# The course of effect in the first month of biological and JAK inhibitor use in inflammatory arthritis: a real-world interim study using the Experience Sampling Method (EARLY study)

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# Abstract

**Background**: The most common primary symptoms of inflammatory rheumatic diseases like rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA) are joint pain, stiffness, and swelling, which can fluctuate day by day. If traditional treatments, including Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Disease Modifying Antirheumatic Drugs (DMARDs) are ineffective, biologic DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs) are used. Although both bDMARDs and tsDMARDs are proven to be effective, little is known about (differences in) the short-time course of the effects of these treatments, nor about interactions with sex and diagnosis. The use of Experience Sampling Method (ESM), a real-time data collection method originally used in psychology, could be used to capture the immediate effects and adverse drug reactions (ADRs) of treatment with bDMARDs or tsDMARDs.

**Aims:** The primary objective of this interim study is to assess the course of pain, stiffness, and swelling over the initial 31 days of starting with bDMARDs or tsDMARDs in RA, PsA, and SpA patients, considering differences in treatment, sex and diagnosis, using ESM and exploring the patients' compliance with the ESM method and the experienced ADRs as secondary objectives.

**Methods:** ESM was applied via a smartphone application to surveying patients twice a day for 31 days after initiating bDMARD or tsDMARD treatment. The primary outcomes pain, stiffness, and swelling were rated on an 0-10 Numeric Rating Scale (NRS) and ADRs could descriptively be reported. Linear Mixed Models (LMMs) were used to analyze primary outcomes over time. Line graphs were created to visualize the estimated marginal means of each primary outcome. A p-value of $<0.05$ was considered significant. Compliance to ESM was assessed by calculating the response rate, indicating percentage of completed surveys, and the frequency of ADRs and type of ADRs were noted according to Medical Dictionary for Regulatory Activities (MedDRA) terminology.

**Results:** This interim analysis included 23 participants, with per-protocol data from 18 participants analyzed (72.2% female, age 58.6±11.2 years, 77.8% rheumatoid arthritis, 22.2% psoriatic arthritis). Joint pain (b = -0.08, se = 0.02, $p$ = .001), stiffness (b = -0.07, se = 0.02, $p$ = .001), and swelling (b = -0.08, se = 0.02, $p < .001$) significantly decreased over time, with no significant differences in changes between bDMARD vs. tsDMARD treatment, sex, and diagnosis ($p > 0.05$) over time. The median compliance to the ESM surveys was 72.8% (±16.9). The most frequently reported ADRs were nervous system disorders, reported by 5 (38.5%) patients.

**Conclusion:** This interim analysis showed significant reduction of pain, stiffness, and swelling in the initial 31 days of bDMARD and tsDMARD treatment, with no significant differences in treatment, sex and diagnosis. A notably high compliance of 72.8% was found and nervous system disorders emerged as the most frequently reported ADR. While definitive conclusions cannot yet be drawn due to the interim nature, this interim study showed potential in using ESM for detecting significant decreases in pain, stiffness, and swelling.

# 1.Introduction

Rheumatology is the medical specialty concerned with the study, diagnosis and treatment of non-trauma induced complaints of joints, muscles, or bones. Approximately one in nine residents of the Netherlands is estimated to have a form of rheumatism [1]. Rheumatic conditions can be categorized into two primary groups: inflammatory rheumatic diseases and non-inflammatory rheumatic diseases [2]. The various inflammatory rheumatic diseases include rheumatoid arthritis (RA), spondyloarthritis (SpA), and psoriatic arthritis (PsA). RA, the most prevalent peripheral arthritis, is a chronic autoimmune disease characterized by synovitis, leading to inflammation of small joints like hands, wrists, and knees. The most common symptoms of RA are swelling and pain of joints and fatigue [3, 4], with joint pain (88.0%) as the most common reported symptom [5]. SpA encompasses diseases with inflammation in the spine, pelvis, and the large peripheral joints of the limbs [6]. SpA is associated with gene variation HLA-B27, which is one of the genes that controls the immune responses and is hereditarily transferable. SpA can be divided into axial spondyloarthritis (axSpA), mainly affecting the spine, and peripheral spondyloarthritis, primarily involving joints outside the spine [7]. The most common symptoms of SpA are inflammatory back pain, morning stiffness, fatigue and reduced spinal mobility [8]. PsA, a form of peripheral spondyloarthritis, is characterized as asymmetric arthritis, primarily involves inflammation in the large limb joints and is associated with skin psoriasis and musculoskeletal features such as tendinitis, enthesitis and dactylitis [9]. PsA patients often experience painful skin and joint pain [9].

## 1.1 Treatment of RA, SpA, and PsA

Advances in understanding inflammatory arthritis to date have led to diverse effective treatment options. The goal of treatment is to inhibit inflammation, preventing irreversible long-term damage, as well as to improve physical functioning and quality of life [1]. Treatment approaches vary based on the specific condition and follow different guidelines [10]. Common treatments include pain relievers [11] like paracetamol, and Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as ibuprofen and diclofenac [12]. In some cases, corticosteroids like prednisone may be prescribed for rapid anti-inflammatory effects [11]. Disease-Modifying Antirheumatic Drugs (DMARDs) are prescribed early in the disease onset to suppress long-term disease activity and reduce symptoms [11, 13]. Conventional synthetic DMARDs (csDMARDs) like methotrexate (MTX), leflunomide, sulfasalazine and hydroxychloroquine are commonly used

as first-line treatment [14], and their effectiveness has been extensively studied. A review shows that 40% to 50% of patients reach remission or low disease activity (LDA) with an optimal weekly dose of 25mg MTX in combination with glucocorticoids [15]. csDMARDs can be administrated orally or subcutaneously and can be combined with other csDMARDs to increase effectiveness [16].

If csDMARDs, alone or in combination, are insufficient in reducing disease activity, biologic DMARDs (bDMARDs) can be introduced. bDMARDs, like tumor necrosis factor inhibitors (TNFi) or interleukin (IL) inhibitors [17], target specific immune components to reduce inflammation and halt disease progress. TNFi inhibit tumor necrosis factor-alpha, a cytokine promoting inflammation, while IL inhibitors target specific interleukins such as IL-6 and IL-23 [17]. bDMARDs for example adalimumab, a TNFi, effectively manages inflammation in rheumatic diseases [18], with most patients reporting pain improvement after 12 weeks of treatment [19]. When considering administration of bDMARDs, they are administered subcutaneously. Specific IL-6 receptor-targeting bDMARDs, for example sarilumab, show efficacy in reducing symptoms in RA patients with inadequate response to csDMARDs [20]. Previous research has shown that combining bDMARDs with MTX have allowed up to 75% of patients to reach treatment targets over time, after MTX monotherapy alone fails [15]. If bDMARDs are ineffective, tsDMARDs like the Janus Kinase Inhibitor (JAKi) tofacitinib [21], which offers oral administration [17], can be considered [22]. JAKi may lead to more frequent clinical remission as a meta-analysis of 5 studies found that bDMARDs were 14.0% less effective in reducing disease activity in RA compared to JAKi [23]. Additionally, JAKi may provide better short-term efficacy than TNFi [24]. While studies indeed indicate that JAKi work even faster than TNFi [24, 25], the existing literature primarily compares the effectiveness of tsDMARDs and bDMARDs with placebos [26], with limited head-to-head research on their effect differences, especially early in treatment.

In most rheumatic conditions, joint symptoms like pain, stiffness, and swelling are consistently reported as the primary complaints [27] and are often assessed as patient-reported outcomes. A study on RA patients showed that arthritis pain is the top priority for improvement, chosen by 88.0% of the patients [28]. It also showed that after one year of TNFi treatment, pain improvement remained the top priority of patients (71.1%) [28]. While bDMARDs and tsDMARDs effectively reduce symptoms and disease activity at the group level, their effect on symptom relief may vary with clinical factors such as treatment type, sex and diagnosis [29]. A

study by Genovese et al. [30], found significant differences in pain improvement between bDMARD and tsDMARD treatment comparing bDMARD treatment with tsDMARD treatment [30]. Additionally, a study by Albrecht and Strangfeld (2023), investigating gender-specific differences in the treatment of inflammatory rheumatic diseases, showed that women achieved lower remission and treatment response rates to antirheumatic medication compared to men [10]. Moreover, according to Boytsov et al. (2020), RA and PsA are heterogeneous diseases with interindividual differences, leading to varied responses to the same therapy among different diagnosed patients [31].

Notwithstanding their effectiveness, bDMARDs and tsDMARDs may cause various adverse drug reactions (ADRs). According to a study investigating ADRs of bDMARDs, the most common reported serious ADRs are infections (52.9%) for the age group 55-64 years [32]. A meta-analysis of 71 trials revealed that an increase of 40% of serious infections were linked to TNFi use [33]. Particularly concerning is the increased risk of tuberculosis with TNFi treatment, as shown in a meta-analysis [34]. Therefore, screening for latent and active tuberculosis is mandatory before initiating bDMARDs or tsDMARDs in clinical practice [35]. Additionally, patients with cardiovascular risk factors treated with tsDMARDs, particularly JAKi, may have a higher incidence of malignancies. A meta-analysis has shown that one study reported a significant increase in malignancies for patients with cardiovascular risk factors using JAKi compared to those using TNFi, but not placebo or csDMARDs such as MTX [36].

Randomized controlled trials (RCTs) typically assess the effectiveness of bDMARDs or tsDMARDs in reducing symptoms at a limited number of fixed time points over several weeks or months [37, 38]. For this, these trials often rely on retrospective methods such as questionnaires to evaluate pain, stiffness, and swelling progression. This only provides insights into past experiences [39], such as pain experienced in the past week or month and the occurrence of infections after several weeks. While some studies suggest that effects and ADRs already manifest within days or weeks [26, 40], there's limited research on the daily fluctuations of symptoms and ADRs during the first month of treatment. Research on the daily symptom fluctuations and ADRs could provide valuable insights for tailoring treatments to patient needs and increasing overall treatment effectiveness and satisfaction [41].

## 1.2 Experience Sampling Method (ESM)

Because retrospective questionnaires have limitations due to recall bias [39], researchers increasingly turn to intensive longitudinal methods such as the Experience Sampling Method (ESM) [42], commonly used in psychology and behavioral sciences [43, 44]. ESM involves structured diaries completed by patients in their natural environment, capturing real-time feelings and thoughts [45]. One of the most used ways for implementing ESM is through smartphone applications. Given that smartphones are nearly always with us, these devices provide an opportunity to frequently assess momentary experiences and behaviors in the natural environment of patients [46]. The application of ESM in smartphones could also be beneficial in the clinical practice of rheumatology for more precise and accurate measurement of the frequency, fluctuation, and magnitude [42] of primary symptoms like pain, stiffness and swelling of joints, and the potential ADRs during early treatment in RA, SpA, and PsA patients. However, application of ESM in clinical practice also comes with certain barriers, such as the potential burden on participants due to frequent prompts, technical issues with smartphone applications, and the possibility of missing data [47]. Consequently, to test the feasibility of ESM, observing compliance with the intended assessment scheme is often required [48].

Although bDMARDs and tsDMARDs are proven to be effective on inflammatory rheumatic conditions, their precise impact on the course of pain, stiffness, and swelling, and the ADRs experienced by patients in the first month of treatment, remains understudied. This study aims to explore the effects and ADRs experienced by patients by using ESM during the first 31 days after initiating bDMARDs or tsDMARDs, comparing the differences in effectiveness and ADRs between bDMARDs and tsDMARDs. Considering the known association of treatment type, sex and diagnosis with the effect of these medicines, the current interim analysis investigates the effect of these associations on the course of the primary effects.

Therefore, the primary objective of this interim study is to assess the course of pain, stiffness, and swelling over the initial 31 days of starting with bDMARDs or tsDMARDs in RA, SpA, and PsA patients, considering differences in sex, diagnosis, and treatment, using ESM and exploring the compliance to ESM and the number of ADRs as secondary objectives.

# 2. Methods

This monocentric prospective observational study is ongoing at the Rheumatology department of Medisch Spectrum Twente (MST) hospital (Enschede, the Netherlands), from October 2023. In this study, ESM is applied through a mobile health application programmed using the online web application of Avicenna Data (Avicenna) [49]. The study protocol was approved by the BMS ethics committee of University of Twente (UT) under the case number 231279. Ethical approval for the study, with study number K23-42, was waived for the Dutch Medical Research Involving Human Subjects Act (WMO) by the medical research ethical committee of MST Enschede, the Netherlands.

## 2.1 Sample size

For power calculations, the least square means (LSMs) of the variable Worst Joint Pain from the RA-BEAM study were used [50]. The LSM for barticinib treatment on day 28 was 3.9 (95% CI: 3.7 - 4.1), and for adalimumab, it was 4.4 (95% CI: 4.2 - 4.7), resulting in a between-group Cohens d effect size of 0.47. Based on a one-sample t-test with $\alpha = 0,05$, a power of 0.8, and considering a 10% dropout rate, an initial sample size of 113 was determined to investigate the course of the effect of bDMARDs and tsDMARDs and their differences in RA, SpA, and PsA patients.

## 2.2 Study participants

Eligible for inclusion were outpatients diagnosed with RA, SpA, or PsA, starting treatment with, or switching between a TNF-α inhibitor, IL-6 inhibitor, IL-17 inhibitor, IL-23 inhibitor, or JAK inhibitor. Additionally, participants had to be 18 years or older, possess a smartphone, be willing to install Avicenna, and provide signed informed consent. Patients who did not sufficiently speak or understand the Dutch language were excluded. In this interim analysis, all participants were included that had been recruited between October 2023 and May 2024.

## 2.3 Procedure

Eligible patients were informed about the study by their attending rheumatologist during the consultation and received a patient information form. If interested, the researcher explained the study further in a face-to-face session, addressing any queries. Upon the patients' comprehension and agreement, they signed the informed consent. Subsequently, the Avicenna app was installed on their smartphones, and patients completed the baseline questionnaire

within the app. They also filled out three baseline paper questionnaires, which included several patient-reported outcomes measures (PROMs) and baseline characteristics, such as sex, and the DAS-28 score. The entire process took around 30 minutes. Afterwards, patients could obtain their medication from the outpatient pharmacy in line with usual practice, and participation in the study was recorded in their medical file. The 31-day study period commenced with a standard follow-up call after 1 day to address progress and technical issues. Additionally, during the study period, the researcher regularly monitored participants' completion of the questionnaires contacted them by phone if many or more than half of the questionnaires were missed consecutively.

### 2.3.2 ESM protocol

Not all participants immediately started taking the medication after inclusion due to various reasons. Some medications could only be collected from the pharmacy approximately five working days after being requested by the rheumatologist. If a patient was included right after the consultation, they began taking the medication a few days later once it became available by the pharmacy. In addition, participants had to be free from previous rheumatic medication for at least 14 days before starting the new medication. To tract medication initiation, a daily questionnaire (completion time ~ 1 minute) was provided for participants to indicate if they had started the medication. Participants were reminded every evening at 8:00 PM via a notification. Once the patient confirmed starting the medication, this questionnaire was no longer presented.

From the first day onwards, participants received questionnaire twice a day at semi-random time intervals between 10:00 AM and 2:00 PM and between 3:00 PM and 8:00 PM, for the next 30 days. These intervals were chosen because literature suggests that pain and stiffness are most pronounced in the morning [51], indicating that symptom severity might differ between the morning and afternoon. The questionnaire addressed primary outcomes: pain, stiffness, swelling of joints, and medication ADRs. It included items on the current level of joint pain, stiffness, and swelling, measured on a 0-to-10-point Numeric Rating Scale (NRS). It also asked about any ADRs, specifying the ADR and its burden on a 1-to-5 Likert scale, where 1 indicated no burden and 5 indicated very severe burden.

All ESM questionnaires remained available for one hour after notification, allowing participants enough time to complete them while still providing accurate assessments. Participants received a reminder on the penultimate day of the study to submit the final paper

questionnaires. They could choose to discontinue the medication at any time in consultation with their physician, which could be indicated in a continuously available questionnaire in the app. Despite discontinuation, participants were asked to continue completing the questionnaires for the remaining study period.

## 2.4 Outcome measures

This study employed both daily ESM measurements and baseline PROMs. The primary objective was to investigate the progression of pain, stiffness, and swelling in RA, SpA, and PsA patients after the initiation of bDMARDs or tsDMARDs. ESM measurements were conducted using the Avicenna (Ethica) smartphone application. The first measurement on the day of starting the study considered the baseline measurement for each participant. These twice-daily ESM measurements were also used to determine the compliance rate and explore ADRs, addressing the study's secondary objective. To assess the impact of the treatments on patients' functional status and overall health-related quality of life, an additional measurement included baseline Patient Reported Outcome Measures (PROMs), specifically The Dutch Health Assessment Questionnaire and the 36-Item Short Form Health Survey.

### 2.4.1 Baseline questionnaires

The Dutch Health Assessment Questionnaire (HAQ) [52] measures self-reported disability and contains 20 items measuring physical disabilities over the past week. It consists of 8 categories of daily living, dressing and grooming, rising, eating, walking, hygiene, reach, grip, and activities. Each item is scored on a 4-point rating scale from 0 to 3, where 0 indicates 'without any difficulty' and 3 indicates 'unable to do'. The overall score is calculated by summing and averaging the highest item score of each category [53].

The 36-Item Short Form (SF-36) Health Survey [54] is a multidimensional questionnaire that assess eight different aspects of health in the past year: physical functioning (10 items), bodily pain (2 items), social functioning (2 items), mental health (5 items), general health (5 items), vitality (4 items), role physical (4 items), role emotional (3 items) and health change (1 item). The items are rated on Likert-type or frequency response scales, varying from 3 to 6 response categories. The overall score is calculated by linearly transforming the scales scores to range from 0 to 100. The scale scores can be aggregated into two scores: physical component summary (PCS) and a mental component summary (MCS) [55], with the US norm-based

scoring in which the scale and component summary scores have a mean of 50 and standard deviation of 10 [56].

### 2.4.3 Compliance of ESM

ESM compliance is assessed by monitoring the response rate to scheduled ESM-questionnaires to identify patterns of non-compliance which may influence the reliability and validity of the study findings.

## 2.5 Statistical analysis

Analyses were performed using R Studio (version 1.4.1103) and IBM SPSS Statistics (version 29.0.2.0) for the additional SF-36 and HAQ-DI analysis. Baseline demographic characteristics were presented as means with standard deviation (SD) for normally distributed continuous data, medians with interquartile range (IQR) for non-normally distributed continuous data, and proportions for categorical data.

This interim analysis employed a per-protocol analysis based on ESM compliance, including only participants who adhered to the arbitrary rule of thumb for validity of ESM data [57], which indicated that the primary ESM analyses included all data from participants who completed at least 21 out of 62 (1/3) assessments in total. The ESM results were based on the daily average scores for pain, stiffness, and swelling, calculated from the two daily questionnaires.

Given the hierarchical, multi-level structure of ESM data with repeated measurements (level 1), nested within subjects (level 2), linear mixed models (LMM) were employed for the three outcome measures. The NMLE R package with the function lme was used to conduct the LMMs [58]. LMMs can handle missing data on the dependent variable using Restricted Estimation Maximum Likelihood (REML), since each missing value represents only a single observation within an individual [59]. Consequently, the effect of missing data remains relatively small, which is important in ESM studies, as these often experience low response rates due to the substantial demands placed on participants [60]. REML was used due to the small sample size. The mixed models assessed primary outcome scores over time and differences in changes between subgroups categorized by treatment types (bDMARD vs. tsDMARDs), sex (female vs. male) and diagnosis (RA vs. SpA) over time. For comparison purposes, SpA and PsA were

grouped due to their common features [61]. Primary outcomes were the daily average scores for pain, stiffness, and swelling, serving as the dependent variable, with groups, time, and group*time interaction as the independent variables. Individual patients were treated as random effects, with both random intercept and random slope, while group, time, and group*time were treated as fixed effects. To confirm the validity of LMMs, assumptions were checked on the unconditional model, including normality, homoscedasticity, and model accuracy. This was achieved by examining QQ-plots of residuals for normality, plotting residuals versus fitted values to assess homoscedasticity, and comparing predicted values against original observations to evaluate model accuracy [62]. This revealed minimal violations in the assumptions of normality and homoscedasticity. Based on the LMMs, line graphs were created with ggplot2 to visualize the estimated marginal means of each primary outcome throughout the 31-day study period, including the 95% confidence intervals.

To provide a more accurate description of the significance of fixed effects, various covariance structures were explored on the unconditional models. After statistically comparing these models using the Anova.lme test, the first-order autoregressive (AR1) structure was determined to be the best fit and was therefore adopted for all models. This structure assumes that the correlation decreases as the time interval between data points increases. A significance level of $P < 0.05$ was considered statistically significant for the fixed effects.

Compliance to ESM was measured by calculating the response rate, the percentage of completed responses out of the total prompts issued to participants. The frequency and types of ADRs were descriptively analyzed and grouped according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Frequencies with percentages were established by dividing the number of cases reporting the ADR by the total number of cases reporting at least one ADR.

## 3. Results

Out of 23 participants initially included in the study, four participants were excluded due to incomplete participation within the designated study period, and one was excluded for discontinuing the prescribed medication. The final sample therefore consisted of 18 participants, which all completed at least 1/3 of the total number of ESM questionnaires and

where therefore included in further analyses. Because of a high number of missing data on day 31 of the study, it was chosen to examine the course of pain, stiffness, and swelling over a 30-day period. Baseline patient characteristics and PROM scores are shown in Table 1. Most identified as female (72.7%), and most were RA patients (77.8%). The majority received bDMARD treatment (88.9%), the other 11.1% was treated with JAKi. Physical and mental health status scores were more than one and two standard deviations below the general population scores, respectively.

Table 1.

Baseline characteristics and Patient-Reported Outcome Measures (PROMs)

| **Patient characteristics** | N = 18 |
|---|---|
| Age (years), mean (SD) | 58.6 (11.2) |
| Sex (female), n (%) | 13 (72.7) |
| Diagnosis | |
| Rheumatoid arthritis (RA), n (%) | 14 (77.8) |
| Psoriatic arthritis (PsA), n (%) | 4 (22.2) |
| Spondyloarthritis (SpA), n (%) | 0 (0.0) |
| Biologic Disease Modifying Anti Rheumatic Drugs (bDMARDs) | 16 (88.9) |
| Tumor necrosis factor inhibitors (TNFi) | |
| Etanercept, n (%) | 6 (37.5) |
| Adalimumab, n (%) | 6 (37.5) |
| Interleukin (IL)-6 inhibitor | |
| Sarilumab, n (%) | 2 (12.5) |
| Tocilizumab, n (%) | 1 (6.3) |
| Interleukin (IL)-17 inhibitor | |
| Secukinumab, n (%) | 1 (6.3) |
| Janus Kinase Inhibitor (JAKi) | 2 (11.1) |
| Tofacitinib, n (%) | 1 (50.0) |
| Upadacitinib, n (%) | 1 (50.0) |
| Prior non-conventional synthetic DMARD use, n (%)* | 9 (50.0) |
| Disease activity score (DAS)28-CRP, mean (SD) | 3.9 (1.2) |
| **Patient-reported outcomes** | |
| Pain score baseline, mean (SD) | 5.8 (2.3) |
| Stiffness score baseline, mean (SD) | 5.1 (2.3) |
| Swelling score baseline, mean (SD) | 5.0 (2.5) |
| 36 item short Form Health Survey (SF-36), mental component summary (MCS), mean (SD) | 38.1 (12.1) |
| 36 item short Form Health Survey (SF-36) physical component score (PCS), mean (SD) | 33.2 (7.0) |
| Dutch Health Assessment Questionnaire (HAQ), mean (SD) | 1.1 (0.7) |

*Number (%) of patients who have previously used bDMARDs or JAKi.

## 3.1 Daily primary outcomes

To address the primary objective, a total of 12 LMMs were constructed. For each primary outcome, four models were run: one unconditional model and three models for evaluating different conditions. This provides an understanding of the progression of joint pain, stiffness, and swelling over time and differences in outcomes across groups. The reference categorwere set as male for sex, SpA for diagnosis, and JAKi (tsDMARD) for treatment.

### 3.1.1 Daily joint pain over time

Table 2 shows the relation between pain and the days within the study, and the interaction with sex, diagnosis, and treatment. Daily momentary joint pain significantly decreased during the 30-day period (b = -0.08, se = 0.02, $p$ = .001). When considering sex (b = -0.01, se = 0.05, $p$ = .901), treatment (b = 0.02, se = 0.06, $p$ = .777), and diagnosis (b = -0.02, se = 0.05, $p$ = .683) interactions (model 1.1 to model 1.3), no significant effects were found, indicating no significant differences in changes between groups.

Table 2

Estimates of fixed effects with sex, diagnosis, treatment, day, and the interaction as the independent variables, and pain as the dependent variable.

| **Model** | **Parameter** | **Estimate (b)** | **Standardized standard error (se)** | ***T (df)*** | ***p*-value** | **95% CI** | |
|---|---|---|---|---|---|---|---|
| | | | | | | **Lower bound** | **Upper bound** |
| *1: Pain ~ day* | Intercept | 4.98 | 0.55 | 9.11 (464) | .000*** | 3.91 | 6.06 |
| | Day | -0.08 | 0.02 | -4.0 (464) | .001** | -0.12 | -0.08 |
| *1.1 pain ~ day * sex* | Intercept | 5.56 | 0.62 | 8.74 (463) | .000*** | 4.23 | 6.68 |
| | Day | -0.08 | 0.02 | -3.24 (463) | .001** | -0.12 | -0.03 |
| | Sex | -1.70 | 1.18 | -1.43 (16) | .171 | -4.21 | 0.81 |
| | Day * sex | -0.01 | 0.05 | -0.1 (463) | .901 | -0.09 | 0.08 |
| | Intercept | 5.01 | 0.59 | 8.38 (463) | .000*** | 3.83 | 6.18 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| *1.2: pain ~ day * treatment* | Day | -0.08 | 0.02 | -3.78 (463) | .002** | -0.12 | -0.03 |
| | Treatment | -0.21 | 1.80 | -0.12 (16) | .905 | -4.02 | 3.59 |
| | Day * treatment | 0.02 | 0.06 | 0.28 (463) | .777 | -0.11 | 0.14 |
| *1.3: pain ~ day * diagnosis* | Intercept | 4.82 | 0.63 | 7.91 (463) | .000*** | 3.57 | 6.07 |
| | Day | -0.07 | 0.02 | -3.26 (463) | .001** | -0.12 | -0.03 |
| | Diagnosis | 0.73 | 1.34 | 0.54 (16) | .595 | -2.12 | 3.58 |
| | Day * diagnosis | -0.02 | 0.05 | -4.10 (463) | .683 | -0.12 | 0.07 |

Note: *$p$<.05 **$p$<.01*** $p$ <.001

**Error! Reference source not found.** shows a line graph of the mean pain scores in the total sample with confidence interval during the 30-day period. It shows a significant decrease of in total 2.3 point on the 0-10 NRS in the mean daily pain during the first 10 days after the treatment started. After the initial decrease, the mean pain stabilized and shows slight fluctuations, but remains predominantly constant around the mean score that is lower than the starting score

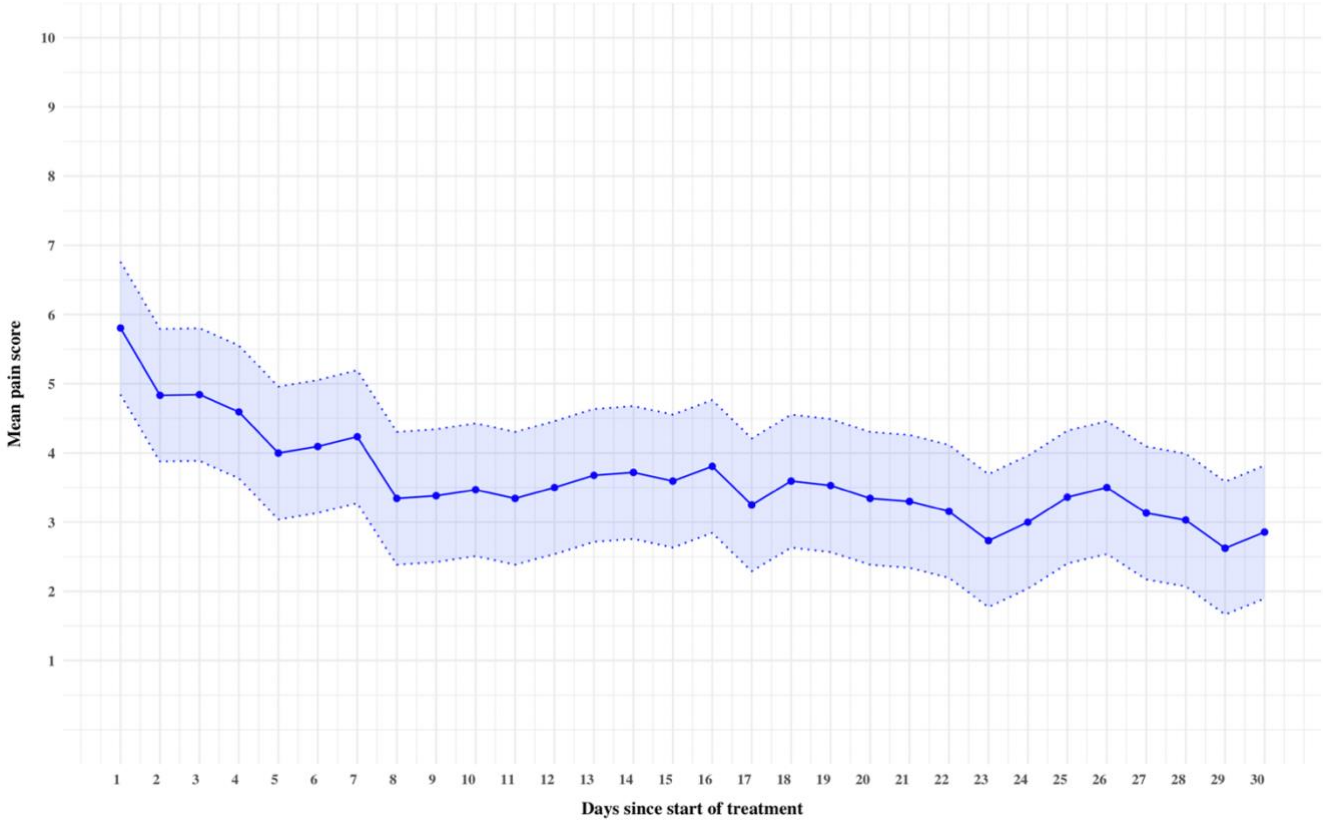


Figure 1

*Line graph of the course of pain throughout the 30-day period.* This figure shows a line graph of the course of the mean pain throughout the 30-day period, based on the estimated marginal means with confidence intervals considered.

Figure 2 visualizes the potential interaction between sex (male vs. female) and the progression of pain over time. Due to the absence of any statistically significant interaction effects, line graphs showing the interaction effects are not illustrated in further analyses. Mean pain score for females remained consistently higher compared to males but tended to reduce in a similar way over the first 30 days. Both groups displayed fluctuations in their mean pain scores; however, the trend for males tended to display fewer fluctuations.

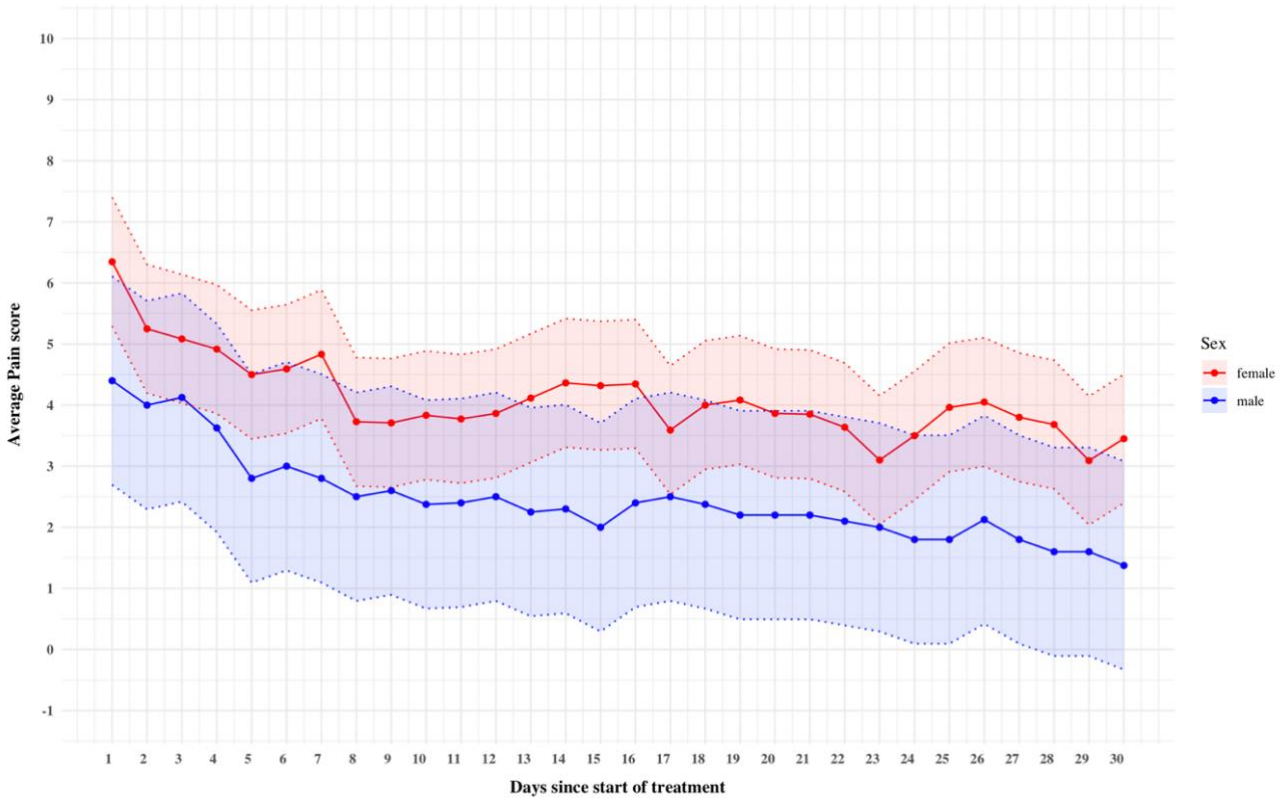


Figure 2

*Line graph of the course of pain throughout the 30-day period, with the interaction of sex.* This figure shows a line graph of the course of pain throughout the 30-day period, with sex as interaction effect. The course of pain for females is displayed in red and the course of pain for males is displayed in blue.

### 3.1.2 Daily joint stiffness over time

Table 3 represents the relation between stiffness and the days within the study, and the interaction with sex, diagnosis, and treatment. It shows a significant decrease in stiffness (b = -0.07, se = 0.02, $p$ = .001) of joints during the 30-day period. No significant interaction was found related to sex (b = -0.03, se = 0.04, $p$ = .497), treatment (b = 0.08, se = 0.06, $p$ = .153), and diagnosis (b = 0.01, se = 0.05, $p$ = .801).

Table 3

Estimates of fixed effects with sex, diagnosis, treatment, day, and the interaction as the independent variables, and stiffness as the dependent variable.

| **Model** | **Parameter** | **Estimate (b)** | **Standardized standard error (se)** | **T (df)** | ***p*-value** | **95% CI** | |
|---|---|---|---|---|---|---|---|
| | | | | | | **Lower bound** | **Upper bound** |
| *2: Stiffness ~ day* | Intercept | 4.41 | 0.47 | 9.33 (464) | .000*** | 3.48 | 5.40 |
| | Day | -0.07 | 0.02 | -3.87 (464) | .001** | -.11 | -.03 |
| *2.1: stiffness ~ day * sex* | Intercept | 4.69 | 0.56 | 8.40 (463) | .000*** | 3.59 | 5.79 |
| | Day | -0.07 | 0.02 | -2.87 (463) | .004** | -.11 | -.02 |
| | Sex | -0.99 | 1.06 | -2.88 (16) | .364 | -3.24 | 1.26 |
| | Day * sex | -0.03 | 0.04 | -0.68 (463) | .497 | -.11 | .05 |
| *2.2: stiffness ~ day * treatment* | Intercept | 4.72 | 0.46 | 10.16 (463) | .000*** | 3.80 | 5.63 |
| | Day | -0.08 | 0.02 | -4.23 (463) | .000*** | -.11 | -.04 |
| | Treatment | -2.75 | 1.40 | -1.97 (16) | .066 | -5.71 | .21 |
| | Day * treatment | 0.08 | 0.06 | 1.43 (463) | .153 | -.03 | .19 |
| *2.3: stiffness ~ day * diagnosis* | Intercept | 4.46 | 0.56 | 8.07 (463) | .000*** | 3.37 | 5.54 |
| | Day | -0.07 | 0.02 | -3.43 (463) | .007** | -.11 | -.03 |
| | Diagnosis | -0.21 | 1.71 | -0.18 (16) | .861 | -2.69 | 2.28 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Day * diagnosis | 0.01 | 0.04 | 0.24 (463) | .801 | -.08 | .10 |

Note: *$p$<.05 **$p$<.01*** $p$ <.001

Figure 3 shows the mean stiffness scores during the 30-day period. It shows a noticeable decrease in mean stiffness during the initial nine days after start with treatment, with a decrease of 2.2 in mean stiffness score. After the initial nine days, the mean stiffness tended to stabilize around 3 on the 0-10 NRS.

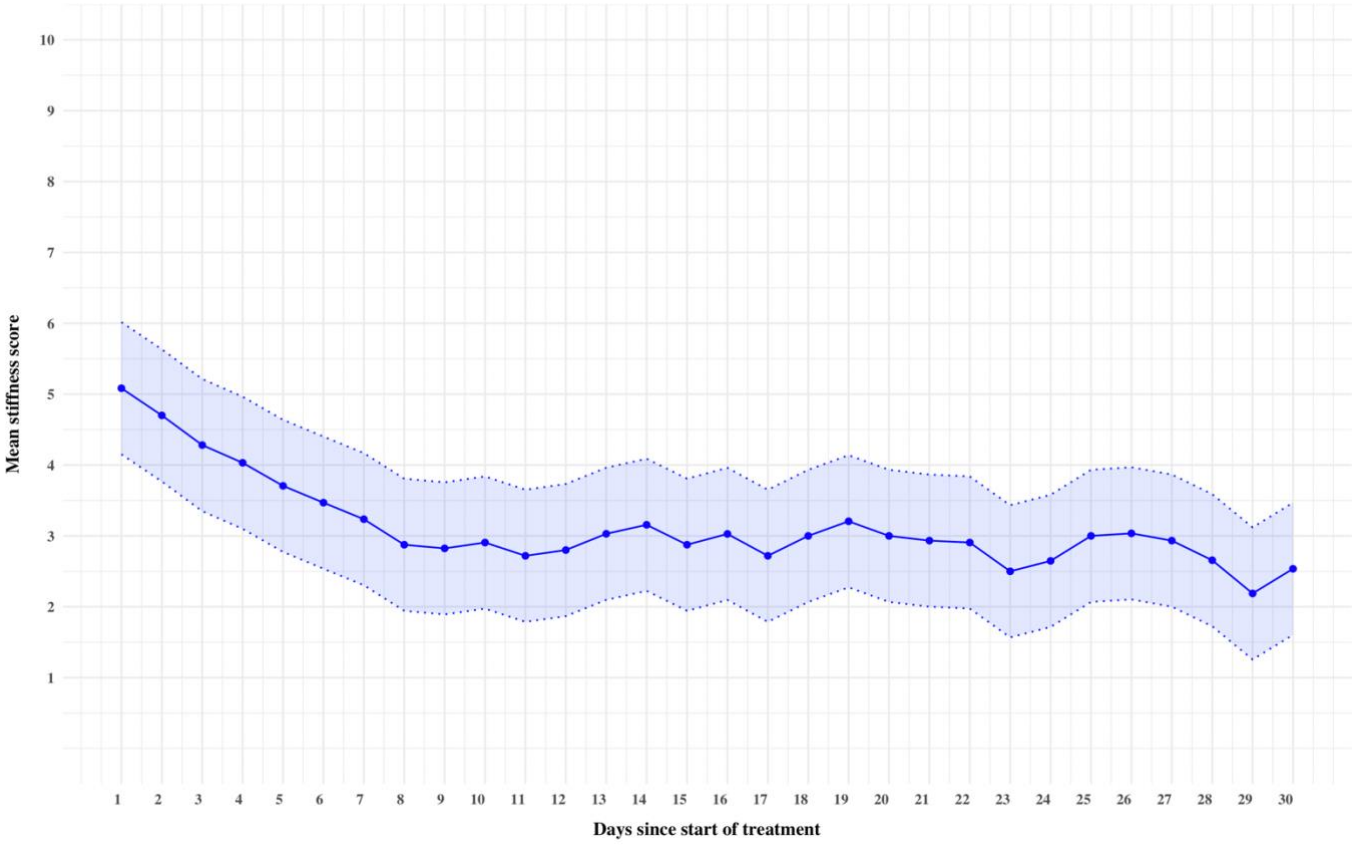


Figure 3

*Line graph of the course of stiffness throughout the 30-day period.* This figure shows a line graph of the course of the mean stiffness throughout the 30-day period, based on the estimated marginal means with considered confidence interval.

### 3.1.3 Daily joint swelling over time

Table 4 shows a notable reduction in self-reported joint swelling over a 30-day period, indicated by a significant decrease (b = -0.08, se = 0.02, p = .000). Additionally, the analysis revealed no significant effects based on sex (b = -0.01, se = 0.04, p = .742), treatment (b = 0.01, se = 0.06, p = .837), or diagnosis (b = -0.06, se = 0.04, p = .162) throughout the study.

Table 4

Estimates of fixed effects with sex, diagnosis, treatment, day, and the interaction as the independent variables, and swelling as the dependent variable.

| | | | | | | 95% CI | |
|---|---|---|---|---|---|---|---|
| **Model** | **Parameter** | **Estimate (b)** | **Standardized standard error (se)** | **T (df)** | ***p*-value** | **Lower bound** | **Upper bound** |
| *3: swelling ~ day* | Intercept | 4.25 | 0.49 | 8.51 (464) | .000*** | 3.27 | 5.23 |
| | Day | -0.08 | 0.02 | -4.57 (464) | .000*** | -.12 | -.04 |
| *3.1: swelling ~ day * sex* | Intercept | 4.43 | 0.59 | 7.39 (463) | .000*** | 3.26 | 5.61 |
| | Day | -0.08 | 0.02 | -3.61 (463) | .003** | -.12 | -.03 |
| | Sex | -0.66 | 1.14 | -0.58 (16) | .570 | -3.07 | 1.75 |
| | Day * sex | -0.01 | 0.04 | -0.33 (463) | .742 | -.10 | .07 |
| *3.2: swelling ~ day * treatment* | Intercept | 4.36 | 0.54 | 8.07 (463) | .000*** | 3.29 | 5.41 |
| | Day | -0.09 | 0.02 | -4.27 (463) | .000*** | -.12 | -.04 |
| | Treatment | -0.97 | 1.62 | -0.59 (16) | .558 | -4.41 | 2.47 |
| | Day * treatment | 0.01 | 0.06 | 0.21 (463) | .837 | -.11 | .13 |
| *3.3: swelling ~ day * diagnosis* | Intercept | 3.94 | 0.56 | 7.04 (463) | .000*** | 2.84 | 5.04 |
| | Day | -0.07 | 0.02 | -3.48 (463) | .001** | -.11 | -.03 |
| | Diagnosis | 1.41 | 1.19 | 1.19 (16) | .252 | -1.10 | 3.93 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Day * diagnosis | -0.06 | 0.04 | -1.40 (463) | .162 | -.15 | .03 |

Note: *$p$<.05 **$p$<.01*** $p$ <.001

Figure 4 illustrates the clear decrease in swelling during the first eight days of treatment, with the mean swelling score decreasing by 2.5. Throughout the remainder of the 30-day period, the mean swelling remained predominantly constant, with a small decrease in the last 4 days of the period.

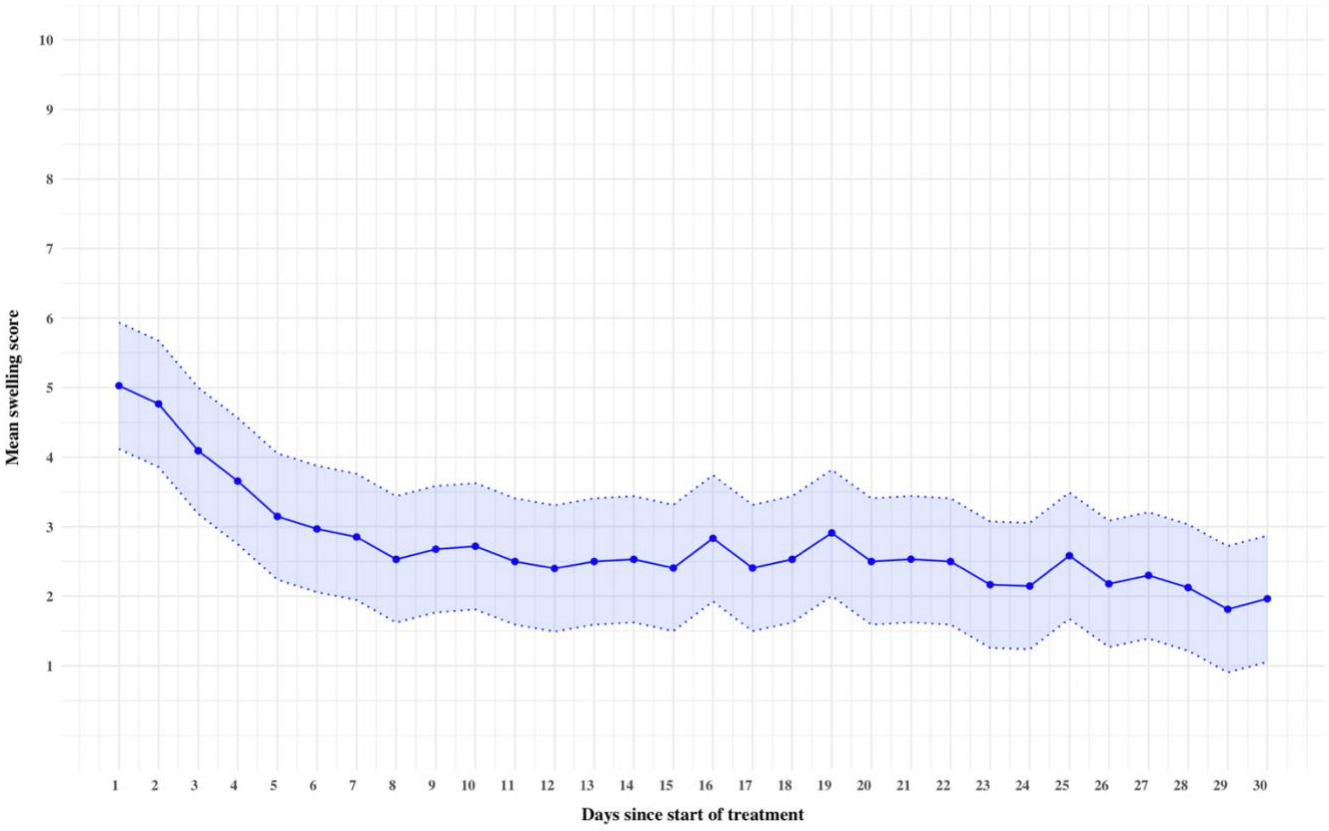


Figure 4

*Line graph of the course of swelling throughout the 30-day period.* This figure shows a line graph of the course of the mean swelling throughout the 30-day period, based on the estimated marginal means with considered confidence interval.

## 3.2 ESM Compliance

Figure 5 visualizes the total compliance to the twice-daily ESM surveys per participant. The mean compliance of the 18 participants included in this report was 72.8% (±16.9). Participants

completed a median of 45.3 of the 62 prompt surveys. Figure 5 shows that most patients filled in at least 50% (n = 13, 72.2%).

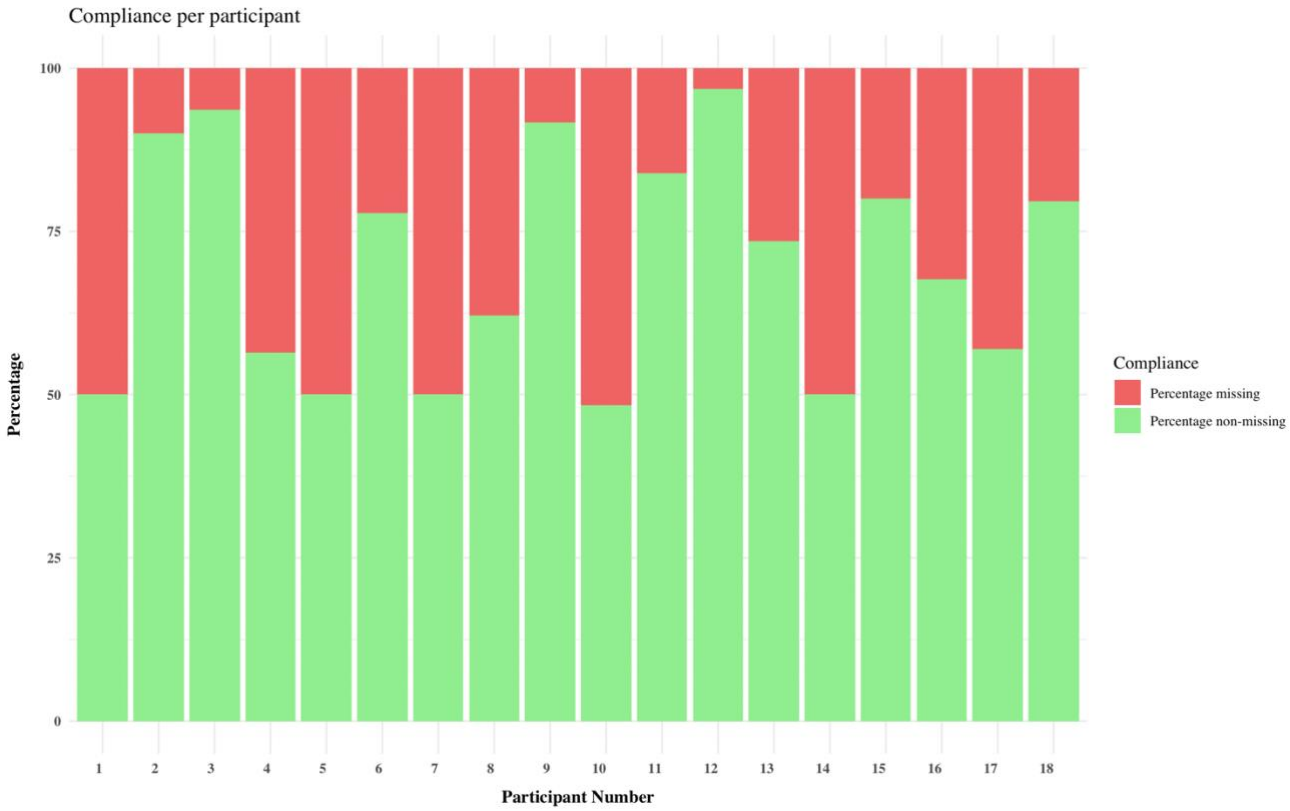


Figure 5

*Compliance per participant.* This figure shows the compliance to Avicenna per participant. Indicating the percentage of missing data and non-missing data.

Figure 6 represents a more detailed heatmap, which visualizes the distribution of missing responses per participant across each day of the study. Substantial variability was observed in compliance among participants. While some participants consistently reported data across most days, others exhibit a varying number of days with one or two missed measurements. There appeared to be no clear pattern or trend in the distribution of missing data over the days, suggesting that missing data may largely occurred at random. The heatmap did reveal a slight increase in missing responses as the study progressed.

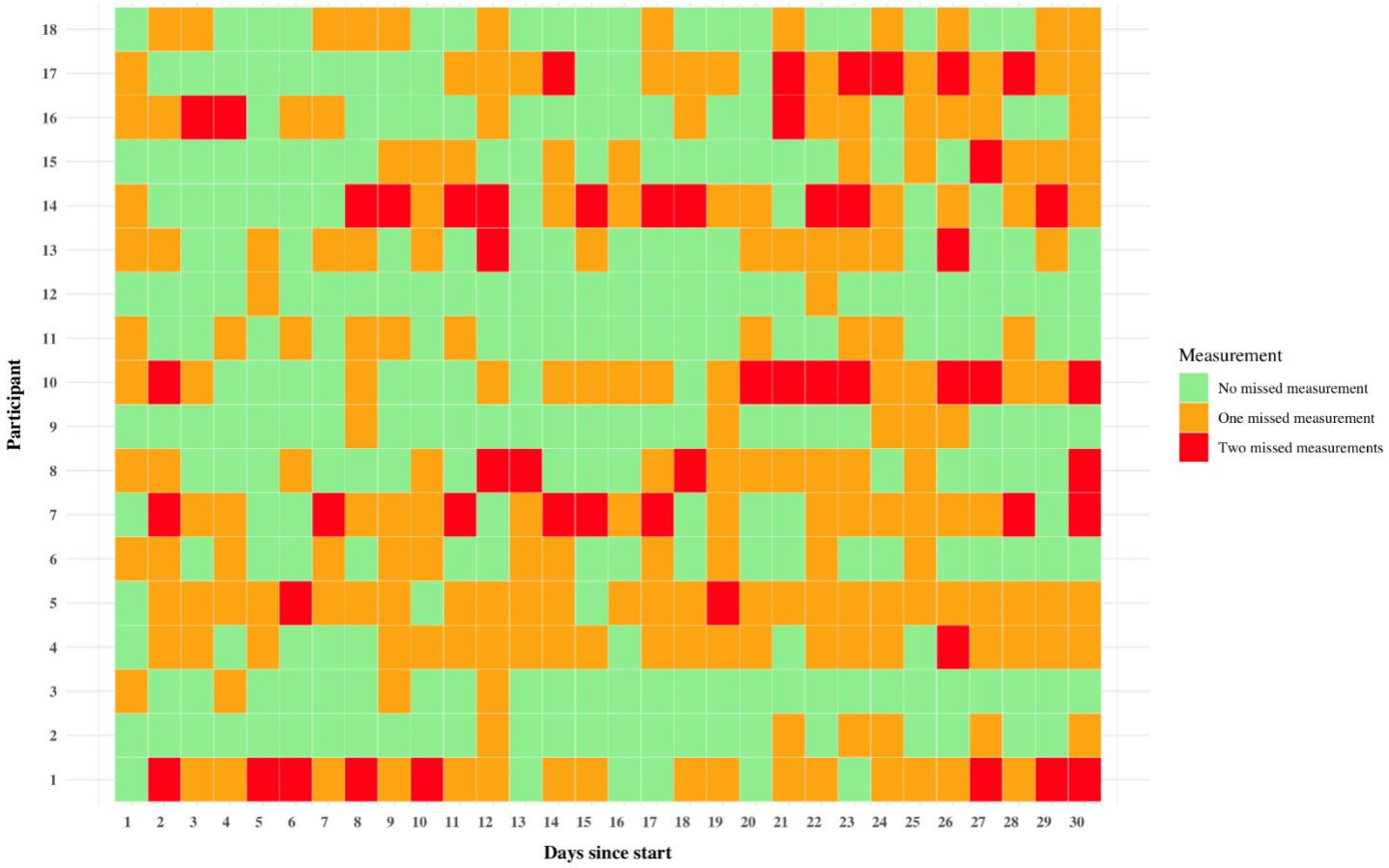


Figure 6

*Heatmap of the distribution of missing data per participant.* This figure shows the distribution of missing data and non-missing data per participant. Indicating the value of missing measurements per day, ranging from no missed measurement to two missed measurements.

Comparison of the number of missing data between the two scheduled measurements each day, did show a noticeable difference in the total number of missing data points. The first measurement session, scheduled between 10am and 2pm had a total of 124 (11.5%) missing responses. The second session had a total of 170 (15.7%) missing responses.

## 3.3 Patient-reported ADRs

In total, 13 participants (72.2%) reported at least one ADR, varying from nervous system disorders to skin and subcutaneous tissue disorders. The frequency and type of these ADRs are presented in Table 5. For a more detailed presentation of the defined subgroups of the ADRs, please refer to Appendix 1.

As shown in Table 5, the most commonly reported ADRs were nervous system disorders (38.5%), including headache and dizziness. This was followed by gastrointestinal disorders, involving symptoms like nausea and diarrhea and musculoskeletal and connective tissue disorders, as arthralgia each reported by 30.8% of participants who reported at least one ADR. General disorders and administration site conditions, as fatigue, and infections and infestations, including cystitis and viral infections were experienced by 23.1% of participants who reported at least one ADR. Lastly, respiratory, thoracic, and mediastinal disorders, and skin and subcutaneous tissue disorders, as cough and rash popular, were reported by 15.4% of participants.

Table 5

Patient-reported ADRs

| **ADRs** | **Number of ADRs (%)** |
|---|---|
| Nervous system disorders | 5 (38.5) |
| Gastrointestinal disorders | 4 (30.8) |
| Musculoskeletal and connective tissue disorders | 4 (30.8) |
| General disorders and administration site conditions | 3 (23.1) |
| Infections and infestations | 3 (23.1) |
| Respiratory, thoracic, and mediastinal disorders | 2 (15.4) |
| Skin and subcutaneous tissue disorders | 2 (15.4) |

## 4. Discussion

This is the first study to examine the course of daily joint pain, swelling and stiffness experienced by RA, SpA and PsA patients over the initial 31 days after starting treatment with bDMARDs or tsDMARDs, using ESM. Secondary objectives included exploring early patient-reported ADRs and compliance with the ESM measurement protocol. Real-time ESM assessment revealed a significant decrease in joint pain, stiffness, and swelling within the first 30 days of treatment with bDMARDs or tsDMARDs. No statistically significant differences in effectiveness were observed between bDMARD vs tsDMARD treatments, sexes or diagnoses. Compliance with the ESM surveys was generally good, with a mean compliance of 72.8%. Nervous system disorders were the most frequently reported ADRs (38.5%). Overall, this interim analysis showed potential in using ESM to detect significant decreases in pain, stiffness, and swelling in RA, SpA and PsA patients during the first 31 days of bDMARD or tsDMARD treatment.

## 4.1 Principal findings

The ESM results showed a significant decrease in self-reported joint pain, swelling, and stiffness over the initial 31 days of treatment. Reductions in pain and swelling appear to be slightly more pronounced than in stiffness, with the most noticeable improvements for all outcomes occurring during the first 10 days after treatment initiation. Following this period, mean pain, stiffness and swelling scores stabilized with slight fluctuations, remaining predominantly constant at lower levels than the starting scores.

The rapid reduction in joint pain and stiffness found in our study aligns with a previous study by Taylor et al. [50] investigating the weekly effect of barticinib (a tsDMARD) versus placebo or adalimumab (a bDMARD) on patient-reported outcomes like joint pain and stiffness. The study showed for both barticinib as adalimumab strong improvements in worst joint pain (WJP) and morning joint stiffness (MJS) as early as week one, with barticinib being more effective in reducing WJP by week two, and more effective in reducing MJS by week four, compared to adalimumab [50]. This suggests that improvements in joint pain and stiffness may occur already within the first weeks of starting tsDMARD or bDMARD treatment. However, the current ESM study's limited sample size, especially for tsDMARD recipients, made it underpowered to detect significant differences between bDMARD and tsDMARD outcomes. In inflammatory rheumatic diseases, the immune system attacks the synovial membrane, causing synovitis and producing inflammatory cytokines like TNF and interleukin, which lead to pain and swelling from synovial fluid accumulation [63]. Since both pain and swelling are positively correlated with joint inflammation [64, 65] and treatment with bDMARDs and tsDMARDs suppresses joint inflammation, both joint pain and swelling tend to improve simultaneously. Based on this knowledge and on Taylor et al. [50] findings, which showed that pain decreased within the first weeks after starting treatment, we anticipated that swelling might also reduce in the initial weeks of bDMARDs or tsDMARDs treatment, as supported by our study.

The above findings demonstrate that bDMARDs and tsDMARDs are quickly effective in reducing patient-reported pain, stiffness, and swelling. Very similar effects are found in a study by van de Laar et al. [66], showing that barticinib and TNFi effectively reduce objective indicators of disease activity, such as DAS28 CRP, within the first weeks of treatment. Given the relationship between disease activity and symptoms like pain, stiffness, and swelling [63], the rapid decreases observed in our study are consistent with these findings.

An additional explanation for the rapid decrease in pain, stiffness, and swelling within the first 31 days of treatment is an ESM limitation noted by Shrout et al. [47], who observed that early ESM responses often show high initial values that then modestly decline and stabilize [47]. In our study, high initial values for pain, stiffness, and swelling, were followed by a decline and stabilization over time. This trend may be partly due to eleven participants who started medication on the first day of inclusion and reported high baseline values. However, since participants were almost equally divided between those who started medication on the first day those who did not, this likely had only a minimal effect on our results.

In our study, reductions of joint pain and swelling appeared slightly stronger than the reduction of stiffness. A previous study by Navarro-Compán et al. (2024), found that median times to initial improvement with tofacitinib were 8 to 10 weeks for joint pain and swelling, and 12 weeks for morning stiffness in SpA patients [67]. The slower reduction in stiffness compared to joint pain and swelling observed in their study may reflect a similar pattern in our study, where stiffness showed a less strong reduction in the first days of treatment. Additionally, while stiffness is a common symptom, it can be influenced by a broader range of factors beyond inflammatory activity, such as age [68] and other conditions like disabilities [69]. Consequently, stiffness may be less directly associated with disease activity compared to pain and joint swelling, which are more directly linked to inflammation [63] .

In the current study, improvements in pain, stiffness, and swelling were noted as early as 10 days after starting treatment with bDMARDs or tsDMARDs. This underscores the potential advantage of using ESM for daily measurements of patient-reported outcomes compared to traditional methods, such as the weekly measurements used in the study by Taylor et al., [50]. ESM provides detailed insights into the daily changes of these primary outcomes.

Three peaks in reported average daily pain, stiffness, and swelling were observed, followed by decreases. These fluctuations might be linked to the administration schedule of bDMARD injections, typically given weekly or bi-weekly [70]. The pattern might suggest that the effects of an injection might wane after one or two weeks, leading to heightened symptom severity, which then decreases after the subsequent injection. It’s important to note that due to the small sample size, interpreting these fluctuations requires caution.

A study by Genovese et al. [30] investigating the effectiveness of tsDMARDs compared to placebo in RA patients refractory to bDMARDs showed a significant difference in pain improvements in the first weeks, favoring the tsDMARD filgotinib [30]. This finding aligns with our study's observation of symptom improvement in the initial days of treatment. However, due to limited sample size, no significant difference between bDMARD and tsDMARD treatments over time was found.

Furthermore, a meta-analysis by Xie et al. [71] found a significant difference in bDMARDs short-term efficacy between male and female SpA patients, with males showing higher ASAS40 response rates [OR 1.89 (95% CI 1.56 – 2.30), $p < .00001$] [71]. It showed that 47.1% of male patients responded to bDMARD treatment compared to 33.5% of female patients, indicating significantly higher short-term efficacy in males. However, our study, being an interim analysis, was underpowered to statistically demonstrate group differences, such as those based on sex, over time.

Although no other study has investigated the differences in the short-term effects of bDMARDs or tsDMARDs on RA versus SpA patients, it is known that RA and SpA differ in pathogenesis and the associated inflammatory processes [72]. Based on this knowledge, we expected RA and SpA patients to react differently to these treatments.

With respect to the feasibility of using ESM in this patient group, the results showed a compliance rate of 72.8% on ESM data, with an average of 45 (out of 60) prompts answered per participant. This percentage was calculated for all patients who adhered to the per-protocol nature of the study, completing at least one-third of the surveys. The compliance rate falls within the average of 70%-80% in ESM studies, as reported by Fritz et al. in their guidelines [73]. A compliance rate of 72.8% suggests that the participants in our study were sufficiently adherent to the study protocol, indicating that ESM is a feasible method for data collection in this patient population.

Furthermore, missing responses appeared random, with slightly more missing responses in the second survey of the day and a slight increase as the study progressed. The slightly higher incidence of non-responses in the second survey may be due to it coinciding with dinner or evening activities. When one of the questionnaires was missed, the average score was calculated from the completed one. The more frequent missing responses in the second survey might have

led to an overestimation of stiffness, which is typically worse in the morning. The increase in missing responses over time might be due to patient fatigue or diminishing interest. potentially explaining the greater fluctuations in daily pain, stiffness, and swelling scores from day 20 onward. With fewer responses, each individual response had a greater impact on the average scores, potentially leading to underestimation or overestimation of these symptoms.

ADRs were reported by 72.2% of the participants. Nervous system disorders, including headache and dizziness, were the most frequently reported by patients who reported at least one adverse drug reaction, affecting five participants (38.5%). This was followed by gastrointestinal disorders, such as nausea and diarrhoea and musculoskeletal and connective tissue disorders, like as arthralgia, each reported by 30.8% of participants who reported at least one ADR. These findings align with a previous study exploring short-term patient-reported ADRs to filgotinib, which found that nasopharyngitis, headache, and nausea were most commonly reported [30].

In our study, 23.1% of participants experiencing ADRs reported infections and infestations as cystitis, sinusitis, and viral infections. These were less serious infections compared to those investigated and reported in other studies [32, 74]. Although patient reported ADRs are not validated as actual ADRs, the application of ESM appears to be a good approach for documenting less serious infections and infestations. Based on this information, it can be hypothesized that the patient-reported ADRs have a temporal relationship with the time.

## 4.2 Strengths

To our knowledge, no other study has studied the course of joint pain, stiffness, and swelling and ADRs within 31 days of starting bDMARDs or tsDMARDs treatment in RA, SpA and PsA patients, using ESM. The application of ESM in clinical effect studies and rheumatology is still in its early stages and has not previously been used to capture the course of short-term effects of treatment. Therefore, our study provides valuable information for current practice and future implementation of ESM in rheumatology.

Joint pain, stiffness, and swelling are subjective experiences that can constantly fluctuate. One of the most important strengths of using ESM in our study is the ability to capture these fluctuations through frequent, repeated measurements. This approach is particularly beneficial give the day-to-day variability in these symptoms. ESM provides a more accurate estimation of

the daily course of pain, stiffness, and swelling compared to retrospective methods by recording real-time data on the effects of these treatment and their fluctuations. This reduces recall bias by gathering information daily [39], enhancing the reliability and validity of the results.

Another strength of this study is the use of LMM to analyze and test the significance of changes in the primary outcomes over time, as we were interested in daily changes and fluctuations of pain, stiffness and swelling over time. This statistical approach is well-suited for the hierarchical and nested structure of the data used in our study. Additionally, LMMs effectively handle instances of missing responses [59], allowing for the inclusion of all available data without needing to exclude cases where data on key outcomes were missing. Despite LMMs' efficient handling of missing responses, a per-protocol analysis was preferred to guarantee high compliance and maximize the assessment of treatment effects independently of LMMs. High participant compliance, combined with the robustness of LMMs, ensured that any missing data due to non-compliance did not distort the primary outcomes.

The high average compliance rate and random missingness are additional strengths of this study. High compliance ensures that the collected data is more representative of participants' actual experiences. Random missing data minimizes the likelihood of systematic errors, increasing the internal validity of our findings [75]. The missing data could be explained as missing at random (MAR) rather than missing completely at random (MCAR), as it may be related to observable variables such as the time of day the survey was administered [76]. This reduces the likelihood of bias, ensuring a more accurate representation of the study population and high validity of our results [75].

Lastly, given the ESM questionnaire is available as a smartphone application, a potential barrier is that the compliance might be hindered by technical issues. However, this concern was addressed by checking for technical issues with patients the first day after inclusion and during the overall study period. Only one participant experienced technical issues, resulting in a minimal number of missed questionnaires. Given the large number of total ESM questionnaires collected, this minor discrepancy is unlikely to have significantly impacted the overall compliance rate or the principal findings related to the course of pain, stiffness, and swelling

## 4.3 Limitations and recommendations for further research

This study has several limitations. Firstly, due to the interim nature of this study, the sample was underpowered, especially for the subgroup comparisons. The current analysis was based on the data from the first 18 patients, following the per-protocol analysis, recruited from the ongoing full study targeting a sample size of 113 patients. Therefore, this interim study is underpowered to make definitive conclusions. Additionally, the final sample might not be representative for overall RA, SpA, or PsA population due to the small and unequal sample sizes, restricting the generalizability of results. While sufficient data was gathered to statistically demonstrate changes in pain, stiffness, and swelling over time in the total sample, there was not enough power to statistically test differences in these changes over time in the subgroups. Future research is needed with a larger sample size and more equal group sizes to achieve sufficient statistical power for definitive conclusions.

Secondly, the frequent measurements, as well as the strict time windows might be burdensome for patients [47]. Despite the high compliance observed in our study, it must be considered that patients could possibly have experienced the participation of this study as a burden. To gain deeper insights into the participants' experiences regarding the study procedures, interviews will be conducted and analyzed as an integral part of the overall study.

Lastly, it is important to note that 50% of the participants in our study where previously treated with bDMARDs or tsDMARDs. Previous studies have shown that effectiveness of a first bDMARD is greater than with of a second bDMARD in patients with RA and PsA [77, 78]. Although these studies investigated long-term use, it might be expected that bDMARD or tsDMARD treatment is less effective in reducing pain, stiffness and swelling in patients with prior bDMARD or tsDMARD treatment compared to bDMARD or tsDMARDs-naïve patients. Patients previously treated with one or more bDMARDs or tsDMARDs often have a longer disease duration and more severe rheumatoid arthritis. This is evidenced by a previous study that showed that, in their study population, patients with prior bDMARD failure significantly differed from bDMARD-naïve patients, exhibiting more erosive changes, longer disease duration, and more severe symptoms [79]. Further research should investigate whether baseline characteristics, including the severity of symptoms such as pain, stiffness, and swelling, significantly differ between these groups. If such differences are found, they should be considered when interpreting the results.

# 5. Conclusion

In conclusion, the current study investigated the effect of bDMARDs and tsDMARDs on the course of pain, stiffness, and swelling of joints in RA, SpA, and PsA patients during the initial 30 days of treatment using ESM. The secondary objective was to explore patient-reported ADRs and compliance with ESM. Due to the interim nature of the study, no firm conclusion can be drawn about the short-term effects of bDMARDs and tsDMARDs on joint symptoms in these patients. However, ESM showed potential for detecting significant decreases in pain, stiffness and swelling in the initial 30 days of treatment, considering day-to-day symptom variability. The observed compliance rate (72.8%) was high and in line with average compliance rates in ESM studies. Among the adverse drug reactions, nervous system disorders were the most frequently reported occurring in 38.5% of cases, as aligns with previous literature. A temporal relationship between the patient-reported ADRs and the treatment period was hypothesized. Future research with a larger sample size is needed to confirm these findings and further evaluate the short-term effects of bDMARDs and tsDMARDs on joint symptoms in RA, SpA, and PsA patients.

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# Appendix

## Appendix 1

This table gives a detailed overview of the patient-reported adverse drug reactions. A total of 13 out of 18 patients (72.2%) reported at least one adverse drug reaction (ADR) over the 30-day study period. The grouping of the ADRs were conform the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The table should be interpreted as follows: out of the 13 patients who reported at least one ADR, five of these patients reported experiencing the ADR of headache at least once.

| **Adverse drug reaction** | **N = 13** |
|---|---|
| Nervous system disorders | |
| Headache | 5 |
| Dizziness | 2 |
| Disturbance in attention | 1 |
| Gastrointestinal disorders | |
| Nausea | 4 |
| Diarrhoea | 3 |
| Abdominal pain | 1 |
| Musculoskeletal and connective tissue disorders | |
| Arthralgia | 4 |
| Back pain | 1 |

| | |
|---|---|
| General disorders and administration site conditions | |
| Fatigue | 3 |
| Infections and infestations | |
| Cystitis | 3 |
| Sinusitis | 2 |
| Viral infections | 2 |
| Skin and subcutaneous tissue disorders | |
| Rash popular | 2 |
| Psoriasis | 1 |
| Pruritus | 1 |
| Alopecia | 1 |
| Respiratory, thoracic, and mediastinal disorders | |
| Cough | 2 |