# Certolizumab Inhibits Radiographic Progression Even in RA Patients with High Rheumatoid Factor Levels: A Pooled, Post-Hoc Analysis of Two Phase 3 Trials

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## Objective

**To assess radiographic progression in certolizumab pegol (CZP) versus placebo (PBO)-treated patients with rheumatoid arthritis (RA), stratified by rheumatoid factor (RF) level, in a pooled analysis of the C-EARLY and C-OPERA phase 3 randomized trials.**

## Background

- In patients with RA, including those treated with disease-modifying antirheumatic drugs (DMARDs), high RF levels are a poor prognostic factor, associated with higher disease activity and risk of radiographic progression.[1,2,3,4]
- Such patients have reduced response to monoclonal antibodies targeting tumor necrosis factor (TNF),[5] but may experience greater clinical response to TNF inhibitors (TNFi) without a fragment crystallizable (Fc) portion, such as CZP.[6,7,8]
- Pertinently, progression of radiographic joint damage drives irreversible changes and is linked with functional disability; prevention of radiographic progression is therefore a key goal to improve clinical outcomes and patients' quality of life.[9,10,11]
  - However, there is limited evidence regarding radiographic progression in patients with RA and high RF levels; available studies have demonstrated that Fc-containing TNFis less effectively control radiographic progression in patients with high RF than in those with low RF.[1]

## Methods

### Study Design

- C-EARLY (NCT01519791) was a phase 3, randomized, PBO-controlled study that assessed efficacy and safety of CZP+dose-optimized methotrexate (MTX) versus PBO+dose-optimized MTX in inducing and sustaining clinical remission in DMARD-naïve patients with moderate-to-severe, active, progressive RA with poor prognostic factors, over 52 weeks.[12]
- C-OPERA (NCT01451203) was a phase 3, randomized, PBO-controlled study that evaluated the efficacy and safety of combination therapy using CZP+MTX versus PBO+MTX as first-line treatment for MTX-naïve patients with early RA and poor prognostic factors, over 52 weeks.[13]
- In both trials, at Week 24, PBO-treated non-responders could switch to CZP for the remaining 28 weeks (early escapers).
- A pooled post-hoc analysis of participants from both trials is presented (full analysis set).

### Analyses

- Participants were stratified by baseline RF level (low: <200 IU/mL; high: ≥200 IU/mL), per published strata.[1,7]
- Change from baseline (CfB) in modified Total Sharp Score (mTSS) and mTSS over time were analyzed.
- Proportions of participants experiencing minimum clinically important difference (worsening) of mTSS (>5)[14] at Week 24 and Week 52 were also assessed.
- Descriptive data are presented; no formal hypothesis testing was undertaken.

## Results

### Baseline Characteristics

- 813 CZP-treated (low RF: N=571; high RF: N=242) and 367 PBO-treated (low RF: N=242; high RF: N=125) participants were included in the pooled analysis; 56 PBO-treated participants were early escapers.
- Baseline characteristics were similar between treatment groups within each RF stratification (**Table 1**).
  - Participants with high RF had more severe disease at baseline than those with low RF, with higher mean C-reactive protein (CRP), anti-citrullinated protein antibodies (ACPA), mTSS, and erosion scores.

### Change from Baseline in mTSS

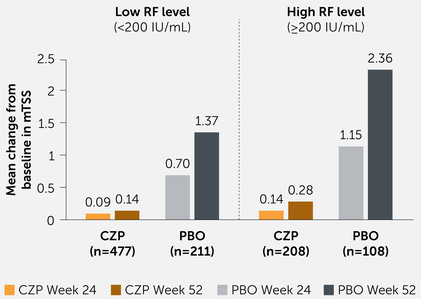
- By Week 52, mean (standard deviation [SD]) mTSS numerically increased from baseline in PBO-treated participants with both high RF (CfB: 2.36 [6.20]) and low RF (CfB: 1.37 [3.43]), but was similar among CZP-treated participants (high RF: CfB: 0.28 [2.63]; low RF: CfB: 0.14 [3.11]) (**Table 2**).
  - Similar trends were observed with CfB in median mTSS.

### Proportion of Participants with Worsening Radiographic Progression

- The proportion of participants with meaningfully worsening radiographic progression was numerically higher in the overall group of PBO-treated participants with high RF compared to low RF at both Week 24 (6.48% vs 2.84%) and Week 52 (17.59% vs 10.43%) (**Figure 1**).
  - By contrast, a smaller proportion of CZP-treated participants experienced meaningful worsening, and the proportion was similar between participants with high and low RF (Week 24: 0.00% vs 1.05%; Week 52: 5.29% vs 3.14%, respectively).

## Summary

**Radiographic progression** was investigated over 52 weeks in patients with **rheumatoid arthritis** and high or low levels of rheumatoid factor, who received **certolizumab pegol** or placebo treatment, in a pooled analysis of the C-EARLY and C-OPERA phase 3 randomized trials.




**CZP-treated participants had lower radiographic progression** at Week 52 than those treated with placebo, **irrespective of baseline RF levels**.

## Conclusions

**Participants with high baseline RF levels had more severe RA and baseline radiographic damage than those with low RF. Certolizumab pegol-treated participants demonstrated consistently lower radiographic progression than those treated with PBO, irrespective of baseline RF levels. This suggests, uniquely, that RF level does not adversely influence radiographic response to certolizumab pegol.**

**Table 1** Baseline demographics and disease characteristics, stratified by baseline RF level

| | Low RF level (<200 IU/mL) | | | | High RF level (≥200 IU/mL) | | | |
|---|---|---|---|---|---|---|---|---|
| | CZP | PBO | | | CZP | PBO | | |
| **Baseline characteristic, mean (SD) unless stated otherwise** | **All (N=571)** | **All (N=242)** | **Early escapers (n=33)** | **Continuers (n=209)** | **All (N=242)** | **All (N=125)** | **Early escapers (n=23)** | **Continuers (n=102)** |
| **Age**, years | 49.8 (13.3) | 50.3 (11.7) | 50.9 (8.3) | 50.2 (12.2) | 51.4 (12.4) | 50.4 (12.5) | 50.6 (13.0) | 50.3 (12.5) |
| **Female**, n (%) | 451 (79.0) | 195 (80.6) | 29 (87.9) | 166 (79.4) | 175 (72.3) | 100 (80.0) | 19 (82.6) | 81 (79.4) |
| **BMI**, kg/m$^2$ | 26.5 (5.9) | 25.8 (6.1) | 24.0 (6.2) | 26.1 (6.1) | 27.7 (6.4) | 26.8 (6.4) | 25.2 (5.6) | 27.1 (6.5) |
| **Disease duration**, years | 3.18 (4.92) | 3.52 (2.91) | 3.59 (2.68) | 3.51 (2.96) | 2.83 (2.69) | 3.35 (3.03) | 3.91 (3.38) | 3.22 (2.95) |
| **Rheumatoid factor**, IU/mL | 71.22 (50.96) | 71.96 (45.64) | 65.48 (34.20) | 72.98 (47.18) | 518.72 (486.17) | 472.98 (355.38) | 398.52 (161.60) | 489.77 (384.47) |
| **CRP**, mg/dL | 15.16 (23.20) | 10.13 (17.10) | 5.48 (11.64) | 10.86 (17.72) | 23.18 (34.06) | 18.48 (31.76) | 7.49 (11.66) | 20.95 (34.28) |
| **DAS28-ESR** | 6.38 (1.05) | 6.14 (1.20) | 6.32 (1.13) | 6.11 (1.21) | 6.55 (1.15) | 6.50 (1.18) | 6.53 (0.84) | 6.49 (1.25) |
| **Anti-CCP (ACPA)**, IU/mL | 381.25 (693.93) | 419.29 (854.94) | 247.35 (211.56) | 446.44 (913.55) | 605.58 (972.45) | 648.68 (1531.15) | 451.14 (630.78) | 693.23 (1667.56) |
| **mTSS** | | | | | | | | |
| Mean | 6.24 (12.11) | 6.38 (14.56) | 4.89 (7.64) | 6.62 (15.37) | 8.18 (14.83) | 9.56 (20.10) | 18.15 (34.92) | 7.60 (14.42) |
| Median (IQR) | 2.00 (0.50, 7.00) | 2.00 (0.50, 6.00) | 2.00 (0.50, 6.00) | 2.00 (0.50, 6.00) | 3.00 (0.50, 9.00) | 2.75 (0.50, 6.50) | 3.00 (1.00, 12.00) | 2.50 (0.50, 5.50) |
| **Erosion score** | 6.96 (13.75) | 5.92 (17.09) | 2.47 (2.77) | 6.46 (18.30) | 9.22 (18.34) | 9.49 (18.82) | 10.48 (21.47) | 9.27 (18.27) |
| **HAQ-DI score** | 1.46 (0.65) | 1.38 (0.75) | 1.34 (0.62) | 1.39 (0.77) | 1.56 (0.67) | 1.48 (0.72) | 1.51 (0.75) | 1.47 (0.71) |

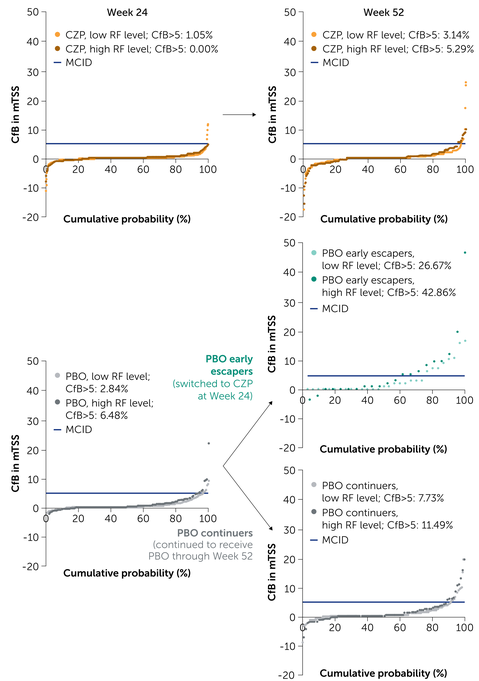
Full analysis set.

**Table 2** Change from baseline in mTSS, stratified by baseline RF level, over time (OC)[a,b]

| | Low RF level (<200 IU/mL) | | | | High RF level (≥200 IU/mL) | | | |
|---|---|---|---|---|---|---|---|---|
| | CZP | PBO | | | CZP | PBO | | |
| | **All (n=477)** | **All (n=211)** | **Early escapers (n=30)** | **Continuers (n=181)** | **All (n=208)** | **All (n=108)** | **Early escapers (n=21)** | **Continuers (n=87)** |
| **Mean change from baseline (SD)** | | | | | | | | |
| **Week 24** | 0.09 (1.50) | 0.70 (1.65) | 1.60 (2.29) | 0.55 (1.48) | 0.14 (1.24) | 1.15 (2.93) | 2.82 (5.10) | 0.74 (1.95) |
| **Week 52** | 0.14 (3.11) | 1.37 (3.43) | 3.46 (4.94) | 1.02 (3.00) | 0.28 (2.63) | 2.36 (6.20) | 6.12 (11.00) | 1.45 (3.93) |
| **Median change from baseline (IQR)** | | | | | | | | |
| **Week 24** | 0.00 (−0.23, 0.46) | 0.00 (0.00, 1.00) | 0.50 (0.00, 3.00) | 0.00 (0.00, 0.69) | 0.00 (−0.23, 0.50) | 0.23 (0.00, 1.50) | 1.00 (0.00, 4.00) | 0.00 (0.00, 1.15) |
| **Week 52** | 0.00 (−0.50, 0.51) | 0.00 (0.00, 1.85) | 1.09 (0.00, 6.50) | 0.00 (0.00, 1.50) | 0.00 (−0.50, 1.00) | 0.50 (0.00, 2.89) | 2.17 (0.00, 8.67) | 0.00 (0.00, 2.50) |

Full analysis set; **[a]** Data presented are observed case, except for PBO early escapers, where linear extrapolation was employed; **[b]** Not all participants with baseline mTSS data had Week 24 and Week 52 change from baseline data available, hence differing n values.

**Figure 1** Individual patient CfB in mTSS at Week 24 and Week 52, stratified by baseline RF level (OC)




Full analysis set; Data presented as cumulative probability in rank order; MCID in mTSS defined as CfB>5; PBO Week 24 discontinuers are participants who discontinued at Week 24 due to lack of efficacy (using time to discontinuation up to 168+5 days maximum); **[a]** Observed case data are used except for PBO early escapers, where linear extrapolation was employed.

**ACPA:** anti-citrullinated protein antibodies; **anti-CCP:** anti-cyclic citrullinated peptide; **BMI:** body mass index; **CfB:** change from baseline; **CRP:** C-reactive protein; **CZP:** certolizumab pegol; **DAS28-ESR:** Disease Activity Score 28 - Erythrocyte Sedimentation Rate; **DMARD:** disease-modifying antirheumatic drug; **Fc:** fragment crystallizable; **HAQ-DI:** Health Assessment Questionnaire - Disability Index; **IQR**: interquartile range; **IU/mL:** international units per milliliter; **MCID:** minimum clinically important difference; **mg/dL:** milligrams per deciliter; **mTSS:** modified Total Sharp Score; **MTX:** methotrexate; **OC:** observed case; **PBO:** placebo; **RA:** rheumatoid arthritis; **RF:** rheumatoid factor; **SD:** standard deviation; **TNF:** tumor necrosis factor; **TNFi:** tumor necrosis factor inhibitor.

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