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ADIS DRUG EVALUATION

Certolizumab Pegol: A Review of Its Use in Patients with Axial Spondyloarthritis or Psoriatic Arthritis

Sohita Dhillon

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Abstract Certolizumab pegol (Cimzia®) is a polyethylene glycolylated antigen-binding fragment of a recombinant human monoclonal antibody that binds to and selectively neutralizes tumour necrosis factor (TNF) α. In the EU, subcutaneous certolizumab pegol is indicated for the treatment of adults with severe active axial spondyloarthritis (axSpA), comprising ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), and for adults with active psoriatic arthritis (PsA). In the USA it is indicated for the treatment of adults with active AS or active PsA. This article reviews the efficacy and tolerability of certolizumab pegol in these patients and briefly summarizes its pharmacology. In two ongoing, well-designed studies, data at 12 and 24 weeks showed that treatment with certolizumab pegol (200 mg every 2 weeks or 400 mg every 4 weeks) was effective in improving the clinical signs and symptoms of disease, health-related quality of life and productivity in patients with axSpA (the RAPID-axSpA study) or PsA (the RAPID-PsA study), with the improvements maintained during longer-term (48 weeks) treatment. Within the axSpA population, clinical benefits with certolizumab pegol were seen both in patients with AS and in those with nr-axSpA. In addition, 12 weeks' treatment with certolizumab pegol reduced inflammation in the sacroiliac joints and spine in patients with axSpA and 24 weeks' treatment with the agent slowed radiographic disease progression in patients with PsA. Certolizumab pegol was generally well tolerated in these studies, with a tolerability profile consistent with that seen in previous clinical trials in other indications. Although additional long-term and comparative data are needed to position certolizumab pegol with respect to other TNFα antagonists, current evidence indicates that certolizumab pegol is an effective option for the treatment of axSpA (including AS and nr-axSpA) and PsA.

Certolizumab pegol in axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA): a summary

Neutralizes soluble and membrane-bound tumour necrosis factor α, thereby inhibiting its role as a key mediator of inflammation
In patients with axSpA, is effective in improving the clinical signs and symptoms of disease and reduces inflammation in sacroiliac joints and spine
Efficacy seen both in patients with ankylosing spondylitis and in those with non-radiographic axSpA
In patients with PsA, is effective in improving clinical signs and symptoms of disease and slows radiographic disease progression
Clinical benefits maintained during longer-term treatment (48 weeks)
Generally well tolerated, with non-serious infections being the most common adverse event

The manuscript was reviewed by: ***R. Alten,*** Internal Medicine II, Rheumatology, Clinical Immunology, Schlosspark-Klinik, Charite-University Medicine Berlin, Berlin, Germany; ***M. Bergman,*** Division of Rheumatology, Department of Medicine, Drexel University College of Medicine, Philadelphia, PA, USA; ***I. Olivieri,*** Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Italy; ***R. Scarpa,*** Rheumatology Research Unit, Department of Clinical and Experimental Medicine, Universita Federico II, Napoli, Italy; ***D. Wendling,*** Service de Rhumatologie, Centre Hospitalier Universitaire de Besancon, Besancon, France.

S. Dhillon (✉)
Adis, Level 1, 5 The Warehouse Way, Northcote 0627; Private Bag 65901, Mairangi Bay 0754, Auckland, New Zealand
e-mail: demail@springer.com

1 Introduction

Spondyloarthritis (SpA) is a heterogeneous disorder, comprising ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis, enteropathic-related spondylitis and arthritis, and undifferentiated SpA [1]. These diseases are closely related and present with symptoms including back pain, oligoarthritis largely of the lower limbs, dactylitis, enthesitis and extra-articular manifestations, such as psoriasis, uveitis and inflammatory bowel disease. According to a more recent classification, SpA can also be categorized according to clinical presentation into axial SpA (axSpA) predominantly affecting the axial skeleton (the sacroiliac joints, spine or both) and peripheral SpA demonstrating peripheral joint manifestations (peripheral arthritis, enthesitis and dactylitis) [1]. AxSpA is further subdivided into (early) non-radiographic axSpA (nr-axial SpA) and radiographic axSpA or AS [2, 3].

Tumour necrosis factor (TNF) α, a pro-inflammatory cytokine secreted mainly by macrophages and activated T cells, plays a central role in the spinal inflammatory process of spondyloarthropathy [4]. Elevated levels of TNFα have been observed in the synovial tissue [5, 6] and serum [7] of patients with SpA, suggesting its role in the pathogenesis of the disease and providing a rationale for the development of treatments targeting TNFα.

Certolizumab pegol (Cimzia®) is a TNFα antagonist approved for use in various indications, including rheumatoid arthritis (RA), axSpA and PsA (approved indications vary between regions; see Sect. 5 for details). This article reviews the efficacy and tolerability of certolizumab pegol in patients with axSpA or PsA, and briefly summarizes its pharmacology. Data selection details are presented at the end of Sect. 6.

2 Pharmacological Properties

The pharmacological properties of certolizumab pegol have been reviewed previously [8, 9]; therefore this section briefly summarizes its key properties, with some data obtained from the manufacture's prescribing information [10, 11].

2.1 Mechanism of Action

Certolizumab pegol is a recombinant human anti-TNFα antibody antigen-binding fragment (Fab′) conjugated to a 40 kDa polyethylene glycol (PEG) moiety [10, 11], which increases the plasma half-life of certolizumab pegol to a value similar to that of the whole antibody [12]. Certolizumab pegol binds to human TNFα with high affinity (dissociation constant of 90 pmol/L) and selectively neutralizes TNFα, but not TNFβ [10]. The key pharmacodynamic effects of certolizumab pegol are summarized in Table 1.

2.2 Pharmacokinetic Properties

The key pharmacokinetic properties of certolizumab pegol are summarized in Table 1. The plasma concentrations of certolizumab pegol are largely dose-proportional [10] and the concentrations achieved in patients with axSpA or PsA in two pivotal studies [13, 14] (see Sect. 3) were consistent with those observed previously in patients with RA [15, 16]. Based on data from phase II and III clinical trials, it was estimated that the typical average plasma concentration of certolizumab pegol that produces half the maximum probability of achieving a 20 % improvement in the American College of Rheumatology (ACR20) response criteria was 17 μg/mL (95 % CI 10–23 μg/mL) [10].

No studies have been performed to assess the effect of hepatic or renal impairment on certolizumab pegol pharmacokinetics [10, 11]. However, the pharmacokinetics of the PEG moiety are expected to be dependent on renal function, as it is excreted via the kidneys [10]. Age and gender had no effect on the pharmacokinetics of certolizumab pegol in a population pharmacokinetic analysis [10, 11].

Co-administration of certolizumab pegol with methotrexate, corticosteroids, NSAIDs or analgesics did not affect the pharmacokinetics of certolizumab pegol, according to a population pharmacokinetic analysis [10]; the pharmacokinetics of methotrexate were also unaffected during concomitant treatment with certolizumab pegol. Combination treatment of other TNFα antagonists with anakinra or abatacept was associated with an increased risk of serious adverse events, with no added clinical benefit [10, 11]. Owing to the nature of adverse events seen with these combination therapies, similar toxicities may also occur during coadministration of anakinra or abatacept with certolizumab pegol; therefore, coadministration of these agents is not recommended [10, 11]. Although drug interactions studies have not been undertaken with rituximab or natalizumab [11], concomitant use of these agents with certolizumab pegol is not recommended [11].

3 Therapeutic Efficacy

This section focuses on the two ongoing, randomized, double-blind, multicentre trials assessing the efficacy of subcutaneous certolizumab pegol in patients with axSpA (the RAPID-axSpA study; Sect. 3.1) [13] or PsA (the RAPID-PsA study; Sect. 3.2) [14]. Some data have been obtained from abstract presentations [17–27].

Table 1 Key pharmacological properties of certolizumab pegol

Pharmacodynamic properties
Dose-dependently neutralized soluble and membrane-bound TNFα, thereby inhibiting its role as a key mediator of inflammation [11, 12, 40]
Inhibited lipopolysaccharide-induced TNFα and interleukin-1ß production in human monocytes [12, 40]
Lacks a Fc region and, therefore, does not induce complement-dependent or antibody-dependent cell-mediated cytotoxicity in vitro, unlike other TNFα antagonists (infliximab, etanercept, adalimumab, golimumab) [40, 41]
Induced non-apoptotic cell death, probably via signalling through transmembrane TNFα, which may contribute to its clinical efficacy [41]
Attenuated pro-inflammatory state in human aortic endothelial cells in vitro (e.g. reduced the expression of adhesion molecules and prevented TNFα induced activation of the nuclear factor-κB pathway) [42]
In an animal model of arthritis, exposure to certolizumab pegol was more prolonged and it distributed into inflamed tissues to a greater extent than infliximab and adalimumab, probably because of PEGylation [43]
Pharmacokinetic properties [10, 11]
After SC administration[a], a mean C_{max} of 43–49 μg/mL is reached at week 5 after an initial loading dose in pts with RA
Bioavailability is ≈80 % (range 76–88 %) and C_{max} is reached 54–171 h after SC administration
Estimated apparent volume of distribution was 8.01 L in a population pharmacokinetic analysis in pts with RA
Fab′ fragment is expected to be proteolyzed to peptides and amino acids and the de-conjugated PEG moiety is rapidly eliminated from plasma by renal excretion
Half-life was ≈14 days for all doses tested
Clearance after SC administration was estimated to be 21.0 mL/h in RA pts in a population pharmacokinetic analysis (intersubject variability 30.8 % [coefficient of variation] and inter-occasion variability 22.0 %)[b]

C_{max} peak plasma concentration, *Fab′* antigen-binding fragment, *Fc* fragment crystallisable region, *PEG* polyethylene glycol, *pts* patients, *RA* rheumatoid arthritis, *SC* subcutaneous, *TNF* tumour necrosis factor

[a] Loading dose of 400 mg at weeks 0, 2 and 4 followed by 200 mg every 2 weeks

[b] Presence of anti-certolizumab pegol antibodies increased clearance by ≈3-fold. Compared with RA pts weighing 70 kg, clearance was 29 % lower in pts with bodyweight 40 kg and 38 % higher in pts with bodyweight 120 kg

Both studies were double-blind and placebo controlled until week 24, dose-blind until week 48 and open-label thereafter (see Fig. 1 for design details) [13, 14]. In the double-blind phase, patients were randomized to receive placebo or subcutaneous certolizumab pegol 400 mg at weeks 0, 2 and 4 followed by certolizumab pegol 200 mg every 2 weeks (hereafter referred to as certolizumab pegol 200 mg q2w) or 400 mg every 4 weeks (hereafter referred to as certolizumab pegol 400 mg q4w). In the dose-blind phase, patients initially randomized to certolizumab pegol continued with their assigned dosage, while those who had received placebo were re-randomized to certolizumab pegol 200 mg q2w or 400 mg q4w following a certolizumab pegol 400 mg loading dose. Patients in the placebo group who did not meet response criteria at weeks 14 and 16, underwent mandatory escape and were re-randomized in a dose-blind manner to treatment with certolizumab pegol 200 mg q2w or 400 mg q4w, after an initial loading dose of certolizumab pegol 400 mg (see Sects. 3.1 and 3.2 for details) [13, 14].

3.1 In Patients with Axial Spondyloarthritis (AxSpA)

The ongoing 204-week RAPID-axSpA study randomized 325 patients with axSpA, including those with AS ($n = 178$) or nr-axSpA ($n = 147$) [13]. Eligible patients were aged ≥18 years and had adult-onset axSpA (as defined by the Assessment of SpondyloArthritis international Society [ASAS] criteria) for at least 3 months and active disease, as defined by a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score of ≥4 and spinal pain scores of ≥4 [10, 11, 13]. Patients had C-reactive protein (CRP) levels of greater than the upper limit of normal (ULN) [>7.9 mg/L] and/or sacroiliitis on magnetic resonance imaging (MRI), as defined by the ASAS/Outcome Measures in Rheumatology criteria [13]. Patients were also required to have had an inadequate response to or be intolerant of at least one NSAID during 30 days or more of continuous therapy (at the maximum tolerated dose) or for at least 2 weeks each for at least two NSAIDs [13]. Exclusion criteria included exposure to more than two other biologic agents or more than one TNFα antagonist, primary failure of prior TNFα antagonist therapy, diagnosis of total spinal ankylosis, and active or high risk of tuberculosis (TB), hepatitis B/C or HIV [13]. Patients who had discontinued prior TNFα antagonist therapy for reasons other than primary failure could be included (up to 40 % of the study population) [13].

At baseline, patients had a mean age of ≈40 years, the median symptom duration was 7.7 years; ≈62 % of patients were male; 16 % of them had prior exposure to TNFα antagonists; 87.8 % of patients received concomitant NSAIDs and 30.7 % received concomitant disease modifying anti-rheumatic agents (DMARDs; sulfasalazine

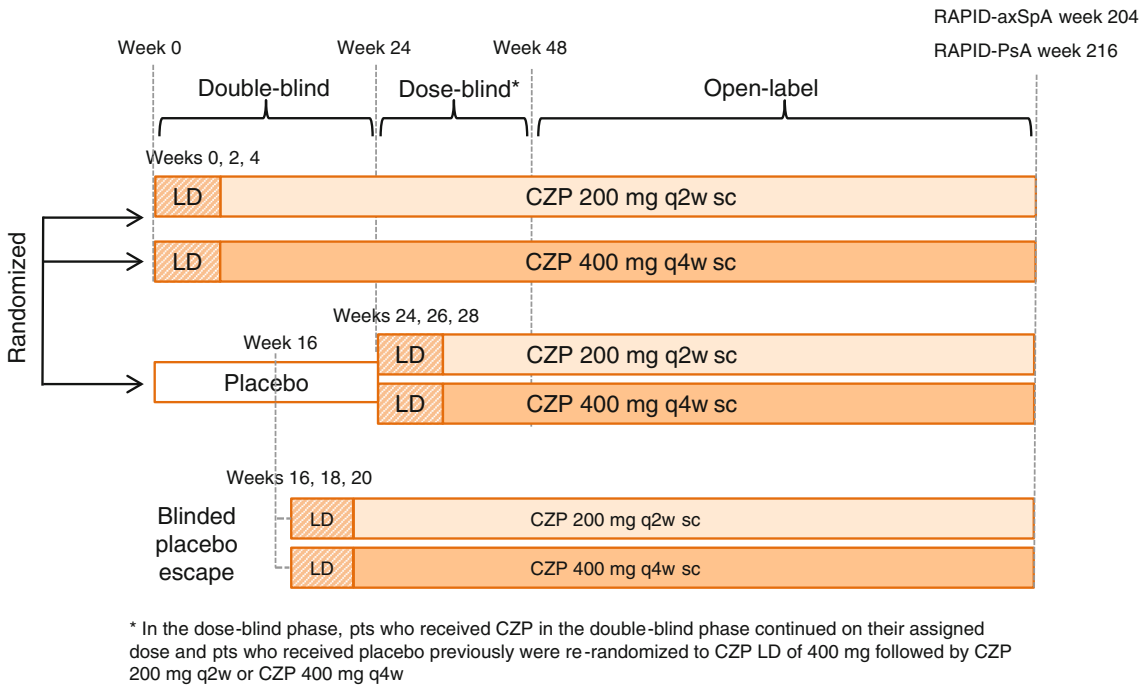

Fig. 1 Study design details of the RAPID-axSpA [13] and RAPID-PsA studies [14]. Adapted from Mease et al. [14] with permission. *CZP* Certolizumab pegol, *LD* loading dose of 400 mg, *qxw* every x weeks, *sc* subcutaneous

or methotrexate) [13]. With the exception of higher exposure to TNFα antagonists in the placebo group than in the certolizumab pegol 200 mg q2w or 400 mg q4w groups (24.3 vs. 13.5 and 10.3 % of patients), the three treatment groups were generally well-balanced in terms of demographic and disease activity/health status characteristics. Within the overall axSpA population, the AS subpopulation was older (41.5 vs. 37.4 years), had a higher proportion of males (72.5 vs. 48.3 %), longer symptom duration (median 9.1 vs. 5.5 years) and higher CRP levels (median 14.3 vs. 11.9 mg/L) than the nr-axSpA population. Except for the CRP levels, these two subpopulations had similar disease activity at baseline, but patients with AS had more limitations in physical function (mean Bath Ankylosing Spondylitis Functional Index [BASFI] score of 5.7 vs. 4.9) and spinal mobility (mean Bath Ankylosing Spondylitis Metrology Index [BASMI] score of 4.4 vs. 3.2) [13].

Of the patients randomized to treatment, 93 % completed 24 weeks and 88 % completed 48 weeks of treatment [18]. Placebo recipients who did not achieve ASAS20 response criteria at weeks 14 and 16 ($n = 56$) underwent mandatory escape and were re-randomized in a dose-blind manner to treatment with certolizumab pegol 200 mg q2w ($n = 27$) or 400 mg q4w ($n = 29$) [Fig. 1]; 35 patients in the certolizumab pegol 200 mg q2w group and 25 patients in the certolizumab pegol 400 mg q4w group also met the escape criteria, but continued with the dosage they were initially assigned to receive [13].

Table 2 summarizes the definitions and descriptions of the outcomes measures used in the RAPID-axSpA study.

3.1.1 Clinical Response

Certolizumab pegol was effective in improving the clinical signs and symptoms of disease in patients with axSpA, as indicated by significantly higher ASAS20 response rates with certolizumab pegol (200 mg q2w or 400 mg q4w) than with placebo at week 12 (primary endpoint; Table 3) [13]. Significant ($p \leq 0.004$) between-group differences in ASAS20 response rates were seen as early as week 1 of treatment and were maintained through to week 24. In addition, ASAS40 and ASAS5/6 response rates and ASAS partial remission rates at weeks 12 and 24 were significantly higher with certolizumab pegol (200 mg q2w or 400 mg q4w) than with placebo (Table 3) [13].

Following 24 week's treatment, disease activity was improved in certolizumab pegol recipients, as indicated by a significant ($p < 0.001$) decrease from baseline in the Ankylosing Spondylitis Disease Activity Score (ASDAS) with certolizumab pegol (200 mg q2w or 400 mg q4w) relative to placebo at week 12 (mean change −1.7 and −1.6 vs. −0.5) and week 24 (−1.9 and −1.7 vs. −0.5) [13]. In addition, significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients achieved ASDAS major improvement (i.e. decrease from baseline in ASDAS of ≥2) [41.4 and 34.6

Table 2 Definitions and descriptions of outcome measures assessing treatment response in the RAPID-axSpA trial

Outcome measure	Definition
ASAS20 response	Improvement of ≥20 % and ≥1 unit on a 0–10 NRS in ≥3 of the 4 ASAS domains (patient's global assessment of disease activity, pain, physical function, inflammation), with no deterioration (worsening of ≥20 % or ≥1 NRS unit) in the remaining domain
ASAS40 response	≥40 % improvement in ASAS domains without any deterioration
ASAS5/6 response	≥20 % improvement in 5 out of 6 ASAS domains, including spinal mobility and CRP
ASAS partial remission	Score of ≤2 NRS units in all 4 domains
ASDAS	A composite index assessing disease activity (based on CRP), with lower scores indicating less disease activity
ASspiMRI-a Berlin modification	Berlin modification of the ASspiMRI-a scoring system assessing disease activity in the spine (range 0–69), with higher scores indicating higher disease activity
ASQoL	18-item questionnaire assessing HR-QOL in pts with AS, with lower scores indicating better health
BASDAI	Validated self-reported instrument consisting of 6 horizontal NRS measuring fatigue, spinal and peripheral joint pain and joint swelling, enthesitis, and severity and duration of morning stiffness over the last week (final score range 0–10), with lower scores indicating lower disease activity
BASDAI50	Improvement of ≥50% in BASDAI score
BASFI	Validated disease-specific instrument assessing physical function comprising 10 items relating to past week. Reported as a mean of 10 scores (assessed by NRS of 0 [easy] to 10 [impossible]), with lower scores indicating better physical function
BASMI linear	Disease-specific measure assessing spinal mobility comprising 5 clinical measures reflecting axial status (cervical rotation; targus to wall distance; lumbar flexion; intermalleolar distance; lateral lumbar flexion; score range 0–5 for each item). Reported as a mean of 5 scores, with higher scores indicating more severe limitation of movement
Fatigue and spinal pain	Assessed on NRS scales (range 0 [none] to 10 [severe])
SPARCC SIJ score	Assessing inflammation in the SIJs (range 0–72), with higher scores indicating more joint inflammation

ACR American College of Rheumatology, *AS* ankylosing spondylitis, *ASAS* Assessment of SpondyloArthritis international Society, *ASDAS* Ankylosing Spondylitis Disease Activity Score, *ASQoL* AS-specific quality of life measure, *ASspiMRI-a* Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *CRP* C-reactive protein, *HR-QOL* health-related quality of life, *NRS* numerical rating scale, *pts* patients, *SIJ* sacroiliac joint, *SPARCC* Spondyloarthritis Research Consortium of Canada, *TJC* tender joint count

vs. 0.9 % at week 12; 45.9 and 39.3 vs. 0.9 % at week 24] and ASDAS inactive disease (i.e. ASDAS of <1.3) [25.2 and 20.6 vs. 0.0 % at week 12; 29.7 and 30.8 vs. 3.7 % at week 24]. BASDAI scores were also improved significantly from baseline with certolizumab pegol (200 mg q2w or 400 mg q4w) relative to placebo (Table 4) and significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients achieved a BASDAI50 response at weeks 12 (45.0 and 43.9 vs. 13.2 %) and 24 (50.5 and 54.2 vs. 17.9 %) [13].

Sub-group analyses showed that both the AS and the nr-axSpA subpopulations benefited from certolizumab pegol therapy, with ASAS response rates and ASAS partial remission rates at weeks 12 and 24 generally significantly higher in certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients in both sub-groups (Table 3) [13]. In addition, at these timepoints, BASDAI (Table 4) and ASDAS scores decreased from baseline (indicating improvement) to a significantly ($p < 0.001$) greater extent with certolizumab pegol (200 mg q2w and 400 mg q4w) than with placebo in both subpopulations [13].

The improvement in disease activity seen with certolizumab pegol (200 mg q2w or 400 mg q4w) at week 24 was maintained during longer-term therapy, with ASAS20 and ASAS40 response and ASAS partial remission criteria being met by >70, >50 and ≥28 % of patients, respectively, in the overall axSpA population at week 48 (Table 3) [18]. In addition, 49.5 and 46.7 % of patients in the certolizumab pegol 200 mg q2w and 400 mg q4w groups, respectively, met the ASDAS major improvement criteria, and 35.1 and 26.2 % of patients met the ASDAS inactive disease criteria in this population. Generally similar results were seen in the AS and nr-axSpA subgroups [18].

3.1.2 *Inhibition of Inflammation*

Certolizumab pegol treatment reduced inflammation in the sacroiliac joints and spine in patients with axSpA, as assessed by MRI in an imaging sub-study ($n = 153$) of RAPID-axSpA [19]. At week 12, certolizumab pegol (200 mg q2w or 400 mg q4w) recipients experienced significant ($p \leq 0.001$) improvement from baseline in the Spondyloarthritis Research Consortium of Canada sacroiliac joint (SPARCC SIJ) scores (least-squares [LS] mean difference from placebo in the change from baseline −4.9 and −6.2, respectively) and in the Berlin modification of AS spine MRI score for activity (ASspiMRI-a; LS mean

Table 3 Efficacy of subcutaneous certolizumab pegol in adult patients with axial spondyloarthritis in the randomized, double-blind, multicentre RAPID-axSpA trial [13]

Population	Treatment (mg qxw[a])	Duration	No. of pts[b]	Response rates (% of pts)			ASAS partial remission rate[c]
				ASAS20	ASAS40	ASAS5/6	
axSpA	CZP 200 q2w	Week 12	111	57.7*[d]	43.2**	45.0**	23.4**
	CZP 400 q4w		107	63.6**[d]	48.6**	41.1**	24.3**
	PL		107	38.3[d]	17.8	8.4	3.7
	CZP 200 q2w	Week 24	111	66.7*[e]	51.4*[e]	36.9*[e]	30.6*[e]
	CZP 400 q4w		107	70.1*[e]	52.3*	47.7*[e]	29.9*[e]
	PL		107	29.0	15.0[e]	4.7[e]	8.4[e]
	CZP 200 q2w	Week 48[f]	111	71.2	53.2	NR	31.5
	CZP 400 q4w		107	72.0	61.7	NR	28.0
AS	CZP 200 q2w	Week 12	65	56.9*	40.0*	47.7*[e]	20.0*[e]
	CZP 400 q4w		56	64.3*	50.0**	35.7*[e]	19.6*[e]
	PL		57	36.8	19.3	8.8[e]	1.8[e]
	CZP 200 q2w	Week 24	65	67.7**	47.7**	33.8*[e]	30.8*[e]
	CZP 400 q4w		56	69.6**	58.9**	46.6*[e]	25.0*[e]
	PL		57	33.3	15.8	5.3[e]	7.0[e]
	CZP 200 q2w	Week 48[f]	65	72.3	52.3	NR	29.2
	CZP 400 q4w		56	75.0	64.3	NR	30.4
nr-axSpA	CZP 200 q2w	Week 12	46	58.7	47.8**	41.3*[e]	28.3*[e]
	CZP 400 q4w		51	62.7*	47.1**	47.1*[e]	29.4*[e]
	PL		50	40.0	16.0	8.0[e]	6.0[e]
	CZP 200 q2w	Week 24	46	65.2**	56.5**	41.3*[e]	30.4*[e]
	CZP 400 q4w		51	70.6**	45.1**	49.0*[e]	35.3*[e]
	PL		50	24.0	14.0	4.1[e]	10.0[e]
	CZP 200 q2w	Week 48[f]	46	69.6	54.3	NR	34.8
	CZP 400 q4w		51	68.6	58.8	NR	25.5

AS ankylosing spondylitis, *ASAS20, 40* improvement of ≥20 or ≥40 % in the Assessment of SpondyloArthritis international Society criteria, *ASAS5/6* improvement of ≥20 % in five out of six ASAS domains, *axSpA* axial spondyloarthritis, *CZP* certolizumab pegol, *NR* not reported, *nr-axSpA* non-radiographic axSpA, *PL* placebo, *pts* patients, *qxw* every x weeks

* $p < 0.05$, ** $p < 0.001$ vs. PL

[a] Maintenance dosage following a loading dose of 400 mg at weeks 0, 2 and 4

[b] All pts randomized to treatment with the intention to treat

[c] Score of ≤2 numerical rating scale units in all four ASAS domains

[d] Primary endpoint

[e] Values obtained from an abstract presentation [26]

[f] Data are for all pts initially randomized to CZP treatment in the double-blind phase of the study (abstract presentation) [18]

difference from placebo in change from baseline −3.3 and −2.8) [values estimated from graphs] [19]. Significant ($p < 0.05$) improvements in these scores with certolizumab pegol (200 mg q2w or 400 mg q4w) were observed in both the AS and the nr-axSpA sub-populations, with the exception of SPARCC SIJ scores in patients with AS who received certolizumab pegol 200 mg q2w and the ASs-piMRI-a Berlin modification scores in patients with nr-axSpA who received certolizumab pegol 200 mg q2w [19]. The reduction in inflammation observed at week 12 was maintained at week 48 (no quantitative data available) [18].

3.1.3 *Spinal Mobility, Health-related Quality of Life and Productivity*

In patients with axSpA, certolizumab pegol (200 mg q2w or 400 mg q4w) treatment was associated with significant improvements in spinal mobility (BASMI-linear scores) and physical function (BASFI scores) at weeks 12 and 24 relative to placebo [13], with the improvements in certolizumab pegol recipients sustained at week 48 [18] (Table 4). Other patient-reported outcome measures, including AS-specific Quality Of Life (ASQoL), spinal pain and fatigue scores also improved significantly

Table 4 Effect of subcutaneous certolizumab pegol on key patient-reported outcomes in the RAPID-axSpA study [13]

Population	Treatment (mg qxw[c])	Duration	No. of pts[a]	Mean change from BL (BL scores[b])		
				BASDAI	BASMI linear	BASFI
axSpA	CZP 200 q2w	Week 12	111	−2.8** (6.5)	−0.6** (3.7)	−2.0** (5.3)
	CZP 400 q4w		107	−2.8** (6.4)	−0.5* (3.8)	−2.0** (5.4)
	PL		107	−1.2 (6.4)	−0.1 (4.0)	−0.5 (5.5)
	CZP 200 q2w	Week 24	111	−3.1**	−0.5**	−2.4**
	CZP 400 q4w		107	−3.0**	−0.5**	−2.2**
	PL		107	−1.1	−0.1	−0.4
	CZP 200 q2w	Week 48[d]	111	[3.1[e]]	[3.0[e]]	[2.6[e]]
	CZP 400 q4w		107	[3.1[e]]	[3.2[e]]	[3.0[e]]
AS	CZP 200 q2w	Week 12	65	−2.5** (6.5)	−0.6 (4.2)	−1.7* (5.6)
	CZP 400 q4w		56	−2.4** (6.2)	−0.3 (4.3)	−1.7* (5.7)
	PL		57	−1.0 (6.4)	−0.2 (4.7)	−0.6 (6.0)
	CZP 200 q2w	Week 24	65	−3.0**	−0.6*	−2.4**
	CZP 400 q4w		56	−3.0**	−0.6	−2.3**
	PL		57	−1.1	−0.3	−0.7
	CZP 200 q2w	Week 48[d]	65	[3.3[e]]	[3.5[e]]	[3.0[e]]
	CZP 400 q4w		56	[3.0[e]]	[3.7[e]]	[3.2[e]]
nr-axSpA	CZP 200 q2w	Week 12	46	−3.3** (6.5)	−0.6** (3.1)	−2.3** (4.8)
	CZP 400 q4w		51	−3.4** (6.6)	−0.5** (3.3)	−2.3** (5.1)
	PL		50	−1.5 (6.4)	0.0 (3.1)	−0.4 (4.9)
	CZP 200 q2w	Week 24	46	−3.3**	−0.5**	−2.4**
	CZP 400 q4w		51	−3.2**	−0.4*	−2.1**
	PL		50	−1.0	+0.1	0.0
	CZP 200 q2w	Week 48[d]	46	[2.9[e]]	[2.3[e]]	[2.1[e]]
	CZP 400 q4w		51	[3.3[e]]	[2.7[e]]	[2.8[e]]

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *BASFI* Bath Ankylosing Spondylitis Functional Index, *BASMI* Bath Ankylosing Spondylitis Metrology Index, *BL* baseline, *CZP* certolizumab pegol, *nr-axSpA* non-radiographic axSpA, *PL* placebo, *pts* patients, *qxw* every x weeks

* $p < 0.05$, ** $p < 0.001$ vs. PL

[a] All pts randomized to treatment with the intention to treat. PL pts escaping at week 16 were considered non-responders at weeks 16–24

[b] Mean BL scores for the full analysis set (i.e. pts who received at least 1 dose of the study medication and had a valid BL and post-BL assessment of ASAS20, which included all randomized pts except one pt in the PL group)

[c] Maintenance dosage following a loading dose of 400 mg at weeks 0, 2 and 4

[d] Data are for all pts initially randomized to CZP treatment in the double-blind phase of the study (abstract presentation) [18]

[e] Mean scores at week 48

($p \leq 0.001$) from baseline with certolizumab pegol (200 mg q2w or 400 mg q4w) relative to placebo at weeks 12 and 24 [17], with the improvements sustained during longer-term treatment (week 48) [18].

Sub-group analyses showed that at week 24, with the exception of BASMI-linear scores in patients with AS who received certolizumab pegol 400 mg q4w, BASMI-linear and BASFI scores improved significantly ($p < 0.05$) both in the AS and the nr-axSpA subpopulations (Table 4) [13]. ASQoL, spinal pain and fatigue scores were also improved from baseline in both subgroups at this timepoint, with the improvements maintained at week 48 [18].

Certolizumab pegol improved workplace productivity (e.g. reduced the level of arthritis interference with work productivity per month; $p \leq 0.05$ for both dosages) and household productivity (e.g. household workdays missed because of arthritis per month; $p \leq 0.05$ for both dosages) during 24 weeks of treatment [20], with productivity continuing to improve during 48 weeks of treatment [21].

3.2 In Patients with Psoriatic Arthritis (PsA)

The ongoing 216-week RAPID-PsA study randomized 409 patients aged ≥18 years with a diagnosis of adult-onset PsA of at least 6 months' duration (as defined by the

ClASsification Criteria for Psoriatic Arthritis) [10, 11, 14]. Patients were required to have active joint disease (defined as ≥3 tender joints, ≥3 swollen joints and an erythrocyte sedimentation rate [ESR] of ≥28 mm/h or CRP of greater than the ULN [>7.9 mg/L]), inadequate response to at least one DMARD, and active psoriatic lesions or documented history of psoriasis. Patients who had received prior TNFα antagonist therapy could be included (up to 40 % of the study population) after a washout period [14]. Exclusion criteria included exposure to more than two biologic agents or more than one TNFα antagonist, primary failure of prior TNFα antagonist therapy, and evidence of latent or active TB unless prophylactic treatment of latent TB was initiated at least 4 weeks prior to baseline [14]. Concomitant treatment with stable-dose methotrexate (up to 25 mg/week), sulfasalazine (up to 3 g/day), leflunomide (up to 20 mg/day) or oral corticosteroids (up to 10 mg/day prednisone or equivalent) was permitted [14].

At baseline, patients had a mean age of ≈48 years; the mean duration of disease was ≈8.5 years; 64.3 % of patients had enthesitis (Leeds Enthesitis Index [LEI] of ≥1), 26.4 % had dactylitis (≥1 dactylitis digit with a circumference ≥10 % larger than the contralateral digit), 73.3 % had nail disease and 61.6 % had ≥3 % body surface area psoriatic skin involvement; ≈19.5 % of patients had prior exposure to TNFα antagonists; and 70.2 % of patients received concomitant treatment with methotrexate. The three treatment groups were generally well balanced in terms of demographic and disease activity/health status characteristics at baseline [14].

Of the patients randomized, ≈90 % completed 24 weeks' treatment [14] and 87 % completed 48 weeks' treatment [22]. Placebo recipients who did not achieve a 10 % improvement from baseline in swollen and tender joints at weeks 14 and 16 ($n = 59$) underwent mandatory escape and were re-randomized in a dose-blind manner to treatment with certolizumab pegol 200 mg q2w ($n = 30$) or 400 mg q4w ($n = 29$) [Fig. 1]; 18 patients in the certolizumab pegol 200 mg q2w group and 21 patients in the certolizumab pegol 400 mg q4w group also met the escape criteria, but continued with the dosage they were initially assigned to receive [14].

Table 5 summarizes the definitions and descriptions of the outcomes measures used in the RAPID-PsA study.

3.2.1 Clinical Response

Certolizumab pegol was effective in improving the clinical signs and symptoms of disease in patients with PsA [14]. American College of Rheumatology (ACR) 20 response rates were significantly higher with certolizumab pegol (200 mg q2w or 400 mg q4w) than with placebo at week 12 (clinical primary endpoint) and week 24 (Table 6), with significant ($p < 0.001$) improvements seen as early as week 1 of treatment. ACR50 and ACR70 response rates were also significantly higher with certolizumab pegol (200 mg q2w or 400 mg q4w) than with placebo at these timepoints (Table 6) [14].

Following 24 weeks' treatment with certolizumab pegol, the PsA lesional burden was reduced in patients with ≥3 % body surface area psoriasis involvement at baseline, as indicated by significantly higher Psoriatic Area and Severity Index (PASI) 75 and PASI90 response rates in certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients (Table 6) [14]. According to a post hoc analysis, PASI75 response rates were numerically higher in certolizumab pegol (200 mg q2w or 400 mg q4w) recipients who had more severe skin presentation at baseline (PASI score ≥10; $n = 37$ and 34 in certolizumab pegol 200 mg q2w and 400 mg q4w recipients, and $n = 28$ in placebo recipients) [81.1 and 73.5 vs. 14.3 %] than in those who had less severe presentation at baseline (PASI score <10; $n = 53$, 42 and 58) [49.1 and 50.0 vs. 15.5 %] [14, 27].

In addition, significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients achieved Psoriatic Arthritis Response Criteria by week 1 (33.3 and 35.6 vs. 14 %), with significant ($p < 0.001$) between-group differences maintained through week 24 (78.3 and 77.0 vs. 33.1 %) [14]. Minimal disease activity was also achieved by significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) recipients than placebo recipients at week 24 (33.3 and 34.1 vs. 5.9 %; post hoc analysis) [14].

Certolizumab pegol improved enthesitis, dactylitis and nail disease in patients who had these at baseline, with certolizumab pegol (200 mg q2w or 400 mg q4w) recipients experiencing significantly ($p \leq 0.003$) greater improvements from baseline in LEI (mean change −2.0 and −1.8 vs. −1.1 [baseline 2.9–3.1]), Leeds Dactylitis Index (−40.7 and −53.5 vs. −22.0 [baseline 45.3–65.6]) and modified Nail Psoriasis Severity Index (−1.6 and −2.0 vs. −1.1 [baseline 3.1–3.4]) scores at week 24 than placebo recipients [14].

Moreover, the benefit of treatment was observed regardless of prior exposure to TNFα antagonists (post hoc analysis), with significantly ($p < 0.05$) higher ACR20, ACR50 and ACR70 response rates seen at week 24 with certolizumab pegol (combined dosage) than with placebo both in patients who had ($n = 54$ and 26 in the respective groups) and in those who did not have prior exposure to these agents ($n = 219$ and 110) [14]. In patients with prior exposure to TNFα antagonists compared with patients with no prior exposure, the ACR20 response rates with certolizumab pegol (combined dosage) were 59.3 versus 60.3 % (11.5 vs. 26.4 % in placebo recipients), ACR50 response

Table 5 Definitions and descriptions of outcome measures used to assess treatment response in the RAPID-PsA trial

Measure	Definition
ACR20, 50, 70	Improvement of ≥20, ≥50 or ≥70 % in ACR core components using HAQ-DI and CRP
FAS	A 10-item scale (score 0–10) assessing fatigue, with lower scores indicating less tiredness
HAQ-DI	Measures functional disability (score 0–3), with higher scores indicating greater disability
LDI	Assesses dactylitis by measuring tenderness (score 0–3) and size of each finger to generate an overall score, with higher scores indicating worse dactylitis
LEI	Assesses enthesitis in 6 enthesial sites (including bilateral lateral epicondyles, medial femoral condyles and Achilles tendon insertions) by recording the presence (score of 1) or absence (score of 0) of tenderness (overall score 0–6), with higher scores indicating greater enthesitis burden
MDA	Achieving 5 of the following 7 criteria: TJC ≤1; SJC ≤1; PASI ≤1 or body surface area ≤3; patient's pain VAS score ≤15; patient's global activity VAS score ≤20; HAQ ≤0.5; tender enthesial points ≤1
mNAPSI	Measures nail psoriasis (score 0–13 for each fingernail and 0–130 overall), with higher scores indicating worse nail disease
mTSS	Assesses the degree of joint damage by quantifying the extent of bone erosions and joint space narrowing in distal interphalangeal, proximal interphalangeal, metacarpophalangeal, metatarsophalangeal and wrist joints, with higher scores indicating greater damage
PASI	Measures the surface area and the average redness, thickness and scaliness of the psoriatic skin lesions (range 0–72), with lower scores indicating less severity
PASI50, 75, 90	Reduction of ≥50, ≥75 or ≥90 % in PASI score from baseline
PsARC	A disease-specific responder index that requires achieving at least 2 of the following 4 items: TJC and/or SJC improved by ≥30 % (at least one of these required) and/or patient or physician global assessment improved by ≥1 point and no item has worsened
PsAQoL	A 20-item scale assessing disease-specific health-related quality of life (range 0–20), with higher scores indicating worse health-related quality of life
SF-36	Measure of physical and mental health in 8 domains (range 0–100 VAS for each domain), with higher scores indicating better health

ACR American College of Rheumatology, *BSA* body surface area, *CRP* C-reactive Protein, *FAS* fatigue assessment scale, *HAQ* Health Assessment Questionnaire, *HAQ-DI* HAQ Disability Index, *LDI* Leeds Dactylitis Index, *LEI* Leeds Enthesitis Index, *MDA* minimal disease activity, *mNAPSI* Modified Nail Psoriasis Severity Index, *mTSS* van der Heijde modified total Sharp score, *PASI* Psoriasis Area and Severity Index, *PsAQoL* psoriatic arthritis-specific quality of life scale, *PsARC* Psoriatic Arthritis Response Criteria, *SF-36* Short-Form 36 health survey, *SJC* swollen joint count, *TJC* tender joint count, *VAS* Visual Analogue Scale

rates were 44.4 versus 41.6 % (3.8 vs. 14.5 % in placebo recipients) and ACR70 response rates were 25.9 versus 26.0 % (3.8 vs. 4.5 % in placebo recipients) [14].

With regard to concomitant DMARD use, treatment benefit was seen both in patients who received certolizumab pegol (200 mg q2w or 400 mg q4w) in combination with DMARDs (ACR20 response rates: 59 and 55 vs. 28 % in placebo recipients), as was well as in patients who received certolizumab pegol as monotherapy (56 and 43 vs. 17 %) [post hoc analysis] [14].

The improvement in disease activity seen with certolizumab pegol at week 24 was maintained during longer-term therapy, as assessed by ACR and PASI response rates at week 48 (Table 6) [22]. In addition, 37.7 and 34.8 % of certolizumab pegol (200 mg q2w and 400 mg q4w) recipients, respectively, achieved minimal disease activity at week 48 (post hoc analyses) [22].

3.2.2 Radiographic Response

Certolizumab pegol slowed radiographic progression of disease in patients with PsA, as assessed by the change from baseline in the modified total Sharp score (mTSS; radiographic primary endpoint) [28]. For patients with fewer than two analysable mTSS, it was prespecified that the minimum observed baseline mTSS be used for missing baseline values and the maximum observed week 24 mTSS be used for missing week 24 values. However, as the prespecified imputation methodology inappropriately overestimated radiographic progression in certolizumab pegol versus placebo recipients (LS mean change from baseline in mTSS 18.3 for the combined dosage vs. 28.9), post hoc analyses using alternative methods of imputation were undertaken [28].

One such analysis (using the median mTSS of the entire population to impute missing values) showed that at week 24, mTSS scores increased from baseline to a significantly ($p = 0.007$) smaller extent in certolizumab pegol (combined dosage) than placebo recipients (LS mean change 0.06 vs. 0.28) [28]. The results obtained with this imputation methodology were realistic and trended [16] with the results seen in a recent PsA trial with another TNFα antagonist (golimumab) [29]. Results for the individual dosages of certolizumab pegol 200 mg q2w (LS mean

Table 6 Efficacy of subcutaneous certolizumab pegol in adult patients with active psoriatic arthritis in the randomized, double-blind, multicenter RAPID-PsA trial [14]

Treatment (mg qxw[b])	Duration	No. of pts[a]	Response rates (% of pts)					
			ACR20	ACR50	ACR70	PASI50[a,c]	PASI75[a]	PASI90[a]
CZP 200 q2w	Week 12	138	58.0**[d]	36.2**	24.6**	68.9	46.7**	22.2**
CZP 400 q4w		135	51.9**[d]	32.6**	12.6*	63.2	47.4**	19.7**
PL		136	24.3[d]	11.0	2.9	26.7	14.0	4.7
CZP 200 q2w	Week 24	138	63.8**	44.2**	28.3**	74.4	62.2**	46.7**
CZP 400 q4w		135	56.3**	40.0**	23.7**	72.4	60.5**	35.5**
PL		136	23.5	12.5	4.4	27.9	15.1	5.8
CZP 200 q2w	Week 48[e]	138	66.7	49.3	34.8	NR	66.7	48.9
CZP 400 q4w		135	65.9	45.9	30.4	NR	61.8	42.1

ACR20, 50 or 70 improvement of ≥20, ≥50 or ≥70 % in the American College of Rheumatology standard criteria, *CZP* certolizumab pegol, *NR* not reported, *PASI50, 75 or 90* improvement of ≥50, ≥75 or ≥90 % in the Psoriasis Area and Severity Index in pts with ≥3 % body surface area psoriasis at baseline, *PL* placebo, *pts* patients, *qxw* every x weeks

* $p = 0.003$, ** $p < 0.001$ vs. PL

[a] All pts randomized to treatment with the intention to treat. PL pts escaping at week 16 were considered non-responders from week 16 onwards. PASI responses were assessed in 90, 76 and 86 pts in the CP 200 q2w, CPZ 400 q4w and PL groups, respectively

[b] Maintenance dosage following a loading dose of 400 mg at weeks 0, 2 and 4

[c] No statistical analysis conducted for PASI50 response

[d] Primary endpoint

[e] Data are for all pts initially randomized to CZP treatment in the double-blind phase of the study (abstract presentation) [22]

change from baseline 0.01; $p = 0.004$) and 400 mg q4w (0.11; $p = 0.072$) were consistent with those for the combined dosage, although the *p*-values were considered nominal as the study was not powered to detect significant differences between individual dosages of certolizumab pegol and placebo [28]. Other post hoc analyses using alternative and more conservative imputation methods confirmed the findings of this imputational analysis [28]. Radiographic progression remained low in patients who continued to receive certolizumab pegol until week 48 (LS mean change from baseline 0.13 for combined dosage) [22], including in the subset of patients at a higher risk of radiographic progression (patients with an mTSS score of >6 at baseline) [10].

3.2.3 Health-Related Quality of Life and Productivity

Certolizumab pegol treatment for up to 24 weeks improved several measures of HR-QOL (Table 7) in patients with PsA [30], with these improvements being maintained at week 48 [22, 23]. At weeks 12 and 24, significant improvements in physical function (as assessed by Health Assessment Questionnaire-Disability Index [HAQ-DI]) were seen in certolizumab pegol (200 mg q2w or 400 mg q4w) relative to placebo recipients (Table 7), with significant ($p < 0.01$) between-group differences seen as early as week 2 of treatment [30]. In addition, at week 24, a clinically relevant change from baseline in HAQ-DI (decrease of ≥0.35 points) was observed in significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients (49.3 and 48.1 vs. 15.4 %), with significant ($p < 0.001$) improvements seen from week 4 onwards. Similar results were seen for a minimum clinically important difference of a ≥0.3 point decrease in HAQ-DI [30].

Certolizumab pegol treatment reduced pain and fatigue at weeks 12 and 24 (Table 7), with significant between-group differences seen from weeks 1 and 2, respectively [30]. In addition, significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients at week 24 experienced a clinically relevant improvement from baseline in pain (≥10 point decrease; 69.6 and 68.9 vs. 29.4 %) and fatigue (≥1 point decrease; 65.9 and 63.0 vs. 28.7), with significant ($p < 0.005$) between-group differences in pain seen from week 1 onwards [30].

Significant improvements from baseline in the Psoriatic Arthritis Quality of Life (PsAQoL) scale and the Short-Form 36 (SF-36) physical and mental component summary scores were also observed with certolizumab pegol (200 mg q2w or 400 mg q4w) relative to placebo by week 24 (Table 7). In addition, significantly ($p < 0.001$) more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients experienced clinically relevant improvements from baseline (≥2.5 point decrease in scores) in the SF-36 physical (63.8 and 71.9 vs. 30.1 %) and mental (54.3 and 48.9 vs. 22.8 %) component summary scores at this timepoint [30].

Table 7 Effect of certolizumab pegol on physical function and health-related outcomes in the RAPID-PsA trial [30]

Treatment (mg qxw[a])	Duration	Mean change from BL (BL values)					
		HAQ-DI	PsAQoL	SF-36 PCS	SF-36 MCS	FAS	Pain[b] (mm)
CZP 200 q2w	Week 12	−0.45** (1.3)	−3.6** (11.1)	7.5** (33.1)	4.9* (40.7)	−2.1** (6.3)	−26.9** (59.7)
CZP 400 q4w		−0.39** (1.3)	−2.8** (11.3)	6.7** (33.2)	2.4 (41.9)	−1.4** (6.2)	−22.5** (61.1)
PL		−0.16 (1.3)	−1.0 (10.9)	1.8 (33.8)	1.4 (42.4)	−0.3 (5.8)	−9.9 (60.0)
CZP 200 q2w	Week 24	−0.52**	−4.4**	8.4**	5.5**	−2.2**	−28.6**
CZP 400 q4w		−0.43**	−3.3**	7.6**	3.5*	−1.9**	−28.4**
PL		−0.17	−1.3	2.1	0.7	−0.6	−11.2
CZP 200 q2w	Week 48[c]	−0.56	−4.8	8.6	4.8	−2.4	−31.6
CZP 400 q4w		−0.49	−3.5	8.4	3.2	−2.0	−29.5

Results for the intent-to-treat population ($n = 138$, 135 and 136 in the CZP 200 q2w, CZP 400 q4w and PL groups)

CZP certolizumab pegol, *FAS* fatigue assessment scale, *HAQ-DI* Health Assessment Questionnaire Disability Index, *MCS* mental component summary, *PCS* physical component summary, *PL* placebo, *PsAQoL* psoriatic arthritis-specific quality of life scale, *qxw* every x weeks, *SF-36* Short-Form 36 health survey

* $p < 0.05$, ** $p < 0.001$

[a] Maintenance dosage following a loading dose of 400 mg at weeks 0, 2 and 4

[b] Assessed on a 0–100 mm visual analogue scale

[c] Data are for all pts initially randomized to CZP treatment in the double-blind phase of the study (abstract presentations) [22, 23]

The benefit of treatment at week 24 was observed regardless of prior exposure to TNFα antagonists, with significant ($p < 0.05$ vs. placebo) improvements seen in most HR-QOL measures in patients receiving certolizumab pegol (combined dosage) with or without TNFα antagonists (with the exception of SF-36 mental component summary scores in patients previously treated with TNFα antagonists) [30].

Certolizumab pegol improved workplace productivity (e.g. reduced the level of arthritis interference with work productivity; $p \leq 0.05$ for both dosages) and household productivity (e.g. household workdays missed because of arthritis; $p \leq 0.05$ for both dosages) during 24 weeks of treatment [24], with these benefits being maintained at week 48 [25].

4 Tolerability

This section discuses the tolerability of subcutaneous certolizumab pegol in patients with axSpA or PsA, based on data available from the RAPID-axSpA [13] and RAPID-PsA [14] studies reviewed in Sect. 3. These data are supplemented with data available from the EU summary of product characteristics [10]. Some data are available only as abstract presentations [18, 22].

4.1 General Profile and Postmarketing Experience

Certolizumab pegol was generally well tolerated in pooled data from randomized clinical trials and their open-label extensions in patients with RA ($n = 4{,}049$; total exposure of 9,277 patient-years) [10, 31] and during postmarketing surveillance [10]. Commonly occurring (incidence ≥1/100 to <1/10) adverse reactions in certolizumab pegol recipients included infections and infestations (e.g. abscess, herpes virus, papillomavirus and influenza virus infections), injection-site reactions, headache, nausea, hepatitis (including increased levels of hepatic enzymes), hypertension, eosinophilic disorders and leukopenia [10].

Infections occurred at an incidence rate of 1.03 per patient-year in certolizumab pegol recipients (vs. 0.92 per patient-year in placebo recipients) in placebo-controlled RA trials, with upper and lower respiratory tract infections, urinary tract infections and herpes viral infections being reported most commonly [10]. Serious infections (including sepsis and TB) and opportunistic infections (e.g. histoplasmosis and candidiasis) infections have also been reported in patients receiving certolizumab pegol [31], some of which resulted in fatalities [10]. In pooled data from RA trials, the most frequent serious infectious events in certolizumab pegol recipients included pneumonia (0.77 events per 100 patients-years), cellulitis (0.31 events/100 patients-years) and urinary tract infection (0.16 events/100 patient-years); 44 patients developed TB during this period (0.47 events per 100 patient-years) [31]. Certolizumab pegol, like other TNFα antagonists, has been associated with the reactivation of hepatitis B virus (HBV) in chronic carriers of HBV, with fatal outcomes reported in some cases [10]. Patients should be tested for TB (latent or active) and hepatitis B infection prior to initiating therapy and should be closely monitored for signs and symptoms of

infections during treatment with certolizumab pegol, with monitoring continued even after treatment discontinuation, as the agent may take up to 5 months to be eliminated (see local prescribing information for further details and treatment recommendations) [10].

Malignancies (excluding non-melanoma skin cancer [NMSC]) occurred at an incidence rate of 0.76 per 100 patient-years with certolizumab pegol in pooled data from RA trials, with lymphomas and solid tumours occurring at an incidence rate of 0.05 and 0.71 per 100 patient-years, respectively [31]. Of the solid tumours, breast cancer occurred most frequently in women (incidence rate 0.12 per 100 patient-years) [31]. No increased risk of malignancy was seen with certolizumab pegol, with the standardized incidence rate for all malignancies (excluding NMSC) being 1.27 (95 % CI 0.99–1.61) using the WHO general population and 1.06 (95 % CI 0.82–1.33) using the US general population [31]. However, caution is advised when considering TNFα antagonist therapy in patients with a history of malignancy or if continuation of therapy is being considered in patients who develop a malignancy [10].

There have been reports of congestive heart failure in patients with RA who were receiving certolizumab pegol [10]; therefore, in the EU, it is recommended that the agent be used with caution in patients with mild heart failure (New York Heart Association [NYHA] class I or II) and its use be discontinued in patients with new or worsening symptoms of congestive heart failure. Major adverse cardiovascular events (fatal and serious non-fatal myocardial infarction, cerebrovascular events and congestive heart failure) occurred at an event rate of 0.82 per 100 patient-years in pooled data from RA trials [31].

Certolizumab pegol therapy may result in the formation of antinuclear antibodies and uncommon occurrences of lupus-like syndrome, as well as rare occurrences of neurological disorders (including seizure disorder, neuritis and peripheral neuropathy) [10, 31]. Rare cases of new onset or exacerbation of demyelinating disease (e.g. multiple sclerosis) have also been reported in patients receiving TNFα antagonists [10]. However, there were no reports of multiple sclerosis, optic neuritis or other demyelinating disorders with certolizumab pegol in the pooled data from RA trials [31].

4.2 In Patients with AxSpA or PsA

Certolizumab pegol (200 mg q2w or 400 mg q4w) was generally well tolerated in patients with axSpA or PsA [13, 14], with a tolerability profile generally consistent with that observed in patients with RA and previous experience with the agent [10] (Sect. 4.1). During 24 weeks' double-blind treatment in the RAPID-axSpA and RAPID-PsA studies, most adverse events occurring in certolizumab pegol recipients were of mild (in 57–60 % of patients) or moderate (33–41 %) severity and generally considered unrelated to treatment (Table 8). Serious adverse events occurred in <10 % of patients receiving certolizumab pegol and <5 % of patients discontinued treatment because of adverse events (Table 8).

During 24 weeks' treatment in patients with axSpA, the most common infectious adverse events in certolizumab pegol (200 mg q2w or 400 mg q4w) recipients were nasopharyngitis and upper respiratory tract infections (URTI; Table 8) and the most common non-infectious adverse events were headache (6.3 and 8.4 vs. 6.5 % of placebo recipients) and increased levels of blood creatinine phosphokinase (6.3 and 5.6 vs. 1.9 %) [13]. The increases in creatinine phosphokinase were often considered related to increased physical activity, were transient, resolved spontaneously during continued treatment and were not associated with ischemic cardiac events or treatment discontinuations. There were no deaths, no reported cases of opportunistic infections (including TB), malignancies or adverse events suggestive of demyelinating disorders [13, 15]. Five new cases of uveitis (two in certolizumab pegol and three in placebo recipients) and one new case of inflammatory bowel disease (in a placebo recipient) were reported in the study [13].

In patients with PsA, nasopharyngitis and URTI were the most common infectious adverse events during 24 weeks' treatment with certolizumab pegol (200 mg q2w or 400 mg q4w) [Table 8], while diarrhoea (5.1 and 3.7 vs. 2.9 % of placebo recipients) and headache (4.3 and 3.7 vs. 1.5 %) were the most common non-infectious adverse events in these patients [14]. Liver enzyme levels increased in at least 2-fold more certolizumab pegol (200 mg q2w or 400 mg q4w) than placebo recipients (alanine aminotransferase levels in 2.9 and 5.2 vs. 1.5 %; aspartate aminotransferase levels in 2.9 and 4.4. vs. 0.7 %; hepatic enzyme levels in 3.6 and 3.0 vs. 1.5 %). There were two deaths reported in certolizumab pegol recipients (Table 8), both of which were considered unrelated to treatment. There were no reports of congestive heart failure, serious injection-site reactions, TB or opportunistic infections or adverse events suggestive of demyelinating disorders [14, 16]; one patient in the certolizumab pegol 400 mg q4w group had non-invasive cervical carcinoma (stage 0) [14].

The tolerability profile of certolizumab pegol in patients who continued treatment in the dose-blind phases of RAPID-axSpA and RAPID-PsA was consistent with that observed in the 24-week double-blind phases of the studies. During 48 weeks of treatment with certolizumab pegol (combined dosage), 78.7 % of patients with axSpA [18] and 77.4 % of patients with PsA [22] experienced adverse events, with serious adverse events reported in 7.9 and

Table 8 Tolerability profile of subcutaneous certolizumab pegol during 24 weeks' treatment in patients with axial spondyloarthritis [13] or psoriatic arthritis [14]

	RAPID-axSpA [13] (% of pts)			RAPID-PsA [14] (% of pts)		
	CZP 200[a] ($n = 111$)	CZP 400[a] ($n = 107$)	PL ($n = 107$)	CZP 200[a] ($n = 138$)	CZP 400[a] ($n = 135$)	PL ($n = 136$)
Any TEAE	76.6	74.8	62.6	68.1	71.1	67.6
Mild	58.6	59.8	48.6	56.5	57.0	54.4
Moderate	41.4	40.2	33.6	34.1	33.3	36.0
Severe	3.6	2.8	6.5	5.1	5.2	1.5
Treatment-related TEAEs	36.9	33.6	20.6	28.3	30.4	27.2
Serious TEAEs	3.6	6.5	4.7	5.8	9.6	4.4
Discontinuations due to TEAEs	1.8	3.7	1.9	2.9	4.4	1.5
Infections	38.7	38.3	23.4	43.5	40.0	38.2
Nasopharyngitis	9.9	10.3	6.5	13.0	6.7	7.4
URTI	5.4	3.7	2.8	8.7	9.6	5.1
Serious infections	1.8[b]	0	0	1.4	1.5	0.7
Injection-site reactions	9.0	4.7	0.9	4.3	9.6	2.2
Injection-site pain	0.9	0	0.9	2.2	0.7	1.5
Death	0	0	0	0.7[c]	0.7[c]	0

CZP 200 certolizumab pegol 200 mg every 2 weeks, *CZP 400* certolizumab pegol 400 mg every 4 weeks, *PL* placebo, *pts* patients, *TEAE* treatment-emergent adverse event, *URTI* upper respiratory tract infection

[a] Maintenance dosage following a loading dose of 400 mg at weeks 0, 2 and 4

[b] Haemophilus infection and laryngitis (one each)

[c] A myocardial infarction in the CZP 200 group and sudden death of unknown cause in the CZP 400 group

9.9 % of patients respectively. The incidence of serious infections in patients with axSpA was 3.2 % (including suspected TB in three [1 %] patients, of which one case was confirmed) [18] and the incidence in patients with PsA was 2.0 % (including one case of TB) [22]. In patients with PsA, three malignancies (two cases of breast cancer and one case of lymphoma) were reported during the dose-blind and open-label periods, of which two were fatal (lymphoma and one case of breast cancer) [16]. The profile of malignancies with certolizumab pegol in patients with PsA was generally similar to that seen earlier in patients with RA [16].

5 Dosage and Administration

In the EU, subcutaneous certolizumab pegol is indicated for the treatment of adult patients with severe active axSpA, comprising: (1) patients with severe active AS and (2) patients with severe active axSpA without radiographic evidence of AS, but with objective signs of inflammation as evidenced by elevated CRP and/or MRI [10]. Patients should have had an inadequate response to or be intolerant of NSAIDs [10]. In the USA, certolizumab pegol is indicated for the treatment of adult patients with active AS [11].

Subcutaneous certolizumab pegol (in combination with methotrexate) is indicated in the EU for the treatment of adults with active PsA who have had an inadequate response to previous DMARD therapy [10]. Certolizumab pegol may be administered as monotherapy in patients who are intolerant of methotrexate or when continued therapy with methotrexate is inappropriate [10]. In the USA, certolizumab pegol is indicated for the treatment of adult patients with active PsA [11].

The recommended dosage and administration schedules for certolizumab pegol are summarized in Table 9. In the EU, no dosage adjustment of certolizumab pegol is required in elderly patients (aged ≥65 years) [10]; caution is advised in the USA when certolizumab pegol is used in this population, because of the increased risk of infections in the elderly in general [11]. The use of certolizumab pegol has not been studied in patients with renal [10, 11] or hepatic impairment [10].

Owing to the increased risk of serious infections (which may lead to hospitalization or death) in patients receiving certolizumab pegol, in the EU, its use is contraindicated in patients with active TB or other severe infections (e.g. sepsis or opportunistic infections) [10]; the US prescribing information carries a boxed warning regarding the increased risk of serious infections [11]. It is recommended that patients be monitored prior to and during treatment for

Table 9 Summary of recommended certolizumab pegol dosage and administration in the EU [10] and USA[a] [11]

Indication	Starting dosage	Subsequent/ maintenance dosage
axSpA (EU) or AS (USA)	400 mg on weeks 0, 2 and 4	200 mg q2w or 400 mg q4w
PsA (EU[b] and USA)	400 mg on weeks 0, 2 and 4	200 mg q2w; 400 mg q4w may be considered after clinical response has been confirmed

CZP certolizumab pegol, *AS* ankylosing spondylitis, *axSpA* axial spondyloarthritis, PsA psoriatic arthritis, *qxw* every x weeks

[a] In the USA, CZP may be used as monotherapy or in combination with conventional disease-modifying anti-rheumatic agents

[b] In the EU it is recommended that methotrexate treatment should be continued during CZP therapy if appropriate

the development of serious infections (see also Sect. 4.1) [10, 11]. In the EU, its use is contraindicated in patients with moderate to severe heart failure (NYHA class III or IV) [10].

Local prescribing information should be consulted for comprehensive information on dosage adjustments, contraindications, warnings and precautions.

6 Place of Cerolizumab Pegol in the Management of AxSpA and PsA

According to recent recommendations of an international task force, a major aim of treatment in patients with SpA is to achieve clinical remission (defined as the absence of clinical or laboratory evidence of significant inflammatory disease activity) or, alternatively, to achieve low disease activity of musculoskeletal involvement, taking extra-articular manifestations into consideration [32]. It is recommended that treatment be individualized based on current clinical manifestations of the disease and once treatment target is achieved, it should ideally be maintained over the course of the disease [32].

The clinical signs and symptoms of disease and levels of acute phase reactants should be used to measure disease activity, with the choice of measure and the treatment target influenced by comorbidities, patient characteristics and drug-related risks [32]. For patients with axSpA, which includes (early) nr-axSpA and AS [2, 3], it is recommended that validated composite measures of disease activity (e.g. BASDAI plus acute phase reactants, or the ASDAS with or without measures of function such as BASFI) should be used to guide treatment decisions [32]. Other factors, such as comorbidities, axial inflammation on MRI, radiographic progression, peripheral musculoskeletal and extra-articular manifestations of the disease, may also be considered when determining the course of treatment [32]. Similarly, in patients with PsA, treatment decisions should be guided by validated measures of musculoskeletal disease activity (arthritis, dactylitis, enthesitis, axial disease), with other factors (such as spinal and extra-articular manifestations, imaging results, changes in function or HR-QOL and comorbidities) also taken into consideration [32].

Treatment options for patients with SpA include TNFα antagonists and conventional agents, such as NSAIDs, corticosteroids and analgesics. The ASAS guidelines recommend the use of TNFα antagonists in patients with axSpA who have had inadequate response to first-line treatment with at least two NSAIDs for a minimum of 4 weeks in total [33]. Generally similar recommendations have also been issued by the ASAS/European League Against Rheumatism (EULAR) for patients with AS, with NSAIDs recommended as first-line therapy in patients with pain and stiffness, and TNFα antagonists recommended for patients with persistently high disease activity despite conventional treatment [34]. No pretreatment with conventional DMARDs is required prior to initiating TNFα antagonist therapy in patients with axial disease [33].

For patients with PsA, the EULAR guidelines recommend NSAIDs as first-line therapy to relieve musculoskeletal signs and symptoms [35], with conventional DMARDs to be considered early during therapy in patients who have active disease (especially those with swollen joints, structural damage in the presence of inflammation, high ESR or CRP, and/or clinically relevant extra-articular manifestations) [35]. In patients who have active PsA and clinically relevant psoriasis, conventional DMARDs that also improve psoriasis (e.g. methotrexate) should be preferred [35]. Adjunctive treatment with local corticosteroid injections should be considered and systemic steroids (the lowest effective dose) may be used with caution [35]. It is recommended that TNFα antagonists be commenced in patients who have inadequate response to at least one conventional DMARD, in patients with active enthesitis and/or dactylitis who have inadequate response to NSAIDs or local steroid injections, and in patients with predominantly axial disease that is active and has responded inadequately to NSAIDs [35]. In addition, TNFα antagonists may be considered for patients with very active disease who are DMARD naïve, particularly those with structural damage in the presence of inflammation, many swollen joints and/or clinically relevant extra-articular manifestations (especially extensive skin involvement) [35]. Patients who respond inadequately to one TNFα antagonist may be switched to another TNFα antagonist [35]. Generally similar treatment recommendations have also been issued by the Group for Research and Assessment of Psoriasis and PsA [36], and the British Society for

Rheumatology and British Health Professionals in Rheumatology [37].

Certolizumab pegol is one such TNFα antagonist recently approved for use in patients with active severe axSpA (comprising AS and nr-axSpA) or PsA (Sect. 5). It differs from other currently available TNFα antagonists (Table 10) comprising a PEGylated Fab′ fragment of an anti-TNFα antibody (Sect. 2.1). Owing to the lack of an Fc portion of the antibody, certolizumab pegol does not induce complement mediated or antibody-dependent cytotoxicity (Table 1). Instead, it has been shown to induce non-apoptotic cell death, probably via signalling through transmembrane TNFα (Table 1).

In terms of clinical efficacy, the two ongoing well-designed RAPID-axSpA and RAPID-PsA studies showed that certolizumab pegol (200 mg q2w or 400 mg q4w) was effective in improving the clinical signs and symptoms of disease in patients with axSpA (Sect. 3.1.1) or PsA (Sect. 3.2.1), with the improvements sustained during longer-term (48 weeks) treatment. The onset of response with certolizumab pegol was rapid, with improvements in some measures (e.g. ASAS20 response in patients with axSpA and ACR20 response in patients with PsA) seen as early as week 1 of treatment and maintained until week 48 (Sect. 3). It has been suggested that the certolizumab pegol loading dose may contribute to the rapid response seen within the first 4 weeks of treatment [14]. Although the studies were not designed to demonstrate equivalence between the 200 mg q2w and 400 mg q4w dosages of certolizumab pegol, overall, there did not appear to be clinically relevant differences between the two dosages in terms of efficacy, suggesting dosing flexibility and the convenience of less frequent dosing in some patients [13, 14].

Significant improvements in spinal mobility (in patients with axSpA), HR-QOL and productivity measures were also seen in certolizumab pegol recipients during 48 weeks' treatment (Sects. 3.1.3 and 3.2.3). In addition, certolizumab pegol therapy reduced inflammation in the sacroiliac joints and spine at week 12 in patients with axSpA (Sect. 3.1.2) and slowed radiographic progression of disease at week 24 in patients with PsA (Sect. 3.2.2), with continued benefit seen at week 48. Further long-term data would help to establish the efficacy of certolizumab pegol on radiographic measures in these patients.

Among patients with axSpA, disease activity at baseline was generally similar between patients who had AS and those who had nr-axSpA, suggesting a high disease burden in both subgroups [13]. However, patients with AS had higher BASFI and BASMI linear scores at baseline, indicating more physical damage compared with patients with nr-axSpA, probably because of greater irreversible structural damage [13]. Certolizumab pegol treatment was effective in both subgroups, with significant improvements relative to placebo seen in most measures assessing clinical response, spinal mobility and productivity (Sects. 3.1.1 and 3.1.3). Of the currently available TNFα antagonists, at the moment only certolizumab pegol [10] and adalimumab [38] have been approved in the EU for use in patients with nr-axSpA (Table 10).

In patients with PsA, benefit of certolizumab pegol therapy was seen regardless of prior treatment with TNFα antagonists (Sect. 3.2.1). However, as patients with primary failures to treatment with TNFα antagonists were excluded from RAPID-PsA, further studies are required to assess the efficacy of certolizumab pegol in these patients [14]. With regard to concomitant DMARD use, treatment benefit was seen in patients with PsA who received certolizumab pegol in combination with DMARDs, as well as in those who received certolizumab pegol as monotherapy (Sect. 3.2.1). However, additional analyses favoured combination therapy over monotherapy (at week 24, the difference from placebo in ACR20 response rates was approximately 40 vs. 30 %) [16]; therefore, in the EU, it is recommended that certolizumab pegol be used in combination with methotrexate, with monotherapy recommended in case of intolerance to methotrexate or if continued methotrexate use is not appropriate (Sect. 5) [10].

Certolizumab pegol was generally well tolerated during 48 weeks' treatment in the RAPID-axSpA and RAPID-PsA studies (Sect. 4.2), with a tolerability profile generally consistent with that observed in patients with RA and previous experience with the agent [10]. No new safety

Table 10 Comparative features of tumor necrosis factor α antagonists currently available for the treatment of spondyloarthritis

Drug	Pharmacology	EU Approved for use in	USA
Adalimumab	Anti-TNFα human mAb	AxSpA (AS and nr-axSpA); PsA	AS; PsA
Certolizumab pegol	PEGylated Fab′ fragment from anti-TNFα human mAb	AxSpA (AS and nr-axSpA); PsA	AS; PsA
Etanercept	Recombinant anti-TNFα receptor dimerized on an Ig frame	AS; PsA	AS; PsA
Golimumab	Anti-TNFα human mAb	AS; PsA	AS; PsA
Infliximab	Chimeric human/mouse anti-TNFα mAb	AS; PsA	AS; PsA

AS ankylosing spondylitis, *axSpA* axial spondyloarthritis, *Fab′* antigen-binding fragment, *mAb* monoclonal antibody, *nr-axSpA* non-radiographic axial spondyloarthritis, *PEG* polyethylene glycol, *PsA* psoriatic arthritis, *TNF* tumor necrosis factor

signals were seen in these studies and, overall, the tolerability profile was generally similar between the certolizumab pegol 200 mg q2w and 400 mg q4w dosages [15, 16]. As with other biologic DMARDs, infections were the most common adverse event in certolizumab pegol recipients in these studies, with nasopharyngitis occurring most frequently (Sect. 4.2). Infections with biologic DMARDs are thought to be result of their unique mechanism of action; by blocking overexpressed signalling proteins in diseases like RA, biologic DMARDs also block important signalling proteins of the normal immune response, resulting in an increased risk of infections [39].

It is also thought that biologic DMARDs may inhibit tumour surveillance by affecting immune responses, which may result in increased risk of malignancies [39]. No malignancies were reported in certolizumab pegol recipients in RAPID-axSpA and four malignancies were reported in RAPID-PsA; the malignancy profile in the latter study was generally similar to that seen previously in patients with RA (Sect. 4.2). Congestive heart failure and demyelinating disease, also associated with the use of TNFα antagonists [39], were not reported in certolizumab pegol recipients in these studies [15, 16].

Treatment with certolizumab pegol was associated with increased levels of creatinine blood phosphokinase in patients with axSpA (Sect. 4.2); however, these elevations were mostly mild to moderate, transient in nature and of unknown clinical significance, with no cases leading to withdrawal [13, 15]. In patients with PsA, increased levels of liver enzymes were seen following certolizumab pegol treatment (Sect. 4.2), which were generally transient and did not require treatment discontinuation [16].

Long-term data in patients with axSpA or PsA are currently limited (up to 48 weeks) and there are no direct head-to-head trials comparing certolizumab pegol with other TNFα antagonists. Furthermore, although well-designed, the RAPID-axSpA and RAPIS-PsA trials have some limitations. For example, RAPID-axSpA was not designed to examine if early treatment with certolizumab pegol could prevent structural changes characteristic of AS [13]. In addition, the outcome measures used in this study, though validated for patients with AS, have not been validated for patients with nr-axSpA [13]. In RAPID-PsA, regional variation in the ACR20 response at week 12 in the placebo group may have underestimated the incremental efficacy of certolizumab pegol (the ACR20 response rates in placebo recipients in South America were substantially higher than rates observed in North America and, Eastern or Western Europe; 63 vs. 13–27 %) [14]. Further well-designed and long-term studies would help to establish the efficacy and safety of certolizumab pegol in patients with axSpA or PsA.

To conclude, two well-designed studies (RAPID-axSpA and RAPID-PsA) showed that certolizumab pegol was effective and generally well tolerated in patients with axSpA or PsA. Although additional long-term and comparative data are needed to position certolizumab pegol with respect to other TNFα antagonists, current evidence indicates that certolizumab pegol is an effective option for patients with axSpA (including those with AS or nr-axSpA) and for patients with PsA.

Data selection sources: Relevant medical literature (including published and unpublished data) on certolizumab pegol was identified by searching databases including MEDLINE (from 1946) and EMBASE (from 1996) [searches last updated 23 May 2014], bibliographies from published literature, clinical trial registries/databases and websites. Additional information was also requested from the company developing the drug.
Search terms: certolizumab pegol, Cimzia, spondylitis, ankylosing, ankylosing spondylitis, axial spondyloarthritis, spondyloarthritis, axSpA, nr-axSpA, psoriatic arthritis.
Study selection: Studies in patients with axial spondyloarthritis or psoriatic arthritis who received certolizumab pegol. When available, large, well designed, comparative trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

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