EXTENDED REPORT

Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON)

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ABSTRACT

Objectives To assess baricitinib on patient-reported outcomes (PROs) in patients with moderately to severely active rheumatoid arthritis, who had insufficient response or intolerance to ≥1 tumour necrosis factor inhibitors (TNFis) or other biological disease-modifying antirheumatic drugs (bDMARDs).

Methods In this double-blind phase III study, patients were randomised to once-daily placebo or baricitinib 2 or 4 mg for 24 weeks. PROs included the Short Form-36, EuroQol 5-D, Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F), Health Assessment Questionnaire-Disability Index (HAQ-DI), Patient’s Global Assessment of Disease Activity (PtGA), patient’s assessment of pain, duration of morning joint stiffness (MJS) and Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis. Treatment comparisons were performed with logistic regression for categorical measures or analysis of covariance for continuous variables.

Results 527 patients were randomised (placebo, 176; baricitinib 2 mg, 174; baricitinib 4 mg, 177). Both baricitinib-treated groups showed statistically significant improvements versus placebo in most PROs. Improvements were generally more rapid and of greater magnitude for patients receiving baricitinib 4 mg than 2 mg and were maintained to week 24. At week 24, more baricitinib-treated patients versus placebo-treated patients reported normal physical functioning (HAQ-DI <0.5; p≤0.001), reductions in fatigue (FACT-F ≥3.56; p≤0.05), improvements in PtGA (p≤0.001) and pain (p≤0.001) and reductions in duration of MJS (p<0.01).

Conclusions Baricitinib improved most PROs through 24 weeks compared with placebo in this study of treatment-refractory patients with previously inadequate responses to bDMARDs, including at least one TNFi. PRO results aligned with clinical efficacy data for baricitinib.

Trial registration number NCT01721044; Results.

INTRODUCTION

The inflammatory activity and joint damage associated with rheumatoid arthritis (RA) often result in impairment in physical function, and other impairments important to patients; effective therapy can dramatically improve these outcomes.1–3 Importantly, impairment in physical function is a consequence of both disease activity and irreversible, progressive joint damage.4,5 Patients with long-standing disease who have undergone treatment with several conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapies and also failed to respond sufficiently to biological DMARDs (bDMARDs) constitute a group with severe and particularly treatment-refractory disease.7 These patients may therefore be at increased risk for a lack of significant improvement in physical function or other patient-reported outcomes (PROs) on introduction of new therapies.7–9 Subsequently, despite the availability of several bDMARDs, there is an unmet need for more treatment options for such patients.

Patient input is important for shared decision-making, an overarching principle in most recommendations for the management of RA.10 As improvements in symptoms and health-related quality of life (HRQOL) are usually more relevant to patients than clinical or serological changes alone. Indeed, the burden of RA as reported by patients is considered an important aspect of RA management.11 12 As evaluation of PROs reflects part of the overall effectiveness assessment of csDMARDs and bDMARDs, such measures are included in RA clinical trials.13 14 Many PRO measures are available for this purpose and assess the range of potentially affected health domains such as pain, disease activity, physical functioning, fatigue, sleep disturbance, psychological disorders, well-being at work and QOL.

Baricitinib is a highly selective inhibitor of Janus kinase (JAK)1/JAK2 that interferes with pathways believed to be important in the pathogenesis of RA.15 In the RA-BEACON study, baricitinib was efficacious in patients who had failed previous treatment with several csDMARDs and one or more tumour necrosis factor inhibitors (TNFis) as well as non-TNFi bDMARDs.16 This manuscript describes the PRO data collection in RA-BEACON and assesses whether the efficacy of baricitinib demonstrated in RA-BEACON is reflected by clinically meaningful changes in PROs.
METHODS

Patients and study design

RA-BEACON (NCT01721044) was a randomised, 24-week, double-blind, placebo-controlled, multicentre, international phase III study. Full details of the study have been reported previously.16 Briefly, patients were randomly assigned (1:1:1) to receive once-daily placebo or baricitinib 2 or 4 mg in addition to the therapies they were already receiving at enrolment. Patients whose tender and swollen joint counts at baseline were reduced by <20% at both week 14 and week 16 received rescue treatment, baricitinib 4 mg daily. Patients were ≥18 years of age and had moderately to severely active RA, defined as a tender joint count of ≥6 and a swollen joint count ≥6 (68/66 joint count) and C-reactive protein ≥3 mg/L. Patients were required to have received one or more TNFIs and discontinued treatment due to insufficient response after ≥3 months or to intolerance and could have received other bDMARDs. Biological DMARDs must have been discontinued for ≥4 weeks before randomisation (≥6 months for rituximab). Patients must have been regularly using ≥1 csDMARDs for ≥12 weeks prior to study entry at a stable dose for ≥8 weeks. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and approved by the institutional review board or ethics committee for each centre involved. All patients provided written informed consent.

Patient-reported outcomes

Several PROs were prespecified secondary outcomes of the study.

The Medical Outcomes Study (MOS) Short Form-36 (SF-36; V2, Acute)17 18 was used to assess HRQOL in eight domains scored from 0 to 100 that are normalised into physical (PCS) and mental (MCS) component scores. A minimum clinically important difference (MCID) of 5 was used to assess the clinical relevance of changes in SF-36 scores (both domains and component scores).19 20 and a sensitivity analysis with an MCID of 2.5 was also evaluated. The EuroQol 5-Dimensions (EQ-5D 5L) Health State Profile was also used to assess HRQOL. The EQ-5D 5L consists of two components: a descriptive system of the respondent’s health and a rating of his/her current health state (visual analogue scale, VAS; 0–100 mm), in which the endpoints are labelled ‘best imaginable health state (100)’ and ‘worst imaginable health state (0)’.21 The UK and US scoring algorithms provide an index score using the UK or US population weighting to normalise it to that population;22–24 index scores range from 0 (death) to 1 (perfect health).

Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACT-F) scale (range 0–52), with higher scores representing less fatigue.25 For the FACT-F, a three to four-point change has been considered an MCID.25,26 and in this study a value of 3.56 was used to assess the clinical relevance of changes in FACT-F scores. Duration of morning joint stiffness (MJS) was reported by the patient as the length of time (minutes) that MJS lasted on the patient’s assessment of pain VA (0–100 mm), in which higher scores indicate more disease activity or pain.

The Work Productivity and Activity Impairment Questionnaire-Rheumatoid Arthritis (WPAI-RA) scale was used to measure the health and symptoms of overall work productivity and impairment of regular activities during the past 7 days. Scores are calculated as impairment percentages,31 with higher percentages indicating greater impairment and less productivity.

Most PROs were assessed at baseline and at weeks 1, 2, 4 and every 4 weeks thereafter to week 24, with the exceptions of the WPAI-RA (not collected at week 1) and the SF-36, EQ-5D and FACT-F data (collected at baseline, week 4 and then every 4 weeks until week 24).

Statistical analyses

Patients who were randomised and treated with ≥1 doses of placebo, baricitinib 2 or 4 mg were included in this analysis.

Comparisons of treatment groups (ie, baricitinib 2 mg vs placebo or baricitinib 4 mg vs placebo) for categorical measures were performed using logistic regression with geographical region and number of previous bDMARDs (=3, ≥3) as explanatory factors. When sample size requirements for logistic regression were not met (<5 responders in any category for any factor), the Fisher exact test was used. Comparisons of continuous measures were performed using analysis of covariance, with baseline score, geographical region and number of previous bDMARDs (=3, ≥3) as explanatory factors. For the duration of MJS, the p value for the median difference of change from baseline was calculated using the Wilcoxon rank-sum test. Any duration of MJS lasting >12 hours was truncated to 720 min for the purpose of this analysis.

Patients who were rescued or discontinued from the study or study treatment were thereafter defined as non-responders (non-responder imputation) for analysis of categorical data. These patients also had their last observations before rescue or discontinuation used for analyses of continuous data (modified last observation carried forward). However, the WPAI-RA measures were censored after rescue or discontinuation without imputation applied.

All analyses are based on a significance level of 0.05 (two-sided). p Values were not adjusted for multiple comparisons.

RESULTS

Patients

A total of 527 patients were randomised: 176 received placebo, 174 received baricitinib 2 mg and 177 received baricitinib 4 mg. Patient disposition has been described by Genovese et al.16 Baseline patient characteristics and disease activity were similar between the groups (see online supplementary table S1).16 Overall, almost 60% of the patients had previously received >1 bDMARD; 221 (42%), 160 (30%) and 142 (27%) patients, respectively, had previously received 1, 2 or ≥3 bDMARDs. Indeed, more than one-third of the patients enrolled in the study had an inadequate response to, or side effects associated with, both TNFi and non-TNFi bDMARDs.16 Baseline PRO values were similar across the treatment groups and indicated a significant disease burden, consistent with the combined effect of baseline clinical disease activity and disease duration16 (see online supplementary table S1).

Patient-reported outcomes

Over 24 weeks, most PROs improved significantly among patients receiving baricitinib compared with placebo, with
patients in the baricitinib 4 mg group showing a more rapid and greater magnitude of change than the baricitinib 2 mg group.

Health-related quality of life
The eight SF-36 domain scores at week 12 and week 24 were assessed. Patients treated with baricitinib 2 or 4 mg reported statistically significantly improved differences from baseline compared with placebo in most of the domains at both time points, except for the mental health domain which improved but did not achieve statistical significance (see online supplementary table S2). Compared with placebo, a statistically significantly larger proportion of patients treated with baricitinib met or exceeded the MCID in four domains (physical functioning, bodily pain, vitality and social functioning) for baricitinib 4 mg and in four domains for baricitinib 2 mg (physical functioning, bodily pain, general health and vitality) at week 12 (figure 1A); at week 24, significant differences were observed in three domains for baricitinib 4 mg (physical functioning, vitality and social functioning) and in two domains for the baricitinib 2 mg group (physical functioning and social functioning) (figure 1B).

For the SF-36 PCS, the least-squares mean (LSM) change from baseline for both baricitinib-treated groups were statistically significantly larger than placebo (p<0.001 for both baricitinib groups vs placebo at both time points) (figure 2A). However, for the SF-36 MCS measure, no significant differences in the LSM change from baseline were found between the baricitinib-treated groups and placebo, although numerical differences were observed. The proportion of patients who met or exceeded the MCID at weeks 8 and 20 (figure 2B). Results were similar for the MCID value of 2.5 (see online supplementary table S3).

A statistically significant difference in change in the EQ-5D UK index score was observed at the first postbaseline assessment (at week 4) for baricitinib 4 mg, but not baricitinib 2 mg, compared with placebo (data not shown). By weeks 12 and 24, however, statistically significant improvements in the EQ-5D UK index score were observed for both baricitinib-treated groups versus placebo (table 1). For the EQ-5D VAS at 4 weeks, baricitinib-treated patients reported statistically significantly higher scores than placebo-treated patients (data not shown). These results were maintained to weeks 12 and 24 (table 1). Results were similar with the US algorithm for the EQ-5D index score (table 1).

FACIT-F and duration of MJS
Treatment with baricitinib 2 and 4 mg was associated with significant improvements in the FACIT-F at week 4 compared with placebo, the first assessment of this measure (figure 3A). For duration of MJS, baricitinib 4 mg, but not 2 mg, was statistically significantly improved from placebo at week 1 (figure 3B). Improvements in the FACIT-F score and reductions in the duration of MJS were sustained to week 12 and week 24 (figure 3).

For the FACIT-F, there were more patients in the baricitinib-treated groups who met or exceeded the MCID at week 12 (p=0.004 for baricitinib 2 mg vs placebo and p=0.007 for baricitinib 4 mg vs placebo) as well as at week 24 (p=0.015 for baricitinib 2 mg vs placebo and p=0.005 for baricitinib 4 mg vs placebo) (figure 3A).

HAQ-DI, PtGA and pain
The percentage of patients with HAQ-DI scores <0.5 (the normal function cutpoint for patients with established RA), for placebo, baricitinib 2 mg and baricitinib 4 mg was 6%, 14% and 14%, respectively (p≤0.05 for baricitinib 2 mg and 4 mg vs placebo), at week 12 and was 3%, 16% and 16%, respectively, at week 24 (p≤0.001 for baricitinib 2 and 4 mg vs placebo) (table 1).

As previously reported, for HAQ-DI and PtGA, differences in improvements in the baricitinib-treated groups versus placebo were evident as early as week 1, the first postrandomisation assessment time point; for patient’s assessment of pain, only baricitinib 4 mg was statistically significantly different from placebo at week 1. Significant improvements in HAQ-DI and reductions in PtGA and pain (VAS) were maintained at week 12 and week 24, the end of the study (table 1).

Subgroup analyses
Subgroup analyses according to the type (TNFi vs non-TNFi) or number (<3 vs ≥3) of previous bDMARDs used revealed no consistent, significant differences in outcomes of FACIT-F, duration of MJS, HAQ-DI or patient’s assessment of pain (VAS) at weeks 12 and 24.

Work productivity and activity impairment
At baseline, only 30%–40% of the patients reported employment. Of this number, 90%–94% continued to report
employment at week 12 and 82%–89% continued to report employment at week 24 (see online supplementary table S4).

Patients treated with baricitinib 2 and 4 mg reported a statistically significant reduction in daily activity impairment compared with placebo at weeks 12 and 24 (see online supplementary table S4). Among those patients who were employed at baseline and those who maintained employment at weeks 12 and 24, there were reduced presenteeism (percentage of work-time impaired) and work productivity loss in baricitinib-treated groups but these did not reach statistical significance compared with placebo; similar results were observed for absenteeism at week 12, but were not maintained at week 24 (see online supplementary table S4).

DISCUSSION
This analysis of RA-BEACON evaluated whether the clinical efficacy data for baricitinib (with background csDMARDs) were complemented by respective changes in PROs in patients with a previous inadequate response to one or more bDMARDs, including at least one TNFi, regardless of the number and type of previous csDMARDs and bDMARDs. This question was particularly important given the refractory nature and long disease duration of the patient population studied as the responsiveness of PROs decreases dramatically with increasing failure of prior therapies and disease duration.7 The disease duration of about 14 years in this trial is one of the longest of any recently published RA clinical trial. Disease durations such as these have been associated with a failure to improve physical function significantly on biological agents compared with placebo.7

Prespecified secondary outcomes in the RA-BEACON trial included a number of PROs that reflect disease activity (duration of MJS and fatigue by FACIT-F), physical function (HAQ-DI, SF-36 PCS), work productivity (WPAI-RA) and HRQOL (SF-36, EQ-5D), some of which constitute patient ratings of the American College of Rheumatology core set measures (HAQ-DI, PtGA and patient’s assessment of pain).33 The use of all these measures allowed a thorough evaluation of the effects of baricitinib on the various aspects of patient well-being.
## Table 1: Patient-reported outcomes at week 12 and week 24

<table>
<thead>
<tr>
<th>Health State Index Score</th>
<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baricitinib 4 mg (N=177)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>0.036 (−0.000 to 0.073)</td>
<td>0.114*** (0.077 to 0.150)</td>
</tr>
<tr>
<td>UK algorithm</td>
<td>0.085 (−0.002 to 0.099)</td>
<td>0.169*** (0.133 to 0.205)</td>
</tr>
<tr>
<td>VAS</td>
<td>2.9 (−1.1 to 6.9)</td>
<td>11.3*** (7.3 to 15.4)</td>
</tr>
<tr>
<td><strong>Baricitinib 2 mg (N=174)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>0.026 (0.001 to 0.051)</td>
<td>0.079*** (0.054 to 0.103)</td>
</tr>
<tr>
<td>UK algorithm</td>
<td>1.9 (−3.2 to 6.2)</td>
<td>0.116*** (0.091 to 0.141)</td>
</tr>
<tr>
<td>VAS</td>
<td>13.0 (4.9 to 21.2)</td>
<td>11.6*** (7.5 to 15.8)</td>
</tr>
<tr>
<td><strong>Placebo (N=178)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EQ-5D-5L</td>
<td>−0.15 (−0.32 to 0.02)</td>
<td>−0.38*** (−0.49 to −0.28)</td>
</tr>
<tr>
<td>UK algorithm</td>
<td>−8.8 (−13.1 to −4.6)</td>
<td>−3.8*** (−4.7 to −3.0)</td>
</tr>
<tr>
<td>VAS</td>
<td>−24.6 (−31.3 to −19.0)</td>
<td>−24.0*** (−28.5 to −19.0)</td>
</tr>
<tr>
<td><strong>Baricitinib 4 mg (N=177)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>5.2 (3.5 to 6.9)</td>
<td>8.1*** (6.5 to 9.8)</td>
</tr>
<tr>
<td><strong>Baricitinib 2 mg (N=174)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>−8.1 (−6.6 to 9.9)</td>
<td>−8.3* (−6.6 to 9.9)</td>
</tr>
<tr>
<td><strong>Placebo (N=178)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FACIT-F</td>
<td>−22.3 (−27.2 to −16.4)</td>
<td>−18.8*** (−23.2 to −14.4)</td>
</tr>
</tbody>
</table>
||**Note:** p < 0.05, ***p < 0.001;

**Abbreviations:** EQ-5D-5L, European Quality of Life-5 Dimensions-5 Levels; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; PtGA, Patient’s Global Assessment of Disease Activity; VAS, visual analogue scale.

Improvements in PROs associated with baricitinib in the present analysis were in the range of those reported with bDMARDs in patients with just an inadequate response to csDMARDs or to TNFis. Over 6 months, the difference in the rates of patients showing improvement that was ≥MCID in the HAQ-DI and the SF-36 PCS, amounted to 23% between baricitinib 4 mg and placebo. This difference was similar to that reported with a bDMARD (improvement of ~40%–65%) versus placebo (improvement of ~25%–35%). However, in the current trial, patients had failed to respond to ≥1 bDMARDs, with approximately 60% having previously received two bDMARDs or more. Therefore, these patients with long-standing disease can be considered a refractory population, which is increasing over time and has a substantial unmet need in RA.

To our knowledge, no other randomised controlled trial has evaluated PROs and drug effects in such a refractory population. In a randomised controlled trial of tofacitinib in patients with inadequate response to TNFis (but overall much lower proportions of patients with multiple bDMARD failure), the PROs reported included pain, PtGA, HAQ-DI, FACT-F, SF-36 and MOS Sleep Scale. Treatment effects from that study are consistent with our data showing meaningful outcomes for patients treated with JAK inhibitors.

This study has some limitations. The 24-week follow-up period is insufficient to determine the longer-term effects of baricitinib treatment. Long-term observations are required to assess the durability of the observed changes; such a study is currently ongoing. However, other extension studies have not shown major losses of response over time. Further, a high placebo response, most notably for the FACIT-F score, was observed. This could be related to patients being seen more often than in clinical practice and/or showing better adherence to their medication, but these factors are also potentially true for most other randomised controlled trials. However, the proportion of patients who reported improvements that met or exceeded the MCID for the FACIT-F score was 62.7% and 63.8% for baricitinib 4 and 2 mg, respectively, versus 48.3% in the placebo group. The difference in fatigue improvement between baricitinib and placebo treatment from week 4 onwards was encouraging, since it was not related to increases in haemoglobin, but rather to the improvement in inflammatory response, pain and disability. The fact that the employment status did not significantly improve significantly is not surprising and likely related to the short duration of the trial; patients with long-standing, disease-associated unemployment are unlikely to search for and find a new job within a period of 6 months. Additionally, patients from 21 countries participated in the trial, and different
rates of unemployment and policies related to workplace accommodations may influence a patient’s employment status.

The strengths of this study include the assessment of a number of well-established PRO measures and a patient population with important unmet needs, many of whom had tried several bDMARDs and would not have been very likely to achieve disease control with currently available therapies. Importantly, both physical function and HRQOL measures improved to a relatively large extent across several assessment methods. The major reduction in duration of MJS reflects the patients’ overall improvement in clinical disease activity beyond that assessed by global assessments of pain and activity.

In conclusion, in this treatment-refractory population of patients with previously inadequate responses to bDMARDs, including at least one TNFi, baseline PROs revealed severely impaired physical function and a high level of pain and fatigue. Significant improvements in PROs occurred rapidly with baricitinib and were sustained throughout 24 weeks. Improvements were generally more rapid and of greater magnitude for patients receiving baricitinib 4 mg compared with baricitinib 2 mg. These data are in agreement with previously reported clinical efficacy data for baricitinib in patients with RA, suggesting that baricitinib may be an effective treatment for patients with inadequate response to bDMARDs.

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Acknowledgements This study and manuscript were sponsored by Eli Lilly and Company and Incyte Corporation. The authors would like to acknowledge Claire Lavin and Clare Gurton (Rx Communications) for medical writing assistance with the preparation of this manuscript and Barbara Coffey and Molly Tomlin (Eli Lilly) for their assistance with process support. The authors would also like to thank all patients and study investigators.

Contributors JSS, BC and CG have worked on the major parts of the manuscript and the revisions. All other authors have significantly contributed to the interpretation of the data, participated in the development of later stages of the manuscript and critically reviewed the final version.

Competing interests JSS has received grants for his institution from Abbvie, Janssen, Eli Lilly and Company, MSD, Pfizer, Roche and has provided expert advice to and/or had speaking engagements for Abbvie, Amgen, Astra-Zeneca, Asto, Celgene, Celsion, GSK, ILTOO, Janssen, Eli Lilly and Company, Medimmune, MSD, Novartis-Sandoz, Novo-Nordisk, Pfizer, Roche, Samsung, Sanofi, UCB. MWK has received research grant support and consultation honoraria from Eli Lilly and Company. He is an officer and stockholder in Coronis. He has received research grant support from Abbvie, Novartis, Aman and Pfizer. He is on the speaker’s bureau for Genentech. CLG, AMD, DES, LX, IS and TR are full-time employees of Eli Lilly and Company and DES, LX, IS and TR are minor shareholders of Eli Lilly and Company. PB has received grants and consulting fees from Abbvie, Pfizer, Novartis, Eli Lilly and Company, Roche, BMS and Janssen. JMSB has received grants and consulting fees from Abbvie, Pfizer, UCB and Genbo. MCG has received grants and consulting fees from Abbvie, Astellas, Eli Lilly and Company, Galapagos, Gilead, Pfizer and Vertex. BC has received honorarium from Abbvie, BMS, Eli Lilly and Company, MSD, Pfizer, Roche-Chugai and UCB.

Ethics approval All local ethical committees.

Figure 3 Change in baseline over time for the (A) FACIT-F and (B) duration of morning joint stiffness. FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; LS, least squares; MCID, minimum clinically important difference.
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Ann Rheum Dis published online October 31, 2016

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