

Do High RF Titers Impact Response to TNF Inhibitors? Comparison of Certolizumab Pegol and Adalimumab in Patients with RA and High Titers of RF: A Post Hoc Analysis of a Phase 4 Trial

Alejandro Balsa,¹ Josef S. Smolen,² Peter C. Taylor,³ Yoshiya Tanaka,⁴ Carlos Cara,⁵ Bernard Lauwerys,⁶ Ricardo Xavier,⁷ Jeffrey R. Curtis,⁸ Ted R. Mikuls,⁹ Michael Weinblatt¹⁰

Objective

To report efficacy outcomes of certolizumab pegol (CZP), a PEGylated crystallizable fragment (Fc)-free tumor necrosis factor inhibitor (TNFi), versus adalimumab (ADA), an Fc-containing TNFi, in patients with rheumatoid arthritis (RA) and high rheumatoid factor (RF) levels.

Background

- In patients with RA, high RF levels are considered a poor prognostic factor and are associated with higher disease activity, risk of radiographic progression, and decreased response to TNFi.¹⁻³ RFs bind the Fc of immunoglobulin G and thus also biologics, such as TNFi, resulting in large immune complexes.⁴
- Preliminary data suggest that patients with RA and high RF levels may achieve and maintain greater clinical improvement with TNFi without an Fc compared to TNFi with an Fc, though further data are required to support this.⁵

Methods

- The phase 4 EXXELERATE trial (NCT01500278) compared the efficacy and safety of CZP to ADA in a head-to-head comparison; full study design and primary outcomes have been reported previously.⁶
- Patients were randomized 1:1 to CZP 200 mg every 2 weeks (Q2W) plus methotrexate (MTX), or ADA 40 mg Q2W plus MTX. At Week 12, patients were classified as responders or non-responders; non-responders were switched to the other TNFi with possible follow-up to Week 104.
- Here, we report the following outcomes to Week 104: drug plasma concentrations (stratified by RF quartile [\leq Q3: \leq 204 IU/mL; $>$ Q3: $>$ 204 IU/mL; measured by Roche Tina-quant[®]]), mean DAS28-CRP score (stratified by RF and anti-citrullinated protein antibodies [ACPA; \leq Q3: \leq 761.4 IU/mL; $>$ Q3: $>$ 761.4 IU/mL] quartile), and proportion of patients achieving low disease activity (LDA; threshold: DAS28-CRP \leq 2.7; stratified by RF quartile).

Results

Patient disposition and baseline characteristics

- Baseline data by RF quartile were available for 453 CZP-randomized patients (\leq Q3: n=334; $>$ Q3: n=119) and 454 ADA-randomized patients (\leq Q3: n=347; $>$ Q3 n=107).
- Baseline characteristics were similar between CZP- and ADA-randomized patients with RF level \leq Q3 and $>$ Q3 (Table 1).
- At Week 12, 66 CZP-treated patients switched to ADA and 59 ADA-treated patients switched to CZP.

Drug plasma concentrations

- Through Weeks 0–104, mean drug plasma concentrations were similar in CZP but not ADA-treated patients with RF level \leq Q3 and $>$ Q3. At Week 104, mean ADA plasma concentrations were 22.9% lower in patients with RF $>$ Q3 versus those with RF \leq Q3; in CZP-treated patients, this difference was smaller (13.0%; Figure 1).

Efficacy

- For patients in RF \leq Q3, mean DAS28-CRP scores were similar between CZP- and ADA-treated patients at Week 104. However, for patients with RF $>$ Q3, mean DAS28-CRP scores were lower in CZP- vs ADA-treated patients at Week 104 (Figure 2).
- A similar pattern was observed for the proportion of patients achieving DAS28-CRP LDA at Week 104.
- When patients were stratified by ACPA level, no notable difference in mean DAS28-CRP scores between CZP- and ADA-treated patients was observed for patients with levels \leq Q3 or $>$ Q3 (Figure 3).

Conclusions

In patients with RA and high RF levels, CZP-treated patients sustained drug concentrations and had better clinical outcomes than ADA-treated patients. This pattern was not observed in outcomes stratified by ACPA level.

These data, together with previous reports where CZP showed consistent efficacy irrespective of baseline RF level,^{7,8} suggest CZP may be a suitable therapy for patients with RA and high RF levels; further research is warranted to confirm this.

Summary

At Week 104, CZP-treated patients had consistent clinical outcomes and drug concentrations regardless of baseline RF level. This was not observed in ADA-treated patients:

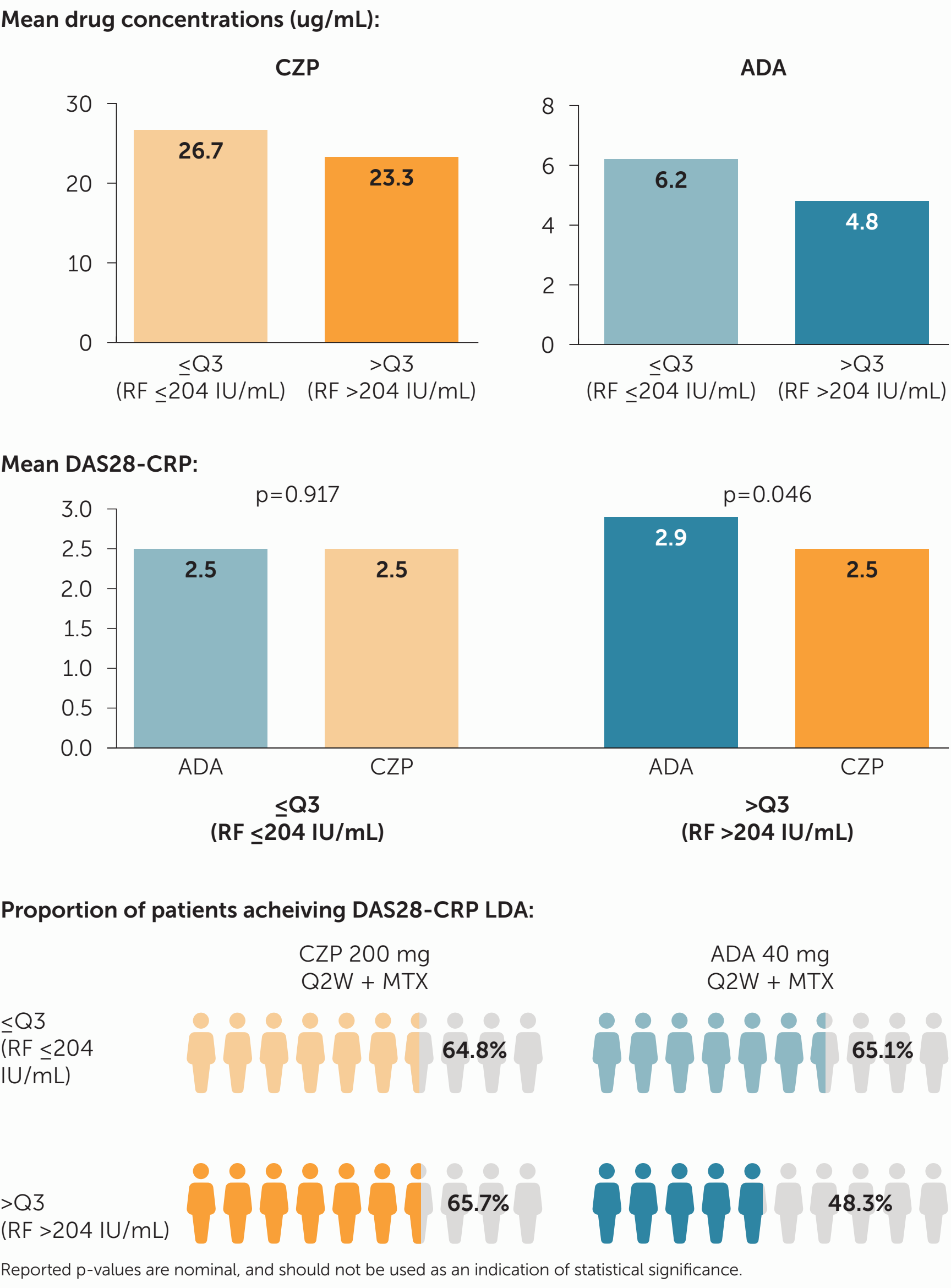


Table 1 Baseline demographics and disease characteristics stratified by RF level

	\leq Q3 (\leq 204 IU/mL)		$>$ Q3 ($>$ 204 IU/mL)	
	CZP + MTX (N=334)	ADA + MTX (N=347)	CZP + MTX (N=119)	ADA + MTX (N=107)
Age, years, mean (SD)	52.7 (12.4)	52.5 (12.9)	55.5 (11.7)	54.2 (12.3)
BMI, kg/m ² , mean (SD)	28.4 (6.4)	28.1 (6.0)	28.8 (6.3)	27.4 (7.0)
Sex, male, (%)	19.2	20.5	26.9	22.4
Steroid use at baseline, yes, (%)	47.9	55.9	68.1	60.7
Previous TNFi use, yes, (%)	<1	<1	<1	<1
Disease duration, years, mean (SD)	5.5 (6.2)	5.5 (6.5)	7.5 (8.6)	6.9 (7.8)
DAS28-CRP, mean (SD)	5.5 (0.9) ^a	5.7 (0.9) ^a	5.9 (0.9) ^c	5.9 (1.0) ^d

[a] n=332; [b] n=346; [c] n=118; [d] n=106

ACPA: anti-citrullinated protein antibodies; ADA: adalimumab; CRP: C-reactive protein; CZP: certolizumab pegol; DAS28: disease activity score 28; Fc: crystallizable fragment; LDA: low disease activity; MTX: methotrexate; OC: observed case; Q2W: every 2 weeks; Q3: third quartile; RA: rheumatoid arthritis; RF: rheumatoid factor; SD: standard deviation; TNFi: tumor necrosis factor inhibitor.

Institutions: ¹Servicio de Reumatología, Hospital Universitario La Paz, Universidad Autónoma de Madrid, Madrid, Spain; ²Division of Rheumatology, Department of Medicine, Medical University of Vienna, Vienna, Austria; ³Bolton Research Centre, University of Oxford, UK; ⁴The First Department of Internal Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan; ⁵UCB Pharma, Madrid, Spain; ⁶UCB Pharma, Brussels, Belgium; ⁷Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil; ⁸Division of Clinical Immunology and Rheumatology, University of Alabama, Birmingham, Alabama, USA; ⁹Division of Rheumatology, Inflammation and Immunity, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA.

References: ¹Vastesaeger N. Rheumatology 2009;48:1114–21. ²Guchacovich M. Clin Rheumatol 2014;33:1707–14. ³Takeuchi T. Arthritis Res Ther 2017;19:140. ⁴Walton-Thomson S. Plus One 2013;14:e0217624. ⁵Nakayama Y. Rheumatol Int 2022;42:1227–34. ⁶Smolen J. Lancet 2016;388:2763–74. ⁷Martinez-Fello A. Ann Rheum Dis 2022;81:594–5. ⁸Tanaka Y. Int J Rheum Dis 2023;26(7):1248–59. **Author Contributions:** Substantial contributions to study conception/design, or acquisition/analysis/interpretation of data: **JSS, PCT, YT, CC, BL, RK, JRC, TRM, MW.** Drafting of the publication, or reviewing it critically for important intellectual content: **AB, JSS, PCT, YT, CC, BL, RK, JRC, TRM, MW.** Final approval of the publication: **AB, JSS, PCT, YT, CC, BL, RK, JRC, TRM, MW.** **Author Disclosures:** **AB:** Research grants from AbbVie, Pfizer, and UCB Pharma; speaker and consultancy fees from AbbVie, Pfizer, and UCB Pharma. **JSS:** Research grants from AbbVie, Bristol Myers Squibb, Eli Lilly, Galapagos, Celgene, Bristol Myers Squibb, Celgene, Celltrion, Chugai, Gilead, ILTOO Pharma, Janssen, Eli Lilly, Merck Sharp & Dohme, Sandoz, Pfizer, R-Pharma, Roche, Samsung, Sanofi, and UCB; editor of Annals of the Rheumatic Diseases; co-editor of Rheumatology 7E/8E; convenor of EULAR Task Forces and T2T Task Forces. **PCT:** Research grants from Galapagos; consultancy fees from AbbVie, Acetylin Inc., Biogen, Eli Lilly, Fresenius, Galapagos, Gilead, GSK, Janssen, Nordic Pharma, Pfizer, Sanofi, and UCB Pharma; participation on a Data Safety Monitoring Board/Advisory Board for Immunovant, Sanofi, and Kymab. **YT:** Speaking fees and/or honoraria from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, Eisai, Eli Lilly, Gilead, GSK, Pfizer, Takeda, and Tashiro; received grants from: Chugai, Eisai, Mitsubishi-Tanabe and Tashiro. **CC, BL:** Employee and stockholder of UCB Pharma. **RK:** Speaker and consultancy fees from: AbbVie, AstraZeneca, Janssen, Organon, and UCB Pharma. **JRC:** Grant/Research and consultancy fees from: AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, and UCB Pharma. **TRM:** Consultant for: Horizon Therapeutics; Pfizer, Sanofi, and UCB Pharma; research support from: Horizon Therapeutics; royalties from: Wolters Kluwer Health | UpToDate. **MW:** Research grants from: AbbVie, Actavis, Amgen, Aquila, BMS, and Janssen; consultant for: AbbVie, Actavis, Amgen, Aquila, BMS, Corbixa, Eli Lilly, GSK, Gilead, Horizon, Johnson and Johnson, Prometheus, Pfizer, Ran Therapeutics, Revado Biotherapeutics, Sanofi, Scipher, Sci Rhom, Set Point, and UCB Pharma. **Acknowledgements:** We would like to thank the patients and their caregivers in addition to all the investigators and their teams who contributed to this study. The authors acknowledge Simone E. Auler, PhD and Ana Barbalillo-Ruiz, MPharm, UCB Pharma, for publication coordination, Erin Clarkson, BSc and Jane Spingardi, DPhil, Costello Medical, UK for editorial assistance, and the Costello Medical Creative team for design support. This study was funded by UCB Pharma. All costs associated with development of this presentation were funded by UCB Pharma.

Figure 1

Mean drug plasma concentrations of (A) CZP and (B) ADA to Week 104, stratified by RF quartiles (OC)

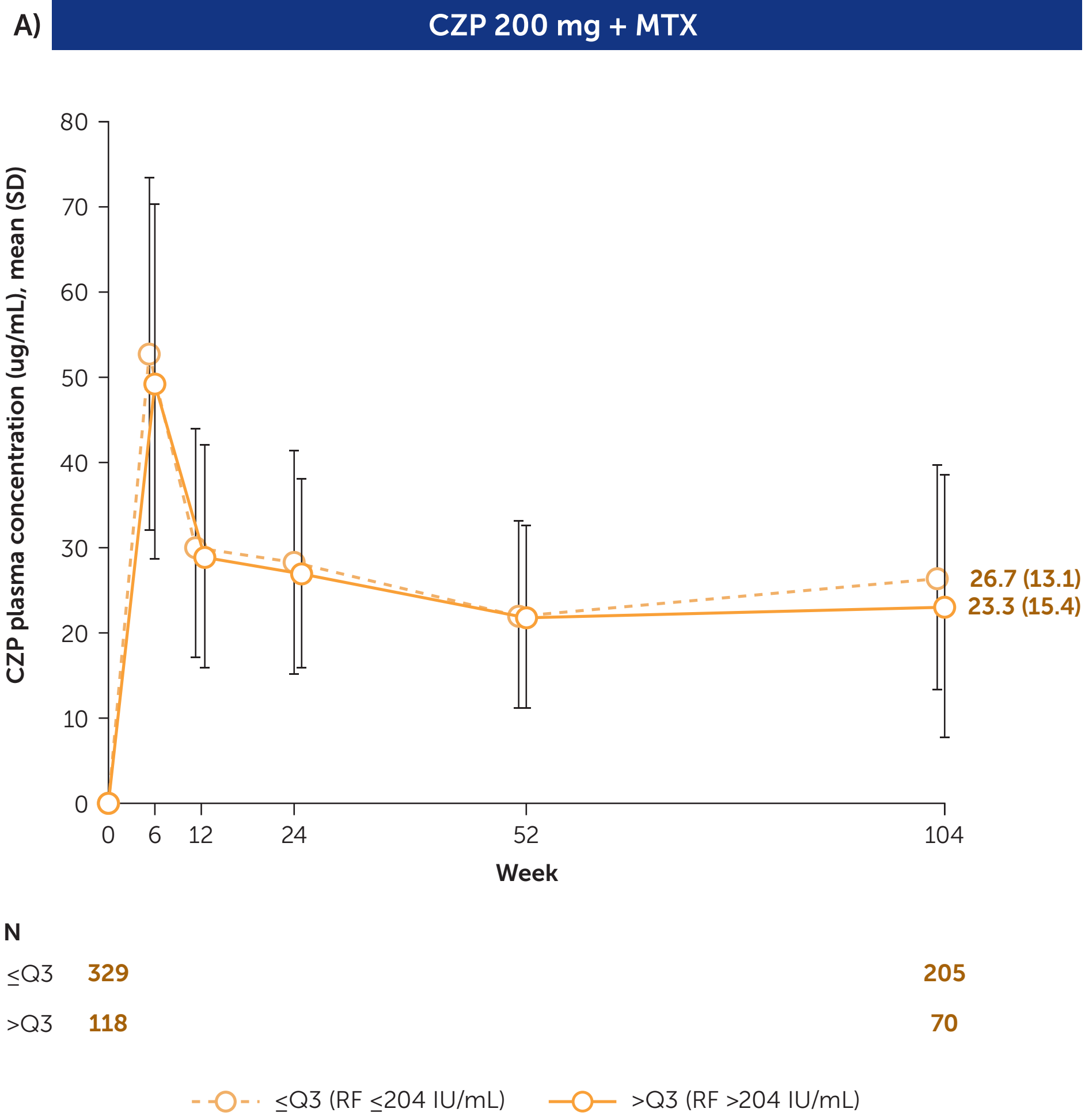


Figure 2

Response to CZP and ADA to Week 104 measured by (A) DAS28-CRP and (B) proportion of patients achieving DAS28-CRP LDA,^a stratified by RF quartiles (OC)

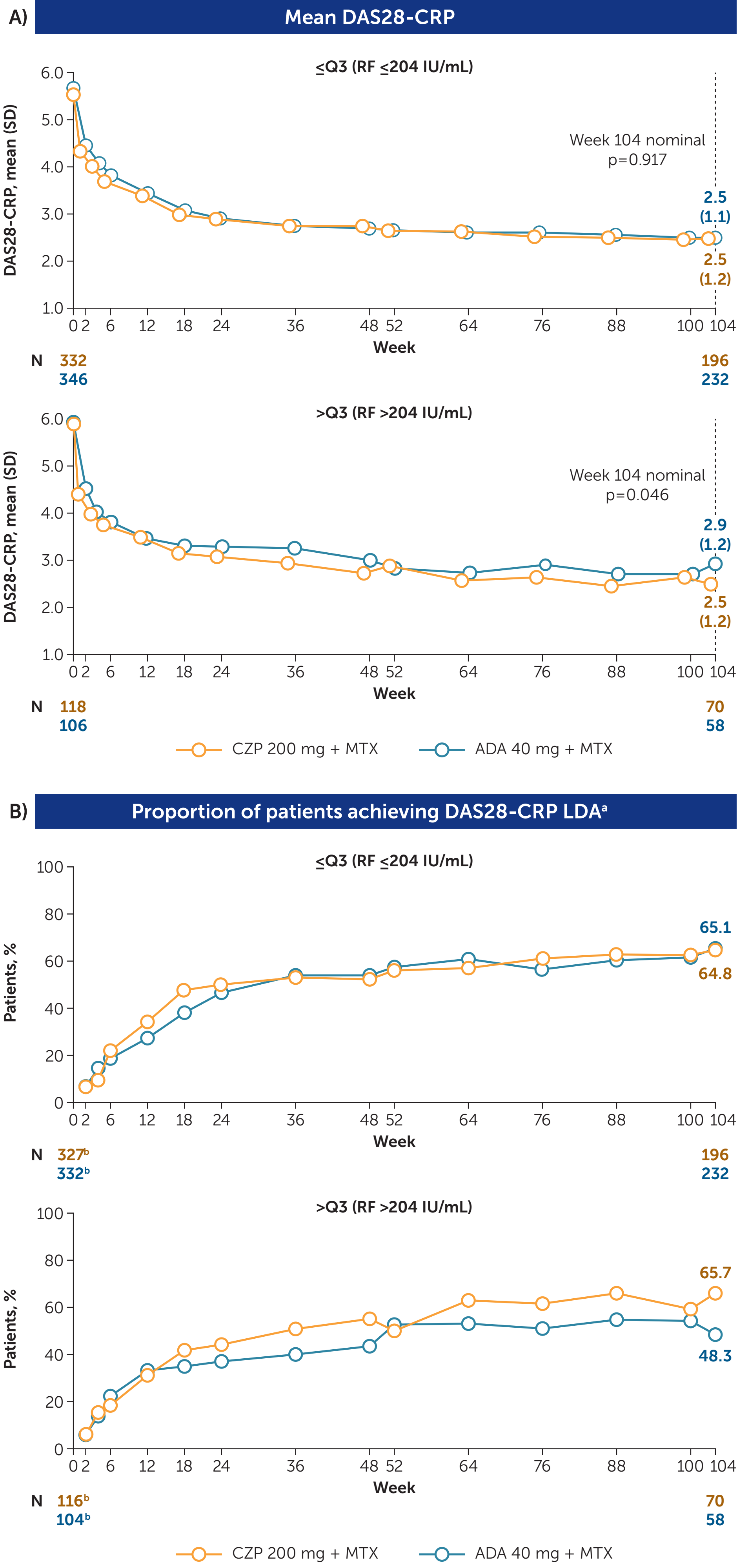


Figure 3

Response to CZP and ADA to Week 104 measured by DAS28-CRP, stratified by ACPA quartile (OC)

