Effect of Certolizumab Pegol With Methotrexate on Home and Work Place Productivity and Social Activities in Patients With Active Rheumatoid Arthritis

ARTHUR KAVANAUGH,1 JOSEF S. SMOLEN,2 PAUL EMERY,3 OANA PURCARU,4 EDWARD KEYSTONE,5 LANCE RICHARD,6 VIBEKE STRAND,7 AND RONALD F. VAN VOLLENHOVEN8

Objective. To assess the impact of certolizumab pegol (CZP), a novel PEGylated anti–tumor necrosis factor, in combination with methotrexate (MTX) on productivity outside and within the home, and on participation in family, social, and leisure activities in adult patients with rheumatoid arthritis (RA).

Methods. The efficacy and safety of CZP (200 mg and 400 mg) plus MTX were assessed in 2 phase III, multicenter, double-blind, placebo-controlled trials (Rheumatoid Arthritis Prevention of Structural Damage [RAPID] 1 and RAPID 2). The novel, validated, RA-specific Work Productivity Survey (WPS-RA) was used to assess work place and home productivity. WPS-RA responses were collected at baseline and every 4 weeks until withdrawal/study completion.

Results. At baseline, 41.6% and 39.8% of subjects were employed outside the home in RAPID 1 and RAPID 2, respectively. Compared with placebo plus MTX, CZP plus MTX significantly reduced work absenteeism and presenteeism among patients working outside the home. Significant reductions in number of household days lost, household days with productivity reduced by >50%, and days lost due to RA for participation in family, social, and leisure activities were reported by patients in active treatment relative to placebo plus MTX. Improvements in all measures were observed with CZP plus MTX as early as week 4, and maintained until the study end (12 months in RAPID 1, 6 months in RAPID 2). Findings were consistent with clinical improvements with CZP plus MTX in both trials.

Conclusion. CZP plus MTX improved productivity outside and within the home and resulted in more participation in social activities compared with placebo plus MTX. These observations suggest that considerable indirect cost gains might be achieved with this therapeutic agent in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a major cause of productivity loss and disability worldwide (1–6). Impairment of physical functioning in RA negatively impacts on patients’ quality of life, translating into low utility values comparable with those reported for multiple sclerosis and chronic ischemic heart disease (6). In adult patients with active...
RA, despite treatment with methotrexate (MTX), impaired physical functioning and radiographic joint damage are associated with loss of full-time employment status (7). In the absence of effective treatment, it has been reported that 40–50% report work loss within 10 years of RA onset (2,8).

RA is associated with significant economic burden. In 2006, the total cost of RA in the US was estimated as the equivalent of $66 billion US (reported as €42 billion, among which €9 billion were medical costs [excluding drugs], €14 billion drug costs, €4 billion nonmedical costs [formal help at home and adaptation of house/transportation costs], €6 billion informal care, and €9 billion indirect costs) (6). Worldwide, at least half of all RA costs represent indirect costs due to lost employment and the need for household help (1.3–6). A cross-sectional analysis of a US patient database reported a loss of household income of 11.8% for all patients with RA, independent of their employment status, and annual earning losses between 9.3% and 10.9% (9).

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) consensus conferences recommended inclusion of work productivity in the assessment of RA therapies (10). The importance of exploring daily activities and participation (International Classification of Function, Disability and Health) was also recently highlighted as an important aspect of an RA patient’s life, and hence of RA outcomes assessment (11). The few studies addressing productivity loss at home (6,12–15) concluded that patients with RA had limited ability to perform household and family activities (e.g., cleaning, cooking, taking care of children), participated less in recreational activities, and were dependent on outside help (14).

Absenteeism, defined as work days missed, is commonly utilized to assess productivity loss in RA (16). Recently, presenteeism, reflecting a decreased ability to be productive while at work, has been shown to account for ~41% of productivity loss in arthritis (including osteoarthritis and RA), compared with 12% due to absenteeism (17). Therefore, an accurate measure of productivity in RA should take into account both presenteeism and absenteeism in the work place and at home.

In addition to a reduction of signs and symptoms, the aim of RA treatment is to prevent or control joint damage, prevent loss of function, and maintain daily activities. Studies have shown that despite early combination therapy with conventional disease-modifying antirheumatic drugs (DMARDs), there are still substantial losses in work productivity in recent-onset active RA (18). Introduction of the biologic DMARDs has been shown to reduce the loss of work productivity in the work place (7,19–25); however, the impact of these therapies on productivity within the home and on family, social, and leisure activities requires further exploration. It has recently been reported in an open-label study of 505 patients with severe established RA refractory to DMARDs that the biologic agent adalimumab maintained productivity at home at a stable rate, by preventing further increases in outside personal aid and transportation help required, over a period of 144 weeks (19).

Recently, certolizumab pegol (CZP) in combination with MTX has been demonstrated to be effective in the treatment of patients with active adult-onset RA who have an inadequate response to MTX (26,27). In the Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and RAPID 2 trials, significantly more patients receiving CZP plus MTX achieved the American College of Rheumatology 20% (ACR20), ACR50, and ACR70 responses compared with patients receiving placebo (24-week ACR20 responses for CZP 200 mg plus MTX versus placebo plus MTX were 58.8% versus 13.6% in the RAPID 1 trial, P < 0.001; and 57.3% versus 8.7% in the RAPID 2 trial, P ≤ 0.001) (26,27). In addition, CZP plus MTX significantly delayed the progression of structural damage and improved physical function (26,27).

The current study demonstrates the impact of CZP as a combination therapy with MTX, administered every other week, on productivity in the work place and at home, and on participation in family, social, and leisure activities, in patients with active RA.

**SUBJECTS AND METHODS**

**Study design.** RAPID 1 (n = 982) and RAPID 2 (n = 619) are phase III, multicenter, double-blind, placebo-controlled trials that assessed the efficacy and safety of 2 different dose regimens of CZP plus MTX versus placebo plus MTX in patients with active RA despite treatment with MTX for ≥6 months (26,27). In each trial, patients were randomized in a 2:2:1 ratio to receive CZP 400 mg, CZP 200 mg (preceded by 3 doses of 400 mg at weeks 0, 2, and 4), or placebo, administered subcutaneously every 2 weeks in combination with MTX, over 52 weeks (RAPID 1) or 24 weeks (RAPID 2). Following screening, eligible patients were assessed for efficacy at baseline: weeks 1, 2, 4, 6, 8, 10 (RAPID 1 only), 12, 14, 16, and every 4 weeks thereafter until week 52 or 24 (or early withdrawal) in RAPID 1 and RAPID 2, respectively. Patients who failed to achieve an ACR20 response at both weeks 12 and 14 were to be withdrawn from the study at week 16. Patients who withdrew at week 16 and those who successfully completed either trial were offered enrollment in an open-label extension study of CZP 400 mg plus MTX every 2 weeks. The studies were conducted in accordance with the International Conference on Harmonisation E6 guideline for Good Clinical Practice (CPMP/ICH/135/95) and the principles that have their origin in the Declaration of Helsinki.

**The RA-Specific Work Productivity Survey (WPS-RA).** The WPS-RA is a novel, validated questionnaire assessing the impact of RA on productivity in the work place and at home, and on participation in family, social, and leisure activities (28). The questionnaire is based on self-report, and is interviewer-administered with a recall period of 1
The survey, which has been shown to be valid and responsive to clinical changes (28), consists of 9 questions. The first question addresses employment status and provides additional information on job type for employed subjects and on the status of those not employed. For employed patients only, 3 questions assess absenteeism (full days of work missed due to arthritis) and presenteeism (days with work productivity reduced by ≥50% due to arthritis, not including days counted in the previous question) in the work place, and the rate of interference with work productivity by RA on a 0–10 scale, where 0 = no interference and 10 = complete interference.

All patients answer the last 5 questions of the survey, which are related to productivity limitations at home and participation in family, social, and leisure activities over the previous month, as follows: number of days with no household work performed due to arthritis; days with household productivity reduced by ≥50% (not including days counted in the previous question); days with outside help hired; days with family, social, or leisure activities missed; and rate of interference with household productivity by RA on a 0–10 scale, where 0 = no interference and 10 = complete interference.

The WPS-RA survey was assessed in the RAPID 1 and RAPID 2 trials at baseline (week 0) and every 4 weeks until the end of the study or until withdrawal from the study. Days missed from work or activities due to scheduled per-protocol study visits were not counted in the assessment.

For clarity of presentation, the results are presented for each trial as the mean and median at weeks 4, 24, and 52 (RAPID 1 only). Statistical comparison between the treatment arms within each trial was performed using a non-parametric bootstrap-t method (29). Last observation carried forward (LOCF) methodology was used to impute missing data at any study visit. The 5% statistical significance level was used. Annualized data for each individual treatment group were also calculated by summing the productivity scores over the entire study duration, starting at week 4. Results are presented as the difference in annualized scores between the active and placebo groups.

### RESULTS

**Patient characteristics.** A total of 982 and 619 patients were randomized into the RAPID 1 and RAPID 2 trials, respectively (Table 1). Overall, patient demographic and clinical characteristics were similar across treatment groups, all with high disease activity at baseline.

Present employment status and productivity measures at baseline for the RAPID 1 and RAPID 2 trial populations are shown in Tables 2 and 3. At study entry, 41.6% and 39.8% (observed data) of all subjects in the intent-to-treat population in the RAPID 1 and RAPID 2 trials, respectively, were employed. Overall, 56.4% were not employed outside the home in RAPID 1 and these subjects were, on average, nearly 7 years older than the employed patients. Patients in RAPID 1 who were not employed were homemakers (14.4%), retired (20.0%), unable to work due to RA (21.1%), or had another not employed status (2.8%); percentages reported for RAPID 2 were largely similar (Table 2). There were no statistically significant differences between the treatment groups with regard to employment status at baseline.

**Burden of disease on productivity in the work place at baseline.** On average at baseline, patients in both trials who were working reported missing 2.8–4.6 days of work per month due to arthritis and had 6.2–9.2 days per month with work productivity reduced by ≥50%, demonstrating that RA affected productivity at work as measured by both absenteeism and presenteeism (Table 3). This was also evidenced by the reported interference of arthritis with work productivity (an average of 5.1–5.6 on a 0–10 scale, where 10 = complete interference). There were no statistically significant differences at baseline in work place productivity between the treatment groups.

### Table 1. Population characteristics at baseline in the RAPID 1 and RAPID 2 trials*

<table>
<thead>
<tr>
<th>Parameter</th>
<th>RAPID 1</th>
<th>RAPID 2</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>CZP 200 mg plus MTX (n = 393)</td>
<td>CZP 400 mg plus MTX (n = 390)</td>
</tr>
<tr>
<td>Age, years</td>
<td>51.4 ± 11.6</td>
<td>52.4 ± 11.7</td>
</tr>
<tr>
<td>Women, %</td>
<td>82.4</td>
<td>83.6</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>6.09 ± 4.22</td>
<td>6.16 ± 4.36</td>
</tr>
<tr>
<td>No. of previous DMARDs†</td>
<td>1.3 ± 1.3</td>
<td>1.3 ± 1.3</td>
</tr>
<tr>
<td>HAQ DI score‡</td>
<td>1.7 ± 0.6</td>
<td>1.7 ± 0.6</td>
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<tr>
<td>DAS28 ESR</td>
<td>6.9 ± 0.8</td>
<td>6.9 ± 0.8</td>
</tr>
<tr>
<td>MTSS</td>
<td>38.4 ± 49.4</td>
<td>38.3 ± 47.1</td>
</tr>
<tr>
<td>Joint erosion score</td>
<td>14.9 ± 24.3</td>
<td>14.4 ± 22.8</td>
</tr>
<tr>
<td>Joint space narrowing score</td>
<td>24.0 ± 27.7</td>
<td>24.0 ± 26.5</td>
</tr>
</tbody>
</table>

* Values are the mean ± SD unless otherwise indicated. RAPID 1 = Rheumatoid Arthritis Prevention of Structural Damage 1; CZP = certolizumab pegol; MTX = methotrexate; DMARDs = disease-modifying antirheumatic drugs; HAQ DI = Health Assessment Questionnaire disability index; DAS28 = Disease Activity Score in 28 joints; ESR = erythrocyte sedimentation rate; MTSS = modified total Sharp Score.
† World Health Organization Drug Classification version Q42004. Excludes MTX.
‡ Ranges from 0–3, with lower scores indicating better physical function.
Burden of disease on productivity within the home at baseline. RA also affected productivity within the home to a high degree. At baseline, all patients, regardless of their employment status, reported missing an average of 6.8–8.8 days of household work per month due to their arthritis and 4.7–6.8 days per month of family, social, and leisure activities. Additionally, they reported experiencing 10.2–11.2 days per month where productivity at home was reduced by 50% and 4.5–6.2 days per month when hiring outside help was necessary (Table 3). The rate of interference of RA with productivity at home was 5.8–6.4, on average, on a 0–10 scale. There were no statistically significant differences at baseline in productivity at home between the treatment groups.

Effect of CZP treatment on productivity in the workplace. In both trials, patients receiving CZP plus MTX experienced rapid improvements in their workplace productivity compared with patients receiving placebo plus MTX, as evidenced by the higher reductions in absenteeism, presenteeism, and the rate of RA interference with work productivity (Figure 1). At week 4 in RAPID 1, patients treated with CZP 200 mg plus MTX reported an average of 1.5 work days per month missed, 4.3 days per month with reduced productivity, and a monthly rate of RA interference with work productivity of 3.5 (on a 0–10 scale), compared with 2.5 days missed per month, 6.5 days with reduced productivity, and a rate of RA interference of 4.2 for patients in the placebo plus MTX group (Figure 1). Improvements in the CZP plus MTX group were further increased over time to the end of the study (week 52 in RAPID 1). Similar reductions in absenteeism, presenteeism, and the rate of RA interference with work productivity were reported in the CZP 400 mg plus MTX group in RAPID 1 and in both CZP groups in RAPID 2, although reductions in absenteeism did not reach statistical significance (at the 0.05 level) in RAPID 2.

On an annual basis, CZP 200 mg plus MTX treatment led to a cumulative gain of 41.95 full work days and 29.43 fewer days with reduced productivity versus placebo plus MTX. Comparable results were observed in the CZP 400 mg plus MTX group in RAPID 1 and in both active arms in RAPID 2.

Effect of CZP treatment on productivity at home. In both trials, patients receiving CZP plus MTX treatment reported less loss of productivity at home and less impact on daily activities compared with patients receiving placebo plus MTX (Figure 2). At week 4 in RAPID 1, patients treated with CZP 200 mg plus MTX reported (on average) fewer household work days missed per month due to RA than patients treated with placebo plus MTX (6.9 versus 7.6) (Figure 2A), fewer days with reduced productivity (8.1 versus 9.8) (Figure 2B), fewer days per month with outside hired help (3.5 versus 4.1) (Figure 2C), and a lower rate of RA interference with household productivity (5.0 versus 5.9 on a 0–10 scale) (Figure 2D). Results were similar in the CZP 400 mg plus MTX group in RAPID 1 and in both active arms in RAPID 2, and improvements in productivity at home continued to improve and were sustained through 24 weeks (RAPID 2) and 52 weeks (RAPID 1).
In the RAPID 1 and RAPID 2 trials, CZP as a combination therapy with MTX resulted in considerable improvement versus placebo plus MTX on all productivity measures, including reduced absenteeism and presenteeism in patients working outside the home, reduced loss of productivity within the home, and fewer days of lost participation in family, social, and leisure activities due to RA. These findings are consistent with the clinical improvements reported with CZP plus MTX treatment in both trials (26,27). Improvements in productivity were observed with CZP plus MTX as early as week 4 and sustained over 6 months (RAPID 2) and 12 months (RAPID 1). Although differences in all productivity measures were noticed at week 4, not all of them reached the statistical significance level. Significant differences were found for all measures in RAPID 1 at weeks 24 and 52, and for all measures except for absenteeism at work in RAPID 2 at week 24.

The patient population studied had active RA with a mean disease duration of 6 years, having failed treatment with an average of 1.3 and 1.2 DMARDs at RAPID 1 and RAPID 2 baseline, respectively. Baseline data confirmed the significant impact of active RA on both employment status and productivity outside and within the home, as well as on participation in family, social, and leisure activities. Using the WPS-RA, an instrument validated for rheumatoid arthritis–specific Work Productivity Survey. See Table 1 for additional definitions.

### Effect of CZP treatment on participation in family, social, and leisure activities.

Patients treated with CZP plus MTX also reported rapid decreases in the number of days of lost participation in family, social, and leisure activities due to their RA compared with placebo plus MTX (Figure 3). In RAPID 1, patients in the CZP 200 mg plus MTX group reported 4.3 days of lost participation, compared with 5.2 days in the placebo group at week 4. Results continued to improve through the entire study duration in both trials and were similar in the 2 active groups (Figure 3). These improvements resulted in an annual cumulative gain of 26.80 days of family, social, and leisure activities in the CZP 200 mg plus MTX group versus placebo plus MTX per year (RAPID 1). Similar trends were observed in the CZP 400 mg plus MTX group in RAPID 1 and in both active arms in RAPID 2.

### DISCUSSION

In the RAPID 1 and RAPID 2 trials, CZP as a combination therapy with MTX resulted in considerable improvement versus placebo plus MTX on all productivity measures, including reduced absenteeism and presenteeism in patients working outside the home, reduced loss of productivity within the home, and fewer days of lost participation in family, social, and leisure activities due to RA. These findings are consistent with the clinical improvements reported with CZP plus MTX treatment in both trials (26,27). Improvements in productivity were observed with CZP plus MTX as early as week 4 and sustained over 6 months (RAPID 2) and 12 months (RAPID 1). Although differences in all productivity measures were noticed at week 4, not all of them reached the statistical significance level. Significant differences were found for all measures in RAPID 1 at weeks 24 and 52, and for all measures except for absenteeism at work in RAPID 2 at week 24.

The patient population studied had active RA with a mean disease duration of 6 years, having failed treatment with an average of 1.3 and 1.2 DMARDs at RAPID 1 and RAPID 2 baseline, respectively. Baseline data confirmed the significant impact of active RA on both employment status and productivity outside and within the home, as well as on participation in family, social, and leisure activities. Using the WPS-RA, an instrument validated for RA (28), CZP plus MTX treatment resulted in significant reductions in absenteeism and presenteeism in the 41.6% and 39.8% of participants in the 2 trials who were employed, respectively. In the context of RA treatment, the rapid improvement of work productivity (within 4 weeks) suggests that CZP combined with MTX is a valuable therapeutic option for RA patients of working age.

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### Table 3. Productivity in the work place and within the home and participation in social activities at baseline in the RAPID 1 and RAPID 2 trials

<table>
<thead>
<tr>
<th>WPS-RA responses at baseline</th>
<th>RAPID 1</th>
<th></th>
<th></th>
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<th>RAPID 2</th>
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<tbody>
<tr>
<td></td>
<td>CZP 200 mg plus MTX</td>
<td>CZP 400 mg plus MTX</td>
<td>Placebo plus MTX</td>
<td>CZP 200 mg plus MTX</td>
<td>CZP 400 mg plus MTX</td>
<td>Placebo plus MTX</td>
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<tr>
<td></td>
<td>(n = 393)</td>
<td>(n = 390)</td>
<td>(n = 199)</td>
<td>(n = 246)</td>
<td>(n = 246)</td>
<td>(n = 127)</td>
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<tr>
<td>Productivity in the work place‡</td>
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<tr>
<td>Employed patients, no.</td>
<td>162</td>
<td>139</td>
<td>69</td>
<td>101</td>
<td>95</td>
<td>49</td>
<td></td>
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<tr>
<td>Work days missed due to arthritis</td>
<td>3.1 (0.0)</td>
<td>4.5 (0.0)</td>
<td>4.6 (0.0)</td>
<td>3.8 (0.0)</td>
<td>2.8 (0.0)</td>
<td>3.0 (0.0)</td>
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<td></td>
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<tr>
<td>Days with work productivity reduced by ≥50% due to arthritis‡</td>
<td>7.2 (5.0)</td>
<td>7.5 (5.0)</td>
<td>6.2 (5.0)</td>
<td>9.2 (8.0)</td>
<td>8.8 (7.0)</td>
<td>7.8 (7.0)</td>
<td></td>
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<tr>
<td>Rate of arthritis interference with work productivity§</td>
<td>5.2 (5.0)</td>
<td>5.1 (5.0)</td>
<td>5.5 (5.0)</td>
<td>5.6 (6.0)</td>
<td>5.4 (5.0)</td>
<td>5.3 (5.0)</td>
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<tr>
<td>Productivity at home</td>
<td></td>
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<tr>
<td>Household work days missed due to arthritis</td>
<td>7.6 (5.0)</td>
<td>8.2 (5.0)</td>
<td>8.8 (7.0)</td>
<td>6.9 (5.0)</td>
<td>6.8 (5.0)</td>
<td>6.9 (5.0)</td>
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</tr>
<tr>
<td>Days with household work productivity reduced by ≥50% due to arthritis‡</td>
<td>10.2 (10.0)</td>
<td>10.5 (10.0)</td>
<td>10.5 (10.0)</td>
<td>11.2 (10.0)</td>
<td>10.3 (10.0)</td>
<td>10.7 (10.0)</td>
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<tr>
<td>Days with family, social, or leisure activities missed due to arthritis</td>
<td>6.2 (2.0)</td>
<td>5.6 (2.0)</td>
<td>6.8 (3.0)</td>
<td>4.7 (2.0)</td>
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<tr>
<td>Days with outside help hired due to arthritis</td>
<td>5.1 (0.0)</td>
<td>5.4 (0.0)</td>
<td>6.2 (0.0)</td>
<td>4.5 (0.0)</td>
<td>4.8 (0.0)</td>
<td>6.2 (0.0)</td>
<td></td>
<td></td>
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<tr>
<td>Rate of arthritis interference with household work productivity§</td>
<td>6.1 (6.0)</td>
<td>6.1 (6.0)</td>
<td>6.4 (7.0)</td>
<td>6.0 (6.0)</td>
<td>5.8 (6.0)</td>
<td>6.0 (6.0)</td>
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</table>

* Values are the mean (median) response per month unless otherwise indicated. WPS-RA = rheumatoid arthritis–specific Work Productivity Survey. See Table 1 for additional definitions.
† Employed patients only.
‡ Does not include days counted in the previous question, “Work days missed due to arthritis.”
§ 0–10 scale, where 0 = no interference and 10 = complete interference.

Over 1 year in RAPID 1, these improvements led to an annual average of 52.10 fewer full days of missed household work and 36.61 fewer days per year with reduced productivity due to RA in the CZP 200 mg plus MTX group compared with the placebo plus MTX group. Similar trends were observed in the CZP 400 mg plus MTX group in RAPID 1 and in both active arms in RAPID 2.

The patient population studied had active RA with a mean disease duration of 6 years, having failed treatment with an average of 1.3 and 1.2 DMARDs at RAPID 1 and RAPID 2 baseline, respectively. Baseline data confirmed the significant impact of active RA on both employment status and productivity outside and within the home, as well as on participation in family, social, and leisure activities. Using the WPS-RA, an instrument validated for RA (28), CZP plus MTX treatment resulted in significant reductions in absenteeism and presenteeism in the 41.6% and 39.8% of participants in the 2 trials who were employed, respectively. In the context of RA treatment, the rapid improvement of work productivity (within 4 weeks) suggests that CZP combined with MTX is a valuable therapeutic option for RA patients of working age.
RA were either not employed outside the home or had lost their employment, but all reported a variety of obligations to be performed within the home. Significant reductions in the number of days of household work lost as well as the number of days with productivity reduced by ≥50% within the home were reported as early as 4 weeks, and sustained over 6 and 12 months in RAPID 2 and RAPID 1, respectively. Compared with placebo plus MTX, productivity within the home was significantly increased by CZP plus MTX in these patients, leading to an average of 44.5–52.1 fewer days of household work lost annually, and an additional 36.6–38.1 fewer days per year with reduced productivity due to RA.

Indirect costs attributed to lost productivity in the work place and at home are a major contributor to the economic burden of RA (1,3–6). Reductions in productivity loss both in the work place and in the home demonstrated in the current trials suggest that CZP plus MTX treatment can lead to savings in indirect costs associated with RA, thereby reducing the burden of RA. Importantly, patients in the active treatment groups in both trials reported fewer days lost engaging in family, social, and leisure activities due to active disease, with annual reductions of ~26 lost days. It can be expected that these reductions in productivity loss contribute to improving patients’ health-related quality of life.

The impact of other biologic DMARDs on work productivity in patients with active RA has been evaluated in a few studies using generic instruments of productivity measurement, but study methodology and patient populations differed, so comparisons should be viewed with care. Productivity in the work place was improved by etanercept treatment in an analysis based on structured telephone interviews of 497 patients of working age with established RA (disease duration 16 years) (20). A positive trend toward improvement of productivity within and outside the home (not statistically significant) was recently reported with adalimumab over a period of 144 weeks in a patient population with severe RA (refractory to 4 DMARD therapies; disease duration 12 years) (19). The need for outside personal aid and transportation help was reported in this case; however, other productivity measures of daily activ-

Figure 1. Reductions in lost productivity in the workplace: mean responses from the Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and RAPID 2 trials (nonparametric bootstrap t-test, last observation carried forward data). Two certolizumab pegol (CZP) plus methotrexate (MTX) combination regimens were compared with placebo plus MTX on the 3 work-related questions of the rheumatoid arthritis-specific Work Productivity Survey. A, Work days missed (absenteeism) due to arthritis per month. B, Days with work productivity reduced by ≥50% (presenteeism) due to arthritis per month. C, Rheumatoid arthritis interference with work productivity per month. Responses were recorded at baseline and every 4 weeks to week 24 in RAPID 2 and week 52 in RAPID 1. * = P ≤ 0.05 versus placebo plus MTX.
ilities within the home and participation in social activities were omitted from all the previous studies.

The strengths of our analyses include the consistency of observations across 2 dose regimens of CZP (200 mg and 400 mg every 2 weeks) in 2 independent clinical trials, RAPID 1 and RAPID 2. Using the WPS-RA instrument facilitated consideration of a broader spectrum of productivity-related dimensions to obtain complementary information on productivity loss with respect to both absenteeism and presenteeism, work within the home, and participation in family, social, and leisure activities.

A limitation of our analyses lies in the use of the LOCF method to impute missing data. Although the WPS-RA was completed by the majority of patients in the 2 studies, some data were missing and the LOCF method was used to impute these data. However, results obtained from observed data (without imputation) up to 16 weeks consistently demonstrated similar decreases in productivity loss

Figure 2. Reductions in lost productivity at home: mean responses from the Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and RAPID 2 trials (nonparametric bootstrap t-test, last observation carried forward data). Two certolizumab pegol (CZP) plus methotrexate (MTX) combination regimens were compared with placebo plus MTX on the 4 home-related questions of the rheumatoid arthritis–specific Work Productivity Survey. A, Household work days missed due to arthritis per month, B, Days with household work productivity reduced by $\geq 50\%$ due to arthritis per month, C, Days with outside help hired due to arthritis per month, and D, Rheumatoid arthritis interference with household work productivity per month. Responses were recorded at baseline and every 4 weeks to week 24 in RAPID 2 and week 52 in RAPID 1.
in the CZP plus MTX versus placebo plus MTX groups (data not shown). Another limitation relates to the control population. Here CZP combined with continued MTX therapy was compared with placebo combined with continued MTX in patients with active disease despite MTX treatment. Therefore, the difference between CZP plus MTX and de novo MTX treatment for the variables studied is not known. However, because other work productivity measures showed better improvement with anti–tumor necrosis factor therapy compared with de novo MTX treatment in other trials (23), it is reasonable to postulate that preseneeism and household performance variables (not measured in other trials) would perform significantly better upon treatment with CZP.

In summary, the RAPID trials demonstrated that CZP plus MTX rapidly improves work productivity in the work place and at home in adult patients with active RA. These observations suggest that considerable indirect cost gains can be achieved in RA with effective therapies in general and with this new therapeutic agent in particular.

AUTHOR CONTRIBUTIONS
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Figure 3. Decrease in days lost of family, social, and leisure activities per month: mean responses from the Rheumatoid Arthritis Prevention of Structural Damage (RAPID) 1 and RAPID 2 trials (nonparametric bootstrap t-test, last observation carried forward data). Two certolizumab pegol (CZP) plus methotrexate (MTX) combination regimens were compared with plus MTX on the daily activities question of the rheumatoid arthritis–specific Work Productivity Survey at baseline and every 4 weeks to week 24 in RAPID 2 and week 52 in RAPID 1. * P = 0.05 versus placebo plus MTX.