RHEUMATOLOGY ADVANCES IN PRACTICE

Rheumatology Advances in Practice 2022;00:1–7
https://doi.org/10.1093/rap/rkac002
Advance Access Publication 1 February 2022

Concise report

Sarilumab reduces disease activity in rheumatoid arthritis patients with inadequate response to janus kinase inhibitors or tocilizumab in regular care in Germany

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Abstract

Objectives. The aim was to evaluate the safety and effectiveness of sarilumab in RA patients after inadequate response (IR) to janus kinase inhibitors (JAKi) and tocilizumab.

Methods. The prospective, observational, 24-month single-arm PROSARA study (SARILL08661) is currently running in Germany at 96 sites. RA patients were prospectively selected at the physician's discretion according to label. This interim analysis included 536 patients over a treatment course of $\leq$6 months. Patients were stratified in four groups according to pretreatment before the start of sarilumab therapy: last prior treatment JAKi (JAKi-IR); last prior treatment tocilizumab (tocilizumab-IR); any other biological DMARD (bDMARD) in treatment history (bDMARD TH); and patients who had not received any bDMARDs or targeted synthetic (ts) DMARDs (b/tsDMARD naive) before.

Results. For this preplanned interim analysis, 536 patients were included in the baseline population, of whom 502 patients had at least one corresponding post-baseline effectiveness assessment documented (main analysis population). In all analysed cohorts, safety was consistent with the anticipated profile of sarilumab, without new safety signals. Six months of sarilumab treatment attenuated disease activity in JAKi-IR, tocilizumab-IR, bDMARD TH and b/tsDMARD-naive patients to a very similar extent. Physical function did not change substantially over the course of treatment. Rates of premature study discontinuation were comparable between cohorts.

Conclusion. Sarilumab treatment was effective in patients with IR to JAKi and tocilizumab, with an expectable safety profile and drug retention over 6 months. Confirmation of these promising results should encourage further studies on this treatment sequence, which is of high practical relevance.

Study registration. Paul-Ehrlich-Institut—Federal Institute for Vaccine and Biomedics, SARILL08661.

Key words: rheumatoid arthritis, sarilumab, janus kinase inhibitor, tocilizumab, inadequate response, safety, effectiveness

CLINICAL SCIENCE

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Submitted 4 August 2021; accepted 6 January 2022

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Key messages

- Sarilumab effectively attenuates disease activity of RA patients with inadequate response to janus kinase inhibitors or tocilizumab.
- Safety in patients pretreated with janus kinase inhibitors or tocilizumab was consistent with the anticipated profile of sarilumab.

Introduction

RA is a chronic inflammatory disease leading to progressive joint destruction, pain and decreased life expectancy. About 1% of the German population is affected by RA [1]. Among others, the cytokine IL-6 plays an important role in onset and sustaining the disease and underlying inflammation [2]. Accordingly, blockade of IL-6 signalling by the monoclonal antibody sarilumab has been demonstrated to be an effective treatment approach for RA in clinical trials [3–6]. Sarilumab is approved for the treatment of adults with moderately to severely active RA and inadequate response (IR) to DMARDs [7].

However, the repertoire of treatments for RA comprises numerous conventional synthetic (cs), biological (b) and targeted synthetic (ts) DMARDs [8, 9]. EULAR recommendations for the management of RA instruct that treatment with a different mode of action of bDMARD or tsDMARD should be considered if a prior bDMARD or tsDMARD treatment has failed [10]. However, clinical data on safety and efficacy are not available for all possible combinations of switches between mode of action among bDMARDs and tsDMARDs. Especially, insights into treatment with bDMARDs after inadequate responses to janus kinase inhibitors (JAKi) or IL-6 receptor inhibitors are sparse.

PROSARA is a PROspective, multicentre, non-interventional study to evaluate the safety and effectiveness of SArilumab for the treatment of active RA in regular care in Germany (SARILL08661). Preliminary PROSARA data showed improvement of RA symptoms in patients switched from JAKi to sarilumab [11]. The aim of the present PROSARA interim analysis is to validate and expand insights into safety and effectiveness of sarilumab after IR to JAKi and tocilizumab over a course of 6 months.

Methods

Study and interim analysis design

PROSARA is currently running in Germany at 96 sites, with 722 enrolled RA patients (last patient in: 1 February 2021) to be treated with sarilumab for $\leq$24 months. RA patients were selected prospectively at the physician's discretion according to label, and medical history was documented before treatment. All patients gave informed consent before study enrolment. The PROSARA protocols were approved by the Ethics Committee of the Charité—Universitätsmedizin Berlin and documented at Paul-Ehrlich-Institute (Federal Institute for Vaccines and Biomedicines).

The frequency of documented visits was scheduled according to German treatment guidelines for RA [12] after 1–2 months, 3, 6, 12 and 24 months. Annual interim analyses were planned prospectively to evaluate real-world patient populations that are often excluded from clinical trials ahead of final database lock.

In order to avoid the possibility that inhibition of the IL-6 pathway via sarilumab makes a disproportionate contribution to the DAS using CRP (DAS28-CRP) [13], we chose, for this analysis, to evaluate the clinical disease activity index (CDAI) instead of the DAS28-CRP. Furthermore, swollen joint count (SJC) and tender joint count (TJC) were assessed to evaluate disease activity and HAQ–disability index (HAQ-DI) to measure physical function.

Patient cohorts

Seven hundred and twenty-two RA patients are currently enrolled in PROSARA. However, the patient cohort for this interim analysis consisted of a baseline population ($n = 536$) and a main analysis population ($n = 502$). The baseline population included all enrolled patients with any baseline data documented, whereas the main analysis population comprised all patients who had been administered sarilumab at least once, with one baseline and at least one corresponding post-baseline efficacy assessment. Therefore, patient numbers differ between the baseline population and the main analysis population.

The baseline population and the main analysis population were stratified into four groups according to pretreatment before the start of sarilumab therapy: (1) last prior treatment JAKi (JAK-IR); last prior treatment tocilizumab (JAK-IR); any other bDMARD in treatment history (bDMARD TH); and patients who had not received any bDMARDs or tsDMARDs (b/tsDMARD naive) before (Supplementary Table S1, available at *Rheumatology Advances in Practice* online).

Data analysis

All analyses within this interim analysis are descriptive only to avoid α error accumulation. Descriptive statistics were presented as absolute and relative frequencies or means (S.D.).

Table 1 Baseline data on patient characteristics, disease activity and serological status

	Parameter	JAKi-IR	Tocilizumab-IR	bDMARD TH	b/tsDMARD naive
	Number of patients, *n*	89	56	209	182
Patient characteristics	Female sex, *n* (%)	69 (77.5)	45 (82.1)	160 (76.6)	133 (73.1)
	Age, mean (S.D.), years	58.4 (9.31)	60.4 (13.80)	58.3 (12.17)	59.2 (10.73)
	BMI, mean (S.D.), kg/m^2	28.7 (6.46)	27.1 (5.95)	28.1 (5.99)	28.3 (6.41)
	Current smokers, %	27.6	17.9	23.9	25.3
	Time since diagnosis of RA, mean (S.D.), years	11.9 (8.18)	13.63 (10.63)	12.7 (10.27)	6.48 (7.24)
	Concomitant csDMARDs with/without/no information, %	18.0/75.3/6.7	14.3/50.0/35.7	38.3/48.8/12.9	33.5/48.4/18.1
Disease activity, mean (S.D.)	CRP, mg/l	9.9 (15.27)	10.1 (40.42)	14.7 (22.46)	17.4 (35.79)
	ESR, mm/h	27.7 (21.64)	12.5 (18.33)	24.9 (19.61)	27.8 (23.92)
	SJC	6.4 (5.62)	3.9 (5.02)	4.4 (4.66)	4.9 (5.11)
	TJC	8.3 (6.81)	6.6 (6.64)	7.2 (6.96)	8.1 (6.99)
	HAQ-DI	1.2 (0.72)	1.1 (0.68)	1.2 (0.70)	1.1 (0.73)
	DAS28 ESR	5.0 (1.36)	3.5 (1.86)	4.7 (1.37)	4.9 (1.45)
	CDAI	26.4 (14.21)	20.0 (15.21)	22.6 (12.56)	24.5 (13.20)
	Fatigue, VAS	53.5 (24.98)	47.6 (29.62)	52.5 (27.64)	54.2 (28.50)
Serological status, *n* (%)	RF-positive, CCP-positive	36 (54.5)	21 (41.2)	89 (56.7)	71 (53.4)
	RF-positive, CCP-negative	9 (13.6)	9 (17.6)	17 (10.8)	14 (10.5)
	RF-negative, CCP-positive	5 (7.6)	6 (11.8)	18 (12.7)	6 (4.5)
	RF-negative, CCP-negative	16 (24.2)	15 (29.4)	31 (19.7)	42 (31.6)

Baseline data of patients, stratified by pretreatment: JAKi (JAKi-IR) or tocilizumab (tocilizumab-IR) as the last treatment before sarilumab, in patients who had received either TNFi or non-TNFi at any time in their treatment history (bDMARD TH) and in patients who had never received bDMARDs or tsDMARDs (b/tsDMARD naive) (see Supplementary Table S1, available at *Rheumatology Advances in Practice* online). The baseline population is shown; therefore, baseline values might differ from baseline values in Fig. 1. bDMARD: biologic DMARD; CDAI: clinical disease activity index; csDMARD: conventional synthetic DMARD; HAQ-DI: HAQ-disability index; IR: inadequate response; JAKi: janus kinase inhibitor; SJC: swollen joint count; TJC: tender joint count; TNFi: TNF inhibitor; tsDMARD: targeted synthetic DMARD; VAS: visual analogue scale.

Results

Patient characteristics

For this preplanned interim analysis, 536 patients (JAKi-IR: $n = 89$; tocilizumab-IR: $n = 56$; bDMARD TH: $n = 209$; and b/tsDMARD naive: $n = 182$) were included in the baseline population, of which 502 patients (JAKi-IR: $n = 82$; tocilizumab-IR: $n = 47$; bDMARD TH: $n = 200$; and b/tsDMARD naive: $n = 173$) were eligible for the main analysis population. In the main analysis population, 56.1% of JAKi-IR, 29.8% of tocilizumab-IR, 51.0% of bDMARD TH and 52.0% of b/tsDMARD-naive patients received glucocorticoids when starting sarilumab therapy. In the baseline population, the mean (S.D.) CDAI was 26.4 (14.2) in JAKi-IR, 20.0 (15.2) in tocilizumab-IR, 22.6 (12.6) in bDMARD TH and 24.5 (13.2) in b/tsDMARD naive (Table 1). HAQ-DI at baseline revealed a mean (S.D.) of 1.2 (0.7) in JAKi-IR, 1.1 (0.7) in tocilizumab-IR, 1.2 (0.7) in bDMARD TH and 1.1 (0.7) in b/tsDMARD-naive patients (Table 1).

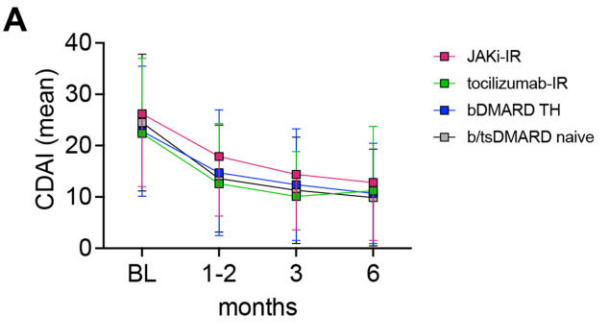
Safety

Safety was consistent with the anticipated profile of sarilumab and without appearance of new signals. Adverse events (AEs)/serious AEs were reported in 75.6%/19.5%, 55.3%/19.1%, 67.5%/15.0% and 61.8%/13.9% of JAKi-IR, tocilizumab-IR, bDMARD TH and b/tsDMARD-naive patients, respectively. According to the Medical Dictionary for Regulatory Activities (MedDRA), documented SAEs ($n > 2$) were categorized into the following system organ classes: blood and lymphatic system disorders, cardiac disorders, gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, musculoskeletal and connective tissue disorders, nervous system disorders and surgical and medical procedures (see Supplementary Table S2, available at *Rheumatology Advances in Practice* online, for more information).

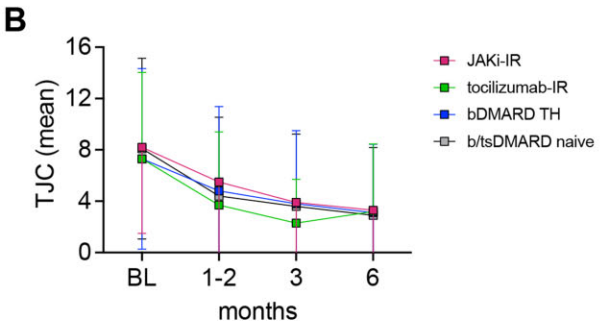
Effectiveness

During 6 months of sarilumab treatment, CDAI improved in JAKi-IR [from 26.2 (14.18) to 12.8 (11.27)] and tocilizumab-IR [from (22.4 (14.60) to 11.2 (12.56)] to the same extent as in the bDMARD TH cohort [from 22.8 (12.69) to 10.7 (9.79)] and b/tsDMARD-naive patients [from 24.5 (13.32) to 9.9 (9.43)] (Fig. 1A). Likewise, the TJC and the SJC decreased over treatment course of 6 months in all four subgroups (Fig. 1B and C).

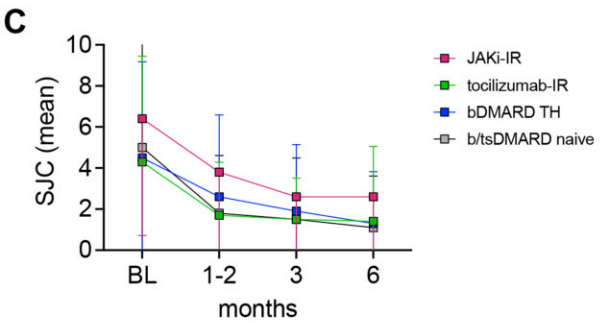
Fig. 1 Treatment effectiveness of sarilumab



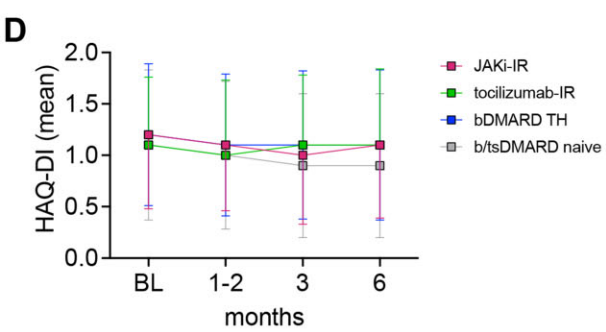
CDAI		Baseline	1-2 months	3 months	6 months
JAKi-IR	*Mean*	26.2	17.9	14.4	12.8
	SD	14.18	11.62	10.82	11.27
	n	80	62	69	64
tocilizumab-IR	*Mean*	22.4	12.6	10.1	11.2
	SD	14.6	11.68	8.75	12.56
	n	47	37	41	40
bDMARD TH	*Mean*	22.8	14.7	12.4	10.7
	SD	12.69	12.26	10.88	9.79
	n	195	146	174	149
b/tsDMARD naive	*Mean*	24.5	13.6	11.3	9.9
	SD	13.32	10.43	10.36	9.43
	n	171	141	151	129



TJC		Baseline	1-2 months	3 months	6 months
JAKi-IR	*Mean*	8.2	5.5	3.9	3.3
	SD	6.72	6.21	4.87	4.96
	n	80	62	69	64
tocilizumab-IR	*Mean*	7.3	3.7	2.3	3.2
	SD	6.72	5.69	3.4	5.26
	n	47	37	41	40
bDMARD TH	*Mean*	7.3	4.8	3.8	3.1
	SD	7.04	6.58	5.7	5.35
	n	196	146	175	153
b/tsDMARD naive	*Mean*	8.1	4.4	3.6	2.9
	SD	7.04	6.14	5.63	5.29
	n	171	141	151	129



SJC		Baseline	1-2 months	3 months	6 months
JAKi-IR	*Mean*	6.4	3.8	2.6	2.6
	SD	5.69	4.34	4.23	3.81
	n	80	62	69	64
tocilizumab-IR	*Mean*	4.3	1.7	1.5	1.4
	SD	5.14	2.58	2.01	3.65
	n	47	37	41	40
bDMARD TH	*Mean*	4.5	2.6	1.9	1.3
	SD	4.68	3.99	3.24	2.52
	n	196	146	175	153
b/tsDMARD naive	*Mean*	5	1.8	1.5	1.1
	SD	5.18	2.81	2.99	2.51
	n	171	141	151	129



HAQ-DI		Baseline	1-2 months	3 months	6 months
JAKi-IR	*Mean*	1.2	1.1	1.0	1.1
	SD	0.72	0.64	0.67	0.71
	n	80	60	67	61
tocilizumab-IR	*Mean*	1.1	1.0	1.1	1.1
	SD	0.66	0.73	0.68	0.74
	n	45	33	41	36
bDMARD TH	*Mean*	1.2	1.1	1.1	1.1
	SD	0.69	0.69	0.72	0.73
	n	194	137	163	141
b/tsDMARD naive	*Mean*	1.1	1.0	0.9	0.9
	SD	0.73	0.72	0.70	0.70
	n	170	131	148	125

Disease activity and physical function during sarilumab treatment over the course of 6 months, assessed by CDAI (**A**), TJC (**B**), SJC (**C**) and HAQ-DI (**D**) in patients with janus kinase inhibitor (JAKi-IR) or tocilizumab (tocilizumab-IR) as the last treatment before sarilumab, in patients who had received either TNFi or non-TNFi at any time in their treatment history (bDMARD TH) and in patients who had never received bDMARDs or tsDMARDs (b/tsDMARD naive) (see Supplementary Table S1, available at *Rheumatology Advances in Practice* online). Symbols show mean values, and error bars present the SD. The main analysis population is shown ($n = 502$). Therefore, the baseline values might differ from those in Table 1. bDMARD: biologic DMARD; BL: baseline; CDAI: clinical disease activity index; HAQ-DI: HAQ-disability index; IR: inadequate response; SJC: swollen joint count; TJC: tender joint count; TNFi: TNF inhibitor; tsDMARD: targeted synthetic DMARD.

During the same time period, HAQ-DI remained relatively stable in all stratified subgroups, without a notable decrease (Fig. 1D).

Study drug discontinuation

Among the main analysis population, 48.8% ($n = 40$) of JAK-IR, 34.0% ($n = 16$) of tocilizumab-IR, 38.5% ($n = 77$) of bDMARD TH and 34.1% ($n = 59$) b/tsDMARD-naive patients discontinued sarilumab prematurely. The reasons for study drug discontinuation were specified as ongoing remission/effectiveness ($n = 3$), intolerance ($n = 55$), lack of effectiveness ($n = 55$), loss of effectiveness (effective at the beginning; $n = 35$), patients' wish ($n = 15$) or other reason ($n = 28$) (see Supplementary Table S3, available at *Rheumatology Advances in Practice* online, for more information).

Discussion

Switching of DMARDs owing to IR or toxicity is a pertinent issue in daily practice. EULAR recommendations advise that a different mode of action should be considered if patients do not respond to treatment with a bDMARD or tsDMARD [10]. Long-term extensions of clinical trials for tofacitinib and baricitinib showed 23.1% [14] and 17.1% [15] of discontinuations owing to AEs, respectively. Also, real-world data on tocilizumab revealed that 21.3% and 6.3% of patients discontinued the study prematurely owing to lack of effectiveness and intolerance, respectively [16]. However, the safety and effectiveness of sarilumab after IR to bDMARDs or tsDMARDs in daily practice has not been evaluated sufficiently. The present interim analysis of PROSARA investigated this question, including pretreatment with JAKi and tocilizumab. To the best of our knowledge, these are the first data addressing this issue over a course of 6 months in daily practice.

Regarding safety, the profile of adverse events was similar to anticipated events, with no new signals. The rate of AEs in this PROSARA interim analysis seems to be somewhat lower than in integrated safety reports for sarilumab [17]. This was also true for SAEs, at least when compared with patients treated with sarilumab in combination therapy with csDMARDs [17]. Long-term safety analysis for $\leq$3.5 years revealed 11.0% SAEs in sarilumab monotherapy, which was comparable to safety data from this PROSARA interim analysis. The lower incidence of (S)AEs might be caused by under-reporting or the shorter duration of the observation period (6 months *vs* $\leq$7 years).

Similar rates of premature discontinuation of sarilumab among JAKi-IR, tocilizumab-IR, bDMARD TH and b/tsDMARD cohorts indicate that drug retention is comparable and that increased drop-out rates are not to be expected in particular switch scenarios when administering sarilumab after the respective pretreatments.

Regarding effectiveness, the present analysis shows a decrease of CDAI, TJC and SJC, not only in patients with IR to a last prior treatment of JAKi or tocilizumab, but also in patients with TNFi- and non-TNFi-bDMARDs in their treatment history and in b/tsDMARD-naive patients. The therapeutic effect was very comparable to a sarilumab switch in b/tsDMARD-naive patients and patients pretreated with other bDMARDs. These results argue for a CRP-independent effect in this cohort.

The data confirm preliminary results on safety and effectiveness of sarilumab after JAKi-IR [11] and extend these insights by increased patient numbers and course of treatment. Additionally, the attenuation of disease activity after IR to tocilizumab supports supplementary data from an open-label extension study evaluating safety and efficacy of sarilumab after switching from i.v. tocilizumab [18].

A substantial change in physical function, assessed by HAQ-DI, was not observed in any of the subgroups analysed. This was contrary to sarilumab clinical trials in which physical function was improved significantly in respective observation periods [3–5]. A reason might be the lower baseline of HAQ-DI scores or short-term follow-up in the present interim analysis compared with the clinical trial populations. Comparison of the present HAQ-DI baseline data with a long-term analysis of sarilumab efficacy [6] shows that physical function is sustained after entering the open-label extension, rather than being improved substantially. However, it is obvious that PROSARA patient populations differ from the clinical trial cohorts. Additionally, the duration of RA was longer in some PROSARA subgroups (JAKi-IR, tocilizumab-IR and bDMARD TH) compared with patients with IR to MTX treated with sarilumab in combination therapy [3] and patients treated with sarilumab in monotherapy [5] in clinical trials. Given that it is known that responsiveness in HAQ-DI scores is inversely associated with the mean duration of RA [19], this explains, in part, the present HAQ-DI irresponsiveness in PROSARA. However, sarilumab-treated patients with IR to TNFi had a comparable duration of RA at baseline and showed an improvement of physical functions in another clinical trial [4].

This PROSARA interim analysis is still limited by low patient numbers in stratified subgroups, especially in the tocilizumab-IR cohort, which also made it impossible to evaluate further the differences of sarilumab monotherapy and combination therapy with concomitant csDMARDs. Also, data on concomitant glucocorticoid use and/or tapering during sarilumab treatment are lacking. However, we believe that the observation period and patient numbers of this interim analysis provide the first evidence in favour of IL-6 receptor inhibitors in patients with RA, especially after failure to JAKi, which is encouraging for clinical practice and further research.

In summary, this analysis suggests that sarilumab might represent an effective treatment option with an expectable safety profile for patients with IR to JAKi or tocilizumab.

Acknowledgements

We thank Cornelia Kühne (Haldensleben), Patrizia Sternad (Munich), Martin Welcker (Munich), Niklas

Thomas Baerlecken (Cologne), Ann-Dörthe Holst (Ludwigslust) and Thilo Klopsch (Neubrandenburg) for substantial contribution to patient recruitment in PROSARA. H.-P.T. and E.F. contributed equally to this work. H.-P.T., E.F., P.M.A., S.Z., H.B., I.A. and S.K. contributed to the conception or design of the study. H.-P.T., E.F., P.M.A., S.Z., H.B., K.K., J.A. and S.K. contributed to the analysis of the data. H.-P.T., E.F., P.M.A., S.Z., H.B. and K.K. contributed to the acquisition of data. All authors were involved in the interpretation of the data and reviewed and approved the letter's content before submission.

Funding: The non-interventional study PROSARA and the current interim analysis were funded by Sanofi-Aventis Deutschland GmbH.

Disclosure statement: H.-P.T. reports personal fees from Abbvie, Amgen, BMS, Chugai, Gilead, Janssen, Lilly, Novartis, Roche, Sanofi, Takeda. E.F. reports grants and personal fees from Sanofi during the conduct of the study; grants and personal fees from Roche, Abbvie, BMS, Lilly outside the submitted work. P.M.A. reports personal fees from Abbvie, Biogen, Berlin Chemie, Celgene, GSK, Hexal, Mylan, Novartis, Pfizer, UCB, Janssen, Medac, Sanofi. S.Z. has no disclosures. K.K. reports personal fees from Sanofi. J.A. and I.A. are employees of Sanofi-Aventis Deutschland GmbH and shareholders of Sanofi. C.B. is employee of Sanofi-Aventis Deutschland GmbH. S.K. reports personal fees from Sanofi-Aventis Deutschland GmbH. H.B. reports personal fees for advisory board and lecture fees from Sanofi, Roche, Chugai, Pfizer, Gilead, Lilly, Abbvie, BMS.

Data availability statement

Qualified researchers may request access to patient-level data and related study documents including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient-level data will be anonymized, 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

Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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