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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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Inclusion and exclusion criteria

Inclusion and exclusion criteria

The inclusion criteria was as follows: 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 DAS28 score ≥ 3.2 at screening who experienced at least one type of disease modifying antirheumatic drugs (DMARDs) failure which is defined as "failure of traditional/conventional DMARD(s) due to lack of efficacy/desired response or side effects" on the basis of *2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis* and received MTX for ≥ 3 months with a stable dose (7.5-15mg/week) at least 4 weeks and without any other DMARDs or any traditional Chinese medicines for no less than 4 weeks before screening. 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 intramuscular, intravenous and intra-articular injection glucocorticoids, oral glucocorticoids without a fixed dose, and intramuscular adrenocorticotrophic hormone were not. Negative pregnancy test and during non-lactation were required of the reproductive age female patients at screening, while every subject was requested to access contraception from the beginning to 6 months after the end of the trial. Patients were asked to be available for regular follow-ups and able to read and fill assessment forms correctly. Written informed consent form should be provided by every patient before any procedure of this study.

The exclusion criteria was as follows: weight > 75 Kg; receiving the live attenuated vaccine during 4 weeks before screening; previous treatment with biological DMARDs (including but not limited to infliximab, etanercept, adalimumab, tocilizumab, and rituximab, etc.) during 3 months prior to screening; history of relatively severe infection (e.g., acute hepatitis, pneumonia, and acute

pyelonephritis), or infection requiring hospitalization, intravenous antibiotics, anti-fungal drugs or antiviral drugs during 2 months before randomization, except for mild infection (e.g., acute upper respiratory infection and simple urinary infection) which is not considered as an exclusion criterion, and whether the subject is enrolled is determined by the investigators; suffering from acute or recurrent infection at screening, e.g., respiratory infection (influenza, upper respiratory infection, bronchiectasia, etc.), acute attack of chronic pyelonephritis, or infectious skin wound; history of opportunistic infection (e.g., herpes zoster, active cytomegalovirus, mycoplasma, pneumocystis carinii, histoplasma, aspergillus, and mycobacteria except tubercle bacillus) within 6 months prior to screening; history of artificial joint infection, or with suspected artificial joint infections which had been treated with antibiotics but not removing the artificial joints; history of serious liver disease, positivity for hepatitis B surface antigen, positive hepatitis B core antibody in five items of hepatitis B but also with positive hepatitis B DNA, or hepatitis C virus infection; acquired immunodeficiency syndrome (AIDS) or human immunodeficiency virus (HIV) infection; the following conditions related to tuberculosis (TB): currently or previously active tuberculosis (chest X-rays suggesting anteroposterior and lateral radiographs must be conducted within 3 months prior to screening to identify either current tuberculosis or prior pulmonary tuberculosis infection), close contact with active tuberculosis patients or as one of high-risk and/or immune deficiency groups (e.g., long-term use of glucocorticoids or immunosuppressants) and with signs of latent tuberculosis infection), PPD test (5 IU TB-PPD is injected intradermally into the forearm and the diameter of the indurated skin reaction is measured at 48–72 h) conducted within 3 weeks prior to screening indicating induration in a diameter of ≤ 15 mm but with blister or necrosis or induration in a diameter of > 15 mm, or positive interferon- γ release test (T-SPOT) for replacing PPD test when it was unavailable, meanwhile with the unsuitability implied by

chest radiograph and clinical evidence; history of organ transplantation surgery (except corneal transplantation performed more than 3 months prior to the first dose); suffering from malignant tumor within 5 years prior to screening or current malignant tumor (except skin squamous cell carcinoma, basal cell carcinoma and cervical carcinoma in situ which had completely been resected without evidence of recurrence); history of lymphoid malignancies (such as lymphoma) or lymphoproliferative disease, or having symptoms and signs suggesting lymphoproliferative disease (e.g., cervical, supraclavicular, or axillary lymph node enlargement), or splenomegaly (≥ 2 cm below the ribs) at screening; currently or previously suffering from central nerve demyelination diseases such as multiple sclerosis; currently or previously suffering from congestive heart failure; currently or previously suffering from other autoimmune diseases that may influence evaluations of the study drugs as expected; suffering from serious, progressive, uncontrolled cardiovascular, cerebrovascular, hepatic, renal, pulmonary, gastrointestinal, hematopoietic, endocrine, or nervous diseases, etc., or other conditions making patients not suitable for the study considered by the investigators; history of serious drug abuse or alcohol abuse with clinical symptoms, medication history without medical order, or other conditions that may interfere with the subjects' compliance to the protocol (e.g., mental disorders, frequent travels, and the absence of intention for participation); hemoglobin < 8.5 g/dL, white blood cell count $< 3.5 \times 10^9/L$, platelet count $< 80 \times 10^9/L$, ALT or AST > 2 times the upper limit of normal, and serum creatinine exceeding the upper limit of normal; sensitive to human immunoglobulin or infliximab or their ingredients; participating in other drug clinical study and receiving the study drugs within 30 days or 5 half-lives of the drug (calculating at maximum value) prior to screening.

A collection of supplementary tables

Table S1 Secondary efficacy endpoints in FAS

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
Secondary endpoint in chronological order				
ACR20 at week 2, m/n (%)	83/191(43.5)	74/193(38.3)	5.11 (-4.62,14.85)	0.265
ACR20 at week 6, m/n (%)	106/186(57.0)	107/192(55.7)	1.26 (-8.64,11.16)	0.789
ACR20 at week 14, m/n (%)	122/180(67.8)	117/185(63.2)	4.53 (-5.17,14.24)	0.344
ACR20 at week 22, m/n (%)	109/176(61.9)	113/181(62.4)	-0.50 (-10.48,9.48)	0.917
ACR50 at week 2, m/n (%)	23/191(12.0)	19/193(9.8)	2.20 (-4.72,9.11)	0.473
ACR50 at week 6, m/n (%)	40/186(21.5)	43/192(22.4)	-0.89 (-9.28,7.50)	0.847
ACR50 at week 14, m/n (%)	70/180(38.9)	61/185(33.0)	5.92 (-3.85,15.68)	0.180
ACR50 at week 22, m/n (%)	67/176(38.1)	65/181(35.9)	2.16 (-7.77,12.08)	0.592
ACR50 at week 30, m/n (%)	80/172(46.5)	75/177(42.4)	4.14 (-6.17,14.45)	0.288
ACR70 at week 2, m/n (%)	7/191(3.7)	3/193(1.6)	2.11 (-3.48,7.70)	0.187
ACR70 at week 6, m/n (%)	14/186(7.5)	8/192(4.2)	3.36 (-2.83,9.55)	0.162
ACR70 at week 14, m/n (%)	27/180(15.0)	20/185(10.8)	4.19 (-3.24,11.62)	0.215
ACR70 at week 22, m/n (%)	40/176(22.7)	31/181(17.1)	5.60 (-2.89,14.09)	0.152
ACR70 at week 30, m/n (%)	53/172(30.8)	40/177(22.6)	8.22 (-1.11,17.54)	0.024*
DAS28 IR at Week 2, %, mean±SD (n)	20.58±16.381(191)	19.44±15.521(192)	1.14 (-2.07,4.34)	0.393
DAS28 IR at Week 6, %, mean±SD (n)	26.83±18.597(186)	25.25±17.184(192)	1.58 (-2.04,5.20)	0.939
DAS28 IR at Week 14, %, mean±SD (n)	30.43±20.240(180)	30.69±17.995(185)	-0.26 (-4.20,3.68)	0.940
DAS28 IR at Week 22, %, mean±SD (n)	32.38±21.676(176)	30.53±20.732(181)	1.84 (-2.57,6.26)	0.391

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
DAS28 IR at Week 30, %, mean±SD (n)	35.18±22.779(172)	33.07±22.433(177)	2.10 (-2.66,6.86)	0.062
IR of morning stiffness duration at week 2, %, mean±SD (n)	42.38±87.271(156)	42.07±88.751(164)	0.30 (-19.07,19.67)	0.408
IR of morning stiffness duration at week 6, %, mean±SD (n)	23.97±313.203(153)	51.29±104.758(164)	-27.32 (-78.24,23.60)	0.899
IR of morning stiffness duration at week 14, %, mean±SD (n)	65.82±67.459(148)	66.72±66.228(159)	-0.90 (-15.92,14.12)	0.313
IR of morning stiffness duration at week 22, %, mean±SD (n)	61.99±88.672(144)	69.56±58.005(156)	-7.57 (-24.47,9.33)	0.956
IR of morning stiffness duration at week 30, %, mean±SD (n)	50.51±167.221(141)	54.49±98.032(154)	-3.98 (-35.08,27.12)	0.107
IR of count of swelling joints at Week 2, %, mean±SD (n)	34.89±43.438(188)	27.89±75.153(187)	7.00 (-5.46,19.46)	0.140
IR of count of swelling joints at Week 6, %, mean±SD (n)	48.92±45.942(183)	49.85±42.852(186)	-0.94 (-10.03,8.16)	0.977
IR of count of swelling joints at Week 14, %, mean±SD (n)	63.75±44.635(177)	58.54±51.336(180)	5.21 (-4.81,15.23)	0.439
IR of count of swelling joints at Week 22, %, mean±SD (n)	49.97±67.063(173)	48.91±62.823(176)	1.06 (-12.61,14.74)	0.284
IR of count of swelling joints at Week 30, %, mean±SD (n)	52.23±67.210(169)	53.00±73.937(173)	-0.77 (-15.81,14.27)	0.381
IR of count of tenderness joints at Week 2, %, mean±SD (n)	28.08±46.359(191)	28.53±47.899(193)	-0.45 (-9.91,9.01)	0.434
IR of count of tenderness joints at Week 6, %, mean±SD (n)	41.29±67.261(186)	38.69±49.305(192)	2.59 (-9.31,14.49)	0.961
IR of count of tenderness joints at Week 14, %, mean±SD (n)	49.24±56.931(180)	52.59±39.595(185)	-3.35 (-13.42,6.73)	0.915
IR of count of tenderness joints at Week 22, %, mean±SD (n)	51.99±73.461(176)	56.59±42.432(181)	-4.60 (-17.05,7.84)	0.656
IR of count of tenderness joints at Week 30, %, mean±SD (n)	57.04±63.239(172)	60.55±39.808(178)	-3.51 (-14.58,7.56)	0.146
IR of subject's VAS score on pain at Week 2, %, mean±SD (n)	24.56±64.915(191)	20.69±72.556(193)	3.86 (-9.96,17.68)	0.356
IR of subject's VAS score on pain at Week 6, %, mean±SD (n)	33.43±49.343(186)	30.27±62.741(192)	3.16 (-8.28,14.59)	0.436
IR of subject's VAS score on pain at Week 14, %, mean±SD (n)	36.67±73.143(180)	30.01±111.546(185)	6.65 (-12.82,26.13)	0.374
IR of subject's VAS score on pain at Week 22, %, mean±SD (n)	42.52±60.835(176)	38.04±83.053(181)	4.48 (-10.71,19.66)	0.717
IR of subject's VAS score on pain at Week 30, %, mean±SD (n)	50.50±49.702(172)	39.20±65.427(177)	11.29 (-0.96,23.55)	0.144

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
IR of subject's VAS score on disease activity at Week 2, %, mean±SD (n)	23.61±57.399(191)	23.64±62.444(193)	-0.04 (-12.07,12.00)	0.752
IR of subject's VAS score on disease activity at Week 6, %, mean±SD (n)	35.30±39.253(186)	32.49±54.578(192)	2.81 (-6.83,12.45)	0.956
IR of subject's VAS score on disease activity at Week 14, %, mean±SD (n)	39.35±70.861(180)	37.50±76.086(185)	1.85 (-13.29,16.99)	0.409
IR of subject's VAS score on disease activity at Week 22, %, mean±SD (n)	44.61±56.737(176)	42.51±77.288(181)	2.11 (-12.04,16.25)	0.647
IR of subject's VAS score on disease activity at Week 30, %, mean±SD (n)	52.48±46.433(172)	44.01±59.711(177)	8.47 (-2.82,19.75)	0.137
IR of investigator's VAS score on disease activity at Week 2, %, mean±SD (n)	20.72±74.060(191)	23.76±85.066(193)	-3.05 (-19.06,12.96)	0.410
IR of investigator's VAS score on disease activity at Week 6, %, mean±SD (n)	31.22±59.284(186)	34.56±59.507(192)	-3.33 (-15.35,8.68)	0.884
IR of investigator's VAS score on disease activity at Week 14, %, mean±SD (n)	41.67±59.475(180)	39.43±94.950(185)	2.23 (-14.13,18.59)	0.712
IR of investigator's VAS score on disease activity at Week 22, %, mean±SD (n)	48.46±46.017(176)	45.66±63.505(181)	2.8 (-8.77,14.37)	0.380
IR of investigator's VAS score on disease activity at Week 30, %, mean±SD (n)	53.80±47.299(172)	47.52±66.131(178)	6.28 (-5.84,18.41)	0.080
IR of HAQ score at Week 2, %, mean±SD (n)	27.23±60.248(189)	23.33±53.163(189)	3.89 (-7.60,15.39)	0.466
IR of HAQ score at Week 6, %, mean±SD (n)	35.74±56.477(184)	37.17±44.954(188)	-1.43 (-11.83,8.96)	0.838
IR of HAQ score at Week 14, %, mean±SD (n)	43.62±49.900(178)	46.74±49.563(181)	-3.12 (-13.44,7.20)	0.765
IR of HAQ score at Week 22, %, mean±SD (n)	48.67±54.889(174)	47.04±52.016(177)	1.64 (-9.59,12.86)	0.092
IR of HAQ score at Week 30, %, mean±SD (n)	48.90±58.218(170)	47.47±65.983(173)	1.43 (-11.80,14.65)	0.229
IR of ESR at Week 2, %, mean±SD (n)	21.19±166.604(191)	16.53±165.139(192)	4.66 (-28.67,37.99)	0.156

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
IR of ESR at Week 6, %, mean±SD (n)	19.06±89.906(187)	24.35±60.156(192)	-5.29 (-20.70,10.13)	0.417
IR of ESR at Week 14, %, mean±SD (n)	5.99±172.995(180)	16.54±107.747(185)	-10.55 (-40.13,19.03)	0.353
IR of ESR at Week 22, %, mean±SD (n)	7.07±176.875(176)	1.44±130.066(181)	5.64 (-26.61,37.89)	0.008*
IR of ESR at Week 30, %, mean±SD (n)	21.10±62.484(172)	4.74±129.320(178)	16.36 (-5.11,37.83)	0.158
IR of CRP at Week 2, %, mean±SD (n)	32.98±124.987(191)	32.74±80.188(193)	0.24 (-20.81,21.29)	0.111
IR of CRP at Week 6, %, mean±SD (n)	-5.67±317.282(187)	16.02±135.342(191)	-21.69 (-70.84,27.47)	0.389
IR of CRP at Week 14, %, mean±SD (n)	-0.38±264.399(180)	18.69±93.800(185)	-19.08 (-59.70,21.55)	0.052
IR of CRP at Week 22, %, mean±SD (n)	0.76±253.841(176)	-3.16±141.358(181)	3.92 (-38.69,46.54)	0.017*
IR of CRP at Week 30, %, mean±SD (n)	12.78±111.259(172)	-9.28±160.043(178)	22.07 (-7.01,51.14)	0.213

*p<0.05

ACR20, American College of Rheumatology criteria (28 joints) for 20%; ACR50, American College of Rheumatology criteria (28 joints) for 50%; ACR70, American College of Rheumatology criteria (28 joints) for 70%; CI, confidence interval; CRP, C-reactive protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IR, improvement rate; “m” was the number of subjects reaching ACR20/ACR50/ACR70 into FAS in each group; “n” was the number of subjects included into FAS in each group; RD, rate difference, CMAB008 - infliximab; SD, standard deviation; VAS, visual analogue scale.

Table S2 Secondary efficacy endpoints in PPS

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
Secondary endpoint in chronological order				
ACR20 at week 2, m/n (%)	71/172(41.3)	68/177(38.4)	2.86 (-7.31,13.03)	0.489
ACR20 at week 6, m/n (%)	96/172(55.8)	102/177(57.6)	-1.81 (-12.10,8.48)	0.784
ACR20 at week 14, m/n (%)	117/172(68.0)	111/177(62.7)	5.31 (-4.63,15.25)	0.254
ACR20 at week 22, m/n (%)	107/172(62.2)	111/177(62.7)	-0.50 (-10.58,9.58)	0.913
ACR50 at week 2, m/n (%)	20/172(11.6)	16/177(9.0)	2.59 (-4.56,9.73)	0.439
ACR50 at week 6, m/n (%)	37/172(21.5)	41/177(23.2)	-1.65 (-10.43,7.12)	0.730
ACR50 at week 14, m/n (%)	67/172(39.0)	60/177(33.9)	5.06 (-4.95,15.07)	0.262
ACR50 at week 22, m/n (%)	66/172(38.4)	65/177(36.7)	1.65 (-8.41,11.71)	0.589
ACR50 at week 30, m/n (%)	80/172(46.5)	75/177(42.4)	4.14 (-6.17,14.45)	0.271
ACR70 at week 2, m/n (%)	6/172(3.5)	3/177(1.7)	1.79 (-4.02,7.61)	0.314
ACR70 at week 6, m/n (%)	13/172(7.6)	7/177(4.0)	3.60 (-2.84,10.04)	0.174
ACR70 at week 14, m/n (%)	27/172(15.7)	20/177(11.3)	4.40 (-3.29,12.09)	0.209
ACR70 at week 22, m/n (%)	39/172(22.7)	31/177(17.5)	5.16 (-3.44,13.76)	0.166
ACR70 at week 30, m/n (%)	53/172(30.8)	40/177(22.6)	8.22 (-1.11,17.54)	0.022*
DAS28 IR at Week 2, %, mean±SD (n)	20.26±16.809(172)	19.11±15.655(177)	1.15 (-2.26,4.57)	0.570
DAS28 IR at Week 6, %, mean±SD (n)	26.47±18.575(172)	25.55±17.439(177)	0.92 (-2.87,4.71)	0.524
DAS28 IR at Week 14, %, mean±SD (n)	30.61±19.966(172)	30.59±18.113(177)	0.01 (-4.00,4.02)	0.842
DAS28 IR at Week 22, %, mean±SD (n)	32.88±21.619(172)	30.57±20.722(177)	2.31 (-2.15,6.77)	0.210
DAS28 IR at Week 30, %, mean±SD (n)	35.18±22.779(172)	33.07±22.433(177)	2.10 (-2.66,6.86)	0.089
IR of morning stiffness duration at week 2, %, mean±SD (n)	44.29±88.482(141)	41.40±90.987(154)	2.89 (-17.71,23.49)	0.588

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
IR of morning stiffness duration at week 6, %, mean±SD (n)	22.16±325.631(141)	50.77±107.691(154)	-28.62 (-83.25,26.02)	0.786
IR of morning stiffness duration at week 14, %, mean±SD (n)	66.60±67.449(141)	66.94±66.872(154)	-0.34 (-15.74,15.07)	0.409
IR of morning stiffness duration at week 22, %, mean±SD (n)	62.25±89.288(141)	70.90±56.660(154)	-8.65 (-25.64,8.34)	0.925
IR of morning stiffness duration at week 30, %, mean±SD (n)	50.51±167.221(141)	54.49±98.032(154)	-3.98 (-35.08,27.12)	0.114
IR of count of swelling joints at Week 2, %, mean±SD (n)	33.49±44.895(169)	28.42±77.717(172)	5.07 (-8.48,18.62)	0.249
IR of count of swelling joints at Week 6, %, mean±SD (n)	48.75±47.175(169)	50.17±43.525(172)	-1.42 (-11.09,8.24)	0.949
IR of count of swelling joints at Week 14, %, mean±SD (n)	63.79±45.118(169)	57.98±52.181(172)	5.81 (-4.59,16.21)	0.647
IR of count of swelling joints at Week 22, %, mean±SD (n)	50.09±67.746(169)	48.42±63.294(172)	1.68 (-12.28,15.64)	0.207
IR of count of swelling joints at Week 30, %, mean±SD (n)	52.23±67.210(169)	52.72±74.065(172)	-0.50 (-15.57,14.58)	0.336
IR of count of tenderness joints at Week 2, %, mean±SD (n)	26.30±47.938(172)	26.93±47.981(177)	-0.63 (-10.73,9.47)	0.674
IR of count of tenderness joints at Week 6, %, mean±SD (n)	40.26±69.408(172)	39.08±50.046(177)	1.17 (-11.54,13.89)	0.833
IR of count of tenderness joints at Week 14, %, mean±SD (n)	49.14±57.791(172)	52.81±39.712(177)	-3.67 (-14.09,6.74)	0.966
IR of count of tenderness joints at Week 22, %, mean±SD (n)	52.09±74.179(172)	57.11±42.252(177)	-5.02 (-17.69,7.64)	0.766
IR of count of tenderness joints at Week 30, %, mean±SD (n)	57.04±63.239(172)	60.32±39.809(177)	-3.29 (-14.38,7.81)	0.169
IR of subject's VAS score on pain at Week 2, %, mean±SD (n)	23.57±67.664(172)	20.07±75.266(177)	3.51 (-11.58,18.59)	0.545
IR of subject's VAS score on pain at Week 6, %, mean±SD (n)	32.64±50.615(172)	30.42±64.520(177)	2.23 (-10.01,14.46)	0.822
IR of subject's VAS score on pain at Week 14, %, mean±SD (n)	37.32±74.038(172)	29.74±113.924(177)	7.58 (-12.71,27.87)	0.361
IR of subject's VAS score on pain at Week 22, %, mean±SD (n)	43.15±60.917(172)	37.85±83.830(177)	5.30 (-10.16,20.77)	0.731
IR of subject's VAS score on pain at Week 30, %, mean±SD (n)	50.50±49.702(172)	39.20±65.427(177)	11.29 (-0.96,23.55)	0.137
IR of subject's VAS score on disease activity at Week 2, %, mean±SD (n)	22.94±60.173(172)	23.00±64.403(177)	-0.06 (-13.20,13.07)	0.833
IR of subject's VAS score on	34.65±39.959(172)	32.43±56.398(177)	2.22	0.978

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
disease activity at Week 6, %, mean±SD (n)			(-8.10,12.53)	
IR of subject's VAS score on disease activity at Week 14, %, mean±SD (n)	39.34±72.254(172)	37.50±77.636(177)	1.83 (-13.97,17.63)	0.495
IR of subject's VAS score on disease activity at Week 22, %, mean±SD (n)	44.90±57.181(172)	42.23±78.048(177)	2.67 (-11.77,17.11)	0.673
IR of subject's VAS score on disease activity at Week 30, %, mean±SD (n)	52.48±46.433(172)	44.01±59.711(177)	8.47 (-2.82,19.75)	0.122
IR of investigator's VAS score on disease activity at Week 2, %, mean±SD (n)	23.09±66.722(172)	22.92±88.540(177)	0.16 (-16.38,16.70)	0.423
IR of investigator's VAS score on disease activity at Week 6, %, mean±SD (n)	33.35±51.346(172)	34.63±61.691(177)	-1.28 (-13.25,10.69)	0.715
IR of investigator's VAS score on disease activity at Week 14, %, mean±SD (n)	42.21±60.409(172)	39.49±97.059(177)	2.71 (-14.37,19.79)	0.679
IR of investigator's VAS score on disease activity at Week 22, %, mean±SD (n)	49.09±45.931(172)	45.66±64.145(177)	3.42 (-8.35,15.20)	0.411
IR of investigator's VAS score on disease activity at Week 30, %, mean±SD (n)	53.80±47.299(172)	47.22±66.200(177)	6.58 (-5.56,18.72)	0.084
IR of HAQ score at Week 2, %, mean±SD (n)	26.03±62.684(170)	22.88±53.857(173)	3.16 (-9.25,15.56)	0.435
IR of HAQ score at Week 6, %, mean±SD (n)	35.30±57.153(170)	37.05±45.981(173)	-1.75 (-12.76,9.26)	0.760
IR of HAQ score at Week 14, %, mean±SD (n)	43.71±50.697(170)	47.20±49.457(173)	-3.49 (-14.12,7.15)	0.580
IR of HAQ score at Week 22, %, mean±SD (n)	48.94±55.261(170)	46.77±52.172(173)	2.17 (-9.24,13.58)	0.109
IR of HAQ score at Week 30, %, mean±SD (n)	48.90±58.218(170)	47.47±65.983(173)	1.43 (-11.80,14.65)	0.239
IR of ESR at Week 2, %, mean±SD (n)	20.69±173.513(172)	15.98±171.755(177)	4.71 (-31.64,41.07)	0.355
IR of ESR at Week 6, %, mean±SD (n)	21.50±79.766(172)	24.56±61.106(177)	-3.06 (-18.00,11.87)	0.609
IR of ESR at Week 14, %, mean±SD (n)	17.32±86.959(172)	15.62±109.758(177)	1.70 (-19.19,22.58)	0.400

Parameter	CMAB008	Infliximab	Difference (95% CI)	P value
IR of ESR at Week 22, %, mean±SD (n)	18.42±112.815(172)	1.28±131.061(177)	17.14 (-8.64,42.92)	0.013*
IR of ESR at Week 30, %, mean±SD (n)	21.10±62.484(172)	4.42±129.616(177)	16.68 (-4.84,38.21)	0.274
IR of CRP at Week 2, %, mean±SD (n)	30.30±130.905(172)	32.21±82.840(177)	-1.91 (-24.91,21.09)	0.168
IR of CRP at Week 6, %, mean±SD (n)	4.13±306.158(172)	22.48±94.314(176)	-18.35 (-65.89,29.19)	0.391
IR of CRP at Week 14, %, mean±SD (n)	0.10±269.671(172)	18.25±95.289(177)	-18.15 (-60.50,24.20)	0.095
IR of CRP at Week 22, %, mean±SD (n)	5.14±251.575(172)	-3.25±142.656(177)	8.40 (-34.51,51.30)	0.016*
IR of CRP at Week 30, %, mean±SD (n)	12.78±111.259(172)	-9.62±160.433(177)	22.40 (-6.74,51.55)	0.315

*p<0.05

ACR20, American College of Rheumatology criteria (28 joints) for 20%; ACR50, American College of Rheumatology criteria (28 joints) for 50%; ACR70, American College of Rheumatology criteria (28 joints) for 70%; CI, confidence interval; CRP, C-reactive protein; DAS28, disease activity score 28; ESR, erythrocyte sedimentation rate; HAQ, health assessment questionnaire; IR, improvement rate; “m” was the number of subjects reaching ACR20/ACR50/ACR70 into FAS in each group; “n” was the number of subjects included into FAS in each group; RD, rate difference, CMAB008 - infliximab; SD, standard deviation; VAS, visual analogue scale.

Table S3 TEAEs with an incidence of $\geq 2\%$

SOC	CMAB008 (n = 192)				Infliximab (n = 195)			
	Incidence n (%)	Severity			Incidence n (%)	Severity		
		Mild	Moderate	Severe		Mild	Moderate	Severe
Total	160(83.3)	90(56.3)	57(35.6)	13(8.1)	159(81.5)	91(57.2)	55(34.6)	13(8.2)
Metabolism and nutrition disorders	9(4.7)	8(88.9)	1(11.1)	0	13(6.7)	12(92.3)	1(7.7)	0
Hyperuricemia	4(2.1)	4(100.0)	0	0	3(1.5)	3(100.0)	0	0
Immune system disorders	7(3.6)	2(28.6)	3(42.9)	2(28.6)	9(4.6)	4(44.4)	3(33.3)	2(22.2)
Drug hypersensitivity	5(2.6)	0	3(60.0)	2(40.0)	5(2.6)	2(40.0)	1(20.0)	2(40.0)
General disorders and administration site conditions	16(8.3)	14(87.5)	2(12.5)	0	22(11.3)	20(90.9)	1(4.5)	1(4.5)
Asthenia	1(0.5)	1(100.0)	0	0	4(2.1)	4(100.0)	0	0
Pyrexia	7(3.6)	6(85.7)	1(14.3)	0	10(5.1)	9(90.0)	0	1(10.0)
Chest pain	2(1.0)	2(100.0)	0	0	4(2.1)	4(100.0)	0	0
Chest discomfort	2(1.0)	2(100.0)	0	0	5(2.6)	4(80.0)	1(20.0)	0
Musculoskeletal and connective tissue disorders	17(8.9)	11(64.7)	5(29.4)	1(5.9)	18(9.2)	12(66.7)	4(22.2)	2(11.1)
Arthralgia	7(3.6)	4(57.1)	3(42.9)	0	7(3.6)	4(57.1)	3(42.9)	0
Investigations	59(30.7)	52(88.1)	7(11.9)	0	50(25.6)	47(94.0)	3(6.0)	0
Alanine transferase increased	5(2.6)	4(80.0)	1(20.0)	0	7(3.6)	6(85.7)	1(14.3)	0
Neutrophil count increased	5(2.6)	4(80.0)	1(20.0)	0	2(1.0)	2(100.0)	0	0
Neutrophil count decreased	9(4.7)	8(88.9)	1(11.1)	0	12(6.2)	11(91.7)	1(8.3)	0
Aspartate aminotransferase increased	5(2.6)	5(100.0)	0	0	6(3.1)	5(83.3)	1(16.7)	0
Blood urine present	8(4.2)	8(100.0)	0	0	2(1.0)	2(100.0)	0	0
Lymphocyte count decreased	6(3.1)	6(100.0)	0	0	3(1.5)	2(66.7)	1(33.3)	0
White blood cell count increased	5(2.6)	4(80.0)	1(20.0)	0	3(1.5)	3(100.0)	0	0
White blood cell count decreased	14(7.3)	12(85.7)	2(14.3)	0	14(7.2)	13(92.9)	1(7.1)	0
Nervous system disorders	14(7.3)	12(85.7)	2(14.3)	0	20(10.3)	16(80.0)	4(20.0)	0
Dizziness	5(2.6)	5(100.0)	0	0	13(6.7)	13(100.0)	0	0
Headache	3(1.6)	3(100.0)	0	0	4(2.1)	4(100.0)	0	0
Hypoesthesia	1(0.5)	1(100.0)	0	0	4(2.1)	3(75.0)	1(25.0)	0
Respiratory, thoracic and mediastinal disorders	31(16.1)	23(74.2)	6(19.4)	2(6.5)	32(16.4)	26(81.3)	5(15.6)	1(3.1)
Cough	14(7.3)	12(85.7)	2(14.3)	0	17(8.7)	14(82.4)	3(17.6)	0

SOC	PT	CMAB008 (n = 192)				Infliximab (n = 195)			
		Incidence n (%)	Severity			Incidence n (%)	Severity		
			Mild	Moderate	Severe		Mild	Moderate	Severe
	Nasal obstruction	4(2.1)	3(75.0)	1(25.0)	0	3(1.5)	3(100.0)	0	0
	Rhinorrhea	4(2.1)	3(75.0)	1(25.0)	0	1(0.5)	1(100.0)	0	0
	Cardiac disorders	8(4.2)	7(87.5)	1(12.5)	0	11(5.6)	11(100.0)	0	0
	Palpitations	2(1.0)	1(50.0)	1(50.0)	0	5(2.6)	5(100.0)	0	0
	Infections and infestations	90(46.9)	54(60.0)	29(32.2)	7(7.8)	91(46.7)	64(70.3)	26(28.6)	1(1.1)
	Upper respiratory tract infection	64(33.3)	44(68.8)	20(31.3)	0	57(29.2)	38(66.7)	19(33.3)	0
	Pharyngitis	6(3.1)	4(66.7)	2(33.3)	0	4(2.1)	3(75.0)	1(25.0)	0
	Urinary tract infection	9(4.7)	6(66.7)	3(33.3)	0	18(9.2)	16(88.9)	1(5.6)	1(5.6)
	Pneumonia	5(2.6)	1(20.0)	1(20.0)	3(60.0)	4(2.1)	3(75.0)	1(25.0)	0
	Bronchitis	1(0.5)	1(100.0)	0	0	5(2.6)	4(80.0)	1(20.0)	0
	Nasopharyngitis	1(0.5)	1(100.0)	0	0	4(2.1)	4(100.0)	0	0
	Skin and subcutaneous tissue disorders	23(12.0)	19(82.6)	4(17.4)	0	21(10.8)	9(42.9)	12(57.1)	0
	Pruritus	5(2.6)	4(80.0)	1(20.0)	0	4(2.1)	4(100.0)	0	0
	Rash	10(5.2)	9(90.0)	1(10.0)	0	6(3.1)	5(83.3)	1(16.7)	0
	Urticaria	4(2.1)	3(75.0)	1(25.0)	0	5(2.6)	1(20.0)	4(80.0)	0
	Dermatitis allergic	3(1.6)	1(33.3)	2(66.7)	0	5(2.6)	1(20.0)	4(80.0)	0
	Hepatobiliary disorders	31(16.1)	22(71.0)	8(25.8)	1(3.2)	32(16.4)	22(68.8)	10(31.3)	0
	Hepatic function abnormal	24(12.5)	16(66.7)	7(29.2)	1(4.2)	22(11.3)	14(63.6)	8(36.4)	0
	Drug-induced liver injury	4(2.1)	4(100.0)	0	0	5(2.6)	3(60.0)	2(40.0)	0
	Gastrointestinal disorders	28(14.6)	23(82.1)	5(17.9)	0	47(24.1)	36(76.6)	9(19.1)	2(4.3)
	Abdominal pain upper	4(2.1)	4(100.0)	0	0	6(3.1)	5(83.3)	1(16.7)	0
	Vomiting	4(2.1)	3(75.0)	1(25.0)	0	3(1.5)	3(100.0)	0	0
	Nausea	2(1.0)	1(50.0)	1(50.0)	0	7(3.6)	7(100.0)	0	0
	Chronic gastritis	1(0.5)	1(100.0)	0	0	6(3.1)	3(50.0)	2(33.3)	1(16.7)
	Toothache	4(2.1)	3(75.0)	1(25.0)	0	8(4.1)	8(100.0)	0	0
	Diarrhea	4(2.1)	4(100.0)	0	0	4(2.1)	4(100.0)	0	0
	Abdominal pain	1(0.5)	1(100.0)	0	0	4(2.1)	3(75.0)	1(25.0)	0
	Abdominal discomfort	4(2.1)	2(50.0)	2(50.0)	0	7(3.6)	5(71.4)	2(28.6)	0
	Blood and lymphatic system disorders	10(5.2)	9(90.0)	1(10.0)	0	13(6.7)	8(61.5)	5(38.5)	0
	Lymphadenopathy	1(0.5)	1(100.0)	0	0	4(2.1)	3(75.0)	1(25.0)	0
	Anemia	7(3.6)	6(85.7)	1(14.3)	0	7(3.6)	4(57.1)	3(42.9)	0
	Vascular disorders	9(4.7)	5(55.6)	4(44.4)	0	6(3.1)	3(50.0)	3(50.0)	0
	Hypertension	5(2.6)	2(40.0)	3(60.0)	0	4(2.1)	2(50.0)	2(50.0)	0

PT, preferred terms; SOC, system organ classification

In the summary (Overall, SOC, PT) of the incidences at each level, for an event that occurred more than once in subjects, the one at most severe severity was counted.

Table S4 The names of all the ethics committees

Name of Ethics Committee	Approval No
Peking University People's Hospital Ethics Committee	2017PHA070-01
Ethics Committee of the First Affiliated Hospital of Zhengzhou University	Drug-2017-69
Ethics Committee of the First Affiliated Hospital of Kunming Medical University	2017ECYL31
Qinghai University Affiliated Hospital Ethics Committee	2017LLPJ-008
Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine Ethics Committee	2017-Y-04
Ethics Committee of the Southwest Hospital of Army Medical University	YW201738
Ethics Committee of West China Hospital Sichuan University	2017CT(130)
Ethics Committee of Qilu Hospital of Shandong University	2017046
Ethics Committee of the Affiliated Hospital of Shandong University of Traditional Chinese Medicine	2018EC(003)-XY
Ethics Committee of the Affiliated Hospital of Nanjing University Medical School	2017-141-01
Pingxiang People's Hospital Ethics Committee	2017D016-E02
Ethics Committee of the First Affiliated Hospital of Harbin Medical University	EC201807
Ethics Committee of the Second Affiliated Hospital of Fujian Medical University	2017002-01
Ethics Committee of Changhai Hospital of Shanghai	CHEC2017-186
Ethics Committee of the First Affiliated Hospital of Xiamen University	XMY-2017Y048-01
Ethics Committee of the First Hospital of Jilin University	(2017)CT171025-206
Ethics Committee of Zhongda Hospital Southeast University	2017ZDSYLL085-P01
Zhuzhou Central Hospital Ethics Committee	ZZCHGCPEC2018002-01
Peking University First Hospital Ethics Committee	2017DrugReg 72
Anhui Provincial Hospital Ethics Committee	2017EC272
Ethics Committee of the Second Affiliated Hospital of Harbin Medical University	2018-Drug-004
Ethics Committee of the Third Affiliated Hospital of Southern Medical University	2017EC012
Ethics Committee of China-Japan Union Hospital of Jilin University	2017121102
Tianjin Medical University General Hospital Ethics Committee	IRB2017-121-01
Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University	Drug2017(041)
Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University	XJTU1AF2018LSY-8
Ethics Committee of the Second Xiangya Hospital of Central South University	2017EC[Drug]-137
Tangdu Hospital Ethics Committee	201712-04
Ethics Committee of Guangdong Provincial Hospital of Chinese Medicine	A2017-022-01
Ethics Committee of Shengjing Hospital of China Medical University	2018PS43
Peking University Third Hospital Ethics Committee	2017EC109-01
Shanghai Xuhui Central Hospital Ethics Committee	2019CT 036