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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 02-008005- -00016-0000

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Señora Jefe de la
DIVISION DE NUEVAS CREACIONES
Superintendencia de Industria y Comercio
E. S. D.

Trámite : 011
Evento : 379
Actuación : 412

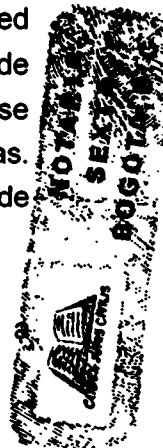
Referencia : Expediente No. 02.008.005
Asunto : SOLICITUD DE PATENTE PARA: "MOLÉCULAS DE ANTICUERPO
QUE TIENEN ESPECIFICIDAD POR EL FACTOR DE NECROSIS
TUMORAL ALFA HUMANO Y USO DE LAS MISMAS"
Solicitante : CELLTECH R&D LIMITED
Clase : C12N 015/013
Fecha de solicitud : Febrero 1 de 2002

1. Yo, Emilio Ferrero, abogado con Tarjeta Profesional No. 31.929, obrando como apoderado de CELLTECH R&D LIMITED, en el asunto antes identificado, atentamente manifiesto a Usted que, en tiempo oportuno, interpongo recurso de reposición contra la resolución No. 44911 de fecha 31 de Agosto de 2009, para que el artículo primero sea revocado y en consecuencia se conceda el privilegio de patente de invención para las once (11) reivindicaciones presentadas. Dicha resolución fue notificada por edicto fijado el 9 de Septiembre de 2009 y desfijado el 22 de Septiembre de 2009 y por lo tanto, el presente recurso es interpuesto oportunamente.

2. Los motivos de inconformidad sobre los cuales sustento este recurso aparecen continuación en este escrito.

3. FUNDAMENTO DE LA RESOLUCIÓN N. 44911

La Resolución en su parte considerativa afirma que realizado el examen de patentabilidad se encontró que la invención no cumple con los requisitos de patentabilidad. Específicamente, la invención no cumple con el requisito de nivel inventivo, pues según sostiene el Examinador la materia reivindicada en la solicitud bajo estudio resultaría obvia y se hubiese podido llegar de manera evidente a la misma a partir de los documentos D1 (WO9825971) y D2 (WO92011383).



4. FUNDAMENTOS DEL RECURSO

Respetuosamente me permito disentir de lo expuesto por ese Despacho en la Resolución objeto del presente recurso, ya que la presente solicitud no carece de nivel inventivo a la luz de los documentos D1 y D2.

La anterior afirmación tiene justificación jurídica y técnica por las siguientes razones:

4.1 VIOLACIÓN DEL ARTÍCULO 18 DE LA DECISIÓN 486 DE LA COMISIÓN DE LA COMUNIDAD ANDINA

El artículo 18 de la Decisión 486 de la Comisión de la Comunidad Andina, establece lo siguiente:

"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".

De acuerdo con lo anterior, queremos reiterar que el documento D2 menciona un anticuerpo anti-TNF humanizado (CDP571), el cual se diferencia del que se presenta en la solicitud de mi representada por las secuencias de amino ácidos de sus cadenas pesada y ligera. Por lo tanto no se podría obtener de D2 información alguna que lleve de manera obvia a la solución de la presente solicitud pues mi representada no esta reivindicando cualquier anticuerpo anti-TNF sino un anticuerpo anti-TNF específico, el cual se define por las secuencias de la cadena ligera (SEQ ID NO: 8 o 113) y la cadena pesada (SEQ ID NO: 11 o 115).

De esta forma, una persona versada en la materia, a partir del anticuerpo que enseña D2, no podría identificar las secuencias de amino ácidos de los anticuerpos reivindicados mediante ingeniería genética porque dicho anticuerpo CDP571, como se mencionó anteriormente, es diferente al que reivindica mi representada, por lo tanto la afirmación de su Despacho no es correcta.

Además, es importante mencionar las ventajas del anticuerpo reivindicado en la presente solicitud en comparación con el anticuerpo que enseña el documento D2 pues debido a pruebas clínicas realizadas al anticuerpo CDP571 del documento D2, dicho anticuerpo nunca llegó al mercado porque no mostró eficacia alguna en los ensayos realizados, por ejemplo, en los relacionados a la enfermedad de Crohn (por favor vea el resumen y discusión de Feagan BG, Sandborn WJ, Lichtenstein G, Radford-Smith G, Patel J, Innes A, CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial, Aliment Pharmacol Ther. 2006 Mar 1;23(5):617-28, documento adjunto al

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presente recurso). Por el contrario, el anticuerpo de la presente solicitud (CDP870) mostró ser eficaz y posteriormente aprobado para el tratamiento de la enfermedad de Crohn y la artritis reumatoide (por favor ver documento anexo: *Keystone E. et al., Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, Arthritis Rheum. 2008 Nov;58(11):3319-29* and *Allez M. et al., Efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF, Aliment Pharmacol Ther. 2009 Aug 26, Epub ahead of print*). Por lo tanto, la aplicabilidad terapéutica del anticuerpo que reivindica mi representada no se deriva de forma obvia por el documento D2.

Con respecto al documento D1, dicha anterioridad no menciona ninguna información con respecto a la secuencia de un anticuerpo anti-TNF.

Por lo tanto, las reivindicaciones de la presente solicitud se refieren a un anticuerpo anti-TNF específico, el cual difiere de los anticuerpos anti-TNF del arte previo (D1 y D2) *inter alia* por las secuencias de amino ácidos de las cadenas pesada y ligera, además de su perfil y utilidad terapéutica.

Por último, es importante mencionar que el anticuerpo de la presente solicitud (CDP870, INN= certolizumab pegol) tiene una afinidad mayor que otro tipo de anticuerpos anti-TNF útiles para los tratamientos (por favor vea el resumen de *Sorbera, L.A., Leeson, P.A, Certolizumab Pegol, Drugs of the Future, Drugs Fut 2005, 30(11): 1087*). El CDP870 también presente una mayor afinidad que el anticuerpo CDP571 de D2 (~90 pM para CDP870, tal y como se presenta en Sorbera et al. en la página 1088 en la sección "Pharmacological Actions" con respecto a 140 pM para CDP571 en D2 en la página 37, última línea).

Por lo anterior, queda demostrado el nivel inventivo de la presente solicitud en vista de los documentos D1 y D2, pues la solicitud de mi representada demuestra efectos sorprendentes que no fueron enseñados o sugeridos en las referencias citadas. Además, una persona versada en la materia no podría suponer de los documentos D1 y D2 las secuencias de aminoácidos y el perfil y/o utilidad farmacéutica de los anticuerpos reivindicados por mi representada.

5. ANEXOS

- Copia de los documentos:
 - *Feagan BG, Sandborn WJ, Lichtenstein G, Radford-Smith G, Patel J, Innes A, CDP571, a humanized monoclonal antibody to tumour necrosis factor-alpha, for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial, Aliment Pharmacol Ther. 2006 Mar 1;23(5):617-28*
 - *Keystone E. et al., Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter,*

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randomized, double-blind, placebo-controlled, parallel-group study, Arthritis Rheum. 2008 Nov;58(11):3319-29 and Allez M. et al., Efficacy and safety of a third anti-TNF monoclonal antibody in Crohn's disease after failure of two other anti-TNF, Aliment Pharmacol Ther. 2009 Aug 26, Epub ahead of print

o Sorbera, L.A., Leeson, P.A, Certolizumab Pegol, *Drugs of the Future, Drugs Fut* 2005, 30(11): 1087-1091

6. PETICIONES

Ruego a Usted entonces, lo siguiente:

6.1. Que se revoque el artículo PRIMERO de la Resolución No. 44911 en cuanto niega el privilegio de patente para el capítulo reivindicatorio de la presente invención.

6.2. Que se otorgue la respectiva patente de invención para todas (11) las reivindicaciones del último pliego reivindicatorio.

7. NOMBRE Y DIRECCIÓN DEL RECURRENTE

El nombre y la dirección del recurrente son:

CELLTECH R&D LIMITED

208 Bath Road, Slough,

Berkshire SL1 3WE,

Reino Unido



8. NOTIFICACIONES

Manifiesto a Usted que recibiré notificaciones en la Secretaría de su Despacho y en mis oficinas de abogado situadas en el Edificio Siski, Carrera 4a. No. 72-35, piso 4o. de esta ciudad.

Señor Superintendente,

A handwritten signature in black ink, appearing to read 'Emilio Ferrero'.

EMILIO FERRERO

T.P.A. No. 31.929

COLO-17184-843-001-2

COLO-11773-843-001-8

COLO-13115-841-001-2

LMAILMAID-158903WPC17184

No. M-2009-158903/LMA

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NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
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CDP571, a humanized monoclonal antibody to tumour necrosis factor- α , for steroid-dependent Crohn's disease: a randomized, double-blind, placebo-controlled trial

B. G. FEAGAN*, W. J. SANDBORN†, G. LICHTENSTEIN‡, G. RADFORD-SMITH¶, J. PATELS
& A. INNESS

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Accepted 8 December 2005

SUMMARY

Background

More than 50% of patients with Crohn's disease become either steroid resistant or dependent. Accordingly, development of new treatments for steroid-dependent Crohn's disease is a research priority.

Aim

To evaluate CDP571, a humanized antibody to tumour necrosis factor- α , for the treatment of steroid-dependent Crohn's disease.

Methods

Patients with steroid-dependent Crohn's disease ($n = 271$) were enrolled in a 36-week, double-blind, placebo-controlled trial. Steroid dependence was defined as use of prednisolone or prednisone (15–40 mg/day) or budesonide (9 mg/day) for ≥ 8 weeks, a previous failed attempt to decrease or discontinue steroids within 8 weeks of screening, and a Crohn's Disease Activity Index score of ≤ 150 points. Patients were randomized to receive intravenous CDP571 10 mg/kg or placebo 8-weekly through to week 32. Steroids were then tapered using a defined schedule. The primary efficacy endpoint was the percentage of patients with steroid sparing, defined as discontinuation of steroid therapy without a disease flare (Crohn's Disease Activity Index score ≥ 220 points) at week 36.

Results

Steroid sparing occurred in 53 of 181 (29.3%) CDP571 patients and 33 of 90 (36.7%) placebo patients ($P = 0.24$). Adverse events occurred at similar frequencies in both treatment groups.

Conclusions

CDP571 was ineffective for sparing steroids in patients with steroid-dependent Crohn's disease. CDP571 was well tolerated.

Aliment Pharmacol Ther 23, 617–628

INTRODUCTION

Steroids are highly effective for the induction of remission in patients with active Crohn's disease.¹ However, the long-term prognosis of these patients is poor. More than 50% of patients become steroid-dependent or undergo a surgical resection within 1 year of commencing treatment with these agents.² Although controlled trials have demonstrated that azathioprine and mercaptopurine are effective for maintenance of steroid-induced remission in patients with active Crohn's disease,^{3, 4} these agents have not been evaluated in steroid-dependent patients. Methotrexate is effective for the induction and maintenance of remission and for steroid-sparing in patients with steroid-treated Crohn's disease.^{5, 6} Nevertheless, for various reasons, acceptance of this drug by gastroenterologists has been modest.

Infliximab is an IgG1 chimeric monoclonal antibody to tumour necrosis factor- α (TNF- α) that is effective for the induction and maintenance of remission in patients with moderate to severe Crohn's disease.^{7, 8} Although a subgroup analysis within a maintenance study demonstrated that infliximab is effective for steroid sparing in patients,⁸ this indication has not been independently evaluated in steroid-dependent patients. Furthermore, infliximab is immunogenic and patients frequently develop human anti-chimeric antibodies (HACAs). These antibodies may cause infusion reactions and loss of efficacy.⁹⁻¹¹

Consequently, humanized monoclonal antibodies were designed to reduce the immunogenicity associated with murine and chimeric antibodies. The process of humanization entails grafting a human antibody to the antigen binding complementarity determining regions (CDRs) of a murine antibody variable domain, resulting in a protein that is approximately 95% human.¹²

CDP571, a humanized monoclonal antibody specific to human TNF- α , was created by linking a human IgG4 antibody framework to the CDR of a murine TNF- α monoclonal antibody.¹³ Previous trials indicated that intravenous (i.v.) CDP571 might be effective for the short-term treatment of active Crohn's disease^{14, 15} and possibly for steroid sparing.¹⁶ A large-scale study subsequently demonstrated that i.v. CDP571 was effective for the short-term treatment of active Crohn's disease, but failed to demonstrate long-term efficacy over 28 weeks [(Sandborn, 2004 no. 1855)]. *Post hoc* analyses of the data from this study showed that CDP571 had both short- and long-term efficacy in a subgroup

of patients with increased serum concentrations of C-reactive protein (CRP) [(Sandborn, 2004 no. 1855)]. Here we describe the results of a 36-week Phase-III trial in which patients with steroid-dependent Crohn's disease received i.v. CDP571 10 mg/kg or placebo 8-weekly through to week 32.

METHODS

Selection of patients

Eligible patients were at least 18 years of age and had steroid-dependent Crohn's disease defined as: (i) the requirement for steroid treatment with prednisolone or prednisone (15–40 mg/day), or budesonide (9 mg/day) for at least 8 weeks (although the dose could have been temporarily reduced during an attempt at steroid withdrawal), with a stable dose for at least 2 weeks prior to study entry; (ii) an unsuccessful attempt to decrease or discontinue steroid treatment, owing to disease flare within 30 days of the attempt, on at least one occasion in the 8 weeks prior to study entry. All patients had a baseline score of ≤ 150 points on the Crohn's Disease Activity Index (CDAI).¹⁷ The diagnosis of Crohn's disease was made using radiological, endoscopic, or histological evidence.

Patients with infection of a fistula (abscess); ulcerative colitis; bowel perforation or evidence of a non-inflammatory obstruction (within 6 months); obstructive symptoms owing to significant mechanical obstruction (within 3 months); small bowel resection >100 cm and/or more than the right colon resected (to avoid patients with significant postoperative diarrhoea that could confound measurement of the CDAI); or a colostomy or ileostomy (to avoid patients in whom stool frequency cannot be determined as this would confound measurement of the CDAI) were not eligible. In addition, patients were ineligible if they had an infectious enteritis or other serious infection; a clinically important chronic disease in the 3 months before study entry; previous history of blood dyscrasia (pancytopenia or aplastic anaemia) or demyelinating disease; current or previous malignancy other than successfully treated carcinoma of the cervix or basal cell carcinoma (> 5 years prior to entry); current or previous bowel dysplasia (5 years before screening); or clinically important allergies or multiple drug allergies. Furthermore, patients with drug or alcohol abuse, significant abnormal haematology or biochemical values, or a history of or concurrent tuberculosis,

CDP571
IgG4 human
+
AcM TNF- α
murine

Efficacy
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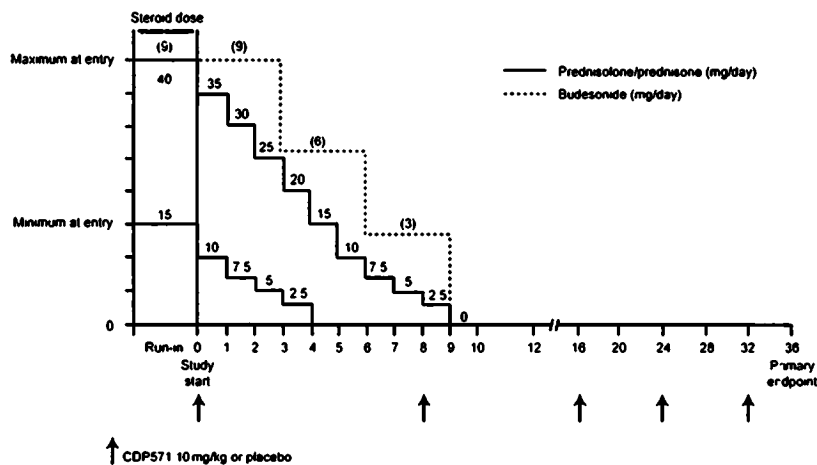


Figure 1. Dosing schedule and steroid withdrawal strategy.

hepatitis, or human immunodeficiency virus were not entered. Pregnant and lactating women were also excluded. The institutional review board at each centre approved the study and all the participants gave written informed consent.

Steroid-tapering regimen

An attempt was made to discontinue patients' existing steroid therapies within 4–9 weeks of starting treatment with CDP571 or placebo. A defined steroid-tapering schedule specific to the baseline dose was utilized (Figure 1). If at any time a patient required rescue therapy for a flare (CDAI ≥ 220 points), the dose of prednisolone, prednisone or budesonide was increased to the daily dose that the patient was receiving at the initial visit. Re-tapering was then resumed on the day of the next scheduled study infusion (unless the flare was within 2 weeks of the next scheduled infusion, in which case re-tapering was resumed after the following infusion 8 weeks later). The steroid dose was then tapered down to the daily steroid dose above that at which the disease had flared. If patients experienced a second flare, or could not be maintained on their dose of steroid at study entry, they were withdrawn from the study.

Concomitant medications

Treatment with azathioprine (minimum allowed dose 1.5 mg/kg/day) or mercaptopurine (minimum allowed dose 0.75 mg/kg/day) at a stable dose for ≥ 16 weeks, or methotrexate (minimum allowed dose 15 mg/weeks) at a stable dose for ≥ 12 weeks, was permitted. Patients who discontinued these agents in the 4 weeks prior to

study entry were ineligible. Sulfasalazine, mesalamine, olsalazine, or balsalazide at a stable dose for ≥ 12 weeks was also permitted. Treatment with antibiotics at a stable dose for ≥ 8 weeks was also allowed provided that the patient agreed to continue the antibiotic during screening and throughout the 36-week trial. Patients who had received sodium cromoglycate, mycophenolate, or ciclosporin within 4 weeks of study entry were excluded, as were those who had been treated with >4 doses of an opioid-containing analgesic or non-steroidal anti-inflammatory drug [including cyclooxygenase (COX)-1 and COX-2 inhibitors] within 2 weeks of entry. Taking specific opioids (i.e. loperamide, diphenoxylate and codeine) for the control of diarrhoea was permitted.

Patients who had previously participated in a clinical trial of CDP571 or who had been treated with another biological anti-TNF- α therapy within 12 weeks of study entry were excluded. Patients who had previously received anti-TNF- α therapy and subsequently experienced either a lack of response to the first dose or an infusion reaction that was suspected or confirmed to be associated with an immune response (e.g. presence of HACA) were also ineligible. Other exclusion criteria included participation in a clinical trial involving an antibody, cytokine, or other immunomodulatory therapy in the 3 months prior to entry and participation in any other clinical trial within 1 month of study entry.

Study medication

Pharmacists at each centre prepared the i.v. infusions of CDP571 or placebo. Placebo was a 5% w/v solution of dextrose. CDP571 at a dose of 10 mg/kg body weight or placebo was administered to patients as a 2-h i.v.

infusion using a 0.2 µm filter. CDP571 and placebo had a similar clear and colourless appearance. Patients received infusions every 8 weeks up to week 32.

Design of the study

This randomized, double-blind, placebo-controlled, parallel-group study was performed at 59 centres in Australia, Bulgaria, Canada, the Czech Republic, Hungary, Poland and the USA (see Appendix). The randomization procedure was stratified according to: (i) geographic region (Europe, the USA, Canada and Australia); and (ii) concomitant medication (treatment with at least one of azathioprine, mercaptopurine, methotrexate, corticosteroids, or antibiotics; and none of these treatments). After a 1- to 2-week screening period, eligible patients were randomly assigned in a 2 : 1 ratio to receive CDP571 or placebo. The randomization schedules for each of the two stratified groups were computer generated by an independent statistician.

Outcomes and statistical analyses

Disease activity was assessed at the baseline (randomization) visit, and at week 2, 4, 8, 12, 16, 24, 32 and 36. Using diary cards, patients recorded the frequency of loose stools, the extent of their abdominal pain and their general well-being in the 7 days before each visit. At each visit, a physical examination, fistula evaluation, quality of life assessment and laboratory tests were conducted and patients were asked whether adverse events had occurred. Clinical disease activity was assessed using the CDAI.¹⁷ Patients were assessed for the presence of open and actively draining perianal or abdominal enterocutaneous fistulae (defined as open fistulae with either spontaneous drainage or the ability to express drainage with gentle compression), or fistulae closure.¹⁸ Disease-specific health-related quality of life was assessed using the self-administered Inflammatory Bowel Disease Questionnaire (IBDQ).^{19, 20} Blood samples were taken for haematological and biochemical assessments and for measurement of plasma anti-CDP571 antibody (immunogenicity assay) and CRP concentrations.

Response measures

The efficacy intention to treat (ITT) population included all patients who received at least one dose of study treatment and had at least one efficacy and/or quality of

life measurement after the first study medication infusion. The primary efficacy endpoint was the percentage of patients with steroid sparing [defined as not experiencing a disease flare (CDAI ≥ 220 points) and no longer requiring steroid therapy at week 36]. Secondary efficacy endpoints included: the percentages of patients who had steroid sparing (as defined above) at week 16, 24 and 32; the time from baseline to the first increase in steroid therapy; the total amount of steroid taken during the study as a proportion of the amount taken if the patient had remained on their baseline dose throughout the study; the percentage of patients in the subgroup with fistulae who showed a closure of ≥ 50% or 100% of fistulae at any visit and on two consecutive visits over an 8-week period (closure defined as no drainage on gentle compression); the mean CDAI and IBDQ scores; and the median serum CRP concentration (week 0, 8, 16, 24, 32 and 36).

Safety measures

The safety population included all patients who received at least one dose of study treatment and had at least one postbaseline safety evaluation after the first infusion. All adverse events were recorded and graded according to Medical Dictionary for Regulatory Activities (MedDRA, Version 3.0, Reston, VA, USA) criteria. Infusion reactions were defined as any adverse events occurring within 2 h of the start of the infusion.

Other safety measures were laboratory data and the presence of antibodies to CDP571 at week 0, 8, 16, 24, 32 and 36. We also performed exploratory comparisons to determine the impact of concomitant therapy with immunosuppressive medications (azathioprine, mercaptopurine, or methotrexate) and past therapy with infliximab on the percentage of patients with steroid sparing at week 16, 24, 32 and 36.

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Statistical methods

The percentages of steroid-dependent patients with steroid sparing at week 16, 24, 32 and 36 were summarized and compared between treatment groups using the Mantel-Haenszel test, adjusting for geographic region and concomitant medication usage. A Kaplan-Meier analysis of the time to the first increase in steroid therapy measured from baseline was also performed. In this analysis, the first increase in steroid therapy was considered an event. Patients with no reported events by week 36 were censored at this

timepoint. Patients without events who withdrew from the study at any time during the period of analysis were censored at their time of withdrawal. The total steroid dose taken throughout the study, as a proportion of the amount the patient would have taken if retained on their baseline dose throughout the study, was compared between treatment groups using the van Elteren's test. Exploratory comparisons to determine the impact of concomitant immunosuppressive therapy or past therapy with infliximab on the percentage of patients who were steroid sparing at week 16, 24, 32 and 36 were performed using Fisher's exact test. Of the subgroup of patients with fistulae, the percentage showing a closure of $\geq 50\%$ and 100% of fistulae at any visit and on two consecutive visits over an 8-week period at any time during the study, were summarized and comparisons made between treatment groups using Fisher's exact test. The mean CDAI and IBDQ scores and the median serum CRP concentrations, were presented graphically. For the analyses of CDAI scores, IBDQ scores and CRP concentrations, data for patients who were lost to follow up or who withdrew from the study because of deterioration in their condition or adverse events were shown using the last observation carried forward approach. Descriptive statistical techniques were used to summarize the adverse events by body system, preferred term and severity, as well as by body system, preferred term and relationship to study drug. The percentages of patients with antibodies to CDP571 were also summarized descriptively. All statistical tests were two-sided and P -values ≤ 0.05 were considered statistically significant.

Sample size

We estimated that 186 patients in the CDP571 group and 93 patients in the placebo group were needed to have 90% power to detect a true difference in the proportion of steroid-dependent patients who achieved steroid sparing at week 36, assuming a true difference of 17% and a placebo rate of 10%. These calculations are based on the observation from a previous Phase-II study of CDP571 for steroid sparing where 44% of patients treated with CDP571 were off steroid therapy at week 16 and 33% remained off steroid therapy at week 40.¹⁶ Because a similar success rate could not be assumed in a larger population, we made the assumption that a lower proportion of patients (27%) would remain off steroid therapy at week 36. We planned to recruit a total of 279 patients.

RESULTS

The study was conducted between 30 November, 2000 and 13 May, 2002. Two hundred and ninety-eight patients were screened, of whom 271 were randomized: 90 patients received placebo and 181 received CDP571. These 271 patients comprised the ITT population. Two patients randomized to placebo did not have postbaseline safety evaluations; the remaining 269 patients comprised the safety population. Baseline characteristics were similar for the two treatment groups (Table 1). The disposition of participating patients is shown in Figure 2.

Major protocol violations were recorded for 152 (56.1%) patients (Table 2). The most common protocol deviation was errors in steroid titration, which occurred in 90 patients (33%). Forty-four patients (48.9%) in the placebo group and 73 patients (40.3%) in the CDP571 treatment group completed the study according to the protocol.

Efficacy

The percentage of steroid-dependent patients who achieved steroid sparing at week 36 was not different between patients treated with CDP571 (53/181, 29.3%) and those who received placebo (33/90, 36.7%; $P = 0.24$) (Figure 3). Likewise, the percentages of steroid-dependent patients who achieved steroid sparing at week 16, 24 and 32 were not significantly different between the two treatment groups (Figure 3). Exploratory comparisons demonstrated that there were no significant differences in the primary outcome according to the stratification criteria of geographic region and concomitant medication use (data not shown).

The median time to first increase in steroid dose measured from baseline was 24.1 weeks in CDP571-treated patients and week 36 in placebo-treated patients ($P = 0.38$). The total amount of steroid taken during the study, as a proportion of the amount taken if the patient had remained on their baseline dose throughout the study, was similar in the two treatment groups (24% and 36% for the CDP571 and placebo groups, respectively). The median CRP concentrations at week 8, 16, 24, 32 and 36 were similar in the two groups (data not shown). The mean CDAI scores (Figure 4a) and the mean IBDQ scores (Figure 4b) at week 8, 16, 24, 32 and 36 were also similar for patients treated with placebo and CDP571.

Variable	Placebo (n = 88)	CDP571 10 mg/kg (n = 181)	Table 1. Baseline characteristics (safety population)
White, n (%)	87 (98.9)	179 (98.9)	
Male, n (%)	47 (53.4)	104 (57.5)	
Mean (s.d.) age at entry, years	34.7 (12.0)	35.3 (12.7)	
Mean (s.d.) weight, kg	72.2 (16.0)	70.2 (16.5)	
Mean (s.d.) duration of Crohn's disease, years	6.6 (6.2)	6.4 (6.4)	
Location of Crohn's disease*, n (%)			
Duodenum	1 (1.1)	10 (5.5)	
Ileum	64 (72.7)	135 (74.6)	
Caecum	55 (62.5)	102 (56.4)	
Ascending colon	46 (52.3)	86 (47.5)	
Transverse colon	31 (35.2)	73 (40.3)	
Descending colon	43 (48.9)	83 (45.9)	
Rectum	29 (33.0)	58 (32.0)	
Perianal	12 (13.6)	29 (16.0)	
Other	6 (6.8)	19 (10.5)	
Open and draining perianal or abdominal enterocutaneous fistulae, n (%)	8 (9.1)	17 (9.4)	
Previous intestinal resection, n (%)	24 (27.3)	60 (33.1)	
Mean (s.d.) Crohn's Disease Activity Index score	93 (47)	94 (48)	
Mean (s.d.) Inflammatory Bowel Disease Questionnaire score	176 (26)	171 (30)	
Geometric mean (95% CI) C-reactive protein concentration, mg/L	4.21 (2.91, 6.09)	3.78 (2.97, 4.81)	
Concomitant medications, n (%)			
Budesonide	23 (26.1)	32 (17.7)	
Prednisone or prednisolone	67 (76.1)	150 (82.9)	
¹ Azathioprine or mercaptopurine	21 (23.9)	44 (24.3)	
² Methotrexate	2 (2.3)	5 (2.8)	
³ Antibiotics	2 (2.3)	14 (7.7)	
⁴ 5-aminosalicylates†	73 (83.0)	130 (71.8)	
One or more of 1 or 2	23 (26.1)	49 (27.1)	
One or more of 1, 2, 3, or 4	76 (86.4)	146 (80.7)	
Previous anti-TNF- α therapy, n (%)	9 (10.2)	19 (10.5)	

CI, confidence intervals; s.d., standard deviation; TNF- α , tumour necrosis factor- α .
 * Patients may have Crohn's disease involving more than one location.
 † Mesalamine, sulfasalazine and olsalazine.

At the start of the study, 17 (9.4%) patients in the CDP571 group and eight (8.9%) patients in the placebo group had at least one open fistula. No statistically significant differences were apparent between the percentages of patients treated with CDP571 or placebo who had closure of $\geq 50\%$ (53% and 38% respectively) or 100% (41% and 25% respectively) of their fistulae at any visit.

Safety

Adverse events occurred at similar frequencies in the placebo and CDP571 groups (Table 3). Patients

discontinued treatment because of an adverse event at similar frequencies in the placebo (10.2%) and CDP571 (12.7%) groups, most commonly owing to an exacerbation of Crohn's disease. The most frequently reported adverse events ($>5\%$) in both treatment groups were similar (Table 3). Serious adverse events occurred in 6.8% of patients in the placebo group and 12.2% of patients in the CDP571 group (Table 3). No cancers occurred during the study. One patient treated with CDP571 died during the study, but the death was considered unrelated to the study medication. The patient underwent surgery for small intestinal obstruction complicated by ileal perforation and faecal peritonitis

525
560

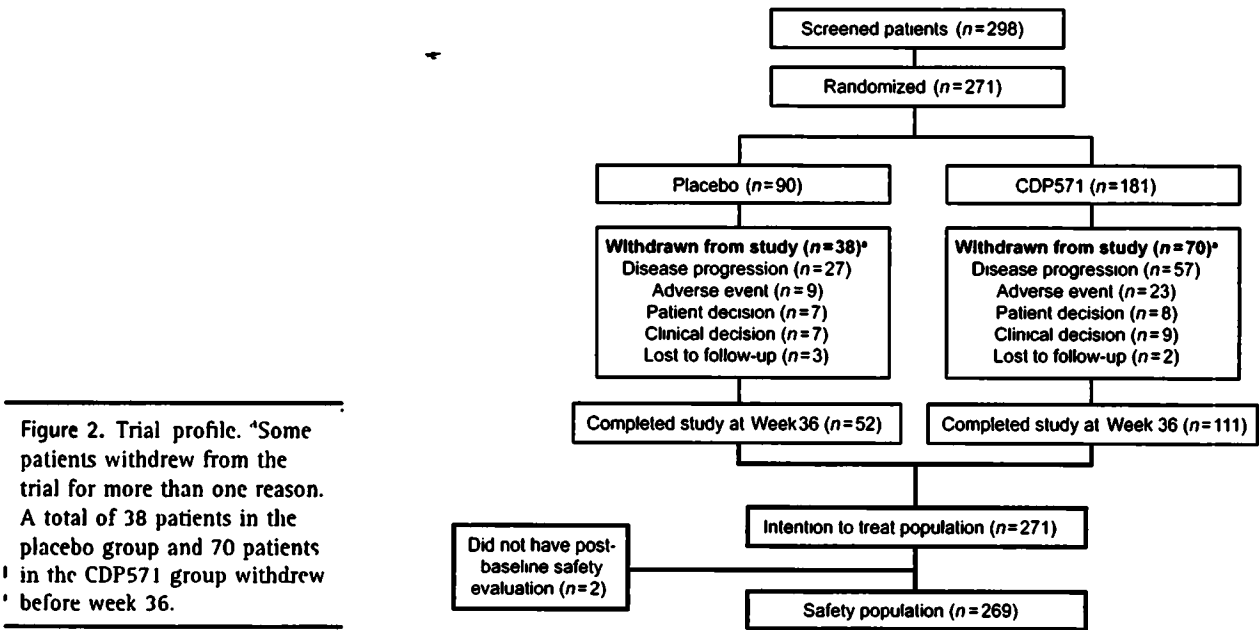


Table 2. Major protocol deviations	
Variable	Number of patients n (%)
Efficacy population	271 (100)
Total major protocol deviations	151 (56.1)
Errors in the titration of steroids. These errors included incorrect down-titration of steroids following flare, failure to stop titration following flare, incorrect steroid titration, incorrect timing of steroid titration and stopping down titration.	90 (33)
Other steroid dosing errors. These errors included incorrect steroid dose or incorrect increase in dose, changing dose postflare and addition of a steroid.	30 (11.1)
CDAI score was either out of range (>150) at the week 0 assessment or not calculated.	25 (9.2)
Concomitant medications were changed during the study.	16 (5.9)
Medications not allowed (e.g. methylprednisolone, intravenous hydrocortisone, triamcinolone, dexamethasone, prednisolone sodium phosphate, prednisone for an allergic reaction, and prednisolone combined with budesonide).	16 (5.9)
Mesalazine dose was not stable for at least 12 weeks prior to screening, methotrexate dose was less than 15 mg/week, or azathioprine dose was less than 1.5 mg/kg/day or not stable for at least 16 weeks prior to screening.	11 (4.1)
There were more than 5 weeks between week 32 and 36 assessments.	9 (3.3)
Concomitant medications were not stable prior to infusion.	8 (3.0)
Steroid dose was not stable for at least 2 weeks prior to the first infusion.	5 (1.8)
The incorrect volume of CDP571 or placebo was infused.	5 (1.8)
Miscellaneous	9 (3.3)

* In addition, protocol deviations occurred in three patients whose steroid dose was too low or incorrect on study entry, two patients who were taking long-term anti-antibiotics, two patients who had a 'visit out of window', one patient who withdrew after a second increase of steroid dose and one patient who did not have a chest X-ray performed until week 2.

and died after 3 days because of gastrointestinal bleeding. There were no clinically significant changes in laboratory values in either treatment group.

Infections occurred at similar frequencies in the placebo and CDP571 groups (Table 3); specific type of infections occurring at a frequency of $\geq 4.5\%$ are

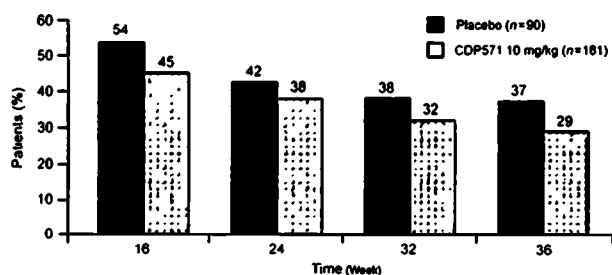


Figure 3. Percentages of patients with steroid-dependent Crohn's disease treated with CDP571 10 mg/kg or placebo at week 0, 8, 16, 24 and 32 who showed steroid sparing (defined as patients who no longer required steroid therapy and who did not experience a disease flare [Crohn's Disease Activity Index (CDAI) score ≥ 220 points] at any postfirst infusion scheduled visit at which a CDAI score was available) (intention to treat population).

tabulated. Serious infections occurred in six patients (3.3%) in the CDP571 group and none in the placebo group (Table 3); the specific types of serious infections are described in Table 3. No patient developed tuberculosis or other opportunistic infections.

Infusion reactions occurred in 13 (14.8%) patients in the placebo group and 39 (21.5%) patients in the CDP571 group (Table 3). Hypersensitivity reactions occurred in none of the patients in the placebo group and in 3.9% of patients treated with CDP571 (Table 3).

Anti-CDP571 antibodies

Of the 181 patients treated with CDP571, post-treatment samples were available for 164 patients, 10 (6.1%) of whom tested positive for anti-idiotypic antibodies to CDP571. None of the patients who tested positive for antibodies were receiving concomitant treatment with immunosuppressive medications.

Sixty per cent of patients (6/10) in the CDP571 treatment group who tested positive for anti-CDP571 antibodies experienced an acute infusion reaction (one of whom also experienced a delayed hypersensitivity-like reaction), compared with 7% of patients (12/171) in the CDP571 group who tested negative for antibodies. Of the 10 patients in the CDP571 treatment group who tested positive for anti-CDP571 antibodies, CDP571 plasma concentrations measured pre-infusion were below the limit of quantification at all visits when anti-CDP571 antibodies were present (except for one instance in one patient, when the CDP571 plasma level was just above the limit of quantification).

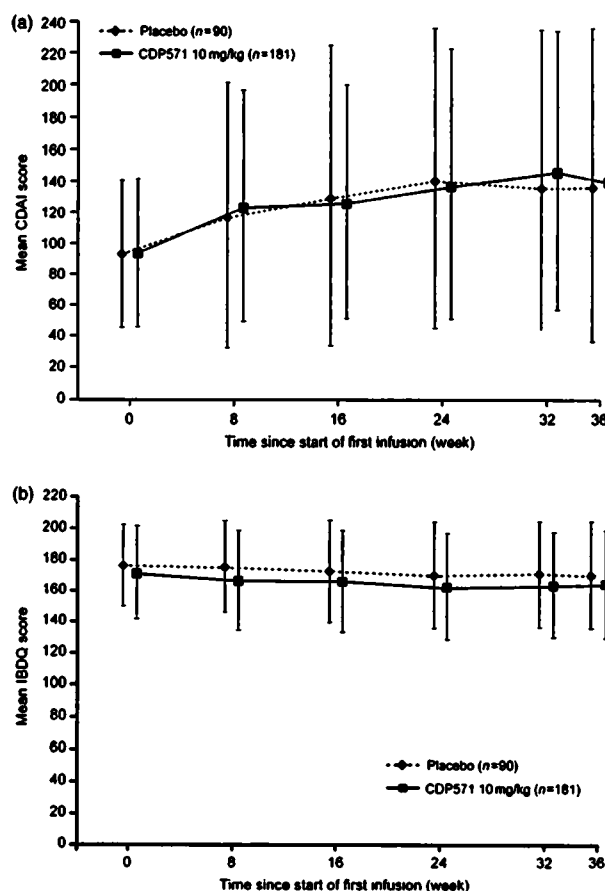


Figure 4. Mean scores at each study visit since the start of the first infusion, according to treatment group (last observation carried forward) for the Crohn's Disease Activity Index (CDAI) (a) and Inflammatory Bowel Disease Questionnaire (IBDQ) (b) for patients treated with CDP571 10 mg/kg or placebo at week 0, 8, 16, 24 and 32 (intention to treat population; limits correspond to one standard deviation from the mean).

DISCUSSION

Withdrawal of steroids while maintaining remission in patients with steroid-dependent Crohn's disease is an important unmet medical need. In this study, we found that CDP571 was ineffective as a steroid-sparing agent. Furthermore, no significant differences were identified between the two treatment groups in other efficacy endpoints, including the time to the first increase in steroid therapy; the total amount of steroid taken; the percentage of patients who showed a closure of $\geq 50\%$ or 100% of fistulae at any visit or on two consecutive visits over an 8-week period;

No evidence
verifying CDP571

Table 3. Adverse events (safety population)

Variable	No. of patients (%)	
	Placebo (n = 88)	CDP571 10 mg/kg (n = 181)
Patients with adverse events	62 (70.5)	128 (70.7)
Patients with serious adverse events	6 (6.8)*	22 (12.2)†
Patients with severe adverse events	9 (10.2)	32 (17.7)
Patients with possibly, probably, or definitely drug-related adverse events	37 (42.0)	76 (42)
Patients with adverse events leading to withdrawal	9 (10.2)	23 (12.7)
Deaths	0 (0)	1 (0.6)
Adverse events possibly or probably related to study treatment occurring in ≥5% of patients in at least one of the treatment groups‡		
Crohn's disease aggravated	12 (13.6)	34 (18.8)
Headache	11 (12.5)	30 (16.6)
Nausea	4 (4.5)	16 (8.8)
Arthralgia	3 (3.4)	16 (8.8)
Abdominal pain	3 (3.4)	14 (7.7)
Dermatitis	6 (6.8)	12 (6.6)
Sore throat	2 (2.3)	11 (6.1)
Pyrexia	3 (3.4)	9 (5.0)
Viral infection	6 (6.8)	8 (4.4)
Upper respiratory tract infection	6 (6.8)	7 (3.9)
Nasopharyngitis	6 (6.8)	6 (3.3)
Back pain	6 (6.8)	6 (3.3)
Urinary tract infection	7 (8.0)	5 (2.8)
Patients with adverse events occurring within 2 h of the start of the infusion		
Any	13 (14.8)	39 (22.8)
Hypersensitivity	0	7 (3.9)
Urinary tract infection	2 (2.3)	4 (2.2)
Headache	2 (2.3)	2 (1.1)
Chest tightness	0	2 (1.1)
Flushing	0	2 (1.1)
Hypertension	0	2 (1.1)
Nausea	0	2 (1.1)
Taste disturbance	0	2 (1.1)
Urticaria	0	2 (1.1)
Patients with infections		
Any infection	32 (36.4)	57 (31.5)
Urinary tract infection	7 (8.0)	5 (2.8)
Viral infection	6 (6.8)	8 (4.4)
Upper respiratory tract infection	6 (6.8)	7 (3.9)
Nasopharyngitis	6 (6.8)	6 (3.3)
Sinusitis	0	7 (3.9)§
Influenza	4 (4.5)	1 (0.6)
Abdominal abscesses	0	2 (1.2)§
Skin/subcutaneous tissue abscess	0	1 (0.6)§

Table 3. (Continued.)		
Variable	No. of patients (%)	
	Placebo (n = 88)	CDP571 10 mg/kg (n = 181)
Scrotal infection	0	1 (0.6)§
<i>Escherichia coli</i> sepsis	0	1 (0.6)§

* Six placebo patients experienced 18 serious adverse events, seven of which (cardiac failure, anaemia, myocardial ischaemia, pneumonitis, thyrotoxicosis, conjunctivitis and cataract) were reported in one patient. One placebo patient experienced gastric ulcer, one patient abdominal distension and pain, one patient Crohn's disease aggravated (two events) and pyrexia, one patient appendicitis and one patient deep limb venous thrombosis, anaemia, leucopenia, and pancytopenia.

† Twenty-two CDP571-treated patients experienced a total of 38 serious adverse events. There was one patient with nine Crohn's disease related events, six patients with Crohn's disease aggravated (one with septicaemia escherichial), three patients with hypersensitivity, two patients with arthralgia, two patients with intestinal obstruction (one with peritonitis), and three patients with abdominal pain (one with vomiting and one with abdominal abscess). A further three patients experienced a serious adverse event of sinusitis, calculus, renal or ileitis aggravated. The remaining three patients each had three events: scrotal infection, venous thrombosis, and gastrointestinal haemorrhage in one case, and abdominal abscess, ileus and ileostomy in the other.

‡ None of the differences between the placebo and CDP571 groups was significant.

§ Infection was classified as a serious adverse event.

the mean CDAI and IBDQ scores; and the median serum CRP concentration. These findings contrast with those of a smaller study by Feagan *et al.*,¹⁶ who reported that 44% of steroid-dependent patients treated with CDP571 were able to withdraw from steroids without disease flare at week 40 (compared with the placebo rate of 22%). The current study involved a greater number of study centres and a higher proportion of patients from Eastern Europe than the trial conducted by Feagan *et al.*¹⁶ Hence, differences in the characteristics of the patients' Crohn's disease, the duration of steroid use and the extent to which patients had previously attempted to withdraw from steroids may have been present. It is also notable that the current study had a high rate of protocol violations, which may have influenced the outcome. In particular, the steroid-tapering protocol was not followed correctly in many patients. A second possible reason that CDP571 failed to demonstrate efficacy is that the patients enrolled in the current trial were not truly steroid-dependent, thus leading to a higher than expected placebo response rate. In keeping with this possibility, the 36.7% response rate observed at week 36 was substantially higher than the placebo rates observed in previous trials of CDP571 (21.9% at week 16)¹⁶ and methotrexate (19% at 16 weeks).⁵

Finally, another possible reason why our study failed is that CDP571 is ineffective for the long-term

treatment of Crohn's disease. Previous studies in patients with moderately to severely active Crohn's disease failed to demonstrate efficacy at week 24–28,^{15, 21} except in a selected subgroup of patients with baseline CRP concentrations ≥ 10 mg/L.²¹ These results are in contrast to those observed with infliximab, which is effective for maintenance of remission and steroid sparing in patients with moderately to severely active Crohn's disease.⁸ The apparent differences in efficacy between CDP571 and infliximab may, among other reasons, be due to differences in antibody binding affinity for TNF- α or immunoglobulin isotype.

Analysis of the adverse events associated with the administration of CDP571 showed that the antibody was well tolerated. It is notable that no cases of pneumonia or opportunistic infection occurred. One patient who received CDP571 died; however, this event was judged to be unrelated to treatment with the study medication. These findings are similar to those reported in other studies of CDP571 that included a total of 689 additional patients. Overall, no increased rate of serious infections, opportunistic infections, lymphoma or other cancers, autoimmune diseases, or death has been observed.^{14–16, 21, 22}

The overall frequency of antibodies against CDP571 was low (6.1%). Data from this trial suggest that concomitant use of immunosuppressants reduced

of efficacy
CDP571 v
Infliximab

anti-CDP571 antibody formation to a nearly undetectable level. When antibodies do occur, they may be associated with relative increases in the rates of infusion reactions and loss of efficacy. These data are in contrast with data that have been reported for infliximab, where as many as 60% of re-treated patients have developed antibodies.⁹⁻¹¹

In conclusion, CDP571 was ineffective for steroid sparing and maintenance of remission in patients with steroid-dependent Crohn's disease. A relatively high placebo response rate may have contributed to this outcome. CDP571 was well tolerated and demonstrated a low frequency of immunogenicity.

CONFLICTS OF INTEREST

Brian Feagan, William Sandborn and Gary Lichtenstein have served as consultants for UCB Pharma Limited. Jatin Patel is a former employee of Celltech (which subsequently merged with UCB Pharma Limited). Alison Innes is an employee of UCB Pharma Limited.

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Certolizumab Pegol Plus Methotrexate Is Significantly More Effective Than Placebo Plus Methotrexate in Active Rheumatoid Arthritis

Findings of a Fifty-Two-Week, Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

Edward Keystone,¹ Désirée van der Heijde,² David Mason, Jr.,³ Robert Landewé,⁴ Ronald van Vollenhoven,⁵ Bernard Combe,⁶ Paul Emery,⁷ Vibeke Strand,⁸ Philip Mease,⁹ Chintu Desai,¹⁰ and Karel Pavelka¹¹

Objective. To evaluate the efficacy and safety of 2 dosage regimens of lyophilized certolizumab pegol (a novel PEGylated anti-tumor necrosis factor agent) as

adjunctive therapy to methotrexate (MTX) in patients with active rheumatoid arthritis (RA) with an inadequate response to MTX therapy alone.

Methods. In this 52-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group trial, 982 patients were randomized 2:2:1 to receive treatment with subcutaneous certolizumab pegol at an initial dosage of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 mg or 400 mg given every 2 weeks, plus MTX, or placebo plus MTX. Co-primary end points were the response rate at week 24 according to the American College of Rheumatology 20% criteria for improvement (ACR20) and the mean change from baseline in the modified total Sharp score at week 52.

Results. At week 24, ACR20 response rates using

ClinicalTrials.gov identifier: NCT00152386.

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Lux Biosciences, Merck Serono, Novartis, Novo Nordisk, Noxxon Pharma, Nuon, Ono Pharmaceutical, Pfizer, Procter & Gamble, Rigel, RiGEN, Roche, Sanofi-Aventis, Savient, Schering-Plough, Scios, SKK, UCB, VLST, Wyeth, XDx, and Zelos Therapeutics (less than \$10,000 each) and receives fees as a member of the advisory board for Abbott, Amgen, Biogen Idec, Bioseek, Bristol-Myers Squibb, Can-Fite, Centocor, Chelsea, Cypress, Euro-Diagnostica, Forest, Idcra, Incyte, Jazz, Novartis, Pfizer, Rigel, RiGEN, Roche, Savient, Schering-Plough, UCB, XDx, and Wyeth (less than \$10,000 each). Dr. Mease has received consulting fees, speaking fees, and/or honoraria from UCB (less than \$10,000). Mr. Desai owns stock or stock options in UCB.

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nonresponder imputation for the certolizumab pegol 200-mg and 400-mg groups were 58.8% and 60.8%, respectively, as compared with 13.6% for the placebo group. Differences in ACR20 response rates versus placebo were significant at week 1 and were sustained to week 52 ($P < 0.001$). At week 52, mean radiographic progression from baseline was reduced in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) as compared with that in placebo-treated patients (2.8 Sharp units) ($P < 0.001$ by rank analysis). Improvements in all ACR core set of disease activity measures, including physical function, were observed by week 1 with both certolizumab pegol dosage regimens. Most adverse events were mild or moderate.

Conclusion. Treatment with certolizumab pegol 200 or 400 mg plus MTX resulted in a rapid and sustained reduction in RA signs and symptoms, inhibited the progression of structural joint damage, and improved physical function as compared with placebo plus MTX treatment in RA patients with an incomplete response to MTX.

The introduction of the tumor necrosis factor (TNF) inhibitors constituted a major advance in the treatment of rheumatoid arthritis (RA). Treatment with the 3 currently available TNF inhibitors in combination with methotrexate (MTX) can significantly improve the signs and symptoms of disease (1-3), decrease the progression of joint damage (3-5), and improve physical function and health-related quality of life (3,5). Although these agents have shown similar efficacy in clinical trials, they have different modes of action and exhibit individual pharmacokinetics, safety, and efficacy profiles (1-5), and patient responses to them in clinical practice may be variable (6). Some patients may respond to one anti-TNF but not to another, while others may discontinue therapy because of poor tolerability or loss of efficacy over time (6,7).

Certolizumab pegol is a novel TNF inhibitor, consisting of a humanized Fab' fragment fused to a 40-kd polyethylene glycol (PEG) moiety. This unique structure may avoid potential Fc-mediated effects seen in vitro, such as complement-dependent or antibody-dependent cell-mediated cytotoxicity or apoptosis (8). PEGylation increases the half-life of certolizumab pegol to ~14 days and may contribute to its preferential distribution to inflamed tissues (as observed in animal models) (9). Intravenous monotherapy with certolizumab pegol was shown to effectively control the signs and symptoms of RA in a phase II trial (10). Phase III

clinical trials were subsequently designed to evaluate the efficacy of subcutaneous certolizumab pegol monotherapy and to evaluate the efficacy of 2 different certolizumab pegol formulations (liquid and lyophilized) as add-on therapy to MTX.

We present here the results of the RA Prevention of Structural Damage 1 (RAPID 1) trial, which evaluated the efficacy and safety of 2 dosage regimens of subcutaneous lyophilized certolizumab pegol as add-on therapy to MTX in patients with active RA despite treatment with MTX alone.

PATIENTS AND METHODS

Patients. Eligible patients were ≥ 18 years of age and had a diagnosis of RA, as defined by the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria (11) for ≥ 6 months prior to screening but for < 15 years. Active disease was defined as ≥ 9 tender and 9 swollen joints at screening and at baseline, with either an erythrocyte sedimentation rate (ESR; Westergren) ≥ 30 mm/hour or a C-reactive protein (CRP) level > 15 mg/liter. Patients were required to have received MTX for ≥ 6 months, with a stable dosage of ≥ 10 mg/week for ≥ 2 months prior to baseline.

Exclusion criteria consisted of diagnoses of any other inflammatory arthritis or a secondary noninflammatory arthritis that could have interfered with our evaluation of the effects of certolizumab pegol on RA. Patients with a history of tuberculosis or a chest radiograph showing active or latent tuberculosis were also excluded. Patients with positive findings on a purified protein derivative (PPD) skin test were excluded, unless the PPD positivity was associated with previous vaccination with BCG (PPD positive by local standard). If there was no clinical or radiographic suspicion of tuberculosis in these latter patients, they were enrolled at the discretion of the investigator. Patients who, in the investigator's opinion, were at a high risk of infection were excluded, as were patients who had a history of malignancy, demyelinating disease, blood dyscrasias, or severe, progressive, and/or uncontrolled renal, hepatic, hematologic, gastrointestinal, endocrine, pulmonary, cardiac, neurologic, or cerebral disease. Patients who had received any biologic therapy within 6 months (or had received etanercept and/or anakinra within 3 months) of baseline and/or any previous biologic therapy that resulted in a severe hypersensitivity or anaphylactic reaction were excluded, as were patients who had previously failed to respond to treatment with an anti-TNF agent.

Protocol. The RAPID 1 trial was a 52-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult patients with active RA despite treatment with MTX. The study was conducted at 147 centers worldwide between February 2005 and October 2006. The Institutional Review Board or Ethics Committee at each participating center approved the study protocol. All patients gave their written consent, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Eligible patients were randomized 2:2:1 to receive treatment with 1 of 2 regimens of lyophilized certolizumab

Beneficio
Certolizumab

Certolizumab pegol CS = CD4870??

pegol (400 mg at weeks 0, 2, and 4, followed by 200 mg or 400 mg every 2 weeks thereafter, administered subcutaneously as a reconstituted, preservative-free injection) plus MTX or with a regimen of placebo (saline) plus MTX. All patients had to continue MTX at the same dosage they were taking at study entry.

In consideration of the disease severity in these study patients, those who failed to achieve a response according to the ACR criteria for 20% improvement (ACR20) (12) at weeks 12 and 14 were designated treatment failures and were withdrawn from the study at week 16. Patients who withdrew at week 16 or who successfully completed the trial were offered enrollment in an open-label extension study of certolizumab pegol 400 mg every 2 weeks. Patients who withdrew early for reasons other than withdrawal of consent underwent mandatory radiographic assessment at the time of withdrawal and at week 52.

Concomitant treatment with oral corticosteroids (≤ 10 mg/day of prednisone or equivalent, with a stable dosage for 4 weeks prior to baseline and continuing throughout the study), nonsteroidal antiinflammatory drugs/cyclooxygenase 2 inhibitors, and analgesics were allowed. Parenteral corticosteroids were not permitted. Disease-modifying antirheumatic drugs (DMARDs; exclusive of MTX) had to be discontinued 28 days prior to baseline, except for leflunomide, which had to be discontinued 6 months prior to baseline unless a cholestyramine washout was performed.

Efficacy and safety evaluations. Efficacy and safety assessments were performed at weeks 1 and 2, then every 2 weeks until week 16, and then every 4 weeks thereafter until week 52 or at the time of withdrawal. Radiographs of the hands (anteroposterior) and feet (posteroanterior) were obtained at baseline, week 24 or early withdrawal, and week 52. Radiographs were read at a central location by 3 independent readers, such that radiographs from every patient were scored by 2 readers; each reader reviewed two-thirds of the radiographs, and radiographs were read in equal pairs between the readers. Readers were blinded as to the patient's identity, clinical data, treatment, and time point (sequence) at which the radiograph was taken. The modified total Sharp score (13), erosion score, and joint space narrowing score of the 2 radiograph readings per patient were used. Interobserver and intraobserver reliability were assessed before and during the treatment phase of the study.

Co-primary end points were the ACR20 response rate at week 24 and the mean change from baseline in the modified total Sharp score at week 52. Major secondary end points included the change from baseline in modified total Sharp score at week 24, the change from baseline in the disability Index (DI) of the Health Assessment Questionnaire (HAQ) (14) at weeks 24 and 52, the ACR20 responder rate at week 52, and the ACR50 and ACR70 responder rates at weeks 24 and 52.

Additional secondary end points included mean changes from baseline in the following features: erosion and joint space narrowing scores, swollen ($n = 66$ joints) and tender ($n = 68$ joints) joint counts, physician's and patient's global assessments of disease activity, patient's assessment of arthritis pain, physical function (according to the HAQ DI), the Disease Activity Score 28-joint assessment (DAS28) (15), the ESR, and the CRP level. The proportion of patients

achieving clinically meaningful improvements in physical function was indicated by the minimum clinically important difference (MCID), which was defined as a decrease in the HAQ DI of ≥ 0.22 points from baseline (16).

Safety assessments included measurement of vital signs, physical examination, hematologic analysis, serum biochemical analysis, and urinalysis. Systolic and diastolic blood pressure was measured at each visit, before and after injection of the study drug. Adverse events were monitored at every visit. Treatment-emergent adverse events were defined as adverse events occurring after the first administration of study drug and up to 12 weeks after the last dose was administered. These were classified according to the Medical Dictionary for Regulatory Activities (version 9.0), by primary system organ class and preferred term. Concomitant medications were monitored at each visit according to protocol requirements. Plasma concentrations of anti-certolizumab pegol antibodies were measured by an enzyme-linked immunosorbent assay; levels > 2.4 units/ml were considered positive.

Statistical analysis. Sample size was determined on the basis of anticipated differences between the certolizumab pegol groups and placebo for both of the primary efficacy end points. For the ACR20 response, a sample size of 590 patients was required in order to have 90% power to detect a statistical difference of $\geq 20\%$ between the certolizumab pegol groups and placebo with a 2-sided significance level of 2.5%. For the modified total Sharp score, a sample size of 950 patients was determined to be sufficient to detect differences of ≥ 2.2 Sharp units between an active drug group and a control group with $\geq 90\%$ power (assuming an SD of 7 Sharp units). The sample size was based on the larger estimate to control for Type II error.

Efficacy analyses were conducted on an intent-to-treat (ITT) population, which consisted of all patients who were randomized into the study. Primary analyses were performed using nonresponder imputation. Patients who received rescue medication or who withdrew for any reason, including safety, were considered nonresponders from that time point onward. Hypothesis testing for the co-primary end points was performed in a hierarchical manner. First, comparisons of the ACR20 responses at week 24 between the placebo group and each of the 2 certolizumab pegol dosage groups were performed using logistic regression, with treatment and geographic region as factors. The treatment effect was estimated using odds ratios and corresponding 97.5% confidence intervals obtained by fitting this model. Rejection of the null hypothesis for the ACR20 response enabled comparison of each active treatment with placebo in terms of the change from baseline in the modified total Sharp score at week 52. This latter analysis was performed using analysis of covariance (ANCOVA) on the ranks, with treatment and geographic region as factors and with the ranked baseline modified total Sharp score as the covariate.

For patients who withdrew early (before week 52) and who had radiographs taken at their withdrawal visit, the modified total Sharp score at week 52 was estimated by linear extrapolation of the scores on the radiographs taken at the early withdrawal visit or, if this was not performed, at week 24. Multiple sensitivity analyses were performed on the radiographic data under various assumptions on the imputation of missing values, including an analysis of the per-protocol pop-

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Table 1. Baseline characteristics of the intent-to-treat population of 982 patients with active rheumatoid arthritis despite treatment with MTX*

	Placebo plus MTX (n = 199)	CZP 200 mg plus MTX (n = 393)	CZP 400 mg plus MTX (n = 390)
Patient demographics and characteristics			
Age, mean ± SD years	52.2 ± 11.2	51.4 ± 11.6	52.4 ± 11.7
Sex, % female	83.9	82.4	83.6
Duration of disease, mean ± SD years	6.2 ± 4.4	6.1 ± 4.2	6.2 ± 4.4
No. of previous DMARDs (except MTX), mean ± SD	1.4 ± 1.4	1.3 ± 1.3	1.3 ± 1.3
MTX dosage, mean ± SD mg/week	13.4 ± 4.2	13.6 ± 4.3	13.6 ± 4.0
% RF positive (≥14 IU/ml)	82.8	79.6	83.6
Disease activity status			
No. of tender/painful joints, mean ± SD	29.8 ± 13.0	30.8 ± 12.4	31.1 ± 13.3
No. of swollen joints, mean ± SD	21.2 ± 9.7	21.7 ± 9.9	21.5 ± 9.8
HAQ DI, mean ± SD	1.7 ± 0.6	1.7 ± 0.6	1.7 ± 0.6
DAS28 using the ESR, median (minimum, maximum)	7.0 (4.9, 8.7)	6.9 (4.3, 8.9)	6.9 (4.8, 9.1)
CRP, median (minimum, maximum) mg/liter	16.0 (2.0, 162)	16.0 (1.0, 234)	14.0 (2.0, 273)
ESR, median (minimum, maximum) mm/hour	45.0 (14.0, 138)	43.5 (5.0, 138)	42.5 (3.0, 141)

* MTX = methotrexate; CZP = certolizumab pegol; DMARDs = disease-modifying antirheumatic drugs; RF = rheumatoid factor; HAQ = Health Assessment Questionnaire; DI = disability index; DAS28 = Disease Activity Score 28-joint assessment; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein (normal 0–6 mg/liter).

ulation, which consisted of a subset of the ITT population, excluding patients who had at least 1 major protocol deviation, as confirmed during a preanalysis review prior to unblinding of the data. Sensitivity analyses were also performed using the last observation carried forward (LOCF) method for imputation of missing scores.

Comparison of active treatment versus placebo for the major secondary end points was tested at the 5% level of significance. Analysis of the ACR20, ACR50, and ACR70 responder rates was performed using logistic regression, with treatment and geographic region as factors. Analysis of secondary continuous efficacy end points was performed using ANCOVA, with geographic region and treatment as factors and baseline values as the covariate. Analysis of the responders according to the MCID for the HAQ DI values was post hoc and was analyzed using a repeated-measures logistic regression.

Safety analyses were conducted on the safety population, which consisted of all patients who received at least 1 dose of medication. Adverse events are presented as either the number of events or the incidence rate per 100 patient-years to adjust for differences between certolizumab pegol and placebo exposure.

RESULTS

Patient characteristics. Overall, 982 patients were randomized into the study. A total of 255 of the 393 patients (64.9%) randomized to receive 200 mg of certolizumab pegol plus MTX and 274 of the 390 patients (70.3%) randomized to receive 400 mg of certolizumab pegol plus MTX completed 52 weeks of treatment, as compared with 43 of the 199 patients (21.6%) randomized to receive placebo plus MTX. At week 16 of the study, 62.8% of the placebo-treated

patients withdrew because of lack of efficacy, as compared with 21.1% and 17.4% of patients in the groups receiving certolizumab pegol 200 mg and 400 mg, respectively. One patient in each group was lost to followup. The baseline demographic features and disease activity status of the study patients were similar among the 3 treatment groups (Table 1).

Treatment efficacy. Treatment with certolizumab pegol plus MTX significantly reduced the signs and symptoms of RA as compared with placebo plus MTX. At week 24, ACR20 response rates for the groups taking 200 mg and 400 mg of certolizumab pegol plus MTX were 58.8% and 60.8%, respectively, compared with 13.6% for the placebo plus MTX group (Figure 1A). These differences in ACR20 responses were statistically significant ($P < 0.001$ for each comparison) and remained significant through week 52 ($P < 0.001$ for each comparison) (Figure 1B). The proportions of patients taking the 2 certolizumab pegol dosages who achieved an ACR20 response were not significantly different at any time point examined. ACR50 and ACR70 responses with certolizumab pegol plus MTX treatment were also superior to placebo plus MTX ($P < 0.001$).

The onset of action of certolizumab pegol was rapid and was evident after the first injection. At week 1, significantly more patients in the certolizumab pegol 200-mg and 400-mg groups achieved an ACR20 response than did those in the placebo group ($P < 0.001$); responder rates were 22.9% and 22.3% versus 5.6%, respectively. The ACR20 response rate peaked at week 12 and was sustained to week 52 (Figure 1B). By week 2,

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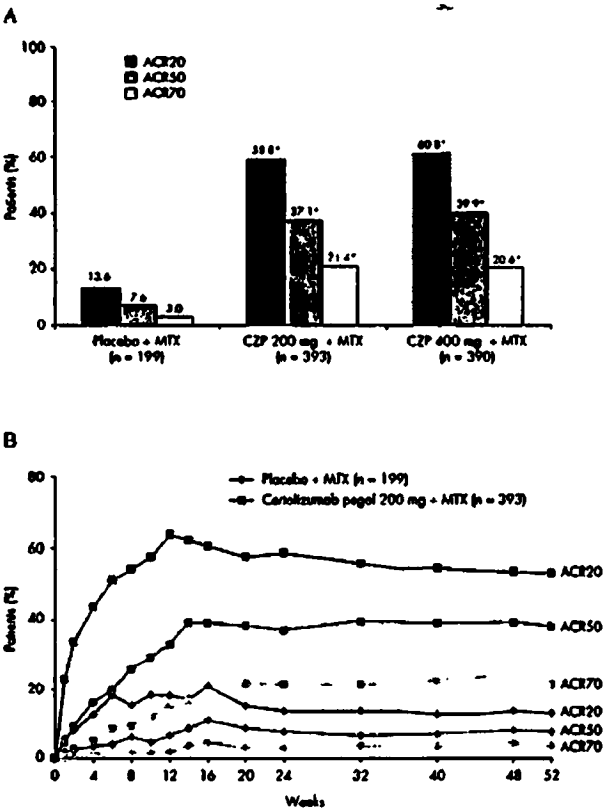


Figure 1. Efficacy of certolizumab pegol (CZP) 200 mg or 400 mg plus methotrexate (MTX) versus placebo plus MTX in the treatment of patients with active rheumatoid arthritis (RA) despite MTX therapy, as determined by the American College of Rheumatology criteria for 20% improvement (ACR20), in the intent-to-treat population of 982 patients. **A**, Percentages of patients who achieved a response according to the ACR20 criteria, as well as the ACR criteria for 50% improvement (ACR50) and the ACR criteria for 70% improvement (ACR70) at week 24. Values at the top of the bars are the actual percentages represented by the bars. * = $P < 0.001$ versus placebo. **B**, Percentages of patients treated with certolizumab pegol 200 mg plus MTX versus placebo plus MTX who achieved an ACR20, ACR50, or ACR70 response over time. Responses to this dosage of certolizumab pegol were statistically significant compared with placebo (for the ACR20 response, $P < 0.001$ at weeks 1–52; for the ACR50 response, $P < 0.01$ at week 2 and $P < 0.001$ at weeks 4–52; and for the ACR70 response, $P \leq 0.05$ at week 4, $P \leq 0.01$ at weeks 6 and 8, and $P < 0.001$ at weeks 10–52).

the ACR50 responses in the certolizumab pegol groups (200 and 400 mg) were significantly higher than that in the placebo group ($P \leq 0.01$ for each comparison). ACR70 responses were significantly higher by week 4 in the certolizumab pegol 200-mg group ($P \leq 0.05$ versus placebo) and by week 6 in the certolizumab pegol 400-mg group ($P \leq 0.05$ versus placebo). Maximum

ACR50 and ACR70 response rates in the group taking 200 mg of certolizumab pegol were achieved by weeks 14–20 of treatment (Figure 1B).

Significant improvement in each component of the ACR core set of disease activity measures was evident at week 1 with certolizumab pegol therapy. These improvements continued rapidly over the first 4–12 weeks of treatment (Table 2) and remained significant relative to placebo at weeks 24 and 52 (data not shown). Treatment with certolizumab pegol plus MTX was also associated with greater improvement in the DAS28-ESR at week 52, with a mean $\pm$ SD change from baseline of -3.3 ± 1.3 in the 200-mg group and -3.4 ± 1.4 in the 400-mg group, as compared with -2.4 ± 1.3 in the placebo group. The improvement with certolizumab pegol compared with placebo was statistically significant at all time points examined ($P < 0.001$).

Findings of radiographic evaluations. Certolizumab pegol plus MTX therapy inhibited the progression of structural damage to a significantly greater extent than did placebo plus MTX therapy. At week 52, the mean change from baseline in the modified total Sharp score was smaller in patients treated with certolizumab pegol 200 mg (0.4 Sharp units) or 400 mg (0.2 Sharp units) than in placebo-treated patients (2.8 Sharp units) ($P < 0.001$ by rank analysis) (Figure 2A). Significant differences between the certolizumab pegol and placebo groups were also observed at 24 weeks ($P < 0.001$) (Figure 2A). Results from the primary analysis were confirmed by multiple sensitivity analyses. Using linear extrapolation in the per-protocol population, changes from baseline in the modified total Sharp score were 0.4 and 0.3 Sharp units, respectively, in the groups taking 200 mg and 400 mg of certolizumab pegol and 2.7 Sharp units in the group taking placebo ($P < 0.001$ by rank analysis). Results from the LOCF analysis in the ITT population, which reflect data from 60% of the placebo-treated patients at week 16 as compared with 60–70% of the certolizumab pegol-treated patients at week 52, also showed a significant improvement ($P < 0.001$) (Figure 2D). Similar improvements in the modified total Sharp score scores were observed with analyses of the observed data and the log-transformed data (data not shown). In addition, for patients who withdrew at week 16, there was significantly less radiographic progression in those treated with either of the certolizumab pegol dosages (combined data) at week 16 as compared with those treated with placebo (Figure 2D). In a post hoc analysis, linear extrapolation of these data suggested that a significant treatment difference would also have been observed at week 52.

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Table 2. Percentage change from baseline or ratio to baseline values for each component of the ACR core set of disease activity measures assessed at weeks 1, 4, and 12 in the intent-to-treat population of 982 patients with active rheumatoid arthritis despite treatment with MTX*

	Week 1			Week 4			Week 12		
	Placebo (n = 199)	CZP 200 mg (n = 393)†	CZP 400 mg (n = 390)†	Placebo (n = 199)	CZP 200 mg (n = 393)†	CZP 400 mg (n = 390)†	Placebo (n = 199)	CZP 200 mg (n = 393)†	CZP 400 mg (n = 390)†
% change from baseline, mean									
Swollen joint count	-4.5	-18.2	-18.8	-10.3	-37.3	-40.4	-10.7	-56.7	-61.5
Tender joint count	-6.7	-18.9	-19.1	-11.4	-36.2	-37.0	-10.8	-52.6	-56.8
Physician's global assessment	-3.3	-19.0	-18.8	-9.4	-35.2	-33.6	-11.8	-49.7	-47.9
Patient's global assessment	-2.9	-12.9	-16.1	-6.5	-10.4	-27.9	-4.9	-38.3	-39.2
Patient's assessment of arthritis pain	-1.0	-20.6	-19.0	-5.0	-26.6	-28.8	-4.8	-38.2	-39.6
HAQ DI	-2.4	-13.5	-10.9	-5.4	-21.5	-21.9	-8.2	-30.4	-27.6
Ratio to baseline values of acute-phase reactants, geometric mean (CV)									
ESR	0.96	0.73	0.70	0.90	0.59	0.54	0.84	0.53	0.52
CRP	1.01	0.35	0.34	0.97	0.44	0.41	0.87	0.45	0.43

* Analyses were performed using the last observation carried forward method for imputation of missing scores. The percentage change from baseline was calculated as follows: % change from baseline = (initial visit - baseline visit)/baseline visit × 10. ACR = American College of Rheumatology; MTX = methotrexate; CZP = certolizumab pegol; HAQ = Health Assessment Questionnaire; DI = disability index; CV = coefficient of variation. † $P < 0.001$ for change from baseline versus placebo, as determined by analysis of covariance (ANCOVA), with geographic region and treatment as factors and with baseline values as the covariate, except for the erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) level, which were determined by ANCOVA using log-transformed data, with geographic region and treatment as factors and log-transformed baseline values as the covariate.

Rank analysis also demonstrated significantly greater inhibition of the progression of erosions ($P < 0.001$) and joint space narrowing ($P \leq 0.01$) in patients treated with certolizumab pegol plus MTX as compared with placebo plus MTX at weeks 24 and 52 (Figures 2B and C). No difference between the groups receiving 200 mg and 400 mg of certolizumab pegol was observed with regard to inhibition of the progression of erosions and joint space narrowing. Post hoc analysis revealed that 69.0% and 71.6% of patients taking 200 mg and 400 mg of certolizumab pegol, respectively, exhibited no radiographic progression (defined as ≤ 0 -unit increase in the modified total Sharp score) as compared with 51.9% of patients taking placebo ($P \leq 0.05$).

Changes in physical function. Patients in both of the certolizumab pegol dosage groups experienced significant improvement in physical function as compared with patients in the placebo group ($P < 0.001$) (Figure 3). These improvements were evident at week 1 and were sustained to week 52. Significantly more certolizumab pegol-treated patients also experienced clinically meaningful improvements in physical function as compared with placebo-treated patients, as indicated by the MCID in the HAQ DI values from week 1 through study end ($P < 0.001$) (data not shown).

Treatment safety. Since the mean exposure to study treatment was markedly longer in the 2 certoli-

zumab pegol groups than in the placebo group, adverse events were analyzed as the number of patients experiencing the event per 100 patient-years or as the incidence rate per 100 patient-years (Table 3). The overall rates of treatment-emergent adverse events were 125.9 per 100 patient-years in the placebo group and 96.6 per 100 patient-years and 94.6 per 100 patient-years in the certolizumab pegol 200-mg and 400-mg dosage groups, respectively. Most adverse events were mild or moderate in intensity. An analysis of adverse events leading to withdrawal versus time revealed a similar pattern of withdrawals for the placebo and active treatment arms. More withdrawals happened in the first quartile as compared with later quartiles; however, it should be noted that at each quartile, the number of patients in the study had decreased. The rates of adverse events that led to withdrawal were 3.3, 5.6, and 7.0 per 100 patient-years in patients treated with placebo, certolizumab pegol 200 mg, and certolizumab pegol 400 mg, respectively.

Infections led to discontinuation of the study drug in 6 patients in each certolizumab pegol dosage group and in 0 patients in the placebo group. Other reasons for early withdrawal were protocol noncompliance (7 patients overall) and the patient's decision (10–15 patients in each group).

All adverse events leading to death (8 overall) were considered unlikely to be related, or were unre-

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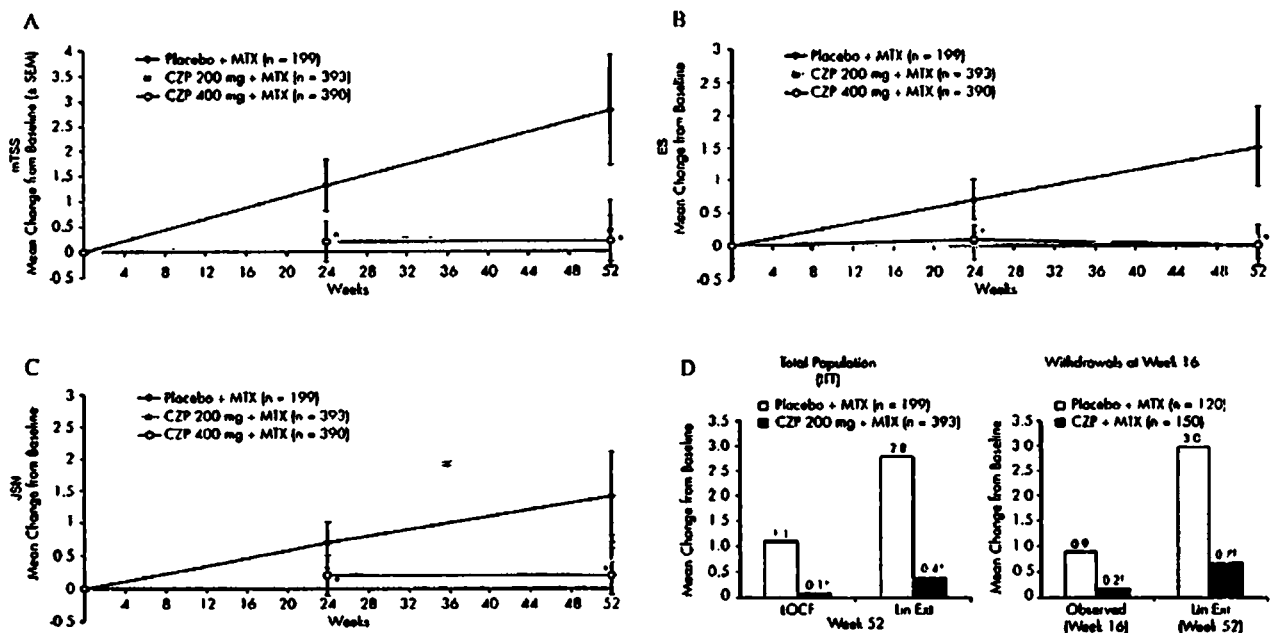


Figure 2. Efficacy of certolizumab pegol (CZP) 200 mg or 400 mg plus methotrexate (MTX) versus placebo plus MTX in the treatment of patients with active rheumatoid arthritis (RA) despite MTX therapy, as determined by radiographic evidence of response, in the intent-to-treat (ITT) population of 982 patients. A, Change from baseline in the modified total Sharp score (mTSS) at weeks 24 and 52. * = $P < 0.001$ for both dosages of active drug versus placebo. B, Change from baseline in erosion scores (ES) at weeks 24 and 52. * = $P < 0.001$ for both dosages of active drug versus placebo. C, Change from baseline in joint space narrowing (JSN) scores at weeks 24 and 52. * = $P \leq 0.05$ for both dosages of active drug versus placebo. Values in A–C are the mean $\pm$ 95% confidence interval. D, Change from baseline in the modified total Sharp score in the total ITT population of patients taking 200 mg of certolizumab pegol and placebo at week 52 (left) and in the population of patients taking active drug (both dosages) and placebo who withdrew at week 16 (right). Analyses were performed using the last observation carried forward (LOCF) method for imputation of missing scores in the total ITT population and the actual scores (observed) in those who withdrew at week 16. In addition, post hoc analyses using linear extrapolation (Lin Ext) of these data to week 52 were performed. Values at the top of the bars are the actual percentages represented by the bars. * = $P < 0.001$; † = $P < 0.05$ for both dosages of active drug versus placebo.

lated, to administration of the study drug. Seven patients died during treatment. One patient taking placebo plus MTX died of a myocardial infarction (after 7 injections of study drug). Two deaths occurred in the group taking 200 mg of certolizumab pegol plus MTX: one patient died of a hepatic neoplasm (after 2 injections of study drug), and the other patient died of cardiac arrest (after 9 injections). One other patient in this dosage group died of peritonitis, cirrhosis, and general deterioration of physical health during the posttreatment period (>84 days after the last injection). Four deaths occurred in the group taking 400 mg of certolizumab pegol plus MTX: 1 patient each died of cerebral stroke (after 2 injections of study drug), myocardial necrosis (after 8 injections), cardiac arrest (after 2 injections), and atrial fibrillation and fatigue (after 19 injections).

The most frequent noninfectious adverse events were headache, hypertension, and back pain. Of these, headache occurred more frequently in patients treated

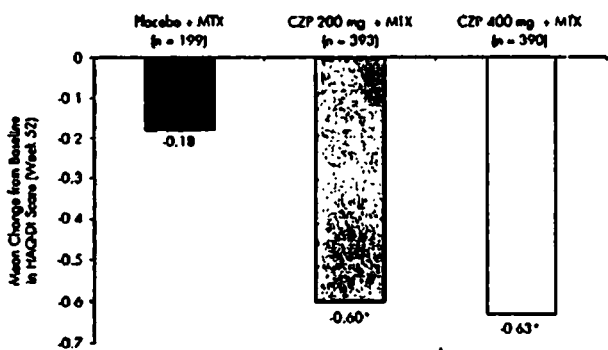


Figure 3. Efficacy of certolizumab pegol (CZP) 200 mg or 400 mg plus methotrexate (MTX) versus placebo plus MTX in the treatment of patients with active rheumatoid arthritis (RA) despite MTX therapy, as determined by the Health Assessment Questionnaire (HAQ) disability index (DI), in the intent-to-treat population of 982 patients. The mean change from baseline in the HAQ DI score at week 52 is shown for each treatment group. Values at the bottom of the bars are the actual values represented by the bars. * = $P < 0.001$ for both dosages of active drug versus placebo.

Table 3. Treatment-emergent adverse events in the safety population*

	Placebo plus MTX (n = 199)	CZP 200 mg plus MTX (n = 392)	CZP 400 mg plus MTX (n = 389)
Exposure, no. of patient-years	91.4	303.3	315.2
Treatment-emergent adverse events			
Any treatment-emergent adverse event	125.9	96.6	94.5
Intensity			
Mild	98.5	80.4	80.6
Moderate	72.2	57.4	56.2
Severe	14.2	10.5	12.1
Related to study drug	54.7	55.1	52.7
Serious adverse events	12.0 (11)	14.8 (45)	15.2 (48)
Adverse events leading to death	1.1 (1)	0.7 (2)	1.3 (3)
Adverse events leading to withdrawal	3.3 (3)	5.6 (17)	7.0 (22)
Most frequent noninfectious adverse events			
Headache	12.0	7.3	5.7
Hypertension	2.2	8.2	10.2
Back pain	2.2	5.6	6.4
Malignancy	1.1	2.3	1.3
Most frequent infectious adverse events			
Infections and infestations	56.9	56.4	58.4
Urinary tract infection	14.2	7.6	10.5
Nasopharyngitis	3.3	6.9	9.5
Upper respiratory tract infection	5.5	7.9	6.7
Most frequent serious infectious adverse events			
Serious infections and infestations	2.2	5.3	7.3
Lower respiratory tract/lung infection	0	1.0	1.3
Gastroenteritis	1.1	0	0
Urinary tract infection	0	0.7	1.0
Tuberculosis infection	0	0.7	1.0
Upper respiratory tract infection	0	0.3	0.6
Herpes viral infection	0	0.3	0.3
Bacterial peritonitis	0	0.3	0
Opportunistic infection	0	0	0

* Treatment-emergent adverse events, defined as adverse events occurring after the first administration of study drug and up to 12 weeks after administration of the last dose, were classified according to the Medical Dictionary for Regulatory Activities (version 9.0), by system organ class and preferred term. Values are the incidence rate per 100 patient-years; numbers in parentheses are the number of cases. MTX = methotrexate; CZP = certolizumab pegol.

with placebo plus MTX, whereas hypertension was more common in patients receiving certolizumab pegol plus MTX (Table 3). The reporting of hypertension was at the discretion of the investigator, and no preset guidelines for changes in the systolic or diastolic blood pressure were defined. Hypertensive events were not related to previous hypertensive status, were transitory, and were not related to the study injection. Mean changes in the systolic and diastolic blood pressure, respectively, at the last visit or at the time of withdrawal as compared with baseline were as follows: -2.1 mm Hg and -0.7 mm Hg in the group taking 200 mg of certolizumab pegol, -1.3 mm Hg and -0.6 mm Hg in the group taking 400 mg of certolizumab pegol, and -0.7 mm Hg and -0.4 mm Hg in the group taking placebo. The incidence of hematologic abnormalities was low: 1 case each of decreased hemoglobin was reported in the

groups taking placebo and 400 mg of certolizumab pegol, and 2 cases were reported in the group taking 200 mg of certolizumab pegol. One case of increased platelet count was reported in the group taking placebo, with 0 and 2 cases reported in the groups taking 200 mg and 400 mg of certolizumab pegol, respectively. There was a low incidence of injection site pain and injection site reaction in those taking 200 mg (2% and 2.3%, respectively) or 400 mg (1.3% and 0.8%, respectively) of certolizumab pegol. There were no reports of injection site pain or reaction in the placebo group.

The frequency of infectious adverse events was comparable between groups (56–58 per 100 patient-years). Urinary tract infections, nasopharyngitis, and upper respiratory tract infections were the most frequently reported infectious adverse events. Serious infections were observed more frequently with certoli-

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zumab pegol treatment than with placebo (5.3 per 100 patient-years and 7.3 per 100 patient-years in the 200-mg and 400-mg certolizumab pegol groups, respectively, versus 2.2 per 100 patient-years in the placebo group). Among the most frequent serious infectious adverse events were lower respiratory tract infections, gastroenteritis, urinary tract infections, and tuberculosis infections. A total of 5 patients (1 each from Estonia, Bulgaria, and Ukraine, and 2 from Russia) developed tuberculosis after 1.5–9 months of treatment. Three of these 5 patients were PPD positive at baseline (≥ 5 -mm reaction; allowed to enroll according to protocol because of a history of BCG vaccination with negative findings on chest radiography), and 1 patient (PPD negative) was a worker in a tuberculosis clinic. Overall, in the ITT population, 172 patients (17.5%) with a PPD test result of ≥ 5 mm at baseline were enrolled according to protocol at the physician's discretion. No cases of tuberculosis with certolizumab pegol treatment were reported in patients living in North America.

Malignant neoplasms were observed in 12 patients: 1 receiving placebo (1.1 per 100 patient-years; thyroid neoplasm), 7 receiving 200 mg of certolizumab pegol (2.3 per 100 patient-years; 3 basal cell carcinomas [1 with metastasis to the central nervous system], 1 adrenal adenoma, 1 hepatic neoplasm, 1 esophageal carcinoma, and 1 uterine cancer), and 4 receiving 400 mg of certolizumab pegol (1.3 per 100 patient-years; 2 tongue neoplasms, 1 extranodal marginal-zone B cell lymphoma, and 1 papilloma). Anti-certolizumab pegol antibodies were detected at week 52 in 6.4% of patients receiving certolizumab pegol.

DISCUSSION

Treatment with certolizumab pegol plus MTX met both primary study end points, significantly reducing the signs and symptoms of RA and inhibiting the progression of structural damage in patients with active RA who had had an inadequate response to MTX alone. The unique design of this study required withdrawal at week 16 for patients who failed to achieve an ACR20 response by weeks 12 and 14. This design facilitated the identification of differences between active treatment and placebo early during the course of treatment and allowed patients who failed to respond within a reasonable clinical time frame to receive active treatment for their disease. No statistically significant or clinically meaningful differences were observed between the 200-mg and 400-mg doses of certolizumab pegol for any of the reported outcomes, and the ACR response rates

observed with certolizumab pegol treatment were comparable with those observed with other anti-TNF agents in combination with MTX (5,17,18). Although the mean weekly dosage of MTX in this trial was low by US standards, a post hoc analysis showed that the clinical response to certolizumab pegol is not affected by the baseline dosage of MTX (data not shown).

The onset of benefit with certolizumab pegol therapy was rapid, with a significant proportion of patients achieving an ACR20 response after the first week of treatment and with maximum ACR50 and ACR70 responses achieved by weeks 14–20. Furthermore, all of the individual components of the ACR20 improvement criteria showed significant improvement by week 1, the earliest time point evaluated. One published study of adalimumab plus MTX therapy reported a statistically significant improvement in the ACR20 response rate by week 2 (5). In addition, the effects of certolizumab pegol on the signs and symptoms of RA were sustained, with significant ACR20, ACR50, and ACR70 response rates persisting to week 52.

At weeks 24 and 52, patients treated with certolizumab pegol plus MTX exhibited significantly less radiographic progression than did those treated with placebo plus MTX. Inhibition of radiographic progression was demonstrable as early as 24 weeks despite the fact that $>60\%$ of the patients in the placebo arm withdrew at week 16 and entered open-label treatment with certolizumab pegol. No differences were observed between the 2 certolizumab pegol dosage regimens in terms of inhibition of radiographic progression. Multiple sensitivity analyses also demonstrated that certolizumab pegol was effective in inhibiting radiographic evidence of disease progression. An additional analysis of the radiographs from the patients who withdrew early per protocol for failing to achieve an ACR20 response found that the progression of joint damage was inhibited by certolizumab pegol even though they had not achieved a clinical response, thereby confirming that radiographic response is not always associated with clinical response criteria. Taken together, these data suggest that certolizumab pegol, administered as add-on therapy with MTX, rapidly inhibits structural joint damage in the early stages of treatment and provides potential long-term benefits to the patient in terms of slowing radiographic evidence of disease progression.

The inhibition of structural joint damage and the reduction in signs and symptoms of active disease with certolizumab pegol therapy were accompanied by significant, clinically meaningful improvements in physical function. These benefits were rapid (occurring as early

as week 1), were sustained for up to 1 year, and were evident regardless of the dosage of certolizumab pegol.

Both doses of certolizumab pegol were associated with a low incidence of treatment discontinuation because of adverse events. The incidence of serious infectious adverse events observed in this study (5.3 and 7.3 per 100 patient-years for the 200-mg and 400-mg dosage groups, respectively) was also comparable with the findings of other certolizumab pegol studies (UCB: unpublished observations). The cases of tuberculosis reported during this trial all occurred in patients living in Eastern Europe, where the prevalence of latent tuberculosis is particularly high (19), mainly in PPD-positive individuals. No other differences in safety were observed across geographic regions or over time, and no regional differences were observed within any of the efficacy analyses. The incidence of injection site pain or injection site reaction observed with the combination of certolizumab pegol and MTX in this study was low, occurring at a rate of <3 per 100 patient-years.

The results of this trial demonstrate that the Fc region of an antibody, which is present in the currently available anti-TNF monoclonal antibody preparations, but is absent from certolizumab pegol, is not required for therapeutic efficacy in RA. The PEGylation of certolizumab pegol may minimize adverse events, such as injection site pain/reaction, may aid in maintaining effective plasma concentrations, and may promote its preferential distribution into inflamed tissues, as was observed in an animal model (9). Increased exposure to the drug at sites of inflammation may be particularly relevant for the effective treatment of inflammatory disorders such as RA and may account for the rapid onset of action and peak response seen with certolizumab pegol therapy.

Taken together, these results demonstrate that the combination of certolizumab pegol plus MTX has an acceptable safety profile and is effective in causing a rapid and sustained reduction in the signs and symptoms of RA and in inhibiting disease progression in patients with active RA who had an inadequate response to MTX therapy. Combination therapy with certolizumab pegol plus MTX in these patients can thus be considered an effective treatment option.

AUTHOR CONTRIBUTIONS

Dr Keystone had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Mason, Emery, Strand.

Acquisition of data. Van der Heijde, Emery, Strand, Pavelka, person-

nel at Quintiles, a contract research organization (Research Triangle Park, NC; nonauthors), Kristel Luijters (UCB, Braine l'Alleud, Belgium; nonauthor).

Analysis and interpretation of data. Keystone, van der Heijde, Landewé, van Vollenhoven, Strand.

Manuscript preparation. Keystone, van der Heijde, Landewé, van Vollenhoven, Combe, Emery, Strand, Mease, Pavelka.

Statistical analysis. Strand, Desai.

Advice on selection of contract research organization and statistical analysis plan: analysis and interpretation of data for regulatory authorities. Strand.

ROLE OF THE STUDY SPONSOR

A committee of academic investigators and UCB scientists designed the study. The trial was registered with clinicaltrials.gov (trial identifier: NCT00152386). Data were collected by Quintiles (Research Triangle Park, NC) and were analyzed by UCB (performed by Kristel Luijters, PhD, Senior Biostatistician, UCB, Braine l'Alleud, Belgium). The academic authors vouch for the veracity and completeness of the data and data analyses.

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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 IgG₄ 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 IgG₄ 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 $\gamma 1\kappa$). 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 with 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

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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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