Supplementary Materials

Table S1: Summary of clinical trials and patients included in the integrated safety update

Type of Study	Study	Study duration	Treatment dose	Steroid use	Number of placebo-treated patients	Number of CZP-treated patients (≥1 dose of CZP)
Uncontrolled, single dose pharmacokinetic interaction study	Study 001	Single dose	Single dose CZP 400mg SC	Patients on a stable dose of MTX	0	16
Randomized controlled trials (RCTs)	Study 002 (NCT00993317)	8 weeks	Single IV dose of CZP 1mg/kg, 5mg/kg, or 20mg/kg or PBO	Not applicable	12	24
	Study 004	12 weeks	CZP 50mg, 100mg, 200mg, 400mg or PBO; CZP 600mg, 800mg or PBO Q4W SC	Concomitant corticosteroid use (≤ 10 mg prednisone or equivalent/day) was allowed during the study provided the doses had been stabilized prior to entry into the study	83	240
	Study 014 [1] (NCT00544154)	24 weeks	CZP 400mg Q4W SC + MTX or PBO + MTX	Corticosteroids at a dosage of ≤10 mg/day prednisone equivalent were allowed if stable for ≥4 weeks prior to study entry and thereafter	119	124
	FAST4WARD [2] (NCT00548834)	24 weeks	CZP 400mg Q4W SC or PBO		109	111
	RAPID 1 [3] (NCT00152386)	52 weeks	CZP initial dose then 200mg Q2W SC + MTX or CZP initial dose then 400mg Q2W SC + MTX or PBO + MTX		199	781
	RAPID 2 [4] (NCT00160602)	24 weeks	CZP initial dose then 200mg Q2W SC + MTX or CZP initial dose then 400mg Q2W SC + MTX or PBO + MTX		125	494
	REALISTIC [5] (NCT00717236)	12 weeks	CZP initial dose then 200mg Q2W SC +/- DMARDs or	Corticosteroids at a dosage of ≤10 mg/day prednisone equivalent were allowed if stable	209	846

			PBO +/- DMARDs	for 7 days prior to study entry		
	CERTAIN (NCT00674362)	52 weeks	CZP initial dose then 200mg Q2W SC + DMARDs or PBO + DMARDs	Corticosteroids at a dosage of ≤10 mg/day prednisone equivalent were allowed if stable for ≥4 weeks prior to study entry	98	96
	DOSEFLEX (NCT00580840)	16 weeks	CZP initial dose then 200mg Q2W SC up to wk 16 ACR20 responders randomized to CZP 200mg Q2W SC + MTX or CZP 400mg Q4W SC + MTX or or PBO + MTX		69	139
	Study RA0017 (vaccination study; NCT00993668)	6 weeks	CZP initial dose then 200 mg Q2W SC or PBO	Patients were allowed to continue their prestudy dosages of oral corticosteroids (prednisone equivalent ≤ 10 mg/day)	114	110
Open label extensions (OLEs) or open label portions of studies	002	8 weeks	Single IV dose of CZP 1mg/kg, 5mg/kg, or 20mg/kg	Not applicable	-	32
	004 OLE	Up to 104 weeks	CZP 200 mg or 400 mg Q4W SC	Concomitant corticosteroid use (≤ 10 mg prednisone or equivalent/day) was allowed during the study provided the doses had been stabilized prior to entry into the study	-	298
	015 (OLE of FAST4WARD and 014; NCT00160693)	Up to 364 weeks	CZP 400 mg SC Q4W	Corticosteroids at a dosage of ≤10 mg/day prednisone equivalent were allowed if stable for ≥4 weeks prior to study entry and thereafter	-	402
	028 (OLE of RAPID 1; NCT00175877)	Ongoing	CZP 400 mg SC Q2W decreased to CZP 200 mg SC Q2W		-	846
	051 (OLE of RAPID 2; NCT00160641)	Ongoing	CZP 400 mg SC Q2W decreased to CZP 200 mg SC Q2W		-	567

	REALISTIC OLE	16 weeks	CZP 200 mg SC Q2W	Corticosteroids at a dosage of ≤10 mg/day prednisone equivalent were allowed if stable for 7 days prior to study entry	-	954
	DOSEFLEX (pre-randomisation open label run-in period for the RCT) (NCT00580840)	18 weeks	CZP initial dose then CZP 200 mg SC Q2W	Corticosteroids at a dosage of ≤10 mg/day prednisone equivalent were allowed if stable for ≥4 weeks prior to study entry	-	333
	Study RA0017 OLE	26 weeks	CZP 200 mg SC Q2W	Patients were allowed to continue their prestudy dosages of oral corticosteroids (prednisone equivalent ≤ 10 mg/day)	-	215
PBO=placebo; SC=subcutaneous; Q4W=every 4 weeks; Q2W=every 2 weeks CZP initial dose = CZP 400 mg SC at W0, 2, and 4						

Table S2: Overall serious infection event ER and IR over time in the RCT and RCT+OLE populations

Population	Exposure (months)	Treatment group	ER / 100 PY	ER OR	ER 95% CI Low*	ER 95% CI High*	IR / 100 PY	IR OR	IR 95% CI Low*	IR 95% CI High*
RCT	All	Placebo	1.34	4.81	0.72	31.99	1.35	4.35	0.65	29.30
		CZP all doses	6.14				5.61			
	Onset between 0-<3	Placebo	0.79	10.67	1.04	109.74	0.79	9.67	0.93	100.30
		CZP all doses	7.87				7.19			
	Onset between 3-<6	Placebo	3.19	1.77	0.43	7.25	3.21	1.57	0.37	6.60
		CZP all doses	5.52				4.94			
	Onset between 6-12	Placebo	0	-	-	-	0	-	-	-
		CZP all doses	2.88				2.90			
RCT+OLE	All	CZP all doses	4.33	**	**	**	3.65	**	**	**

CI=Confidence interval, ER=Event rate, IR=Incidence rate, OR=Odds ratio, '-'=OR and 95% CI impossible to calculate due to 0 event in the placebo group, CZP all dose group includes CZP 400 Q2W data (twice the registered dose)

Odds ratio is the ratio of the probability that an event will happen within 100 PY to the probability that it will not happen within 100 PY in the CZP group as compared to the control group

*CIs were created using a normal approximation to the sampling distribution of the natural log odds ratio, CI around OR of rare events should be interpreted with caution with respect to rare events due to the asymptotic approximation of the CI's.

** As there is no placebo during OLE, OR are not relevant for long term exposure.

Table S3: List of OIs developed by independent physicians and validated by the SC

- Actinomyces
- Aspergillus (invasive forms only)
- Bartonella
- Blastomyces species
- Brucella
- Campylobacter (invasive disease only)
- Candida species (excluding vaginal candidiasis)
- Chagas disease (T. cruzi)
- Coccidioides immitis/posadasii
- Coxiella (Q fever)
- Cryptococcus neoformans/gatii
- Cryptosporidium species
- Cytomegalovirus
- Fusarium
- Herpes simplex (all forms)
- Herpes zoster (all forms)
- Histoplasma species
- Isosporiasis
- Leishmaniasis
- Leptospirosis
- Listeria monocytogenes (systemic)
- Malaria
- Microsporidia
- Mucomycosis (=zygomycosis) [Rhizopus, Mucor, and Absidia)
- Mycobacterium tuberculosis
- Nocardia species
- Nontuberculous mycobacterium
- Paracoccidioides infections
- Progressive multifocal leukoencephalopathy (PML, JC virus)
- Pneumocystis jiroveci (carinii)
- Salmonella (invasive disease only)
- Scedosporum / Pseudallescheria boydii
- Shigella (invasive disease only)
- Sporothrix schenckii
- Toxoplasmosis

Table S4: Serious adverse events by preferred term reported at an event rate of ≥0.3/100 PY for CZP-treated patients (all doses) in RCTs or RCT+OLEs

Preferred Term	***RCTs*** PBO (n=1137)		***RCTs*** CZP (n=2965)		***RCTs & OLEs*** CZP (n=4049)	
	ER/100 PY (95% CI)	Number of events	ER/100 PY (95% CI)	Number of events	ER/100 PY (95% CI)	Number of events
Pneumonia	0.54 (0.09-2.14)	2	0.77 (0.39-1.46)	10	0.77 (0.60-0.97)	71
Osteoarthritis	0.27 (0.01-1.72)	1	0.08 (0.00-0.50)	1	0.52 (0.39-0.69)	48
Cellulitis	0	0	0.38 (0.14-0.95)	5	0.31 (0.21-0.45)	29
Cholelithiasis	0	0	0.31 (0.10-0.84)	4	0.20 (0.13-0.33)	19
Cerebrovascular accident	0.54 (0.09-2.14)	2	0.31 (0.10-0.84)	4	0.17 (0.10-0.29)	16
Osteonecrosis	0	0	0.38 (0.14-0.95)	5	0.16 (0.09-0.27)	15

Preferred Term	*RCTs* PBO (n=1137)		*RCTs* CZP (n=2965)		*RCTs & OLEs* CZP (n=4049)	
	ER/100 PY (95% CI)	Number of events	ER/100 PY (95% CI)	Number of events	ER/100 PY (95% CI)	Number of events
Erysipelas	0	0	0.38 (0.14-0.95)	5	0.11 (0.05-0.21)	10
Pyrexia	0.27 (0.01-1.72)	1	0.46 (0.19-1.05)	6	0.14 (0.08-0.25)	13
Abdominal pain	0.27 (0.01-1.72)	1	0.38 (0.14-0.95)	5	0.12 (0.06-0.22)	11
Acute myocardial infarction	0.27 (0.01-1.72)	1	0.38 (0.14-0.95)	5	0.12 (0.06-0.22)	11

Table S5: Shift in biochemistry values from normal at baseline to markedly abnormal grade 3 or 4 post-baseline (safety population)

Parameter	*RCTs*[a] **Placebo** (n=1125)		*RCTs*[a] **CZP** (n=2941)		*Open label* CZP[b] (n=3630)	
	Low grade 3 or 4 n (%)	High grade 3 or 4 n (%)	Low grade 3 or 4 n (%)	High grade 3 or 4 n (%)	Low grade 3 or 4 n (%)	High grade 3 or 4 n (%)
Alkaline phosphatase (U/L)	NA	1 (0.1)	NA	2 (0.1)	NA	4 (0.1)
Alanine aminotransferase (U/L)	NA	10 (0.9)	NA	39 (1.3)	NA	66 (1.8)
Aspartate aminotransferase (U/L)	NA	8 (0.7)	NA	25 (0.9)	NA	46 (1.3)
Bilirubin (µmol/L)	NA	0	NA	2 (0.1)	NA	5 (0.1)
Calcium (mmol/L)	1 (0.1)	0	2 (0.1)	0	6 (0.2)	0
Creatine phosphokinase (U/L)	NA	3 (0.3)	NA	16 (0.5)	NA	15 (0.4)
Creatinine (µmol/L)	NA	1 (0.1)	NA	2 (0.1)	NA	16 (0.4)
Glucose (mmol/L)	0	5 (0.4)	5 (0.2)	15 (0.5)	7 (0.2)	43 (1.2)
Potassium (mmol/L)	1 (0.1)	2 (0.2)	1 (0.0)	3 (0.1)	9 (0.2)	10 (0.3)
Sodium (mmol/L)	0	NA	3 (0.1)	NA	5 (0.1)	NA
Urate (µmol/L)	NA	0	NA	0	NA	0

NA=not applicable, 'High' and 'Low' refer to parameter levels that were abnormally high or abnormally low. Only Grade 3 and 4 adverse events are reported, as defined by the RCTC.[25]
Note: Baseline refers to data collected prior to study medication administration in any study or study phase.
[a]C87002 was not included due to its single-dose design. The total number of subjects (excluding those in C87002) was used as the denominator for percentages.
[b]CZP-treated patients in open label studies or open label portions of studies only. PHA001 and C87002 were not included due to their single-dose design. The total number of subjects (excluding those in PHA001 and C87002) was used as the denominator for percentages. CZP all dose, including 400 mg Q2W (twice registered dose)

Figure S1: Study designs of the trials included in this CZP RA data pooling

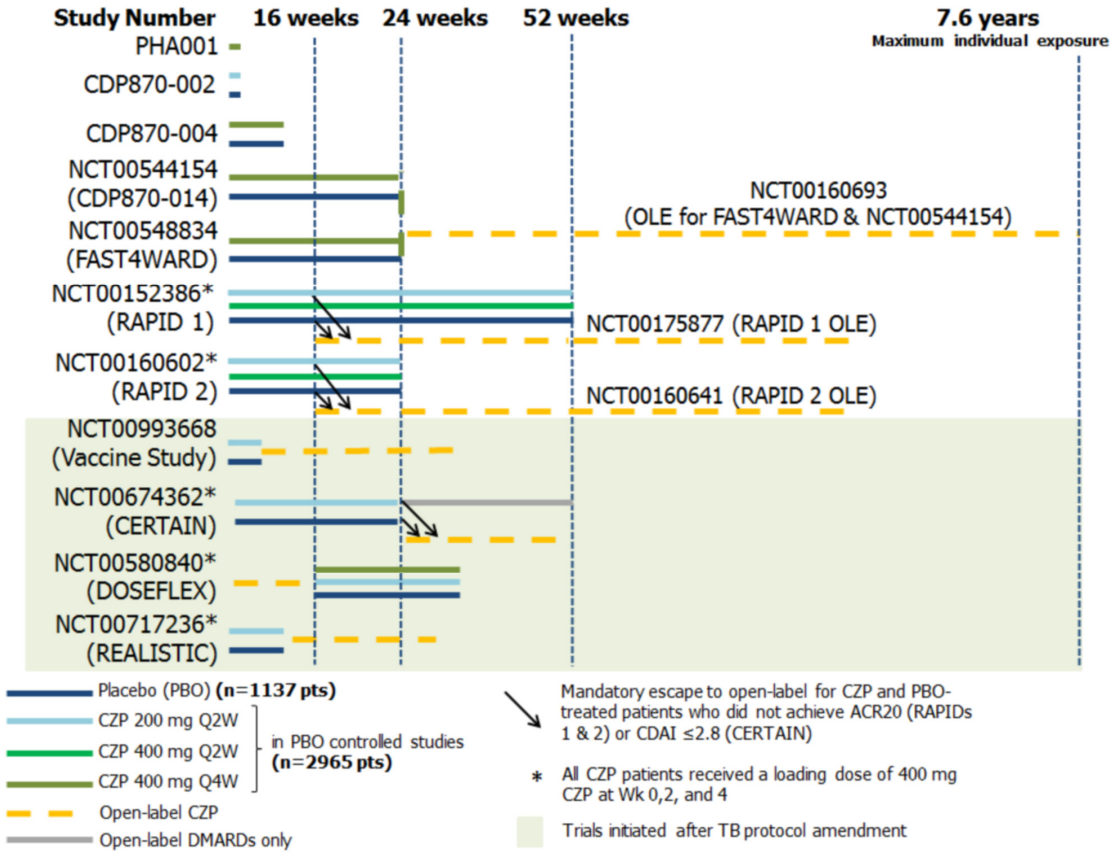
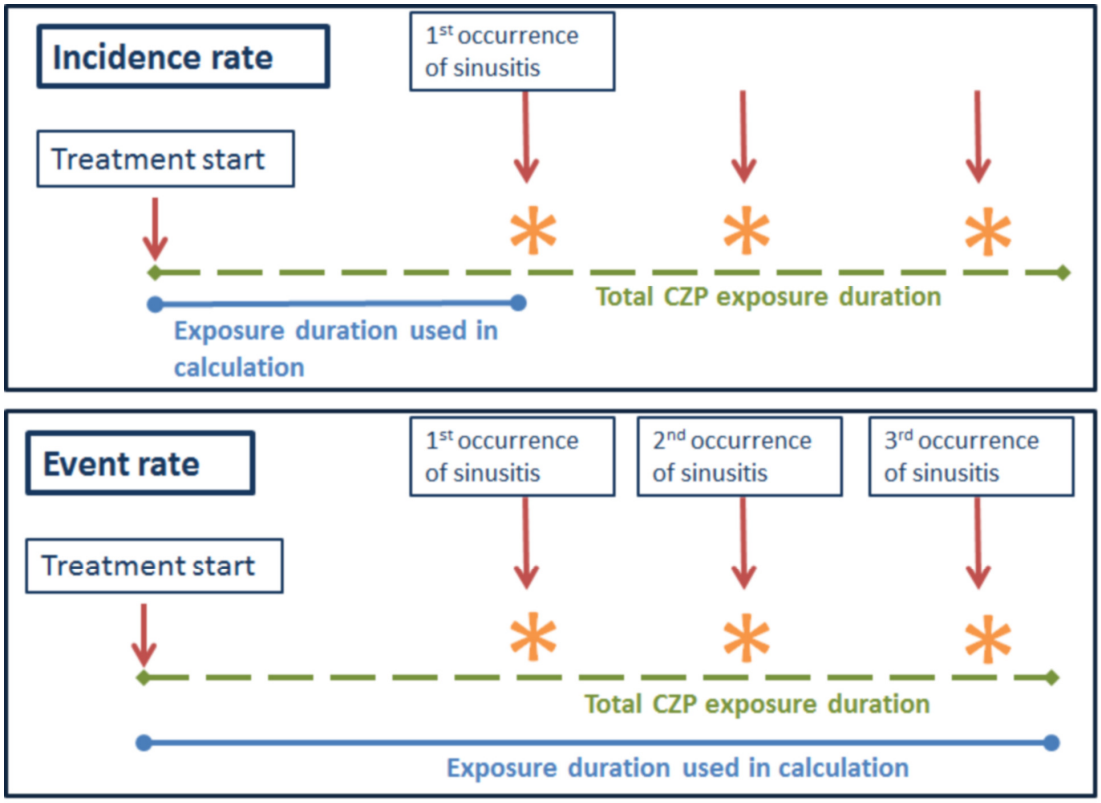


Figure S2: Exposure durations used in the calculation of incidence and event rates



1. Choy E, McKenna F, Vencovsky J, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. Rheumatology (Oxford) 2012;51(7):1226-34 doi: 10.1093/rheumatology/ker519 [published Online First: 22 February 2012].

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