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RANDOMISED CLINICAL TRIAL: CERTOLIZUMAB PEGOL FOR FISTULAS IN CROHN'S DISEASE – SUBGROUP RESULTS FROM A PLACEBO-CONTROLLED STUDY

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Running title: Certolizumab pegol for the treatment of fistulas

SUMMARY

Background: Background: Treatment options for fistulizing Crohn's disease (CD) are limited.

Aims: To examine whether fistula closure is maintained at week 26 following treatment with certolizumab pegol (CZP).

Methods: Patients with draining fistulas at baseline from PRECiSE 2 (n =108) received open-label induction with CZP 400 mg at weeks 0 (baseline), 2 and 4. Response was defined as ≥100-point decrease from baseline in the Crohn's Disease Activity Index. Nonresponders (50/108) were excluded. At week 6, responders with draining fistulas (N = 58) were randomized to CZP 400 mg (n = 28) or placebo (n = 30) every 4 weeks across weeks 8–24. Fistula closure was evaluated throughout the study, with a final assessment at week 26.

Results: The majority of patients (55/58) had perianal fistula. At week 26, 36% of patients in the CZP group had 100% fistula closure compared with 17% of patients receiving placebo (P = 0.038). Protocol-defined fistula closure (≥50% closure at two consecutive post-baseline visits ≥3 weeks apart) was not statistically significant (P = 0.069) with 54% and 43% of patients treated with CZP and placebo achieving this endpoint, respectively.

Conclusion: Continuous treatment with CZP improves the likelihood of sustained perianal fistula closure compared with placebo.

INTRODUCTION

Development of fistulas occurs frequently in patients with Crohn's disease (CD). A population-based study demonstrated that after 10 years of disease the cumulative risk for developing fistulas is 33%, and this increases to 50% after 20 years.[1,2] Perianal fistula is the most common fistula type; it occurs in 25–50% of patients with CD[3] and often causes severe impairment in their quality of life.[4]

Treatment options for fistulas are limited.[5,6] Until recently, surgery has been the mainstay for treating fistulas; however, invasive surgical treatments such as extensive dissection can lead to incontinence in some patients.[3] In addition, while corticosteroids have potent anti-inflammatory actions and are effective in the treatment of luminal CD, they have not been demonstrated to benefit patients with fistulizing disease.[4] Antibiotics are a widely used short-term treatment for fistulas in patients with CD; however, despite their widespread use, there are limited controlled studies demonstrating their symptomatic efficacy in patients with fistulizing CD.[7] In an open-label case series of 21 patients with perianal CD treated with 20 mg/kg/day of metronidazole, 56% of patients had complete fistula healing and all had a positive clinical response. However, follow-up of 17 of these patients showed that when the dosage was decreased, the symptoms reappeared.[8] Immunosuppressive agents such as azathioprine and 6-mercaptopurine have been shown to successfully treat the intestinal inflammation of CD; however, data on their ability to treat fistulas in these patients are limited. In a meta-analysis of 5 randomized, controlled trials in which closure of various fistulas (including perianal, enterocutaneous, enteroenteric, recto-vaginal and vulvar types) was a secondary end point, a beneficial effect of azathioprine and 6-mercaptopurine was shown in 54% (22 of 41) of patients compared with 21% (6 of 29) in the placebo group after 6 months of treatment (pooled odds ratio of 4.4; 95% confidence interval [CI], 1.5–13.2).[9] The formation of a CD fistula can, therefore, be considered a difficult to treat and sometimes

irreversible form of structural damage as a consequence of incompletely controlled inflammation.

Meta-analysis of the anti-tumour necrosis factor (TNF) agents infliximab, adalimumab and certolizumab pegol has shown success with their use in fistulizing CD. In an overall analysis, anti-TNF therapy was more effective than placebo for complete fistula closure.[10] Detailed reports on the efficacy of infliximab and adalimumab for closure of fistulas have been published previously.[11-13]

Limited data on the effectiveness of certolizumab pegol in the treatment of fistulas in the PRECiSE 2 study have been published.[14] In the PRECiSE 2 study, 14% of patients in the overall population who had a response to induction therapy with certolizumab pegol and were included in the intent-to-treat population (58 of 425) had draining fistulas (28 patients in the certolizumab group and 30 in the placebo group). In the present study, additional post hoc analyses were performed to further examine the fistula closure effects of certolizumab pegol and to determine whether fistula closure observed at week 6 is maintained through to week 26.

METHODS

Patients

The methods and results of PRECiSE 2 (Clincaltrials.gov identifier: NCT00152425) have been reported previously.[14] Adult patients were eligible if they had at least a 3-month history of active CD, defined as a Crohn's Disease Activity Index score of 220–450.[14,15] A total of 108 patients had open draining fistulas at week 0. Among these patients, 58 had a clinical response to induction with certolizumab pegol (defined as reduction of at least 100 from the baseline score on CDAI) at week 6. These patients ($N = 58$) were randomized to double-blind maintenance treatment (Figure 1). For each patient, each individual fistula was

assessed at every visit to determine whether it was closed or not. Physicians assessed if a fistula was closed by the absence of drainage on gentle compression.

Efficacy analyses

Data are presented for the intention to treat population ($N = 58$). Fistula closure was defined as the absence of drainage on gentle compression at any two consecutive post-baseline visits at least 3 weeks apart.[14] The following efficacy variables were analyzed: 1) assessment of fistula closure at weeks 2, 4, 6, 8, 12, 16, 20, 24 and 26 compared with week 0 (≥50% closure of fistulas open at baseline and 100% closure of fistulas open at baseline); 2) maintenance of fistula closure, defined as at least 50% closure of fistulas at any two consecutive post-baseline visits (≥3 weeks apart) at any time during the study and at least 50% or 100% closure at week 26; 3) fistula closure based on the prespecified definition in the PRECiSE 2 study (closure of ≥50% of fistulas at any two consecutive post-baseline visits ≥3 weeks apart); 4) CDAI response and remission (CDAI was calculated using established methods;[15] remission was defined as a CDAI score of ≤150 points and response was defined as a decrease from week 0 in CDAI score of ≥100 points); and 5) Inflammatory Bowel Disease Questionnaire (IBDQ) efficacy measures. The IBDQ efficacy measure was calculated using established methods.[16,17] The mean increase in the IBDQ score from week 0 and the mean increase in the score of the individual domains of the IBDQ score (bowel symptoms, systemic symptoms, emotional function, social function) from week 0 were calculated.

Statistical analyses

All data presented are exploratory; nominal *P* values were calculated using logistic regression including factors for treatment, C-reactive protein (CRP) strata at entry (<10 mg/L / ≥ 10 mg/L), steroid use at entry, immunosuppressant use at entry and geographical region (this was done as subjects had been stratified for these variables when randomized).

Missing data were imputed as not achieving the end point for binary outcomes. For IBDQ efficacy measures, the last observation carried forward was imputed for continuous outcomes.

RESULTS

Patients

After three induction doses of certolizumab pegol 400 mg, a total of 58 patients with draining fistulas at baseline responded according to CDAI criteria. These 58 patients were randomized in the double-blind phase: 28 to certolizumab pegol 400 mg q4w and 30 to placebo q4w. Reasons for withdrawal are shown in Figure 1.

The demographic features of these patients are shown in Table 1. Anal fistulas were the most common type of fistula and accounted for 95% (55 of 58) of all fistulas at baseline. Non-anal fistulas among the placebo group (n = 4 patients) were recto-vaginal, posterior to anus, left thigh, right buttock, left lateral, mid abdominal/right side, left perineum, and lower abdomen. Non-anal fistulas in the certolizumab pegol group (n = 3 patients) were inguinal right, perineal (left posterior), and left buttock. The mean number of open fistula at baseline was 2.0 in the placebo group and 1.6 in the certolizumab pegol group.

Efficacy: prespecified definition of fistula closure

The fistula closure definition that was prespecified in the PRECiSE 2 study was closure of at least 50% of fistulas at any two consecutive post-baseline visits at least 3 weeks apart. Using this definition, fistula closure occurred in 54% (15 of 28) of patients randomized to maintenance therapy with certolizumab pegol 400 mg q4w and 43% (13 of 30) randomized to placebo (P = 0.247). Time to closure in both groups was similar; mean time to closure was

13.4 days (s.d. = 3.5) in the certolizumab pegol 400 mg group and 13.3 days (s.d. = 3.3) in the placebo group.

Efficacy: 50% and 100% fistula closure at weeks 2, 4, 6, 8, 12, 16, 20, 24 and 26

Figure 2 shows the percentage of patients with at least 50% fistula closure (Figure 2A) and the percentage of patients with 100% fistula closure (Figure 2B) at weeks 2–26. Certolizumab pegol maintenance did not demonstrate a statistically significant increase in the percentage of patients with at least 50% fistula closure. However, the proportions of patients in the certolizumab pegol maintenance group who had at least 50% fistula closure across the range of time points from weeks 2 to 26 were numerically greater than those receiving placebo (Figure 2A). The decrease in the percentage of patients who had at least 50% fistula closure from weeks 8 to 26 in both arms may reflect a lessening of the effect from the 3 induction doses of certolizumab pegol in both the certolizumab pegol and placebo arms. There was a statistically significant increase in the percentage of patients with 100% fistula closure in the certolizumab pegol group compared with patients in the placebo group (Figure 2B). At week 26, 36% (10 of 28) of patients in the certolizumab pegol group had 100% fistula closure compared with 17% (5 of 30) of patients in the placebo group (P = 0.038).

Efficacy: maintenance of fistula closure

The differences between certolizumab pegol 400 mg and placebo for the primary endpoint of prespecified definition of fistula closure did not reach statistical significance at week 26. However, among patients who achieved the prespecified definition of fistula closure during the study, a numerically higher proportion of patients treated continuously with certolizumab pegol group versus the patients who received induction followed by placebo maintained 50% fistula closure at week 26 (73.3% [11 of 15] vs. 38.5% [5 of 13]; P = 0.069) and had 100% closure at week 26 (66.7% [10 of 15] vs. 30.8% [4 of 13]; P = 0.064) (Figure 3).

Efficacy: CDAI

In the examined subpopulation of 58 randomized patients with open fistulas at baseline, CDAI response and remission rates were higher in the certolizumab pegol–treated patients than in those given placebo (Figure 4). At week 26, 71% of patients in the certolizumab pegol group vs. 33% in the placebo group achieved a CDAI response ($P = 0.005$), and 54% vs. 20% patients were in CDAI remission ($P = 0.026$).

In those patients who achieved the prespecified definition of fistula closure during the study and achieved 100% fistula closure at week 26, CDAI response was observed in 80% (8 of 10) of patients in the certolizumab pegol group vs. 75% (3 of 4) patients in the placebo group. This compares with 67% (12 of 18) vs. 27% (7 of 26) of patients who did not achieve the prespecified definition of fistula closure and 100% closure at week 26. In patients who achieved the prespecified definition of fistula closure during the study and 100% fistula closure at week 26 CDAI remission rates were 60% (6 of 10) in the certolizumab pegol and 50% (2 of 4) in the placebo group. In contrast, CDAI remission rates in patients who did not achieve the prespecified definition of fistula closure during the study and achieved 100% fistula closure at week 26 were 50% (9 of 18) and 15% (4 of 26), in the certolizumab pegol and placebo groups, respectively. The mean decrease from week 0 in CDAI score was 170 points in the certolizumab pegol group ($n = 23$) compared with 131 in the placebo group ($n = 15$) at week 26.

Health-related quality of life

At week 26, patients in the certolizumab pegol group who had open and draining fistulas at week 0 showed a mean change from baseline in total IBDQ scores of 36.7 vs. 20.7 in the placebo group (Figure 5). Mean changes from week 0 to week 26 in IBDQ scores were 39.5 in the certolizumab pegol group and 30.5 in the placebo group.

Of patients who had open and draining fistulas at week 0, mean changes in the IBDQ from week 0 to week 26 were greater in those who received certolizumab pegol than those who received placebo for all four individual domains of the IBDQ: bowel symptoms (11.2 vs. 6.9), systemic symptoms (7.2 vs. 3.8) and emotional (12.6 vs. 6.1) and social function (5.9 vs. 3.9), as well as the overall score (34.0 vs. 23.0).

Safety

In the overall population, certolizumab pegol 400 mg q4w was well tolerated, with a safety profile consistent with that of other anti-TNF therapies.[14] The adverse events that occurred in the 58 patients with open and draining fistulas at week 0 are summarized in Table 2. One patient in the certolizumab pegol group had a serious adverse event of a perineal abscess. The abscess was of moderate intensity and unlikely related to the study drug. The patient underwent surgery and the abscess resolved with sequelae. The adverse events that occurred in the patients with fistulas were generally similar to those that occurred in the PRECiSE 2 study overall.[14]

DISCUSSION

The data reported in this study support the efficacy of certolizumab pegol in patients with fistulizing CD. Although the differences between certolizumab pegol 400 mg and placebo for the primary endpoint of prespecified definition of fistula closure did not reach statistical significance at week 26, more patients in the certolizumab pegol 400 mg q4w maintenance group achieved fistula closure compared with the placebo q4w group. Several reasons may account for why the difference between the certolizumab pegol 400 mg and placebo for the primary endpoint of prespecified definition of fistula closure did not reach statistical significance. First, the overall sample size of each group was small. Second, 100% fistula closure may have been a better primary endpoint than the protocol-defined outcome for

fistula closure. Lastly, the placebo group was not a true representation of a placebo response. Patients in the placebo group had received a successful course of induction therapy with certolizumab pegol before they had been randomized to placebo maintenance. In the certolizumab pegol group, 73% of patients maintained at least 50% fistula closure by week 26 and 67% maintained 100% closure by week 26. In the placebo group, 39% of patients maintained at least 50% fistula closure by week 26 and 31% maintained 100% closure by week 26. The findings summarized above demonstrate a generally consistent numeric advantage in favor of certolizumab pegol.

The different definitions of fistula closure and time point of measurement not withstanding, these results are generally similar to those reported for the anti-TNF agents infliximab and adalimumab. In ACCENT II, a randomized, controlled study of infliximab in fistulizing CD, 36% of patients in the infliximab 5 mg/kg q8w maintenance group had a complete absence of draining fistulas vs. 19% of patients in the placebo maintenance group ($P = 0.009$) at week 54.[13] At the end of the CHARM study (week 56), 33% (23 of 70) of patients who had fistulas at baseline and were randomized to adalimumab (combined results from patients in the 40 mg q2w and 40 mg weekly groups) had fistula healing (defined as no drainage, either spontaneous or with gentle compression) compared with 13% (6 of 47) in the corresponding placebo group ($P < 0.05$).[11] The number of smokers in the certolizumab pegol group (8/28) was less than in the placebo group (15/30), a difference that could potentially affect the primary endpoint, as many,[18-20] but not all,[21-23] studies have shown an unfavourable effect of smoking on disease course. In the present study, statistical analyses were not performed for differences based on baseline demographic characteristics. However, other studies have shown no effect of active smoking on the efficacy of anti-TNF agents in patients with CD.[24-26]

Patients assigned to certolizumab pegol maintained fistula closure and had higher rates of CDAI response and remission than patients in the placebo group. In the certolizumab pegol group, 71% of patients achieved clinical response and 54% of patients achieved clinical

remission based on CDAI criteria. However, it should be noted that since fistula is a component of the CDAI, the CDAI score does not represent an independent variable.

In addition to the clinical improvements, certolizumab pegol showed a greater improvement on patients' health-related quality of life compared with placebo, as demonstrated by improvements in the overall and individual domain scores of the IBDQ. Among the individual IBDQ domains, bowel symptoms (11.2 vs. 6.9), systemic symptoms (7.2 vs. 3.8) and emotional function (12.6 vs. 6.1) showed the greatest improvement in the certolizumab pegol group compared with placebo. Notably, the mean IBDQ score in PRECiSE 2 was 175 at week 6. In the present study, which comprised patients with open fistulas at baseline, the mean IBDQ score at week 6 was 128, indicating that fistulas are associated with a worse health-related quality of life.

Following stricter and more clinically relevant definitions of fistula closure than those that were initially prespecified to examine data from patients with open fistulas in the PRECiSE 2 study, it was shown that fistula closure is maintained following continuous treatment with certolizumab pegol compared with placebo. These data suggest that certolizumab pegol maintenance therapy provides fistula closure and other clinical benefits in patients with moderate to severe CD and open draining fistulas. (Clincaltrials.gov identifier: NCT00152425).

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Table 1. Demographic characteristics at screening of patients with open, draining fistulas in the double-blind maintenance phase

	Placebo (*n* = 30)	Certolizumab pegol 400 mg q4w (*n* = 28)
Age, y		
Mean ± standard deviation (s.d.)	37.6 ± 10.1	37.3 ± 9.4
Range	21–55	20–54
Gender, male, n (%)	20 (66.7)	14 (50.0)
Duration of disease, y		
Mean ± s.d.	10.2 ± 8.9	7.8 ± 5.9
Median	8.2	6.2
Range	0.4–32.7	1.1–25.8
Current smoker, n (%)	15 (50.0)	8 (28.6)
Crohn's Disease Activity Index (CDAI) score*		
Mean ± s.d.	317.1 ± 69.4	299.8 ± 58.3
Range	215–439	191–442
Location of disease, n (%)		
Terminal ileum	2 (6.7)	5 (17.9)
Colon	10 (33.3)	11 (39.3)
Ileocolon	16 (53.3)	12 (42.9)
Upper gastrointestinal	2 (6.7)	0
Disease behaviour, n (%)		
Inflammatory	5 (16.7)	2 (7.1)
Stricturing	1 (3.3)	2 (7.1)
Penetrating	24 (80.0)	24 (85.7)
Mean number of fistulas per patient		
Mean ± s.d.	2.0 ± 1.9	1.6 ± 0.7
Median	1.0	1.0
Range	1.0–9.0	1.0–3.0
Number of resections, n (%)		
0	19 (63.3)	23 (82.1)
1	6 (20.0)	4 (14.3)
2	2 (6.7)	1 (3.6)
3	2 (6.7)	0
>3	1 (3.3)	0
Fistula type, n (%)		
Anal	28 (93.3)	27 (96.4)
Other	3 (10.0)	1 (3.6)
Prior anti-tumour necrosis factor use		
Yes, n (%)	11 (36.7)	11 (39.3)
Concomitant medication, n (%)		
Corticosteroids (with or without immunosuppressants)	6 (20.0)	5 (17.9)
Immunosuppressants (with or without corticosteroids)	13 (43.3)	17 (60.7)
Corticosteroids and immunosuppressants	5 (16.7)	2 (7.1)
No corticosteroids and no immunosuppressants	16 (53.3)	8 (28.6)

*CDAI scores were subsequently re-calculated based on the Week 0 hematocrit value.

q4w = every 4 weeks.

Table 2. Summary of adverse events (AEs) during induction and maintenance treatment with certolizumab pegol or placebo in patients with open, draining fistulas at baseline

AE	Open-label induction (*N* = 58)	Double-blind phase: Placebo (*n* = 30)	Double-blind phase: Certolizumab pegol 400 mg q4w (*n* = 28)
Patients who reported AEs, n (%)	30 (51.7)	24 (80.0)	15 (53.6)
Total number of AEs	54	63	40
AEs occurring at frequency of ≥10% in any treatment group, n (%)			
Headache	8 (13.8)	2 (6.7)	1 (3.6)
Arthralgia	0	1 (3.3)	3 (10.7)
Injection site pain	0	3 (10.0)	1 (3.6)
Pyrexia	1 (1.7)	3 (10.0)	0
Patients who reported drug-related AEs, n (%)	6 (10.3)	9 (30.0)	6 (21.4)
Patients in whom AEs led to permanent study drug discontinuation, n (%)	0	4 (13.3)	1 (3.6)
Patients who reported serious AEs, n (%)	1 (1.7)	3 (10.0)	1 (3.6)
Total number of serious AEs	1	4	1
Patients who reported infections, n (%)	12 (20.7)	7 (23.3)	9 (32.1)
Patients who reported serious infections, n (%)	0	0	1 (3.6)*
Patients who reported injection-site pain, n (%)	10 (1.7)	1 (0.0)	0 (0.0)
Patients who died, n (%)	0	0	0

*Perineal abscess.

q4w = every 4 weeks.

Figure 1. Patient disposition.

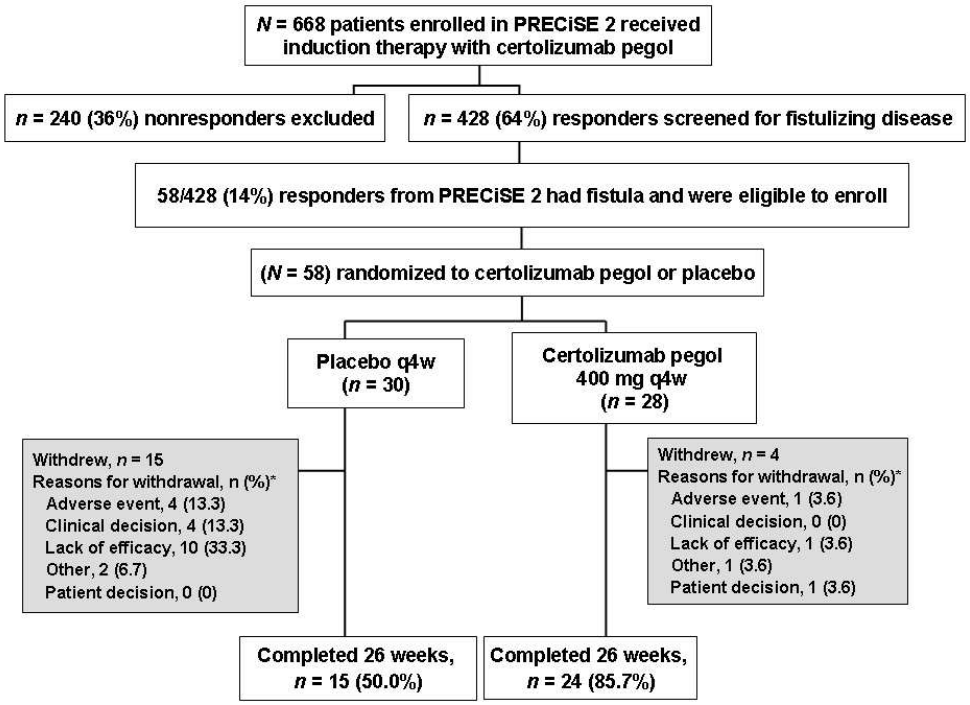
Figure 2. Percentage of patients with (A) at least 50% fistula closure and (B) 100% fistula closure at weeks 2–26. Error bars represent 95% confidence intervals for percentage response. q4w = every 4 weeks.

Figure 3. Fistula closure based on prespecified definition in the PRECiSE 2 study (closure of ≥50% of fistulas at any two consecutive post-baseline visits ≥3 weeks apart) at week 26. Error bars represent 95% confidence intervals for percentage frequency. q4w = every 4 weeks.

Figure 4. Crohn's Disease Activity Index (CDAI) response (≥100 point decrease from baseline) and remission (CDAI ≤150 points) at week 26. Error bars represent 95% confidence intervals for percentage response. q4w = every 4 weeks.

Figure 5. Mean change from baseline in Inflammatory Bowel Disease Questionnaire (IBDQ) score at week 26 (last observation carried forward).* Error bars represent 95% confidence intervals for mean change. q4w = every 4 weeks.

*One patient did not provide post-baseline data; thus last observation carried forward analysis was not applied.



*More than one reason could be specified. q4w = every 4 weeks.

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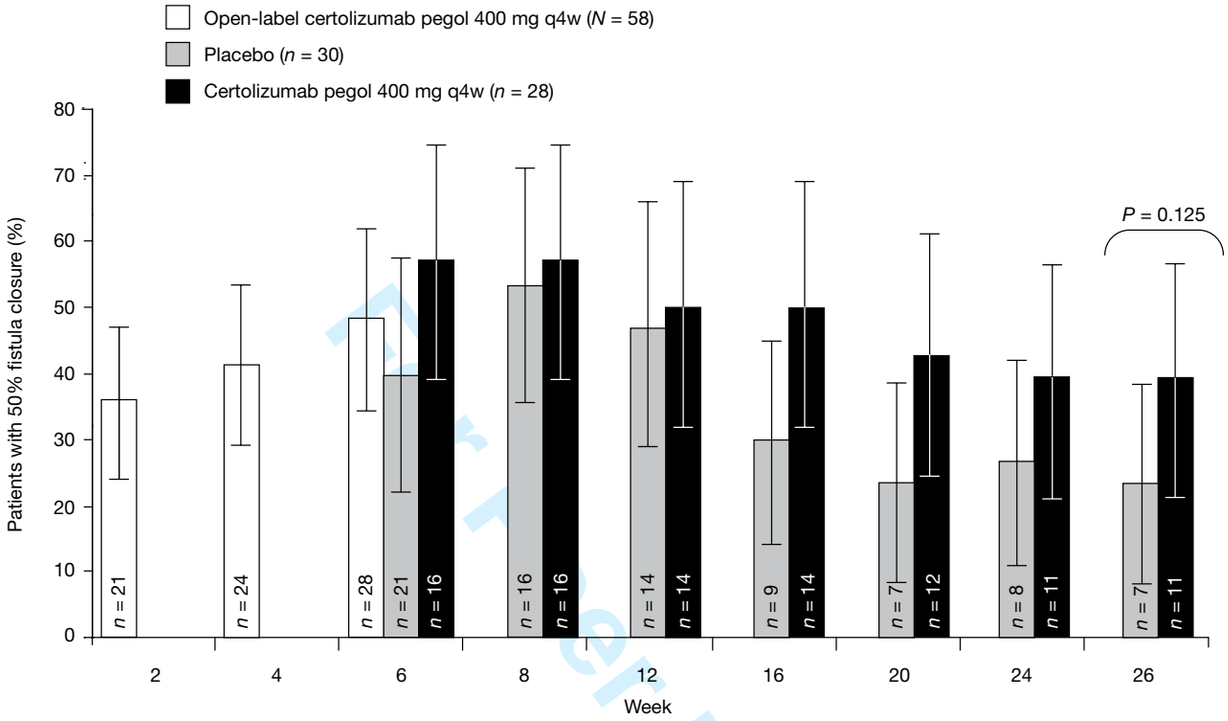

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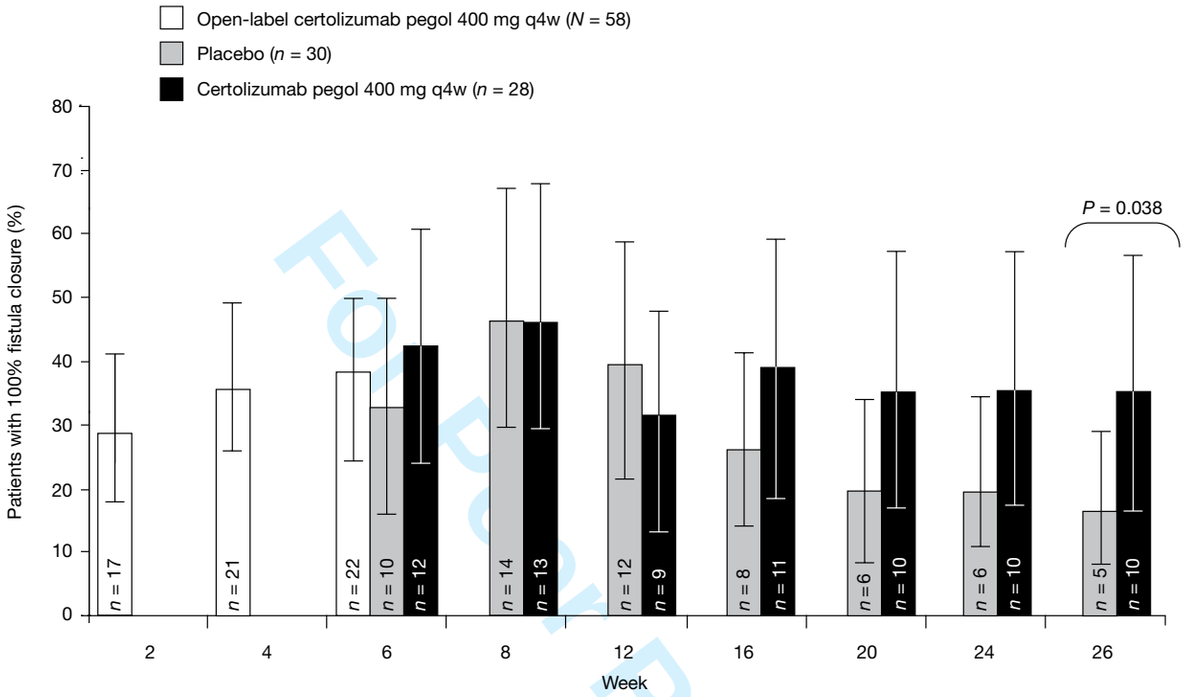

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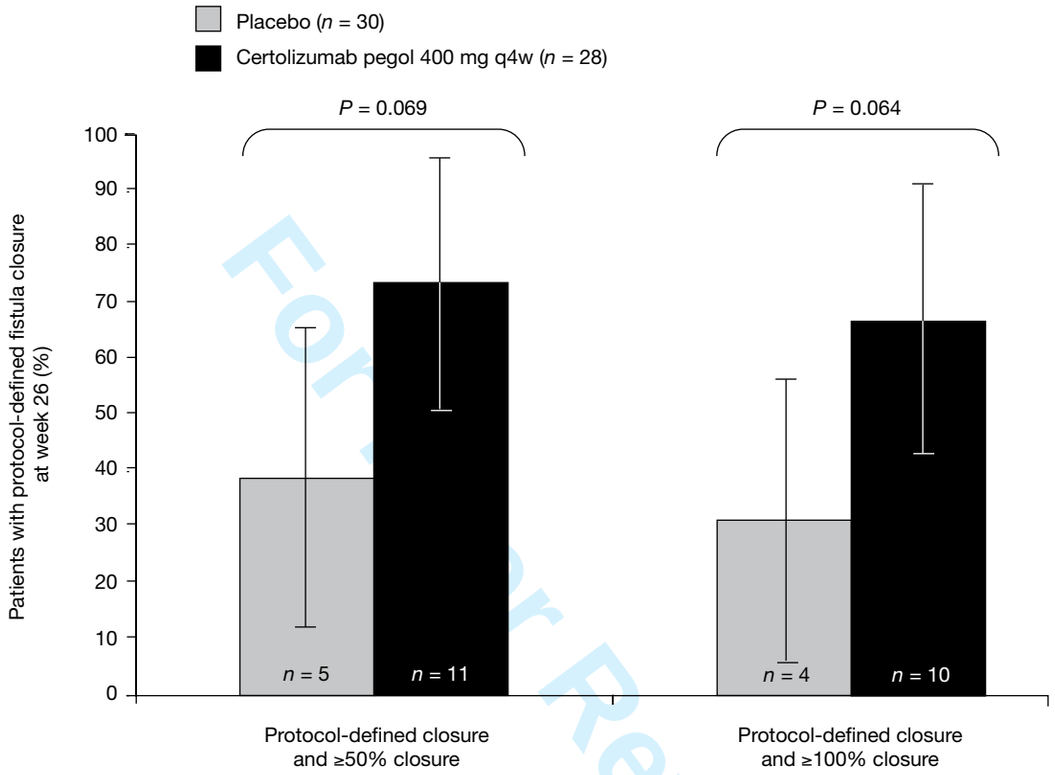

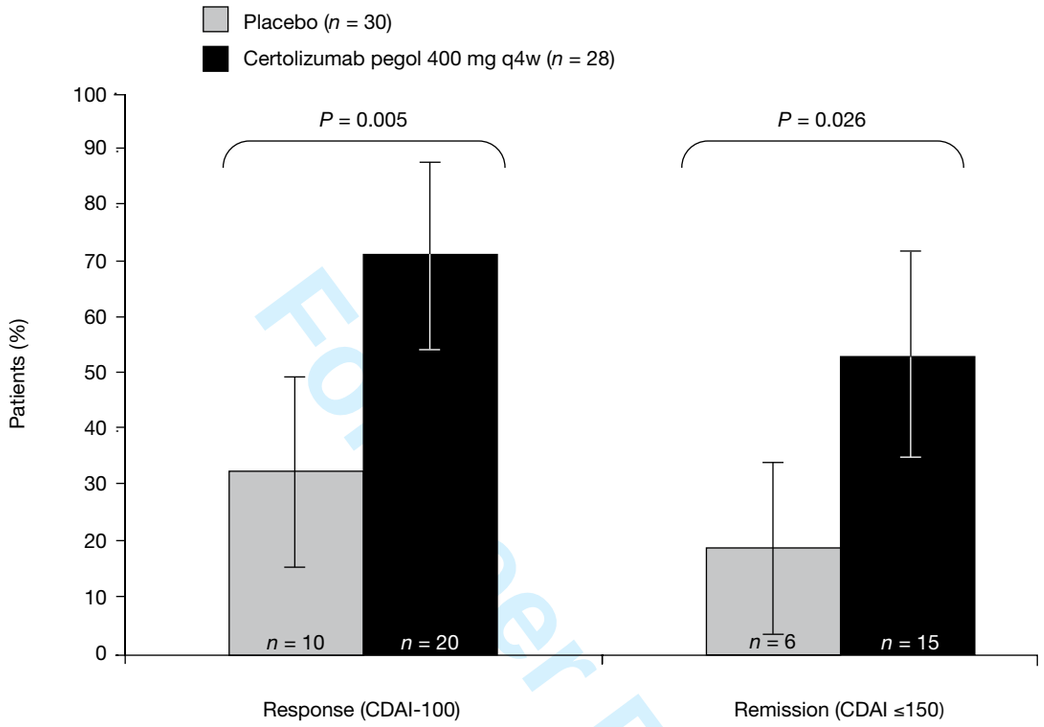

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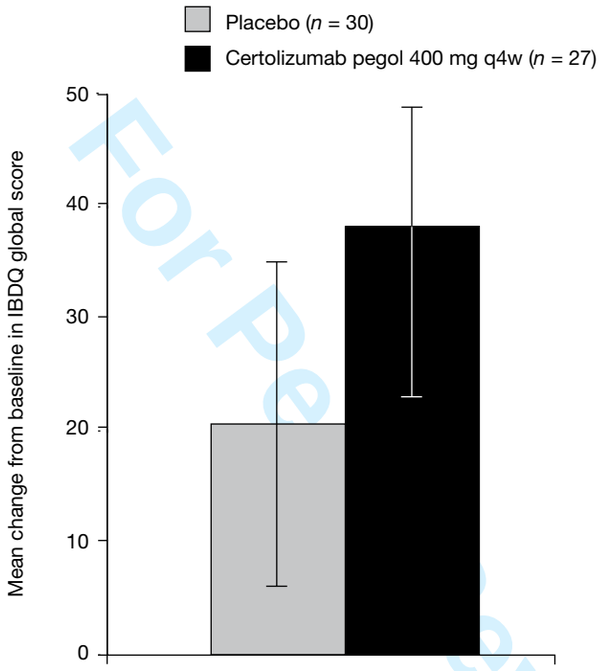

Statement of Interests

Authors' declaration of personal interests

S. Schreiber has served as a speaker, a consultant and/or an advisory board member for Abbot Laboratories, BayerSchering, Centocor, Dr. Falk Pharma, Essex/Schering Plough, Ferring, Genentech, Glaxo-SmithKline, Novartis, Novo-Nordisk, Pfizer, Schering-Plough and its subsidiary Essex Pharma., UCB and owns stocks and shares in Conaris Research Institute.

I.C. Lawrance has served as a speaker, consultant and an advisory board member for Abbott Australasia, Schering-Plough, Janssen-Cilag Pharmaceuticals, Pharmatel Fresenius Kabi and has received research funding from Abbott Australasia.

O.Ø. Thomsen has served as a consultant and an advisory board member for UCB, Zealand Pharma and as a speaker for Schering-Plough and UCB.

S.B. Hanauer has served as a consultant and advisory board member for Abbot Laboratories, AstraZeneca, Bristol Myers Squibb, Centocor, Elan Pharmaceuticals, Ferring Pharmaceuticals, Genentech, GlaxoSmithKline, Millenium Pharmaceuticals, Proctor and Gamble, Prometheus, Salix, Shire, UCB and has received research funding from Abbot Laboratories, Bristol Myers Squibb, Centocor, Elan Pharmaceuticals, Ferring Pharmaceuticals, Genentech, Proctor and Gamble, Prometheus, Salix, Shire and UCB.

R. Bloomfield is an employee of UCB.

W.J. Sandborn has served as consultant and advisory board member for Abbott Laboratories (fees paid to Mayo), ActoGenix, AGI Therapeutics, Albireo, Alfa Wassermann,

AM-Pharma, Amgen, Anaphore, Astellas Pharma, Athersys, Atlantic Healthcare Limited, Axcan Pharma, BioBalance Corporation, Bristol Meyers Squibb (fees paid to Mayo), Celek Pharmaceuticals, Celgene, Cellerix, CentocorOrthoBiotech (fees paid to Mayo), Chemocentryix, CoMentis, Cosmo Technologies, Cytokine Pharmasciences, Eagle Pharmaceuticals, Eisai Medical Research, Elan Pharmceuticls (fees paid to Mayo), Eli Lilly, Enteromedics, Ferring Pharmaceuticals, Flexion Therapeutics, Funxional Therapeutics Limited, Genentech (fees paid to Mayo), Given Imaging, GlaxoSmithKline, KaloBios Pharmaceuticals, Merck Research Laboratories, Merck Serono, Novo Nordisk, Pfizer Inc (fees paid to Mayo), Procter & Gamble (fees paid to Mayo), Purgenesis Technologies, Regeneron Pharmaceuticals, Salient Pharmaceuticals, Salix Pharmaceuticals, Santarus, Schering Plough Corporation, Shire Pharmaceuticals (fees paid to Mayo), Sigmoid Pharma, Sitrtis Pharmaceuticals, SLA Pharma, Takeda (fees paid to Mayo), Tillotts Pharma, UCB (fees paid to Mayo), Vascular Biogenics, Viamet Pharmaceuticals and Wyeth and has received research funding from Abbott Laboratories, Bristol Meyers Squibb, CentocorOrthoBiotech, Genentech, Millennium Pharmaceuticals, Novartis, Pfizer Inc, Shire Pharmaceuticals, UCB, Warner Chilcott (previously Procter & Gamble).

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