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ORIGINAL ARTICLE

Efficacy of certolizumab pegol across baseline rheumatoid factor subgroups in patients with rheumatoid arthritis: Post-hoc analysis of clinical trials

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Abstract

Aim: Certolizumab pegol (CZP), an Fc-free, PEGylated tumor necrosis factor inhibitor (TNFi), has shown rapid and sustained reduction in signs and symptoms of rheumatoid arthritis (RA). Elevated rheumatoid factor (RF) level has been associated with RA disease progression and poorer TNFi response. We assessed the efficacy of CZP in patients with early and established RA across baseline RF levels.

Methods: This post-hoc analysis included data from 6 trials: C-OPERA (NCT01451203), pooled RAPID trials (RAPID-1 [NCT00152386], RAPID-2 [NCT00160602], J-RAPID [NCT00791999], RAPID-C [NCT02151851]), and EXXELERATE (NCT01500278). Patients who received CZP or placebo/comparator with methotrexate (MTX) were categorized by baseline RF quartiles. Efficacy was assessed with Disease Activity Score-28 erythrocyte sedimentation rate (DAS28-ESR).

Results: Overall, 316, 1537, and 908 patients were included in C-OPERA, pooled RAPID trials, and EXXELERATE, respectively. Patient demographics and baseline

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disease characteristics were similar between treatment groups and across RF quartiles. DAS28-ESR low disease activity (LDA) and remission (REM) rates were numerically higher in the CZP + MTX group than PBO + MTX group at weeks 12 and 24, across RF quartiles. LDA and REM rates in the CZP + MTX groups were comparable across RF quartiles at weeks 12 and 24. Mean DAS28-ESR decreased from week 0 to week 24 in the CZP + MTX groups, across RF quartiles.

Conclusion: CZP showed steady efficacy across baseline RF quartiles in patients with early and established RA, over 24 weeks. CZP treatment may be considered in patients with RA irrespective of baseline RF levels and time from diagnosis.

KEYWORDS
certolizumab pegol, rheumatoid arthritis, rheumatoid factor, tumor necrosis factor inhibitor

1 | INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease which causes joint pain and damage.[1] RA results in a progressive impairment of physical function.[1] Most patients with RA have detectable levels of rheumatoid factor (RF), a physiologic antibody which targets the fragment crystallizable (Fc) region of immunoglobulin (Ig) G, with high reactivity to the IgG1 isotype.[2] In its physiological role, pentameric IgM-RF, the most prevalent RF subtype, increases the clearance of immune complexes by binding up to 10 IgG1-Fc regions per molecule of RF.[2–4] These large immune complexes are subsequently eliminated by endocytosis through binding to the Fc gamma receptor (FcγR).[5] RF positivity (>20 U/mL) in patients with RA has been associated with higher disease activity and disease progression.[6,7] Specifically, high RF titer ≥50 U/mL has been significantly associated with RA disease activity compared with low titer or negative RF.[7]

Tumor necrosis factor (TNF) is an inflammatory cytokine involved in the pathogenesis of RA. Certolizumab pegol (CZP) is an Fc-free, PEGylated TNF inhibitor (TNFi) which has established efficacy in RA.[8–14] Treatment with CZP has resulted in inhibition of radiographic progression and improvements in physical function in patients with early RA[8,9] as well as rapid and sustained reduction in signs and symptoms of established RA.[10–13] Other currently available TNFi comprise a range of human or chimeric monoclonal antibodies (adalimumab [ADA], golimumab, and infliximab) and an IgG1–TNFR2 fusion protein (etanercept).[15,16] In a head-to-head study evaluating efficacy of CZP versus ADA in patients with established RA, with prognostic factors for severe disease progression, no significant difference in efficacy was found between the 2 treatments in the study population.[14]

While TNFi have demonstrated efficacy in patients with RA,[1] their effectiveness has been associated with the levels of RF present.[4,17–20] Studies on TNFi (eg, ADA, golimumab, infliximab, etanercept) in patients with established RA (>6 months disease duration) have observed better responses in patients with negative versus positive and low versus high baseline RF titers.[4,17–19] When followed up to 6 months, patients with RA who were receiving ADA, etanercept, or infliximab, who were RF-positive (>20 IU/mL) at baseline were less likely to achieve disease remission compared with those who were RF-negative.[17] Positive serum RF (≥40 U/μL) at baseline was also associated with less improvement in Disease Activity Score 28 (DAS28) response at 6 months following TNFi treatment (ADA, etanercept, or infliximab) in patients with long-standing established RA.[18] In another study, DAS28 remission was less frequent and severe disability more frequent in patients who received TNFi in the RF-positive group (≥15 IU/mL) compared with the RF-negative group.[4] A study in Japan that investigated the association between baseline RF and anti-citrullinated peptide antibodies (ACPA) seropositivity and discontinuation of TNFi therapy (ADA, CZP, etanercept, golimumab, or infliximab assessed collectively) found RF positivity was predictive of TNFi discontinuation due to ineffectiveness.[20]

The association between CZP efficacy and RF levels has been briefly investigated in a Japanese retrospective cohort study, in comparison with other TNFi.[21] Studies with a focus on CZP have so far explored the association in patients with early RA[22] and established RA.[23] However, these results have not been discussed together in the context of overall course of the disease. This post-hoc analysis of multiple clinical trials (phase 3 and 4) aimed to assess the efficacy of CZP across baseline RF quartiles in patients with early RA and established RA.

2 | MATERIALS AND METHODS

2.1 | Study design

This post-hoc analysis included data from 6 clinical trials of CZP in patients with RA: C-OPERA (NCT01451203),[9] RAPID-1 (NCT00152386),[10] RAPID-2 (NCT00160602),[11] J-RAPID (NCT00791999),[12] RAPID-C (NCT02151851)[13] and EXXELERATE (NCT01500278).[14] The study designs of the trials are presented in Figure 1. The full study designs, patient populations, and results of all 6 clinical studies have been previously published.[9–14] Data from

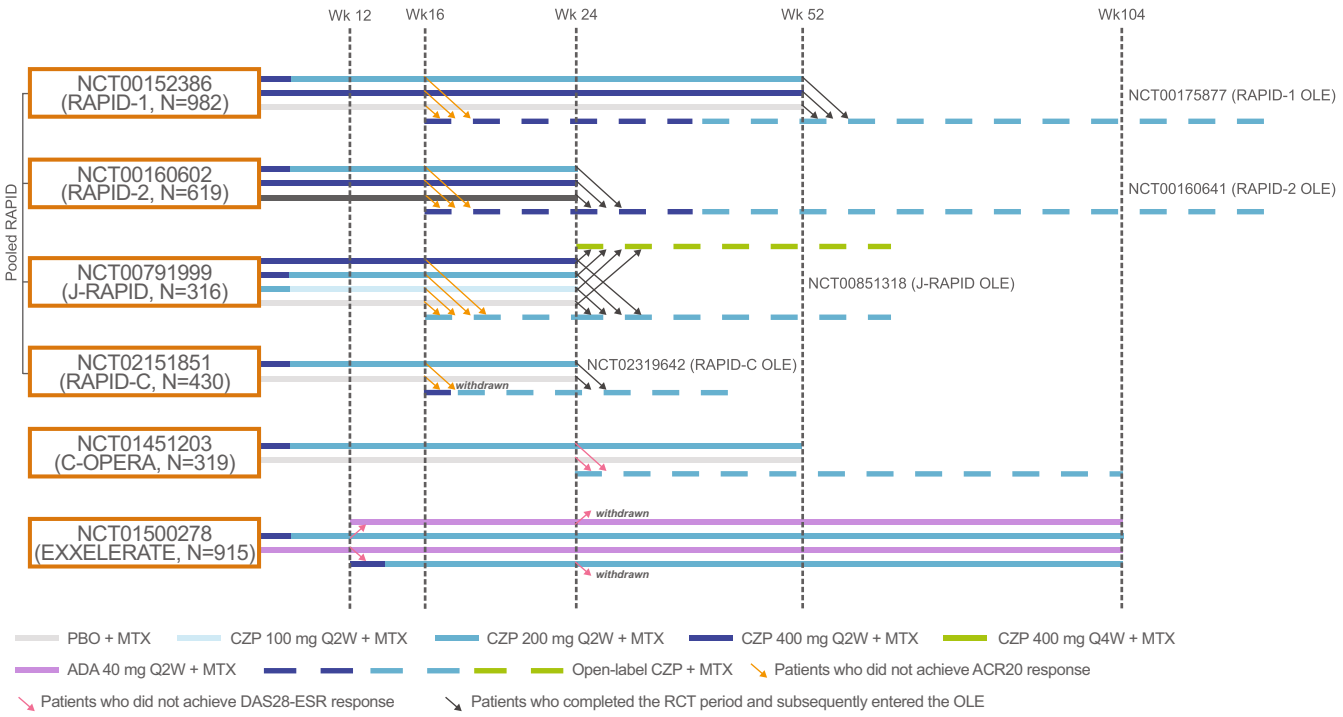


FIGURE 1 Study designs of the clinical trials RAPID-1, RAPID-2, J-RAPID, RAPID-C, C-OPERA, and EXXELERATE. ACR20: ≥20% improvement based on American College of Rheumatology criteria; ADA, adalimumab; CZP, certolizumab pegol; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; MTX, methotrexate; OLE, open-label extension; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; RCT, randomized-controlled trial; Wk, week.

RAPID-1, RAPID-2, J-RAPID, and RAPID-C were pooled in this article.

2.2 | Study participants

The full inclusion and exclusion criteria of the included trials have been previously published.[9–14]

C-OPERA included Japanese patients with early RA. Briefly, methotrexate (MTX)-naïve patients aged 20–64 years with active RA ≤12 months (defined by 2010 American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria[24]) were randomized to receive placebo (PBO) every 2 weeks plus methotrexate (PBO + MTX) or CZP 200 mg every 2 weeks (loading dose of CZP 400 mg at weeks 0/2/4) plus MTX (CZP + MTX) for 52 weeks.

Pooled RAPID included patients from 2 global trials (RAPID-1[10] and RAPID-2[11]), a Japanese trial (J-RAPID),[12] and a Chinese trial (RAPID-C).[13] Briefly, patients ≥18 years (≥20 years for J-RAPID) with active RA for ≥6 months (defined by ACR 1987 criteria[25]), who received MTX for ≥6 months (≥3 months for RAPID-C) prior to baseline, were randomized to receive PBO + MTX or CZP 400 mg every 2 weeks plus MTX or CZP 200 mg every 2 weeks (loading dose of CZP 400 mg at weeks 0/2/4) plus MTX (CZP + MTX) for at least 24 weeks (52 weeks for RAPID-1, 24 weeks for RAPID-2, J-RAPID, and RAPID-C).

EXXELERATE was a head-to-head superiority study comparing CZP with ADA in patients with active RA with prognostic factors for severe disease progression. Briefly, patients ≥18 years with active RA (defined by 2010 ACR/EULAR classification criteria[24]) were randomized to receive CZP 200 mg every 2 weeks (loading dose of CZP 400 mg at weeks 0/2/4) plus MTX (CZP + MTX), or ADA 40 mg every 2 weeks plus MTX (ADA + MTX) for 104 weeks.

2.3 | Assessment of RF level

RF levels (IgM-RF) were measured using validated immunoassays in local hospitals, by nephelometry or enzyme-linked immunosorbent assay (ELISA). There is a good correlation between the 2 methods of RF quantification despite potential variations in cut-off levels; both methods are adequately sensitive for routine laboratory purposes.[26] Patients were classified into quartiles (Q) based on overall baseline RF levels of each study. For C-OPERA, the RF quartiles were defined as <59.0 IU/mL, ≥59.0–<93.0 IU/mL, ≥93.0–<275.0 IU/mL, and ≥275.0 IU/mL for Q1–4, respectively. For Pooled RAPID, the RF quartiles were defined as <25.0 IU/mL, ≥25.0–<78.5 IU/mL, ≥78.5–<207.0 IU/mL, and ≥207.0 IU/mL for Q1–4, respectively. For EXXELERATE, the RF quartiles were defined as ≤32.0 IU/mL, >32.0–≤75.0 IU/mL, >75.0–≤204.0 IU/mL, and >204.0 IU/mL for Q1–4, respectively.

2.4 | Outcomes

The efficacy of CZP was assessed by DAS28-erythrocyte sedimentation rate (DAS28-ESR); efficacy assessments (mean DAS28-ESR) were performed through weeks 0–24. In this analysis, DAS28-ESR 2.6–≤3.2 was classified as low disease activity (LDA) and DAS28-ESR <2.6 was classified as remission (REM). The proportion of patients who achieved DAS28-ESR LDA and REM were evaluated at week 12 and week 24.

Here, we report data for the PBO + MTX and CZP 200 mg every 2 weeks plus MTX (CZP + MTX) groups from the C-OPERA and Pooled RAPID trials. From the EXXELERATE trial, we report efficacy data for the CZP + MTX and ADA + MTX groups only (patients who switched between CZP and ADA at week 12 were excluded from this analysis).

2.5 | Statistical analysis

All analyses were performed using the full analysis set, unless otherwise stated. The full analysis set included all patients who received ≥1 dose of study drug and provided any efficacy data thereafter. Observed data for DAS28-ESR response are reported. As this was a post-hoc subgroup analysis, all data reported are descriptive only.

3 | RESULTS

3.1 | Patient demographics and baseline characteristics

The demographic and baseline disease characteristics for the overall study population are presented in Table 1. In C-OPERA, 316 patients (CZP + MTX $n = 159$; PBO + MTX $n = 157$) were included in this post-hoc analysis. In Pooled RAPID, 1537 patients (CZP + MTX $n = 1025$; PBO + MTX $n = 512$) were included in this post-hoc analysis. In EXXELERATE, 908 patients (CZP + MTX $n = 454$; ADA + MTX $n = 454$) were included in the full analysis set which was used for the analysis of baseline demographics and weeks 0–12 efficacy outcomes in this post-hoc analysis. For weeks 12–24, the week 12 full analysis set (CZP + MTX $n = 352$; ADA + MTX $n = 361$), consisting of CZP + MTX patients randomized to CZP who responded at week 12 and continued on CZP and ADA + MTX patients randomized to ADA who responded at week 12 and continued on ADA, was analyzed.

At baseline, patient demographics and disease characteristics were similar between treatment groups for C-OPERA, Pooled RAPID, and EXXELERATE. Within each treatment group (PBO + MTX or CZP + MTX or ADA + MTX), mean DAS28-ESR scores at baseline were similar across RF quartiles for C-OPERA, Pooled RAPID, and EXXELERATE.

3.2 | DAS28-ESR LDA and REM rates

For C-OPERA, DAS28-ESR LDA and REM rates were numerically higher in the CZP + MTX group compared with the PBO + MTX group at weeks 12 and 24, across RF quartiles. In the CZP + MTX group, DAS28-ESR LDA and REM rates improved from week 12 to week 24, across RF quartiles. At weeks 12 and 24, DAS28-ESR LDA and REM rates were comparable across RF quartiles in the CZP + MTX group (Figure 2A).

For Pooled RAPID, DAS28-ESR LDA and REM rates were numerically higher in the CZP + MTX group compared with the PBO + MTX group at weeks 12 and 24, across RF quartiles. In the CZP + MTX group, DAS28-ESR LDA and REM rates improved from week 12 to week 24, across RF quartiles. At weeks 12 and 24, DAS28-ESR LDA and REM rates were comparable across RF quartiles in the CZP + MTX group (Figure 2B).

For EXXELERATE, DAS28-ESR LDA and REM rates were similar in CZP + MTX compared to ADA + MTX at weeks 12 and 24, across all RF quartiles. In both CZP + MTX and ADA + MTX groups, DAS28-ESR LDA and REM rates improved from week 12 to week 24, across RF quartiles (Figure 2C). In the CZP + MTX group, this improvement was consistent across RF quartiles. In the ADA + MTX group, the improvement was numerically lower in the subgroup with the highest RF levels (Q4) compared with other RF quartiles.

3.3 | Mean DAS28-ESR over 24 weeks

For C-OPERA and Pooled RAPID, in both CZP + MTX and PBO + MTX groups, mean DAS28-ESR decreased from week 0 to week 24, across RF quartiles (Figure 3A,B, respectively). Mean DAS28-ESR was numerically lower in CZP + MTX compared with PBO + MTX over 24 weeks, across RF quartiles. At week 24, mean DAS28-ESR scores across RF quartiles in the CZP + MTX group were 2.5–2.8 for C-OPERA (Figure 3A) and 3.8–3.9 for Pooled RAPID (Figure 3B).

For EXXELERATE, in both CZP + MTX and ADA + MTX groups, mean DAS28-ESR decreased from weeks 0–12 and weeks 12–24 across RF quartiles (Figure 3C). Mean DAS28-ESR for CZP + MTX and ADA + MTX groups were similar over 24 weeks, across RF quartiles. At week 24, mean DAS28-ESR scores across RF quartiles were 3.0–3.5 in the CZP + MTX group and 3.1–3.7 in the ADA + MTX group (Figure 3C).

4 | DISCUSSION

In this post-hoc analysis, efficacy of CZP was comparable across baseline RF subgroups over 24 weeks, in patients with early RA (C-OPERA) and established RA (Pooled RAPID and EXXELERATE). Additionally, in patients with established RA (EXXELERATE), CZP demonstrated consistent efficacy across baseline RF quartiles through week 104 (data not shown).

TABLE 1 Demographics and baseline disease characteristics.

C-OPERA	CZP + MTX				PBO + MTX			
	Q1 <59.0 IU/mL (*n* = 40)	Q2 ≥59.0–<93.0 IU/mL (*n* = 39)	Q3 ≥93.0–<275.0 IU/mL (*n* = 37)	Q4 ≥275.0 IU/mL (*n* = 43)	Q1 <59.0 IU/mL (*n* = 38)	Q2 ≥59.0–<93.0 IU/mL (*n* = 38)	Q3 ≥93.0–<275.0 IU/mL (*n* = 45)	Q4 ≥275.0 IU/mL (*n* = 36)
Demographics								
Age, y, mean (SD)	49.4 (11.3)	47.2 (9.7)	48.8 (10.1)	52.1 (11.0)	51.4 (7.7)	47.2 (10.2)	47.2 (11.8)	50.7 (10.6)
Female, *n* (%)	33 (82.5)	37 (94.9)	28 (75.7)	31 (72.1)	30 (78.9)	33 (86.8)	36 (80.0)	28 (77.8)
BMI, kg/m^2, mean (SD)	20.8 (2.3)	23.7 (5.3)	22.2 (3.2)	23.0 (3.5)	21.5 (2.2)	22.9 (4.1)	23.3 (4.4)	22.3 (3.2)
Prior DMARD use, *n* (%)	9 (22.5)	11 (28.2)	3 (8.1)	8 (18.6)	12 (31.6)	4 (10.5)	6 (13.3)	7 (19.4)
Weekly MTX dose through the study period, mg/wk, mean (SD)	11.7 (3.0)	11.8 (2.8)	11.8 (3.5)	10.3 (2.9)	11.0 (2.8)	11.2 (2.5)	12.2 (2.7)	11.4 (3.0)
Disease activity status								
Disease duration, mo, mean (SD)	4.5 (3.1)	3.8 (2.9)	3.8 (3.1)	3.8 (2.6)	4.5 (3.0)	4.0 (2.3)	3.8 (2.6)	4.8 (3.4)
DAS28-ESR, mean (SD)	5.0 (1.1)	5.5 (0.9)	5.2 (0.9)	5.7 (1.3)	5.2 (1.2)	5.5 (1.2)	5.6 (1.2)	5.8 (1.1)
mTSS, mean (SD)	3.3 (4.5)	2.7 (6.3)	5.3 (10.9)	5.0 (6.9)	4.6 (8.0)	3.3 (6.3)	3.2 (6.8)	11.4 (28.1)
mTSS ≤0.5, *n* (%)	15 (37.5)	17 (43.6)	20 (54.1)	13 (30.2)	17 (44.7)	16 (42.1)	20 (44.4)	14 (38.9)
Pooled RAPID[a]								
	CZP + MTX				PBO + MTX			
	Q1 <25.0 IU/mL (*n* = 251)	Q2 ≥25.0–<78.5 IU/mL (*n* = 254)	Q3 ≥78.5–<207.0 IU/mL (*n* = 246)	Q4 ≥207.0 IU/mL (*n* = 274)	Q1 <25.0 IU/mL (*n* = 123)	Q2 ≥25.0–<78.5 IU/mL (*n* = 130)	Q3 ≥78.5–<207.0 IU/mL (*n* = 137)	Q4 ≥207.0 IU/mL (*n* = 122)
Demographics								
Age, y, mean (SD)	49.3 (12.9)	50.7 (11.2)	50.6 (11.5)	51.4 (10.9)	50.0 (12.2)	50.3 (11.8)	50.2 (11.5)	53.1 (10.3)
Female, *n* (%)	215 (85.7)	220 (86.6)	199 (80.9)	223 (81.4)	108 (87.8)	116 (89.2)	117 (85.4)	90 (73.8)
BMI, kg/m^2, mean (SD)	25.7 (5.8)	24.6 (4.8)	25.1 (5.1)	25.7 (5.7)	25.5 (5.5)	25.4 (5.6)	25.2 (5.4)	25.4 (5.8)
Prior TNFi use, *n* (%)	24 (9.6)	23 (9.1)	25 (10.2)	25 (9.1)	11 (8.9)	13 (10.0)	16 (11.7)	10 (8.2)
MTX dose, *n* (%)								
<15 mg/wk	167 (66.5)	195 (76.8)	185 (75.2)	201 (73.4)	83 (67.5)	99 (76.2)	105 (76.6)	93 (76.2)
≥15 mg/wk	83 (33.1)	59 (23.2)	61 (24.8)	73 (26.6)	39 (31.7)	31 (23.8)	32 (23.4)	29 (23.8)
Race, *n* (%)								
Asian	70 (27.9)	116 (45.7)	99 (40.2)	110 (40.1)	30 (24.4)	61 (46.9)	51 (37.2)	48 (39.3)
Caucasian	178 (70.9)	136 (53.5)	147 (59.8)	159 (58.0)	93 (75.6)	68 (52.3)	84 (61.3)	73 (59.8)

TABLE 1 (Continued)

Pooled RAPID[a]								
	CZP + MTX				PBO + MTX			
	Q1 <25.0 IU/mL (*n* = 251)	Q2 ≥25.0–<78.5 IU/mL (*n* = 254)	Q3 ≥78.5–<207.0 IU/mL (*n* = 246)	Q4 ≥207.0 IU/mL (*n* = 274)	Q1 <25.0 IU/mL (*n* = 123)	Q2 ≥25.0–<78.5 IU/mL (*n* = 130)	Q3 ≥78.5–<207.0 IU/mL (*n* = 137)	Q4 ≥207.0 IU/mL (*n* = 122)
Disease activity status								
Disease duration, y, mean (SD)	5.4 (4.5)	6.1 (5.0)	6.7 (4.9)	7.0 (5.4)	5.4 (4.5)	5.8 (4.2)	6.8 (6.3)	6.5 (4.6)
DAS28-ESR, mean (SD)	6.7 (0.9)	6.6 (0.9)	6.8 (0.9)	7.0 (0.9)	6.8 (1.0)	6.5 (0.9)	7.0 (0.9)	6.9 (0.9)
EXXELERATE[b]								
	CZP + MTX				ADA + MTX			
	Q1 ≤32.0 IU/mL (*n* = 120)	Q2 >32.0–≤75.0 IU/mL (*n* = 99)	Q3 ≥75.0–≤204.0 IU/mL (*n* = 115)	Q4 >204 IU/mL (*n* = 119)	Q1 ≤32.0 IU/mL (*n* = 115)	Q2 >32.0–≤75.0 IU/mL (*n* = 122)	Q3 ≥75.0–≤204.0 IU/mL (*n* = 110)	Q4 >204 IU/mL (*n* = 107)
Demographics								
Age, y, mean (SD)	52.5 (12.4)	50.6 (12.2)	54.6 (12.5)	55.6 (11.7)	51.7 (13.1)	52.4 (13.5)	53.5 (12.2)	54.2 (12.3)
Female, *n* (%)	104 (86.7)	77 (77.8)	89 (77.4)	87 (73.1)	96 (83.5)	101 (82.8)	79 (71.8)	83 (77.6)
BMI, kg/m^2, mean (SD)	28.5 (6.1)	26.7 (6.7)	28.0 (6.4)	28.8 (6.3)	28.4 (6.3)	28.0 (5.9)	27.9 (5.9)	27.4 (7.0)
Prior TNFi use, *n* (%)	2 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	1 (0.9)
MTX dose, *n* (%)								
<15 mg/wk	5 (4.2)	3 (3.0)	3 (2.6)	9 (7.6)	4 (3.5)	4 (3.3)	3 (2.7)	6 (5.6)
≥15 mg/wk	114 (95.0)	96 (97.0)	111 (96.5)	110 (92.4)	111 (96.5)	118 (96.7)	107 (97.3)	101 (94.4)
Race, *n* (%)								
Asian	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	2 (1.6)	1 (0.9)	0 (0.0)
Caucasian	114 (95.0)	89 (89.9)	100 (87.0)	104 (87.4)	106 (92.2)	106 (86.9)	95 (86.4)	95 (88.8)
Disease activity status								
Disease duration, y, mean (SD)	5.8 (6.4)	4.7 (5.7)	6.0 (6.4)	7.5 (8.6)	4.5 (6.3)	6.5 (7.3)	5.3 (5.7)	6.9 (7.8)
DAS28-ESR, mean (SD)	6.3 (0.8)	6.4 (0.9)	6.5 (0.9)	6.7 (0.9)	6.4 (0.8)	6.5 (0.9)	6.6 (0.7)	6.7 (0.9)

Abbreviations: ADA, adalimumab; BMI, body mass index; CZP, certolizumab pegol; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; DMARD, disease-modifying anti-rheumatic drugs; mo, month; mTSS, modified Total Sharp Score; MTX, methotrexate; PBO, placebo; Q, quartile; SD, standard deviation; TNFi, tumor necrosis factor inhibitor; wk, week; y, year.

[a]Pooled RAPID comprised RAPID-1, RAPID-2, RAPID-C, and J-RAPID trials; only data for the CZP 200 mg every 2 weeks group were reported.

[b]EXXELERATE: 1 patient from the CZP + MTX group had a missing rheumatoid factor assessment at baseline and was not included in this table.

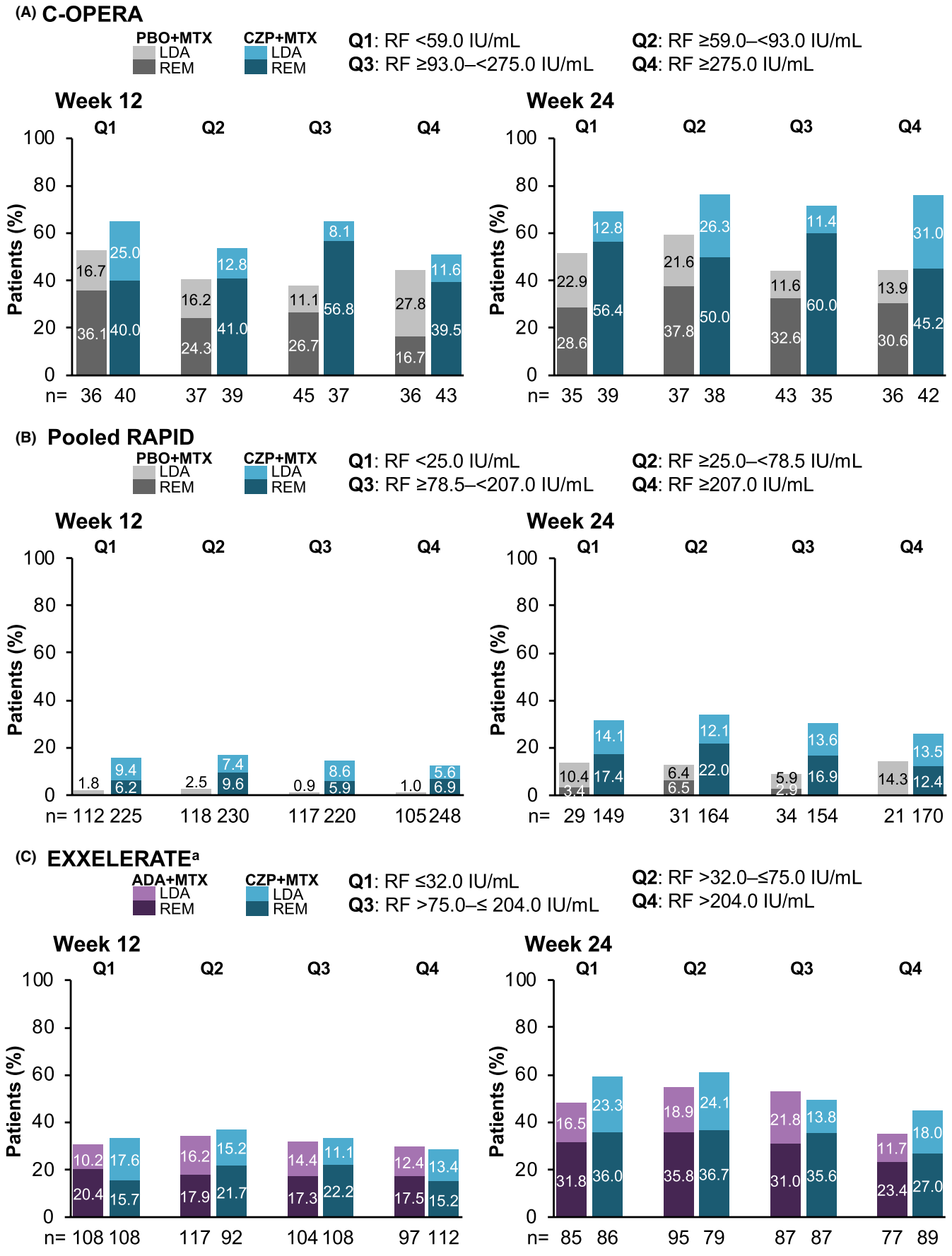


FIGURE 2 DAS28-ESR LDA and REM rates at weeks 12 and 24 for (A) C-OPERA, (B) Pooled RAPID, and (C) EXXELERATE. [a]EXXELERATE data for weeks 0–12 included patients initially randomized to CZP + MTX and ADA + MTX (Full Analysis Set) while weeks 12–24 data included week 12 responders who continued on the same treatment, not including patients who switched between CZP and ADA at week 12 (Week 12 Full Analysis Set). RF quartiles for week 24 were defined as ≤32.0 IU/mL, >32.0–≤74.0 IU/mL, >74.0–≤203.0 IU/mL, and > 203.0 IU/mL for Q1–4, respectively. Observed case. In this analysis, DAS28-ESR 2.6–≤3.2 was classified as LDA and DAS28-ESR <2.6 was classified as REM. ADA, adalimumab; CZP, certolizumab pegol; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; LDA, low disease activity; MTX, methotrexate; PBO, placebo; Q, quartile; REM, remission; RF, rheumatoid factor.

In patients with established RA (EXXELERATE), the proportion of patients with high baseline RF levels (Q4) who achieved DAS28-ESR LDA or REM at week 24 was approximately 10 percentage points higher in the CZP + MTX group (45.0%) compared to the ADA + MTX group (35.1%). Although inferential statistics were not performed in this analysis, when compared to the other RF quartiles, a slightly lower but still comparable proportion of patients with high baseline RF levels (Q4) responded to CZP + MTX treatment at week 24 (49.4–60.8% vs 45.0%, respectively). However, only 35.1% of patients with high baseline RF levels (Q4) in the ADA + MTX group responded at week 24, lower than the 48.3–54.7% observed in the other RF quartiles. This suggests that the effect of high baseline RF levels is not as evident on CZP efficacy as it is on ADA efficacy. A similar trend was observed at week 104 (data not shown; inferential statistics not performed), with approximately 15 percentage points more patients in the highest baseline RF level quartile (Q4) achieving DAS28-ESR LDA or REM in the CZP + MTX group than the ADA + MTX group. Indeed, a recent study of Japanese RA patients grouped by RF quartiles likewise reported higher efficacy of CZP compared with other currently available TNFi (analyzed collectively) in the highest baseline RF level quartile (Q4: 166–7555 IU/mL).[21] At 3, 6, and 12 months after treatment, DAS28-ESR improvement from baseline was significantly greater in patients who received CZP versus other TNFi in the highest baseline RF level quartile.[21]

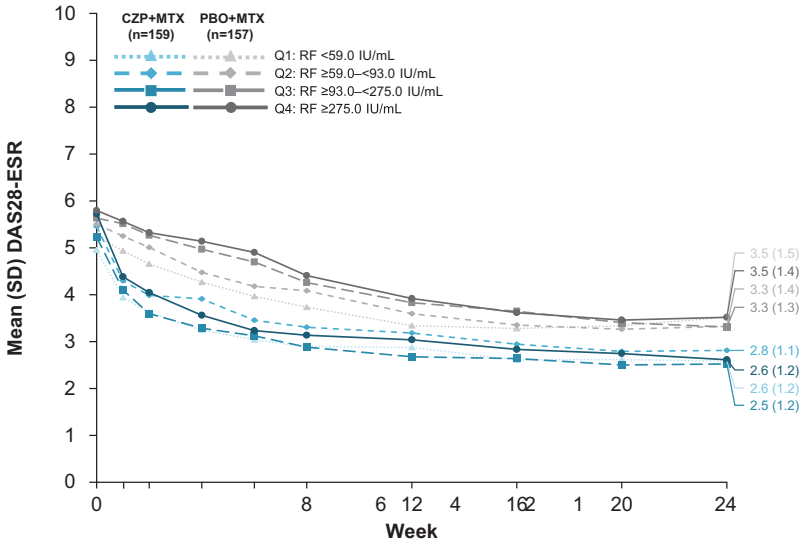
Studies on TNFi so far have observed lower efficacy in patients with high RF levels compared with patients with low RF levels.[4,17–20] However, CZP demonstrated consistent efficacy across all RF groups in the current study, including in the highest RF quartile compared with decreased ADA efficacy in the same quartile. This observation may be related in part to its unique molecular Fc-free structure. Complete monoclonal antibody TNFi, and the IgG1-TNFR2 fusion protein etanercept, include the IgG1-Fc fragment which IgM-RF bind to;[16,21] it is reasonable to speculate that TNFi drug bioavailability is reduced when the resulting immune complexes are cleared.[4] Thus, the higher the RF levels are, the higher the impact on clearance of the complete monoclonal antibody TNFi, which may explain the lower efficacy observed in patients with high RF levels versus those with low RF levels.[21] In this context, CZP, being Fc-free, is cleared at a lower rate even in the presence of high RF levels and remains available to inhibit TNF pro-inflammatory actions. Interestingly, RF positivity has been associated with better response to rituximab and tocilizumab, both monoclonal antibodies with IgG1-Fc fragments, in patients with RA.[3,27,28] However, for these therapies, the association may relate to RF positivity as a B-cell activation marker rather than its role in drug clearance.[3,28]

ACPA are also important in the pathophysiology of RA and potentially influence efficacy outcomes in patients with RA.[1,3] In a post-hoc analysis of Japanese patients with RA, a combination of high baseline RF (≥160 IU/mL) and ACPA (≥100 U/mL) levels was associated with low drug (infliximab) levels and reduced clinical responses.[29] Given that patients with higher baseline ACPA levels often also have high baseline RF levels, there could be a confounding effect for any inferences on baseline ACPA levels and TNFi efficacy. In the current study, we classified patients by RF levels only due to the hypothesized effect of RF on the clearance of CZP and other TNFi. ACPA targets citrullinated proteins and not IgG1[1] and is therefore unlikely to be involved in the IgG1-Fc clearance process. Furthermore, RF-positive patients were found to have high levels of RA disease activity regardless of ACPA levels,[6] suggesting that the value of determining baseline ACPA levels may be in RF-negative or low-titer RF-positive patients rather than in patients with very high baseline RF levels.

A strength of this study is that patients included were from different populations and with a range of disease durations and severity. However, the relatively low patient numbers in the individual clinical trial subgroups may limit the interpretation of results. Furthermore, this diversity may also represent a limitation due to variations in inclusion and exclusion criteria and study periods. The 6 clinical studies were conducted over different periods (C-OPERA: 2011–2013, RAPID-1 and RAPID-2: 2005–2006, J-RAPID: 2008–2010, RAPID-C: 2014–2016, and EXXELERATE: 2011–2013) and may have reflected changes in clinical practice. Nevertheless, our findings demonstrate that CZP showed consistent efficacy trends across the heterogenous trial populations and study periods.

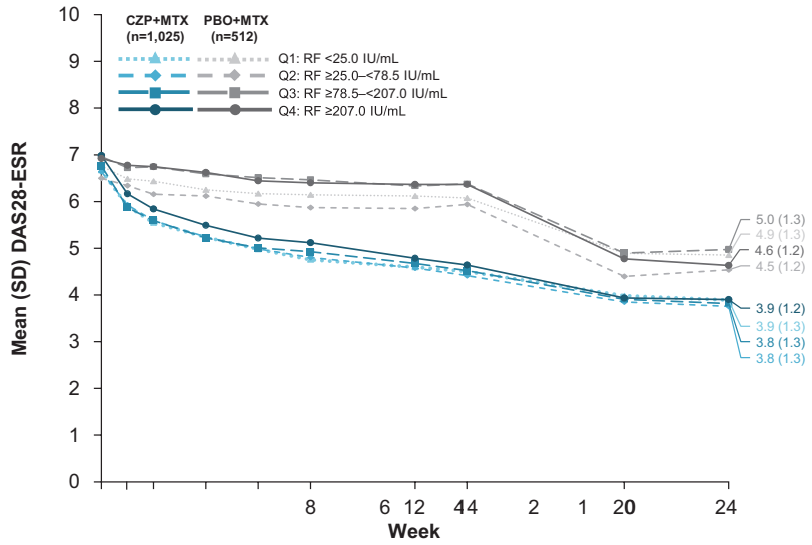
Other potential limitations of the analysis are that observed case data were presented, taking into account responders who continued until at least week 24, but excluding non-responders who dropped out of the trials. In this study, RF assays may have differed across local hospitals, although all assays were performed using validated techniques. Given that the effect on efficacy is only evident in patients with very high baseline RF levels, the potential variability of RF assays used most likely has a negligible impact on the inferences drawn in this study. Additionally, only IgM-RF levels were assayed in this study, although other RF isotypes have also been associated with response rates in patients with RA. For example, high levels (>100 U/mL) of IgA-RF have been found to predict poor response rate to TNFi treatment compared with low (20–100 U/mL) or negative (<20 U/mL) levels.[19] Regardless, the most commonly detected RF subtype in patients with RA is IgM-RF and RF levels measured in clinical diagnostic settings usually refer to IgM-RF.[2,3] As this was

(A) C-OPERA



n										
Q1	40	40	40	40	40	40	40	40	40	39
Q2	39	39	39	39	39	39	39	39	36	38
Q3	37	37	36	37	37	37	37	37	36	35
Q4	43	43	43	43	43	42	43	42	40	42
Q1	38	38	38	37	37	36	36	35	34	35
Q2	38	38	36	38	38	38	37	37	37	37
Q3	45	45	45	45	45	44	45	45	44	43
Q4	36	36	36	36	36	36	36	36	36	36

(B) Pooled RAPID



n										
Q1	251	239	246	244	240	234	225	226	148	149
Q2	254	246	246	246	240	237	230	227	158	164
Q3	246	234	240	240	234	231	220	220	152	154
Q4	272	258	265	264	256	255	248	246	173	170
Q1	120	117	120	117	117	112	112	111	29	29
Q2	129	127	127	126	123	119	118	117	33	31
Q3	136	124	135	133	128	124	117	115	33	34
Q4	122	114	114	113	109	107	105	103	22	21

FIGURE 3 (Continued)

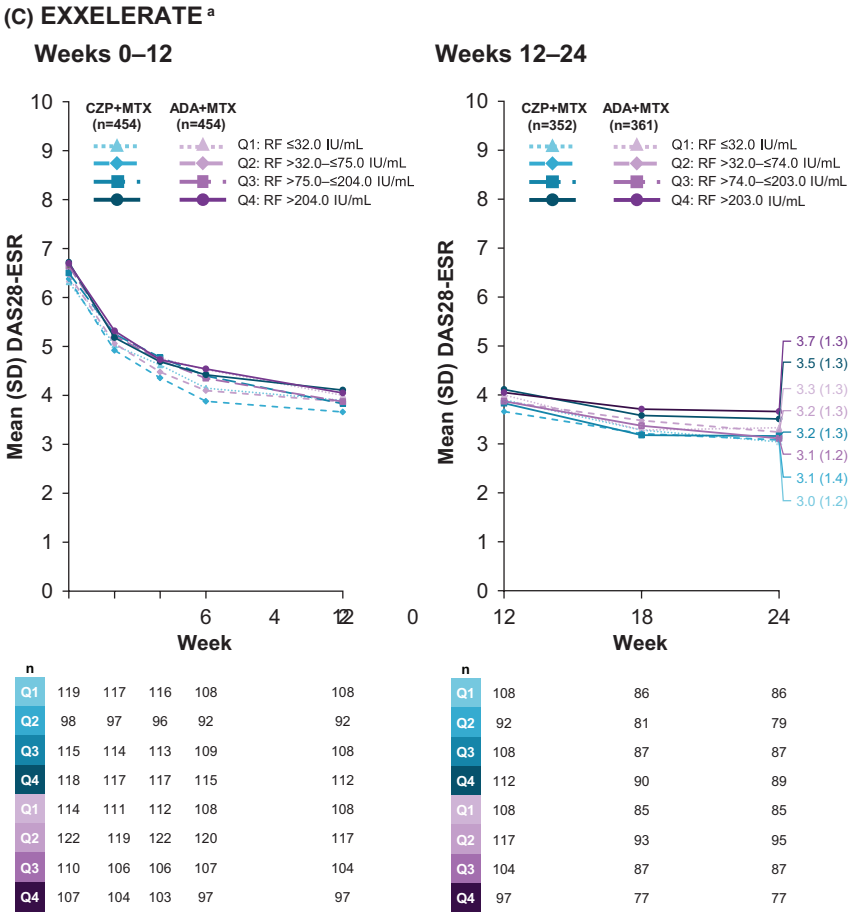


FIGURE 3 Mean DAS28-ESR over 24 weeks for (A) C-OPERA, (B) Pooled RAPID, and (C) EXXELERATE. [a]EXXELERATE data for weeks 0–12 included patients initially randomized to CZP + MTX and ADA + MTX (Full Analysis Set) while weeks 12–24 data included week 12 responders who continued on the same treatment, not including patients who switched between CZP and ADA at week 12 (Week 12 Full Analysis Set). Observed Case. Week 24 data are mean (SD). ADA, adalimumab; CZP, certolizumab pegol; DAS28-ESR, Disease Activity Score 28-erythrocyte sedimentation rate; MTX, methotrexate; PBO, placebo; Q, quartile; RF, rheumatoid factor; SD, standard deviation.

a post-hoc analysis, we have not provided quantitative statistical inferences. This study was not powered for hypothesis testing. Nonetheless, we have discussed the numerical differences and potential clinical importance of such differences. Finally, this post-hoc analysis did not assess the safety of CZP specific to baseline RF levels. However, the full safety results of all 6 clinical studies have been published previously and most adverse events were mild or moderate.[9–14]

5 | CONCLUSION

In conclusion, this post-hoc analysis provides evidence to support the clinical benefit of CZP treatment in association with MTX in RA irrespective of baseline RF status. CZP efficacy was consistent across RF quartiles, including in patients in the quartile with the highest baseline RF levels who are at the highest risk of disease progression.

AUTHOR CONTRIBUTIONS

Substantial contributions to study conception and design: YT, TT, DH, SH, NI, ZL, RMX, CC, NT, PCT. Substantial contributions to analysis and interpretation of the data: YT, TT, DH, SH, NI, ZL, RMX, CC, NT, PCT. Drafting the article or revising it critically for important intellectual content: YT, TT, DH, SH, NI, ZL, RMX, CC, NT, PCT. Final approval of the version of the article to be published: YT, TT, DH, SH, NI, ZL, RMX, CC, NT, PCT.

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CONFLICT OF INTEREST STATEMENT

Yoshiya Tanaka and Tsutomu Takeuchi are Editorial Board members of the *International Journal of Rheumatic Diseases* and were excluded from all editorial decision-making related to the acceptance of this article for publication to minimize bias.

DATA AVAILABILITY STATEMENT

Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents which may include: analysis-ready datasets, study protocol, annotated case report form, statistical analysis plan, dataset specifications, and clinical study report. Prior to use of the data, proposals need to be approved by an independent review panel at www.Vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password protected portal.

ETHICS STATEMENT

Ethics approval was not required for this study as this was a post-hoc analysis. The original study protocols were reviewed by the institutional review board of each institution prior to implementation. Written informed consent was obtained from all patients. All studies were carried out in accordance with the applicable regulatory and International Council for Harmonization-Good Clinical Practice requirements, and the Helsinki Declaration of 1964, and its later amendments.

DISCLOSURES

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