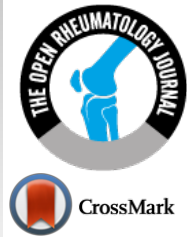# The Open Rheumatology Journal

RESEARCH ARTICLE

Patient Satisfaction with the Etanercept Biosimilar SB4 Device, Among Rheumatoid Arthritis and Spondyloarthropathy Patients - A German Observational Study

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Abstract:

Background:

The etanercept biosimilar SB4 is a TNF inhibitor authorised for use as a targeted Biological Disease-Modifying Anti-Rheumatic Drug (bDMARD). Various administration devices have been developed for subcutaneous self-injection of bDMARDs.

Objective:

This study surveyed patient satisfaction with their experience of using the SB4 pre-filled pen device.

Methods:

This non-interventional, cross-sectional, multi-centre study enrolled adult rheumatoid arthritis and spondyloarthropathy patients who had been treated for at least three months with the SB4 pre-filled pen. Based on a standardized questionnaire, patients rated general satisfaction, handling, user-friendliness, physical characteristics, and training material received. A total of 492 eligible patients completed questionnaires at 43 centres across Germany between August 2017 and June 2018. Data were analysed descriptively. Pre-defined subgroup analyses by previous therapy and by indication were performed.

Results:

Overall, 87% (95% CI 83% - 90%) of patients reported being 'satisfied' or 'very satisfied' with the pen. 89% of patients reported that the pen was 'simple' or 'very simple' to use. Most patients (87%) self-injected. 93% of patients who received training on the use of the pen were 'satisfied' or 'very satisfied' with the training provided. In this cross-sectional study, 12 patients reported an Adverse Event (AE) and one patient reported a treatment-related AE (nausea).

Conclusion:

The results demonstrated a high level of general satisfaction among patients using the SB4 pre-filled pen as well as satisfaction with ease of use for patients who were either naïve to bDMARDs or who had switched to SB4 from other bDMARDs.

Keywords: Biological disease-modifying anti-rheumatic drug, Etanercept biosimilar, Patient satisfaction, Pre-filled pen, Rheumatoid arthritis, SB4 (Benepali®), Spondyloarthropathy, TNF inhibitor.

1. INTRODUCTION

Etanercept, a Tumor Necrosis Factor (TNF) inhibitor was the first targeted Biological Disease-Modifying Anti-Rheumatic Drug (bDMARD) approved to treat rheumatoid arthritis, psoriatic arthritis, plaque psoriasis, and ankylosing spondylitis [1]. Since initial approval in 1998, a number of other bDMARDs have become available for prescription. SB4 (Benepali®, Biogen Manufacturing ApS, Hillerød, Denmark) was the first etanercept biosimilar approved in the European Union (EU) in January 2016 for the treatment of moderate to severely active rheumatoid arthritis, active and progressive psoriatic arthritis, axial spondyloarthritis and plaque psoriasis [2].

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The administration route of most bDMARDs is subcutaneous injection, for which a variety of product-specific administration devices are available. These devices were developed to enable safe and comfortable self-injection, which is an important aspect of patient compliance [3]. A number of studies reported that rheumatoid arthritis patients prefer pre-filled pens to conventional injection methods. Reasons reported by patients included 'easier handling', 'more practical', 'better acceptance', 'less painful', and 'less time-consuming' [4 - 6].

This study aimed to ascertain satisfaction with the day-to-day use of the SB4 pre-filled pen in patients with Rheumatoid Arthritis (RA) or Spondyloarthropathy (SpA). Besides, it investigated whether differences in satisfaction exist between subgroups of patients who were either naïve to the use of bDMARDs, were switching from a pre-filled syringe or were switching from another bDMARD pre-filled pen. Patients were asked to complete a questionnaire to evaluate various aspects of use based on their personal experiences, such as handling, user-friendliness, and features of the SB4 pre-filled pen, as well as satisfaction compared to the previous administration device and satisfaction with the training received on safe injection with the SB4 pre-filled pen.

2. PATIENTS AND METHODS

2.1. Study Design

This was a non-interventional, cross-sectional, multi-centre study that enrolled patients with RA or SpA who had been treated for at least three months with the SB4 pre-filled pen. Medical care with the SB4 pre-filled pen followed the product information [2] and routine practice. The SB4 pre-filled pen is 13 cm long and contains 1.0 ml injection solution. A more detailed description of the device is included in the authorised product information [2]. The study was registered with clinicaltrials.gov under the number NCT03327454. Patients were recruited for the study between August 2017 and June 2018 at 43 private practices across Germany. Based on considerations regarding the precision for the estimate of the primary endpoint, an overall sample size of approximately 500 patients was calculated. Patient participation in the study included providing informed consent and completing a single questionnaire on satisfaction with the SB4 pre-filled pen during a scheduled visit with the treating physician. This study was funded by Biogen GmbH, Ismaning, Germany. An independent ethics committee (Ethics Committee of the Department of Medicine, University of Giessen; AZ 41/17) approved the study on 06 April 2017.

2.2. Patients

Eligible patients were ≥18 years of age with a diagnosis of moderate to severe active RA or severe, active and progressive RA (henceforth referred to as RA), or of active and progressive psoriatic arthritis (PsA), severe active ankylosing spondylitis (AS) or severe non-radiographic axial spondyloarthritis (axSpA) (henceforth referred to as spondyloarthropathies, SpA), had received SB4 via the pre-filled pen in accordance with the prescribing information for at least three months prior to enrolment (to ensure sufficient experience with its use), and had provided informed consent to participate. Patients were excluded if they had contraindications according to the prescribing information for SB4 or if they had received SB4 for the treatment of moderate to severe plaque psoriasis since these patients are usually seen in dermatology practices and not in rheumatology practices.

2.3. Procedures

Study data originated from routine documentation captured by the treating physicians (patient demographics, medical history, disease activity measures, *i.e.* Disease Activity Score 28 (DAS28 for RA and PsA) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI for axSpA), previous and concomitant medications, comorbidities, adverse events and product complaints) and from a standard questionnaire on satisfaction with the SB4 pre-filled pen [7]. This paper questionnaire evaluated the following variables based on a 5-point Likert scale (0 = worst rating, 4 = best rating): General satisfaction, handling and user-friendliness, physical characteristics, satisfaction in comparison with the previous application system, evaluation of the training material received. All variables were entered into an electronic case report form by the physicians and their staff. Automatic data checks for plausibility and completeness were built into the electronic data entry system.

2.4. Outcomes and Safety Variables

The primary endpoint was based on the patient's general satisfaction with the SB4 pre-filled pen. It was determined as the proportion of patients who rated their general satisfaction with the SB4 pre-filled pen as 4 ('very satisfied') or 3 ('satisfied') on a 5-point Likert scale.

Secondary endpoints were the number and proportion of patients who answered questions on their personal experience of various aspects of using the SB4 pre-filled pen with (3) or (4) on a 5-point Likert scale (0 = worst rating, 4 = best rating). The questions included the areas of handling, user-friendliness and features of the SB4 pre-filled pen, satisfaction compared with the previous application system and satisfaction with the training on injection with the training pen.

Other secondary endpoints were the number and proportion of patients who evaluated the training materials received in terms of adequate effectiveness, clarity, and extent of information with 'yes' ('yes'/'no' answers).

For all endpoints, sub-groups by previous treatment (patients naïve to bDMARDs, patients who were switched from a pre-filled injection to the SB4 pre-filled pen, patients who were switched from another pre-filled pen to the SB4 pre-filled pen) and by treatment indication (RA, SpA) were considered.

Adverse Events (AEs) and product complaints were collected. Reported AEs were classified according to MedDRA System Organ Class (SOC) and Peferred Term (PT), a causal relationship with SB4 pre-filled pen according to the reporter and seriousness. Product complaints included the following responses in the patient satisfaction questionnaire: injection procedure 'difficult' or 'very difficult', acoustic signal (clicking) 'unclear' or 'very unclear', and an indication of fully completed injection 'unclear' or 'very unclear'.

2.5. Statistical Analysis

All data processing, summarisation, and analyses were performed using the statistical software suite SAS 9.4® (SAS Institute Inc, Cary, North Carolina, U.S.). Data were tabulated and analysed descriptively. Categorical variables were presented as absolute numbers and proportions (%) and 95% confidence intervals (CI; Clopper Pearson). Percentages for categorical variables were based on all non-missing values (=100%). Continuous variables were summarized with the number of observations (number of missings), mean value, standard deviation, median, quartile, minimum and maximum.

A regression model was used to investigate the potential influence of other variables on the primary endpoint (patient satisfaction). Firstly, the effects of other covariates were evaluated individually in univariate analyses and then with multivariable analyses using a multiple logistic regression model. The potential effects of covariates on patient satisfaction were measured by the odds ratio (OR) and 95% CI. All potentially important covariates were included in a full model and a step-down procedure was used to evaluate the impact of the covariates in the model. The following covariates were evaluated: age (<55 years, 55+ years), RA and SpA subgroups, previous treatment (naïve to bDMARDs), previous injection, disease duration (<6 years, 6+ years), disease remission, presence of comorbidity, use of concomitant medications, and self-injection.

3. RESULTS

512 patients from 43 RA treatment sites across Germany provided written consent to participate and were analysed in the 'All Patients Set'. All patients participated in the one-time visit, had used the device, and received SB4. Twenty of these patients did not meet the inclusion criterion of at least three months of therapy with the SB4 pre-filled pen prior to observation. The remaining 492 patients (96%) were included in the 'Full Analysis Set' (FAS). All results below refer to the FAS except for the results section 'Safety and product complaints', which refers to the All Patients Set.

3.1. Demographics, Description of Disease and Treatment

The 492 patients in the FAS Table **1** included 309 patients (63%) with rheumatoid arthritis and 183 patients (37%) with spondyloarthropathies (88 patients (18%) with psoriatic arthritis and 95 patients (19%) with axial spondyloarthritis). The median age in the FAS was 56 years (59 years for RA patients and 49 years for SpA patients), 63% of the patients were female (72% for RA patients and 49% for SpA patients) and the median duration of disease was 6 years (7 years for RA patients and 5 years for SpA patients).

Most patients (460; 93%) had at least one prior medication before they started using the SB4 pre-filled pen. Only the last therapy directly prior to SB4 pre-filled pen was documented: Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) were used by 338 patients (69%; the most frequently used csDMARD was methotrexate in 246/492 patients, 50%), steroids (256 patients, 52%), non-steroidal anti-inflammatory drugs (NSAIDs) (202 patients, 41%), and bDMARDs (160 patients, 33%; the most frequently used bDMARD was etanercept in 92/492 patients, 19%). Sixty-seven percent of study participants (331/492) were previously naïve to bDMARDs (71% (220/309) of RA patients and 61% (111/183) of SpA patients). Table **1** shows previous treatment in the FAS by indication.

The median duration of use was 201 days (range 90 - 699 days). The median duration of use was longer in RA patients (216 (90 - 699) days) than in SpA patients (177 (90 - 651) days).

The majority of patients (384, 78%) reported receiving at least one concomitant medication. csDMARDs (219 patients; 45%) were the most frequently reported concomitant medications among both the RA patients (174, 56%) and SpA patients (45, 25%).

3.2. Patient Satisfaction

For the primary endpoint, general patient satisfaction, 87% (95% CI 83% - 90%) of patients in the FAS, reported being 'satisfied' (3) or 'very satisfied' (4) with the SB4 pre-filled pen. Overall, 193 patients (39%) were 'very satisfied' with the SB4 pre-filled pen, 233 (47%) were 'satisfied', 23 (5%) were 'neutral', 11 (2%) were 'dissatisfied', and 32 (7%) were 'very dissatisfied' Table **2**.

Table 1. Population characteristics (Full Analysis Set).

-	-	RA	SpA	Total
-	n (missing)	(N=309)	(N=183)	(N=492)
Age in years	492 (0)	59·0 (19·0 - 85·0)	49·0 (19·0 - 87·0)	55·5 (19·0 - 87·0)
Gender - percent female	492 (0)	221 (72%)	90 (49%)	311 (63%)
Duration of disease in years	485 (7)	7·0 (0·0 - 61·0)	5·0 (0·0 - 46·0)	6·0 (0·0 - 61·0)
Indication	492 (0)	-	-	-
Rheumatoid arthritis (RA)	-	..	..	309 (63%)
Psoriatic arthritis	-	..	..	88 (18%)
Axial spondyloarthritis	-	..	..	95 (19%)
Disease Activity Score	-	-	-	-
Rheumatoid arthritis DAS28	163 (146)	3·0 (0·0 - 7·0)	..	3·0 (0·0 - 7·0)
Psoriatic arthritis DAS28	44 (44)	..	2·9 (1·0 - 7·0)	2·9 (1·0 - 7·0)
Axial spondyloarthritis BASDAI	71 (24)	..	3·0 (0·0 - 9·0)	3·0 (0·0 - 9·0)

(Table 1) cont.....

-	-	RA	SpA	Total
-	n (missing)	(N=309)	(N=183)	(N=492)
Type of previous therapy[a]	492 (0)	-	-	-
bDMARD	-	88 (28%)	72 (39%)	160 (33%)
csDMARD	-	255 (83%)	83 (45%)	338 (69%)
NSAID	-	106 (34%)	96 (52%)	202 (41%)
Glucocorticoids	-	213 (69%)	43 (23%)	256 (52%)
Previous bDMARD therapy	492 (0)	-	-	-
Naïve to bDMARDs	-	220 (71%)	111 (61%)	331 (67%)
Switch from injection to pen	-	37 (12%)	22 (12%)	59 (12%)
Switch from pen to pen	-	45 (15%)	48 (26%)	93 (19%)
Other bDMARD therapy (i.v.)	-	7 (2%)	2 (1%)	9 (2%)

Data are n (%) or median (range). Percentages based on all non-missing subjects. [a] Multiple responses possible. RA=Rheumatoid Arthritis, SpA=Spondyloarthropathies, DAS=Disease Activity Score, BASDAI=Bath Ankylosing Spondylitis Disease Activity Index, DMARD=Disease-Modifying Antirheumatic Drug, b=Biological, cs=Conventional Synthetic, NSAID=Non-Steroidal Anti-Inflammatory Drug, i.v.= Intravenous Infusion

Table 2. General satisfaction - number and percent of patients by 5-point Likert scale category, by previous treatment and overall (Full Analysis Set).

-	Naïve to bDMARDs	Switch from another pen to SB4 pen	Switch from syringe to SB4 pen	Other bDMARD therapy	Total
5-point Likert scale	(N=331)	(N=93)	(N=59)	(N=9)	(N=492)
Very satisfied (4)	143 (43%)	27 (29%)	19 (32%)	4 (44%)	193 (39%)
Satisfied (3)	141 (43%)	53 (57%)	35 (59%)	4 (44%)	233 (47%)
Neutral (2)	15 (5%)	5 (5%)	2 (3%)	1 (11%)	23 (5%)
Dissatisfied (1)	7 (2%)	3 (3%)	1 (2%)	..	11 (2%)
Very dissatisfied (0)	25 (8%)	5 (5%)	2 (3%)	..	32 (7%)

bDMARD = Biological Disease-Modifying Antirheumatic Drug.

In the subgroup analyses by indication, the proportions of patients who rated their general satisfaction positively were similar for a patient with RA (86%) and patients with SpA (88%). Likewise, when general satisfaction was considered by previous treatment, 86% of patients naïve to bDMARDs, 92% of patients who switched from injection with a syringe, 86% of patients who switched from another pre-filled pen, and 89% of patients who had previously used another form of bDMARD therapy, reported being 'satisfied' (3) or 'very satisfied' (4) with the SB4 pre-filled pen Table **2**.

The influence of other covariates on the general satisfaction rate was evaluated in a logistic regression model. The following covariates of interest were evaluated in the full model: age (<55 years, 55+ years), RA subgroup (yes/no), ankylosing spondylitis (SpA) subgroup (yes/no), previous medication subgroup (new to bDMARD) (yes/no), previous injection (yes/no), disease duration (<6 years, 6+ years), disease remission (BASDAI/DAS28) (yes/no), comorbidity (yes/no), concomitant medication (yes/no), and self-injection (yes/no). Only disease remission was shown to have a statistically significant effect on a positive general satisfaction response in the multivariable full model. Patients who were in disease remission at the time of completion of the questionnaire were more likely to have a positive general satisfaction response (OR = 3·25, 95% CI 1·29 – 8·17, full multiple logistic regression model) (Table **S1**). A disease activity score at the time of questionnaire completion was missing for 43% of patients Table **1**, thus the impact of this covariate on patient satisfaction must be interpreted with caution.

3.3. Patient Evaluation of Various Aspects of the Device

The overall patients' response to ease of administration with the SB4 pre-filled pen was positive, 89% of patients (n = 439) reported that the pen was 'simple' or 'very simple' to use Table **3**. Holding the pre-filled pen was rated as 'simple' or 'very simple' by 89% of patients (n = 432). Most patients (82%; n = 402) reported that they were 'satisfied' or 'very satisfied' with the duration of the injection. Most patients (87%; n = 424) reported that they were 'satisfied' or 'very satisfied' with being able to carry out the injection without additional pressing of a button. The majority of patients (91%; n = 445) reported that the acoustic signal (click) was 'clear' or 'very clear'. A 'clear' or 'very clear' indication of completed injection was reported by 429 patients (87%). The surface feeling was rated as 'comfortable' or 'very comfortable' by 375 patients (77%). The weight of the pen was rated as 'comfortable' or 'very comfortable' by 394 patients (82%).

When patients were asked to compare the SB4 pre-filled pen to their previous application system, 340/388 patients (88%) were 'satisfied' or 'very satisfied' with the SB4 pre-filled pen. This response was similar between RA patients (212/240 'satisfied' or 'very satisfied'; 88%) and SpA patients (128/148 patients 'satisfied' or 'very satisfied'; 86%). Among patients who had previously experienced another application system for bDMARDs (another pen, syringe or i.v. infusion), 136/157 (87%) of the patients were 'satisfied' or 'very satisfied'.

Table 3. Personal experience of various aspects of using the SB4 pre-filled pen – by previous treatment and overall (Full Analysis Set).

-	Naïve to bDMARDs	Switch from another pen to SB4 pen	Switch from syringe to SB4 pen	Other bDMARD therapy	Total
-	(N=331)	(N=93)	(N=59)	(N=9)	(N=492)
Aspect	n (missing) (%)	n (missing) (%)	n (missing) (%)	n (missing) (%)	n (missing) (%)
Ease of execution of the injection ('simple' or 'very simple')	296 (89%)	84 (90%)	50 (1) (86%)	9 (100%)	439 (1) (89%)
Holding the pre-filled pen ('simple' or 'very simple')	294 (6) (90%)	84 (90%)	46 (78%)	8 (89%)	432 (6) (89%)
Duration of the injection ('satisfied' or 'very satisfied')	271 (1) (82%)	75 (1) (82%)	48 (2) (84%)	8 (89%)	402 (4) (82%)
Injection without add. pressing of a button ('satisfied' or 'very satisfied')	293 (5) (90%)	75 (1) (82%)	48 (1) (83%)	8 (89%)	424 (7) (87%)
Acoustic signal (click) ('clear' or 'very clear')	303 (2) (92%)	82 (88%)	51 (1) (88%)	9 (100%)	445 (3) (91%)
Indication of completed injection ('clear' or 'very clear')	292 (1) (88%)	78 (84%)	50 (85%)	9 (100%)	429 (1) (87%)
Surface feeling ('comfortable' or 'very comfortable')	259 (2) (79%)	70 (1) (76%)	40 (1) (69%)	6 (67%)	375 (4) (77%)
Weight ('comfortable' or 'very comfortable')	268 (6) (82%)	78 (1) (85%)	42 (3) (75%)	6 (67%)	394 (10) (82%)
Satisfaction in comparison with the previous application system for bDMARDS ('satisfied' or 'very satisfied')	NA	79 (1) (86%)	52 (1) (90%)	5 (2) (71%)	136 (4) (87%)[a]

bDMARD = Biological Disease-Modifying Antirheumatic Drug.

[a] 331 patients naïve to bDMARDs not included in calculations.

Among patients who were naïve to bDMARDs and had previously used a csDMARD injection application, 72/81 (89%) of these patients were 'satisfied' or 'very satisfied'. The positive response varied by previous therapy, 35/43 patients (81%) who had used a pre-filled pen, 32/33 patients (97%) who had used a pre-filled syringe and 5 patients (100%) with injection via syringe.

3.4. Patient Evaluation of Training and Information Material Received

Overall, the majority of patients were trained in the use of the device before they started their therapy; 175 patients (36%) were trained by their physician, 225 patients (46%) were trained by a nurse or site staff, and 11 patients (2%) were trained by physician and nurse or site staff. However, 77 patients (16%) did not receive training and for 4 patients, training data were missing.

The majority of patients who had received training with the pen (n=415) were 'satisfied' or 'very satisfied' (386 patients; 93%) with the injection training that they received with the training pen. The training was rated as 'helpful' or 'very helpful' by the majority of patients (381 patients; 92%). According to the majority of patients (361/409 patients; 88%),

the training provided confidence in the execution of the injection. A small number of patients (2 patients) found that the training was 'not helpful'. The reasons why the training was not helpful were: 'the instruction was too short / not extensive enough' (2 patients), 'the injection with the instruction pen was not executed often enough' (3 patients), 'the injection with the instruction pen was different from the real injection pen' (12 patients), and 'other reasons' (16 patients).

Most patients (468/483; 97%) received the package insert material and rated the material as helpful (402/416 patients; 97%), as understandable (392/405 patients; 97%), and the material's scope was sufficient (396/406 patients; 98%) Table **4**. A quick reference guide for handling was received by 414/469 patients (88%) and most of these patients rated the guide as helpful (371/375 patients; 99%), understandable (361/364 patients; 99%), and of sufficient scope (354/360 patients; 98%). A patient information leaflet was received by 351/472 patients (74%) who also rated the leaflet content as helpful (306/318 patients; 96%), understandable (302/310; 97%), and of sufficient scope (293/305 patients; 96%). Among patients who received a video with handling information for the pre-filled pen, most of these patients rated the video as helpful (78/108 patients, 72%), understandable (79/106 patients; 75%), and of sufficient scope (85/111 patients; 77%).

Table 4. Information material received and patients' ratings (Full Analysis Set).

-	Material received	Rated as 'helpful'	Rated as 'understandable'	Rated as 'of sufficient scope'
-	(N=492)	(N=492)	(N=492)	(N=492)
Material	n (missing) (%)	n (missing) (%)	n (missing) (%)	n (missing) (%)
Package insert material	468 (9) (97%)	402 (76) (97%)	392 (87) (97%)	396 (86) (98%)
Quick reference guide for handling	414 (23) (88%)	371 (117) (99%)	361 (128) (99%)	354 (132) (98%)

(Table 4) cont.....

-	Material received	Rated as 'helpful'	Rated as 'understandable'	Rated as 'of sufficient scope'
-	(N=492)	(N=492)	(N=492)	(N=492)
Material	n (missing) (%)	n (missing) (%)	n (missing) (%)	n (missing) (%)
Information leaflet	351 (20) (74%)	306 (174) (96%)	302 (182) (97%)	293 (187) (96%)
Video with handling information	87 (42) (19%)	78 (384) (72%)	79 (386) (75%)	85 (381) (77%)

3.5. Patients' Approach to Self-injection

Most patients (430; 87%) always gave their injection to themselves, 36 patients (7%) self-injected most of the time, and 26 patients (5%) did not inject themselves. Patients who switched from a pre-filled pen to SB4 pre-filled pen were most likely (86 patients; 92%) to do self-injection. Patients who switched from syringe injection to SB4 pre-filled pen were the least likely (46 patients; 78%) to always do self-injection. Among patients who did not self-inject, family members (34 patients; 81%) were most frequently indicated as giving the patient the injection, followed by site staff (8 patients; 19%) and nurses (4 patients; 10%).

Overall, 241/484 patients (50%) 'disagreed' or 'strongly disagreed' that injections generally made them nervous and 248/483 patients (51%) responded that they 'disagreed' or 'strongly disagreed' that needles generally made them nervous Table **5**. Similarly, 231/481 patients (48%) 'disagreed' or 'strongly disagreed' that to inject oneself was unpleasant. Similar results were observed in the subgroups by previous treatment.

3.6. Safety and Product Complaints

The All Patients Set was used for safety analyses because all patients in this set had received at least one injection with the SB4 pre-filled pen and thus included the 20 patients who had not met the inclusion criterion of at least three months therapy. During the study, 12 patients (2%) in the All Patients Set (N=512) reported an AE (one AE reported per patient). None of the patients had a serious AE, nor did any patient discontinue treatment due to an AE. Eight patients (2%) reported an AE included in the SOC 'general disorders and administration site conditions', this included 7 patients (1%) with 'injection site pain' and 1 patient with 'discomfort' (0·2%). AEs related to 'underdose' of medication were reported by 3 patients (1%) who reported that the indication of fully completed injection was 'unclear'. One patient (0·2%) reported 'nausea' which was judged to be related to SB4.

Few product complaints were reported in the All Patients Set (N=512) Table **6**. 18 patients (4%) reported that the injection procedure was 'difficult' or 'very difficult', 13 patients (3%) reported that the acoustic signal was 'unclear' or 'very unclear', and 19 patients (4%) reported that the indication of a fully completed injection was 'unclear' or 'very unclear'.

4. DISCUSSION

The results from this study indicate that patients using the SB4 pre-filled pen are generally satisfied with it and find it comfortable to use. The majority of patients self-inject, which is a major advantage for self-management of their disease [8]. The patient satisfaction and their comfort in using the SB4 pre-filled pen may contribute positively to adherence to their treatment schedule as well as their self-management. The management of RA and SpA aims to timely treatment of patients with bDMARDs to obtain disease remission. Particularly for patients with moderate to severe disease, the general patient satisfaction and ease of use of the SB4 pre-filled pen may help meet these treatment goals through better patient adherence. The results from this study are generalisable to patients with moderate to severe RA or SpA who are eligible for treatment with bDMARDs since the spectrum of sites from which patients were recruited is representative of private practices treating RA and SpA in Germany.

Table 5. Patients' approach to injections, needles, and self-injection by previous treatment (Full Analysis Set).

-	-	Naïve to bDMARDs	Switch from another pen to SB4 pen	Switch from syringe to SB4 pen	Other bDMARD therapy	Total
Statement	**Response**	(N=331)	(N=93)	(N=59)	(N=9)	(N=492)
Injections make me generally nervous	Missing	7 (-)	1 (-)	..	..	8 (-)
	'strongly disagree'	90 (28%)	35 (38%)	18 (31%)	5 (56%)	148 (31%)
	'disagree'	61 (19%)	17 (18%)	14 (24%)	1 (11%)	93 (19%)
	'neutral'	96 (30%)	24 (26%)	18 (31%)	2 (22%)	140 (29%)
	'agree'	49 (15%)	16 (17%)	5 (8%)	1 (11%)	71 (15%)
	'strongly agree'	28 (9%)	..	4 (7%)	..	32 (7%)
Needles make me generally nervous	Missing	7 (-)	1 (-)	1 (-)	..	9 (-)
	'strongly disagree'	94 (29%)	29 (32%)	21 (36%)	4 (44%)	148 (31%)
	'disagree'	67 (21%)	17 (18%)	15 (26%)	1 (11%)	100 (21%)
	'neutral'	92 (28%)	24 (26%)	13 (22%)	2 (22%)	131 (27%)
	'agree'	46 (14%)	19 (21%)	5 (9%)	2 (22%)	72 (15%)
	'strongly agree'	25 (8%)	3 (3%)	4 (7%)	..	32 (7%)

(Table 5) cont.....

-	-	Naïve to bDMARDs	Switch from another pen to SB4 pen	Switch from syringe to SB4 pen	Other bDMARD therapy	Total
Statement	**Response**	**(N=331)**	**(N=93)**	**(N=59)**	**(N=9)**	**(N=492)**
To inject myself is unpleasant	Missing	8 (-)	1 (-)	2 (-)	..	11 (-)
	'strongly disagree'	82 (25%)	33 (36%)	18 (32%)	3 (33%)	136 (28%)
	'disagree'	64 (20%)	17 (18%)	12 (21%)	2 (22%)	95 (20%)
	'neutral'	94 (29%)	27 (29%)	12 (21%)	1 (11%)	134 (28%)
	'agree'	56 (17%)	12 (13%)	9 (16%)	3 (33%)	80 (17%)
	'strongly agree'	27 (8%)	3 (3%)	6 (11%)	..	36 (7%)

bDMARD = Biological Disease-Modifying Antirheumatic Drug.

Table 6. Product complaints: number and percentage of patients by previous treatment (All Patients Set).

-	-	Naïve to bDMARDs	Switch from another pen to SB4 pen	Switch from syringe to SB4 pen	Other bDMARD therapy	Total
Parameter	**Response**	**(N=348)**	**(N=96)**	**(N=59)**	**(N=9)**	**(N=512)**
Injection procedure	Missing	..	..	1 (-)	..	1 (-)
	'neutral', 'simple' or 'very simple'	334 (96%)	93 (97%)	57 (98%)	9 (100%)	493 (96%)
	'difficult' or 'very difficult'	14 (4%)	3 (3%)	1 (2%)	..	18 (4%)
Acoustic signal	Missing	2 (-)	..	1 (-)	..	3 (-)
	'neutral', 'clear', 'very clear'	334 (97%)	95 (99%)	58 (100%)	9 (100%)	496 (97%)
	'unclear' or 'very unclear'	12 (3%)	1 (1%)	..	..	13 (3%)
Indication of completed injection	Missing	1 (-)	..	..	..	1 (-)
	'neutral', 'clear', 'very clear'	335 (97%)	92 (96%)	56 (95%)	9 (100%)	492 (96%)
	'unclear' or 'very unclear'	12 (3%)	4 (4%)	3 (5%)	..	19 (4%)

bDMARD = Biological Disease-Modifying Antirheumatic Drug.

A limitation of the study is that the data collected from the patient satisfaction questionnaire are cross-sectional and therefore do not provide long-term information on patient satisfaction. However, the study was designed to collect patient satisfaction after at least three months of pen use in order to assure that the respondents had sufficient experience with the SB4 pre-filled pen to be able to evaluate it. The patient satisfaction questionnaire that was used in the study was to be completed by the patient. This allowed for the direct source measurement of satisfaction by collecting the data from the patient and there was no questioning by the physician or nurse that may have biased the patient's response.

Twenty patients were not included in the Full Analysis Set because they did not meet the inclusion requirement of at least three months use of the SB4 pre-filled pen before participation. However, patient questionnaire information was available for these patients and only one patient stopped due to dissatisfaction. The majority of the 20 non-eligible patients were satisfied with the device thus the three-month requirement does not appear to bias the study's results.

CONCLUSION

In conclusion, the results from this study demonstrate a high level of patient general satisfaction with the SB4 pre-filled pen as well as satisfaction with the ease of use of the pre-filled pen for patients who were naïve to bDMARDs or who had previously used bDMARDs.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Ethics Committee of the Department of Medicine, University of Giessen, Germany under approval number AZ 41/17.

HUMAN AND ANIMAL RIGHTS

All research procedures were carried out in accordance with the principles laid in STROBE guidelines.

CONSENT FOR PUBLICATION

Every participating patient had provided signed informed consent according to the regulatory and legal requirements.

AVAILABILITY OF DATA AND MATERIALS

All relevant data are within the manuscript and its supplementary material.

FUNDING

CONFLICT OF INTEREST

Dr. C. Maucksch was an employee of Biogen GmbH during the conduct of the study. Dr. P. M. Aries reports investigator fees from Biogen GmbH during the conduct of the study. Dr. S. Zinke reports investigator fees from Biogen GmbH during the conduct of the study. Prof. Dr. U. Müller-Ladner reports investigator fees from Biogen GmbH during the

conduct of the study and served as speaker and advisor for Biogen outside of this study.

SUPPORTIVE/SUPPLEMENTARY MATERIAL

Supplementary Table S1. Univariate and multivariate results of full multiple logistic regression model - Full Analysis Set.

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