EXTENDED REPORT

Long-term efficacy and safety in patients with rheumatoid arthritis continuing on SB4 or switching from reference etanercept to SB4

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ABSTRACT

Objectives SB4 (Benepali, Brenzys) is a biosimilar of reference etanercept (ETN). In a randomised, double-blind, 52-week study, SB4 demonstrated comparable efficacy and safety in patients with rheumatoid arthritis (RA). The open-label extension period evaluated long-term efficacy, safety and immunogenicity when continuing SB4 versus switching from ETN to SB4.

Methods In the randomised, double-blind phase, patients received weekly subcutaneous administration of 50 mg SB4 or ETN with background methotrexate for up to 52 weeks. Patients in the Czech Republic and Poland who completed the 52-week visit were enrolled in the open-label extension period and received SB4 for 48 additional weeks. Efficacy, safety and immunogenicity were assessed up to week 100.

Results Of 245 patients entering the extension period, 126 continued to receive SB4 (SB4/SB4) and 119 switched to SB4 (ETN/SB4). American College of Rheumatology (ACR) response rates were sustained and comparable between SB4/SB4 and ETN/SB4 with ACR20 response rates at week 100 of 77.9% and 79.1%, respectively. Other efficacy results, including radiographic progression, were also comparable between the groups. After week 52, rates of treatment-emergent adverse events were 47.6% (SB4/SB4) and 48.7% (ETN/SB4); one patient/group developed non-neutralising antidrug antibodies. No cases of active tuberculosis or injection-site reactions were reported during the extension period. One patient (SB4/SB4) died of hepatic cancer.

Conclusions SB4 was effective and well tolerated over 2 years in patients with RA. Efficacy, safety and immunogenicity were comparable between the SB4/SB4 and ETN/SB4 groups, showing no risk associated with switching patients from ETN to SB4.

Trial registration number NCT01895309; 2012-005026-30

INTRODUCTION

The tumour necrosis factor inhibitor etanercept was the first approved biologic disease-modifying anti-rheumatic drug and allowed for a major advance in the treatment of rheumatoid arthritis (RA).¹ Eighteen years since its approval, etanercept continues to play a key role in RA management, having demonstrated efficacy and a manageable safety profile in both clinical trial and real-world settings.⁴ Other current indications for etanercept include juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis (European Union only), plaque psoriasis and paediatric psoriasis (USA only).<sup>2,3</sup>

SB4 (Benepali, Samsung Bioepis UK Limited, Surrey, UK; Brenzys, Samsung Bioepis, Republic of Korea) is a biosimilar of reference etanercept (ETN). The structural, physicochemical and biological quality attributes of SB4 have been shown to be highly similar to ETN in a comprehensive comparability exercise designed as part of the European Medicines Agency’s rigorous approval pathway.<sup>4</sup>

A phase 1 study in healthy subjects demonstrated pharmacokinetic equivalence between SB4 and ETN⁵; a phase 3 study (NCT01895309; EudraCT 2012-005026-30) in patients with moderate to severe RA despite treatment with methotrexate (MTX) demonstrated equivalent efficacy in terms of American College of Rheumatology 20% response rate (ACR20) at the 24-week interim analysis (SB4, 78.1%; ETN, 80.3%)<sup>6</sup> and at week 52 (SB4, 80.8%; ETN, 81.5%).<sup>7</sup> Safety was generally comparable between SB4 and ETN.<sup>6,7</sup>

SB4 has been approved for treatment of RA, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis and plaque psoriasis in the European Union.<sup>8,9</sup> However, an important consideration for prescribing physicians is whether switching from ETN to SB4, which may occur in clinical practice, can be achieved without detriment to safety and efficacy. We analysed data from the open-label extension period of the phase 3 study to evaluate the efficacy, safety and immunogenicity of continuing SB4 (SB4/SB4) versus switching from ETN to SB4 (ETN/SB4). Long-term safety and efficacy were assessed up to week 100.

METHODS

Study design and patients

Patients with moderate to severe RA despite treatment with MTX were eligible to enrol in this phase 3, randomised, double-blind, multicentre study, which included an open-label extension period. Detailed patient inclusion/exclusion criteria were previously published.<sup>6</sup> During the double-blind period, patients were randomised 1:1 to receive subcutaneous SB4 50 mg or ETN 50 mg once weekly for 52 weeks. Patients in the Czech Republic or Poland who completed the scheduled 52-week visit were enrolled in the open-label, single-arm...
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extension period. During the extension period, patients from the SB4 group continued to receive SB4 (SB4/SB4), and patients from the ETN group switched to SB4 50 mg (ETN/SB4) once weekly for an additional 48 weeks. All patients took a stable dose of MTX (10–25 mg/week) from 4 weeks before screening until the end-of-treatment visit for the extension period. For patients who entered the extension period, efficacy was assessed at weeks 52, 76 and 100, and safety was assessed at all visits during treatment and at 4 weeks after treatment (or after the early termination visit).

Endpoints
Efficacy endpoints for the extension period included ACR20/50/70 response (≥20%/50%/70% improvement, respectively, from baseline in ACR response criteria), European League Against Rheumatism (EULAR) response and disease activity score based on a 28-joint count (DAS28). Physical function was assessed using the Health Assessment Questionnaire-Disability Index (HAQ-DI). For patients who entered the extension period, radiographs of the hands and feet obtained at weeks 0, 52 and 100 were evaluated by a single reader to determine the modified Total Sharp Score (mTSS), which is the sum of the joint erosion and joint space narrowing (JSN) scores. Post hoc assessments included the proportions of patients achieving low disease activity (LDA) and remission based on the Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI) and DAS28 and the proportions achieving Boolean-based remission (defined as ≤1 swollen and ≤1 tender joint, C-reactive protein ≤1 mg/dL and patient global visual analogue scale score ≤1 using a 0–10 scale). Safety endpoints included the incidence of treatment-emergent adverse events (TEAEs) and adverse events (AEs) of special interest (serious infections and active tuberculosis). Immunogenicity was assessed by determining the incidence of antidrug antibodies (ADAs) and neutralising antibodies; ADAs were detected in serum samples using an electrochemiluminescence bridging assay (Meso Scale Discovery, Maryland, USA), double-antigen format with acid dissociation and neutralising antibodies were measured using a competitive ligand-binding assay.

Statistical analysis
All data were analysed descriptively. Efficacy and safety data were analysed in the extended population, which comprised all patients who provided informed consent for the open-label extension period and received ≥1 dose of study medication in the open-label extension period. Efficacy data obtained up to week 52 were analysed retrospectively in this population. No imputation was made for missing data. Analyses were performed using SAS software, V9.2 or higher (SAS Institute, Cary, North Carolina, USA).

RESULTS
Patients
A total of 245 patients, including 126 who continued on SB4 and 119 who switched to SB4 from ETN, enrolled in the extension period. All patients received ≥1 dose of study drug during the extension period and were included in this analysis. Patient disposition is shown in figure 1; 94.7% of patients (232/245) who entered the extension period completed 100 weeks of treatment, with 5.6% of patients in the SB4/SB4 group and 5.0% of patients in the ETN/SB4 group withdrawing before week 100. Patient demographic and clinical characteristics were well balanced between the two groups (table 1).

Efficacy
ACR responses were comparable between the SB4/SB4 and ETN/SB4 groups and were maintained from weeks 52 through 100, with 79.2%/52.0%/38.4% and 82.4%/53.8%/32.8% of patients achieving ACR20/50/70 in each group, respectively, at week 52%
and 77.9%/59.8%/42.6% and 79.1%/60.9%/41.7% of patients achieving ACR20/50/70 in each group, respectively, at week 100 (figure 2). ACR responses were also comparable between the two groups in the retrospective analysis of this population during the initial 52-week treatment period. Other efficacy results at week 100 are shown in table 2. At this time point, the proportion of patients who had moderate or good EULAR responses; the proportion who achieved LDA and remission based on DAS28, SDAI or CDAI criteria and the proportion who achieved Boolean-based remission were comparable between the SB4/SB4 and ETN/SB4 groups. Further, throughout the study, DAS28, SDAI, CDAI and HAQ-DI scores were also comparable between the two groups (see figure in the online supplementary material 1). The main factor driving the improvement in DAS28 score was the reduction in swollen and tender joint counts; these components demonstrated the largest percentage improvements from baseline during the extension period. At week 100, radiographic progression was comparable and minimal (figure 3), with mean (SD) change from baseline mTSS values of 0.48 (0.503) for the SB4/SB4 group and 1.00 (5.563) for the ETN/SB4 group (table 2). Summary of structural joint damage for each visit can be found in table S1 in the online supplementary material 1.

**Safety**

Safety after week 52 was generally comparable between the SB4/ SB4 and ETN/SB4 groups (table 3). This extension study was not adequately powered to show similar safety and imbalance might be expected as shown in the incidence of serious TEAEs, RA, viral infection, laryngitis and hypertension. Serious infection was reported in one patient in each treatment group, and there were no reports of active tuberculosis. Also during the extension period, no injection-site reactions were reported. One patient in the SB4/SB4 group died of hepatic cancer, which was considered to be related to the study drug. One patient in each treatment group developed non-neutralising ADAs after week 52 (see table S2 in the online supplementary material 1). Both patients had a titre of ≤1, and the ADAs did not affect efficacy. The patient in the SB4/SB4 and ETN/SB4 group tested positive at week 100 with a titre of 1 and achieved an ACR50 response at week 100. The patient from the ETN/SB4 group tested positive at week 100 with a titre of 1 and achieved an ACR70 response at week 100.

**DISCUSSION**

This open-label extension period of a phase 3, randomised, double-blind study evaluated the long-term efficacy, safety and immunogenicity of SB4 in patients with moderate to severe RA despite MTX treatment and compared outcomes between patients who continued SB4 (n=126) and those who switched from ETN to SB4 (n=119). Results showed SB4 to be effective...
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Figure 3  Cumulative probability of mTSS change from baseline at week 100 (extended population). Data based on patients with available radiographic assessment results at each visit. ETN, reference etanercept; mTSS, modified Total Sharp Score.

Table 2  Efficacy results at week 100 (extended population)

<table>
<thead>
<tr>
<th></th>
<th>SB4/SB4 (n=126)</th>
<th>ETN/SB4 (n=119)</th>
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<tbody>
<tr>
<td><em><em>EULAR response, n/N</em> (%)</em>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Good</td>
<td>59/121 (48.8)</td>
<td>63/115 (54.8)</td>
</tr>
<tr>
<td>Moderate</td>
<td>54/121 (44.6)</td>
<td>40/115 (34.8)</td>
</tr>
<tr>
<td>No response</td>
<td>8/121 (6.6)</td>
<td>12/115 (10.4)</td>
</tr>
<tr>
<td><strong>DAS28</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement from baseline, mean (SD)</td>
<td>2.9 (1.5)</td>
<td>3.0 (1.5)</td>
</tr>
<tr>
<td>Disease activity, n/N* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (≤3.2)</td>
<td>60/122 (49.2)</td>
<td>63/115 (54.8)</td>
</tr>
<tr>
<td>Remission (&lt;2.6)</td>
<td>37/122 (30.3)</td>
<td>40/115 (34.8)</td>
</tr>
<tr>
<td><strong>SDAI score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement from baseline, mean (SD)</td>
<td>27.4 (15.5)</td>
<td>28.7 (14.6)</td>
</tr>
<tr>
<td>Disease activity, n/N* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&gt;3.3 and≤11)</td>
<td>41/123 (33.3)</td>
<td>44/115 (38.3)</td>
</tr>
<tr>
<td>Remission (≥s3.3)</td>
<td>39/123 (30.9)</td>
<td>39/115 (33.9)</td>
</tr>
<tr>
<td><strong>CDAI score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improvement from baseline, mean (SD)</td>
<td>26.8 (15.0)</td>
<td>27.9 (14.1)</td>
</tr>
<tr>
<td>Disease activity, n/N* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (&gt;2.8 and≤10)</td>
<td>38/123 (30.9)</td>
<td>46/115 (40.0)</td>
</tr>
<tr>
<td>Remission (≥s2.8)</td>
<td>40/123 (32.5)</td>
<td>33/115 (28.7)</td>
</tr>
<tr>
<td>Boolean-based remission, n/N* (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31/123 (25.2)</td>
<td>23/115 (20.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Radiographic results</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline in JSN score, mean (SD)</td>
<td>0.19 (1.98)</td>
<td>0.39 (2.86)</td>
</tr>
<tr>
<td>Change from baseline in joint erosion score, mean (SD)</td>
<td>0.28 (2.57)</td>
<td>0.61 (3.08)</td>
</tr>
<tr>
<td>Change from baseline in mTSS, mean (SD)</td>
<td>0.48 (4.05)</td>
<td>1.0 (5.56)</td>
</tr>
</tbody>
</table>

* Number of patients with available data at each time point.
  † Based on number of patients who completed week 100 visit with available radiographic assessment results at weeks 0 and 100 (SB4/SB4, n=108; ETN/SB4, n=104).

Table 3  Safety after week 52 (extended population)

<table>
<thead>
<tr>
<th></th>
<th>SB4/SB4 (n=126)</th>
<th>ETN/SB4 (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 TEAE†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frequently reported TEAEs (≥3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>10 (7.9)</td>
<td>9 (7.6)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>9 (7.1)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>7 (5.6)</td>
<td>3 (2.5)</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>6 (4.8)</td>
<td>7 (5.9)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6 (4.8)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>4 (3.2)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>4 (3.2)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (0.8)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>≥1 serious TEAE</td>
<td>6 (4.8)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>TEAE leading to study drug discontinuation</td>
<td>4 (3.2)</td>
<td>2 (1.7)</td>
</tr>
<tr>
<td>Serious infection</td>
<td>1 (0.8)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Active tuberculosis</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Injection-site reaction*</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Malignancy†</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Death†</td>
<td>1 (0.8)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

*TEAE with high-level group term of administration site reaction.
† Hepatic cancer, which was considered related to study drug.
ETN, reference etanercept; TEAE, treatment emergent adverse event.

and well tolerated over 2 years. In patients who switched from ETN to SB4, comparable efficacy to the SB4/SB4 group was observed, with no new safety signals identified.

Among the patients entering the extension period, 94.4% in the SB4/SB4 group and 95.0% in the ETN/SB4 group completed an additional 48 weeks of SB4 treatment. The discontinuation rate due to lack of efficacy or TEAEs was very low, which suggests the long-term tolerability of SB4 treatment.

Efficacy outcomes in the extended population were comparable between the SB4/SB4 and ETN/SB4 groups at all visits up to week 100, sustained from weeks 52 to 100 and unaffected by switching. Comparable inhibition of radiographic progression was previously reported after 52 weeks of treatment with SB4 or ETN (mean change in mTSS: 0.45 for SB4 vs 0.74 for ETN). In both groups, continued inhibition of radiographic progression was observed with an additional year of SB4 treatment, with mean changes from baseline in joint space narrowing and joint erosion of <1. This is consistent with historical results from randomised studies of etanercept with or without MTX in patients with RA.11–13 Two-year radiographic findings in patients with early RA continuing ETN+MTX therapy from year 1 showed a mean Sharp/van der Heijde score change of −0.02 and an improvement in mean 28-swollen joint count from 1.7 to 1.3.11 Similarly, 2-year data from the Canadian Methotrexate and Etanercept Outcome study showed that patients continuing ETN+MTX therapy after the first 6 months had mean changes from baseline in mTSS and JSN of 0.0 at month 24 and those switching to ETN monotherapy had mean changes from baseline in mTSS and JSN of <1.12 Lastly, the Trial of Etanercept and Methotrexate with Radiographic Patient Outcomes (TEMPO) demonstrated mean changes from baseline in mTSS, joint erosion scores and JSN of <1 at years 1, 2 and 3 of treatment with ETN+MTX.13

In the extension period, SB4 demonstrated a safety profile similar to that observed in the pivotal etanercept trials.11–13 There were no reports of active tuberculosis or injection-site reactions. One patient in each group reported a serious infection and one...
patient in the SB4/SB4 group died from hepatic cancer. After week 52, one patient in each group developed non-neutralising ADAs. The low incidence of non-neutralising ADAs observed in the study was expected given the low rates reported in short-term and long-term studies of etanercept-treated patients with RA (0%–6%).14–16 The ADAs developed prior to switching did not affect the efficacy or safety of SB4 in the ETN/SB4 group.

Results from this extended-period switching study showed maintenance of response after switching from ETN to SB4 with no newly identified safety issues (eg, no increase in immunogenicity or immune-related TEAEs of anaphylaxis, hypersensitivity or injection-site reactions). In extensions of PLANETaRA (Program Evaluating the Autoimmune Disease iNvestigational Drug CT-p13 in RA Patients)17 and PLANETAS (Program Evaluating the Autoimmune Disease iNvestigational Drug CT-p13 in AS patients)18 which had similar study designs with the present study, switching from reference infliximab to the biosimilar infliximab CT-P13 was not associated with diminished efficacy or change in safety profile. These results are further corroborated by findings from the randomised, non-inferiority NOR-SWITCH study which demonstrated that switching to CT-P13 is not inferior to continued treatment with reference infliximab.19 In addition, data from the DANBIO registry where switching from ETN to SB4 was well tolerated and effective over 2 years in patients with RA. Switching from ETN to SB4 was not associated with treatment-emergent issues such as loss of efficacy or increases in TEAEs or immunogenicity. Postmarketing surveillance and registry studies are ongoing to monitor the efficacy and safety of SB4 in various indications.

CONCLUSIONS

SB4 was well tolerated and effective over 2 years in patients with RA. Switching from ETN to SB4 was not associated with treatment-emergent issues such as loss of efficacy or increases in clinical and epidemiological research.

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Contributors

PE, SYC, and JG contributed to the study conception and design, analysis and interpretation of data and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. JV, AS, PL, WP, BS, JH and ZM contributed to the acquisition of data. All the authors equally contributed to the drafting the manuscript and revising it critically for important intellectual content, final approval of the version published.

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Competing interests

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Patient consent

Obtained.

Ethics approval

This study was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation Good Clinical practice guidelines. Protocols were reviewed and approved by the independent ethics committee or institutional review board for each study centre. All patients provided written informed consent.

Provenance and peer review

Not commissioned; externally peer reviewed.

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