Rheumatology International (2019) 39:1537–1546
https://doi.org/10.1007/s00296-019-04359-9

Rheumatology
INTERNATIONAL

CLINICAL TRIALS

A phase III study of BCD-055 compared with innovator infliximab in patients with active rheumatoid arthritis: 54-week results from the LIRA study

Alexander M. Lila[1,2] · Vadim I. Mazurov[1] · Lev N. Denisov[2] · Olga B. Nesmeyanova[3] · Elena P. Ilivanova[4] · Anna V. Eremeeva[5] · Julia Valentinovna Usacheva[5] · Ekaterina A. Dokukina[5] · Ekaterina V. Chernyaeva[5] · Roman A. Ivanov[5]

Received: 28 March 2019 / Accepted: 28 June 2019 / Published online: 10 July 2019

Abstract

BCD-055 is a biosimilar of innovator infliximab (IFX). Here we present the 54-week results from phase 3 clinical study in patients with rheumatoid arthritis (RA). The aim of this study was to demonstrate the equivalent efficacy and safety of BCD-055 and IFX in patients with active rheumatoid arthritis. 426 adults with active RA were enrolled. Patients were randomized into 2 study arms in 2:1 ratio to receive BCD-055 or IFX innovator in dose of 3 mg/kg at week 0, 2, 6 and then every 8 weeks up to week 54. Primary efficacy endpoint was the rate of American College of Rheumatology (ACR) 20 response at week 14. The equivalence margin was set as 15%. Immunogenicity and safety were also assessed. Rate of ACR20 at week 14 in PP (Per-Protocol) population was 71.2% in BCD-055 group and 67.9% in IFX group. Difference in ACR20 rates between groups was 3.2% with 95% CI [− 7.0%; 13.5%] ($p = 0.587$). Throughout 54-week study period, both groups were characterized by similar rates of ACR20/50/70 response at all timepoints without significant differences ($p > 0.05$). The rates of adverse events (AE) were similar in groups (74.64% in BCD-055 arm vs 66.67% in IFX arm, $p = 0.111$). Antibodies to infliximab were detected in 28.46% patients for BCD-055 arm and 26.56% for IFX arm ($p = 0.786$). BCD-055 and IFX were comparable in efficacy (including radiographic progression), safety and immunogenicity throughout the 54-week study.
Trial registration ClinicalTrials.gov ID, number NCT02762838.

Keywords Biosimilar · Infliximab · BCD-055 · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disorder with unknown etiology characterized by chronic erosive arthritis and systemic lesions that lead to early disability and reduce life expectancy [1]. The current strategy of RA treatment strives for early referral, early diagnosis and early start of effective therapy to prevent progression of the disease and optimize physical functioning, work and social participation. Identification of key cells and cytokines in RA pathogenesis, development of targeted drugs and their rational use radically improved the treatment effectiveness of many inflammatory disorders including RA [2].

The widespread use of biologics in the therapy of rheumatic diseases started with tumor necrosis factor α (TNFα) blockers. TNFα is one of the key cytokines involved in a local and systemic inflammation [3]. The first results of

The results of 14 week study period were presented at EULAR2018 Ann Rheum Dis 2018; 77:316–317.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00296-019-04359-9) contains supplementary material, which is available to authorized users.

✉ Julia Valentinovna Usacheva
usacheva@biocad.ru

1 North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

2 V.A. Nasonova Research Institute of Rheumatology, Moscow, Russia

3 State Budgetary Institution of Healthcare "Chelyabinsk Regional Clinical Hospital", Chelyabinsk, Russia

4 State Budgetary Institution of Healthcare "Leningrad Region Clinical Hospital", Saint Petersburg, Russia

5 JSC BIOCAD, Saint Petersburg, Russia

treatment with anti-TNFα monoclonal antibody infliximab were published in 1993 [4]. The following years were characterized with rapid growth in the number of new biological products that act against TNFα and other targets. However, treatment with biologics is associated with high costs. This caused the development of biosimilars that increase the availability of highly effective therapies to patients. Biosimilar is a biotechnological product that is proved to be comparable to an already approved reference product in quality, non-clinical and clinical evaluation [6]. Several biosimilar products were authorized for marketing over the last decade. From 2006, 50 biosimilars were approved in the European Union (EU) for the treatment of wide range of diseases including inflammatory diseases, cancer and other medical conditions [7].

Infliximab is an effective medicinal product which is used in the treatment of many chronic inflammatory diseases (ankylosing spondylitis, psoriasis and psoriatic arthritis, inflammatory bowel diseases). Innovator infliximab (IFX) is a chimeric anti-TNFα monoclonal antibody that has showed it efficacy for RA treatment in ATTRACT clinical trial [5] and was approved for the treatment of this disease in 1999.

BCD-055 (Infliximab developed by Russian Biotechnology Company JSC BIOCAD) is a biosimilar of IFX. Preclinical studies confirmed the equivalence of BCD-055 and IFX in structure, physical, chemical and biological properties. Equivalence in pharmacokinetics and comparability in efficacy and safety profiles between BCD-055 and IFX were evaluated in phase 1 and 3 clinical trial (ASART-1, ASART-2) in patients with active ankylosing spondylitis [8]. BCD-055 has been approved in Russian Federation for all IFX licensed indications, including RA. This article reports the results of LIRA clinical phase 3 trial which evaluated the equivalent efficacy and safety of BCD-055 and IFX in patients with active RA.

Patients and methods

Patients

Patients 18–75 years of age diagnosed with RA based on ACR 2010 criteria at least 6 months before the date of signing informed consent form (IC), which remained active despite standard disease-modifying antirheumatic drugs (csDMARD) treatment (MTX or other) were enrolled into the study. Active disease was defined as having ≥ 6 swollen joints, ≥ 6 tender joints and at least two of the following: morning stiffness for at least 45 min, erythrocyte sedimentation rate (ESR) ≥ 28 mm/h or serum C-reactive protein (CRP) concentration > 10 mg/l [9].

Main exclusion criteria were: previous use of any monoclonal antibodies, low activity of RA based on DAS28-CRP(4) < 3.2, Felty's syndrome, RA Class IV based on ACR 1991 Revised Criteria for the Classification of Global Functional Status, hepatitis B, C, HIV-infection, tuberculosis (active or latent), severe comorbidities, pregnancy. Additional details of patient eligibility criteria are provided online (see Online Supplementary Material A).

Study design

This was an international multicenter randomized double-blind phase 3 clinical study (named LIRA), which was conducted in accordance with WMA Declaration of Helsinki, good clinical practice, and local legislation of participating countries, and was approved by institutional review boards of the investigational sites. Patients were enrolled in 39 study sites in three countries: Russia (29 study sites), Belarus (4 study sites) and India (6 study sites) (ClinicalTrials.gov NCT02762838). The study was approved by the ethical review board at each participating site before the start of the study. All patients signed IC before inclusion into the screening.

After completion of 28-day screening period all eligible patients were centrally randomized in 2:1 ratio into BCD-055 or IFX groups. Patients in study groups were balanced by country, age, Disease Activity Score in 28 joints (DAS28) score, and methotrexate dose prior the randomization (block randomization). Block randomization was performed by a computer generated random number list prepared by an employee of sponsor with no clinical involvement in the trial. Patients and Investigators were blinded to the allocated arm. BCD-055 and IFX were in identical vials. They were prepacked and consecutively numbered for each patient according to the randomization schedule. BCD-055 or IFX were used at a dose of 3 mg/kg intravenously at weeks 0, 2, 6 and then every 8 weeks until week 54 inclusively. Throughout the study period, patients received stable doses of methotrexate (10–25 mg/week) and folic acid (5 mg/week). Use of oral steroids at a stable prednisolone-equivalent dose not exceeding 10 mg/day was allowed for patients who received such treatment immediately before inclusion into the study.

The primary objective of the study was to demonstrate equivalent efficacy of BCD-055 and IFX in patients with active RA. Secondary goals were to prove equivalent safety and immunogenicity of these two products.

Assessments

Primary efficacy endpoint in LIRA study was the rate of ACR20 response at week 14 which was defined as at least 20% decrease in tender joint count (TJC)/swollen joint count (SJC) (68/66) and at least 20% decrease in 3 or more following parameters: Patient's Global Pain Assessment (PGPA) by 0–100 mm visual analogue scale (VAS); Patient's Global

Activity Assessment (PGAA) by 0–100 mm VAS; Physician's Global Activity Assessment (PhGAA) by 0–100 mm VAS; Health Assessment Questionnaire Disability Index (HAQ-DI) score; ESR and/or CRP.

Secondary efficacy endpoints included ACR20 rate at weeks 30 and 54, ACR50/70 rates (at least 50%/70% decrease in TJC/SJC (68/66) and at least 50%/70% decrease in 3 or more following parameters: PGPA by 0–100 mm visual analogue scale (VAS); PGAA by 0–100 mm VAS; PhGAA by 0–100 mm VAS; HAQ-DI score; ESR and/or CRP); remission and low RA activity by DAS28-CRP(4), Simplified Disease Activity Score (SDAI) and Clinical Disease Activity Score (CDAI) scores; quality of life by the Medical Outcomes Study Short Form Health Survey (SF36). DAS28-CRP(4), CDAI, SDAI higher scores represented higher disease activity. Assessment of secondary efficacy endpoints was done at weeks 14, 30, and 54. X-ray of hands and feet was performed at the baseline and week 54. Endpoints for radiographic progression were the change of total Sharp score at week 54 compared to baseline and rates of patients with increase of RA radiographic stage based on Steinbrocker's classification [10, 11].

Safety was assessed as the incidence and severity of adverse events (AEs) in all patients who have received at least one dose of BCD-055 or IFX according to with Common Terminology Criteria for Adverse Events version 4.03 (CTCAE, v.4.03).

All patients were screened for tuberculosis (TB) by Interferon Gamma Release Assay using the two antigens and chest X-ray. Patients with signs of lung TB, definite or latent TB infection (positive Interferon Gamma Release Assay using the two antigens with the absence of lung TB according to chest X-ray) were not included in the study. During the study, Interferon Gamma Release Assay using the two antigens and chest X-ray was rechecked at weeks 14, 30, and 58 to identify positive conversion from negative results at baseline. If definite signs of active or latent TB have been revealed, the patient should be immediately withdrawn from the study.

All patients were screened for hepatitis B, hepatitis C, HIV-infection, syphilis by serological tests.

Blood samples for anti-drug antibodies (ADA) screening were collected before the first infusion of BCD-055/IFX, and then at weeks 14, 30 and 54. Immunogenicity assay for binding ADA was performed by validated ELISA with horseradish peroxidase as an indicator enzyme and included screening and confirmatory stages.

Statistical analysis

The primary efficacy analysis was performed in both Per-Protocol (PP) and modified Intent-To-Treat (mITT) population, whereas the safety was assessed in mITT population.

Sample size calculation was based on literature data on IFX and its currently approved biosimilars efficacy in RA patients. The number of subjects was determined with the formula for calculating the sample size in parallel-group equivalence studies with unequal randomization [12]. Therapeutic equivalence to IFX in both PP and mITT populations was based on expected responder rates of 65.3% in the main and reference groups. Specifying a 2-sided alpha level of 0.05, power of 80%, and 2-sided equivalent margin of 15% required 387 patients to be included in PP population for primary efficacy endpoint assessment (the total sample size was enlarged up to 426 which considered 10% drop-out rate). The equivalence was considered proven if 95% CI for the difference in ACR20 rates at week 14 lied in a range [− 15%; 15%].

Data were statistically processed using Statistica 10.0 and R3.5.1 software. Quantitative data, which included some demographics and clinical/laboratory data (physical signs and laboratory tests) were tested for normality of distribution using Shapiro–Wilk test and the graphical method. Main quantitative parameters obtained during the study were processed using descriptive statistics. Normally distributed quantitative data were described using mean values and standard deviations. Quantitative non-normally distributed data were described using median values and quartiles.

Statistical comparison methods were selected based on raw data type and distribution. Normally distributed quantitative data were analyzed using the two-sample Student's t test and ANOVA. Non-normally distributed data were analyzed using the Mann–Whitney test and Wilcoxon test.

Percentages or proportions were used to describe categorical data. Categorical data were processed using the Fisher's exact test and Pearson's χ^2 test.

Results

Population

530 patients signed IC and underwent screening procedures. 104 (19.6%) were not randomized: 86 patients did not meet eligibility criteria and 18 patients withdrew IC prior to randomization. 426 patients were randomized into the study within the recruitment period from January 20th to December 30th 2016. 345 patients have completed 54 weeks of the study in accordance with the protocol. Reasons for early withdrawal were IC withdrawal, adverse events, protocol violation or lost to follow up (Fig. 1). Baseline and disease characteristics were highly similar in the groups (Table 1). The medians of received dosed were 213.8 [185.5–246.0] mg for BCD-055 and 208.6 [183.0–240.0] mg for IFX. The median number of received infusions was 9 [1–9] for both BCD-055 and IFX.

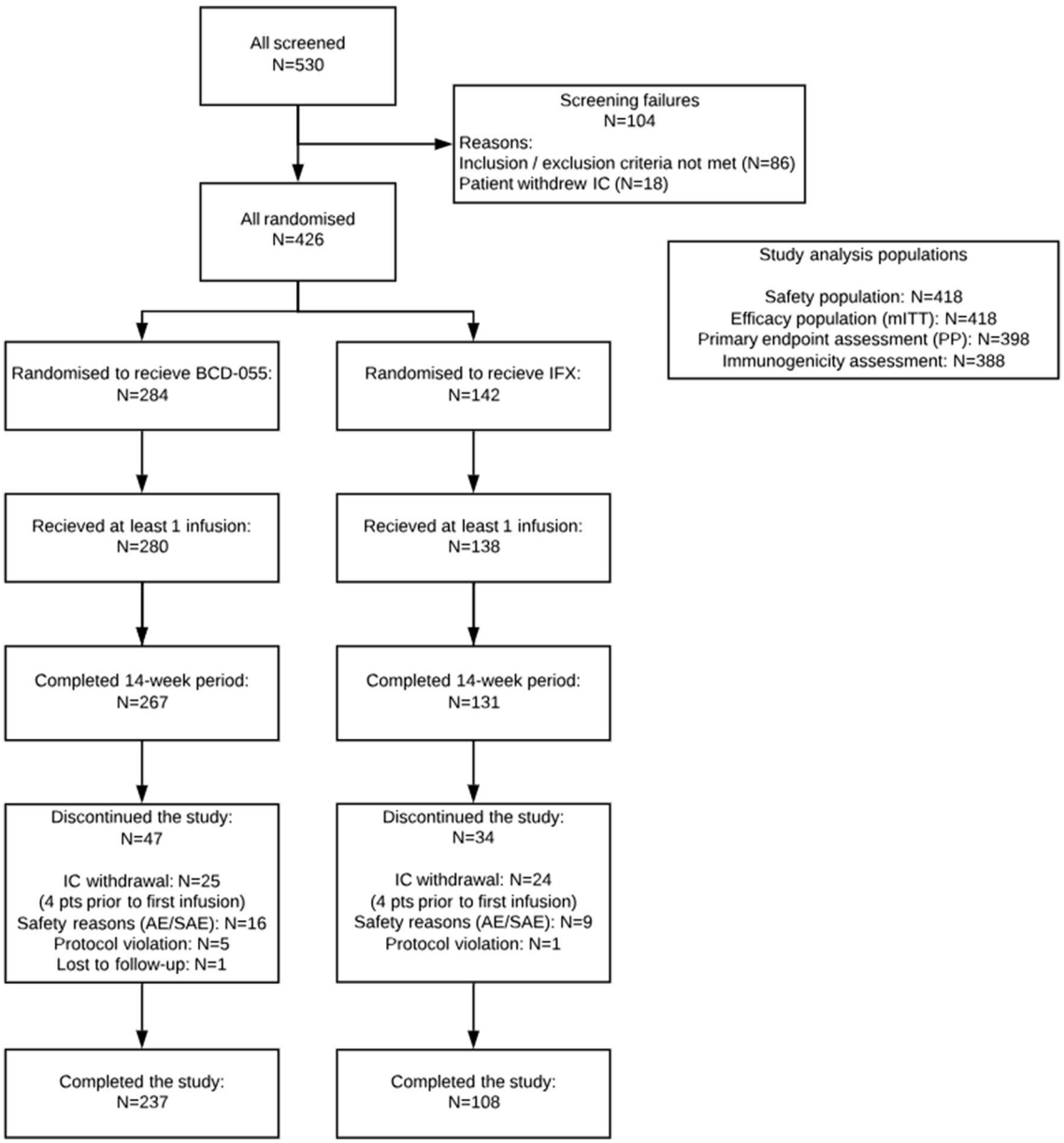

Fig. 1 Study flow

Primary efficacy endpoint

Rate of ACR20 at week 14 in PP population was similar in both groups (71.2% in BCD-055 arm, 67.9% in IFX arm). Difference in ACR20 rates between groups was 3.2% with 95% CI [− 7.0%; 13.5%] ($p = 0.587$). Obtained 95% CI was entirely within set equivalence margin $\delta = |0, 15|$, which proves the hypothesis of the study and confirms equivalence of BCD-055 and IFX. The same results were obtained in mITT population, 95% CI for the treatment difference also lied within predefined equivalence margin ($\delta = |0, 15|$) (Fig. 2).

Secondary efficacy endpoints

Evaluation of secondary efficacy endpoints also did not reveal differences between BCD-055 and IFX. Throughout the study period, both groups were characterized by similar rates of ACR20/50/70 response at all timepoints without significant differences ($p > 0.05$) (Fig. 3). At week 54 69.6% of patients in BCD-055 arm and 65.2% in IFX arm had ACR20 response. It should be emphasized that percentage of patients with ACR50 response increased throughout the study up from 36.1% of ACR50 responders at week 14–48.5% at week 54 in BCD-055 arm and from 32.6 to

Table 1 Basic demographic and disease characteristics (mITT population)

Parameter	BCD-055 ($n=280$)	IFX ($n=138$)
Age, (years)	53.0 (41.0–61.0)	53.0 (40.0–59.0)
Females[a]	227 (81.1)	110 (79.7)
Males[a]	53 (18.9)	28 (20.3)
Race		
Caucasian[a]	265 (94.64)	123 (89.13)
Mongoloid[a]	15 (5.36)	14 (10.15)
Black[a]	0 (100.0)	1 (0.72)
Body weight, (kg)	70.0 (60.0–82.0)	68.0 (60.4–80.0)
RA duration, (years)	3.8 (1.5–8.0)	4.4 (1.3–10.1)
Patient's Global Pain Assessment, (mm)	70.0 (60.0–80.0)	68.5 (56.0–80.0)
Patient's Global Activity Assessment, (mm)	71.0 (60.0–81.0)	70.0 (60.0–80.0)
Physician's Global Activity Assessment, (mm)	67.0 (57.0–78.00)	70.0 (60.0–77.0)
DAS28-CRP(4), score	6.2 (5.7–6.7)	6.0 (5.6–6.5)
CDAI, score	39.2 (31.5–46.0)	36.9 (31.9–42.0)
SDAI, score	42.5 (35.2–51.1)	41.2 (34.2–47.5)
Rate of CCPA-positive patients[a]	213 (76.1%)	113 (81.9%)
Systemic manifestations of RA[a]	19 (6.8%)	7 (5.1%)
CRP (mg/l)	27.2 (16.2–50.4)	22.9 (14.0–51.5)
ESR (mm/h)	42.5 (29.0–64.0)	44.5 (30.0–63.0)
MTX dose at baseline	15.0 (12.5–20.5)	15.0 (15.0–20.0)
Oral corticosteroid use[a]	121 (43.2)	67 (48.6)

DAS28-CRP(4) Disease Activity Score in 28 joints (0—indicates absence of disease activity), *CDAI* Clinical Disease Activity Index (0—indicates absence of disease activity), *SDAI* Simple Disease Activity Index (0—indicates absence of disease activity), *CCPA* cyclic citrullinated peptides antibodies, *CRP* C-reactive protein, *ESR* erythrocyte sedimentation rate, *MTX* methotrexate

Medians and interquartile ranges are presented except variables marked with[a], where no. (%) is presented

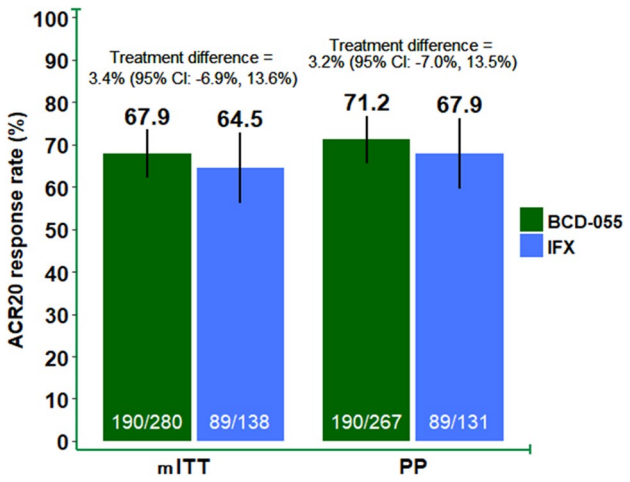

Fig. 2 Percentage of patients achieved ACR20 by week 14 (primary endpoint) for the mITT (modified Intent-To-Treat) population ($n=280$ in BCD-055 arm, $n=138$ in IFX arm) and PP (Per-Protocol) populations ($n=267$ in BCD-055 arm, $n=131$ in IFX arm)

48.2% in IFX arm. Moreover, percentage of patients with ACR70 response also increased during the treatment period from 17.1 to 13% in BCD-055 and IFX arms at week 14 to 37.7% and 34.6% in the same arms at week 54, respectively. This means that a certain number of patients experienced further improvement in ACR response domains after achieving ACR20.

Absolute values of DAS28-CRP(4), CDAI and SDAI scores changed in a similar manner, there was a significant decrease in median rates at week 14 compared to screening, up to the values that correspond to moderate RA activity, then followed by a reliable but less pronounced positive dynamic up to a week 54 ($p<0.05$). At the baseline median DAS28-CRP(4) scores corresponded to high-RA activity (6.2 vs 6.0 in BCD-055 and IFX arms, respectively, $p>0.05$), whereas at week 54 DAS28-CRP(4) scores reflected low RA activity in both arms (3.2 vs 3.0, $p>0.05$). The same dynamics revealed for CDAI and SDAI absolute values. CDAI score decreased from 39.2 at baseline to 9.2 at week 54 in BCD-055 arm ($p<0.0001$) and from 36.9 to 6.85 in IFX arm ($p<0.0001$). SDAI score improved from 42.5 and 41.2 to 10.2 and 7.9 in BCD-055 and IFX arms, respectively ($p<0.0001$).

During the study, the proportion of patients achieving remission or low activity of RA for each of the analyzed criteria progressively increased in each group, without significant intergroup differences (Table 2A). The similar

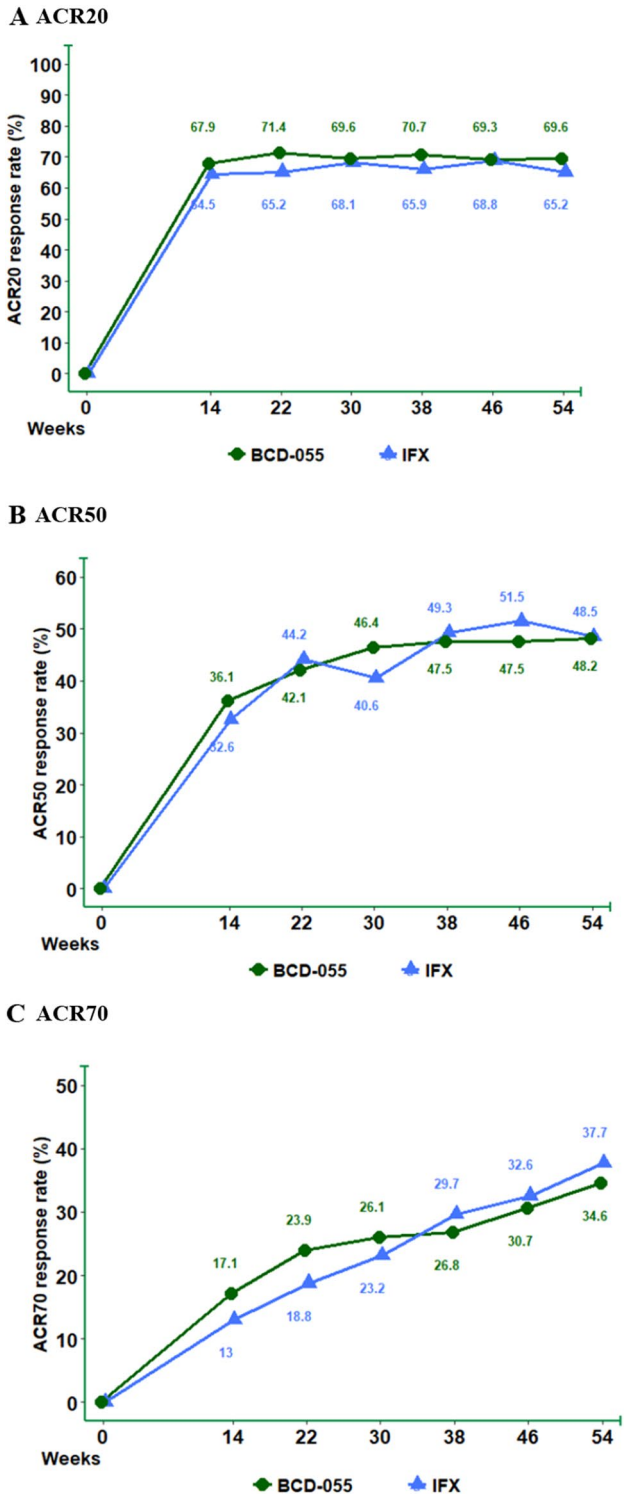

Fig. 3 ACR response rates throughout the study. Percentage of patients achieved ACR20/50/70 for the mITT (modified intent-to-treat) population ($n=280$ in BCD-055 arm, $n=138$ in IFX arm). **a** Percentage of ACR20 responders, [%, $p>0.05$ for all timepoints, Pearson's χ^2 criterion (Yates)]; **b** percentage of ACR50 responders [%, $p>0.05$ for all timepoints, Pearson's χ^2 criterion (Yates)]; **c** percentage of ACR70 responders, [%, $p>0.05$ for all timepoints, Pearson's χ^2 criterion (Yates)]

dynamics was shown for the rate of ACR/EULAR 2011 remission: by week 54 14.3% and 12.3% in BCD-055 and IFX arm had ACR/EULAR 2011 remission ($p>0.05$). Total Sharp score was similar in both groups both at baseline and week 54 (129.4 vs 133.8 at baseline and 129.8 vs 133.9 at week 54 in BCD-055 and IFX arm, respectively, $p>0.05$). Majority of the patients had 2nd and 3rd radiographic stage according to Steinbrocker's classification at screening and throughout the study. Only one episode of stage progression was observed in BCD-055 arm.

Quality of life assessment showed that SF-36 mental and physical components scores significantly improved by week 14. The further limited growth for both components of SF-36 was observed for up to the last observation timepoint at week 54 (Table 2B).

Safety

The rates of adverse events were similar in both groups ($p>0.05$) (Table 3). There were no deaths reported during the study.

The most common AEs were hypertension, anemia, lymphocytosis, neutropenia, ALT/AST increase and upper respiratory tract acute viral infections. Both arms had comparable incidence of all abovementioned AEs apart from hypertension, which was significantly more frequent in BCD-055 arm (28.28% vs 15.94%, $p<0.05$).

The therapy-related AEs (TAE) were reported for 47.14% of patients in BCD-055 arm and 40.58% in IFX arm ($p=0.245$). In general, each of TAEs was observed in < 3% of patients. Relation to study treatment for every AE was defined by Investigator. The grade of severity was established in accordance with CTCAE, v.4.03. Most of TAEs were mild or moderate. Grade 3 TAEs were observed in 8.93% and 5.80% of patients in BCD-055 and IFX arm, respectively ($p=0.356$). None of the patients experienced Grade 4 TAEs.

TAEs, presented with laboratory abnormalities (anaemia, neutropenia, leucopenia, ALT increase, AST increase, hyperglycemia), were established during standard protocol procedures (complete blood count, blood biochemistry). TAEs with clinical manifestations (infusion reaction, allergic reaction, hypertension, atrial fibrillation, bronchospasm, tuberculosis, pneumonia, asthma) were defined by investigator based on clinical symptoms, laboratory and instrumental studies.

AEs of particular interest were reported for both arms. One case of therapy-related tuberculosis and one case of infiltrative colon cancer (unrelated to study therapy) occurred in BCD-055 and IFX arm, respectively. Both patients discontinued the study immediately after the diagnosis was established. The proportion of patient who had a negative interferon gamma release assay using the two

Table 2 Main efficacy parameters (mITT population)

Parameter	Week 14		Week 30		Week 54	
	BCD-055 ($n=280$)	IFX ($n=138$)	BCD-055 ($n=280$)	IFX ($n=138$)	BCD-055 ($n=280$)	IFX ($n=138$)
A. Activity of RA by DAS28-CRP(4), CDAI and SDAI, remission by ACR/EULAR 2011						
DAS28-CRP(4)						
Remission*	54 (19.3)	18 (13.0)	75 (26.8)	28 (20.3)	79 (28.2)	43 (31.2)
Low activity*	33 (11.8)	18 (13.0)	36 (12.9)	27 (19.6)	37 (13.2)	20 (14.5)
CDAI						
Remission*	20 (7.1)	6 (4.4)	35 (12.5)	11 (8.0)	52 (18.6)	27 (19.6)
Low activity*	68 (24.3)	37 (26.8)	80 (28.6)	44 (31.9)	79 (28.2)	43 (31.2)
SDAI						
Remission*	23 (8.2)	6 (4.4)	36 (12.9)	11 (8.0)	52 (18.6)	25 (18.1)
Low activity*	67 (23.9)	36 (26.1)	80 (28.6)	39 (28.3)	79 (28.2)	43 (31.2)
Remission by ACR/EULAR 2011*	13 (4.6)	3 (2.2)	27 (9.6)	7 (5.1)	40 (14.3)	17 (12.3)

Parameter	Baseline**	Week 14**	Week 30**	Week 54**
B. Quality of life (SF-36 survey)				
Physical health				
BCD-055 ($n=280$)†	30.4 (26.4–34.5)	38.1 (33.0–46.4)	39.6 (33.3–49.0)	40.9 (33.2–48.4)
IFX ($n=138$)†	30.7 (27.7–34.0)	37.2 (30.6–44.4)	40.3 (32.6–47.6)	42.5 (34.6–50.3)
Mental health				
BCD-055 ($n=280$)†	36.0 (32.4–39.6)	38.4 (33.8–42.4)	38.6 (34.1–42.3)	39.5 (34.2–43.2)
IFX ($n=138$)†	36.9 (33.4–41.0)	39.3 (34.9–42.9)	38.9 (34.4–42.4)	40.0 (35.4–43.2)

For DAS28-CRP(4), CDAI and SDAI, remission by ACR/EULAR 2011 no. (%) is presented

For quality of life medians and interquartile ranges are presented

DAS28-CRP(4) Disease Activity Score in 28 joints (0—indicates absence of disease activity), *CDAI* Clinical Disease Activity Index (0—indicates absence of disease activity), *SDAI* Simple Disease Activity Index (0—indicates absence of disease activity), Remission by ACR/EULAR 2011 (≥ 1 TJC/SJC, CRP ≤ 1 mg/dl, VAS (Patient's Global Activity Assessment) ≤ 1)

*$p > 0.05$ for all timepoints, Fisher's exact test, Pearson's χ^2 criterion (Yates), if data were unavailable then a patient was considered as no-responder (section A)

**$p > 0.05$ for all timepoints, two-tailed Mann–Whitney test (section B)

†$p < 0.001$ for the intergroup dynamics (repeated measures ANOVA) (section B)

antigens result at screening followed by positive result during the study was similar 3.57% and 5.07% of patients in BCD-055 and IFX arm, respectively, however, active tuberculosis was not confirmed in any of them.

Antibodies to infliximab (ADA) were detected in 28.46% patients for BCD-055 arm and 26.56% for IFX arm ($p=0.786$). ADA formation was mainly detected at Wk30 and Wk54, however, no significant decrease in efficacy or worsening of safety profile were observed.

Discussion

The results of this study demonstrate the equivalence of efficacy and comparable safety and immunogenicity of BCD-055 and IFX in patients with active RA, who did not respond adequately to previous MTX therapy. The similarity of efficacy, safety and immunogenicity of BCD-055 and IFX persisted up to 1 year. BCD-055 and IFX were comparable across all endpoints throughout the study.

Notably, LIRA clinical trial showed higher efficacy results for both IFX and BCD-055 than previous IFX studies. For example, in ATTRACT trial [5] 50%, 27% и 8% of patients in IFX group achieved ACR 20, 50 and 70 responses at week 30, respectively, while in LIRA these parameters were higher for BCD-055 and IFX. In IFX study ASPIR for patients with early RA (not more than 3 years from the first manifestation of the disease), 62%, 46%, and 33% of patients achieved ACR 20, 50 and 70 at week 54, respectively [13]. In LIRA we saw similar results in BCD-055 group at week 54: 69%, 48%, and 34%. Although baseline RA activity in patients enrolled in ATTRACT [5] and ASPIR [13] were similar for CRP level and number of tender/swollen joints, the mean duration of RA was 8.4 years in ATTRAC

Table 3 Summary of safety data

Variables	BCD-055 ($n=280$)	IFX ($n=138$)	p value*
Any AE	209 (74.64)	92 (66.67)	0.111
Therapy-related AE	132 (47.14)	56 (40.58)	0.245
Severe AE	46 (16.43)	14 (10.14)	0.115
Therapy-related severe AE	25 (8.93)	8 (5.80)	0.356
Serious AE	12 (4.29)	3 (2.17)	0.404
Withdrawal due to AE	17 (6.07)	9 (6.52)	0.971
Death	0	0	–
Summary of severe TAEs			
Infusion reaction (Grade 3)	3 (1.07)	2 (1.45)	0.667
Allergic reaction (Grade 3)	1 (0.36)	0	1.00
Hypertension (Grade 3)	6 (2.14)	2 (1.45)	1.00
Atrial fibrillation (Grade 3)	1 (0.36)	0	1.00
Bronchospasm (Grade 3)	1 (0.36)	0	1.00
Anaemia (Grade 3)	1 (0.36)	0	1.00
Neutropenia (Grade 3)	4 (1.43)	3 (2.17)	0.689
Leucopenia (Grade 3)	1 (0.36)	0	1.00
Alanine aminotransferase increased (Grade 3)	6 (2.14)	0	0.184
Aspartate aminotransferase increased (Grade 3)	1 (0.36)	0	1.00
Hyperglycemia (Grade 3)	1 (0.36)	0	1.00
Tuberculosis (Grade 3)	1 (0.36)	0	1.00
Pneumonia (Grade 3)	2 (0.71)	0	1.00
Asthma (Grade 3)	0	1 (0.72)	0.330
Other important AEs			
Infiltrative colon cancer (Grade 3)	0	1 (0.72)	0.330

No. (%) is presented

AE adverse events, *TAEs* treatment-related adverse events

*Fisher's exact test

T patients and 0.8 years in ASPIR. The mean RA duration in LIRA was 3.8 years, baseline RA activity in LIRA, ATT RACT and ASPIR was comparable. These data demonstrate that treatment with infliximab at the earlier stage of RA is associated with a better therapeutic response.

To date, three infliximab biosimilars (CT-P13, SB2 and GP1111) have been approved in the European Union (EU) [7]. Similarly, to BCD-085, the development program of CT-P13 included clinical trials in RA patients (PLANERTA study) [14] and ankylosing spondylitis patients (PLANETAS study) [15]. The efficacy and safety of SB2 and GP1111 compared to innovator infliximab was assessed in RA only [16, 17]. The RA trials were quite similar in terms of eligibility criteria, MTX dosing and study endpoints. Equivalence of efficacy for CT-P13 and SB2 was evaluated according to ACR20 response at week 30. In our study and in GP1111 study, the primary assessment of ACR20 response was performed at week 14. It is believed that early evaluation of ACR20 response—before it reaches the therapeutic plateau—provides greater sensitivity to detect possible differences in the rate of response between treatment arms, as compared with later time points [17]. ACR20 rates at week 14 in LIRA and GP1111 studies demonstrated equivalence of biosimilars compared to the reference product and were similar in numbers for BCD-085 and GP1111 (67.9% and 62.7%, respectively) [17].

The results of our 54-week study are comparable to other long-term studies of infliximab biosimilars in RA. Thus, in PLANETRA study ACR 20, 50, and 70 responses rate at week 54 in CT-P13 group were 74.7%, 43.6%, and 21.3% [18], and in the SB2 study these parameters at week 54 were 64.5%, 40.8%, and 23.3%, respectively [19]. Likewise, the efficacy of BCD-055 and IFX at week 54 was highly comparable across disease activity parameters, including DAS28-CRP, SDAI, SDAI. In addition to disease activity assessment, similarity of BCD-055 and IFX in the inhibition of joint damage progression was also confirmed in LIRA study. The same was assessed and proved for other infliximab biosimilars [18, 19]. Thus, the retention of the effect was demonstrated in the long-term perspective for all infliximab biosimilars, including BCD-055.

BCD-055 was well tolerated. Safety profiles of BCD-055 and IFX were comparable throughout the 1 year of the treatment. In LIRA study an incidence of hypertension was

significantly higher in BCD-055 arm (28.28% vs 15.94%, $p < 0.05$). This difference can be explained by pre-existing comorbidity (37.86% with arterial hypertension in BCD-055 arm vs 27.54% with arterial hypertension in IFX arm, $p < 0.05$). In general, the long-term safety profile for BCD-055 was comparable to the known safety profile of innovator infliximab and other infliximab biosimilars.

In our study, 1 case (0.36%) of active tuberculosis was defined in BCD-055 arm. 3.45% patients in BCD-055 arm and 5.07% patients in IFX arm had positive TB-test, active tuberculosis was not reported in these patients. These results correlate with earlier data (ATTRACT, ASPIR studies) and routine clinical practice [20].

One case of cancer (colon cancer) was observed (in IFX arm) in our study, it was diagnosed right after the first IFX injection. This patient had no symptoms of gastrointestinal tract disease or relevant complaints at the enrollment. Colorectal cancer was diagnosed during colonoscopy that was performed as regular screening clinical examination outside study procedures and can be considered as incidental finding. Overall, long-term follow-up of patients receiving biological DMARDs (TNFα inhibitors, in particular) showed no increase in cancer incidence [21, 22].

Immunogenicity of BCD-055 vs IFX was comparable throughout 1 year of study. One year period is considered to be sufficient for the immunogenicity assessment and complies with the guidelines for biosimilar research [6]. Detection rate of ADA in LIRA clinical trial aligns to literature data that reported ADA in 12–44% of RA patients [23]. In the recent clinical studies of infliximab biosimilar (CT-P13 and SB2), ADA incidences had a trend to be higher than in the innovator infliximab pivotal studies (51.4–62.4% vs 14.5%), which is suggested to be due to the increased sensitivity of the assays [13, 18, 19].

CT-P13, SB2 and GP1111 were approved in EU for the full set of indications of the reference product as well as BCD-055 in Russia. One of the key principles of EMA, FDA, and WHO regulatory guidelines for biosimilars is extrapolation of clinical efficacy and safety data to other indications of the reference product, not specifically studied during the clinical development of the biosimilar [6, 24, 25]. It is assumed that biosimilar due to a highly similar structure, chemical, physical and biological characteristics provides the same pharmacological effects and, therefore, is very similar in terms of safety and efficacy to a reference product in all indications [26].

Current European guidelines on the treatment of RA consider biosimilars as option of the biologic treatment [27]. There are still serious debates whether innovator and biosimilar medicines can be considered interchangeable and whether switching or substitution of biologic medicines is appropriate. The NOR-SWITCH, PLANETRA and PLANETAS studies have demonstrated that switching from innovator infliximab to biosimilar does not result in any loss of efficacy, increase in AEs or immunogenicity in a large group of patients [28–30].

Our study has some limitations. Based on eligibility criteria, we have enrolled biologic-naïve patients, while it could be interesting also to evaluate bDMARDs-experienced patients. The study was not designed to assess switching between innovator and biosimilar. These data will be collected in routine clinical practice.

In conclusion, the results of 54-week LIRA study demonstrated consistent similarity in efficacy, safety, and immunogenicity of BCD-055 and IFX in treatment of patients with active RA, who did not respond adequately to treatment with MTX.

Acknowledgements The authors appreciate Nikita Zolkin and Ivan Kuryshev (JSC BIOCAD, Russia) for statistical analysis, and support in manuscript development. Employees of JSC BIOCAD, the study sponsor, designed the study in collaboration with the academic authors, conducted the study, collected the data, performed statistical analyses, and were involved in the writing of the study manuscript. Contributing centers (principal investigators)—*Russia:* Olga V. Antipova, Anna N. Galustyan, Ivan G. Gordeev, Antonina F. Davidova, Natalya A. Eremina, Alexander A. Kastanyan, Larisa A. Knayzeva, Tatyana V. Kropotina, Irina M. Marusenko, Irina M. Patrikeeva, Tatyana V. Plaksina, Tatyana V. Povarova, Tatyana G. Pokrovskaya, Olga V. Reshetko, Elena A. Smolyarchuk, Irina A. Shumichina, Elena V. Zemerova, Elena V. Zonova, Eduard A. Ponomarev, Svetlana A. Smakotina, Marianna S. Petrova, Galina A. Chumakova, Larisa V. Eliseeva, Maria I. Skalinskaya. *Belarus:* Igor E. Adzericho, Sergey I. Pimanov, Andrey M. Pristom, Elena V. Kunder, Nikolay F. Soroka. *India:* Reema Kashiva, Ajit Bapurao Nalawade, Liyakat Ali Gauri, Vishnu Sharma, Syamasis Bandyopadhyay, Bindumathi P. L.

Author contributions In accordance with ICMJE criteria, all authors were involved in writing and drafting the article or revising it critically for important intellectual content. All authors approved the final version to be submitted for publication and agree to be accountable for all aspects of the work.

Funding This study was sponsored by JSC BIOCAD.

Compliance with ethical standards

Conflict of interest Alexander M. Lila, Vadim I. Mazurov, Lev N. Denisov, Olga B. Nesmeyanova, Elena P. Ilivanova declare that they have no conflict of interest. Anna V. Eremeeva, Julia V. Usacheva, Ekaterina V. Chernyaeva, Ekaterina A. Dokukina and Roman A. Ivanov Employees of JCS BIOCAD.

Ethical approval All patients were informed, and their informed consents were obtained prior to the study. The information on all Ethics Committees and approval dates is presented in Supplementary Material B.

References

1. Smolen JS, Aletaha D, McInnes IB (2016) Rheumatoid arthritis. Lancet 388:2023–2038. https://doi.org/10.1016/s0140-6736(16)30173-8

2. Smolen JS, Aletaha D et al (2018) Rheumatoid arthritis. Nat Rev Dis Prim 4:18001. https://doi.org/10.1038/nrdp.2018.1
3. Mclnnes IB, Schett G (2007) Cytokines in the pathogenesis of rheumatoid arthritis. Nat Rev Immunol 7(6):429–442
4. Elliott M, Maini R, Feldman M et al (1993) Treatment of rheumatoid arthritis with chimeric monoclonal antibodies to tumor necrosis factor α. Arthritis Rheum 36:1681–1690
5. Maini R, Clair EW, Breedveld F, ATTRACT Study Group et al (1999) Infliximab (chimeric anti-tumor necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. Lancet 354(9194):1932–1939
6. World Health Organization, Expert Committee on Biological Standardization (2009) Guidelines on evaluation of similar biotherapeutic products (SBPs). http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf. Accessed 11 Dec 2018
7. Generics and Biosimilars Initiative (2016) Biosimilars approved in Europe. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe. Accessed 28 Aug 2018
8. Denisov L, Gordeev I, Mazurov V et al (2017) FRI0208 Comparison of efficacy, safety and pharmacokinetics of infliximab biosimilar (BCD-055) and innovator infliximab. Ann Rheum Dis 76:560–561
9. Ezard C, Kumari R, Willot R et al (2012) What is meant by active disease in the NICE recommendation on use of combination therapy in early RA? Rheumatology 51(5):947–948
10. van der Heijde D (2000) How to read radiographs according to the Sharp/van der Heijde method. J Rheumatol 27:261–263
11. Steinbrocker O, Traeger CH, Batter-Mann RC (1949) Therapeutic criteria in rheumatoid arthritis. JAMA 140:659–662
12. Glueck DH (2008) Sample size calculations in clinical research. In: Chow SC, Shao J, Wang H (eds) Biometrics, vol 64, 2nd edn. CRC Press, Boca Raton, pp 1307–1308. https://doi.org/10.1111/j.1541-0420.2008.01138_10.x
13. Clair EWS, Van der Heijde D, Smolen JS et al (2004) Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. Arthritis Rheum 50(11):3432–3443
14. Yoo DH, Hrycaj P, Miranda P et al (2013) A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. Ann Rheum Dis 72:1613–1620
15. Park W, Hrycaj P, Jeka S et al (2013) A randomised, double-blind, multicentre, parallel-group, prospective study comparing the pharmacokinetics, safety, and efficacy of CT-P13 and innovator infliximab in patients with ankylosing spondylitis: the PLANETAS study. Ann Rheum Dis 72:1605–1612
16. Choe JY, Prodanovic N, Niebrzydowski J et al (2017) A randomised, double-blind, phase III study comparing SB2, an infliximab biosimilar, to the infliximab reference product remicade in patients with moderate to severe rheumatoid arthritis despite methotrexate therapy. Ann Rheum Dis 76(1):58–64
17. Cohen SB, Alten R, Kameda H et al (2018) A randomized controlled trial comparing PF-06438179/GP1111 (an infliximab biosimilar) and infliximab reference product for treatment of moderate to severe active rheumatoid arthritis despite methotrexate therapy. Arthritis Res Ther. 20(1):155. https://doi.org/10.1186/s13075-018-1646-4
18. Yoo DH, Racewicz A, Brzezicki J et al (2016) A phase III randomized study to evaluate the efficacy and safety of CT-P13 compared with reference infliximab in patients with active rheumatoid arthritis: 54-week results from the PLANETRA study. Arthritis Res Ther. 18:82. https://doi.org/10.1186/s13075-016-0981-6
19. Smolen JS, Jung-Yoon Choe, Prodanovic N et al (2017) Comparing biosimilar SB2 with reference infliximab after 54 weeks of a double-blind trial: clinical, structural and safety results. Rheumatology 56:1771–1779. https://doi.org/10.1093/rheumatology/kex254
20. Dixon WG, Hyrich KL, Watson KD, on behalf of the BSR Biologics Register et al (2010) Drug-specific risk of tuberculosis in patients with rheumatoid arthritis treated with anti-TNF therapy: results from the British Society for Rheumatology Biologics Register (BSRBR). Ann Rheum Dis 69:522–528
21. Wolfe F, Michaud K (2007) Biologic treatment of rheumatoid arthritis and the risk of malignancy: analyses from a large US observational study. Arthritis Rheum 56:2886–2895
22. Askling J, van Vollenhoven RF, Granath F et al (2009) Cancer risk in patients with rheumatoid arthritis treated with anti–tumor necrosis factor α therapies: does the risk change with the time since start of treatment? Arthritis Rheum 60:3180–3189
23. Aikawa NE, de Carvalho JF, Almeida Silva CA, Bonfa E (2010) Immunogenicity of anti-TNF-alpha agents in autoimmune diseases. Clin Rev Allergy Immunol 38(2–3):82–89
24. European Medicines Agency (2014) [Internet] Guideline on similar biological medicinal products. London, UK: Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency; 2014. [updated October 23, 2014]. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176768.pdf. Accessed 23 Apr 2019
25. United States Food and Drug Administration (2015) [Internet] Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. Silver Spring, MD: US Department of Health and Human Services, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER); 2015. [updated April 2015]. http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm291128.pdf. Accessed 23 Apr 2019
26. Vulto AG, Jaquez OA (2017) The process defines the product: what really matters in biosimilar design and production? Rheumatology 56(suppl_4):iv14–iv29. https://doi.org/10.1093/rheumatology/kex278
27. Smolen JS, Landewe R, Breedveld FC et al (2017) EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 76:960–977
28. Yoo DH, Prodanovic N, Jaworski J et al (2017) Efficacy and safety of CT-P13 (infliximab biosimilar) in patients with rheumatoid arthritis: comparison between switching from reference infliximab to CT-P13 and continuing CT-P13 in the PLANETRA extension study. Ann Rheum Dis 76:355–363
29. Park W, Yoo DH, Miranda P et al (2017) Efficacy and safety of switching from reference infliximab to CT-P13 compared with maintenance CT-P13 in ankylosing spondylitis. 102-week data from the PLANETAS extension study. Ann Rheum Dis 76:346–354
30. Goll GL, Jørgensen KK, Sexton J, Olsen IC et al (2019) Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: open-label extension of the NOR-SWITCH trial. J Intern Med. https://doi.org/10.1111/joim.12880