

# Effectiveness and safety of a biosimilar-to-biosimilar switch of the TNF inhibitor etanercept in patients with chronic inflammatory rheumatic diseases

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## Abstract

**Background:** Biosimilar disease-modifying anti-rheumatic drugs (bsDMARDs) has created a financial incentive to encourage switching to cheaper products.

**Objectives:** We aim to study the effectiveness and safety of a non-medical bsDMARD-to-bsDMARD switch from originator etanercept (ETN) to bsDMARD ETN (SB4) and successive to another bsDMARD ETN (GP2015) in patients with chronic inflammatory rheumatic diseases in a real-life setting.

**Methods:** Retrospective chart review of patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) who had been treated with originator ETN and were switched twice to ETN bsDMARD for non-medical reasons thereafter. All patients received ETN 50 mg/week. Disease activity and physical function was assessed every 12 weeks with standardized questionnaires.

**Results:** A total of 100 patients who switched twice [54 RA, 27 axSpA, 19 PsA, mean age 54.3 (15.1), 46% male] were included. Patients with axSpA were younger than RA and PsA patients. Patients with SpA were less likely to receive conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) than RA patients. Duration of treatment with originator ETN before the first switch was 3.3 (2.3) years. Retention rate 6 months after the second ETN bsDMARD switch was 89%. Disease activity and physical function scores remained rather unchanged in patients with RA and axSpA longitudinally, while there was some more fluctuation in PsA patients. Six patients lost efficacy and were switched back to originator ETN in month 6 ( $n=4$ ) or to another mode of action ( $n=2$ ). There were 14 adverse events (AE) reported in eight patients. One patient re-administered bsDMARD GP2015 successfully 3 months after healing of mucosal erosions.

**Conclusion:** No relevant change in disease activity and physical function were observed in a non-medical bsDMARD-to-bsDMARD switch scenario. The retention rate after switches from originator ETN to two ETN bsDMARD was close to 90%. Multiple switches resulted in a high adherence rate without clinically important efficacy or safety signals.

**Keywords:** biosimilar, outcome, switch

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## Background

Following the approval of biosimilars [biosimilar disease modifying anti-rheumatic drugs (bsDMARDs)] in the field of rheumatology by the European Commission in 2015, bsDMARDs

have captured a steadily growing market share in rheumatology.<sup>1</sup> Approval is based on clinical trials demonstrating efficacy, safety and equivalence to the originator biologic DMARD (bDMARD).<sup>2–4</sup> In all countries of the European Union, the

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annual therapy costs of the bsDMARDs are significantly lower than those of the originator bDMARD.<sup>1</sup> The economic factors cause, on one hand, that several bsDMARDs of one originator bDMARD are approved and, on the other hand, that the health authorities pursue different strategies for the implementation of bsDMARDs. Thus, the availability of bsDMARDs has created a financial incentive to encourage switching to cheaper products (‘non-medical switch’). Both internationally and nationally, proposals range from an unregulated approach (i.e. the decision-making authority is solely on the physician’s side) to rigid requirements of a mandatory switch from the originator bDMARD to the bsDMARDs. Data collected in Denmark in the context of a mandatory switch from etanercept (ETN) as the originator bDMARD to SB4 as the ETN bsDMARD showed that the retention rate of the bsDMARD was higher than the retention rate of non-switchers but lower compared with a historical cohort.<sup>5</sup> The authors conclude that patient factors and nonspecific drug effects may have an impact on retention rates. However, we have previously shown that switching from ETN originator bDMARD to ETN bsDMARD SB4 was not associated with a reduction in efficacy or negative impact on safety in routine care.<sup>6</sup>

The prescription of bsDMARDs also varies at the national level, for example, in Germany, by the regional associations of panel physicians [‘Kassenärztliche Vereinigung’ (KV)]. For example, in our area, Westfalen-Lippe, rheumatologists are confronted with a requirement of a bsDMARD quota of >90%—which practically means that almost all patients have to be started on a bsDMARD, and an existing therapy with an originator bDMARD has to be switched to a bsDMARD. In consequence, multiple switches between bsDMARDs are to be expected. Since, as mentioned above, several bsDMARD are approved for some reference biologics, multiple switching will also occur within bsDMARDs, whereas economic factors in the provision of medication are the decisive factor. While the effectiveness and safety of switching in rheumatic and other diseases has been properly assessed, this is not the case for multiple switching. Documentation of such treatment switches is essential in clinical practice, as clinical studies on multiple switches from the originator bDMARD to different bsDMARDs is not required by European Medical Agency (EMA).

### *Objectives*

To assess the effectiveness and safety of a systematic non-medical switch from originator ETN to bsDMARD ETN (SB4) and successive to another bsDMARD ETN (GP2015) in adult patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) or axial spondyloarthritis (axSpA) in a real-life setting.

### **Materials and methods**

#### *Study design*

Retrospective chart review of patients with RA, PsA or axSpA treated with originator ETN in early 2017 in daily routine in our tertiary centre. The local ethics committee at Ruhr-Universität Bochum, Germany, approved the study protocol (Reference number 19-6736). Patients did not need to give written informed consent. The reporting of this study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.<sup>7</sup>

#### *Study population*

Clinical data of all adult patients with RA, PsA or axSpA who had been treated with originator etanercept ETN with a dosage of 50 mg/week and who had been switched subsequently to two different ETN bsDMARD for non-medical reasons thereafter were documented retrospectively. The decision for switching was mandated for all patients on originator etanercept ETN with a dosage of 50 mg/week after a lower price had been negotiated for our department. The first switch from originator ETN to first bsDMARD SB4 occurred between February and May 2017 and the second switch from first to the second bsDMARD (GP2015) occurred between September and December 2017. Patients were switched to bsDMARDs at the same dose and frequency as originator ETN. Patients were informed by their rheumatologist at a clinical face-to-face visit between February–May 2017 about the first switch and between September–December 2017 about the second switch. Patients were informed about the nature of bsDMARDs and the high likelihood that the bsDMARD will be effective and safe. Subsequent visits were scheduled approximately every 12 weeks apart according to the routine visit scheme. Patients who received originator ETN 25 mg/week were not analysed because this formulation was not available as a

bsDMARD. The end of the observation period was July 2018.

### *Clinical data*

Patients and disease characteristics [age, gender, diagnosis, laboratory parameter (rheumatoid factor, HLA-B27, C-reactive protein (CRP)) and current and past drug treatment] were documented at the first clinical visit on which the patient was informed about the switch. Disease activity, physical function and current treatment as well as adverse events were extracted longitudinally from first switch visit until last observed visit in October 2019. Disease activity was assessed in RA and PsA patients by using the 28-joint Disease Activity Score (DAS28) and in axSpA by using the Bath Ankylosing Spondylitis (AS) Disease Activity Index (BASDAI) and the AS Disease Activity Score (ASDAS).<sup>8–10</sup> Physical function was assessed in RA and PsA patients by using the 'Funktionsfragebogen Hannover' (FFbH) score, which strongly correlates with the Health Assessment Questionnaire (HAQ).<sup>11</sup> Values of FFbH were converted into HAQ values by the published formula: HAQ score =  $3.16 - (0.028 \times \text{FFbH score})$ .<sup>11</sup> Physical function was assessed in axSpA patients by using the Bath AS functional index (BASFI).<sup>12</sup> Information about current treatment, switch to bsDMARD or to other mode of actions as well as reports about adverse events were extracted from the hospital information system for each visit. Any change in disease status was assessed as potentially related to the switch or not. All data were taken from the hospital information system, including the date of the visits. Routine visits occur approximately every 12 weeks.

### *Definition of outcome*

The scores documented at the routine visit closest to 24 weeks after the second switch were taken as primary outcome. Secondary outcomes included the retention rate of bsDMARD and occurrence of adverse events.

### *Statistics*

All data are expressed as mean values [standard deviation (SD)] or number and percentage (%) for continuous and categorical variables, accordingly. Categorical variables were compared between groups using chi-square test while quantitative variables were compared using Mann–Whitney U test. All analyses were made using

SPSS version 25.0, and a  $p < 0.05$  was considered statistically significant.

## **Results**

### *First switch visit*

A total of 100 patients who switched twice to ETN bsDMARDs (Enbrel® → SB4 → GP2015) were included [54 RA, 27 axSpA, 19 PsA, mean age 54.3 (15.1), 46% male] (Table 1).

The mean time of treatment with originator ETN prior to the first switch was 3.3 (2.3) years (range 0–10 years), and that was not different between subgroups (Table 1). Outcome over a follow-up period of 21.1 (7.4) with a range of 16–32 weeks were documented.

Patients with axSpA were younger than RA and PsA patients. Patients with axSpA and PsA were less likely to receive csDMARDs than RA patients. Fewer axSpA patients received glucocorticoid treatment compared with RA or PsA patients.

Patients had at first switch visit a moderate to high disease activity [DAS-28 for RA 3.0 (2.2) and PsA 3.8 (2.9); BASDAI 5.1 (2.7) and ASDAS 3.4 (0.9)]. Physical function was impaired as documented by HAQ [RA 1.4 (0.8); PsA 1.2 (0.9)] and BASFI 4.4 (2.7).

### *Outcome of bsDMARD to bsDMARD switch*

The retention rate 6 months after the second ETN bsDMARD switch was 89%. While two patients were lost to follow-up and one patient died (cardiac arrest (categorized as not associated with switch), six patients discontinued due to inefficacy. Patients with loss of effect were switched back to originator ETN in month 6 ( $n = 4$ ) or to another mode of action ( $n = 2$ , abatacept and baricitinib in RA patients). All four patients who switched back to originator ETN reached their former state of low disease activity during follow-up. One patient re-administered GP2015 successfully in month 3 after experiencing a treatment break of 6 weeks because of mucosal erosions. One patient was withdrawn due to pregnancy and one patient was diagnosed with pancreatic cancer.

Disease activity scores remained rather unchanged during follow-up in RA and axSpA patients

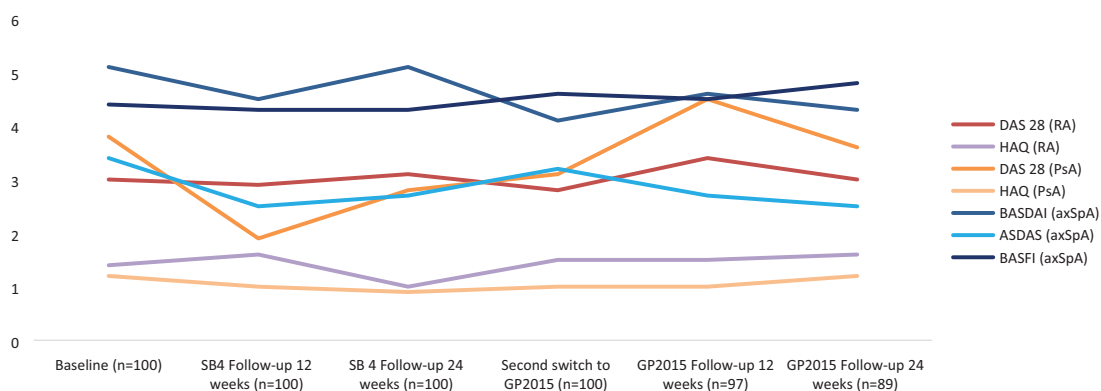
**Table 1.** Study population at first switch visit.

	All patients (n = 100)	RA (n = 54)	PsA (n = 19)	axSpA (n = 27)
Age (years) <sup>a</sup>	54.3 (15.1)	60.2 (13.8)	52.5 (15.6)	43.9 (11.5)
Sex (male), n (%)	46 (46.0)	19 (35.2)	9 (47.4)	18 (66.7)
Disease duration (years), mean (SD)	10.1(10.7)	10.9 (12.7)	9.7 (8.9)	8.6 (7.1)
Time on originator ETN before first switch, years	3.3 (2.3)	3.3 (2.4)	3.4 (2.3)	3.4 (2.3)
CRP, mg/dL, median (IQR)	0.5 (0.5)	0.2 (0.02 to 0.7)	0.2 (0.05 to 0.3)	0.4 (0.1 to 1.0)
csDMARDs, n(%)	43 (43)	32 (59.3)	5 (26.3)	6 (22.2)
Glucocorticoids, n(%)	42 (42)	25 (46.3)	10 (52.6)	7 (25.9)
Disease activity	NA <sup>b</sup>	3.0 (1.2)	3.8 (1.4)	BASDAI: 5.1 (2.7) ASDAS: 3.4 (0.9)
Physical function	NA	1.4 (0.8)	1.2 (0.8)	4.4 (2.7)

ASDAS, AS Disease Activity Score; axSpA, axial spondyloarthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ETN, etanercept; IQR, interquartile range; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SD, standard deviation.

<sup>a</sup>Values are shown as mean (SD)

<sup>b</sup>Since disease-specific measures (DAS-28 in RA and PsA, HAQ in RA and PsA and BASFI in axSpA) were used, no global score can be shown.



**Figure 1.** Longitudinal data of disease activity and physical function in the multiswitch cohort.

(Figure 1). PsA patients showed more fluctuations in the disease activity score but the DAS-28 values at baseline and end of observation were at the same level. Physical function remains stable in all three disease groups.

Overall, 14 AEs were reported in eight patients, all graded 1–3 according to Common Terminology Criteria for Adverse Events (CTCAE). One patient was diagnosed with pancreatic cancer and was withdrawn from bsDMARD in month 2 after the

second bsDMARD switch. The remaining patients had laboratory abnormalities [elevation of liver enzymes ( $n=5$ ), creatinine ( $n=2$ ) or anaemia ( $n=1$ ) or infectious complications (herpes simplex ( $n=1$ ), flue-like symptoms ( $n=1$ ), pneumonia ( $n=1$ ), gingivitis ( $n=1$ ), suspicion of bone tuberculosis ( $n=1$ )]. Patients with pneumonia and suspicion of bone tuberculosis experienced a treatment break of 3 (1.2) weeks. No injection site reactions were documented in our cohort. No retransitioning to originator ETN occurred due to AEs.

## Conclusion

This study shows that the retention rate of multiple switches from originator bDMARD ETN to two different ETN bsDMARDs in a non-medical switch was close to 90%. Furthermore, no major changes in disease activity, physical function or in the frequency of adverse events were observed in all groups including patients with RA, PsA and axSpA. However, one has to consider that the DAS-28 score has limitations as a disease activity measure in PsA.

This result is in line with other studies investigating a switch from originators to bsDMARDs. A systematic review identified 70 articles including many uncontrolled and observational studies related to a switch between originator and bsDMARD infliximab (INF).<sup>13</sup> Nevertheless, no clinically important efficacy or safety signals were reported but there was an increase in patient-reported outcomes (PROs) that was not considered clinically relevant. In the DANBIO registry, a non-medical switch from originator to bsDMARD ETN (SB4) showed somewhat lower retention rates in switchers [83% (95% confidence interval (CI): 79–87%)] compared with a historical originator ETN cohort [90% (95% CI: 88–92%)].<sup>5</sup> In contrast, we have previously demonstrated that switching originator ETN to bsDMARD ETN was not associated with loss of efficacy nor with a negative impact on safety in routine care. Indeed, the retention rate of 96.4% after 12 weeks was high.<sup>6</sup> Other data from the DANBIO registry on a non-medical switch from originator to two different adalimumab (ADA) bsDMARDs (GP2017 *versus* SB5) also showed a high retention rate of 89.5% at year 1.<sup>14</sup> This head-to-head comparison of two different bsDMARD was possible because of different results of price negotiations in two regions of Denmark. Interestingly, the estimated risk of withdrawal was lower for GP2017 compared with SB5 [hazard ratio (HR): 0.60; 95% CI: 0.42 to 0.86], and the 6-month remission rate was also higher [odds ratio (OR): 1.72; 95% CI: 1.25 to 2.37]. The reason for this result remained unclear.

While data on switching from originator to bsDMARD are now increasingly available, data on switching from bsDMARD to bsDMARD are rare. To our knowledge, no bsDMARD-to-bsDMARD switch has been reported in patients with rheumatic diseases to date. This is different in inflammatory bowel disease (IBD) where patients showed no difference in efficacy and safety after a

switch from bsDMARD to bsDMARD but high clinical remission rates.<sup>15–17</sup> The retention rate of about 88% is comparable with our 6-month results. Data on multiple switches have also been published in psoriasis. Multiple switches between ETN bsDMARD GP2015 with originator ETN did not impact efficacy, safety and immunogenicity in patients with chronic plaque-type psoriasis.<sup>18</sup> Even interchangeability between ADA originator and an ADA bsDMARD (BI 695501) was recently shown in a phase III study of patients with moderate to severe plaque psoriasis.<sup>19</sup> These patients who had been switched several times between ADA originator and bsDMARD BI 695501 showed similar outcomes in terms of pharmacokinetics, efficacy, immunogenicity and safety. This study was the first to meet FDA criteria for bDMARD interchangeability. The expected FDA approval will definitely change the bsDMARD landscape in the future. However, in Europe, decisions on interchangeability of bsDMARDs, which implies substitution of drugs by the pharmacist without notification of the prescribing physician, have already occurred in the absence of such data. This is in contrast to the proposal of the Task Force on the Use of Biosimilars to Treat Rheumatological Diseases, which has asked for reliable pharmacovigilance data, including traceability and respect for patient perspectives.<sup>20</sup> However, this is usually not the case in a non-medical switch scenario. In addition, low acceptance of switching DMARDs including nocebo effects may influence the retention rate and increase the rate of transitioning.<sup>21</sup> However, this rate was very low in our cohort. In contrast, in a French cohort study negative perceptions of patients with rheumatic diseases were blamed for the low retention rate after switching from INF to bsDMARD CT-P13.<sup>22</sup> In a subsequent study, patients decided whether to switch or not from ETN to SB4 resulting in a high acceptance rate of 92%.<sup>23</sup> Furthermore, the experience made with the originator bDMARD was shown to influence the attitudes of patients towards switching.<sup>24</sup> In this study, patients with negative perceptions about bsDMARDs were more often female, seeking health information online and were in preference of originators. However, positive message framing was shown to improve perceptions and the willingness to switch to a bsDMARD in patients currently taking bDMARDs.<sup>25</sup> Indeed, a multidisciplinary team intervention with a prominent role of nurses was shown to reduce the nocebo effect in a non-medical switch scenario with an INF bsDMARD.<sup>26</sup>

However, ETN is clearly not the best agent for studying multiple switching as it is the least immunogenic of all tumour necrosis factor (TNF) inhibitors.<sup>27</sup> Therefore, the results of our study should be interpreted with caution and may be different with other bDMARDs. Immunogenicity is a major concern when switching between different bDMARDs including bsDMARDs. However, data in plaque psoriasis showed equivalent efficacy and comparable safety and immunogenicity between pooled continued and pooled switched treatment arms in patients treated with GP2015 or originator ETN.<sup>18,28</sup> Interestingly, the incidence of antidrug antibodies against SB4 in comparison with originator ETN was even lower in a phase III study in patients with RA.<sup>3</sup>

Our study does have some limitations. The main limitation is the retrospective design. Because non-medical switch scenarios in a real-world setting depend on economic decisions, application of a prospective study design is simply not possible. However, the findings of this study offer new information on this patient population by stressing that multiple switches between ETN bsDMARD can be performed without major problems. Of note, the long period of time until our primary endpoint at 24 weeks after the second switch was reached varied between 16 and 32 weeks – this reflects the usual situation of follow-up visits in routine care. Our results are consistent with the real-world evidence for patients treated in regions with rigid requirements to mandatory bsDMARD-to-bsDMARD switching. The second limitation is the relatively small number of participants. Given the fact that multiple switch scenarios do occur in a limited number of drug classes, our sample size was large enough to present meaningful data from a retrospective chart review. Third, due to the retrospective design of our study no comparator group of patients with no change in medication could be studied because the switch was mandatory for all patients on originator etanercept ETN dosed with 50 mg/week.

No relevant change in disease activity and physical function were observed in a non-medical bsDMARD-to-bsDMARD switch scenario. The retention rate after switches from originator ETN to two ETN bsDMARD was very high—close to 90%. In summary, multiple switches between ETN bsDMARD resulted in a high adherence

rate without clinically important efficacy or safety signals.

## Declarations

### *Ethics approval and consent to participate*

The local ethics committee at Ruhr-Universität Bochum, Germany, approved the study protocol (Reference number 19-6736). Patients did not need to give written informed consent.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Uta Kiltz:** Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Writing – original draft.

**Styliani Tsiami:** Formal analysis; Investigation; Writing – review & editing.

**Xenofon Baraliakos:** Formal analysis; Methodology; Writing – review & editing.

**Ioana Andreica:** Formal analysis; Investigation; Writing – review & editing.

**David Kiefer:** Formal analysis; Investigation; Writing – review & editing.

**Jürgen Braun:** Conceptualization; Formal analysis; Methodology; Writing – original draft.

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#### Availability of data and materials

All data generated or analysed during this study are included in this published article.

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