

## Certolizumab pegol in the treatment of Crohn's disease: evidence from the PRECiSE clinical trial program

**Clin. Invest.** (2011) 1(3), 459–465

Certolizumab is an IgG4-binding pegylated humanized Fab' fragment that is the third anti-TNF- $\alpha$  agent available for the treatment of Crohn's disease (CD). It has clearly demonstrated efficacy in the maintenance of CD disease response and remission, with recent data demonstrating that it also has long-term efficacy in CD with no new concerns about its safety. Evidence is mounting for a role of certolizumab pegol in patients who have lost response to infliximab and adalimumab and for a role in the treatment of perianal fistulizing disease. Unfortunately, the pivotal double-blinded, placebo-controlled study investigating its efficacy in the induction of response in CD did not fully meet its primary end points, making registration of this agent for use in CD difficult.

**Keywords:** anti-TNF • certolizumab pegol • Crohn's disease  
• Crohn's Disease Activity Index • C-reactive protein • therapy • TNF- $\alpha$

TNF- $\alpha$  is a proinflammatory cytokine involved in the pathogenesis of the chronic intestinal inflammation observed in Crohn's disease (CD) with increased expression observed in colonic tissue, the fecal stream and the systemic circulation in the presence of active intestinal inflammation [1–5]. Its expression, as well as that of other proinflammatory cytokines (IL-6 and IL-1 $\beta$ ), is increased through the activation of nucleotide-binding oligomerization domain and Toll-like receptors, which signal through the nuclear factor- $\kappa$ B (NF- $\kappa$ B) pathway. At present there are three anti-TNF agents that have demonstrated efficacy in the management of CD. The first two are infliximab (a chimeric monoclonal antibody) and adalimumab (a fully human monoclonal antibody) both of which are IgG1-binding antibodies. The third is certolizumab pegol, an IgG4 binding pegylated humanized Fab' fragment. It has been suggested that much of the clinical efficacy of the IgG1-binding agents occurs through their induction of monocytes and T-cell apoptosis; however, the anti-TNF agent etanercept (a soluble receptor construct), which is also able to neutralize soluble TNF and induce apoptosis, is not efficacious in CD [6]. In contrast, the IgG4-binding certolizumab pegol does not induce complement activation, cellular apoptosis nor cellular cytotoxicity, suggesting that these mechanisms are not essential for the efficacy of anti-TNF agents in CD [7,8]. One common aspect of certolizumab pegol, infliximab and adalimumab, but not etanercept, is the almost complete inhibition of LPS-induced IL-1 $\beta$  release from monocytes, suggesting that this may be required for there to be a clinical effect in CD [7].

### Initial CDP870 studies

The agent CDP870, which was soon to be known as certolizumab pegol, was designed as a subcutaneous injection with the addition of two polyethylene glycol molecules to the antibody fragment to increase the plasma half-life to approximately 2 weeks and reduce the frequency of dosing. However, an initial study investigated its efficacy

**Ian C Lawrance**<sup>1,2</sup>

<sup>1</sup>Centre for inflammatory Bowel Diseases, Fremantle Hospital, WA, Australia

<sup>2</sup>School of Medicine & Pharmacology, University of Western Australia, T Block, Fremantle Hospital, Alma Street, Fremantle 6059, WA, Australia  
Tel.: +61 618 9431 6347

Fax: +61 618 9431 3160

E-mail: ian.lawrance@uwa.edu.au

**FUTURE  
SCIENCE**

part of

**fsg**

as an intravenous injection in order to investigate doses that were greater than could be administered easily as a subcutaneous injection [9]. In this Phase II, placebo-controlled study of 92 patients, doses of certolizumab pegol ranged from 5 to 20 mg/kg of body weight. At week 4, the clinical response, defined as a reduction in the CD activity index (CDAI) of  $\geq 100$  points, was similar for placebo and all the CDP870 doses. The placebo response rate, however, was observed to be over 50% in this study. There were also no statistically significant differences in the remission rates at either week 4 or 12, suggesting either poor efficacy of the intravenous form of this medication, or a lack of a demonstrable difference due to the high placebo response rate. At the doses given, CDP870 appeared to be safe and well tolerated.

This first study was followed by a second Phase II placebo-controlled study that investigated the use of subcutaneous certolizumab pegol 100, 200 or 400 mg compared with placebo administered at weeks 0, 4 and 8 weeks [10]. A total of 292 patients with moderate-to-severe CD were enrolled with the primary end point being a clinical response at week 12 defined as a drop in the CDAI of  $\geq 100$  points or remission (CDAI  $< 150$ ). Again, no significant differences were observed between the three doses of certolizumab pegol and placebo for the primary end point of a clinical response at 12 weeks. A *post hoc* analysis of health-related quality of life (HRQoL) determined by the Inflammatory Bowel Disease Questionnaire (IBDQ) scores, however, did demonstrate a better outcome for patients treated with certolizumab pegol at all time points up to week 12 [11].

This study also suffered from a high placebo response rate that was over 35%. A number of factors could influence this including the time to the primary end point with longer duration associated with a higher placebo response, number of study visits, and the use of a subjective disease scoring system [12]. Of course, it is equally possible that the medication itself was not efficacious. A *post hoc* analysis, however, did provide the company with reason to continue the development of the drug. When taking into account the patients' baseline C-reactive protein (CRP) levels, patients with an elevated CRP ( $> 10$  mg/l), demonstrated significantly better response and remission rates at all time points when treated with certolizumab pegol 400 mg compared with placebo. This suggests that the primary assessment tool used to assess disease activity is not optimal. In this, and many other CD studies, the primary tool used is the CDAI. The CDAI, however, contains numerous subjective patients' assessments and can give equally high scores to patients with active inflammation, and those with functional bowel symptoms without inflammation, suggesting that a better method of assessment is required.

Even without the *post hoc* analysis, there were other encouraging signs of efficacy as all certolizumab pegol groups demonstrated a significantly better clinical effect at week 2 compared with placebo. At a dose of 400 mg, certolizumab pegol had significantly greater efficacy at weeks 4, 8 and 10, but not 12, against placebo. Patients receiving certolizumab pegol 400 mg also demonstrated the highest response rate at all time points compared with the other certolizumab pegol doses. These findings provided enough encouraging data to advance certolizumab pegol 400 mg into the next stage of clinical trials, collectively known as the Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECiSE) studies (Table 1).

## The PRECiSE studies

### ■ PRECiSE 1

The PRECiSE 1 study randomized patients to receive either certolizumab pegol 400 mg or placebo subcutaneously at weeks 0, 2 and 4 and then every 4 weeks to week 26 [13]. Patients were eligible for inclusion if they had a minimum of a 3-month history of CD, and a CDAI of between 220 and 450. As stated earlier, the CDAI is a numerical score derived from the subjective reporting of abdominal pain and overall wellbeing by the patient and more objective components such as stool frequency, weight, use of antidiarrheal agents, presence of fistulae and extra-intestinal manifestations of CD. It is, thus, quite possible that patients with a diagnosis of CD, but without active inflammation, are included in studies such as this due to irritable bowel symptoms (IBS). Other patients may have limited inflammation, but also IBS resulting in a high CDAI that is not truly representative of the level of active disease. In line with the Phase II study findings and in an attempt to control for this, the PRECiSE studies measured the CRP in all patients and then stratified the patients according to their CRP at baseline ( $\geq 10$  or  $< 10$  mg/l). Patients were also stratified according to their use of steroids and immunosuppressive agents.

The primary end points were a  $\geq 100$  point CDAI drop from baseline at week 6 and at both weeks 6 and 26 in patients with a CRP  $\geq 10$  mg/l at baseline. The IBDQ, reduction in the CDAI of  $\geq 70$  points from baseline, disease remission (CDAI  $< 150$ ) and fistulae closure in those patients suffering this aspect of CD were also assessed. In patients treated with certolizumab pegol and a CRP  $\geq 10$  mg/l a modest benefit was observed with statistically more patients with a  $\geq 100$  point CDAI reduction at week 6 ( $p = 0.04$ ) but not at both weeks 6 and 26 ( $p = 0.05$ ) compared with patients who received placebo. Significance, however, was reached at both end points when examining all patients regardless of the CRP at baseline. Statistically

significant differences were detected in remission rates at weeks 4 and 26, but not at week 6, and at both weeks 6 and 26. More certolizumab pegol-treated patients also had an improvement in their IBDQ at week 26 ( $p = 0.001$ ).

#### ■ PRECISE 2

The PRECISE 2 study was undertaken in parallel with PRECISE 1 but at separate sites with the inclusion criteria the same as for PRECISE 1. In PRECISE 2, all patients received open-label therapy with certolizumab pegol 400 mg at weeks 0, 2 and 4, and then those patients who demonstrated a reduction of  $\geq 100$  points in their baseline CDAI at week 6 were randomly assigned to receive either certolizumab pegol 400 mg or placebo every 4 weeks up to week 26 [14]. Again, patients were stratified for baseline CRP, steroid and immunosuppressive use. The primary end point was a clinical response defined as a  $\geq 100$  point reduction in the baseline CDAI at week 26 in patients with a CRP  $\geq 10$  mg/l. A total of 428 of 668 patients responded (64%), and 289 (43%) were in remission following induction therapy. The primary end point was met with 62% of certolizumab pegol-treated patients (69/112) having a response at week 26 compared with 34% (34/101) receiving placebo ( $p < 0.001$ ). At week 26, 48% of those patients who responded to certolizumab pegol at week 6, and were then randomized to continue to receive certolizumab pegol, 48% were in remission compared with 29% who received placebo ( $p < 0.001$ ). Response and remission rates were not different among smokers nor did they correlate with body mass index, the CRP level at baseline or the use of immunomodulators and corticosteroids.

#### ■ PRECISE 1, 2 & WELCOME trials

The PRECISE 2 study clearly demonstrated that continuous subcutaneous certolizumab pegol was superior to placebo in the maintenance of response and remission in CD. There are, however, several observations to be made about the PRECISE 1 and 2 studies. In PRECISE 1, response and remission rates at 6 weeks in the certolizumab pegol-treated patients were 35 and 22%, respectively, compared with the higher rates observed in PRECISE 2 with open-label induction therapy with certolizumab pegol of 64 and 43%, for reasons that remain unclear. Thus, although the primary end points in PRECISE 1 were not met, suggesting a lack of efficacy of the medication, the PRECISE 2 data suggest that there may indeed be efficacy in the induction of CD remission. In addition, the use of CRP, which was noted to be of significance in the Phase II studies, was not of use in predicting patient response in either of these PRECISE studies. *Post hoc* analyses have

**Table 1. Clinical studies on certolizumab pegol.**

	Induction	Maintenance	Safe	Reinduction
<b>Phase II</b>				
CDP870 iv.	No benefit	N/A	Yes	N/A
CDP870 sc.	No benefit	N/A	Yes	N/A
<b>Phase III/IV</b>				
PRECISE 1	Modest benefit	Modest benefit	Yes	N/A
PRECISE 2	N/A	Definite benefit	Yes	N/A
PRECISE 3	N/A	Efficacious	Yes	N/A
PRECISE 4	N/A	N/A	Yes	Efficacious

iv.: Intravenous; N/A: Not applicable; PRECISE: Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy; sc.: Subcutaneous.

further identified that patients with a shorter disease duration ( $< 1$  year) had a better maintenance of remission with certolizumab pegol therapy compared with those with a diagnosis of 5 years or more [15]. On assessment of HRQoL, certolizumab pegol was demonstrated to improve and maintain the patient well-being with a significant number of patients on certolizumab pegol returning to a normal life compared with those who were receiving placebo [16]. Further studies have also identified that patients receiving certolizumab pegol are also significantly more likely to have better work productivity [17].

Fistula healing was a secondary end point of both studies, but neither study was powered to demonstrate a significant difference in fistulae healing. In PRECISE 1, 107 patients had draining fistulae at baseline (46 received certolizumab pegol and 61 placebo) while in PRECISE 2, 58 patients who responded to certolizumab pegol therapy at week 6 also had draining fistulae (28 received certolizumab pegol and 30 placebo after week 6). A similar percentage of patients achieved fistula remission with certolizumab pegol (30%) compared with placebo (31%) in PRECISE 1 with similar findings in PRECISE 2 of 54 and 43%, respectively. Efficacy of certolizumab pegol in the management of CD fistulae has been reported [18,19], but to date there is no controlled evidence indicating a beneficial role of certolizumab pegol on the healing of perianal fistulae related to CD.

Finally, it was noted that certolizumab pegol was efficacious in patients who had previously received infliximab therapy, as had been previously observed with the use of adalimumab [20,21]. Further analysis of the PRECISE 2 data has demonstrated that approximately 50% of patients previously treated with infliximab would benefit from certolizumab pegol therapy [22]. A more recent patient cohort was investigated by the WELCOME trial with the inclusion of 539 CD patients with moderate-to-severe active disease who

had loss of response to infliximab. In this study, following 6 weeks of open-label induction therapy with certolizumab pegol 62% of patients had responded and 39% were in remission, which is very similar to the 64 and 43% of patients in the overall PRECiSE 2 population that was assessed independently of previous exposure to infliximab. Continued response at 26 weeks was also only slightly lower at 38% in the WELCOME trial [23]. In patients who have lost response to, or are intolerant of, two anti-TNF therapies, the use of certolizumab pegol has also been suggested as having benefit, although the efficacy and tolerability would appear to be markedly lower than in anti-TNF therapy naive patients [24].

### ■ PRECiSE 3

The PRECiSE 3 study was designed as an open-label extension study that included patients who completed week 26 of the PRECiSE 2 trial [25]. It was designed to assess the long-term safety and efficacy of certolizumab pegol 400 mg given every 4 weeks. Data up to week 54 from the commencement of PRECiSE 3 (or 80 weeks from commencement of PRECiSE 2) was published in 2010. A total of 141 out of 215 patients (65.6%) who received CPZ ('continuous' group) and 100 of 210 patients (47.6%) who received placebo ('interrupted' group) in PRECiSE 2 were enrolled into PRECiSE 3.

At entry, 56.3% of 'continuous' patients were in remission according to the Harvey–Bradshaw Index compared with 37.6% of 'interrupted' patients. Response rates in patients at week 54 of PRECiSE 3, who were also in response at enrollment into PRECiSE 3, were 66.1 and 63.3% in the two groups, respectively. In relation to all patients entering PRECiSE 2 ( $n = 668$ ), 86 (25.6%) 'continuous' and 57 (17.4%) 'interrupted' patients remained in response at week 54. This is similar to the finding for adalimumab where 24.1% of all patients in the CHARM study remained in response at week 26 [26]. The findings, however, would appear to be lower than those observed for patients receiving adalimumab in the ADHERE study, where after up to 2 years of therapy, between 37 and 50% of patients were in clinical remission [27]. It must be noted, however, that in the ADHERE study, some patients had their dosage of adalimumab increased to weekly subcutaneous injections, whilst in the PRECiSE 3 study, dose escalation was not allowed. For those patients in remission on commencing PRECiSE 3, sustained remission rates were 33.0% at week 54 in the 'continuous' and 30.9% in the 'interrupted' patient groups.

Of particular importance was the collection of adverse events. Injection-site reactions such as bruising, pain and erythema were low ( $\leq 1\%$ ). There were no

anaphylactic reactions and the most commonly reported adverse events were abdominal pain, nasopharyngitis and arthralgia. Of the 78 patients who withdrew from the study, most withdrew due to patient decision, lack of drug efficacy or deterioration of their CD. The rate of serious infections was 7.8 and 6.0% in the 'continuous' and 'interrupted' groups, respectively, with just under half of the patients with serious infections also taking either steroids and/or an immunosuppressant at the time of the infection. The most commonly reported serious infection was a perianal abscess that occurred in five patients. There were two cases of tuberculosis giving a risk of 0.8%/year, which is higher than the general population but expected with anti-TNF therapy.

PRECiSE 3 has now been underway for over 4.5 years and certolizumab pegol continues to be efficacious with 79 serious adverse events in 50 patients. Serious infections occurred 22 times in 19 patients, there had been three cases of tuberculosis markedly reducing the yearly risk observed at 18 months, three malignancies (one small intestine carcinoma, one prostate cancer and one uterine leiomyoma) and two deaths. To date there are no new safety signals from those seen in the original studies and those seen after 18 months of certolizumab pegol therapy [28].

### ■ PRECiSE 4

PRECiSE 4 was designed to determine the efficacy of certolizumab pegol to regain response to therapy following a relapse after initially responding to certolizumab pegol in PRECiSE 2 [29]. Patients who had responded to induction therapy with certolizumab pegol were randomized to receive certolizumab pegol or placebo every 4 weeks to week 26. Those patients who suffered a disease flare prior to week 26 were eligible to enter PRECiSE 4. In this ongoing, open-label extension trial, patients on continuous therapy received a single extra dose of certolizumab pegol 400 mg, while those patients on placebo underwent reinduction receiving certolizumab pegol 400 mg at weeks 0, 2 and 4, followed by maintenance with certolizumab pegol 400 mg every 4 weeks. A response was defined as a  $\geq 100$  point decrease in the CDAI from baseline. A total of 124 patients flared (75 on placebo and 49 on certolizumab pegol 400 mg 4-weekly). At 4 weeks into PRECiSE 4, 63% of patients who relapsed on continuous certolizumab pegol therapy and 65% of patients who relapsed on placebo regained a therapeutic response. This response was maintained in 55 and 59% of patients from the continuously certolizumab pegol- and placebo-treated groups, respectively, through to week 52, indicating that an additional dose of certolizumab pegol to patients who relapsed despite receiving 4 weekly certolizumab pegol is effective, as it is for patients who flare following cessation of active drug.



### Where are we now with certolizumab pegol?

To date, certolizumab pegol is available for use in North America, Switzerland and Russia for the treatment of CD, after failure of conventional treatments. In other European countries, the UK and the Asia-Pacific regions, however, marketing authorization has not been obtained. In 2008, the EMA published a negative opinion on the use of certolizumab pegol for CD and refused to grant marketing authorization owing to two major concerns. The first was concern about insufficient evidence of efficacy, as the effectiveness was considered to be marginal and too low to be clinically relevant, while the second was about concerns on the short duration of the PRECiSE 1 and 2 maintenance phases.

The US FDA, however, approved the use of certolizumab pegol for CD despite differences among the clinical reviewers [101]. Two reviewers recommended not approving certolizumab pegol for CD for reasons similar to those of the EMA, citing that the findings of efficacy were not statistically robust and that the clinical effect beyond 30 weeks had not been evaluated while there were two other TNF inhibitors approved for CD with more long-term clinical experience. The third reviewer did not agree that approval should be withheld due to this as both of the dissenting reviewers had already accepted the primary efficacy analyses of certolizumab pegol in CD.

The 2008 Cochrane review on TNF inhibitors used for CD also determined that the relative efficacy of certolizumab pegol was similar to natalizumab and adalimumab for induction, and similar to natalizumab for maintenance of remission, although inferior to infliximab and adalimumab despite there being no head-to-head trials. It was also noted that those patients who responded to induction therapy with certolizumab pegol were likely to maintain a response similar to infliximab and adalimumab. The short-term safety profile was also considered to be equivalent to that of the other two anti-TNF agents already approved for CD [30].

It is assumed that with the long-term data from PRECiSE 3 going out to over 5 years [28] and the recently published results from the FACTS survey, some of the safety concerns have, at least in some part, been addressed. Unfortunately, patient numbers are small in PRECiSE 3, but no new safety signals have been identified. A recent meta-analysis examining certolizumab pegol in comparison with placebo in 2009 also failed to identify certolizumab pegol as carrying a greater risk of serious adverse events and concluded that certolizumab pegol is safe in treating CD [31]. Safety for the use of certolizumab pegol in pregnancy may also be an important difference for this anti-TNF agent. Despite there being no published

human data, with the exception of case reports [32,33], data taken from *in vitro* and animal studies show that the Fab' fragment, unlike infliximab and adalimumab, does not cross the placenta [34]. It is, however, possible that the cleaved Fab' fragment could cross the placenta, but initial evidence does not suggest an increased risk with the use of certolizumab pegol during pregnancy.

Evidence of efficacy would also appear to be stronger when considering data from the WELCOME trial published in 2010, which clearly demonstrated clinical efficacy in patients who had lost response to infliximab [23]. In addition, preliminary data from the open-label trial investigating endoscopic mucosal improvement in patients with CD demonstrated that in 53 of 78 patients who remained in the trial at week 54, treatment with certolizumab pegol was associated with endoscopic response, endoscopic remission and complete endoscopic remission rates of 62.2, 28.3 and 18.9%, respectively [35].

### Future perspective

At present, certolizumab pegol for the management of CD is limited to a few countries. It would appear that there are unlikely to be additional safety concerns for certolizumab pegol in addition to those already recognized for patients treated with an anti-TNF agent (PRECiSE 3). Unfortunately, the pivotal induction study (PRECiSE 1) did not identify a clear signal for efficacy in the induction of remission of CD with certolizumab pegol, although PRECiSE 2 demonstrated the maintenance of remission in a high percentage of initial responders to open-label therapy compared with placebo over a 6-month period. This, however, may not be enough to convince the regulators to approve its use for induction therapy.

Certolizumab pegol has been shown to be able to reinduce remission if it is lost (PRECiSE 4) and can be effective in patients who have lost response to infliximab. It would, thus, seem that a role of certolizumab pegol has been clearly demonstrated for patients who have achieved disease remission with the use of other agents. For those patients who develop side effects with other agents, or would like a 4-weekly subcutaneous injection as opposed to 2-weekly or an intravenous infusion, there appears to be a place for certolizumab pegol. It can, therefore, be assumed that it is a matter of time before there is enough evidence to allow for the registration of certolizumab pegol alongside that of infliximab and adalimumab for use in CD in countries apart from the USA, Switzerland and Russia. Whether this is purely for maintenance therapy and for patients losing response to other anti-TNF agents, or also for the induction of remission in CD, remains to be seen.

**Financial & competing interests disclosure**

IC Lawrance sits on the Schering-Plough (Merck) Crohn's disease Advisory Board, Abbott Australasia Crohn's Disease Advisory Board and is on the publication review committee for Certolizumab Pegol PRECISE 2/3 studies. He is also a member of the Western Australian Drug Evaluation Panel. The author has no other relevant

affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

**Executive summary**

- Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECiSE) 1 investigated the efficacy of induction of response in Crohn's disease (CD) patients. The primary end points were not fully met but some benefit was demonstrated following *post hoc* analysis and the meeting of secondary end points.
- PRECiSE 2 identified a clear benefit of certolizumab pegol (CZP) over placebo for the maintenance of response and remission in CD patients with moderate to severe disease at week 26.
- PRECiSE 3 demonstrates long-term efficacy and safety of CZP in CD patients for up to 18 months, with data extending out to over 5 years.
- PRECiSE 4 shows that reinduction with CZP is effective following loss of response in CD patients still receiving maintenance CZP therapy every 4 weeks and those having ceased active certolizumab pegol medication.
- CZP has demonstrated benefit in regaining a therapeutic response in CD patients who have lost response to infliximab.
- CZP is only registered for use in the USA, Switzerland and Russia due to concerns that the efficacy for induction of disease response in CD was not statistically robust (PRECiSE 1). The second concern of a lack of long-term follow up may now have been addressed with the publication of the PRECiSE 3 data.

**Bibliography**

Papers of special note have been highlighted as:

- of interest

- 1 Reinecker HC, Steffen M, Witthoef T *et al.* Enhanced secretion of tumor necrosis factor- $\alpha$ , IL-6, and IL-1  $\beta$  by isolated lamina propria mononuclear cells from patients with ulcerative colitis and Crohn's disease. *Clin. Exp. Immunol.* 94(1), 174–181 (1993).
- 2 Murch SH, Lamkin VA, Savage MO, Walker-Smith JA, MacDonald TT. Serum concentrations of tumor necrosis factor  $\alpha$  in childhood chronic inflammatory bowel disease. *Gut* 32(8), 913–917 (1991).
- 3 Schreiber S, Nikolaus S, Hampe J *et al.* Tumor necrosis factor  $\alpha$  and interleukin 1 $\beta$  in relapse of Crohn's disease. *Lancet* 353(9151), 459–461 (1999).
- 4 Braegger CP, Nicholls S, Murch SH, Stephens S, MacDonald TT. Tumor necrosis factor- $\alpha$  in stool as a marker of intestinal inflammation. *Lancet* 339(8785), 89–91 (1992).
- 5 MacDonald TT, Hutchings P, Choy MY, Murch S, Cooke A. Tumor necrosis factor- $\alpha$  and interferon- $\gamma$  production measured at the single cell level in normal and inflamed human intestine. *Clin. Exp. Immunol.* 81(2), 301–305 (1990).
- 6 Sandborn WJ, Hanauer SB, Katz S *et al.* Etanercept for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Gastroenterology* 121(5), 1088–1094 (2001).
- 7 Nesbitt A, Fossati G, Bergin M *et al.* Mechanism of action of certolizumab pegol (CDP870): *in vitro* comparison with other anti-tumor necrosis factor  $\alpha$  agents. *Inflamm. Bowel Dis.* 13(11), 1323–1332 (2007).
- 8 Tilg H, Moschen A, Kaser A. Mode of function of biological anti-TNF agents in the treatment of inflammatory bowel diseases. *Expert Opin. Biol. Ther.* 7(7), 1051–1059 (2007).
- 9 Winter TA, Wright J, Ghosh S, Jahnsen J, Innes A, Round P. Intravenous CDP870, a PEGylated Fab' fragment of a humanized antitumor necrosis factor antibody, in patients with moderate-to-severe Crohn's disease: an exploratory study. *Aliment. Pharmacol. Ther.* 20(11–12), 1337–1346 (2004).
- 10 Schreiber S, Rutgeerts P, Fedorak RN *et al.* A randomized, placebo-controlled trial of certolizumab pegol (CDP870) for treatment of Crohn's disease. *Gastroenterology* 129(3), 807–818 (2005).
- 11 Rutgeerts P, Schreiber S, Feagan B, Keininger DL, O'Neil L, Fedorak RN. Certolizumab pegol, a monthly subcutaneously administered Fc-free anti-TNF $\alpha$ , improves health-related quality of life in patients with moderate to severe Crohn's disease. *Int. J. Colorectal Dis.* 23(3), 289–296 (2008).
- 12 Su C, Lichtenstein GR, Krok K, Brensinger CM, Lewis JD. A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology* 126(5), 1257–1269 (2004).
- 13 Sandborn WJ, Feagan BG, Stoinov S *et al.* Certolizumab pegol for the treatment of Crohn's disease. *N. Engl. J. Med.* 357(3), 228–238 (2007).
- Pegylated Antibody Fragment Evaluation in Crohn's Disease: Safety and Efficacy (PRECiSE) 1 investigated the efficacy of induction of response in Crohn's disease (CD) patients, but the primary end points were not fully met, and the findings have been considered to be marginal by regulatory authorities making the marketing of certolizumab pegol (CZP) for use in CD difficult in many countries.
- 14 Schreiber S, Khaliq-Kareemi M, Lawrance IC *et al.* Maintenance therapy with certolizumab pegol for Crohn's disease. *N. Engl. J. Med.* 357(3), 239–250 (2007).
- PRECiSE 2 identified a clear benefit of CZP over placebo for the maintenance of response and remission in CD patients at week 26.
- 15 Schreiber S, Colombel JF, Bloomfield R *et al.* Increased response and remission rates in short-duration Crohn's disease with subcutaneous certolizumab pegol: an analysis of PRECiSE 2 randomized maintenance trial data. *Am. J. Gastroenterol.* 105(7), 1574–1582 (2010).
- 16 Feagan BG, Coteur G, Tan S, Keininger DL, Schreiber S. Clinically meaningful improvement in health-related quality of life in a randomized controlled trial of certolizumab pegol maintenance therapy for Crohn's disease. *Am. J. Gastroenterol.* 104(8), 1976–1983 (2009).

- 17 Feagan BG, Reilly MC, Gerlier L, Brabant Y, Brown M, Schreiber S. Clinical trial: the effects of certolizumab pegol therapy on work productivity in patients with moderate-to-severe Crohn's disease in the PRECISE 2 study. *Aliment. Pharmacol. Ther.* 31(12), 1276–1285 (2010).
- 18 Danese S, Stefanelli T, Omodei P *et al.* Successful treatment of fistulizing Crohn's disease with certolizumab pegol. *Inflamm. Bowel Dis.* 14(2), 292–293 (2008).
- 19 Schoepfer AM, Vavricka SR, Binek J *et al.* Efficacy and safety of certolizumab pegol induction therapy in an unselected Crohn's disease population: results of the FACTS survey. *Inflamm. Bowel Dis.* 16(6), 933–938 (2010).
- 20 Hanauer SB, Sandborn WJ, Rutgeerts P *et al.* Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 130(2), 323–333 (2006).
- 21 Sandborn WJ, Rutgeerts P, Enns R *et al.* Adalimumab induction therapy for Crohn disease previously treated with infliximab: a randomized trial. *Ann. Intern. Med.* 146(12), 829–838 (2007).
- 22 Hanauer SB, Panes J, Colombel JF, Bloomfield R, Schreiber S, Sandborn WJ. Clinical trial: impact of prior infliximab therapy on the clinical response to certolizumab pegol maintenance therapy for Crohn's disease. *Aliment. Pharmacol. Ther.* 32(3), 384–393 (2010).
- 23 Sandborn WJ, Abreu MT, D'Haens G *et al.* Certolizumab pegol in patients with moderate to severe Crohn's disease and secondary failure to infliximab. *Clin. Gastroenterol. Hepatol.* 8(8), 688–695 (2010).
- The WELCOME study suggests that CZP is of benefit in CD patients who have lost response to infliximab.
- 24 Allez M, Vermeire S, Mozziconacci N *et al.* The efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF antibodies. *Aliment. Pharmacol. Ther.* 31(1), 92–101 (2010).
- 25 Lichtenstein GR, Thomsen OO, Schreiber S *et al.* Continuous therapy with certolizumab pegol maintains remission of patients with Crohn's disease for up to 18 months. *Clin. Gastroenterol. Hepatol.* 8(7), 600–609 (2010).
- PRECISE 3 demonstrates long-term efficacy and safety in CD patients up to 18 months, with data extending out to 5 years.
- 26 Colombel JF, Sandborn WJ, Rutgeerts P *et al.* Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. *Gastroenterology* 132(1), 52–65 (2007).
- 27 Panaccione R, Colombel JF, Sandborn WJ *et al.* Adalimumab sustains clinical remission and overall clinical benefit after 2 years of therapy for Crohn's disease. *Aliment. Pharmacol. Ther.* 31(12), 1296–1309 (2010).
- 28 Lichtenstein G, Thomsen O, Schreiber S *et al.* Long-term remission with certolizumab pegol in Crohn's disease: Efficacy over 4.5 years in patients with no prior TNF inhibitor exposure (PRECISE 3 study). *Gut* 17, S51–S52 (2010).
- 29 Sandborn WJ, Schreiber S, Hanauer SB, Colombel JF, Bloomfield R, Lichtenstein GR. Reinduction with certolizumab pegol in patients with relapsed Crohn's disease: results from the PRECISE 4 Study. *Clin. Gastroenterol. Hepatol.* 8(8), 696–702 (2010).
- PRECISE 4 shows that reinduction with CZP is effective following loss of response in both patients still receiving maintenance CZP therapy and those having ceased active CZP medication.
- 30 Behm BW, Bickston SJ. Tumor necrosis factor- $\alpha$  antibody for maintenance of remission in Crohn's disease. *Cochrane Database Syst. Rev.* (1), CD006893 (2008).
- 31 Shao LM, Chen MY, Cai JT. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. *Aliment. Pharmacol. Ther.* 29(6), 605–614 (2009).
- 32 Oussalah A, Bigard MA, Peyrin-Biroulet L. Certolizumab use in pregnancy. *Gut* 58(4), 608 (2009).
- 33 Mahadevan U, Abreu MT. Certolizumab use in pregnancy: low levels detected in cord blood. *Gastroenterology* 136(5)(Suppl. 1), 960 (2009).
- 34 Kane SV, Acquah LA. Placental transport of immunoglobulins: a clinical review for gastroenterologists who prescribe therapeutic monoclonal antibodies to women during conception and pregnancy. *Am. J. Gastroenterol.* 104(1), 228–233 (2009).
- 35 Colombel JF, Lemann M, Bouhnik Y *et al.* Endoscopic mucosal improvement in patients with active crohn's disease treated with certolizumab pegol: week 10 and 54 results of the music trial. *Gastroenterology* 138(5)(Suppl. 1), 166 (2010).
- Website
- 101 FDA Center for Drug Evaluation and Research Application Number: BLA 235160. Drugs@FDA.gov. Division Director Review – BLA/STN 125160 Cimzia® (certolizumab pegol). [www.accessdata.fda.gov](http://www.accessdata.fda.gov) (Accessed on 9 September 2009)