Benepali™ Etanercept

ESTUDIO BENEFIT
Datos de RWE de Benepali a 6 meses

Biogen

Datos en la práctica real de BENEPALI después del **switch** de ETNo en **artritis reumatoide** (AR) y **espondiloartritis axial** (EspaAx)

ESTUDIO BENEFIT:
efectividad de BENEPALI en práctica clínica real después del switch de etanercept de referencia (ETNo) en artritis reumatoide (AR) y espondiloartritis axial (EspaAx)

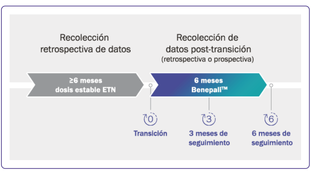
Los biosimilares de los fármacos anti-TNF-α tienen el potencial de mejorar la accesibilidad a los fármacos y reducir el impacto económico del tratamiento de las enfermedades reumáticas inflamatorias. Los datos de práctica clínica real pueden proporcionar a los especialistas evidencia crítica para tomar decisiones informadas, especialmente cuando se realiza switch en pacientes estables, de medicamentos de referencia a biosimilares.

El estudio BENEFIT es un estudio observacional paneuropeo multicéntrico, realizado en 56 centros de Francia, Alemania, Italia y España, que incluyó **358 pacientes con AR y 199 pacientes con EspaAx**.

El **objetivo** del estudio fue proporcionar **evidencia en práctica clínica real sobre la efectividad de Benepali tras el switch** de etanercept de referencia. Para ello se midió el cambio en la puntuación de la enfermedad (DAS-28 y BASDAI en AR y EspaAx respectivamente) a los 3 y a los 6 meses tras el switch.

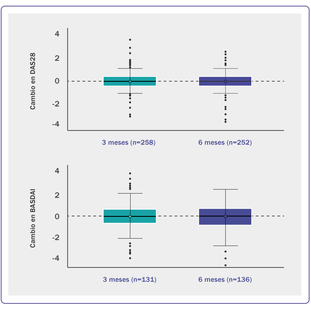
Se estableció un **diseño retrospectivo-prospectivo** en función del momento en que se realizara el switch a Benepali, donde el momento basal era el switch de etanercept de referencia a Benepali. A partir de ese momento se realizó el seguimiento a los 3 y 6 meses.

Los pacientes debían tener una **enfermedad estable** antes de entrar en el estudio y haber tenido, en los **6 meses previos, la misma dosis de etanercept**.



Las puntuaciones de actividad de la enfermedad para los pacientes con AR y aquellos con EspaAx que recibieron Benepali **se mantuvieron estables hasta 6 meses después del switch de ETNo**. El cambio medio individual en la puntuación DAS28 a los 6 meses fue similar en pacientes con AR (**cambio medio en la puntuación DAS28 0,01**; IC del 95%: -0,09; 0,11, n = 252) y la puntuación **BASDAI** también se mantuvo durante el transcurso del estudio en pacientes con EspaAx (**cambio medio en la puntuación BASDAI de -0,11**; IC del 95%: -0,31; 0,10; n = 136).

Los cambios en las puntuaciones medias individuales tanto en el DAS28 como en el BASDAI **fueron consistentes** en todos los países participantes.



El valor de DAS28 fue de 2,01 en el momento de la transición (switch), 2,0 a los 3 meses y 2,07 a los 6 meses y en el caso del BASDAI el valor medio fue de 2,50 en el momento del switch, 2,51 a los 3 meses y 2,30 a los 6 meses.

Ambos grupos de pacientes que recibieron Benepali después del switch, mantuvieron el control de la enfermedad. En la cohorte de **AR, no hubo cambios en la actividad de la enfermedad a los 6 meses** con respecto al **momento basal** en un **90,9% de los pacientes** (n = 229 de 252; IC del 95%: 86,7%, 94,1%). La proporción de pacientes con **baja actividad de la enfermedad** después del switch en la cohorte de AR fue del 10,5% (n = 36 de 342; IC del 95%: 7,5%, 14,2%) y del 78,1% en la cohorte de EspaAx (n = 146 de 187; IC del 95% 71,5%, 83,8%).

A los 6 meses, la proporción de pacientes con **baja actividad de la enfermedad** fue del 12,5% para la cohorte de AR (n = 32 de 256; IC del 95%: 8,7%, 17,1%) y del 79,1% para la cohorte de EspaAx (n = 110 de 139, 95 % IC 71,4%, 85,6%).

La **tasa de retención de pacientes fue alta**, el 90,8% de los pacientes con AR (95% CI 87,2%, 93,4%) y el 92,4% de los pacientes con EspaAx (95% CI 87,5%, 95,4%) continuaron con Benepali 6 meses después del switch.

El perfil de riesgo-beneficio de Benepali se demuestra en la tasa registrada de eventos adversos con 19 pacientes (5,3%) con AR y 12 pacientes (6%) con EspaAx que informaron eventos adversos no graves. Solo un evento adverso grave, neumonía, se consideró relacionado con Benepali.

Este estudio proporciona **evidencia de vida real de la efectividad y seguridad de Benepali** en pacientes con AR y EspaAx estable tras el switch desde etanercept de referencia, **a los 6 meses** de seguimiento.

Los datos de este estudio **fueron consistentes entre los 4 países** participantes.

Benepali™ Etanercept
EL ETANERCEPT DE BIOGEN®

descargar Ficha Técnica

Referencias:

1. Selmi C, Krüger K, Cantagrel A, Abad Hernández MA, Freudensprung U, Farouk Rezk M, et al. BENEFIT: real-world effectiveness of SB4 after transition from reference etanercept in rheumatoid arthritis and axial spondyloarthritis. Clin Exp Rheumatol. 2020 Jun 30. Epub ahead of print. Disponible en: https://www.clinexprheumatol.org/abstract.asp?a=14629. Última fecha de acceso: Febrero 2021.

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BENEFIT: real-world effectiveness of SB4 after transition from reference etanercept in rheumatoid arthritis and axial spondyloarthritis

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Abstract

Objective

The objective of this non-interventional study was to evaluate the effectiveness and safety of the etanercept biosimilar SB4 (Benepali™) following transition from reference etanercept in patients with rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA).

Methods

Data were collected from clinical records of adult patients with stable RA or axSpA, in France, Germany, Italy and Spain. Key outcomes included the change from transition to 3 and 6 months in Disease Activity Score 28 (DAS28) for RA or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for axSpA.

Results

In total, 358 patients with RA and 199 patients with axSpA were enrolled. The mean individual change in disease score from transition was -0.02 (95% confidence interval [CI] -0.11, 0.08) at 3 months and 0.01 (95% CI -0.09, 0.11) at 6 months for DAS28, and -0.01 (95% CI -0.24, 0.21) at 3 months and -0.11 (95% CI -0.31, 0.10) at 6 months for BASDAI. In the RA cohort, 19 (5.3%) and 5 patients (1.4%) reported adverse events and serious adverse events (SAEs), respectively. In the axSpA cohort, 12 (6.0%) and 2 patients (1.0%) reported adverse events and SAEs, respectively. One SAE of pneumonia (RA cohort) was considered to be related to SB4 administration. At 6 months post-transition, the SB4 retention rate was 90.8% (95% CI 87.2%, 93.4%) in the RA cohort and 92.4% (95% CI 87.5%, 95.4%) in the axSpA cohort.

Conclusion

Transition from reference etanercept to SB4 is effective and safe in patients with stable RA and axSpA.

Key words

axial spondyloarthritis, effectiveness, etanercept, real-world, rheumatoid arthritis

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Introduction

Development of anti-tumour necrosis factor-α (TNF-α) drugs, such as etanercept, has led to significant advances in the management of inflammatory rheumatic diseases (1, 2). While effective, biologic medicines are costly, which can have a negative effect on treatment adherence and persistence (3). Biosimilars to anti-TNF-α drugs have the potential to improve drug accessibility and reduce the financial impact of costs in the treatment of these diseases (4).

SB4 (Benepali™), Samsung Bioepis NL B.V.) is a biosimilar of reference etanercept. SB4 was the first etanercept biosimilar to be approved and made available in Europe, in 2016, for the treatment of adults with moderate or severe RA for whom disease-modifying anti-rheumatic drugs (DMARDs) had been ineffective, and for the treatment of adults with axSpA for whom conventional therapy had been ineffective (5).

Marketing authorisation was granted by the European Medicines Agency (EMA) on the basis of robust evidence of biosimilarity obtained from comprehensive quality, physicochemical and biological comparisons together with confirmatory clinical phase I and phase III randomised controlled trials (6, 7), resulting in approval for SB4 in all indications covered in the reference etanercept label. However, real-world data on the use of SB4 were needed to provide healthcare professionals with evidence obtained outside the controlled setting of a randomised clinical trial, providing greater external validity and a better understanding of the outcomes of transitioning stable patients from the reference etanercept to SB4 in real life settings (8). To this end, a pan-European non-interventional study (the BENEFIT study) was designed to evaluate clinical practice outcomes in patients receiving SB4 at specialist treatment centres located in four European countries. The key objectives of the study were to evaluate the effectiveness and safety of SB4 over 6 months following transition from reference etanercept in routine practice in patients with stable RA or axSpA.

Methods

Study design and patients

This multicentre, non-interventional study was conducted at 56 specialist rheumatology centres in France, Germany, Italy and Spain. Patients were enrolled between June 2017 and November 2018.

Inclusion criteria were: age ≥18 years; diagnosis of RA or axSpA (according to local practice); stable disease throughout the 2 months before entering the study, according to physician opinion; transition from reference etanercept to SB4 at the discretion of the treating physician prior to entering the study; treatment with the same dose of etanercept for ≥6 months before transition to SB4; data on ≥1 effectiveness outcome, *i.e.* Disease Activity Score-28 (DAS28) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) during etanercept treatment.

Exclusion criteria were: hypersensitivity to the active substance or excipients of SB4; any medical condition that would preclude the continuation of etanercept treatment; treatment with another biologic agent or with investigational drugs within 6 months prior to transition or during the observation period; initiation or change of treatment which would affect disease status within 2 months prior to transition; or any other reason that would render the patient unsuitable for enrolment.

All treatment decisions were at the discretion of the treating physician as part of routine medical practice. There were no predefined visits, tests or procedures. Physicians completed case report forms for each patient, recording data from clinic visits at transition through to 6 months after transition (Fig. 1). All data relating to demographic and clinical characteristics, medical history and disease status were obtained from routine clinical records. Adverse events were recorded from SB4 initiation to study completion/early withdrawal.

Outcomes

The primary outcome measure of the study was the change in disease activity score (DAS28 for RA and BASDAI for axSpA) from transition to 3 months

post-initiation of SB4. To calculate DAS28, C-reactive protein (CRP) was used preferentially, if captured in the case report form; if CRP was not available then erythrocyte sedimentation rate was used; if neither variable was provided by the site but a score had been provided, then this score was used.

Other variables assessed included patient clinical characteristics, effectiveness and safety. For patients with RA, key effectiveness outcomes included the change in DAS28 at 6 months and the proportions of patients with low disease activity, or in remission, or with worsening disease or with an improvement in DAS28 relative to transition at 3 and 6 months (see Supppl. Table S1 for disease status definitions). For patients with axSpA, key effectiveness outcomes included the change in the BASDAI score at 6 months, the proportions of patients with low disease activity at transition and at 6 months, or with low disease activity at transition and at 3 and 6 months (Supplementary Table S1).

Safety outcomes included the nature and severity of adverse events considered to be causally related to SB4, and all serious adverse events (SAEs) regardless of causality.

Analytic approach

The main analysis was conducted in the full analysis population, which included all patients who met the inclusion and exclusion criteria and received at least one dose of SB4. Analyses were conducted separately for the RA and the axSpA cohorts. All analyses within this non-interventional study were descriptive in nature.

For categorical variables, the number of patients, frequency, percentage and 95% CI were presented. For continuous variables – including the primary outcome measure of change in disease activity scores – the number of patients, mean and 95% CI were presented. The Kaplan-Meier method was used to present estimates of retention on SB4 therapy and the corresponding two-sided 95% CIs at 3 and 6 months.

For the analysis of change in disease activity scores at 3 and 6 months, scores were assigned in the following manner: the score obtained closest to the date of transition, within the time window of 6 months prior to or up to 1.5 months after SB4 initiation, was assigned as the disease score at transition; the score obtained between 1.5 and 4.5 months after SB4 initiation was used as the disease score at 3 months, and the score obtained between 4.5 and 7.5 months after SB4 initiation as the disease score at 6 months. To be included in the effectiveness analysis at 3 or at 6 months, patients needed a disease activity score at transition and at 3 or at 6 months, respectively.

No imputation of missing values (including for the primary outcome measure at 3 months) was made.

To assess the robustness of the results, a sensitivity analysis including only those patients who had received the same dose of reference etanercept for at least 5 months prior to transition to SB4 was conducted. As a further sensitivity analysis, a mixed model for repeated measurements (MMRM) was fitted into the longitudinal data, adjusting for important confounders at transition (*e.g.* disease score at transition and duration of etanercept treatment prior to transition).

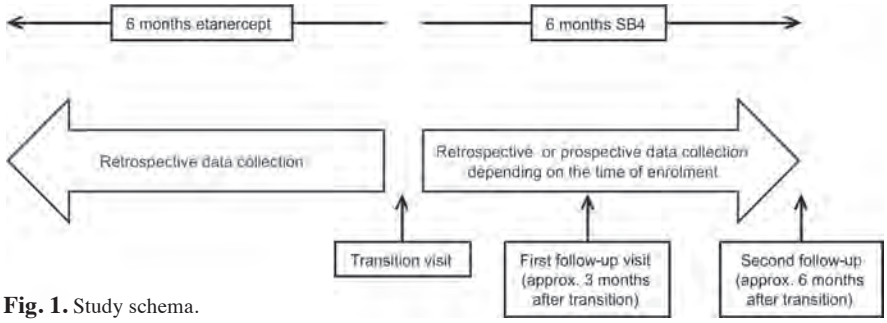

Fig. 1. Study schema.

Ethics

The study was conducted in accordance with the International Conference on Harmonisation and Good Pharmacovigilance Practices (ICH GCP) guidelines, the World Medical Association Declaration of Helsinki and local regulations. Patients provided written informed consent prior to being enrolled in the study. The study protocol was approved by each participating institution's ethics committee. The statistical analysis plan expanded on the pre-defined analysis outlined in the study protocol and was finalised prior to database lock.

Results

Patient clinical characteristics at transition

Overall, 358 patients with RA and 199 patients with axSpA were enrolled (Table I, Suppl. Fig. S1). Patients in the RA cohort were older than patients in the axSpA cohort (mean 60.9 *vs*. 49.9 years), and the gender distribution, employment status and smoking history differed between the two cohorts (Table I). In the RA cohort, the mean duration of disease at transition was 14.6 years. The mean DAS28 score was 2.01 (95% CI 1.92, 2.10); 277 patients (81.0%) were in remission, 36 patients (10.5%) had low disease activity and 29 patients (8.5%) had active disease. In the axSpA cohort, the mean duration of disease at transition was 12.9 years. The mean BASDAI score was 2.50 (95% CI 2.22, 2.78) and 146 patients (78.1%) had low disease activity.

Patient characteristics at the time of transition by country are presented in Supplementary Table S2.

Treatments

In the RA cohort, the mean (SD) duration of reference etanercept therapy was 68.3 (46.5) months and the mean (SD) time from the last dose of reference etanercept to transition was 0.5 (1.8) months. The mean (SD) duration of the course of reference etanercept immediately prior to transition was 49.7 (40.6) months, with most patients (n=286, 79.9%) receiving 50 mg once per week. The majority of patients who had previously received etanercept 50 mg once per week transitioned to SB4 at the same dose (n=267, 74.6%); (Table II). Concomitant medication was prescribed in 73.7% of patients, most commonly conventional synthetic disease-modifying anti-rheumatic drugs

Table I. Patient characteristics at transition.

	RA cohort n=358	axSpA cohort n=199
Age, mean (SD), years	60.9 (11.9)	49.9 (13.3)
Sex, n (%)		
Male	94 (26.3)	145 (72.9)
Female	264 (73.7)	54 (27.1)
Country, n (%)		
France	89 (24.9)	65 (32.7)
Germany	147 (41.1)	87 (43.7)
Italy	79 (22.1)	32 (16.1)
Spain	43 (12.0)	15 (7.5)
Weight, kg		
n	162	72
mean (SD)	74.8 (16.0)	82.4 (15.6)
Height, cm		
n	141	60
mean (SD)	165.5 (8.5)	171.7 (10.2)
BMI, kg/m^2		
n	141	58
mean (SD)	27.5 (5.6)	27.5 (3.8)
Employment status, n (%)		
Full-time	125 (34.9)	126 (63.3)
Part-time	19 (5.3)	18 (9.0)
Unemployed	210 (58.7)	48 (24.1)
Smoking history, n (%)		
Current smoker	47 (13.1)	41 (20.6)
Ex-smoker	30 (8.4)	22 (11.1)
Non-smoker	279 (77.9)	135 (67.8)
Duration of smoking, mean (SD), years[a]	28.0 (13.6)	20.5 (10.9)
Duration of disease, mean (SD), years	14.6 (9.4)	12.9 (10.3)
median	12.4	10.2
Q1, Q3	7.3, 21.0	5.9, 16.6
Disease activity		
Patients with available disease score at transition, n (%)	342 (95.5)	187 (94)
Remission (DAS28 ≤2.8), n (%)	277 (81.0)	
Low disease activity (DAS28 ≤3.2 for RA or BASDAI <4 for axSpA), n (%)	36 (10.5)	146 (78.1)
Active disease (DAS28 >3.2), n (%)	29 (8.5)	41 (21.9)
Receiving concomitant therapy, n (%)	264 (73.7)	92 (46.2)
Conventional synthetic DMARD, n (%)	190 (53.1)	29 (14.6)
NSAID, n (%)	49 (13.7)	42 (21.1)
Steroid, n (%)	99 (27.7)	6 (3.0)

[a]Data for 71 patients in the RA cohort and 50 patients in the axSpA cohort.
axSpA: axial spondyloarthritis; BMI: body mass index; DAS28: Disease Activity Score 28; DMARD: disease-modifying anti-rheumatic drug; NSAID: non-steroidal anti-inflammatory drug; RA: rheumatoid arthritis; SD: standard deviation.

Table II. Dose regimen at transition and at 6 months.

	RA cohort	axSpA cohort
Dose regimen at transition, etanercept: SB4, n (%)		
n	358	199
50 mg once per week: 50 mg once per week	267 (74.6)	132 (66.3)
50 mg other frequency: 50 mg other frequency	59 (16.5)	46 (23.1)
Other[a]	32 (8.9)	21 (10.5)
Dose regimen at 6 months, SB4, n (%)		
n	337	189
50 mg once per week	268 (79.5)	132 (69.8)
50 mg other frequency	53 (15.7)	43 (22.8)
25 mg other frequency	16 (4.7)	14 (7.4)

[a]Includes 25 mg other: 50 mg other; 25 mg other: 25 mg other; and 50 mg other: 25 mg other.

(csDMARDs, 53.1%), steroids (27.7%) and non-steroidal anti-inflammatory drugs (NSAIDs, 13.7%) (Table I).

In the axSpA cohort, the mean (SD) duration of reference etanercept therapy was 62.0 (45.5) months and the mean (SD) time from the last dose of reference etanercept to transition was 0.3 (1.2) months. The mean (SD) duration of the last course of reference etanercept prior to transition was 46.4 (39.1) months, with most patients (n=145, 72.9%) receiving 50 mg once per week. The majority of patients who had previously received etanercept 50 mg once per week also received SB4 at a dose of 50 mg once per week at transition (n=132, 66.3%) (Table II). Fewer than 50% of patients received concomitant medications to SB4 (46.2%); the most commonly prescribed types of concomitant medications were NSAIDS (21.1%) and csDMARDs (14.6%) (Table I).

Effectiveness

- RA cohort

The mean individual change in DAS28 score from transition to 3 months was -0.02 (n=258, 95% CI -0.11, 0.08) and at 6 months was 0.01 (n=252, 95% CI -0.09, 0.11); individual change in DAS28 is presented in Figure 2. The mean DAS28 score was 2.01 (n=342, 95% CI 1.92, 2.10) at transition, 2.00 (n=261, 95% CI 1.90, 2.10) at 3 months and 2.07 (n=256, 95% CI 1.96, 2.17) at 6 months. The results of the sensitivity analyses for missing data were broadly consistent with those of the main analysis (Suppl. Table S3, Suppl. Fig. S2A).

The proportion of patients in remission was 81% (n=277 of 342 patients with available disease score; 95% CI 76.4%, 85%) at transition, 81.6% (n=213 of 261; 95% CI 76.4%, 86.1%) at 3 months and 75.8% (n=194 of 256; 95% CI 70.1%, 80.9%) at 6 months. The proportion of patients with low disease activity was 10.5% (n=36 of 342; 95% CI 7.5%, 14.2%) at transition, 8.8% (n=23 of 261; 95% CI 83.4%, 91.7%) at 3 months and 12.5% (n=32 of 256; 95% CI 8.7%, 17.1%) at 6 months.

There was no change in disease activity relative to transition in 91.1% of patients (n=235 of 258; 95% CI 86.9%,

94.3%) at 3 months and 90.9% of patients (n=229 of 252; 95% CI 86.7%, 94.1%) at 6 months. The proportion of patients whose disease activity had worsened was 3.5% (n=9 of 258; 95% CI 1.6%, 6.5%) at 3 months after transition and 4.8% (n=12 of 252; 95% CI 2.5%, 8.2%) at 6 months. The proportion of patients with improvement in disease activity relative to transition was 5.4% (n=14 of 258; 95% CI 3%, 8.9%) at 3 months and 4.4% (n=11 of 252; 95% CI 2.2%, 7.7%) at 6 months. The mean individual change in the DAS28 score and the corresponding 95% CIs were broadly consistent across all countries (Fig. S3A).

- axSpA cohort

The mean individual change in BASDAI score from transition to 3 months was -0.01 (n=131; 95% CI -0.24, 0.21), and at 6 months was -0.11 (n=136; 95% CI -0.31, 0.10); individual change in BASDAI is presented in Figure 3. The mean BASDAI score was 2.50 (n=187; 95% CI 2.22, 2.78) at transition, 2.51 (n=135; 95% CI 2.18, 2.84) at 3 months and 2.30 (n=139; 95% CI 2.00, 2.61) at 6 months. The results of the sensitivity analyses for missing data were broadly consistent with those of the main analysis (Suppl. Table S4, Suppl. Fig. S2B). The proportion of patients with low disease activity was 78.1% (n=146 of 187; 95% CI 71.5%, 83.8%) at transition and 79.1% (n=110 of 139; 95% CI 71.4%, 85.6%) at 6 months.

The mean individual change in the BASDAI score and the corresponding 95% CIs were broadly consistent across all countries (Suppl. Fig. S3B).

Safety

Non-serious adverse events considered to be causally related to SB4 were reported by 19 patients (5.3%) in the RA cohort and 12 patients (6.0%) in the axSpA cohort.

One adverse event of pneumonia was reported as Serious (SAE) and related to SB4 administration, and led to patient discontinuation from the RA cohort. Six SAEs unrelated to SB4 were reported: relapsing pancreatitis, coronary artery disease, chronic obstructive pulmonary disease and lithium overdose in the RA cohort, and umbilical hernia and uveitis in the axSpA cohort, the latter leading to discontinuation of SB4.

In the RA cohort, 10 patients discontinued SB4 due to causally-related non-serious adverse events: sepsis, rash (two patients), pruritus (two patients), urinary tract infection, hypersensitivity and increased psoriasis and hot flushes, nausea, urticaria, and cutaneous lesion. Two patients in this cohort discontinued due to unrelated non-serious adverse event of rheumatoid nodule and hunger (n=1, 0.3% for all). In the axSpA cohort, four patients discontinued SB4 because of causally-related non-serious adverse events: injection site erythema and swelling, pruritus and rash, pyrexia and skin infection, and psoriasis, and one patient discontinued due to an unrelated non-serious event of uveitis (n=1, 0.5%).

Discontinuation and retention on SB4

In the RA cohort, reasons for discontinuation of SB4 included lack of effectiveness (n=21, 5.9%), adverse events (n=13, 3.6%), investigator's decision (n=1, 0.3%) and other (n=5, 1.4%). (Fig. S1).

In the axSpA cohort, reasons for discontinuation of SB4 included lack of effectiveness (n=12, 6.0%), adverse events (n=6, 3.0%), investigator's decision (n=1, 0.5%) and other (n=1, 0.5%) (Suppl. Fig. S1).

Based on Kaplan-Meier estimates, 90.8% (95% CI 87.2%, 93.4%) of patients in the RA cohort (Suppl. Fig. S4A) and 92.4% (95% CI 87.5%, 95.4%) of patients in the axSpA cohort continued to receive SB4 at 6 months (Suppl. Fig. S4B).

A total of 25 patients (7.0%) in the RA cohort and 14 patients (7.0%) in the axSpA cohort resumed treatment with reference etanercept after discontinuing SB4.

Method of SB4 administration

In the RA cohort, 213 patients (60.0%) initiated SB4 with a pre-filled pen and 142 patients (40.0%) with a pre-filled syringe. At 6 months, 200 patients

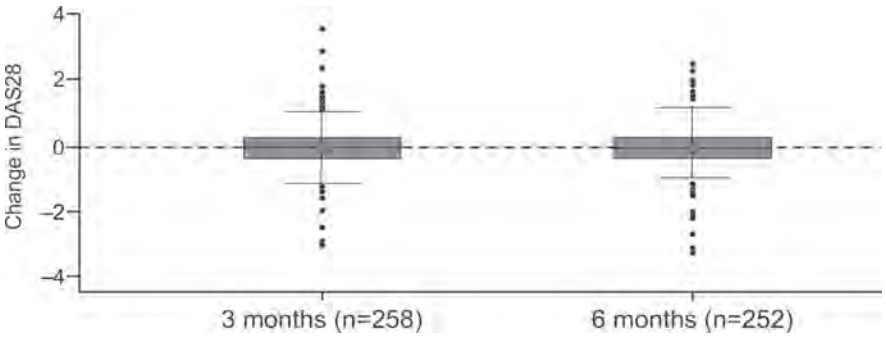

Fig. 2. Individual change in DAS28 scores from the SB4 transition point in the RA cohort for patients with a score at transition and the timepoint presented (*i.e.* at 3 months and at 6 months)
DAS28: Disease Activity Score 28; RA: rheumatoid arthritis.

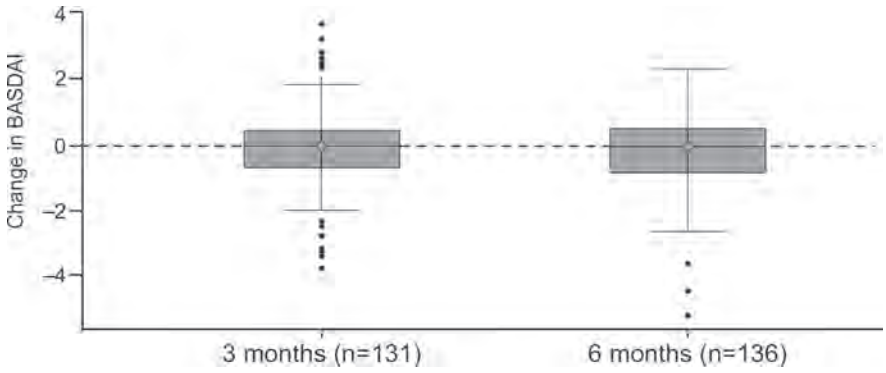

Fig. 3. Individual change in BASDAI scores from the SB4 transition point in the axSpA cohort for patients with a score at transition and the timepoint presented (*i.e.* at 3 months and at 6 months)
axSpA: axial spondyloarthritis; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.

(59.9%) were using a pre-filled pen and 134 (40.1%) were using a pre-filled syringe. At transition, 64.0% of patients in France used a pre-filled pen and 36.0% used a pre-filled syringe; a similar proportion of patients in Germany used the two devices (68.0% and 32.0%, respectively). In Italy, the proportion of patients who used a pre-filled syringe (73.4%) was higher than the proportion of those who used a pre-filled pen (26.6%). The opposite was true in Spain, where 86.0% of patients used a pre-filled pen and 14.0% used a pre-filled syringe. At 6 months, these differences were maintained.

In the axSpA cohort, 141 patients (71.6%) initiated SB4 with a pre-filled pen and 56 patients (28.4%) with a pre-filled syringe. At 6 months, a pre-filled pen was used by 136 patients (72.7%) and a pre-filled syringe by 51 patients (27.3%). At transition, a similar proportion of patients in France and Germany used a pre-filled pen (79.4% and 75.9%, respectively) or a pre-filled syringe (20.6% and 24.1%, respectively). In Italy, the proportion of patients who used a pre-filled syringe (62.5%) was higher than the proportion of those who used a pre-filled pen (37.5%). The proportion of patients using a pre-filled pen was highest in Spain, where 86.7% used the pen and only 13.3% used a pre-filled syringe. These differences were maintained at 6 months.

Discussion

This real-world analysis of European patients with stable RA or axSpA who transitioned from reference etanercept to SB4 found no clinically meaningful change in disease control after transition: overall and by country, disease scores remained stable with no change in biologic therapy. This finding is in line with those of previous phase I and phase III clinical studies of SB4 in patients with RA, in which bioequivalence of SB4 to the reference etanercept was demonstrated (6, 7).

The results of the present study are also consistent with those of a systematic review of real-world studies of SB4 (9). The review identified 33 publications describing a total of 11,053 patients who transitioned from reference etanercept to SB4. Three journal articles (10-12) reported effectiveness outcomes and none found any clinically significant changes in disease activity as assessed via changes in DAS28 or Ankylosing Spondylitis Disease Activity Score over 3 or 6 months. This was also true for most congress abstracts, including an interim analysis of this study (13-21). The incidences of adverse events and SAEs were similar between SB4 and reference etanercept. In one study, the incidence of injection site reactions was higher with reference etanercept than with SB4 (7.3% *vs*. 2.6%) (22).

High retention rates were reported in most studies, with a minimum of 75% at 12 months of follow-up (9). In two studies, lower retention rates compared with historical etanercept cohorts were reported (10, 11); these were at least partially attributable to non-treatment-related factors including nocebo effect, different treatment practices and lack of knowledge on the part of physicians. In studies that included large cohorts of patients (11, 23), the rate of switching back to etanercept ranged from 7% to 14%, consistent with the rate seen in the present study (7.0%).

This non-interventional, real-world study had some limitations, being a single-cohort study in which the reason for switch was not reported into the study database, hence it is not possible to know whether switch was mandated by the health authority or was the free choice of the physician or patient. This could limit the applicability of the results to all switched patients. However, all eligible patients enrolled into this study had to have stable disease at the time of switch, which helps to mitigate this limitation. Multiple confounding factors, such as concomitant therapies and variations in clinical practice across sites and countries, could have influenced the results. Secondly, a proportion of patients in both cohorts had missing disease activity scores at 3 and/or at 6 months. This is perhaps not surprising since not all physicians routinely measure disease activity at 3 months after initiation of new treatment as part of regular clinical practice. However, the results of the sensitivity analyses were consistent with the main analysis, which suggests that neither missing data points nor heterogeneity across sites and/or countries markedly affected the results.

This study also had a number of strengths. Firstly, it was conducted in real-world populations in the routine practice setting. This gives its findings greater external validity than those of randomised controlled trials. Secondly, the study provided country-specific insights into clinical practice, effectiveness and safety. Furthermore, to the best of our knowledge, this study included the largest studied cohort of patients with axSpA receiving SB4.

In conclusion, this study provides real-world evidence that SB4 is effective and safe in patients with stable RA and axSpA who transitioned from reference etanercept, followed for 6 months.

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References

1. HARAOUI B, BYKERK V: Etanercept in the treatment of rheumatoid arthritis. *Ther Clin Risk Manag* 2007; 3: 99-105.
2. VASANTHI P, NALINI G, RAJASEKHAR G: Role of tumor necrosis factor-alpha in rheumatoid arthritis: A review. *APLAR J Rheumatol* 2007; 10: 270-4.
3. KIM YA, RASCATI KL, PRASLA K, GODLEY P, GOEL N, DUNLOP D: Retrospective evaluation of the impact of copayment increases for specialty medications on adherence and persistence in an integrated health maintenance organization system. *Clin Ther* 2011; 33: 598-607.
4. DORNER T, STRAND V, CORNES P *et al*.: The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016; 75: 974-82.
5. EUROPEAN MEDICINES AGENCY. Benepali: Epar – product information. European Medicines Agency; 2016 [updated 21 June 2019; cited 2019 25 July]; Available from: https://www.ema.europa.eu/en/documents/product-information/benepali-epar-product-information_en.pdf.
6. LEE YJ, SHIN D, KIM Y, KANG J, GAULIARD A, FUHR R: A randomized phase l pharmacokinetic study comparing sb4 and etanercept reference product (Enbrel®) in healthy subjects. *Br J Clin Pharmacol* 2016; 82: 64-73.
7. EMERY P, VENCOVSKY J, SYLWESTRZAK A

et al.: A phase III randomised, double-blind, parallel-group study comparing SB4 with etanercept reference product in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2017; 76: 51-7.

8. SILVAGNI E, DI BATTISTA M, BONIFACIO AF, ZUCCHI D, GOVERNATO G, SCIRÈ CA: One year in review 2019: novelties in the treatment of rheumatoid arthritis. *Clin Exp Rheumatol* 2019; 37: 519-34.
9. EBBERS HC, PIEPER B, ISSA A, ADDISON J, FREUDENSPRUNG U, REZK MF: Real-world evidence on etanercept biosimilar sb4 in etanercept-naive or switching patients: A systematic review. *Rheumatol Ther* 2019; 6: 317-38.
10. TWEEHUYSEN L, HUISKES VJB, VAN DEN BEMT BJF *et al*.: Open-label, non-mandatory transitioning from originator etanercept to biosimilar SB4: Six-month results from a controlled cohort study. *Arthritis Rheumatol* 2018; 70: 1408-18.
11. GLINTBORG B, LOFT AG, OMEROVIC E *et al*.: To switch or not to switch: Results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry. *Ann Rheum Dis* 2019; 78: 192-200.
12. PESCITELLI L, LAZZERI L, DI CESARE A, TRIPO L, RICCERI F, PRIGNANO F: Clinical experience with the etanercept biosimilar SB4 in psoriatic patients. *Int J Clin Pharm* 2019; 41: 9-12.
13. DYBALL S, HOSKINS V, CHRISTY-KILNER S, HAQUE S: Effectiveness and tolerability of benepali in rheumatoid arthritis patients switched from enbrel. *Arthritis Rheumatol* 2017; 69 (Suppl. 10).
14. AL TABAA O, ETCHETO A, MICELI-RICHARD C, ANNA M, DOUGADOS M: Sat0199 switch from innovator etanercept to biosimilar etanercept in inflammatory rheumatic diseases: The experience of Cochin University Hospital Paris-France. *Ann Rheum Dis* 2018; 77: 960.
15. ALKOKY H, PAKOZDI A, TAHIR H: Benepali switches in clinical practice – a positive single centre experience. *Arthritis Rheumatol* 2018; 70 (Suppl. 10).
16. BRITES L, COSTA F, FREITAS J *et al*.: Impact of block switch to biosimilar etanercept in practice, accross different rheumatic diseases. *Arthritis Rheumatol* 2018; 70 (Suppl. 10).
17. HAUGEBERG G, BAKLAND G, RØDEVAND E, FEVANG BT, HANSEN IJW, DIAMANTOPOULOS A: Ab0441 drug survival and reason for drop-out in rheumatoid arthritis patients with a non-medical switch from originator to biosimilar etanercept – preliminary data from a Norwegian multicenter study. *Ann Rheum Dis* 2018; 77: 1383.
18. KRÜGER K, SELMI C, CANTAGREL A *et al*.: Benefit study: Results of interim analysis of a pan-european observational study to evaluate real-world effectiveness of sb4 following transition from originator etanercept (ETN) in patients with rheumatoid arthritis (RA) or axial spondyloarthritis (axSpA). *Arthritis Rheumatol* 2018; 70 (Suppl. 10).
19. MÜSKENS WD, RONGEN-VAN DARTEL SAA, ADANG E, VAN RIEL PL: Ab0475 the influence of switching from etanercept originator to its biosimilar on effectiveness and and the impact of shared decision making on retention and withdrawal rates. *Ann Rheum Dis* 2018; 77: 1399.
20. SHAH K, FLORA K, PENN H: 232 clinical outcomes of a multi-disciplinary switching programme to biosimilar etanercept for patients with rheumatoid arthritis. *Rheumatology* 2018; 57 (Suppl. 3): 075.
21. SIGURDARDOTTIR V, SVARD A: Repeated switches between reference product etanercept and biosimilar do not affect disease activity or retention rate of etanercept over 24 months - a cohort study with historical controls. *Joint Bone Spine* 2019; 86: 529-30.
22. BAGANZ L, MEIßNER Y, HERZER P *et al*.: Treatment continuation on the etanercept original in comparison with a biosimilar. *Arthritis Rheumatol* 2018; 70 (Suppl. 10).
23. ALTEN R, JONES H, CURIALE C, MENG T, LUCCHESE L, MIGLIO C: Sat0201 real world evidence on switching between etanercept and its biosimilar in rheumatic diseases. *Ann Rheum Dis* 2018; 77: 961.

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