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Certolizumab pegol

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Abbreviations: ACR, American College of Rheumatology; ADCC, antibody-dependent cell-mediated cytotoxicity; AE, adverse event; CD, Crohn disease; CDAI, Crohn disease activity index; CDC, complement-dependent cytotoxicity; CDEIS, Crohn disease endoscopic index of severity; CERTAIN, certolizumab pegol in the treatment of RA: remission induction and maintenance in patients with low disease activity; CRP, C-reactive protein; CZP, certolizumab pegol; DAS28, disease activity score 28; DLQI, dermatology life quality index; DMARD, disease-modifying antirheumatic drug; EU, european union; Fab', antigen binding fragment; FAS, fatigue assessment scale; FAST4WARD, efficacy and safety of certolizumab pegol—4 weekly dosage in rheumatoid arthritis; FDA, Food and Drug Administration; GES, global evaluation scale; HAQ-DI, health assessment questionnaire-disability index; mTSS, modified total sharp score; MTX, methotrexate; MUSIC, endoscopic mucosal improvement in patients with active Crohn disease treated with certolizumab pegol; NSAID, non-steroidal anti-inflammatory drug; PASI, psoriasis area and severity index; PCDAI, pediatric Crohn disease activity index; PEG, polyethylene glycol; PRECiSE, PEGylated antibody fragment evaluation in Crohn disease: safety and efficacy; RA, rheumatoid arthritis; RAPID, rheumatoid arthritis prevention of structural damage; REALISTIC, RA evaluation in subjects receiving TNF inhibitor certolizumab pegol; SC, subcutaneous; SF-36, short form 36-item health survey; TNFα, tumor necrosis factor alpha; US, united states; VAS, visual analog scale; WELCOME, phase 3b multicentre, 26 week open label trial evaluating the clinical benefit and tolerability of certolizumab pegol induction and maintenance in patients suffering from Crohn disease with prior loss of response or intolerance to infliximab; wk, week; WPS-RA, work productivity survey-rheumatoid arthritis

Certolizumab pegol (Cimzia®) is currently the only PEGylated anti-TNFα biologic approved for the treatment of rheumatoid arthritis and Crohn disease. The product, developed by UCB, is a humanized antigen-binding fragment (Fab') of a monoclonal antibody that has been conjugated to polyethylene glycol. Certolizumab pegol was approved as a treatment for rheumatoid arthritis in the EU, US and Canada in 2009, and as a treatment for Crohn disease in Switzerland in 2007 and the US in 2008. Certolizumab pegol is entering into an increasingly competitive marketplace, especially in rheumatoid arthritis, but clinical data demonstrate benefits across a range of clinical, radiographic and patient reported outcomes.

Introduction

Tumor necrosis factor alpha (TNFα) is a pro-inflammatory cytokine implicated in the pathogenesis of various immunological diseases including rheumatoid arthritis (RA) and Crohn disease (CD). In RA, a disease that affects an estimated 5 million people worldwide,[1] TNFα is a key mediator of the inflammation-induced joint damage that is a hallmark of this disease.[2] Reduction in TNFα levels improves signs and symptoms of RA and other autoimmune diseases such as CD[3,4] and the availability of TNFα-inhibitors has revolutionized treatment of these illnesses.

Despite the fact that TNFα-inhibitors have the same primary mode of action, patient responses to these therapeutics remain variable. The observed lack of response, loss of response over time and tolerability issues suggest the need for additional treatment options.[5,6] One TNFα-receptor fusion protein (etanercept), three anti-TNFα monoclonal antibodies (infliximab, adalimumab and golimumab) and one anti-TNFα PEGylated Fab' (certolizumab pegol) are currently approved as anti-TNFα therapies for autoimmune disorders. Biologics with other modes of action that are marketed for the treatment of RA include abatacept (T cell signaling inhibitor), rituximab (B cell depleting, anti-CD20 antibody), anakinra (IL-1 receptor antagonist) and tocilizumab (anti-interleukin-6 receptor antibody). For CD, certolizumab pegol, infliximab, adalimumab and natalizumab (an antibody that targets the cellular adhesion molecule α4-integrin) are approved therapeutics.

Certolizumab pegol, marketed as Cimzia® by UCB, has demonstrated a fast and lasting effect on the signs and symptoms, inhibition of joint damage and improvement in physical function in RA.[7,8] The product was approved in May 2009 as a monotherapy or for use concomitantly with disease-modifying antirheumatic drugs (DMARDs) for the treatment of moderate-to-severe RA in adult patients by the US Food and Drug Administration (FDA). In September and October 2009, Health Canada and the European Medicines Agency, respectively, approved certolizumab pegol in combination with methotrexate (MTX)

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for patients where the response to DMARDs, including MTX, has been inadequate. In Canada and the European Union (EU), monotherapy can be initiated in case of intolerance to MTX or when continued treatment with MTX is inappropriate. In all countries, the recommended dosing regimen in RA is 400 mg certolizumab pegol administered subcutaneously at weeks 0, 2 and 4, followed by 200 mg every 2 weeks. In the US and Canada, 400 mg certolizumab pegol every 4 weeks can also be considered as a maintenance dose.

Certolizumab pegol has received approval in the US and Switzerland for the reduction of signs and symptoms of CD and maintenance of a clinical response in adult patients with moderate-to-severe active disease who have had an inadequate response to conventional therapy. The dosing for CD is 400 mg certolizumab pegol administered subcutaneously at weeks 0, 2 and 4, followed by 400 mg every 4 weeks in patients who experienced a response to the treatment. The drug is supplied as a liquid formulation in a pre-filled syringe containing a dose of 200 mg. A lyophilized formulation is also available in the US. Self-injection of the liquid formulation by the patient is possible if deemed appropriate by the physician.

Characterization and Preclinical Evaluation

Certolizumab pegol is a novel Fc-free, PEGylated, anti-TNFα monoclonal antibody. The parent antibody was selected from a screen of hybridomas for human TNFα binding. The complementarity determining regions from the murine antibody were then inserted into a human Fab' IgG framework, along with several other framework residues of the variable domain that were essential for maintenance of affinity.[9,10] The certolizumab Fab' was subsequently PEGylated via the site-specific attachment of a 40 kDa polyethylene glycol (PEG) moiety. Certolizumab pegol binds and neutralizes both soluble and transmembrane TNFα[11] and inhibits signaling through both the p55 and p75 TNFα receptors in vitro.[12]

Certolizumab pegol differs from the other TNFα-inhibitors in its lack of an Fc region, which minimizes potential Fc-mediated effects such as complement-dependent cytotoxicity (CDC) or antibody dependent cell-mediated cytotoxicity (ADCC). In vitro studies have shown that adalimumab, infliximab and etanercept induce CDC and ADCC, whereas certolizumab pegol does not.[11] In vitro studies have also demonstrated that certolizumab pegol, unlike other TNFα-inhibitors, does not cause activated peripheral blood lymphocytes to undergo apoptosis and that it inhibits lipopolysaccharide-induced cytokine production to a greater extent than other TNFα-inhibitors, in particular etanercept.[11]

The lack of an Fc region may also be a factor in the prevention of active transfer of certolizumab pegol across the placenta during pregnancy. To evaluate this possibility, reproduction studies were performed in rats using a rodent anti-murine TNFα PEGylated Fab' (cTN3 PF) that was similar in structure to certolizumab pegol, as certolizumab pegol does not bind to mouse or rat TNFα. Reproduction studies were performed in rats at doses up to 100 mg/kg and revealed no evidence of impaired fertility or harm to the fetus due to cTN3 PF. Data on the placental transfer of cTN3 PF in five pregnant rats showed that the PEGylated Fab' was undetectable in 3 out of 5 fetal samples, and detectable at very low levels in the other 2.[13]

A case-study of a 22-year old CD patient who received certolizumab pegol 400 mg every 4 weeks during the second and third trimesters of pregnancy indicated that certolizumab pegol does not appear to be actively transported across the human placenta; at the time of delivery, the mother's blood certolizumab pegol level was 18.83 mcg/ml, whereas the cord blood certolizumab pegol level was 1.65 mcg/ml.[14] The neonate was delivered at 37 weeks gestation, weighed 2,700 g and had no congenital abnormalities. The clinical significance of this finding is currently unknown as there have been no controlled studies with certolizumab pegol in pregnant women. Therefore, certolizumab pegol is classified in the US as pregnancy category B, indicating that animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. The US label advises that the product should only be used during pregnancy if clearly needed, whereas the EU label for certolizumab pegol advises that the product should not be used in pregnant woman at all.

Certolizumab pegol also differs from the other TNFα-inhibitors as it is PEGylated. PEGylation is widely used to improve drug pharmacokinetics and bioavailability.[15,16] It has been demonstrated that PEGylation significantly increases the circulating half-life of Fab' molecules,[17] permitting a minimum dosing interval of 2 weeks for certolizumab pegol.[10] Biofluorescence imaging in arthritic mice has shown that certolizumab pegol preferentially penetrates inflamed tissue compared to non-inflamed tissue, and does so to a greater extent than adalimumab or infliximab.[18] Furthermore, the persistence of drug in the inflamed tissue was more prolonged for certolizumab pegol compared to either adalimumab or infliximab.[18] These phenomena are most likely due to the PEGylation of the molecule, although the persistence in the tissue could also be due to the lack of Fc receptor-mediated recycling of the Fab'. These features of certolizumab pegol may be relevant to its action in RA, although they have not been demonstrated in human patients to date, and consequently the clinical relevance and importance of these animal data are unknown.

In animal models, the 40 kDa PEG moiety is cleaved from the Fab' and is excreted intact via the renal route. At 84 days after drug administration in rats, the mean urinary and fecal excretion was 83%, which was extrapolated to a final total of more than 90%.[19] In a study in healthy humans, unchanged certolizumab pegol accounted for 87–92% of the total PEG present in samples of blood plasma, with only 8–13% present as de-conjugated 40 kDa PEG. This result suggests that PEG is rapidly excreted once cleaved from the Fab' portion of the molecule. The majority of PEG is estimated to be removed by the kidneys, as PEG was readily detected in the urine of all six human subjects in which it was studied.[20]

Clinical Trials Overview

The clinical development program for certolizumab pegol currently includes a total of 47 completed or ongoing clinical

studies: 19 RA studies, 19 CD studies, two psoriasis studies and seven healthy subject studies. In RA, the product has been studied in three published Phase 3 trials (RAPID 1,[7] RAPID 2,[8] and FAST4WARD[21]) and one further completed Phase 3 trial (NCT00544154); it is still being evaluated in five placebo-controlled Phase 3 trials, seven open-label Phase 3 trials and one Phase 4 trial. In CD, three published Phase 3 trials (PRECiSE 1,[22] PRECiSE 2,[23] and WELCOME[24]) and one further Phase 3 trial (CONCiSE) have been completed. In addition, one Phase 2 pediatric trial, one placebo-controlled Phase 3 trial, six open-label Phase 3 trials and one observational registry are ongoing.

Clinical Trials in Rheumatoid Arthritis

The safety and efficacy of certolizumab pegol in moderate-to-severe RA has been assessed in combination with MTX or alone as a monotherapy. In all studies, patients were allowed to continue a stable dose of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose oral glucocorticoids (≤10 mg prednisone or equivalent daily).

Phase 2 study of certolizumab pegol monotherapy in severe RA patients. A double-blind, placebo-controlled, dose-ranging Phase 2 study (CDP870-004)[25] was conducted to test the efficacy of certolizumab pegol in treating advanced RA symptoms. A total of 203 adult patients with active RA who had a mean duration of disease of more than 9 years and had on average received four prior DMARDs were randomized to placebo or to certolizumab pegol at 50 mg, 100 mg, 200 mg or 400 mg subcutaneously every 4 weeks for 12 weeks. The ACR20 (20% improvement of symptoms based on American College of Rheumatology criteria) response rates at week 12 were 21, 20, 34 and 60% for patients treated with certolizumab pegol 50, 100, 200 and 400 mg, respectively, compared to 15% for patients treated with placebo. Similarly, the degree of improvement appeared to be related to the dose of certolizumab pegol administered to patients who showed ACR50 and ACR70 (50 and 70% improvement of symptoms based on American College of Rheumatology criteria, respectively) responses (**Table 1**).[25] In the second section of this study, doses of 600 mg and 800 mg every 4 weeks showed no increase in efficacy compared to results for the 400 mg dose administered every 4 weeks. The study demonstrated that certolizumab pegol was effective in the reduction of signs and symptoms of active RA. The most common adverse events (AEs) reported in this study were headache, nausea and infection.

Phase 3 studies with certolizumab pegol in combination with MTX. Certolizumab pegol has been tested as an add-on therapy to MTX treatment in three completed Phase 3 trials. The two pivotal Phase 3 RAPID (rheumatoid arthritis prevention of structural damage) studies were double-blind, placebo-controlled, multicenter trials that assessed the efficacy and safety of certolizumab pegol in combination with MTX in patients with active RA who had previously had an incomplete response to MTX. In the 52-week RAPID 1 (NCT00152386)[7] and 24-week RAPID 2 (NCT00160602)[8] studies, 982 and 619 patients, respectively, were randomized 2:2:1 to certolizumab pegol 200 mg, certolizumab pegol 400 mg or placebo.

Table 1. Phase 2 study in RA

CDP870-004[25] Phase 2 trial: Active RA patients (n = 203)					
SC CZP or placebo every 4 weeks for 12 weeks.					
Endpoints (week 12)	Placebo	CZP 50 mg	CZP 100 mg	CZP 200 mg	CZP 400 mg
ACR20	15%	21%	20%	34%	60%
ACR50	0%	8%	5%	17%	40%
ACR70	0%	5%	3%	7%	29%

RA, rheumatoid arthritis; SC, subcutaneous; CZP, certolizumab pegol; ACR, American College of Rheumatology.

All subjects continued background MTX. Certolizumab pegol was administered every 2 weeks via subcutaneous injection following an initial loading dose of 400 mg at weeks 0, 2 and 4 in both trials. A lyophilized formulation was administered in the RAPID 1 study, while a liquid formulation was employed in RAPID 2. The patient baseline demographics were comparable between the two RAPID trials. In consideration of disease severity, patients who did not have an ACR20 response at week 12 and week 14 were withdrawn from the study at week 16 in both studies. These patients were eligible for inclusion in the open-label extension studies.

The co-primary endpoints of RAPID 1 were the ACR20 response at week 24 and the mean change from baseline in the van der Heijde modified total Sharp score (mTSS), a radiographic measurement of structural joint damage, at week 52. RAPID 2 had a single primary endpoint of ACR20 response at week 24, with structural joint damage assessment at week 24 as a major secondary endpoint. Certolizumab pegol significantly reduced the signs and symptoms of RA compared to placebo in both RAPID trials. In RAPID 1 the ACR20 response rates at week 24 for the certolizumab pegol 200 mg and 400 mg groups were 58.8 and 60.8%, respectively, compared to 13.6% for the placebo group ($p < 0.001$).[7] The ACR20 response rates at week 24 in RAPID 2 were 57.3 and 57.6% for the 200 mg and 400 mg certolizumab pegol groups, respectively, compared to 8.7% for the placebo group ($p < 0.001$) (**Table 2**).[8]

Certolizumab pegol also significantly inhibited the progression of structural damage in RA patients in the RAPID trials (**Table 2**). At week 52 in RAPID 1, the mean changes in mTSS from baseline for the certolizumab pegol 200 mg and 400 mg treated patients were 0.4 Sharp units and 0.2 Sharp units, respectively, in comparison to 2.8 Sharp units for the placebo group ($p < 0.001$).[7] In RAPID 2, the mean changes in mTSS from baseline at week 24 for the certolizumab pegol 200 mg and 400 mg groups were 0.2 Sharp units ($p < 0.01$) and -0.4 Sharp units ($p < 0.001$), respectively, compared to 1.2 Sharp units for the placebo group.[8]

Physical functioning, a major secondary endpoint in both studies, was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI). In both RAPID 1 and 2, certolizumab pegol-treated patients had a significantly greater reduction in HAQ-DI score (i.e., improved physical functioning), compared to placebo-treated patients (**Table 2**).[7,8] In addition, significantly

Table 2. Major phase 3 studies in RA: RAPID 1, RAPID 2 and FAST4WARD

RAPID 1 (NCT00152386)[7] **Phase 3 trial: Moderate-to-severe RA patients who have had an inadequate response to MTX (n = 982)**				
SC CZP 200 mg (400 mg loading dose at weeks 0, 2 and 4) or 400 mg, or placebo every 2 weeks for 52 weeks. All patients received stable entry dose MTX (≥10 to 25 mg/wk). Study has an open-label extension of 3 years.				
	Endpoints	**Placebo + MTX** (n = 199)	**CZP 200 mg + MTX** (n = 393)	**CZP 400 mg + MTX** (n = 390)
Co-primary	**ACR20 wk 24**	13.6%	58.8% ($p < 0.001$)	60.8% ($p < 0.001$)
	mTSS mean change from baseline wk 52	2.8	0.4 ($p < 0.001$*)	0.2 ($p < 0.001$*)
Selected Secondary	**ACR20 wk 52**	13.1%	53.1% ($p < 0.001$)	54.9% ($p < 0.001$)
	ACR50 wk 52	7.6%	38.0% ($p < 0.001$)	39.9% ($p < 0.001$)
	ACR70 wk 52	3.5%	21.2% ($p < 0.001$)	23.2% ($p < 0.001$)
	mTSS mean change from baseline wk 24	1.3	0.2 ($p < 0.001$)	0.2 ($p < 0.001$)
	HAQ-DI mean change from baseline wk 52	-0.18	-0.60 ($p < 0.001$)	-0.63 ($p < 0.001$)
RAPID 2 (NCT00160602)[8] **Phase 3 trial: Moderate-to-severe RA patients who have had an inadequate response to MTX (n = 619)**				
SC CZP 200 mg (400 mg loading dose at weeks 0, 2 and 4) or 400 mg, or placebo every 2 weeks for 24 weeks. All patients received stable entry dose MTX (≥10 to 25 mg/wk). Study has an open-label extension of 3 years.				
	Endpoints at week 24	**Placebo + MTX** (n = 127)	**CZP 200 mg + MTX** (n = 246)	**CZP 400 mg + MTX** (n = 246)
Primary	**ACR20**	8.7%	57.3% ($p < 0.001$)	57.6% ($p < 0.001$)
Selected Secondary	**ACR50**	3.1%	32.5% ($p < 0.001$)	33.1% ($p < 0.001$)
	ACR70	0.8%	15.9% ($p \leq 0.01$)	10.6% ($p \leq 0.01$)
	mTSS mean change from baseline	1.2	0.2 ($p \leq 0.01$*)	-0.4 ($p \leq 0.001$*)
	HAQ-DI mean change from baseline	-0.14	-0.50 ($p < 0.001$)	-0.50 ($p < 0.001$)
FAST4WARD (NCT00548834)[21] **Phase 3 trial: Moderate-to-severe RA patients who have failed ≥1 prior DMARD (n = 220)**				
SC CZP or placebo every 4 weeks for 24 weeks. No concomitant DMARD therapy.				
	Endpoints at week 24	**Placebo** (n = 109)	**CZP 400 mg** (n = 111)	
Primary	**ACR20**	9.3%	45.5% ($p < 0.001$)	
Selected Secondary	**ACR50**	3.7%	22.7% ($p < 0.001$)	
	ACR70	0%	5.5% ($p \leq 0.05$)	
	HAQ-DI mean change from baseline	0.13	-0.36 ($p < 0.001$)	

p values calculated by odds ratios, unless indicated. *by rank analysis. RA, rheumatoid arthritis; MTX, methotrexate; SC, subcutaneous; CZP, certolizumab pegol; wk, week; ACR, American College of Rheumatology; mTSS, modified total Sharp score; HAQ-DI, Health Assessment Questionnaire-Disability Index; DMARD, disease-modifying antirheumatic drug.

greater reductions in pain (measured using a visual analog scale [VAS]) and fatigue (measured using the Fatigue Assessment Scale [FAS]) and improvements in health-related quality of life (measured using the Short Form 36-item Health Survey [SF-36]) were seen with certolizumab pegol plus MTX therapy compared to MTX monotherapy.[26,27]

In both RAPID studies, a fast onset of response to certolizumab pegol treatment was seen. Certolizumab pegol with MTX had significantly greater ACR20 response compared to placebo with MTX at week 1 ($p < 0.001$) in both trials, and significantly greater ACR50 response than placebo at week 2 for RAPID 1 ($p < 0.01$) and week 6 for RAPID 2 ($p \leq 0.01$). These differences remained significant through the remainder of the trials. Significant inhibition of progression of structural damage was seen as early as week 16 in certolizumab pegol-treated patients who withdrew from the trials due to lack of ACR20 response.[7,8] In addition, an early response by week 12 was found to be predictive of long-term low disease activity; at week 12 in RAPID 1, 57% of patients taking certolizumab pegol 200 mg plus MTX achieved a disease activity (DAS28) response of at least 1.2 units improvement from baseline and these patients were more likely to achieve low disease activity (DAS28 ≤ 3.2) at one year compared to patients who did not achieve a DAS28 response at week 12 (37 vs. 6%).[28]

In the RAPID trials and their extension studies, RA-dependent productivity at work and in the home was measured every 4 weeks using the validated Work Productivity Survey (WPS-RA).[29] Over one year in RAPID 1, patients treated with certolizumab pegol 200 mg plus MTX gained an annual average of 52.1 full days of household activities compared to placebo with MTX.[30] Similarly, patients treated with certolizumab pegol 200 mg plus MTX in RAPID 1 gained an annual average of 42.0 work days

versus placebo with MTX.[30] Results for the 200 mg dose were comparable to those for the 400 mg dose of certolizumab pegol, and those of the RAPID 2 trial.

The majority of AEs reported in the RAPID trials were mild-to-moderate in nature. The most common AE leading to withdrawal was infection. Serious infection was observed more frequently in the certolizumab pegol arms than in the placebo arm; in pooled RAPID 1 and 2 populations, serious infections occurred at the rate of 6.0 and 7.1 per 100 patient-years in the certolizumab pegol 200 mg and 400 mg plus MTX groups, respectively, compared to 1.5 per 100 patient-years in the placebo plus MTX group.[26] The most common serious infections were tuberculosis, pneumonia and erysipelas. This safety profile is similar to that reported for the other TNFα-inhibitors. Of note, injection site pain was reported in very few cases with either dose of certolizumab pegol in both studies (<3 new cases per 100 patient-years, compared to none in the placebo plus MTX group).

Overall, in the RAPID studies certolizumab pegol plus MTX demonstrated rapid and sustained reductions in the signs and symptoms of moderate-to-severe RA, inhibition of the progression of structural joint damage and improved physical functioning, when the response to MTX had previously been inadequate. Certolizumab pegol was also shown to have a favorable risk-benefit profile. The open-label extension studies of the RAPID trials (NCT00175877 and NCT00160641), in which all patients received 400 mg drug for at least 6 months and then switched to 200 mg every 2 weeks, are ongoing. The two-year data from the RAPID 1 extension demonstrate that the ACR20/50/70 response rates and the inhibition of radiographic progression were sustained throughout two years in patients who had received certolizumab pegol and completed the 52 weeks of RAPID 1.[31]

A 24-week double-blind, parallel group Phase 3 study (NCT00544154)[32] assessed the efficacy of certolizumab pegol 400 mg plus MTX dosed every 4 weeks in RA patients who had active disease despite receiving MTX previously. The study randomized 247 subjects to receive either certolizumab pegol 400 mg or placebo subcutaneously every 4 weeks. Both groups continued to receive MTX at their standard dose. The study achieved its primary endpoint of a significantly greater ACR20 responder rate at week 24 in the certolizumab pegol plus MTX group than in the placebo plus MTX group ($p < 0.001$) (**Table 3**).[32] The open-label extension (NCT00160693) is currently ongoing.

Phase 3 studies with certolizumab pegol monotherapy. To assess the efficacy of certolizumab pegol monotherapy, the Phase 3 FAST4WARD (efficacy and safety of certolizumab pegol—4 weekly dosage in rheumatoid arthritis) study (NCT00548834)[21] evaluated the drug in 220 patients who had failed treatment with at least one prior DMARD (**Table 2**). In this 24-week, multicenter, double-blind, placebo-controlled study, the subjects were randomized to receive subcutaneous lyophilized certolizumab pegol 400 mg (n = 111) or placebo (n = 109) every 4 weeks. Patients were allowed to continue their baseline dose of NSAIDs or glucocorticoids. The FAST4WARD primary outcome measure was the ACR20 response rate at week 24, which was 45.5% for certolizumab pegol-treated patients and 9.3% for the placebo group ($p < 0.001$).[21] The secondary endpoints, which included ACR50 and ACR70 response, physical functioning, ACR component scores and patient-reported outcomes (health-related quality of life, pain and fatigue), all indicated significant benefits of certolizumab pegol compared to placebo. Overall, FAST4WARD demonstrated that treatment with certolizumab pegol 400 mg monotherapy every 4 weeks compared to placebo improved the signs and symptoms of active RA in patients who had previously failed at least one prior DMARD. The rapidity of certolizumab pegol onset of action was also apparent in FAST4WARD; by week 1 both the ACR20 and ACR50 response rates were significantly greater in the certolizumab pegol group than in the placebo group ($p \leq 0.05$). In particular, the HAQ-DI physical function assessment and VAS pain scale mean changes from baseline were also significantly greater after only 1 week in the certolizumab pegol arm compared to the placebo arm ($p < 0.001$).[21] Treatment-emergent AEs were reported in 57.8% of placebo-treated patients and 75.7% of certolizumab pegol-treated patients; the majority of AEs were mild or moderate in nature. Serious infections were reported in 0% of patients on placebo and 1.8% of patients treated with certolizumab pegol. No cases of tuberculosis or opportunistic infections were reported. Injection site pain and injection site reactions were reported in a low proportion of certolizumab pegol-treated patients (0 and 4.5%, respectively).[21] In comparison, a greater proportion of patients receiving placebo reported injection site pain or reaction (1.8 and 13.8%, respectively), with this difference resulting from the use of sorbitol as placebo.[21]

Ongoing phase 3 studies in patients with RA. Several phase 3 studies with certolizumab pegol in RA are ongoing (**Table 3**). A large-scale Phase 3b trial, REALISTIC (RA evaluation in subjects receiving TNF inhibitor certolizumab pegol; NCT00717236), will evaluate the efficacy of subcutaneous certolizumab pegol 200 mg (after an initial loading dose of 400 mg at weeks 0, 2 and 4) in an estimated 1,000 subjects. It will have a 12-week double-blind period followed by an open-label extension that is due to end in 2010.

Dose Flex (NCT00580840) is a Phase 3b trial that is currently recruiting and will evaluate the efficacy of two different maintenance treatment regimens, certolizumab pegol 200 mg every 2 weeks or 400 mg every 4 weeks, in addition to background MTX. There will be an open-label run-in period when patients will receive 400 mg certolizumab pegol at weeks 0, 2 and 4 and then 200 mg certolizumab pegol plus placebo every 2 weeks from weeks 6 to 16, before the patients who respond (based on ACR20 response at week 16) are randomized at week 18 to one of the two certolizumab pegol treatment regimens, or to placebo for up to an additional 16 weeks. Subjects may enter the open-label extension study (NCT00753454) in which they will receive certolizumab pegol at 200 mg every 2 weeks.

An ongoing placebo-controlled Phase 3b trial, CERTAIN (Certolizumab pegol in the treatment of RA: remission induction and maintenance in patients with low disease activity; NCT00674362), will assess the efficacy of certolizumab pegol (200 mg every 2 weeks after loading with 400 mg at weeks 0, 2 and 4) in combination with DMARDs in patients with a moderate-to-low RA disease activity. This 52-week study has an estimated

Table 3. Additional studies in RA

Clinical study number/name	Study phase	Study details	Status
NCT00175877 RAPID 1 extension[13]	Phase 3 extension	Open-label extension to NCT00152386 (RAPID 1). 400 mg CZP q2w + MTX for at least 6 months. 200 mg CZP q2w + MTX thereafter.	Ongoing
NCT00160641 RAPID 2 extension	Phase 3 extension	Open-label extension to NCT00160602 (RAPID 2). 400 mg CZP q2w + MTX for at least 6 months. 200 mg CZP q2w + MTX thereafter.	Ongoing
NCT00544154[32]	Phase 3	24 wk, double-blind, placebo-controlled study. Placebo (+MTX) or 400 mg CZP (+MTX) q4w. N = 247 adult active RA patients. Primary endpoint: ACR20 at wk 24 (achieved).	Completed
NCT00160693	Phase 3 extension	Open-label extension to NCT00544154	Ongoing
NCT00717236 REALISTIC	Phase 3b	12 wk, double-blind, placebo-controlled study followed by an open-label extension. Placebo q2w or 400 mg CZP at wks 0, 2 and 4, followed by 200 mg CZP q2w thereafter. N = 1000 (estimated) adult established RA patients. Primary endpoint: ACR20 at wk 12.	Ongoing
NCT00580840 Dose Flex	Phase 3b	34 wk, double-blind, placebo-controlled study. Open-label run-in: 400 mg CZP at wks 0, 2 and 4 (+MTX). 200 mg CZP q2w thereafter (+MTX). Responders at wk 16 randomized to 200 mg CZP q2w, 400 mg CZP q4w, placebo q2w or placebo q4w (+MTX) for a further 16 wks. N = 335 (estimated) adult active RA patients. Primary endpoint: ACR20 at wk 34.	Ongoing
NCT00753454	Phase 3 extension	Open label extension to NCT00580840 (Dose Flex).	Ongoing
NCT00674362 CERTAIN	Phase 3b	52 wk, double-blind, placebo-controlled study. Placebo q2w (+DMARDs) or 400 mg CZP at wks 0, 2 and 4, followed by 200 mg CZP q2w (+DMARDs) thereafter. N = 170 (estimated) adult RA patients with moderate-to-low disease activity. Primary endpoint: clinical remission at both wks 20 and 24.	Ongoing
NCT00843778	Phase 3 extension	Open label extension to NCT00674362 (CERTAIN)	Ongoing
NCT00791921	Phase 3	Japanese, 24 wk, double-blind, placebo-controlled study. Placebo q2w or 400 mg CZP at wks 0, 2 and 4, followed by 200 mg CZP q2w thereafter. N = 200 (estimated) active RA patients >20 years of age. Co-primary endpoints: ACR20 at wks 12 and 24.	Ongoing
NCT00850343	Phase 3 extension	Japanese open-label extension to NCT00791921	Ongoing
NCT00993317	Phase 3	Japanese, 24 wk, double-blind, placebo-controlled study. Placebo q2w (+MTX) or 400 mg CZP at wks 0, 2 and 4, followed by 200 mg CZP q2w (+MTX) thereafter. N = 126 (estimated) adult active RA patients. Primary endpoint: ACR20 at wk 24.	Ongoing
NCT00851318	Phase 3 extension	Japanese open-label extension to NCT00993317	Ongoing
NCT00993668	Phase 4	6 wk single-blind, placebo-controlled study to assess the effect of CZP on the antibody response to a T cell dependent and a T cell independent immunization in RA patients. Placebo or 200 mg CZP q2w. Pneumococcal and influenza vaccines administered. N = 270 (estimated) adult active RA patients Co-primary endpoints: • % of subjects without baseline protective titers achieving a ≥2-fold titer increase in ≥3 of six pneumococcal antigens at wk 6. • % of subjects without baseline protective titers achieving a ≥4-fold titer increase in ≥2 of three influenza antigens at wk 6.	Ongoing

CZP was administered subcutaneously in all studies. RA, rheumatoid arthritis; wk, week; CZP, certolizumab pegol; MTX, methotrexate; q2w, every 2 weeks; q4w, every 4 weeks; DMARD, disease-modifying antirheumatic drug.

Table 4. Major phase 3 studies in CD: PRECiSE 1 and PRECiSE 2

PRECiSE 1 (NCT00152490)[22] **Phase 3 trial: Moderate-to-severe CD patients (n = 662)**			
SC CZP (400 mg) or placebo at weeks 0, 2 and 4 and then every 4 weeks for 26 weeks. Completers entered PRECiSE 3 and withdrawers entered PRECiSE 4 ongoing open-label studies of 7-years duration.			
	Endpoints	**Placebo**	**CZP 400 mg**
Co-primary	**CDAI100 response wk 6 (baseline CRP ≥10 mg/L)**	26% (n = 154)	37% (p = 0.04) (n = 145)
	CDAI100 response wk 6 and wk 26 (baseline CRP ≥10 mg/L)	12% (n = 154)	22% (p = 0.05) (n = 144)
Selected Secondary	**Remission (CDAI ≤150) wk 6 (baseline CRP ≥10 mg/L)**	17% (n = 154)	22% (p = NS) (n = 146)
	Remission (CDAI ≤150) wk 6 and wk 26 (baseline CRP ≥10 mg/L)	8% (n = 154)	13% (p = NS) (n = 145)
PRECiSE 2 (NCT00152425)[23] **Phase 3 trial: Moderate-to-severe CD patients (n = 668, responders at week 6 = 428)**			
Induction therapy: SC CZP (400 mg) at weeks 0, 2 and 4. Responders at week 6 (n = 428) then received placebo or CZP (400 mg) SC every 4 weeks to week 26. Completers entered PRECiSE 3 and withdrawers entered PRECiSE 4 ongoing open-label studies of 7-years duration.			
	Endpoints at week 26	**Placebo**	**CZP 400 mg**
Primary	**CDAI100 response (baseline CRP ≥10 mg/L)**	34% (n = 101)	62% (p < 0.001) (n = 112)
Selected Secondary	**CDAI100 response (all patients)**	36% (n = 210)	63% (p < 0.001) (n = 215)
	Remission (CDAI ≤150) (all patients)	29% (n = 210)	48% (p < 0.001) (n = 215)

CD, Crohn disease; SC, subcutaneous; CZP, certolizumab pegol; CDAI, Crohn disease activity index; CDAI100, decrease of at least 100 CDAI points; wk, week; CRP, C-reactive protein; NS, not significant.

enrollment of 170 subjects. Those who complete NCT00674362 may enter the open-label extension study NCT00843778.

Two ongoing Phase 3 studies (NCT00791921 and NCT00993317) that further assess the efficacy of certolizumab pegol as a monotherapy and as an add-on therapy to MTX in RA, respectively, are being carried out in Japan by Otsuka Pharmaceuticals, UCB's Japanese development partner. Subjects from these studies may be eligible to enter their respective open-label safety extensions (NCT00850343 and NCT00851318).

Phase 4 study in patients with RA. An ongoing Phase 4 study (NCT00993668) will assess the immune response to influenza and pneumococcal vaccines in patients with RA who are taking certolizumab pegol. The study will include an estimated 270 subjects and is due to end in October 2010 (**Table 3**).

Clinical Trials in Crohn Disease

Phase 3 studies in patients with active CD. Two published Phase 3 trials, PRECiSE 1 (PEGylated antibody fragment evaluation in Crohn disease: safety and efficacy 1; NCT00152490)[22] and PRECiSE 2 (NCT00152425),[23] studied the efficacy and safety of certolizumab pegol in the treatment of patients with moderately-to-severely active CD (**Table 4**). Both studies had a 26-week duration and permitted background therapy with immunosuppressants and low dose oral glucocorticoids.

The design of PRECiSE 1 is distinctive amongst biologic trials in CD because patients were randomized to drug or placebo from baseline, whereas previous studies of drugs for CD involved randomization of only patients who responded to treatment. PRECiSE 1 also evaluated both induction and maintenance of response in a single trial rather than in separate studies. The results of PRECiSE 1 should therefore not be compared to those of other CD trials. In total, 662 subjects were randomized 1:1 to receive subcutaneously either 400 mg certolizumab pegol or placebo at weeks 0, 2 and 4, and then every 4 weeks thereafter. The co-primary endpoints were induction of a clinical response at week 6 and the proportion of patients that had a response at both weeks 6 and 26 in patients with a baseline serum C-reactive protein (CRP) level of at least 10 mg per liter (mg/L). A response was defined as a decrease in Crohn Disease Activity Index (CDAI) score of at least 100 points. The primary endpoints were met; 37% of patients taking certolizumab pegol who had a baseline CRP level of at least 10 mg/L had a response at week 6 compared to 26% of placebo-treated patients (p = 0.04) and 22% of certolizumab pegol-treated patients had a response at both weeks 6 and 26 compared to 12% for the placebo group (p = 0.05).[22] However, the remission rates (CDAI score of ≤150) at weeks 6 and 26 between the two groups did not differ significantly.[22] The PRECiSE 1 study conclusion was that induction and maintenance therapy with certolizumab pegol in patients with moderate-to-severe CD offered a modest improvement in response rates compared to placebo.

PRECiSE 2,[23] evaluated the efficacy of certolizumab pegol in the maintenance of a response in patients who responded at week 6 following open-label induction therapy. CD patients (n = 668) received certolizumab pegol 400 mg subcutaneously at weeks 0, 2 and 4 as open-label induction therapy. Responders at week 6, defined as those who had a decrease of at least 100 points on the CDAI (428 of 662 subjects; 64.7%), were then randomized 1:1 to receive either placebo or certolizumab pegol 400 mg every 4 weeks. In patients who had a baseline CRP level of at least 10 mg/L and achieved a response at week 6, 62% of certolizumab pegol-treated patients versus 34% of placebo-treated patients had a response at week 26 (p < 0.001) (primary endpoint).[23] The overall population also showed a significantly greater proportion of patients achieving a response, as well as remission, at week

26 in the certolizumab pegol group compared to the placebo group.[23] The conclusion of PRECiSE 2 was that patients with moderate-to-severe CD who had achieved a clinical response to certolizumab pegol by week 6 were more likely to have a maintained response, or achieve remission, when continuing with certolizumab pegol than if switched to placebo.

PRECiSE 1 and 2 both demonstrated that certolizumab pegol had a favorable risk-benefit profile; 10% and 6% of patients in the certolizumab pegol groups in PRECiSE 1 and 2, respectively, reported a serious AE compared to 7% in the placebo group in both trials. Serious infection occurred in 2 and 3% of patients in the certolizumab pegol groups in PRECiSE 1 and 2, respectively, compared to <1% in the placebo groups in both trials.[22,23]

Two ongoing, 7-year, open-label studies have evolved from PRECiSE 1 and 2; PRECiSE 3 (NCT00160524) involves 595 subjects who completed PRECiSE 1 and 2, whereas PRECiSE 4 (NCT00160706) involves 310 subjects who withdrew from the first two studies due to exacerbation of CD. All patients in the open-label studies receive certolizumab pegol 400 mg subcutaneously every 4 weeks. The PRECiSE four subjects also received the loading dose of certolizumab pegol again at the start of the open-label study. Of the 141 certolizumab pegol-treated patients who completed PRECiSE 2 and entered PRECiSE 3, 75% were in remission at the start of PRECiSE 3.[33] After 1.5, 2.5 and 3.5 years of continued certolizumab pegol treatment, the remission rates were 56% (79/141), 38% (54/141) and 31% (44/141), respectively, based on last observation carried forward analysis.[33] Data from PRECiSE 4 have demonstrated that in patients who experienced disease exacerbation during maintenance treatment in PRECiSE 2, re-induction with certolizumab pegol may be effective to regain response and remission.[34] The continuing PRECiSE extension studies will provide further long-term assessment of the efficacy and safety of certolizumab pegol in the treatment of moderate-to-severe CD.

A short, randomized, placebo-controlled Phase 3 study (NCT00552058) aimed to provide further evidence for the efficacy and safety of certolizumab pegol in the induction of remission in patients with CD. A total of 421 subjects were enrolled in this study, in which the primary endpoint was the proportion of subjects achieving clinical remission (CDAI score ≤150) at 6 weeks. Patients received either certolizumab pegol 400 mg or placebo at weeks 0, 2 and 4 (**Table 5**). This study has a 5-year open-label extension (NCT00552344) that will assess the long-term safety and efficacy of certolizumab pegol in CD patients.

The Phase 3b study WELCOME (26 week open label trial evaluating the clinical benefit and tolerability of certolizumab pegol induction and maintenance in patients suffering from Crohn disease with prior loss of response or intolerance to infliximab; NCT00308581)[24] was designed to assess the clinical efficacy of certolizumab pegol at week 6 following open-label induction therapy in patients with active CD who had previously responded to infliximab but were no longer responding or had developed intolerance (**Table 5**). The major secondary outcome was the comparison of two maintenance dose regimens: 400 mg every 2 or 4 weeks until week 26. The open-label induction schedule was 400 mg subcutaneous certolizumab pegol at weeks 0, 2 and 4. Responders (≥100 CDAI point decrease, i.e., CDAI 100) at week 6 were then randomized to 400 mg certolizumab pegol every 2 weeks or every 4 weeks for 26 weeks. The primary endpoint was response rate at week 6. At Week 6, 62% of 539 enrolled patients achieved CDAI 100.[24] At week 26 there was no significant difference between the 2-weekly and 4-weekly dosing regimens in the proportion of patients who achieved CDAI 100 (36.6% and 39.9%, respectively, $p = 0.55$).[24] The extension study (NCT00333788) is ongoing.

A 36-week Phase 3b study, known as CONCiSE (NCT00349752), assessed the corticosteroid-sparing effect of certolizumab pegol in patients with CD (**Table 5**). The primary objective was to compare certolizumab pegol and placebo treatments for the proportion of patients who were successfully withdrawn from a forced-taper of corticosteroids (prednisone and prednisolone) and are in disease remission (CDAI score ≤150) at week 36. Although the target sample size for primary efficacy analysis was 352, the study had to be prematurely stopped due to slow enrollment (174 patients enrolled). The open-label extension of this study (NCT00356408) is ongoing.

An open-label Phase 3b study in CD, MUSIC (endoscopic mucosal improvement in patients with active Crohn disease treated with certolizumab pegol; NCT00297648),[35] was carried out to evaluate the effect of certolizumab pegol on endoscopic mucosal improvement (**Table 5**). The product was assessed in 89 subjects using the Crohn Disease Endoscopic Index of Severity (CDEIS) score. Subjects received certolizumab pegol 400 mg at weeks 0, 2 and 4, and then 400 mg every 4 weeks thereafter. After week 10, the dose could be escalated to certolizumab pegol 400 mg every 2 weeks if there had been a loss of response. The primary endpoint, change from baseline in CDEIS score at week 10, was achieved; by week 10 there was a mean change in CDEIS from baseline of -6.5 points (95% confidence interval -7.6 to -5.3, $p < 0.0001$).[35] Certolizumab pegol is the first anti-TNFα to show endoscopic improvement in CD at such an early time-point.

Ongoing phase 2 pediatric study. Certolizumab pegol is currently being studied in children and adolescents with CD in a Phase 2 trial (NCT00899678). This 62-week study is still recruiting; it is estimated that it will enroll 160 subjects aged 6–17 years. Patients 20–40 kg and over 40 kg will receive an induction dose of 200 or 400 mg, respectively, at weeks 0, 2 and 4. Following this induction, the patients will be randomized to a high or low dose regimen: in the high dose arm, patients over 40 kg will receive certolizumab pegol 400 mg and patients 20–40 kg will receive 200 mg every 4 weeks, while in the low dose arm patients over 40 kg and patients 20–40 kg will receive certolizumab pegol 200 mg and 100 mg, respectively, every 4 weeks. The primary outcome will be the proportion of patients in clinical remission (a Pediatric Crohn Disease Activity Index (PCDAI) score ≤10) at week 62 (**Table 5**).

Observational registry. An observational registry, SECURE (NCT00844285), is tracking the safety outcomes of CD patients currently being prescribed certolizumab pegol. Each patient will be tracked for at least 10 years, even if they discontinue certolizumab pegol therapy. The estimated enrollment is 4,000 patients, consisting of patients on certolizumab pegol and control patients

Table 5. Additional studies in CD

Clinical study number/name	Study phase	Study details	Status
NCT00160524 PRECiSE 3[33]	Phase 3 extension	7 year, open-label study of patients who completed NCT00152490 (PRECiSE 1) and NCT00152425 (PRECiSE 2). 400 mg CZP q4w.	Ongoing
NCT00160706 PRECiSE 4[34]	Phase 3 extension	7 year, open-label study of patients who withdrew from NCT00152490 (PRECiSE 1) and NCT00152425 (PRECiSE 2) due to exacerbation of CD. 400 mg CZP q4w.	Ongoing
NCT00552058	Phase 3	6 wk, double-blind, placebo-controlled study. 400 mg CZP or placebo at wks 0, 2 and 4. N = 421 adult active CD patients. Primary endpoint: % patients in remission at wk 6.	Completed
NCT00552344	Phase 3 extension	5 year open-label extension to NCT00552058. 400 mg CZP q4w.	Ongoing
NCT00308581 WELCOME[24]	Phase 3b	26 wk, open-label study of patients who had previously failed with infliximab. 400 mg CZP at wks 0, 2 and 4, followed by 400 mg CZP q2w or q4w. N = 539 adult active CD patients. Primary endpoint: Response rate at wk 6 (62% patients achieved CDAI100). Secondary endpoint: Comparison of the two maintenance dose regimens (no significant difference between % patients achieving CDAI100 at wk 26, p = 0.55).	Completed
NCT00333788	Phase 3 extension	Open-label extension to NCT00308581 (WELCOME).	Ongoing
NCT00349752 CONCiSE	Phase 3b	36 wk, double-blind, placebo-controlled study to assess the corticosteroid sparing effect of CZP in CD patients. Placebo or 400 mg CZP at wks 0, 2 and 4 and then placebo or 400 mg CZP q4w thereafter. Patients followed a corticosteroid forced-taper regimen. N = 174 adult CD patients with moderate-to-severe disease. Primary endpoint: % patients who remained off corticosteroids are in remission at wk 36.	Completed (prematurely terminated due to slow enrollment)
NCT00356408	Phase 3 extension	Open-label extension to NCT00349752 (CONCiSE)	Ongoing
NCT00297648 MUSIC[35]	Phase 3b	54 wk open-label study to assess endoscopic mucosal healing in CD patients. 400 mg CZP at wks 0, 2 and 4, followed by 400 mg CZP q4w thereafter. Escalated to 400 mg CZP q2w if there has been a loss of response. N = 89 adult active CD patients suffering from at least 2 segments with endoscopic ulcerative lesions with baseline CDEIS ≥8. Primary endpoint: Change from baseline CDEIS at wk 10 (achieved).	Completed
NCT00899678	Phase 2	62 wk, open-label pediatric study. **Loading:** Patients 20–40 kg: 200 mg wk 0, 2 and 4 Patients >40 kg: 400 mg wk 0, 2 and 4 Treatment arms (wks 6–62): **High dose:** Patients 20–40 kg: 200 mg q4w Patients >40 kg: 400 mg q4w **Low dose:** Patients 20–40 kg: 100 mg q4w Patients >40 kg: 200 mg q4w N = 160 (estimated) CD patients aged 6–17 years. Primary endpoint: % patients in remission at wk 62.	Ongoing
NCT00844285 SECURE	Observational registry	Observational registry for CD patients in the USA. N = 4000 CD patients; CZP cohort and non-CZP comparators (estimated).	Ongoing

CZP was administered subcutaneously in all studies. CD, Crohn disease; wk, week; CZP, certolizumab pegol; q2w, every 2 weeks; q4w, every 4 weeks; CDAI, Crohn disease activity index; CDAI100, decrease of at least 100 CDAI points; CDEIS, Crohn Disease Endoscopic Index of Severity.

Table 6. Phase 2 study in psoriasis

NCT00245765[36,37] Phase 2 trial: Moderate-to-severe psoriasis patients (n = 176)				
SC CZP 200 mg (400 mg initial dose) or 400 mg, or placebo every 2 weeks for 12 weeks.				
Endpoints at week 12		**Placebo** (n = 59)	**CZP 200 mg** (n = 59)	**CZP 400 mg** (n = 58)
Co-primary	**PASI 90**	1.7%	39.0% (p < 0.001)	46.6% (p < 0.001)
	GES marked improvement	13.5%	80.8%	90.2%
Selected Secondary	**DLQI mean change from baseline**	0.8	8.3 (p < 0.001)	9.9 (p < 0.001)

SC, subcutaneous; CZP, certolizumab pegol; PASI, Psoriasis Area and Severity Index; GES, Global Evaluation Scale; DLQI, Dermatology Life Quality Index.

Table 7. Additional study in psoriasis

Clinical study number/name	Study phase	Study details	Status
NCT00329303	Phase 2 extension	Extension of NCT00245765 to assess the re-treatment of those patients who responded to treatment in the first trial but relapsed during the no-treatment period. No placebo patients from NCT00245765 entered this study due to their lack of response in the first study. Patients continued with their dosing schedule from NCT00245765. N = 75 active CD patients from NCT00245765. Primary endpoint: No difference between the PASI scores at the end of the initial and the re-treatment periods (achieved).	Completed

CZP was administered subcutaneously. CD, Crohn disease; PASI, Psoriasis Area and Severity Index.

who are on any medication for CD apart from certolizumab pegol and who have never taken certolizumab pegol (**Table 5**).

Clinical Trials in Psoriasis

Two Phase 2 studies with certolizumab pegol have been completed in patients with chronic plaque psoriasis. The first (NCT00245765),[36,37] was a multicenter, dose-response, randomized, double-blind, placebo-controlled study that aimed to evaluate the efficacy and safety of certolizumab pegol at two different dose regimens (**Table 6**). Psoriasis patients (n = 176) received 12 weeks of treatment and were then followed for an additional 12 weeks with no certolizumab pegol treatment. Subjects were randomized to receive subcutaneously either certolizumab pegol 200 mg (after an initial dose of 400 mg at week 0), certolizumab pegol 400 mg or placebo every 2 weeks. The co-primary endpoints were PASI 90 (Psoriasis Area and Severity Index ≥90% decrease from baseline) and marked improvement on the global evaluation scale (GES) at week 12. Significantly more patients treated with certolizumab pegol achieved a PASI 90 response at week 12 than patients treated with placebo (200 mg, 39.0% (p < 0.001); 400 mg, 46.6% (p < 0.001); placebo, 1.7%).[36] Of the patients treated with certolizumab pegol 200 or 400 mg, 80.8 and 90.2% respectively achieved a marked improvement on the GES, compared to 13.5% of patients treated with placebo.[36] Psoriasis patients treated with certolizumab pegol also experienced a significantly greater mean improvement from baseline in health-related quality of life than placebo-treated patients.[37] It was concluded from this Phase 2 study that certolizumab pegol has significant superior efficacy over placebo in the treatment of moderate-to-severe chronic plaque psoriasis. In addition, certolizumab pegol was well tolerated and the frequency of AEs was similar across all treatment groups.[36]

The second study (NCT00329303) was a follow-up of the first study that aimed to evaluate the efficacy and safety of re-treatment with certolizumab pegol in psoriasis patients who responded to treatment in NCT00245765 but subsequently relapsed when treatment was discontinued (**Table 7**). Subjects (n = 75) received the same certolizumab pegol dose regimen as they did in the first psoriasis trial, after an initial dose of 400 mg. No placebo subjects entered the second trial, due to their relative lack of response in the first trial. There was no clinically significant difference between the mean and median PASI scores between the first treatment period (week 12) and the re-treatment. Overall, fewer patients reported AEs during the re-treatment period.

Summary

Certolizumab pegol (Cimzia®) is currently the only PEGylated anti-TNFα approved for the treatment of RA and CD. Four other TNFα-inhibitors, infliximab (Remicade), adalimumab (Humira), etanercept (Enbrel) and golimumab (Simponi), for the treatment of RA are direct market competitors of certolizumab pegol, and biologics with other modes of action are also on the market for the treatment of RA, e.g., abatacept (Orencia), rituximab (Rituxan, MabThera), anakinra (Kineret) and tocilizumab (Actemra). Three biologic products, infliximab, adalimumab and natalizumab (Tysabri), are approved as treatments for CD.

Certolizumab pegol has been evaluated in numerous Phase 3 studies and results have indicated that the product has a favorable

benefit to risk ratio when used as directed. The product has a similar safety profile to other TNFα-inhibitors and in particular has a favorable low level of injection site pain. Certolizumab pegol is available with an ergonomically designed syringe, which may facilitate use by RA patients with different grip styles and strengths.[38]

Declaration of Interest

The authors are employees of UCB, Inc., which markets certolizumab pegol.

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