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ORIGINAL ARTICLE

# Safety and efficacy of switching from adalimumab to sarilumab in patients with rheumatoid arthritis in the ongoing MONARCH open-label extension

Gerd R Burmester ,[1] Vibeke Strand,[2] Andrea Rubbert-Roth,[3] Howard Amital,[4] Tatiana Raskina,[5] Antonio Gómez-Centeno,[6] Claudia Pena-Rossi,[7] Leon Gervitz,[8] Karthinathan Thangavelu,[9] Gregory St John,[10] Susan Boklage,[10] Mark C Genovese [11]

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For numbered affiliations see end of article.

**Correspondence to**
Dr Gerd R Burmester;
gerd.burmester@charite.de

## ABSTRACT

**Objective** Evaluate open-label sarilumab monotherapy in patients with rheumatoid arthritis switching from adalimumab monotherapy in MONARCH (NCT02332590); assess long-term safety and efficacy in patients continuing sarilumab during open-label extension (OLE).

**Methods** During the 48-week OLE, patients received sarilumab 200 mg subcutaneously once every 2 weeks. Safety (March 2017 cut-off) and efficacy, including patient-reported outcomes, were evaluated.

**Results** In the double-blind phase, patients receiving sarilumab or adalimumab monotherapy showed meaningful improvements in disease activity; sarilumab was superior to adalimumab for improving signs, symptoms and physical function. Overall, 320/369 patients completing the 24-week double-blind phase entered OLE (155 switched from adalimumab; 165 continued sarilumab). Sarilumab safety profile was consistent with previous reports. Treatment-emergent adverse events were similar between groups; no unexpected safety signals emerged in the first 10 weeks postswitch. Among switch patients, improvement in disease activity was evident at OLE week 12: 47.1%/34.8% had changes ≥1.2 in Disease Activity Score (28 joints) (DAS28)-erythrocyte sedimentation rate/DAS28-C-reactive protein. In switch patients achieving low disease activity (LDA: Clinical Disease Activity Index (CDAI) ≤10; Simplified Disease Activity Index (SDAI) ≤11) by OLE week 24, 70.7%/69.5% sustained CDAI/SDAI LDA at both OLE weeks 36 and 48. Proportions of switch patients achieving CDAI ≤2.8 and SDAI ≤3.3 by OLE week 24 increased through OLE week 48. Improvements postswitch approached continuation-group values, including scores ≥normative values.

**Conclusions** During this OLE, there were no unexpected safety issues in patients switching from adalimumab to sarilumab monotherapy, and disease activity improved in many patients. Patients continuing sarilumab reported safety consistent with prolonged use and had sustained benefit.

## Key messages

### What is already known about this subject?

- In the 24-week phase III MONARCH study (NCT02332590), both sarilumab 200 mg every 2 weeks and adalimumab 40 mg every 2 weeks were associated with a meaningful improvement in disease activity in adult patients with rheumatoid arthritis (RA) who were intolerant of, or inadequate responders to, methotrexate (MTX) or who were deemed inappropriate for MTX treatment. Sarilumab monotherapy demonstrated superiority to adalimumab monotherapy for improving RA signs and symptoms and physical function.

### What does this study add?

- Findings from this open-label extension (OLE) study support the long-term safety and efficacy of sarilumab in patients who continued sarilumab from double-blind through OLE for a total of 72 weeks. Safety profile and incidence of treatment-emergent adverse events were similar for patients who switched from adalimumab to sarilumab on entry into the OLE versus patients who continued on sarilumab.
- Patients switching from adalimumab to sarilumab achieved additional clinically meaningful improvements in disease activity and in patient-reported outcomes in the OLE, primarily within 12 weeks of switching. These improvements approached levels of improvement observed in patients who continued sarilumab after completing the double-blind phase.

## INTRODUCTION

Rheumatoid arthritis (RA) is a debilitating, chronic condition requiring early treatment with disease-modifying antirheumatic drugs (DMARDs) to provide symptom

## Key messages

### How might this impact on clinical practice or future developments?

- Treatment guidelines endorse a 'treat-to-target' approach to RA management, aiming for sustained remission or low disease activity. Sustained clinical improvement following the switch from adalimumab to sarilumab provides support for therapy switching as a management option for select patients.
- These data may help optimise treatment approaches in RA requiring not only proactive, early identification of suboptimal disease control but also a collaborative goal-setting approach between rheumatologists and patients in deciding when potential changes in therapy, including the use of biological disease-modifying antirheumatic drug monotherapy, may be warranted.

relief, reduce disease activity and slow progression, as well as improve health-related quality of life (HRQoL).[1 2] Although treatment guidelines recommend the addition of biological or targeted synthetic DMARDs (b/tsDMARD) following inadequate responses to initial conventional synthetic DMARDs (csDMARDs), registry data suggest that at least one third of patients use bDMARDs as monotherapy.[3–6] Driving factors for b/tsDMARD monotherapy include poor adherence and intolerance/contraindications to methotrexate (MTX) or other csDMARDs.[7 8]

Expansion of therapeutic options in RA has increased the need to better understand comparative safety and efficacy among bDMARDs, particularly in head-to-head randomised controlled trials (RCTs). Such trials present opportunities to evaluate patient-reported outcomes (PROs) for safety and efficacy during open-label extension (OLE) periods, during which patients previously randomised to an active comparator are switched to the bDMARD being investigated. Switching to a bDMARD with a different mechanism of action offers an option for patients who do not achieve target responses with first-line treatment, as well as for patients unsuited to csDMARD therapy.[1 2]

The efficacy and tolerability of sarilumab administered subcutaneously as monotherapy and in combination with csDMARDs have been demonstrated in phase III trials in adults with RA.[9–14] In the 24-week RCT, MONARCH (NCT02332590), monotherapy with sarilumab was superior to adalimumab at reducing disease activity and improving signs and symptoms of RA, as well as improving physical function and several PROs: Health Assessment Questionnaire-Disability Index (HAQ-DI), Medical Outcomes Study Short-Form (36-item) Health Survey (SF-36) physical component summary (PCS) and four of eight domains, patient global assessment of disease activity (PtGA) by visual analogue scale (VAS) and pain VAS.[9 12] The objective of this paper is to understand and report the safety and efficacy of monotherapy with open-label sarilumab for up to 48 weeks in the ongoing MONARCH OLE among patients who switched to sarilumab from adalimumab, and in those who continued sarilumab, at the completion of the double-blind phase (DBP).

## MATERIALS AND METHODS

### Study design and patient population

The methodology and results of the 24-week, phase III superiority RCT have been published previously.[9 12] Briefly, adult patients (aged ≥18 years) with active RA who were intolerant of, or inadequate responders to, MTX or who were deemed inappropriate for MTX treatment, were eligible for inclusion. Patients were randomised to sarilumab 200 mg plus placebo every 2 weeks or adalimumab 40 mg plus placebo every 2 weeks, administered subcutaneously for 24 weeks. After 16 weeks, dose escalation to weekly administration of adalimumab or matching placebo was permitted for patients who failed to achieve ≥20% improvement in tender or swollen joint counts.

Patients who completed the 24-week DBP in the head-to-head trial were eligible to enter the OLE phase, during which patients who had been randomised to adalimumab were switched to open-label sarilumab 200 mg (switch group), and patients who had been randomised to sarilumab 200 mg every 2 weeks continued treatment at this dosage (continuation group). The last visit of the DBP was the first visit (baseline) of the OLE. Per protocol, patients could reduce their dosage to sarilumab 150 mg every 2 weeks to manage laboratory abnormalities or per investigator's discretion, or could withdraw from the OLE at any time, for any reason, or per investigator's discretion. All patients who withdrew from treatment were asked to complete an early discontinuation visit 6 weeks afterwards.

Each patient gave written informed consent before study participation. The study was conducted in compliance with institutional review board regulations, the International Conference on Harmonisation Guidelines for Good Clinical Practice and the Declaration of Helsinki.

### Patient and public involvement

The clinical trial was recorded on public registry websites prior to the enrolment of the first patient. This research was done without patient consultation. At the time this study was conducted, there were no funds or time allocated for patient/public involvement in study design or result-dissemination planning.

### Safety

Safety data were reported for all patients in the OLE as of March 2017. Safety assessments included incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and laboratory measures. Adverse events (AEs) were described by the Medical Dictionary for Regulatory Activities (V.18.1) preferred term; AEs of special interest (AESIs) were identified using prespecified search criteria. Sarilumab was to be temporarily or permanently discontinued in cases of opportunistic infections (eg, tuberculosis), symptoms of hypersensitivity, severe

neurological disease, acute renal failure, pregnancy or significant laboratory abnormalities (eg, neutropenia, thrombocytopenia or increased alanine aminotransferase (ALT) levels), as previously described.[9]

### Efficacy endpoints

Efficacy data were reported complete through OLE week 48. Efficacy endpoints included the proportion of switch patients achieving the following through week 48 in the OLE: Disease Activity Score (28 joints; DAS28) ≥minimally important difference (MID) for DAS28-erythrocyte sedimentation rate (ESR) ≥1.2 change from OLE entry and DAS28-C-reactive protein (CRP) ≥1.2 change from OLE entry; Clinical Disease Activity Index (CDAI) ≤2.8 (remission) and ≤10 (low disease activity (LDA)); Simplified Disease Activity Index (SDAI) ≤3.3 (remission) and ≤11 (LDA); American College of Rheumatology 20%/50%/70% (ACR20/50/70) response and improvement of HAQ-DI ≥0.22 units from baseline. Change from OLE at baseline to OLE at week 48 in DAS28-ESR, DAS28-CRP, CDAI, SDAI and HAQ-DI was also evaluated.

PROs included PtGA VAS; pain VAS; Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F); SF-36 PCS and mental component summary (MCS) and domain scores; EuroQol 5-Dimensions questionnaire (EQ-5D) VAS and EQ-5D single-index utility; Rheumatoid Arthritis Impact of Disease (RAID) and morning stiffness VAS. Details of each PRO assessed in the DBP, including minimally clinically important differences (MCIDs) and scores ≥normative values, have been reported previously.[12] PROs were assessed at OLE baseline and OLE week 24; PtGA and pain VAS were also assessed at week 48. Patients reporting scores ≥normative values for the US general population in HAQ-DI (≤0.25),[15] FACIT-F (≥40.1),[16] SF-36 PCS and MCS (≥50) and for each of the SF-36 domains were also assessed.

### Statistical analysis

Safety data were reported for the OLE period, the baseline of which coincided with week 24 of the DBP. Efficacy results were reported for the OLE period and, for select endpoints, for both DBP and OLE periods. Responder rates were reported using frequency and percentages for the full intent-to-treat (ITT) population, counting patients with missing data as nonresponders. Continuous efficacy outcomes were reported as observed cases (without imputation of missing data) using means (±SE) at each visit or as least-squares mean changes from mixed models for repeated measures. Data collected after discontinuation from treatment were excluded from analyses of continuous data.

## RESULTS

### Patient population and exposure

Of 369 patients who enrolled in the RCT, 321 completed the DBP and 320 (87%) entered the OLE. Patients either switched from adalimumab 40 mg every 2 weeks to sarilumab 200 mg every 2 weeks (switch group, n=155) or continued sarilumab (continuation group, n=165; figure 1).

Characteristics of the OLE patient population at entry to the DBP, including age, weight and disease severity, were similar between switch and continuation groups; overall mean age was 51.6 years, and the majority (>80%) were female (table 1). Mean time since RA diagnosis was 6.7 years in the switch group and 8.2 years in the continuation group; both groups had moderate-to-high baseline disease activity.

At the time of data cut-off, 46/320 (14%) patients had discontinued the OLE before week 48 (72 weeks since DBP randomisation). Proportions of discontinued patients were similar in the switch (24/155, 15%) and continuation (22/165, 13%) groups; the most common reason for discontinuation (20/46, 43%) being AEs (figure 1).

### Safety

Safety findings reported for the OLE period were based on 165.7 and 182.4 patient-years (PY) of exposure in switch and continuation groups, respectively. AEs, SAEs, AESIs and laboratory abnormalities reported in the OLE were consistent with those previously reported in the DBP.[9] AEs, SAEs and AESIs that occurred within 70 days (≈5.5 drug half-lives) postswitch were also reported.

### AEs (serious and non-serious) and AESIs

The overall incidence and exposure-adjusted rates of TEAEs were 76.1%, and 267.4 events/100 PY, respectively, in the switch group and 70.9% and 230.2 events/100 PY, respectively, in the continuation group (table 2). The proportion of patients with TEAEs occurring within 70 days postswitch was 42.6% and 420.5 events/100 PY in the switch group and 38.2% and 386.4 events/100 PY in the continuation group (online supplementary table 1). During the OLE, the most common AESIs were infection (switch: 41.9%, 66.4/100 PY; continuation: 35.8%, 53.2/100 PY), neutropenia (switch: 13.5%, 27.8/100 PY; continuation: 12.7%, 28.5/100 PY) and injection-site reactions (switch: 9.0%, 39.8/100 PY; continuation: 10.3%, 55.4/100 PY), including erythema (table 2). There were no reports of gastrointestinal (GI) ulcerations or perforations in either group.

TEAEs leading to treatment discontinuation during the OLE were similar between the switch (n=10, 6.5%) and continuation (n=12; 7.3%) groups (table 2). The most common reasons for discontinuation were infection (n=2 in both groups; 1.3% and 1.2% in switch versus continuation groups, respectively), neoplasms (switch group, n=2; 1.3%) and blood and lymphatic system disorders (switch group, n=1; 0.6%, continuation group, n=2; 1.2%). As of March 2017, three deaths had been reported: two in the switch (1.2/100 PY) group and one in the continuation (0.5/100 PY) group. In the switch group, one death was due to malignancy and the other due to a cerebrovascular accident. The death in the continuation group was due to a subarachnoid haemorrhage. None of the deaths were considered treatment related.

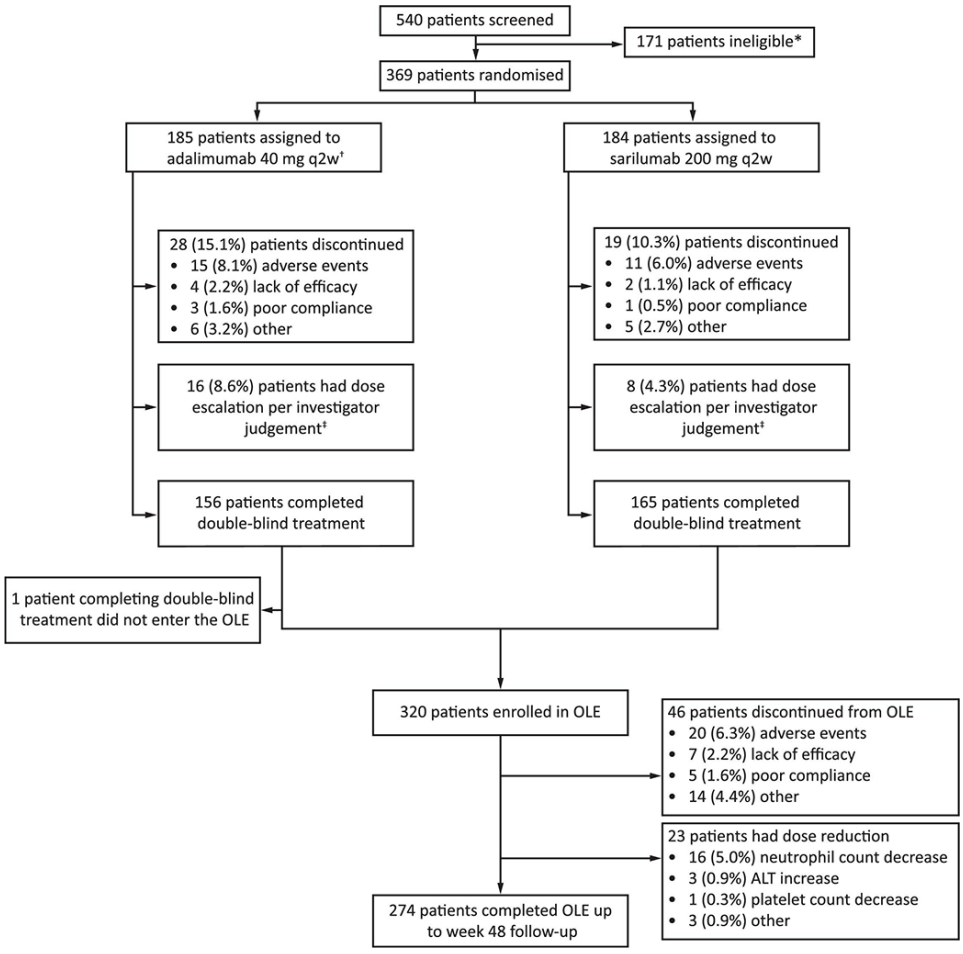



**Figure 1** Consolidated Standards of Reporting Trials flow diagram of the DBP and OLE stages of MONARCH. *Primary reasons for patient ineligibility were meeting the exclusion criteria related to tuberculosis (12.0%) or failure to meet the inclusion criterion for severity of disease (8.1%). †One patient was randomised but not treated in the adalimumab group. ‡The actual numbers of patients who received a dose-escalation kit on the basis of meeting protocol criteria were six (3.2%) in the adalimumab group and five (2.7%) in the sarilumab group. ALT, alanine aminotransferase; DBP, double-blind phase; OLE, open-label extension; q2w, every 2 weeks.

A greater incidence of treatment-emergent SAEs was noted in the switch versus continuation groups (table 2): rates of treatment-emergent SAEs were 11.0%, 15.1 events/100 PY in the switch group and 3.6%, 4.4 events/100 PY in the continuation group. However, there were no unexpected SAEs and no changes in the overall safety profile reported during the OLE. The most common (≥1%) treatment-emergent SAEs that occurred in switch patients were infections and infestations, three patients (1.9%); neoplasms, three (1.9%); cardiac disorders, three (1.9%); nervous system disorders, two (1.3%); vascular disorders, two (1.3%); musculoskeletal disorders, two (1.3%); and product issues, two (1.3%). Three serious infections occurred in the switch group (1.9%; 1.8/100 PY): pharyngotonsillitis (83 days after first dose in OLE), osteomyelitis (142 days after first dose) and pneumonia (94 days after first dose); none occurred in the continuation group.

## Laboratory abnormalities

During the OLE, an absolute neutrophil count (ANC) <lower limit of normal was found in 57.7% and 56.4% of patients in the switch and continuation groups, respectively (online supplementary table 2). Nineteen patients in the switch group (12.3%) and 19 in the continuation group (11.5%) had an ANC ≥500 and ≤1000/mm$^3$, and one patient (continuation group, 0.6%) had an ANC <500/mm$^3$. Permanent treatment discontinuation due to neutropenia occurred in one patient in the switch group (with ANC ≥500–1000/mm$^3$) and two in the continuation group (ANC ≥500–1000/mm$^3$ and <500/mm$^3$). There was no evidence of an association between an ANC decrease and infection or serious infection (online supplementary table 2).

The majority of ALT elevations in both groups were >1.0× and ≤1.5× the upper limit of normal (ULN): switch, 23.4%; continuation, 24.8%. ALT levels >3× to 5× ULN occurred in 5.2% and 3.0% of switch and continuation patients, respectively, and ALT >5× ULN occurred in 1/154 (0.6%) switch patient and 4/165 (2.4%) continuation patients, respectively (online supplementary table 2).

**Table 1** Patient demographics and disease characteristics of the OLE patient population at entry to the DBP and disease characteristics of the OLE population at entry to the OLE (ITT population)

| | Adalimumab/sarilumab (n=155) | Sarilumab/sarilumab (n=165) | All (n=320) |
|---|---|---|---|
| DBP entry | | | |
| Mean age, years (SD) | 53.1 (11.80) | 50.1 (12.80) | 51.6 (12.40) |
| Female, n (%) | 126 (81.30) | 142 (86.10) | 268 (83.80) |
| Caucasian/White, n (%) | 137 (88.40) | 153 (92.70) | 290 (90.60) |
| Mean weight, kg (SD) | 71.35 (17.69) | 71.90 (16.59) | 71.63 (17.11) |
| BMI ≥30 kg/m$^2$, n (%) | 42 (27.10) | 36 (21.80) | 78 (24.40) |
| Mean time since RA diagnosis, years (SD) | 6.66 (7.68) | 8.23 (8.25) | 7.47 (8.01) |
| Mean CDAI (SD) | 42.24 (11.68) | 43.30 (11.76) | 42.79 (11.71) |
| Mean HAQ-DI (SD) | 1.62 (0.65) | 1.63 (0.53) | 1.63 (0.59) |
| Mean DAS28-CRP (SD) | 6.00 (0.88) | 5.99 (0.87) | 5.99 (0.87) |
| Mean DAS28-ESR (SD) | 6.74 (0.83) | 6.81 (0.76) | 6.78 (0.79) |
| OLE entry | | | |
| Mean CDAI (SD) | 16.53 (10.45) | 13.73 (11.39) | 15.09 (11.01) |
| Mean HAQ-DI (SD) | 1.21 (0.67) | 1.01 (0.64) | 1.10 (0.66) |
| Mean DAS28-CRP (SD) | 3.92 (1.25) | 3.07 (1.21) | 3.48 (1.30) |
| Mean DAS28-ESR (SD) | 4.46 (1.29) | 3.45 (1.44) | 3.94 (1.46) |

BMI, body mass index; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score (28 joints); DBP, double-blind phase; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; OLE, open-label extension; RA, rheumatoid arthritis.

Among switch patients, 11/150 (7.3%) had antidrug antibodies (ADAbs) and 11/163 (6.7%) continuation patients had ADAbs. Three of these 22 (13.6%) ADAb-positive patients had hypersensitivity reactions (dermatitis, pruritic rash), compared with 19/291 (6.5%) patients who were ADAb-negative. There were no cases of anaphylaxis. The incidence of injection-site reactions was similar in ADAb-positive and ADAb-negative patients, and no ADAb-positive patients permanently discontinued treatment because of a lack of efficacy.

## Efficacy

In the DBP, the mean change from baseline in DAS28-ESR, DAS28-CRP and HAQ-DI and the proportion of patients achieving LDA (CDAI≤10) were greater with sarilumab monotherapy versus adalimumab monotherapy (figure 2).[9]

At DBP week 24/OLE baseline, the mean (SD) change from DBP baseline in DAS28-ESR was −2.28 (1.31) in the switch group and −3.36 (1.36) in the continuation group, and the change in DAS28-CRP was −2.08 (1.22) and −2.93 (1.25), respectively. Following the switch from adalimumab to sarilumab, rapid improvement was observed in the mean DAS28-ESR and DAS28-CRP, trending towards values observed in the sarilumab continuation group (figure 2A,B). The mean change (SD) from DBP baseline to OLE week 48 (total treatment: 72 weeks) in DAS28-ESR was −4.06 (1.25) in the switch group and −4.18 (1.35) in the continuation group, while the mean change in DAS28-CRP was −3.61 (1.23) and −3.63 (1.32), respectively.

In the OLE ITT population, within 12 weeks of switching from adalimumab to sarilumab, 47.1% (95% CI 39.2% to 55.0%) of patients in the switch group showed improvement in disease activity ≥MID for DAS28-ESR (≥1.2 change from OLE baseline) and 34.8% (95% CI 27.3% to 42.3%) exceeded MID for DAS28-CRP (≥1.2 change from OLE baseline). This proportion increased to 45.8% (95% CI 38.0% to 53.7%) for DAS28-CRP at week 48 (figure 3A). A similar trend in improvement was observed for DAS28-ESR during OLE (data not shown); by week 48, 52.9% (95% CI 45.0% to 60.8%) of patients exceeded MID for DAS28-ESR. Patients in the continuation group also showed continued improvement during the OLE, with an additional 16.4% (95% CI 10.7% to 22.0%) and 11.5% (95% CI 6.6% to 16.4%) of patients exceeding the MID for DAS28-ESR and DAS28-CRP, respectively, at OLE week 12 and 28.5% (95% CI 21.6% to 35.4%) and 18.8% (95% CI 12.8% to 24.7%), respectively, exceeding MID at OLE week 48 (data not shown).

Improvement in CDAI (achievement of LDA or improvement exceeding the MID) was observed in both groups during the OLE (figures 2D and 3B). In switch patients who achieved LDA (CDAI≤10 or SDAI ≤11) by OLE week 24, the majority sustained LDA at weeks 36 and 48 (70.7% and 69.5%, respectively; online supplementary figure 1). The proportion of switch patients who achieved CDAI (≤2.8) or SDAI (≤3.3) remission through week 48 (online supplementary figure 2) increased

**Table 2** TEAEs reported during the OLE

| OLE period (as of March 2017) | Patients, n (%) | | $n_E$ ($n_E$/100 PY) | |
|---|---|---|---|---|
| | Adalimumab/ sarilumab (n=155) | Sarilumab/ sarilumab (n=165) | Adalimumab/ sarilumab (PY=165.7) | Sarilumab/ sarilumab (PY=182.4) |
| Any TEAE | 118 (76.1) | 117 (70.9) | 443 (267.4) | 420 (230.2) |
| Any treatment-emergent SAE | 17 (11.0) | 6 (3.6) | 25 (15.1) | 8 (4.4) |
| Any TEAE leading to death | 2 (1.3) | 1 (0.6) | 3 (1.8) | 1 (0.5) |
| Any TEAE leading to permanent treatment discontinuation | 10 (6.5) | 12 (7.3) | 12 (7.2) | 15 (8.2) |
| AESI type | | | | |
| Infection | 65 (41.9) | 59 (35.8) | 110 (66.4) | 97 (53.2) |
| Serious infection | 3 (1.9) | 0 | 3 (1.8) | 0 |
| Opportunistic infection | 3 (1.9) | 1 (0.6) | 3 (1.8) | 1 (0.5) |
| Tuberculosis | 1 (0.6) | 0 | 1 (0.6) | 0 |
| Leucopenia | 21 (13.5) | 22 (13.3) | 46 (27.8) | 56 (30.7) |
| Thrombocytopenia | 3 (1.9) | 1 (0.6) | 5 (3.0) | 1 (0.5) |
| Hepatic disorders | 10 (6.5) | 13 (7.9) | 15 (9.1) | 20 (11.0) |
| Diverticulitis/GI perforation | 0 | 0 | 0 | 0 |
| GI ulceration | 0 | 0 | 0 | 0 |
| Elevation in lipids | 4 (2.6) | 6 (3.6) | 4 (2.4) | 7 (3.8) |
| Hypersensitivity | 8 (5.2) | 7 (4.2) | 16 (9.7) | 8 (4.4) |
| Anaphylaxis | 0 | 0 | 0 | 0 |
| Injection-site reaction | 14 (9.0) | 17 (10.3) | 66 (39.8) | 101 (55.4) |
| Malignancy | 3 (1.9) | 0 | 4 (2.4) | 0 |
| Malignancy excluding NMSC | 3 (1.9) | 0 | 4 (2.4) | 0 |
| Lupus-like syndrome | 0 | 0 | 0 | 0 |
| Demyelinating disorder | 0 | 0 | 0 | 0 |

AESI type was based on Standardised Medical Dictionary for Regulatory Activities Query or predefined search criteria.
AESI, adverse event of special interest; GI, gastrointestinal; $n_E$, number of events; $n_E$/100 PY, number of events per 100 patient-years; NMSC, nonmelanoma skin cancer; OLE, open-label extension; PY, patient-years; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

rapidly (within 2–4 weeks) from the point of switch and continued to increase to week 48.

Among adalimumab patients who achieved CDAI-based or SDAI-based LDA or remission by the end of DBP, the majority maintained or improved their response after switching to sarilumab for OLE. By the end of the DBP/OLE entry, 41 switch patients had achieved CDAI LDA without remission (2.8<CDAI≤10), and 43 had achieved SDAI LDA without remission (3.3<SDAI≤11). Of the 41 switch patients who had achieved a CDAI-based LDA during DBP, 30 (73.2%) at least maintained LDA through OLE week 48, including 13 (31.7%) who had newly achieved remission during OLE and 12 (29.3%) who had achieved a better CDAI score within the limits of LDA. Findings were similar through OLE week 48 for the 43 switch patients who had achieved an SDAI-based LDA score in DBP: 34 (79.1%) at least maintained their LDA score, 12 (27.9%) of whom achieved remission and 15 (34.9%) of whom achieved a better SDAI score within the limits of LDA. Five and six adalimumab patients achieved CDAI and SDAI remission, respectively, during DBP and entered OLE. Of these, three (60%) and two (33%) maintained remission through week 48 of OLE after switching to sarilumab.

The proportion of patients achieving an ACR20/50/70 response before, at and after switch is shown in the online supplementary figure 3. In the DBP, ACR20/50/70 response rates were greater in sarilumab-treated versus adalimumab-treated patients. Following switch from adalimumab to sarilumab, ACR20/50/70 response rates improved rapidly in the switch group, increasing from the point of switch (within 4 weeks) and approaching rates observed in the continuation group by OLE week 48.

By OLE week 48, the mean (SE) change in HAQ-DI score from DBP baseline was −0.70 (0.06) in the switch group versus −0.77 (0.06) in the continuation group (figure 2C). In the ITT population, within 12 weeks of switch, 43.2% (95% CI 35.4% to 51.0%) of patients reported improvement in HAQ-DI ≥MCID (≥0.22 units); the same proportion of

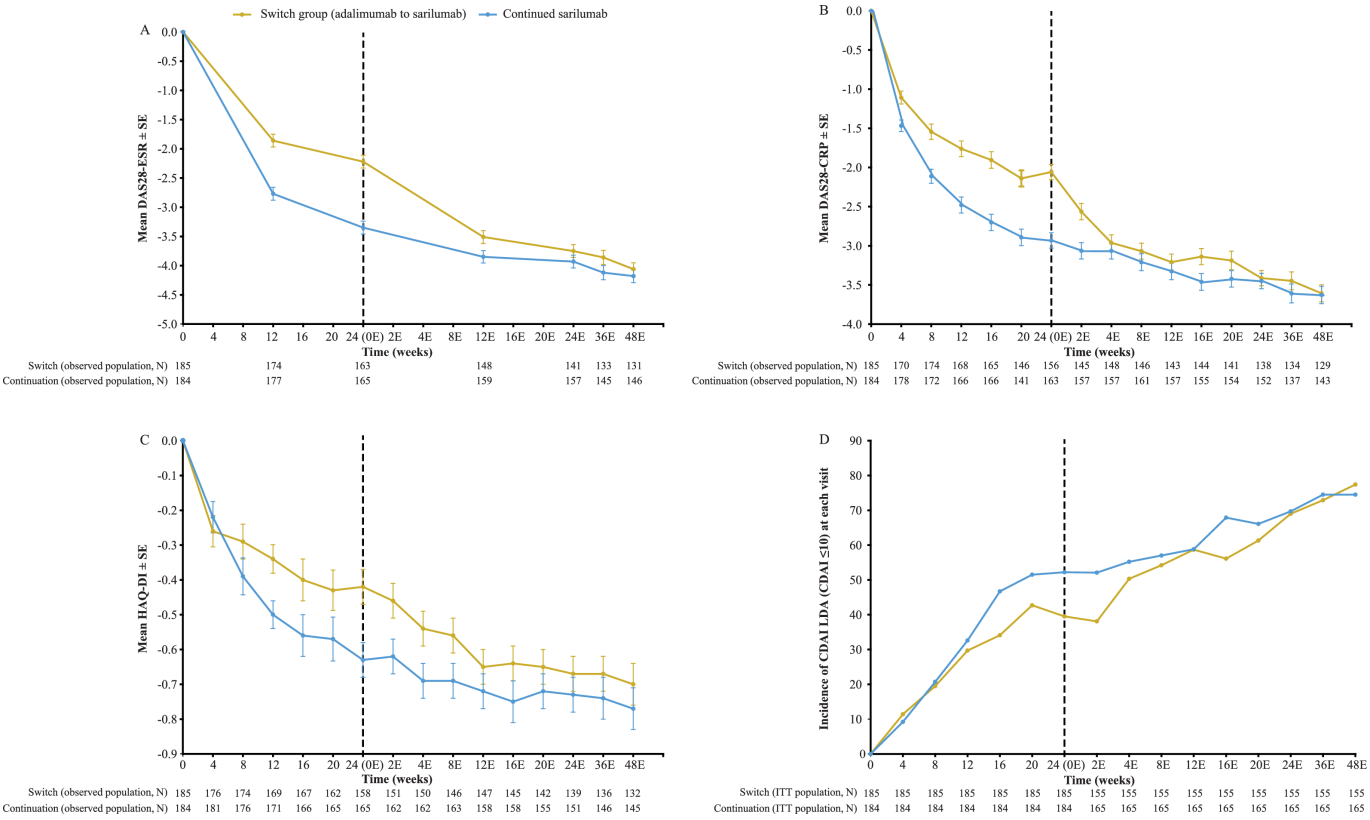



**Figure 2** Mean (±SE) change from DBP baseline in (A) DAS28-ESR, (B) DAS28-CRP, (C) HAQ-DI and (D) the proportion of patients achieving LDA (CDAI≤10) in the DBP and OLE. Mean change from baseline (panels A, B and C) is reported for observed cases, with no imputation for missing patients. Proportion of patients achieving LDA (panel D) is reported for the full ITT population, counting missing patients as nonresponders. Note: point of switch/continuation is indicated with a dotted vertical line; week number followed by an E refers to the number of weeks since entry into the OLE. CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score (28 joints); DBP, double-blind phase; ESR, erythrocyte sedimentation rate; HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; LDA, low disease activity; OLE, open-label extension.

patients, 43.2% (95% CI 35.4% to 51.0%), reported such improvement at week 48 (figure 3C).

### Patient-reported outcomes

PRO scores at DBP baseline through DBP week 24 have previously been reported.[12] By DBP week 24, patients treated with sarilumab reported greater improvement in PROs compared with adalimumab. The majority of patients completing the DBP enrolled in the OLE; hence, at the OLE baseline, patients in the sarilumab continuation group had better PtGA, HAQ-DI, pain VAS and SF-36 PCS domain scores than patients in the switch group.[12] Continued improvement from OLE baseline to OLE week 24 was reported across all PROs in the switch and continuation groups (figure 4), demonstrating a reduction in pain, morning stiffness, fatigue and HRQoL. Given the difference in PRO scores at OLE baseline, mean improvement in PROs was more pronounced in the switch group (from OLE baseline to OLE week 24) than in the continuation group; and by OLE week 24, the switch group reported similar PRO scores to those of the continuation group (data not shown). The magnitude of PRO improvement exceeded MCID, and for many patients, the scores approached or met age-matched and sex-matched population normative values (online supplementary table 3). By OLE week 24, the proportion of switch patients reporting scores at or exceeding normative values for the US general population for FACIT-F ≥40.1 was 34.2% (53/155); for pain VAS ≤20 mm, 40.6% (63/155); for HAQ-DI ≤0.25, 16.8% (26/155); for SF-36 PCS ≥50, 11.0% (17/155); and for SF-36 MCS ≥50, 34.8% (54/155).

By OLE week 24, 47.1% (73/155) of patients switching from adalimumab reported additional improvements ≥MCID in PtGA (above those already achieved in the DBP), 47.1% (73/155) in pain score and 39.4% (61/155) in morning stiffness VAS ≥10. PtGA and pain scores remained similar in the switch and continuation groups from weeks 24 through 48 (data not shown).

## DISCUSSION

Findings from the OLE demonstrate the benefits of monotherapy with sarilumab among patients who switched to sarilumab from adalimumab, and they support the long-term safety and efficacy of sarilumab monotherapy in those patients who continued it from DBP through the OLE for a total of up to 72 weeks.

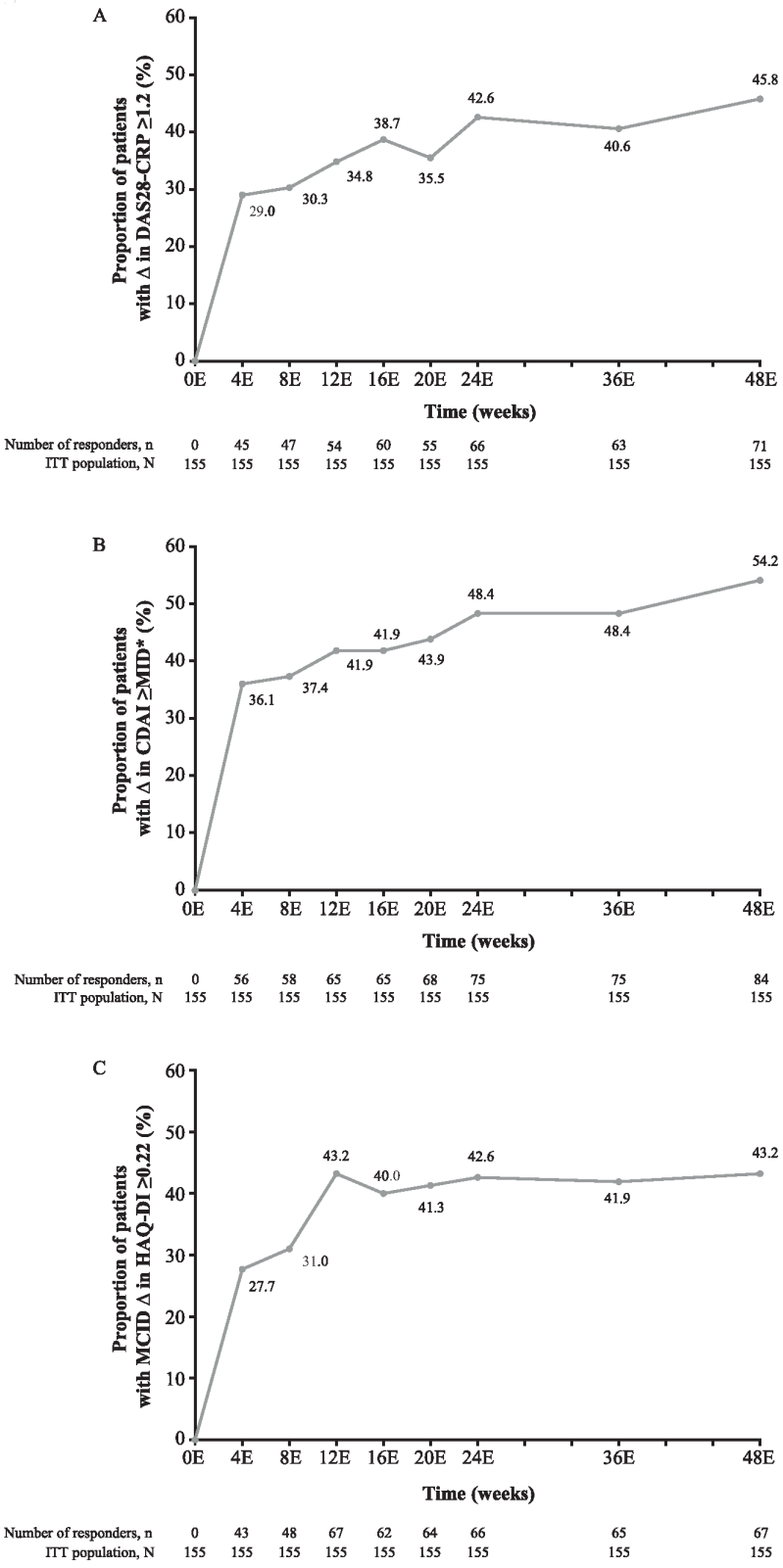
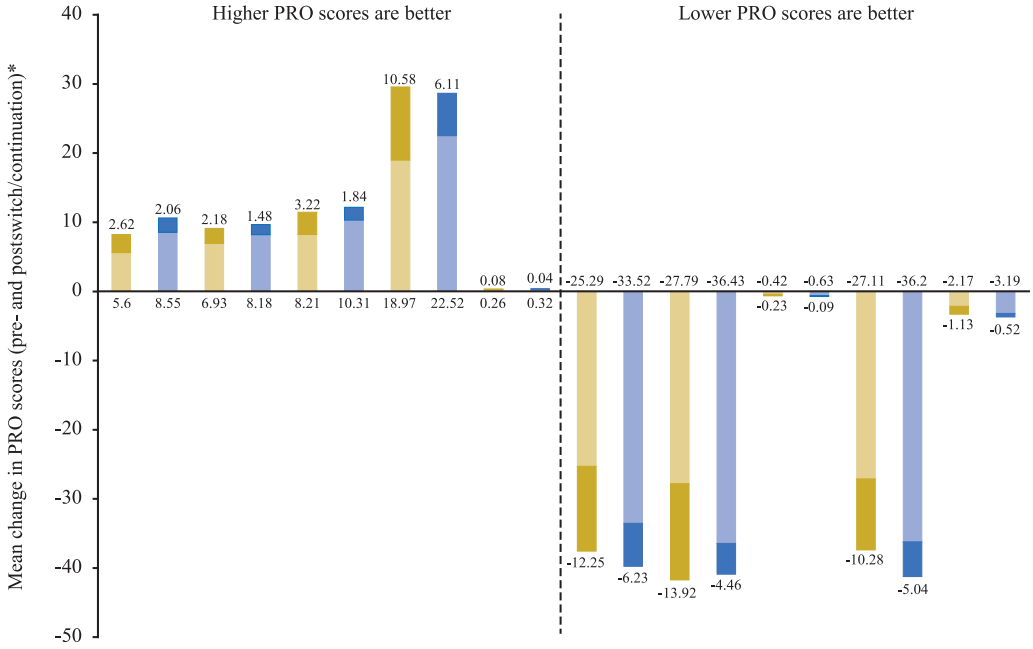



**Figure 3** Proportions of switch patients (A) achieving MID in DAS28-CRP (≥1.2 change from OLE entry), (B) reporting improvements from OLE entry ≥MID in CDAI* and (C) reporting improvements from OLE entry ≥MCID (≥0.22 units) in HAQ-DI. Proportions of patients meeting or exceeding these levels are reported for the full ITT population, counting missing patients as nonresponders. Note: baseline=week 0E; a week number followed by an E refers to the number of weeks since entry into the OLE. *For CDAI, the definitions of MID were: MID=12 if baseline CDAI>22; MID=6 if baseline CDAI=10–22; MID=1 if baseline CDAI<10. CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28, Disease Activity Score (28 joints); HAQ-DI, Health Assessment Questionnaire-Disability Index; ITT, intent-to-treat; MCID, minimally clinically important difference; MID, minimally important difference; OLE, open-label extension.




| Number of patients, n | PCS | MCS | FACIT-F | EQ-5D VAS | EQ-5D single utility | PtGA | Pain VAS | HAQ-DI | Morning stiffness | RAID |
|---|---|---|---|---|---|---|---|---|---|---|
| **Change from DBP Week 0 to DBP Week 24** | | | | | | | | | | |
| Switch group (DB adalimumab), n | 154 | 154 | 155 | 153 | 153 | 155 | 154 | 155 | 153 | 155 |
| Continuation group (DB sarilumab), n | 158 | 158 | 164 | 163 | 159 | 164 | 164 | 164 | 164 | 160 |
| **Change from OLE Week 0 to OLE Week 24** | | | | | | | | | | |
| Switch group (adalimumab to OLE sarilumab), n | 135 | 135 | 135 | 128 | 134 | 140 | 139 | 139 | 137 | 134 |
| Continuation group (OLE sarilumab), n | 140 | 140 | 149 | 141 | 139 | 153 | 153 | 151 | 150 | 144 |

**Figure 4** Mean change in PRO scores at the end of DBP (OLE week 0) and through OLE week 24. *Light-coloured bars and data at the x-axis show change during the DBP, when patients in the switch group were receiving adalimumab and patients in the continuation group were receiving sarilumab. Dark-coloured bars and data at the end of the bars show change from OLE week 0 to OLE week 24, when patients in both the switch and continuation groups were receiving sarilumab. PtGA, pain VAS, PCS, MCS, morning stiffness and EQ-5D VAS: score range 0–100; HAQ-DI: score range 0–4; FACIT-F: score range 0–52; RAID: score range 0–10 and EQ-5D single index utility: score range 0–1. DBP, double-blind phase; EQ-5D, EuroQoL 5-Dimensions questionnaire; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI, Health Assessment Questionnaire-Disability Index; MCS, mental component summary; OLE, open-label extension; PCS, physical component summary; PRO, patient-reported outcome; PtGA, patient global assessment of disease activity; RAID, Rheumatoid Arthritis Impact of Disease; VAS, visual analogue scale.

In the DBP, improvements in RA signs and symptoms observed in patients receiving adalimumab monotherapy were clinically meaningful and included improvements at week 24 in DAS28-ESR and DAS28-CRP, achievement of CDAI remission and LDA and ACR20/50/70 responses and reported improvements in HAQ-DI scores, PtGA, pain scores, FACIT-F and SF-36 PCS, MCS and domain scores.[9 12] Additionally, sarilumab monotherapy was superior to adalimumab monotherapy in reducing disease activity, improving signs and symptoms of RA and improving physical function and several PROs in the DBP. These findings are consistent with those reported for tocilizumab, a humanised monoclonal antibody against the interleukin-6 receptor (IL-6R), which also showed superiority as monotherapy versus adalimumab monotherapy in reducing signs and symptoms of RA,[17] and they suggest that IL-6R inhibitors are more effective than TNF inhibitors when used as monotherapy to reduce patients' signs and symptoms of RA.

To further support the outcomes with sarilumab versus adalimumab monotherapy in the DBP, findings from the OLE indicate that additional, clinically meaningful improvement in disease activity and PROs was achieved following the switch from adalimumab to sarilumab. Improvements in the OLE were noted primarily within 12 weeks of switching and approached levels of improvement similar to those seen in patients who continued sarilumab after completing the DBP. Response by 12 weeks was considered a good indicator of long-term efficacy, given that improvement in efficacy was sustained in the majority of patients up to 48 weeks after switching.

Throughout the DBP and OLE, patients who continued treatment with sarilumab demonstrated continuous and sustained improvements in mean clinical scores through OLE week 48, including in DAS28-ESR and DAS28-CRP scores. Similarly, the proportion of patients

with improvement in CDAI (a measure of clinical response independent of acute-phase reactants that may favour IL-6 inhibition) increased and was sustained throughout the DBP and OLE.

Improvement in all PROs, including pain, fatigue and morning stiffness, was reported in both the switch and continuation groups—often exceeding MCIDs and, in some patients, meeting or exceeding age-matched and gender-matched normative values. The change in PROs reflects similar improvement in clinical outcomes and provides further evidence of the broad benefits of IL-6 inhibition in reducing the daily impact of RA. Overall, mean improvement in PRO scores from OLE baseline to OLE week 24 was greater in the switch versus continuation group, and by OLE week 24, mean PRO scores reported by patients in the switch group had reached those of patients in the continuation group.

Treatment guidelines endorse a 'treat-to-target' approach to RA management, with the aim of achieving sustained remission or LDA.[1 2] Sustained clinical improvement following the switch from adalimumab to sarilumab provides support for therapy switching as a management option for select patients. The potential benefits of switching from a TNF inhibitor to an agent with a different mechanism of action have also been highlighted in a 1-year OLE comparing a switch to tofacitinib after blinded treatment with adalimumab or tofacitinib.[18] Among switch patients who had achieved LDA or remission based on either CDAI or SDAI score prior to OLE entry, the majority either maintained their LDA/remission status or achieved additional improvement while taking sarilumab through OLE week 48.

Safety observations in the OLE were generally consistent with the DBP and consistent with previous phase III studies of sarilumab.[9–11] No new safety concerns were identified, and safety profiles were similar in the switch and continuation groups, indicating that patients can be switched directly from adalimumab to sarilumab without introducing new safety or tolerability concerns. The rate of treatment-emergent SAEs during the OLE was higher in the switch versus continuation group, with the most common treatment-emergent SAEs among switch patients occurring at rates less than 2%. Three serious infections were reported in the switch group (vs none in the continuation group), two of which occurred within 10 weeks after switching; however, the overall exposure-adjusted rate of infection was similar between the two groups. Neutropenia occurred at similar frequencies in the switch and continuation groups and, importantly, was not associated with an increased risk of infection and serious infection. This potential paradox of neutropenia without increased risk of infection is thought to be related to neutrophil margination induced by IL-6 blockade without any apparent effect on neutrophil function.[19]

An important limitation of the present analysis is the open-label nature of the trial phase. Although a necessary component for evaluating long-term safety and efficacy, in addition to the inclusion/exclusion criteria initially used for entry into the RCT, identifying and analysing a 'completer' population (ie, patients who do well in the blinded phase of an RCT and enter the OLE), introduces a potentially confounding effect. To reduce further impact of such a confounding effect, a nonresponder imputation has been employed that considers the entire OLE ITT population and considers discontinuers as nonresponders, irrespective of their reason for discontinuation. The safety and efficacy analyses of the OLE excluded patients who discontinued the DBP. However, clinical responses (notably during the early phase of the trial) and the safety profile were similar between the switch and continuation groups. An additional limitation of the safety analysis is the relatively small number of patients in the OLE, which yielded a total of 165.7 PY (n=155) versus 182.4 PY (n=165) for follow-up in the switch versus continuation group. A further limitation of the study is the lack of long-term PRO data for this analysis, which were only available to OLE week 24 for most measures. The OLE is ongoing and will provide valuable additional evidence for the long-term safety and efficacy of sarilumab monotherapy in patients with RA. Lastly, given that the study was not designed as a crossover study, it was not possible to evaluate the effects of switching from sarilumab to adalimumab.

Collectively, these data demonstrate that patients who initiated and remained on treatment with sarilumab during the DBP had significant improvement in the signs and symptoms of RA and reported clinically meaningful improvement in physical function and multiple PROs. Findings from the switch analysis indicate that patients who switched from adalimumab monotherapy to sarilumab monotherapy experienced, within 3 months, additional and clinically relevant improvement in signs and symptoms of RA and in PROs, which were sustained to the end of the current analyses. The safety profile during the OLE was generally consistent with that in the DBP and similar between the switch and continuation groups, with no new safety signals emerging. These data may help optimise treatment approaches in RA requiring not only proactive, early identification of suboptimal disease control but also a collaborative goal-setting approach between rheumatologists and patients in deciding when potential changes in therapy, including the use of bDMARD monotherapy, may be warranted. Indeed, these findings address a real issue where patients who are no longer tolerant to MTX but are maintained on adalimumab monotherapy can safely and effectively be switched to sarilumab monotherapy when treatment targets have not been reached or are not maintained.

**Author affiliations**
[1]Department of Rheumatology and Clinical Immunology, Charité – Medical University Berlin, Free University, and Humboldt University Berlin, Berlin, Germany

[2]Department of Immunology and Rheumatology, Stanford University, Palo Alto, California, USA
[3]Klinik für Rheumatologie, Kantonsspital St. Gallen, St. Gallen, Switzerland
[4]Department of Medicine 'B' and Zabludowicz Center for Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel
[5]Faculty of Therapeutics, Kemerovo State Medical Academy of Roszdrav, Kemerovo, Russian Federation
[6]Servicio de Reumatología, Parc Taulí Hospital Universitari, Barcelona, Spain
[7]Immunology and Inflammation, Sanofi, Bridgewater, New Jersey, USA
[8]Medical Operations and Effectiveness, Sanofi Genzyme, Cambridge, Massachusetts, USA
[9]Biostatistics, Sanofi Genzyme, Cambridge, Massachusetts, USA
[10]Medical Affairs, Regeneron Pharmaceuticals, Inc, Tarrytown, New York, USA
[11]Immunology and Rheumatology, Stanford University Medical Center, Palo Alto, California, USA

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**Competing interests** GRB has received research grants or consulting fees or participated in speakers' bureaus from/for AbbVie, Eli Lilly, Merck Sharp & Dohme, Pfizer, Roche, Sanofi and UCB. VS has received consulting fees from AbbVie, Amgen, AstraZeneca, Biogen, Bristol-Myers Squibb, Celltrion, CORRONA, Crescendo, Eli Lilly, Genentech/Roche, GlaxoSmithKline, Janssen, Novartis, Pfizer, Regeneron Pharmaceuticals, Inc., Sandoz, Sanofi and UCB. AR-R has attended speakers' bureaus for AbbVie, Bristol-Myers Squibb, Chugai, Eli Lilly, Hexal/Novartis, Janssen, Merck Sharp & Dohme, Pfizer, Roche and Sanofi and has provided consultancy for Chugai, Eli Lilly, Roche and Sanofi. HA has received grant/research support from AbbVie, Janssen and Pfizer, has attended speakers' bureaus for Bristol-Myers Squibb, Janssen, Merck Sharp & Dohme, Pfizer and Sanofi and has provided consultancy for Merck Sharp & Dohme and Pfizer. TR has nothing to declare. AG-C has received research grants from Boehringer Ingelheim, Celltrion, Eli Lilly, Galapagos-Gilead, Novartis, Pfizer, Roche, Sanofi, UCB and YL Biologics and consulting/speakers' fees or other remuneration from AbbVie, Biogen, Bristol-Myers Squibb, Celgene, Eli Lilly, Gebro, Hospira, Janssen, Menarini, Merck Sharp & Dohme, Pfizer, Roche, Rubio, Sandoz, Sanofi and UCB. CP-R was formerly an employee of Sanofi, and may hold stock and/or stock options in the company. LG is an employee of Sanofi Genzyme, and may hold stock and/or stock options in the company. KT is a former employee of Sanofi Genzyme, may hold stock and/or stock options in the company, and is currently employed by EMD Serono. GSJ and SB are employees of Regeneron Pharmaceuticals, Inc., and may hold stock and/or stock options in the company. MCG has received research grants and/or consulting fees from GlaxoSmithKline, R-Pharm, Roche, and Sanofi.

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**Data availability statement** Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies and process for requesting access can be found at: https://www.clinicalstudydatarequest.com.

**Author note** CP-R was working at Sanofi Genzyme, Bridgewater, NJ, USA, for the study duration, data analyses, and the majority of the manuscript development, and has since left the company. CP-R's current address is 17, Route des Crans, Celigny 1298, Switzerland. KT was working at Sanofi Genzyme, Cambridge, MA, USA, for the study duration, data analyses, and the majority of the manuscript development, and has since left the company. KT is currently employed by EMD Serono.



**ORCID iDs**
Gerd R Burmester http://orcid.org/0000-0001-7518-1131
Mark C Genovese http://orcid.org/0000-0001-5294-4503

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