Long-term Safety of Certolizumab Pegol in Rheumatoid Arthritis, Axial Spondyloarthritis, Psoriatic Arthritis, Psoriasis, and Crohn's Disease: A Pooled Analysis of 11,317 Patients across Clinical Trials

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SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLES AND FIGURES

Supplementary Table S1. Opportunistic infections as defined by the OICC and associated MedDRA coded terms

OICC term[a]	MedDRA coded term (v18.1)
Definite[b/c]	
Aspergillosis (invasive disease only)	Aspergillosis
Bartonellosis (disseminated disease only)	Bartonellosis
BK virus disease including PVAN	Polyomavirus-associated nephropathy
Blastomycosis	Blastomycosis
Candidiasis (invasive disease or oral)	Oral candidiasis or split to oral candidiasis and Candida infection
Coccidioidomycosis	Coccidioidomycosis
Cryptococcosis	Cryptococcosis
Cytomegalovirus disease	Cytomegalovirus infection
HBV reactivation	Hepatitis B
Herpes simplex (invasive disease only)	Herpes simplex
Herpes zoster (any form)	Herpes zoster
Histoplasmosis	Histoplasmosis
Legionellosis	Legionella infection
Listeria monocytogenes (invasive disease only)	Listeriosis
Nocardiosis	Nocardiosis
Nontuberculous mycobacterium disease	Mycobacterial infection
Other invasive fungi: Mucormycosis (=zygomycosis) [Rhizopus, Mucor, and Lichtheimia], Scedosporum/Pseudallescheria boydii, Fusarium]	1) 'Mucormycosis (=zygomycosis-) [Rhizopus, Mucor, and Lichtheimia] (Invasive fungi)'- coded to 'Zygomycosis'; 2) 'Scedosporum (Invasive fungi)' coded to 'Scedosporium infection'; 3) 'Pseudallescheria boydii (Invasive fungi)'- coded to 'Pseudallescheria infection'; 4) 'Fusarium (II) (Invasive fungi)'- coded to 'Fusarium infection'
Pneumocystis jiroveci	Pneumocystis jiroveci infection
Post-transplant lymphoproliferative disorder (EBV)	Post-transplant lymphoproliferative disorder
Progressive Multifocal Leukoencephalopathy	Progressive multifocal leukoencephalopathy
Salmonellosis (invasive disease only)	Salmonellosis
Stronglyoides (hyperinfection syndrome and disseminated forms only)	Strongyloidiasis
Toxoplasmosis	Toxoplasmosis
Tuberculosis	Tuberculosis
Probable[d]	
Campylobacter (invasive disease only)	Campylobacter infection
Cryptosporidium species (chronic disease only)	Cryptosporidiosis infection
HCV progression	Hepatitis C
Leishmaniasis (visceral only)	Visceral leishmaniasis
Microsporidiosis	Microsporidia infection
Paracoccidioides infections	Paracoccidioides infection
Penicillium marneffei	Penicilliosis
Shigella (invasive disease only)	Shigella infection
Sporothrix schenckii	Sporotrichosis
Trypanosoma cruzi infection (Chagas' Disease) (disseminated disease only)	American trypanosomiasis
Vibriosis (invasive disease due to V. vulfnificus)	Bacterial infection

[a]Based on OICC consensus recommendations.[15] [b]Generally do not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity. [c]Can occur in patients without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity. [d]Published data are currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy. OICC: Opportunistic Infections Consensus Committee.

Supplementary Table S2. Validated MedDRA terms included as potential autoimmune events

Event type	MedDRA coded term (v18.1)
Demyelination events	Multiple sclerosis Optic neuritis Primary progressive multiple sclerosis Demyelinating polyneuropathy
Lupus and lupus-like events	Lupus-like syndrome Subacute cutaneous lupus erythematosus
Pulmonary events	Acute pulmonary oedema Bronchial hyperreactivity Idiopathic pulmonary fibrosis Pulmonary granuloma
Vasculitis events	Arteritis Cutaneous vasculitis Haemorrhagic vasculitis Henoch-Schönlein purpura Rheumatoid vasculitis Vasculitis

MedDRA: Medical Dictionary for Regulatory Activities.

Supplementary Table S3. Validated MedDRA terms included as GI-specific SIEs in the sensitivity analysis

MedDRA coded terms (v18.1)		
Abdominal abscess	Douglas' abscess	Oesophageal candidiasis
Abdominal sepsis	Enteritis infectious	Oral candidiasis
Abscess intestinal	Enterocolitis viral	Rectal abscess
Anal abscess	Gallbladder empyema	Subdiaphragmatic abscess
Anal fistula infection	Gastroenteritis	Pelvic abscess
Anorectal infection	Gastroenteritis clostridial	Perineal abscess
Appendiceal abscess	Gastroenteritis salmonella	Perineal infection
Campylobacter gastroenteritis	Gastroenteritis viral	Perirectal abscess
Clostridium difficile colitis	Gastroenteritis fungal infection	Peritoneal tuberculosis
Clostridium difficile infection	Gastrointestinal infection	Peritonitis
Cytomegalovirus colitis	Gastrointestinal viral infection	Pseudomembranous colitis
Diverticulitis	Helicobacter infection	Tuberculosis gastrointestinal

GI: gastrointestinal; MedDRA: Medical Dictionary for Regulatory Activities; SIE: serious infectious event.

Supplementary Table S4. Adverse events reported for CZP-treated patients in the combined RCT and OLE periods (RCT+OLE) and PBO-controlled and CZP-treated patients (all doses) in the RCT period

	Overall		**RA**		**axSpA**		**PsA**		**PSO**		**CD**	
	RCT+OLE (n=11,317)		**RCT+OLE (n=6,927)**		**RCT+OLE (n=315)**		**RCT+OLE (n=393)**		**RCT+OLE (n=1,112)**		**RCT+OLE (n=2,570)**	
Total exposure (PY)	21,694.9		13,541.6		977.8		1,316.1		1,481.3		4,378.1	
Mean exposure (days)	700.2		714.0		1,133.7		1,223.2		486.5		622.2	
Median exposure (days)	420.0		413.0		1,371.0		1,456.0		550.0		313.0	
	IR/100 PY [n (%)]											
AEs	212.43 [9,805 (86.6)]		200.38 [5,951 (85.9)]		173.45 [303 (96.2)]		162.33 [367 (93.4)]		181.08 [899 (80.8)]		305.26 [2,285 (88.9)]	
Severe AEs	11.43 [2,192 (19.4)]		9.44 [1,148 (16.6)]		5.46 [49 (15.6)]		5.90 [71 (18.1)]		7.67 [109 (9.8)]		23.28 [815 (31.7)]	
Deaths	0.40 [87 (0.8)]		0.50 [68 (1.0)]		0		0.46 [6 (1.5)]		0.27 [4 (0.4)]		0.21 [9 (0.4)]	
AEs leading to withdrawal	8.65 [1,842 (16.3)]		6.92 [924 (13.3)]		4.96 [48 (15.2)]		3.82 [50 (12.7)]		4.29 [63 (5.7)]		18.07 [757 (29.5)]	
SAEs	14.33 [2,655 (23.5)]		13.01 [1,505 (21.7)]		7.81 [69 (21.9)]		8.76 [100 (25.4)]		9.06 [127 (11.4)]		24.19 [854 (33.2)]	
	RCT PBO (n=3,092)	**RCT CZP (n=6,467)**	**RCT PBO (n=1,759)**	**RCT CZP (n=4,248)**	**RCT PBO (n=107)**	**RCT CZP (n=218)**	**RCT PBO (n=136)**	**RCT CZP (n=273)**	**RCT PBO (n=215)**	**RCT CZP (n=809)**	**RCT PBO (n=875)**	**RCT CZP (n=919)**
Total exposure (PY)	1184.3	3016.9	774.7	2259.9	38.5	98.9	50.6	122.0	58.8	237.3	261.7	298.7
Mean exposure (days)	139.9	170.4	160.9	194.3	131.4	165.7	135.9	163.3	99.8	107.1	109.3	118.7
Median exposure (days)	112.0	137.0	113.0	168.0	113.0	168.0	116.0	168.0	112.0	112.0	84.0	112.0
	IR/100 PY [n (%)]											
AEs	378.62 [2069 (66.9)]	343.09 [4555 (70.4)]	328.87 [1,166 (66.3)]	322.86 [3,058 (72.0)]	311.86 [67 (62.6)]	323.39 [162 (74.3)]	340.56 [92 (67.6)]	311.71 [192 (70.3)]	386.69 [134 (62.3)]	346.91 [496 (61.3)]	560.88 [610 (69.7)]	514.28 [647 (70.4)]
Severe AEs	21.86 [247 (8.0)]	16.42 [478 (7.4)]	16.61 [124 (7.0)]	14.91 [326 (7.7)]	18.85 [7 (6.5)]	8.20 [8 (3.7)]	6.01 [3, (2.2)]	11.75 [14 (5.1)]	22.98 [13 (6.0)]	11.52 [27 (3.3)]	41.71 [100 (11.4)]	37.56 [103 (11.2)]
Deaths	0.25 [3 (0.1)]	0.50 [15 (0.2)]	0.26 [2 (0.1)]	0.58 [13 (0.3)]	0	0	0	1.64 [2 (0.7)]	0	0	0.38 [1 (0.1)]	0.00 [0 (0.0)]
AEs leading to withdrawal	15.61 [181 (5.9)]	12.05 [357 (5.5)]	10.51 [80 (4.5)]	11.26 [250 (5.9)]	5.24 [2 (1.9)]	5.09 [5 (2.3)]	6.00 [3 (2.2)]	7.42 [9 (3.3)]	5.13 [3 (1.4)]	5.08 [12 (1.5)]	37.03 [93 (10.6)]	28.14 [81 (8.8)]
SAEs	15.46 [177 (5.7)]	18.00 [521 (8.1)]	12.80 [96 (5.5)]	17.18 [372 (8.8)]	13.35 [5 (4.7)]	11.43 [11 (5.0)]	14.29 [7 (5.1)]	17.78 [21 (7.7)]	13.97 [8 (3.7)]	12.41 [29 (3.6)]	24.33 [61 (7.0)]	31.35 [88 (9.6)]

n (%) refers to the number of patients with events; zeros indicate that there were no cases. All reported confidence intervals can only be interpreted in an exploratory manner, i.e. are nominal. AE: adverse event; axSpA: axial spondyloarthritis; CD: Crohn's disease; CI: confidence interval; ER: event rate (includes repeat occurrences of the same AE in individual patients, with the denominator being the total duration of exposure); IR: incidence rate (the number of new cases per 100 PY, with the denominator being the exposure duration up to the first occurrence of a particular AE); OLE: open-label extension; PBO: placebo; PsA: psoriatic arthritis; PSO: psoriasis; PY: patient-years; RA: rheumatoid arthritis; RCT: randomized controlled trial; SAE: serious adverse event.

Supplementary Table S5. Adverse events reported for patients treated with 200 mg Q2W CZP or 400 mg Q2W CZP in the RCT CZP population

	Overall, RCT CZP		RA		PSO	
	CZP 200 mg Q2W (n=3,560)	CZP 400 mg Q2W (n=1,391)	CZP 200 mg Q2W (n=2,871)	CZP 400 mg Q2W (n=737)	CZP 200 mg Q2W (n=410)	CZP 400 mg Q2W (n=399)
Total exposure (PY)	1812	617	1574	467	120	117
Mean exposure (days)	185.9	162.1	200.3	231.3	106.8	107.5
Median exposure (days)	131.5	112.0	167.0	182.0	112.0	112.0
	IR/100 PY (95% CI) n (%)					
AEs	322.39 (309.86, 335.30) [2493 (70.0)]	300.51 (281.22, 320.78) [902 (64.8)]	321.47 (307.73, 335.68) [2056 (71.6)]	242.52 (221.93, 264.51) [510 (69.2)]	328.28 (288.06, 372.54) [240 (58.5)]	366.41 (322.90, 414.15) [256 (64.2)]
Severe AEs	12.20 (10.62, 13.95) [215 (6.0)]	16.47 (13.37, 20.07) [98 (7.0)]	12.56 (10.85, 14.47) [192 (6.7)]	13.83 (10.60, 17.73) [62 (8.4)]	9.28 (4.63, 16.61) [11 (2.7)]	13.82 (7.90, 22.44) [16 (4.0)]
Deaths	0.50 (0.23, 0.94) [9 (0.3)]	0.81 (0.26, 1.89) [5 (0.4)]	0.51 (0.22, 1.00) [8 (0.3)]	1.07 (0.35, 2.50) [5 (0.7)]	0	0
AEs leading to withdrawal	9.65 (8.26, 11.20) [172 (4.8)]	10.87 (8.41, 13.83) [66 (4.7)]	10.34 (8.80, 12.07) [160 (5.6)]	10.89 (8.08, 14.36) [50 (6.8)]	5.03 (1.85, 10.95) [6 (1.5)]	5.14 (1.89, 11.19) [6 (1.5)]
SAEs	14.25 (12.54, 16.14) [249 (7.0)]	20.79 (17.26, 24.82) [122 (8.8)]	15.13 (13.23, 17.22) [229 (8.0)]	19.05 (15.19, 23.58) [84 (11.4)]	5.89 (2.37, 12.13) [7 (1.7)]	19.16 (12.01, 29.01) [22 (5.5)]
SIEs	4.40 (3.48, 5.49) [79 (2.2)]	5.44 (3.74, 7.64) [33 (2.4)]	4.75 (3.73, 5.96) [74 (2.6)]	5.69 (3.72, 8.33) [26 (3.5)]	0.83 (0.02, 4.65) [1 (0.2)]	3.42 (0.93, 8.76) [4 (1.0)]
OIs including TB disease	0.94 (0.55, 1.51) [17 (0.5)]	0.81 (0.26, 1.89) [5 (0.4)]	1.02 (0.58, 1.65) [16 (0.6)]	0.86 (0.23, 2.20) [4 (0.5)]	0	0.85 (0.02, 4.75) [1 (0.3)]
TB disease	0.44 (0.19, 0.87) [8 (0.2)]	0.81 (0.26, 1.89) [5 (0.4)]	0.51 (0.22, 1.00) [8 (0.3)]	0.86 (0.23, 2.20) [4 (0.5)]	0	0.85 (0.02, 4.75) [1 (0.3)]
Herpes zoster	0.22 (0.06, 0.57) [4 (0.1)]	0	0.19 (0.04, 0.56) [3 (0.1)]	0	0	0
All malignancies	0.77 (0.42, 1.30) [14 (0.4)]	0.65 (0.18, 1.66) [4 (0.3)]	0.89 (0.49, 1.49) [14 (0.5)]	0.43 (0.05, 1.55) [2 (0.3)]	0	0.85 (0.02, 4.75) [1 (0.3)]
All malignancies excluding NMSC	0.61 (0.30, 1.09) [11 (0.3)]	0.49 (0.10, 1.42) [3 (0.2)]	0.70 (0.35, 1.25) [11 (0.4)]	0.43 (0.05, 1.55) [2 (0.3)]	0	0
Melanoma	0.06 (0.00, 0.31) [1 (0.0)]	0	0.06 (0.00, 0.35) [1 (0.0)]	0	0	0
Lymphoma, including Hodgkin's disease[a]	0.06 (0.00, 0.31) [1 (0.0)]	0.16 (0.00, 0.90) [1 (0.1)]	0.06 (0.00, 0.35) [1 (0.0)]	0.21 (0.01, 1.19) [1 (0.1)]	0	0
NMSC	0.17 (0.03, 0.48) [3 (0.1)]	0.16 (0.00, 0.90) [1 (0.1)]	0.19 (0.04, 0.56) [3 (0.1)]	0	0	0.85 (0.02, 4.75) [1 (0.3)]
Other Events of Interest						
MACE	0.77 (0.42, 1.30) [14 (0.4)]	0.97 (0.36, 2.12) [6 (0.4)]	0.76 (0.39, 1.33) [12 (0.4)]	1.07 (0.35, 2.50) [5 (0.7)]	0	0.85 (0.02, 4.75) [1 (0.3)]
GI perforations	0	0	0	0	0	0
New-onset or worsening psoriasis[b]	0	0.16 (0.00, 0.90) [1 (0.1)]	0	0	0	0.85 (0.02, 4.75) [1 (0.3)]
Venous thromboembolism[c]	0.28 (0.09, 0.64) [5 (0.1)]	0.16 (0.00, 0.90) [1 (0.1)]	0.32 (0.10, 0.74) [5 (0.2)]	0.21 (0.01, 1.20) [(1, 0.1)]	0	0
Pulmonary embolism (SAEs only)[d]	0.06 (0.00, 0.31) [1 (0.0)]	0.16 (0.00, 0.90) [1 (0.1)]	0.06 (0.00, 0.35) [1 (0.0)]	0.21 (0.01, 1.20) [1 (0.1)]	0	0

n (%) refers to the number of patients with events; zeros indicate that there were no cases. NMSC includes serious and non-serious cases. All reported confidence intervals can only be interpreted in an exploratory manner, i.e. are nominal. [a]There were no Hodgkin's disease cases in these patient subgroups. [b]Worsening psoriasis defined as psoriasis reported as an adverse event in a patient enrolled in a PSO study; new-onset psoriasis defined as psoriasis in a patient enrolled in a non-PSO study. [c]Includes serious and non-serious deep vein thrombosis and pulmonary embolism events. [d]There were no non-serious pulmonary embolism events in these subgroups of patients. CI: confidence intervals; GI: gastrointestinal; IR: incidence rate (the number of new cases per 100 PY, with the denominator being the exposure duration up to the first occurrence of a particular AE); MACE: major adverse cardiovascular events; NMSC: non-melanoma skin cancer; OI: opportunistic infection; PSO: psoriasis; PY: patient-years; Q2W: every two weeks; RA: rheumatoid arthritis; SAE: serious adverse event; SIE: serious infectious event; TB: tuberculosis.

Supplementary Figure S1. Summary of RA study designs (data cut-off: August 2017)

Concomitant MTX dosing not shown. [#]For maintenance in RA, CZP 100 mg Q2W is not an approved dose in the European Union. [†]For maintenance in RA, CZP 400 mg Q2W is not an approved dose in the European Union. *For maintenance in RA, CZP 400 mg Q4W before clinical response is confirmed is not an approved dose in the European Union. ACR20: American College of Rheumatology 20 criteria; ADA: adalimumab; CDAI: Crohn's Disease Activity Index; CZP: certolizumab pegol; DMARD: disease-modifying antirheumatic drug; MTX: methotrexate; OLE: open-label extension; Q2W: every 2 weeks; Q4W: every 4 weeks; RCT: randomized controlled trial.

Supplementary Figure S2. RAPID-axSpA and RAPID-PsA study designs (data cut offs: both April 2016)

ASAS20: Assessment of SpondyloArthritis international Society 20 criteria; axSpA: axial spondyloarthritis; CZP: certolizumab pegol; OLE: open-label extension; PBO: placebo; PsA: psoriatic arthritis; Q2W: every 2 weeks; Q4W: every 4 weeks; SJC: swollen joint count; TJC: tender joint count; Wk: week.

Supplementary Figure S3. Summary of PSO study designs (data cut-off: August 2017)

The use of 400 mg loading doses of CZP at Weeks 0, 2 and 4, or upon re-randomization to CZP, was consistent across all studies, except for C87040 and C87044, where single CZP 400 mg loading doses were given at study entry. *Responders at Week 12 of study C87040 with relapse between Week 12 and Week 36 were eligible for retreatment with C87044. Patients received same treatment dose as received in first treatment study. No patients who received placebo were eligible for enrolment in the re-treatment study as no placebo responders relapsed. [a]During the CIMPACT study, any patients who did not achieve PASI75 at Week 16 entered the escape arm for treatment with CZP 400 mg Q2W. For all other patients, those randomized to ETN 50 mg BIW at Week 0 were re-randomized at Week 16 to treatment with CZP 200 mg Q2W (after a 400 mg Q2W loading dose at Weeks 16, 18 and 20) or PBO. Patients randomized to CZP 200 mg Q2W at Week 0 were re-randomized at Week 16 to treatment with CZP 200 mg Q2W, CZP 400 mg Q4W or PBO. Patients randomized to CZP 400 mg Q2W at Week 0 were re-randomized at Week 16 to treatment with CZP 200 mg Q2W, CZP 400 mg Q2W or PBO. BIW: twice every week; CZP: certolizumab pegol; ETN: etanercept; OL: open-label; PBO: placebo; PSO: psoriasis; Q2W: every 2 weeks; Q4W: every 4 weeks.

Supplementary Figure S4. Summary of CD study designs (data cut-off: April 2012)

*Patients received one subcutaneous injection of 200 mg CZP and one injection of PBO on Weeks 0, 2 and 4. [†]Dosing started at Week 2 of COSPAR II/CONCiSE 2. Non-completers of COSPAR/CONCiSE received the loading dose of 400 mg Q2W at Weeks 2, 4 and 6. CD: Crohn's disease; CZP: certolizumab pegol; DB: double-blind; OL: open-label; OLE: open-label extension; PBO: placebo; Q2W: every 2 weeks; Q4W: every 4 weeks; wk: week.

Supplementary Figure S5. Incidence rates over time of SAEs, malignancies, and TB pre-2007 and from 2007 onwards across the different indications for CZP-treated patients in the combined RCT and OLE periods (RCT+OLE)

A. SAE incidence rates over time by indication in RCT+OLE patients

B. TB disease incidence rates pre-2007 and from 2007 onwards over time in RA and CD RCT+OLE patients

C. Malignancy incidence rates over time by indication in RCT+OLE patients

Pre-2007 and 2007 onwards refer to the date of treatment initiation with CZP. Before 2007, the threshold for a positive result on the purified protein derivative (PPD) tuberculin skin test varied (from ≥5 to ≥20 mm) according to geographic region. Since 2007, CZP recommendations internationally mandate that all patients with PPD ≥5 mm receive treatment for latent TB infection. After 50 months in axSpA, the malignancy IR was noticeably higher, but due to the small population at this point (after the end of the 4-year RAPID-axSpA study); the CI is therefore wide and the significance unknown. axSpA: axial spondyloarthritis; CD: Crohn's disease; CZP: certolizumab pegol; IR: incidence rate; OLE: open-label extension; PsA: psoriatic arthritis; PSO: psoriasis; PY: patient-years; RA: rheumatoid arthritis; SAE: serious adverse event.

Supplementary Figure S6. Kaplan-Meier graphs for time to first expert-confirmed SIE

A. Kaplan-Meier graph of time to first expert-confirmed SIE: 0–8 years exposure

B. Kaplan-Meier graph of time to first expert-confirmed SIE: 0–2 years exposure (taken from panel A)

axSpA: axial spondyloarthritis; CD: Crohn's disease; CZP: certolizumab pegol; PsA: psoriatic arthritis; PSO: psoriasis; RA: rheumatoid arthritis; SIE: serious infectious event.