INFLAMMATORY BOWEL DISEASE

Clinically Meaningful Improvement in Health-Related Quality of Life in a Randomized Controlled Trial of Certolizumab Pegol Maintenance Therapy for Crohn's Disease

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OBJECTIVES: **Moderate-to-severe Crohn's disease (CD) is associated with important impairment in health-related quality of life (HRQOL). The aim of this study was to assess the effects of certolizumab pegol (CZP) maintenance therapy on HRQOL.**

METHODS: **During an open-label induction phase, study participants with moderate-to-severe CD were treated with 400 mg CZP every other week. Responders were randomized to monthly maintenance therapy with CZP or placebo. Clinically meaningful improvement in HRQOL was evaluated with three patient-reported outcome (PRO) instruments. Quality-adjusted life-years (QALYs) were calculated from utility scores derived from the EuroQoL-5 dimensions (EQ-5D). Normal life rating was measured by combining clinical disease activity, HRQOL, and measures of professional work productivity and daily activity.**

RESULTS: **A total of 425 responders to induction therapy were randomized to CZP maintenance ($n=215$) or placebo ($n=210$). Participants assigned to CZP maintenance reported clinically meaningful improvements in HRQOL relative to baseline and to placebo-treated participants. More participants receiving treatment with CZP reported clinically meaningful improvement in Inflammatory Bowel Disease Questionnaire (IBDQ) score (60 vs. 43%, $P<0.001$) and in Short-Form 36-Item Health Survey (SF-36) physical (51 vs. 34%, $P<0.001$) and mental component summary responses (44 vs. 32%, $P=0.016$) than did those receiving placebo. The proportion of participants who achieved clinically meaningful improvement in the EQ-5D plus health status visual analogue scale (VAS) was significantly greater in those assigned to CZP maintenance than in those assigned placebo (57 vs. 38%, $P<0.001$). There was also a significantly greater gain in QALYs for the CZP group as compared with the placebo group (mean±s.d. 0.25±0.10 and 0.21±0.11; $P=0.001$). Significantly more participants receiving CZP maintenance reported living a normal life (21.4%) than did those receiving placebo (12.9%, $P=0.019$).**

CONCLUSIONS: **Maintenance therapy with CZP resulted in statistically significant and clinically meaningful improvements in HRQOL, as assessed by multiple PRO instruments. CZP improved and maintained the quality and quantity of the remission and response, as measured by QALYs. Furthermore, a significant proportion of study participants who received CZP returned to a normal life compared with those who received placebo.**

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract. Typical symptoms include diarrhea, abdominal pain, and fatigue.

The morbidity of CD often limits patients' physical functioning, social interactions, and emotional well-being (1). Physical limitations result in reduced work productivity, impaired sexual function, and diminished interaction with family and friends (2,3). Moreover, CD patients are at increased risk for depression and often fear that they may lose their independence or require surgery (2–5).

The severity of CD is typically measured by clinical indices, which are frequently used as outcome measures in clinical trials. The most commonly used instrument, the Crohn's Disease Activity Index (CDAI), is heavily weighted toward physical symptoms (6). However, a strong correlation has been observed between disease activity and CD-specific measures of health-related quality of life (HRQOL). Despite this relationship, the inclusion of HRQOL assessments in clinical trials provides an additional level of information regarding patients' emotional and social functioning that is not assessed by conventional disease activity indices (7,8).

The relevance of obtaining the perspective of the patient has recently been supported in an FDA guidance document. According to the FDA, patient-reported outcomes (PRO) may be more valid and reliable than observer-reported measures, because they are not subject to interobserver variability and can provide valuable information that is not available when the patient's perspective is filtered by physician evaluation (9).

Patient-reported outcome questionnaires are instruments that measure aspects of a patient's health status, including multidimensional HRQOL, as reported directly by the patient (9). Several PRO instruments have demonstrated validity and reliability for use in CD clinical trials. The Inflammatory Bowel Disease Questionnaire (IBDQ), a disease-specific instrument (3,8,10), is the one most commonly used (7). However, generic HRQOL instruments, such as the Short-Form 36-Item Health Survey (SF-36) (11–13) and the EuroQOL-5 dimensions (EQ-5D) plus health status visual analogue scale (VAS) (1,2,14), have also been used for this purpose. An additional PRO questionnaire, the Work Productivity and Activity Impairment-Specific Health Problem (15), has been adapted for CD patients (WPAI: CD) to evaluate the impact of disease on work productivity and daily activities.

These instruments have been used to assess health outcomes in phase III trials of biologics. The efficacy of infliximab was measured using the IBDQ and SF-36 (16). The efficacy of adalimumab maintenance therapy was evaluated using the IBDQ (17). In trials of natalizumab, the impact of maintenance treatment on HRQOL was assessed with the IBDQ, SF-36 (18), and EQ-5D (19).

Certolizumab pegol (CZP; Cimzia) is the first polyethylene glycolated (PEGylated) anti-tumor necrosis factor-α (anti-TNFα) antibody fragment. Unlike conventional anti-TNFα agents, CZP lacks a fragment crystallizable region, thus potentially avoiding cytotoxic effects (20). The safety and efficacy of CZP has been demonstrated in two large phase III trials, PEGylated antibody fRagment Evaluation in Crohn's disease: Safety and Efficacy (PRECiSE 1 (21) and PRECiSE 2 (22)). We evaluated the effect of CZP maintenance therapy in PRECISE 2 using three distinct PRO instruments.

METHODS

Study population

Study participants were recruited from the university hospitals, medical centers, and clinical research centers between February 2004 and October 2004. A total of 147 investigational sites in four geographic regions encompassing 17 countries participated: Eastern Europe (27 sites), Western Europe (33 sites), North America (52 sites), and other areas around the world (35 sites).

Study participants were adults (≥18 years old) with a confirmed diagnosis of moderate-to-severe CD (CDAI ≥220 and <450) for 3 months or more. Treatment with anti-TNFα therapy for >12 weeks before screening was allowed. Preexisting concomitant medications for CD were also permitted, including 5-aminosalicylic acids or antibiotics (at a stable dose for 4 weeks before screening), corticosteroids (≤30 mg prednisone/day at a stable dose for 2 weeks), azathioprine, 6-mercaptopurine, or methotrexate (at a stable dose for 8 weeks).

Patients were not eligible if they had an abscess at screening, a bowel perforation or evidence of noninflammatory obstruction during the 3 months before screening, extensive bowel resection, a functional colostomy or ileostomy, a positive stool culture for enteric pathogens, or a known history of tuberculosis. Other exclusion criteria were treatment for CD with sodium cromoglycate, mycophenolate mofetil, or cyclosporin within 4 weeks of study entry.

Study protocol and masking

This was a 26-week, phase III, double-blind, placebo-controlled, parallel-group study. All study participants received CZP during a 6-week, open-label induction phase. The intent-to-treat population consisted of study participants who had a clinical response (defined as a ≥100-point decrease in CDAI score from baseline at week 6) to open-label therapy, who were subsequently randomized to maintenance with CZP or placebo, and who received at least one injection of the study drug. To facilitate blinding, study participants received their treatment from a nurse or physician who was not involved in assessment of study outcomes. All other study personnel were unaware of treatment assignments.

Study treatments

An open-label induction regimen of 400 mg CZP was administered to all participants by subcutaneous injection on weeks 0, 2, and 4. A maintenance regimen of 400 mg CZP or placebo was administered by subcutaneous injection on weeks 8, 12, 16, 20, and 24. All study injections were administered in the clinic during scheduled visits.

PRO assessment instruments

The IBDQ and SF-36 were self-administered on weeks 0, 6, 16, and 26 or at the withdrawal visit; the EQ-5D was self-administered at every scheduled visit.

The IBDQ is a disease-specific, 32-item questionnaire consisting of four domains: Bowel symptoms (10 items), Systemic symptoms (5 items), Emotional function (12 items), and Social function (5 items) (8). Response options are presented on a 7-point Likert scale (1 indicating *worst HRQOL* to 7 indicating *best HRQOL*), yielding a total score that ranges from 32 to 224 points. A ≥16-point increase from baseline is considered a minimum clinically important difference (MCID) (10). A total score of ≥170 points is observed in patients with clinical remission (3).

The SF-36 is a widely used generic HRQOL instrument (23). Items on the SF-36 are aggregated into eight multi-item domains: Physical Functioning, Role Limitations Due to Physical Problems (Role-Physical), Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations Due to Emotional Problems (Role-Emotional), and Mental Health. Scores range from 0 for *worst HRQOL* to 100 for *best HRQOL*. Domain scores are aggregated into two summary scores, the Physical Component Summary (PCS) and the Mental Component Summary (MCS). For both summary scores, a score of 50±10 is considered the norm for the general US population (23).

The EQ-5D is a generic questionnaire with five items and a 20-cm VAS measuring patients' perceptions of their current health status. The five items assess Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression. Each item is evaluated using a three-point response from *no problem* (level 1) to *extreme problem* (level 3). The EQ-5D VAS score ranges from 0 for *worst imaginable health state* to 100 for *best imaginable health state* (24).

The domains of these three PRO instruments provide a comprehensive assessment of HRQOL as they include, at a minimum, the three key domains of HRQOL: physical, emotional, and social function. In addition to these measures of HRQOL, the WPAI:CD was used to assess the impact of CD and its treatment on work productivity (25).

The CDAI, IBDQ, and WPAI:CD were used to determine the proportion of participants who achieved *normal life* at week 26, a composite measure defined here for the first time. Participants with *normal life* met all of the following criteria: clinical remission, as measured by CDAI (≤150 points); HRQOL remission, as measured by IBDQ (≥170 points); no or almost no impact from CD on daily activities (WPAI:CD daily activities score of 0 or 1 point); and no or almost no absenteeism or presenteeism if currently employed (WPAI:CD score of 0 on absenteeism and 0 to 1 on presenteeism).

Until recently, no MCID for SF-36 domains and EQ-5D VAS had been determined for patients with active CD. However, MCIDs were recently derived for the SF-36 summary scores (4.1 for PCS, 3.9 for MCS) and the EQ-5D VAS (9.2) through the use of data from a companion trial of CZP therapy (PRECiSE 1 (ref. (26)). The MCIDs for the three instruments were used to define HRQOL response variables (participants with a score change from baseline ≥MCID were considered to have achieved an HRQOL response).

Statistical analysis

Study participants' baseline demographic attributes and disease characteristics were evaluated using descriptive statistics. HRQOL scores (IBDQ, SF-36, and EQ-5D) were calculated at baseline and week 6 and compared with the specified MCIDs and normative values for the general US population. The effect of CZP maintenance on HRQOL was compared with that of placebo by means of a stepwise repeated-measures analysis of covariance of score changes from baseline for IBDQ, SF-36, and EQ-5D VAS or by stepwise repeated-measures logistic regression for EQ-5D items. The EQ-5D responses collected at each scheduled and withdrawal visit were converted into utility scores using an established algorithm (27). An estimate of quality-adjusted life-years (QALYs) was computed for each patient from the area under the utility curve during the randomization period. Mean QALYs and s.d. were calculated by treatment group and compared using the Wilcoxon rank-sum test.

Binary variables (response, remission, and *normal life* status) were compared at each assessment using logistic regression with adjustment for the baseline score. Missing items were replaced using single-mean imputation, provided the respondent completed at least 50% of the items for a given scale. For binary outcomes, study participants with missing scores were considered as nonresponders.

RESULTS

Study population flow and assignment

Of the 930 patients screened for eligibility, 668 participants entered the open-label induction phase of the trial. Of these, 428 study participants (64.1%) who were clinical responders at week 6 were randomized to maintenance treatment with CZP or placebo and received at least one injection of study drug. However, three participants, one in the CZP group and two in the placebo group, were excluded because of possible unblinding of their treatment assignment. Thus, 425 study participants were included in intent-to-treat analyses: 215 participants randomized to CZP maintenance and 210 to placebo. The baseline demographics of the intent-to-treat population are shown in **Table 1**.

HRQOL at baseline

At the baseline visit, impairment in HRQOL was observed on most domain scores of all three instruments. The mean total IBDQ score was substantially lower than that observed in patients in remission, and most SF-36 and EQ-5D scores were demonstrably below those observed in the general US population. The SF-36 domain most affected was Role-Physical, and the least affected was Physical Functioning (**Table 2**, **Figure 1a**). The most affected EQ-5D domain was Pain/Discomfort, and the least affected was Self-Care (**Table 2**, **Figure 1b**). No study participants had a *normal life* at baseline according to our prespecified composite definition.

Table 1. Demographic attributes and clinical characteristics of ITT population

	Placebo (n=210)	Certolizumab pegol (n=215)
Demographic variables		
Mean age, years (±s.d.)	37.6 (±12.1)	37.5 (±11.2)
Gender, % male	51.9	42.8
Region, %		
Eastern Europe	30.5	30.7
Western Europe	17.1	21.4
North America	29.0	22.3
Rest of the world	23.3	25.6
Clinical variables		
Mean duration of CD, years (±s.d.)	7.3 (±7.8)	8.6 (±7.1)
Mean CDAI baseline score (±s.d.)	301.1 (±61.2)	305.6 (±60.8)
Location of CD, %		
Terminal ileum	23.3	20.9
Colon	27.1	26.0
Ileocolon	42.4	48.4
Upper gastrointestinal tract	7.1	4.7
Behavior of CD, %		
Inflammatory	67.1	67.4
Stricturing	9.5	11.6
Penetrating	23.3	20.9
Resection performed, %	34.8	29.8
Preexisting concomitant antineoplastic and immunomodulating agents for CD, %	42.9	41.4
Azathioprine	30.5	34.0
6-Mercaptopurine	7.6	3.3
Methotrexate	4.3	4.7
Infliximab	1.4	0.5

CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; ITT, intent-to-treat.

HRQOL scores at the end of the open-label treatment period (week 6)

Study participants who responded to treatment with CZP reported significant improvement in HRQOL at week 6, approaching levels observed in patients in remission and people in the general US population. The total IBDQ score increased from a baseline mean of 122.6±28.4 to 174.8±25.7 points (P<0.001). Scores in all four IBDQ domains also improved significantly relative to baseline (P<0.001). An IBDQ response (MCID), defined as an increase of ≥16 points from baseline, was observed in 91.0% of study participants (384/422). The mean scores in all eight SF-36 domains improved and approached those of the general US population (**Figure 1a**). The PCS and MCS scores increased from a mean baseline of 37.5±7.3 and 36.9±11 points, respectively, to 47.2±7.1 and 47.6±10.1 points, respectively. EQ-5D items, except Self-Care, were improved (**Figure 1b**), and the EQ-5D VAS score increased by 24 points, from 47.4 to 71.4 points (P<0.001). The proportion of study participants who satisfied the rigorous criteria for a *normal life* increased from 0% at baseline to 25.7% (109/425) at the end of the open-label induction treatment (P<0.001).

HRQOL scores at the end of the maintenance period (week 26)

In study participants, randomized to continued treatment with CZP, the statistical improvements in all IBDQ domain scores achieved at week 6 were sustained to week 26 and were significantly greater than those observed in participants assigned to placebo (**Table 3**). The mean IBDQ total score of CZP-treated participants at week 26 was >170 points. At week 26, a positive IBDQ response (≥16-point increase from baseline) was seen in 60.6% (129/213) of those receiving CZP maintenance, compared with 42.9% (90/210) of those assigned to placebo (P<0.001). Furthermore, IBDQ remission (total score ≥170 points) was achieved by 46.5% (99/213) of study participants treated with CZP maintenance therapy, compared with 26.2% (55/210) of those who received placebo (P<0.001) (**Figure 2**).

Improvements in SF-36 measures were also sustained at week 26. Both component summary scores and all SF-36 domains except Physical Functioning were significantly higher in study participants who continued with CZP maintenance than in those who received placebo (**Table 3**). The PCS and MCS scores approximated those of the general US population (23). Positive SF-36 PCS and MCS responses (≥MCID, defined as a 4.1- or 3.9-point increase from baseline, respectively) were achieved by more study participants receiving continued treatment with CZP than those assigned to placebo (51.2% (107/209) compared with 33.8% (70/207), P<0.001, and 44.2% [92/208) compared with 32.4% (67/207), P=0.016, respectively) (**Figure 2**).

Up to week 26, EQ-5D VAS scores were significantly higher in study participants who received CZP maintenance than in those who received placebo (**Table 3**). The proportion of study participants with a positive EQ-5D VAS response (≥MCID, defined as a minimum 9.2-point increase from baseline) was greater in the maintenance therapy group than in the placebo group (57.2% (115/211) compared with 37.9% (77/203), P<0.001) (**Figure 2**). Improvements in three of the five EQ-5D domains were significantly greater with CZP maintenance than with placebo maintenance (**Table 3**). Patients in the CZP group had higher QALYs than those in the placebo group. The mean±s.d. QALYs were 0.25±0.10 for those treated with CZP and 0.21±0.11 for those receiving placebo (P=0.001). Signifi-

Table 2. Baseline health-related quality of life mean scores (±s.d.)

	Score range	Score results[a]
IBDQ domains		
Total	32–224	122.6 (±28.44)
Bowel symptoms	10–70	38.6 (±8.23)
Systemic symptoms	5–35	15.7 (±4.84)
Emotional function	12–84	47.1 (±13.37)
Social function	5–35	21.2 (±7.28)
*EQ-5D domains % (*n*) reporting no problem*		
Mobility	0–100	63.7 (270)
Usual activities	0–100	25.9 (110)
Pain/discomfort	0–100	4.0 (17)
Self-care	0–100	93.2 (395)
Anxiety/depression	0–100	29.7 (126)
SF-36 domains		
PCS[b]	0–100	37.5 (±7.28)
MCS[b]	0–100	36.9 (±10.96)
Physical functioning	0–100	65.0 (±22.19)
Role—physical	0–100	22.5 (±31.92)
Bodily pain	0–100	39.6 (±17.14)
General health	0–100	31.4 (±15.78)
Vitality	0–100	29.8 (±18.46)
Social functioning	0–100	50.7 (±23.34)
Role—emotional	0–100	44.5 (±41.27)
Mental health	0–100	53.0 (±19.34)
EQ-5D VAS		
VAS	0–100	47.4 (±17.17)

EQ-5D, EuroQoL-5 dimensions; IBDQ, Inflammatory Bowel Disease Questionnaire; MCS, mental component score; PCS, physical component score; SF-36, Short-Form 36-Item Health Survey; VAS, health status visual analogue scale.
[a]Higher scores indicate better outcomes. [b]Normalized to general US population (mean = 50, s.d. = 10).
n = 425.

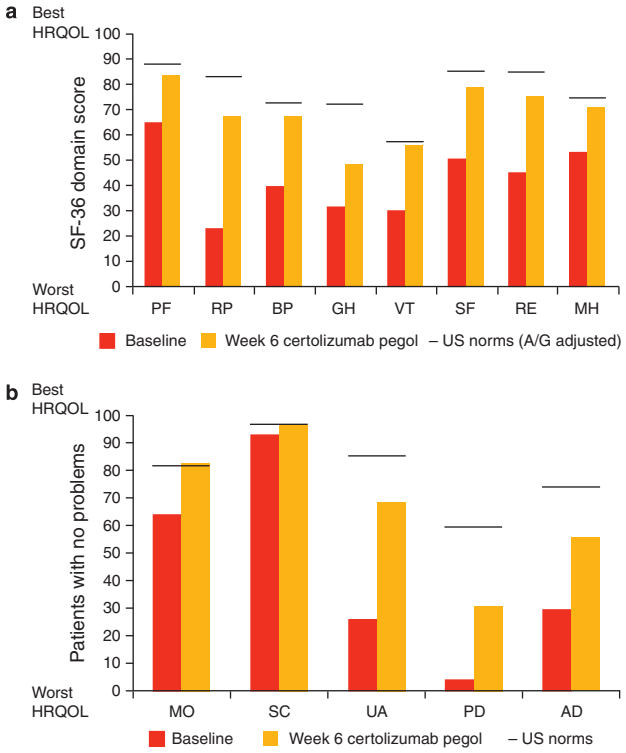

Figure 1. HRQOL scores following certolizumab pegol induction therapy compared to baseline and US population norms. (**a**) Mean SF-36 scores: baseline, certolizumab pegol induction, and US norms. *n* = 425 Study participants receiving open-label induction with certolizumab pegol at baseline and week 6. *n* for US norms = 1,982. PF, physical functioning; RP, role—physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role—emotional; MH, mental health. SF-36 norms for general US population (23) were adjusted for age and gender (A/G adjusted). (**b**) Mean EQ-5D scores: baseline, certolizumab pegol induction, and US norms. *n* = 425 Study participants who received open-label induction with certolizumab pegol at baseline and week 6. *n* for US norms = 4,048 individuals from the general US population who were interviewed face-to-face from 8 June to 31 October 2002 (ref. (28)). MO, mobility; SC, self-care; UA, usual activities; PD, pain/discomfort; AD, anxiety/depression.

cantly more study participants reported a *normal life* at week 26 with CZP maintenance than with placebo: 21.4% (46/215) compared with 12.9% (27/210) ($P = 0.019$) (**Figure 2**).

DISCUSSION

Our results confirm the value of long-term treatment of CD with CZP. At the time of study entry, the HRQOL of these study participants was significantly impaired. Baseline HRQOL scores were consistent with other reports of HRQOL for patients with moderate-to-severe CD (16–18,29,30). Most HRQOL scores were lower than the normative scores of the general US population and the HRQOL levels observed with other gastrointestinal disorders, such as moderate-to-severe irritable bowel syndrome and gastroesophageal reflux disease (31,32). Compared with the HRQOL of the general US population, the HRQOL domains most impaired at baseline in study participants were Role Limitations (limitations at work as a result of physical problems) (SF-36) and Pain/Discomfort (EQ-5D). This suggests that for patients with moderate-to-severe CD, reduced HRQOL is largely the result of physical problems. Not surprisingly, none of the study participants met the criteria defining a *normal life* at baseline.

At week 6, the clinical response to CZP therapy was associated with clinically meaningful improvement in study participants' HRQOL, as measured by all three HRQOL instruments. Mean scores were increased in all four IBDQ domains, and the mean total IBDQ score was 175 points, indicative of disease remission (3). Mean scores in all eight SF-36 domains improved, and component summary scores

Table 3. Health-related quality of life (±s.d.) at week 26

	Certolizumab pegol (n=215)	Placebo (n=210)	P value[a]
IBDQ domains			
Total	175.7 (±29.94)	167.9 (±32.19)	**<0.001**
Bowel symptoms	54.7 (±9.58)	51.8 (±10.24)	**<0.001**
Systemic symptoms	25.3 (±5.21)	23.9 (±5.94)	**<0.001**
Emotional function	65.6 (±12.64)	62.6 (±13.90)	**0.002**
Social function	30.1 (±6.20)	29.5 (±5.99)	**0.048**
EQ-5D domains % (n) reporting no problem			
Mobility	87.0 (127)	79.6 (86)	**<0.001**
Usual activities	78.8 (115)	65.7 (71)	**0.011**
Pain/ discomfort	39.0 (57)	29.6 (32)	**0.045**
Self-care	96.6 (141)	96.3 (104)	0.115
Anxiety/ depression	58.2 (85)	52.8 (57)	0.242
SF-36 domains			
PCS	48.1 (±8.17)	46.4 (±7.69)	**0.014**
MCS	46.9 (±11.53)	45.2 (±11.83)	**0.001**
Physical functioning	84.1 (±19.41)	83.0 (±17.92)	0.120
Role—physical	67.6 (±36.46)	63.0 (±42.07)	**0.006**
Bodily pain	69.4 (±21.87)	61.2 (±21.30)	**<0.001**
General health	50.0 (±19.50)	47.0 (±20.76)	**0.016**
Social functioning	79.2 (±23.32)	74.5 (±25.29)	**0.001**
Role—emotional	72.1 (±36.52)	70.4 (±40.33)	**0.026**
Mental health	70.0 (±19.68)	66.6 (±20.42)	**0.001**
EQ-5D VAS			
VAS	74.6 (±17.13)	70.2 (±18.07)	**0.002**

MCS, Mental Component Score; PCS, Physical Component Score.
[a]Certolizumab pegol maintenance compared with placebo maintenance; repeated-measures stepwise analysis of covariance on changes from baseline.
Certolizumab pegol maintenance compared with placebo maintenance; repeated-measures stepwise logistic regression.
Boldface P values indicate statistical significance.

approached normative levels for the general US population (23). Improvements were observed in EQ-5D VAS and all five EQ-5D items when measured at week 6; only the

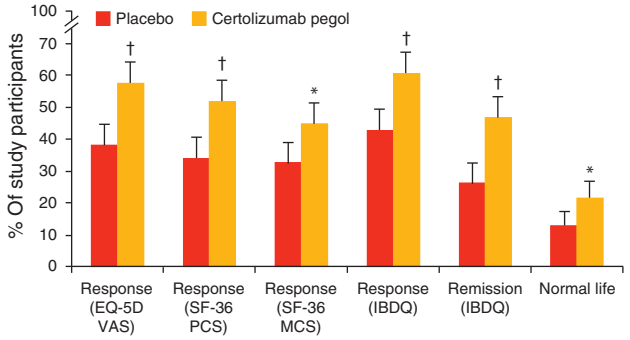

Figure 2. Proportion of participants with response, remission, or normal life, according to the IBDQ, SF-36, and EQ-5D VAS at week 26. *P<0.05 (logistic regression). †P<0.001 (logistic regression). Error bars represent the 95% confidence interval.

Self-Care score was not greatly increased, most likely because 93% of participants reported normal function in this domain at study entry.

Improvements in HRQOL associated with CZP maintenance were sustained up to week 26. At week 26, the mean total IBDQ score with CZP maintenance was 176 points compared with 168 points with placebo maintenance. Over the maintenance period, scores for all IBDQ domains were significantly improved compared with placebo scores. Nearly half the study participants treated with CZP maintenance therapy reported remission, as defined by IBDQ criteria. The mean SF-36 component summary scores with CZP maintenance remained close to normative values in the general US population. Component summary scores and all SF-36 domains except Physical Functioning were significantly greater with CZP maintenance than with placebo. The Physical Functioning domain includes questions about health limitations on physical activities, such as running, walking, or climbing stairs. A ceiling effect, meaning most respondents were at the highest possible score at the baseline visit, was observed for Physical Functioning, indicating that study participants were not severely affected in these activities and improvement at week 26 was not possible. In contrast to the Physical Functioning domain, the Role-Physical domain (which asks about problems with work productivity or other regular daily activities) was the most severely affected at baseline and was markedly improved compared with baseline and with placebo in the maintenance phase. At week 26, the EQ-5D VAS mean score and three of the five EQ-5D domain scores were significantly improved with CZP maintenance compared with placebo maintenance. Although the period of assessment was only 26 weeks, with the first 6 weeks being induction therapy for all, the data clearly showed that patients treated with CZP gained more QALYs (0.03) than those on placebo. QALYs have not previously been calculated using patient level data from clinical trial studies, such as reported here, for other biologics used to treat CD. However, an analysis based on a decision analytic model comparing the risks and benefits of

infliximab therapy with standard of care showed a similar gain of 0.02 QALY per patient (0.77 vs. 0.75) for infliximab in a time horizon of 1 year (33).

Our results show that continued treatment with CZP substantially ameliorates the burden of illness due to CD. Specifically, the HRQOL improvements observed in this study are similar to those reported in other maintenance studies evaluating TNF antagonists in patients with moderate-to-severe CD (16,17,29), providing further support that few, if any, efficacy differences exist among these agents. Anti-TNFα agents, such as CZP, infliximab, and adalimumab, modulate the pathological inflammation of CD by blocking TNFα initiation of the inflammatory cascade. Unlike these other biological agents, CZP is a PEGylated Fab′ fragment of a monoclonal antibody that lacks the fragment crystallizable region. *In vitro*, this modified anti-TNFα agent mediates immune cell death by an action separate from complement-dependent cytotoxicity or antibody-dependent cytotoxicity action (20).

One unique aspect of this study is that the impact of the disease was evaluated according to a new HRQOL measure: *normal life* assessment, which combines measures of disease activity, HRQOL, and work productivity and daily activity. The results of PRECISE 2 show that an important proportion of patients treated with CZP maintenance met our prespecified definition of *normal life*. As the "therapeutic bar" for HRQOL is raised, there is an increasing need for sensitive and specific instruments to evaluate outcomes. We believe the *normal life* assessment will be highly specific for identifying HRQOL differences among competing agents. However, we do recognize that this concept needs to be validated in future clinical trials.

We have shown, using three distinct PRO instruments, that continued treatment with CZP maintained a high quality of life in patients who previously responded to CZP induction.

CONFLICT OF INTEREST

Guarantor of the article: Brian G. Feagan, MD.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ The Crohn's Disease Activity Index, a measure predominantly of physical symptoms, is typically used to assess the severity of Crohn's disease (CD).
- ✓ Although health-related quality of life (HRQOL) is heavily correlated with disease activity, an additional level of information regarding patients' emotional and social functioning is not assessed by conventional disease activity indexes.

WHAT IS NEW HERE

- ✓ This study reports the first evaluation of HRQOL associated with CD that uses three patient-reported outcome (PRO) instruments in response to maintenance therapy with a biological agent.
- ✓ Evaluation by three distinct PRO instruments demonstrated that continued treatment with certolizumab pegol (CPZ) maintained a high quality of life in patients who previously responded to CPZ induction.
- ✓ An important proportion of CPZ-treated patients met the definition of "normal life" when assessed by a new HRQOL instrument that combines measures of disease activity, HRQOL, work productivity, and daily activity.

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