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# Certolizumab Pegol

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*Treatment of Rheumatoid Arthritis*
*Treatment of Crohn's Disease*
*Human Anti-TNF-α Monoclonal Antibody*

CDP-870
PHA-738144
Cimzia™

Immunoglobulin, anti-(human tumor necrosis factor α) Fab' fragment (human-mouse monoclonal CDP870 heavy chain), disulfide with human-mouse monoclonal CDP870 light chain, pegylated at Cys-221

CAS: 428863-50-7

EN: 264195

**Abstract**

Inflammatory bowel diseases (IBDs) such as Crohn's disease and ulcerative colitis are chronic inflammatory disorders of the gastrointestinal (GI) tract that can lead to tissue damage and irreversible impairment of GI tract structure and function. Tumor necrosis factor-α (TNF-α) has been identified as a key mediator in IBDs and in rheumatoid arthritis, where it promotes chronic inflammation and tissue damage. Anti-TNF-α therapies are promising treatment options and anti-TNF monoclonal antibodies (MAbs) in particular have shown efficacy in reducing IBD-associated inflammation and in promoting mucosal healing. Certolizumab pegol is an anti-TNF-α MAb in development for the treatment of both Crohn's disease and rheumatoid arthritis. It is a pegylated Fab' fragment of a humanized anti-TNF-α MAb that lacks the Fc portion of the parent $IgG_4$ antibody. Certolizumab pegol has a higher affinity for TNF-α than other anti-TNF agents and does not induce apoptosis or mediate complement-dependent cytotoxicity or antibody-dependent cellular cytotoxicity. Certolizumab pegol was selected for further development as a treatment for Crohn's disease and rheumatoid arthritis and demonstrated efficacy and safety in clinical trials.

## Introduction

Inflammatory bowel diseases (IBDs) are chronic inflammatory disorders of the gastrointestinal (GI) tract that include Crohn's disease, ulcerative colitis, microscopic (or lymphocytic) colitis, diversion colitis, fulminant colitis and toxic megacolon. IBDs primarily affect Western populations and a higher incidence is noted in urban as compared to rural areas. In the past 25 years, the incidence of IBD has increased up to 6-fold and it is estimated that up to 1 million Americans suffer from IBD. Crohn's disease and ulcerative colitis are the most common forms of IBD and the prevalence of both diseases has been estimated to be 10-200 cases per 100,000 population in North America and Europe (1, 2).

The chronic inflammation characteristic of IBDs can lead to tissue damage and long-term irreversible impairment of GI tract structure and function. Crohn's disease and ulcerative colitis are due to abnormal immune responses. Both disorders involve inflammation and ulceration of the intestines; however, in general, ulcerative colitis is limited to the rectum and colon, while Crohn's disease extends into the intestinal wall and can affect the entire digestive tract from the mouth to the anus. The cause of these disorders has not been elucidated, although it appears that genetic (*e.g.*, mutations in the gene encoding NOD2 are seen in some patients with Crohn's disease) and environmental factors, together with abnormal immune responses, play a crucial role in the pathogenesis of IBDs (1, 2).

The chronic mucosal inflammation present in ulcerative colitis and Crohn's disease is due to immunological defects which result in inappropriate T-cell responses to antigen and overexpression of proinflammatory cytokines such as the interleukins IL-1, IL-8, IL-6, IL-12 and IL-13, interferon gamma (IFN-γ) and tumor necrosis factor-α (TNF-α). Several studies have identified TNF-α in particular as a key mediator that promotes chronic inflammation and tissue damage, and levels of this proinflammatory cytokine have been found to be elevated in mucosa and stools of patients with Crohn's disease. TNF-α appears to play a major role in the pathogenesis and symptomatology of several immune-mediated diseases such as Crohn's disease and rheumatoid arthritis, and anti-TNF-α therapies are promising treatment options. Clinical studies using anti-TNF monoclonal antibodies (MAbs; *e.g.*, infliximab, adalimumab) have demonstrated the efficacy of this treatment strategy (1, 3-14).

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The chimeric MAb infliximab (Remicade®) is currently the only anti-TNF-α MAb available for the treatment of Crohn's disease; the human MAb adalimumab (Humira®) was launched for the treatment of arthritis but is still undergoing phase III development for the treatment of Crohn's disease. Because infliximab is chimeric, it is associated with immunogenicity which can lead to infusion reactions and reductions in efficacy. It has also been associated with immunosuppression (15-18).

Certolizumab pegol (CDP-870, Cimzia™) is a promising anti-TNF-α MAb currently under development for the treatment of both Crohn's disease and rheumatoid arthritis. It is a pegylated Fab' fragment of a humanized anti-TNF-α MAb that lacks the Fc portion of the parent $IgG_4$ antibody. It was constructed by grafting the short hypervariable complementarity-determining regions derived from the murine MAb HTNF40 onto a virtually human Ig fragment (IgG γ1κ). The biological activity of the Fab' fragment is retained. The Fab' fragment is connected via a maleimide linker to two cross-linked chains of polyethylene glycol (20 kDa each), which increases the plasma half-life to approximately 2 weeks. Thus, the frequency of dosing of this anti-TNF-α MAb would be reduced. Certolizumab pegol is intended for s.c. administration and was selected for further development as a treatment for Crohn's disease and rheumatoid arthritis (19, 20).

## Pharmacological Actions

An *in vitro* study compared the affinity and potency of certolizumab pegol with adalimumab and infliximab using a surface plasmon resonance assay and a mouse fibroblast cell line (L929) bioassay, respectively. Certolizumab pegol had higher affinity for TNF-α, with a $K_D$ of 89.3 pM compared to 157.4 and 227.2 pM for adalimumab and infliximab, respectively. Moreover, the monovalent certolizumab pegol was more potent in preventing TNF-α-induced killing of L929 fibroblasts than the other two bivalent antibodies ($IC_{50}$ = 0.35 ng/ml *vs.* 6 and 5 ng/ml, respectively) (21).

Certolizumab pegol was shown *in vitro* to bind peripheral blood lymphocytes and monocytes. However, in contrast to adalimumab, etanercept and infliximab which all induced apoptosis in a comparable manner, certolizumab pegol did not induce apoptosis of these cells. All four MAbs were shown to bind *in vitro* to NS0 cells transfected with human TNF (TNF 6.5). However, while adalimumab and infliximab, and to a lesser degree etanercept, all mediated complement-dependent cytotoxicity (CDC) and antibody-dependently cellular cytotoxicity (ADCC), certolizumab pegol did not kill these cells via CDC or ADCC (22, 23).

## Clinical Studies

A multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II study conducted in 292 patients with moderate to severe Crohn's disease (Crohn's Disease Activity Index [CDAI] = 220-450 points) demonstrated the safety and efficacy of s.c. certolizumab pegol (100, 200 or 400 mg at weeks 0, 4 and 8). Certolizumab pegol was well tolerated and the incidence of adverse events was similar in both treatment and placebo groups. At least 1 positive result for anti-certolizumab pegol antibodies was found for 12.3% of the patients receiving the highest dose. Although plasma certolizumab pegol levels appeared to be lower in antibody-positive patients, the efficacy of the agent was not reduced. All doses resulted in significant efficacy (*i.e.*, a decrease in CDAI of 100 or more points) or remission (CDAI = 150 points or less) at week 2 (29.7%, 30.6% and 33.3%, respectively, *vs.* 15.1% on placebo). The highest dose resulted in the greatest clinical response rates at all time points, with the highest rate seen at week 10 (52.8% *vs.* 30.1% on placebo). However, a significant difference from placebo was not observed for this dose at week 12 (44.4% *vs.* 35.6% on placebo). This may be due to the high percentage of patients (59%) participating in this study with low baseline C-reactive protein (CRP) levels (< 10 mg/l), which are generally high in patients with active Crohn's disease. In fact, individual patient analysis of data revealed that none of the patients with baseline CRP below 10 mg/l achieved a significant response compared to placebo at week 12. Moreover, a significantly higher response rate was observed in a subset of 199 patients with CRP levels of 10 mg/l or greater treated with the highest dose of certolizumab pegol compared to placebo at week 12 due to a lower response rate in the placebo group (53.1% at 400 mg *vs.* 17.9%). *Post hoc* analysis of health-related quality-of-life data from this study indicated that certolizumab pegol doses of 200 and 400 mg are associated with improvement, particularly in patients wtih elevated CRP levels at baseline (19, 24-27).

The safety and efficacy of a single i.v. dose of certolizumab pegol (1.25, 5, 10 or 20 mg/kg) were also assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel-group phase II trial in 92 patients with Crohn's disease (CDAI = 220-450 points). CDAI was determined at baseline and at 2, 4, 8 and 12 weeks. All doses were well tolerated, with only mild to moderate adverse events reported by 43 patients in the certolizumab pegol groups and by 15 on placebo. No infusion-related reactions were reported. Patients in all treatment groups comparably achieved the primary endpoint of a clinical response (*i.e.*, a decrease in CDAI of 100 or more points) or remission (CDAI = 150 points or less) (56.0-60.0% on certolizumab pegol and 47.8% on placebo) at week 12. A significantly higher remission rate at week 2 was observed in the group receiving 10 mg/kg certolizumab pegol compared to the group given placebo (47.1% *vs.* 16%), but this benefit was not sustained at week 12 (20, 28).

The safety of i.v. and s.c. certolizumab pegol was analyzed from results of the two phase II trials described above. From the total of 384 patients with Crohn's disease who participated, 287 were evaluated for safety. The incidence and type of adverse events reported were similar between treatment and placebo groups. Adverse

events were only mild to moderate in intensity, the most frequent being headache, aggravated Crohn's disease, nausea and nasopharyngitis. No increase in opportunistic infections, tuberculosis, death, lupus or malignancies was observed with treatment. The most common infections seen in certolizumab pegol-treated patients were nasopharyngitis, urinary tract infection and influenza. Analysis of pharmacokinetics revealed that $C_{max}$ concentrations for certolizumab pegol were broadly dose-proportional and the half-life was about 2 weeks (29, 30).

Significant positive efficacy and safety results were obtained from two pivotal phase III trials (PRECiSE 1 and 2) in the induction and maintenance of clinical response to certolizumab pegol over 26 weeks as compared to placebo in a total of 1,330 patients with active Crohn's disease. The efficacy of certolizumab pegol was not affected by CRP levels or by previous treatment with anti-TNF therapies (31-33). Although analysis of data from the 26-week, double-blind, placebo-controlled PRECiSE 1 trial is ongoing, all co-primary endpoints were successfully achieved, with significant results obtained. However, results were of a lower magnitude as compared to the PRECiSE 2 trial. In the PRECiSE 2 study, 428 of the 668 patients enrolled with active Crohn's disease (CDAI = 220-450) responded (*i.e.*, a decrease in CDAI of 100 points or more) to open-label induction therapy with certolizumab pegol (400 mg s.c. at weeks 0, 2 and 4). These patients were randomized to receive maintenance certolizumab pegol therapy (400 mg s.c.) or placebo every 4 weeks up to week 24 and stratified according to baseline CRP levels and corticosteroid/immunosuppressant use. Treatment was safe and well tolerated, with generally mild to moderate adverse events reported. The most common adverse event was headache (6.9% and 6.6% on certolizumab pegol and placebo, respectively). Three and 2 serious non-Crohn's disease-related infections were observed in the certolizumab pegol and placebo groups, respectively. One patient receiving certolizumab pegol died from a fentanyl overdose. The clinical response rate at week 26 in the stratum of patients with CRP levels of 10 mg/l or greater was significantly higher in the certolizumab pegol group compared to the placebo group (61.6% *vs.* 33.7%), with remission achieved in 42.0% *vs.* 25.7%. In addition, the clinical response and remission rates for the overall intent-to-treat population were significantly higher at week 26 for the certolizumab pegol-treated group as compared to the placebo-treated group (62.8% and 47.9%, respectively, *vs.* 36.2% and 28.6%, respectively, on placebo) (32, 33).

The ongoing PRECiSE 3 and 4 trials are also part of the phase III development program for certolizumab pegol. Both are open-label trials involving patients who participated in PRECiSE 1 and 2. Each study will assess the long-term safety and tolerability of certolizumab pegol (33).

The efficacy and safety of certolizumab pegol (1, 5 or 20 mg/kg as a single i.v. infusion) as a treatment for rheumatoid arthritis were also examined in a randomized, double-blind, placebo-controlled, dose-escalating phase II trial in 36 patients with active rheumatoid arthritis (30 females and 6 males; mean disease duration = 13 years; mean of 5 previous disease-modifying antirheumatic drugs [DMARDs] or experimental therapies). Continuation of DMARDs and prednisolone (up to 7.5 mg/day) was allowed. Following the blinded period, 32 patients received another single, open-label i.v. infusion of certolizumab pegol (5 or 20 mg/kg). Certolizumab pegol was well tolerated. Of the 12 patients receiving placebo during the blinded period, 6 withdrew due to deteriorating disease by 4 weeks postdosing and 2 certolizumab pegol-treated (1 mg/kg) patients withdrew due to deteriorating disease and were lost to follow-up at more than 4 weeks postdosing. The percentage of patients from the preprotocol population with ACR20 improvement for the certolizumab 1, 5 and 20 mg/kg dose groups was 50%, 87.5% and 62.5%, respectively, at 4 weeks and 25%, 75% and 75%, respectively, at 8 weeks, which was significantly higher than placebo (16.7% at both time points). The percentage of certolizumab pegol patients from the preprotocol population with ACR50 improvement at both 4 and 8 weeks was 12.5%, 12.5% and 50%, respectively, on doses of 1, 5 and 20 mg/kg compared to none of the patients on placebo. Similar results were obtained in the open-label phase, where 72.2% and 55.6%, respectively, of the patients in the 5 and 20 mg/kg certolizumab pegol groups achieved ACR20 improvement at week 4, respectively, and 55.6% and 66.7%, respectively, at week 8 (34).

Several phase III trials are under way for the treatment of rheumatoid arthritis and Crohn's disease (31, 33, 35).

## Source

UCB S.A. (BE).

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