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ORIGINAL RESEARCH

Real-World Effectiveness and Safety of SDZ ETN, an Etanercept Biosimilar, in Patients with Rheumatic Diseases: Final Results from Multi-Country COMPACT Study

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ABSTRACT

Introduction: COMPACT, a non-interventional study, evaluated the persistence, effectiveness, safety and patient-reported outcomes (PROs) in patients with rheumatoid arthritis (RA), axial-spondyloarthritis (axSpA) or psoriatic arthritis (PsA) treated with SDZ ETN (etanercept [ETN] biosimilar) in Europe and Canada.

Methods: Patients (aged ≥ 18 years) who have been treated with SDZ ETN were categorised on the basis of prior treatment status (groups A–D): patients in clinical remission or with low disease activity under treatment with reference ETN or biosimilar ETN and switched to SDZ ETN; patients who received non-ETN targeted therapies and switched to SDZ ETN; biologic-naïve patients who started SDZ ETN after conventional therapy failure; or disease-modifying anti-rheumatic drug (DMARD)-naïve

Prior Presentation: Some of the study results have been presented at the EULAR, EADV and ACR 2022 Congresses, and the Scandinavian Congress of Rheumatology 2023: Schmalzing M, Kellner H, Askari A, et al. POS0640 Real-world effectiveness and safety of GP2015 in patients with rheumatic diseases: final results of the Compact study [abstract]. Ann Rheum Dis. 2022;81:589–90. Askari A, Coleman J, Bazzani C, et al. Abstract No.1626. Safety and patient-reported outcomes in patients with psoriatic arthritis who were treated with Etanercept biosimilar GP2015: final results of the COMPACT study. Submitted to EADV Congress, 7–10 September, 2022. Available at https://eadv.org/scientific/abstract-books/. Askari A, Schmalzing M, Kellner H, et al. Patient-reported outcomes and quality of life in patients with rheumatoid arthritis treated with GP2015: final results from a real-world study [abstract]. Arthritis Rheumatol. 2022;74(suppl 9). Schmalzing M, Askari A, Jeka S, et al. Effectiveness of GP2015 in biologic-naïve patients with early rheumatoid arthritis: results from the COMPACT study [abstract]. Scand J Rheumatol. 2023;52(sup131):60–116.

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patients with RA considered suitable for treatment initiation with a biologic and started on treatment with SDZ ETN. The primary endpoint was drug persistence, defined as time from study enrolment until discontinuation of SDZ ETN treatment.

Results: Of the 1466 patients recruited, 844 (57.6%) had RA, 334 (22.8%) had axSpA and 288 (19.6%) had PsA. Patients had an ongoing SDZ ETN treatment at the time of enrolment for an observed average of 138 days (range 1–841); 22.7% of patients discontinued SDZ ETN through 12 months of study observation. Overall, all the patients receiving SDZ ETN showed good treatment persistence at 12 months with discontinuation rates of 15.2%, 25.7% and 27.8% in groups A, B and C, respectively. Across all patient groups, no major differences were observed in the disease activity and PRO scores between baseline and month 12. Injection-site reactions were low across the treatment groups.

Conclusion: These results support the effectiveness and safety of SDZ ETN treatment in patients with RA, axSpA or PsA in real-life conditions. The treatment persistence rates observed were consistent with previously published reports of patients treated with reference or other biosimilar ETN. No new safety signals were identified.

Keywords: Biosimilar; COMPACT; Persistence; Safety; Effectiveness; PRO; Non-interventional; Real-world; Rheumatic diseases; SDZ ETN

Key Summary Points

Why carry out this study?

The study evaluated the real-world drug persistence, effectiveness and safety in patients with rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) or psoriatic arthritis (PsA) who either initiated SDZ ETN, an etanercept biosimilar, as a first-line biologic, or were switched to SDZ ETN from a stable treatment with reference etanercept or biosimilar etanercept other than SDZ ETN, or were switched to SDZ ETN from other targeted disease-modifying anti-rheumatic drugs.

What was learned from the study?

The results from the study support the effectiveness and safety of SDZ ETN treatment in patients with RA, axSpA or PsA in real-life conditions. The treatment persistence rates observed at 12 months were comparable to the previously published reports of patients treated with reference or other biosimilar ETN.

No impact on effectiveness, drug retention, safety and patient-reported outcomes was observed after the switch from reference etanercept or other biosimilar etanercept to SDZ ETN.

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INTRODUCTION

Rheumatoid arthritis (RA), axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are among the common inflammatory rheumatic diseases that can be associated with progressive irreversible joint damage, resulting in functional deterioration and disability [1].

Timely diagnosis, treatment initiation and continuation are crucial in controlling disease signs and symptoms, preventing structural damage and maximising quality of life (QoL), leading to sustained long-term therapeutic benefits [2] and the potential to reduce healthcare costs, especially when biosimilars are used [3]. Pathogenesis-based, biological disease-modifying anti-rheumatic drugs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), particularly therapies targeting tumour necrosis factor (TNF), have revolutionised the treatment of RA, axSpA and PsA. Studies have shown that anti-TNF agents are effective and have a manageable safety profile in the majority of the patients with musculoskeletal rheumatic diseases, allowing non-steroidal anti-inflammatory drug (NSAID) and corticosteroid dose tapering while also targeting long-term remission and significantly improving QoL [4–10].

Etanercept (ETN), a recombinant human TNF receptor p75Fc fusion protein, is a subcutaneously administered bDMARD approved for the treatment of RA, axSpA, PsA, juvenile idiopathic arthritis (JIA) and plaque psoriasis [11, 12]. The higher estimated annual costs of anti-TNF drugs per treated patient limits their accessibility to patients. In this context, the introduction of biosimilars has gained considerable interest as they are more cost-effective and increase patient access to effective treatment options [13, 14].

A biosimilar is a biological medicine highly similar to another already approved biological medicine (the 'reference medicine'). Biosimilars are approved according to the same standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines [15]. SDZ ETN (Sandoz-etanercept; GP2015; Erelzi™ [Sandoz GmbH, Austria]) is an ETN biosimilar approved by the European Commission for the same indications, including RA, axSpA, PsA and JIA, as the reference ETN (ref-ETN), and approved by the US Food and Drug Administration (FDA) for the treatment of JIA, RA, PsA and ankylosing spondylitis [16, 17].

COMPACT is a multi-country, non-interventional study evaluating the drug persistence, effectiveness, safety and patient-reported outcomes (PROs) in patients with RA, axSpA or PsA treated with SDZ ETN in real-world conditions. Herein, we report the final results from the COMPACT study evaluating the effectiveness and safety through 12 months in patients treated with SDZ ETN.

METHODS

Patients

Patients (aged ≥ 18 years) with RA, axSpA or PsA (diagnosis was according to the treating physician's discretion) were enrolled in the study if treatment with SDZ ETN was initiated by the treating physician (according to the prescribing recommendations in each country) prior to signing informed consent and study enrolment. Of note, there was no established limit for SDZ ETN treatment introduction before informed consent form signature and study enrolment.

DMARD-naïve patients (indicated only for RA), or biologic-naïve patients who have been initiated on treatment with SDZ ETN or who have been switched to SDZ ETN either from stable treatment with ref-ETN (or other ETN biosimilar ([iETN], i.e. in remission [Disease Activity Score 28-joint count Erythrocyte Sedimentation Rate (DAS28-ESR) < 2.6] or with low disease activity [DAS28-ESR ≥ 2.6 to ≤ 3.2]), or from previous treatment with another anti-TNF agent or other biologic or tsDMARD, were eligible to be enrolled in the study.

Patients were categorised into four treatment groups based on prior treatment status:

– Group A: Patients in clinical remission or with low disease activity under treatment with ref-ETN or other biosimilar ETN (iETN) and switched to SDZ ETN

- Group B: Patients who received non-ETN targeted therapies and switched to SDZ ETN
- Group C: Biologic-naïve patients considered uncontrolled with conventional therapy and started on SDZ ETN as the first biologic treatment
- Group D: DMARD-naïve patients with a recent diagnosis of RA considered suitable for treatment initiation with a biologic and started on treatment with SDZ ETN

Exclusion criteria included any contraindications to ETN according to the prescribing recommendations in each country or known hypersensitivity to ETN. Detailed inclusion/exclusion criteria are presented in Supplementary Table 1.

The study was approved for each participating site according to the local regulations. The trial was conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices of the International Society for Pharmacoepidemiology (2008) [18], the Strengthening the Reporting of Observational Studies in Epidemiology guidelines [19], the Declaration of Helsinki [20] and each country's local regulations. All patients signed an informed consent form that was reviewed and approved by an independent ethics committee or institutional review board.

Study Design

This multicentre, prospective, non-interventional cohort study conducted in targeted countries in Europe and Canada was designed to ensure systematic and consistent real-world data collection in a broad spectrum of patients including RA, axSpA or PsA treated with ETN (Supplementary Fig. 1). To ascertain response rates to SDZ ETN, data for various disease activity variables and PROs were collected for all eligible patients at week 12 and week 24, and around 6-month or 1-year intervals. Overall, the patients were enrolled over 2 years, starting 11 October 2017, with last observation recorded on 30 April 2021.

Assessments

The primary objective of this study was to evaluate the real-world drug persistence of SDZ ETN in patients with RA, axSpA or PsA as time from study enrolment until discontinuation of SDZ ETN treatment. As part of the primary analysis, drug persistence from the time of SDZ ETN start to discontinuation was also assessed.

Key secondary objectives included

(a) Assessment of effectiveness of SDZ ETN from enrolment to the end of the study: (i) DAS28-ESR for patients with RA and PsA; (ii) Ankylosing Spondylitis Disease Activity Score (ASDAS); four disease activity states have been defined, namely inactive (ASDAS < 1.3), moderate (≥ 1.3 to < 2.1), high (≥ 2.1 to ≤ 3.5) and very high (> 3.5) and (iii) Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for patients with axSpA. In addition, disease activity was assessed in patients who continued (continuation group) or discontinued (discontinuation group) the treatment at 12 months of drug persistence from SDZ ETN treatment start.

(b) Assessment of PROs and QoL, which included (i) EuroQol-5D overall self-rated health status (EQ-5D visual analogue scale [VAS]); (ii) Patients' functional disability measured by Health Assessment Questionnaire–Disability Index (HAQ-DI); (iii) Patients' general health measured by Short Form Health Survey 12-item (SF-12)-physical/mental health; (iv) Functional Assessment of Chronic Illness Therapy (FACIT)-fatigue and fatigue VAS; (v) Pain as measured by Basic Pain Inventory (BPI)-interference score, pain VAS scores and overall pain (experience of pain during current day) scores.

Safety and tolerability of SDZ ETN were evaluated in terms of adverse events (AEs), serious AEs, adverse drug reactions (ADRs), AEs of special interest (AESIs) and injection-site reactions.

Statistical Analysis

Considering the observational design of the study and its objectives, the statistical analysis

was descriptive in nature. Descriptive statistics for continuous variables included the number of observations (*N*), mean, median, and standard deviation (SD). For categorical variables, *N* and percent were provided.

The primary endpoint, drug persistence, was calculated as the difference in days between the day of discontinuation of SDZ ETN treatment and enrolment in the study (week 0/baseline). Discontinuation was defined as switching to another biologic or an SDZ ETN treatment-free interval of 60 days or more. Drug persistence from the time of SDZ ETN start to discontinuation was mentioned in the study protocol to be assessed as an exploratory analysis; however, this was assessed as part of the primary analysis.

The Kaplan–Meier curve was used to estimate median time of the drug persistence using the complimentary log–log transformation.

All analyses were performed on the basis of the per-protocol set (PPS). The PPS comprised patients from groups A–D. Patients who were enrolled in the study but did not meet inclusion criterion 2 (Supplementary Table 1) were excluded from the PPS.

The primary objective was descriptive, and hence, no formal sample size calculation based on a formal hypothesis test could be performed. However, based on the assumption that the median drug persistence time is 36 months and that the distribution of persistence times follows an exponential distribution, the standard deviation of the persistence times would be 6 months.

With a sample size of around 1400 (between 1200 and 1600) patients and a 10% dropout rate, the standard error of the mean persistence time would be around 1/35.5th of the standard deviation, i.e. 5 days. Hence, this sample size should allow for a highly accurate estimate of the persistence time. For the main secondary endpoints, the sample size of about 1400 (between 1200 and 1600) would allow a 95% probability of detecting an AE that occurred at a background frequency of at least 0.2%.

For all statistical analyses, SAS software was used.

RESULTS

Baseline Characteristics and Patient Demographics

A total of 1575 patients, recruited from nine countries and 98 centres, were enrolled in the study, of which 1466 patients fulfilled the inclusion criteria. Of the 1466 patients, 844 (57.6%) had RA, 288 (19.6%) had PsA and 334 (22.8%) had axSpA as the primary indication (Fig. 1). The use of systemic corticosteroids was the highest in patients with RA (37.0%, Supplementary Table 2); 52.0% of the patients with RA were on methotrexate compared to 42.4% and 13.5% in the PsA and axSpA population, respectively. A total of 572 patients were switched from iETN (group A), 171 were switched from other targeted therapies (group B), 713 were biologic-naïve (group C), and 10 had RA and were DMARD-naïve (group D).

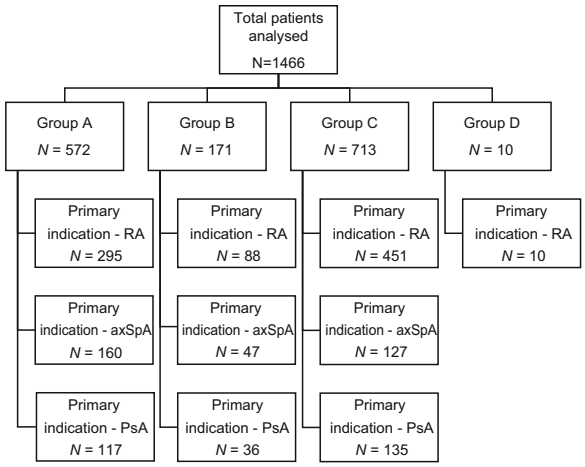

Fig. 1 Patient disposition. *axSpA* axial spondyloarthritis, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis. Group A, patients in clinical remission or with low disease activity under treatment with ref-ETN or other biosimilar ETN and switched to SDZ ETN; group B, patients who received non-ETN targeted therapies and switched to SDZ ETN; group C, biologic-naïve patients considered uncontrolled with conventional therapy and started on SDZ ETN as the first biologic treatment; group D, DMARD-naïve patients with a recent diagnosis of RA considered suitable for treatment initiation with a biologic and started on treatment with SDZ ETN

Patients had an ongoing SDZ ETN treatment at the time of enrolment for an observed average of 138 days (median [88 days], range 1–841). Overall, the mean age of patients was 54.4 years, 59.8% were female, mean body weight was 76.9 kg and mean BMI was 27.2 kg/m^2. Comorbidities were more frequent in patients with RA, followed by those with PsA and axSpA (Table 1).

SDZ ETN Drug Persistence from Enrolment (Primary Outcomes)

Overall, 22.7% of patients discontinued SDZ ETN through 12 months of study observation. The primary reasons for treatment discontinuation were AEs (7.9%) and non-responders (14.4%).

As shown in Fig. 2a, patients in group A who had stable disease under prior treatment with iETN showed a higher treatment persistence rate with reported discontinuation rates of 15.2% at 12 months after study enrolment. While group B patients, who were previously treated with biologic or tsDMARDs, reported discontinuation rates of 25.7%, group C with biologic-naïve patients with uncontrolled disease had discontinuation rates of 27.8% at 12 months. Owing to a lower number of patients in group D (n = 10), drug persistence rates were difficult to interpret.

Drug Persistence from SDZ ETN Treatment Start

The discontinuation rate was 17.2% at month 12 after SDZ ETN start in the overall population. At month 12, patients in group A had a higher treatment persistence rate with reported discontinuation rates of 8.8%, whereas patients in groups B and C reported discontinuation rates of 22.8% and 22.5%, respectively (Fig. 2b), at month 12. The drug persistence rates were difficult to interpret due to a smaller number of patients in group D (n = 10).

The drug persistence rates based on the reasons for discontinuation from SDZ ETN treatment start were also analysed. At month 12, the discontinuation rates due to lack of efficacy and AEs were 8.9% and 5.0%, respectively, in the overall population (Supplementary Figs. 2a, 2b).

Effectiveness of SDZ ETN Treatment

In patients with RA or PsA, the overall mean (SD) DAS28-ESR scores at baseline were 3.0 (1.4) and 2.6 (1.5), respectively (Fig. 3a); corresponding scores at week 12 were 2.7 (1.2) and 2.5 (1.4), respectively, with a mean (SD) change from baseline of −0.5 (1.4) in patients with RA. At month 12, the mean (SD) scores were 2.7 (1.3) and 2.4 (1.5), respectively, with a mean (SD) change from baseline of −0.4 (1.6) in patients with RA.

Overall, 306/729 patients with RA (42.0%) were in remission, and 126 (17.3%) had low disease activity at baseline, whereas of 226 patients with PsA, 120 (53.1%) were in remission and 39 (17.3%) had low disease activity at baseline. At month 12, 218/422 patients with RA (51.7%) were in remission and 78 (18.5%) had low disease activity; 65/105 (61.9%) and 14/105 (13.3%) patients with PsA achieved remission and low disease activity, respectively (Fig. 4a).

At baseline, the mean (SD) ASDAS score was 1.9 (0.9) for 154 patients with axSpA with available data. At month 12, the mean (SD) ASDAS score was 1.8 (0.9) for 70 patients, with a mean (SD) change from baseline of −0.1 (1.0). Overall, the mean (SD) BASDAI score at baseline was 2.9 (2.3) for 304 patients with available data. At month 12, the mean (SD) BASDAI score was 2.5 (2.0) for 192 patients, with a mean (SD) change from baseline of −0.5 (2.2). The ASDAS and BASDAI scores at baseline and over time across all the groups are presented in Fig. 3b.

Overall, of 154 patients with axSpA, 40 (26.0%) had inactive disease and 54 (35.1%) had moderate disease activity at baseline. At month 12, of the 70 patients with available data, 18 (25.7%) had inactive disease and 27 (38.6%) had moderate disease activity (Fig. 4b).

Table 1 Baseline demographics and comorbidities of patients

	RA *N* = 844				PsA *N* = 288				axSpA *N* = 334			
	Group A *n* = 295	**Group B** *n* = 88	**Group C** *n* = 451	**Group D** *n* = 10	**Group A** *n* = 117	**Group B** *n* = 36	**Group C** *n* = 135	**Group D** *n* = 0	**Group A** *n* = 160	**Group B** *n* = 47	**Group C** *n* = 127	**Group D** *n* = 0
Age (years), mean (SD)	59.1 (13.6)	59.4 (11.2)	56.9 (12.8)	55.5 (17.7)	54 (11.7)	51 (12.6)	51 (12.9)	0	50 (12.3)	45 (14.3)	45 (12.5)	0
Female, *n* (%)	229 (77.6)	68 (77.3)	313 (69.4)	6 (60.0)	55 (47.0)	16 (44.4)	78 (57.8)	0	41 (25.6)	20 (42.6)	50 (39.4)	0
BMI (kg/m^2), mean (SD), *n*	26.8 (6.1) [*n* = 198]	28.3 (5.8) [*n* = 51]	27.2 (5.6) [*n* = 331]	25.8 (6.1) [*n* = 8]	28.2 (6.3) [*n* = 77]	27.8 (5.8) [*n* = 29]	27.3 (5.6) [*n* = 92]	0	27.6 (5.6) [*n* = 106]	26.2 (4.8) [*n* = 30]	26.8 (6.2) [*n* = 90]	0
Patients with at least one comorbidity, *n* (%)	207 (70.2)	65 (73.9)	302 (67.0)	6 (60.0)	69 (59.0)	21 (58.3)	81 (60.0)	0	84 (52.5)	20 (42.6)	70 (55.1)	0
Musculoskeletal and connective tissue disorders	96 (32.5)	24 (27.3)	125 (27.7)	3 (30.0)	28 (23.9)	7 (19.4)	25 (18.5)	0	25 (15.6)	10 (21.3)	34 (26.8)	0
Vascular disorders	74 (25.1)	30 (34.1)	125 (27.7)	2 (20.0)	29 (24.8)	10 (27.8)	34 (25.2)	0	24 (15.0)	3 (6.4)	20 (15.7)	0
Metabolism and nutrition disorders	63 (21.4)	17 (19.3)	97 (21.5)	3 (30.0)	24 (20.5)	7 (19.4)	26 (19.3)	0	30 (18.8)	2 (4.3)	19 (15.0)	0
Gastrointestinal disorders	39 (13.2)	10 (11.4)	31 (6.9)	1 (10.0)	7 (6.0)	1 (2.8)	3 (2.2)	0	13 (8.1)	4 (8.5)	9 (7.1)	0
Respiratory, thoracic and mediastinal disorders	37 (12.5)	6 (6.8)	37 (8.2)	0	6 (5.1)	2 (5.6)	6 (4.4)	0	12 (7.5)	3 (6.4)	6 (4.7)	0
Endocrine disorders	32 (10.8)	11 (12.5)	49 (10.9)	2 (20.0)	4 (3.4)	4 (11.1)	12 (8.9)	0	6 (3.8)	3 (6.4)	10 (7.9)	0
Psychiatric disorders	27 (9.2)	11 (12.5)	38 (8.4)	1 (10.0)	8 (6.8)	3 (8.3)	13 (9.6)	0	4 (2.5)	3 (6.4)	7 (5.5)	0

Comorbidities by primary system organ class (> 10%) in patients with RA are listed

axSpA axial spondyloarthritis, *BMI* body mass index, *N* number of patients in the treatment group, *n* number of evaluable patients, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation

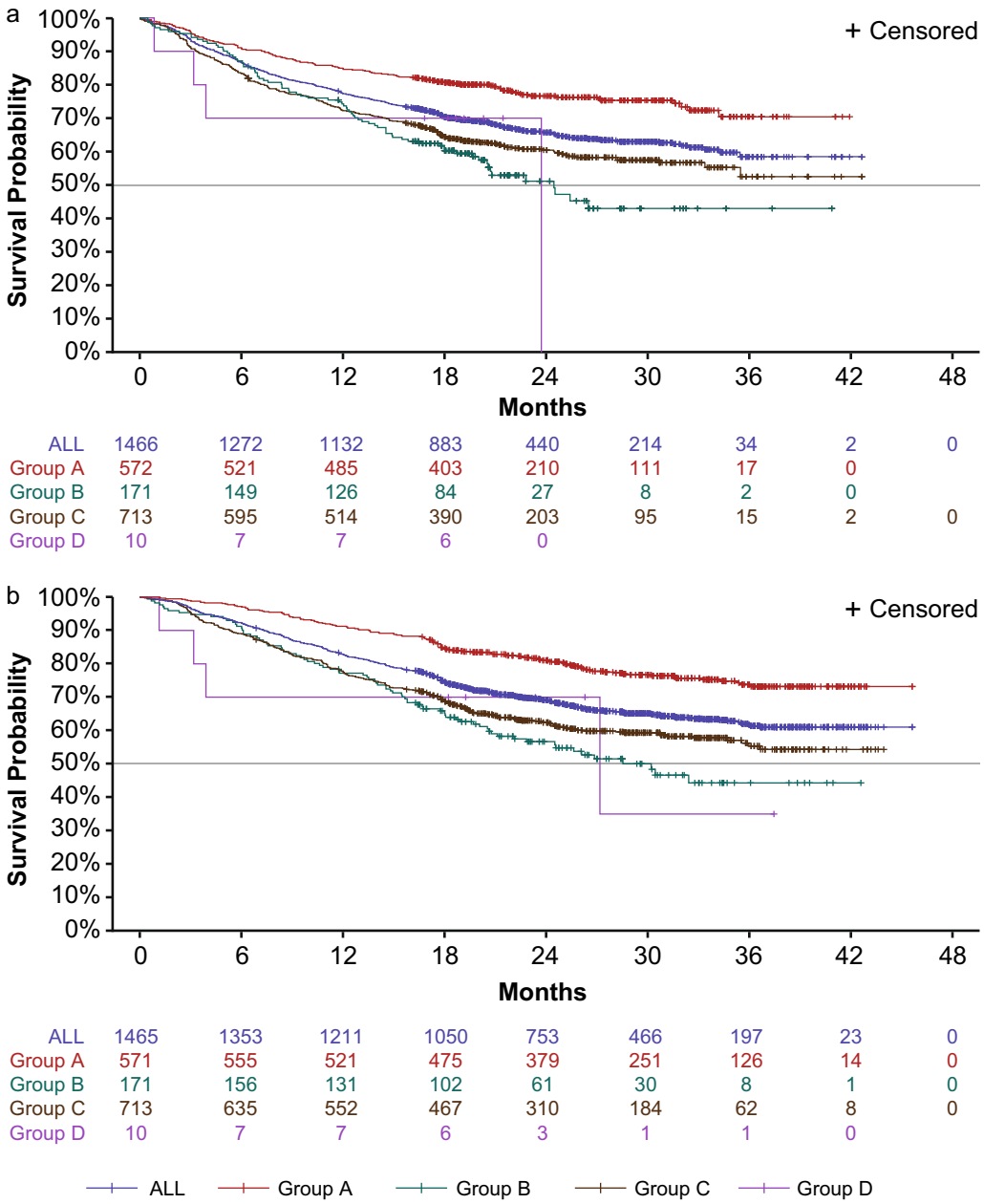

Fig. 2 Kaplan–Meier plot for drug persistence (SDZ ETN) survival analysis (overall population). **a** Drug persistence from enrolment; **b** Drug persistence from SDZ ETN treatment start. Group A, patients in clinical remission or with low disease activity under treatment with ref-ETN or other biosimilar ETN and switched to SDZ ETN; group B, patients who received non-ETN targeted therapies and switched to SDZ ETN; group C, biologic-naïve patients considered uncontrolled with conventional therapy and started on SDZ ETN as the first biologic treatment; group D, DMARD-naïve patients with a recent diagnosis of RA considered suitable for treatment initiation with a biologic and started on treatment with SDZ ETN

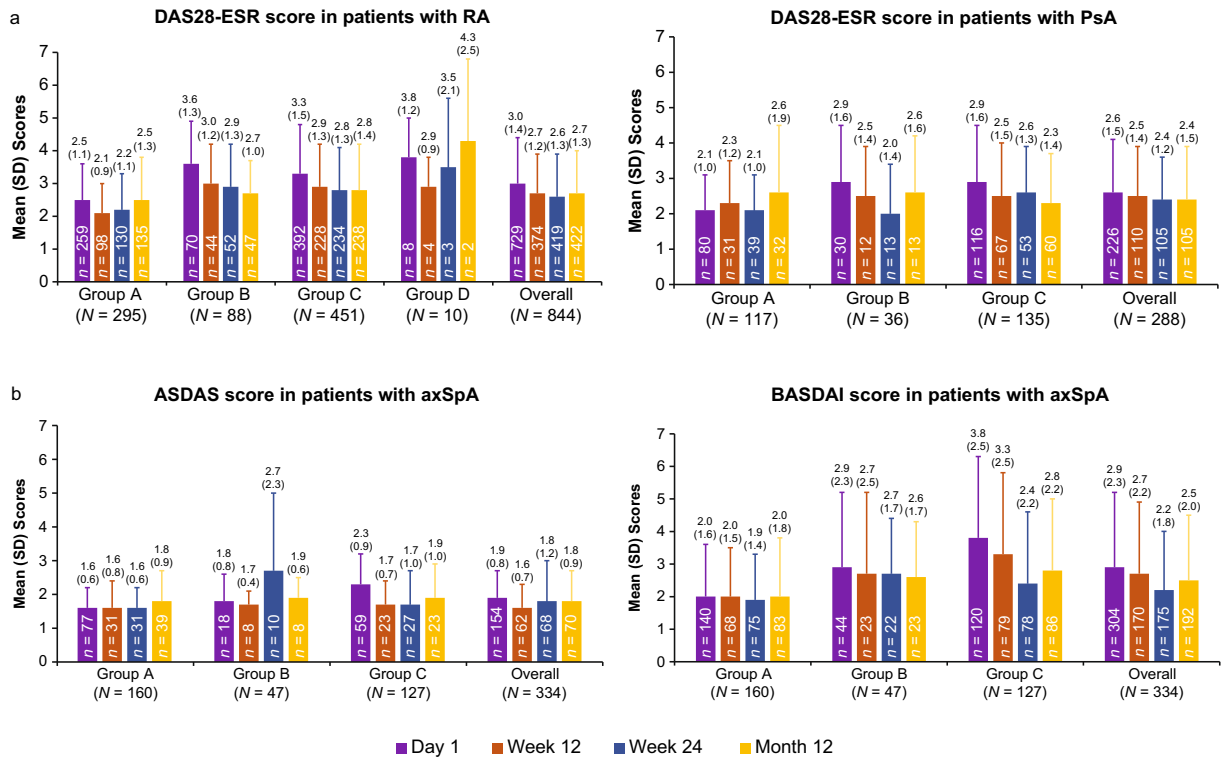

Fig. 3 Effectiveness outcomes across different indications. **a** Disease activity scores in patients with RA and PsA; **b** ASDAS and BASDAI scores in patients with axSpA. *ASDAS* ankylosing spondylitis disease activity score, *axSpA* axial spondyloarthritis, *BASDAI* Bath Ankylosing Spondylitis Disease Activity Index, *DAS28-ESR* Disease Activity Score 28-joint count Erythrocyte Sedimentation Rate, *N* number of patients in the treatment group, *n* number of evaluable patients, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis, *SD* standard deviation

Disease Activity Score in Patients Who Continued or Discontinued the Treatment After Month 12

In patients with RA who continued the treatment after month 12, the overall mean (SD) DAS28-ESR scores at baseline and month 12 were 2.9 (1.4) and 2.6 (1.2), respectively (Supplementary Table 3). In the overall discontinuation group, the mean (SD) DAS28-ESR scores were 3.7 (1.5) and 3.5 (1.5) at baseline and month 12, respectively. In the group that discontinued due to lack of efficacy, the mean (SD) DAS28-ESR scores were 3.8 (1.5) and 3.7 (1.7) at baseline and month 12, respectively.

In patients with PsA who continued the treatment after month 12, the overall mean (SD) DAS28-ESR scores were 2.5 (1.4) and 2.3 (1.5) at baseline and month 12, respectively (Supplementary Table 3). In the overall discontinuation group, the mean (SD) DAS28-ESR scores at baseline and month 12 were 3.4 (1.5) and 3.6 (1.8), respectively. The mean (SD) DAS28-ESR scores at baseline and month 12 were 3.7 (1.3) and 4.6 (1.6), respectively, in the group that discontinued due to lack of efficacy. To note, the number of patients with PsA was limited (12 and 7 patients in the overall discontinuation group and discontinuation due to lack of efficacy group, respectively).

In patients with axSpA who continued the treatment, ASDAS values remain unchanged over 12 months with a mean (SD) of 1.8 (0.8) at baseline versus 1.8 (0.8) at month 12. In the overall discontinuation group, there were only 21 patients at baseline and 4 patients at month 12, for which data on ASDAS were collected (2.4 [0.9] at baseline, 2.9 [1.3] at month 12). In the group that discontinued due to lack of efficacy,

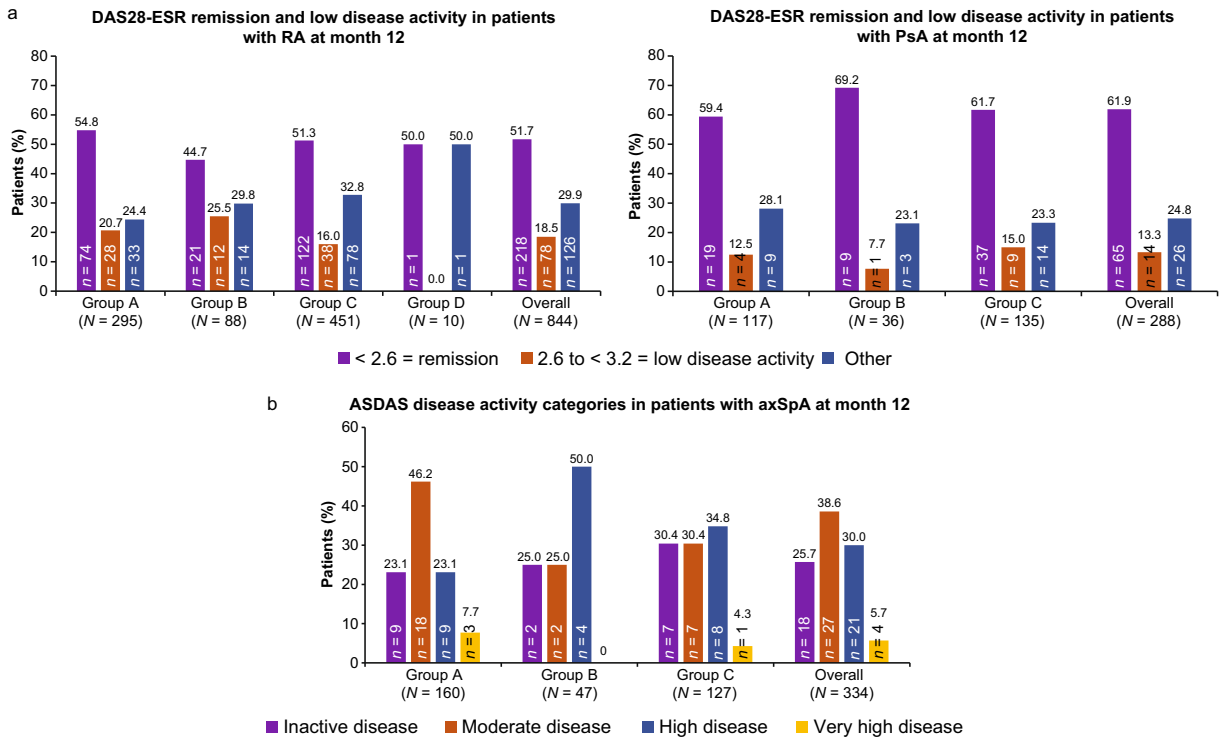

Fig. 4 Disease activity categories across different indications. **a** Disease activity classification in patients with RA and PsA; **b** ASDAS disease activity categories in patients with axSpA at month 12. *ASDAS* ankylosing spondylitis disease activity score, *axSpA* axial spondyloarthritis, *DAS* disease activity score, *N* number of patients in the treatment group, *n* number of evaluable patients, *PsA* psoriatic arthritis, *RA* rheumatoid arthritis

the mean ASDAS at baseline was 2.6 (7 patients), and only 1 patient discontinued due to lack of efficacy at month 12 with an ASDAS of 1.5.

In patients with axSpA who continued the treatment after month 12, the overall mean (SD) BASDAI scores at baseline and month 12 were 2.5 (2.1) and 2.3 (1.9), respectively (Supplementary Table 3). In the overall discontinuation group, the mean (SD) BASDAI scores were 4.7 (2.5) and 3.8 (2.4) at baseline and month 12, respectively. In the group that discontinued due to lack of efficacy, the mean (SD) BASDAI scores were 5.2 (2.6) and 2.9 (2.5) at baseline and month 12, respectively (Supplementary Table 3). To note, the number of patients with axSpA was low; in the group that discontinued treatment due to lack of efficacy, there were only 9 patients for which data on BASDAI could be collected.

PROs and QoL Assessments

In patients with RA, the overall mean (SD) EQ-5D VAS score was 64.9 (22.2) at baseline and 65.5 (21.5) and 64.6 (22.8) at week 12 and month 12, respectively; corresponding scores at baseline, week 12 and month 12 were 61.5 (24.1), 64.8 (21.8) and 69.7 (18.9) in patients with PsA, and 63.6 (22.8), 66.4 (21.1) and 67.5 (22.0) in patients with axSpA, respectively.

Physical function, as assessed by HAQ-DI, indicated mild to moderate difficulty in patient's condition at baseline and over time. Across indications, the majority of the patients had an overall mean (SD) HAQ-DI score < 1, which further reduced through 12 months of treatment.

Other PROs and QoL measures assessed in terms of physical function, health-related QoL, fatigue and pain are presented in Table 2. Overall, the results were comparable across

Table 2 PROs and QoL at baseline and month 12 by indication

Variable, mean ± SD (*n*) unless specified otherwise	RA (*N* = 844)		PsA (*N* = 288)		axSpA (*N* = 334)	
	Day 1	Month 12	Day 1	Month 12	Day 1	Month 12
Physical function						
HAQ-DI	0.9 ± 0.7 (669)	0.8 ± 0.7 (360)	0.7 ± 0.7 (208)	0.6 ± 0.7 (108)	0.7 ± 0.6 (220)	0.5 ± 0.6 (126)
SF-12 physical health	42.1 ± 8.7 (403)	42.7 ± 8.3 (194)	43.8 ± 8.5 (121)	44.3 ± 9.2 (56)	43.6 ± 8.7 (151)	45.4 ± 8.6 (87)
Health-related QoL						
SF-12 mental health	45.9 ± 8.5 (403)	46.8 ± 8.7 (194)	47.1 ± 8.5 (121)	47.4 ± 9.2 (56)	46.9 ± 8.5 (151)	48.3 ± 8.2 (87)
EQ-5D VAS	64.9 ± 22.2 (481)	64.6 ± 22.8 (228)	61.5 ± 24.1 (144)	69.7 ± 18.9 (67)	63.6 ± 22.8 (176)	67.5 ± 22.0 (94)
Fatigue						
FACIT-Fatigue	35.0 ± 9.5 (453)	35.0 ± 9.6 (217)	35.0 ± 9.4 (129)	36.0 ± 9.7 (60)	34.0 ± 9.1 (169)	36.0 ± 8.3 (90)
Fatigue VAS	35.1 ± 26.7 (123)	32.6 ± 25.1 (34)	35.7 ± 28.1 (43)	36.0 ± 25.8 (13)	26.6 ± 25.6 (51)	27.2 ± 29.6 (14)
Pain						
BPI—Interference Score	2.7 ± 2.4 (286)	2.7 ± 2.2 (119)	2.6 ± 2.3 (91)	2.6 ± 2.7 (40)	3.1 ± 2.6 (121)	2.4 ± 2.2 (58)
Pain VAS score	2.9 ± 2.2 (287)	3.0 ± 2.1 (122)	–	–	–	–
Overall pain: experience of pain (Yes), *n* (%)	166 (58.0)	58 (51.3)	53 (57.6)	20 (50.0)	67 (56.3)	28 (51.9)

axSpA axial spondyloarthritis, *BPI* Basic Pain Inventory, *EQ-5D* EuroQoL 5-dimensions, *FACIT* Functional Assessment of Chronic Illness Therapy, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *QoL* quality of life, *PsA* psoriatic arthritis, *PRO* patient-reported outcome, *RA* rheumatoid arthritis, *SD* standard deviation, *SF-12* Short Form Health Survey 12-item, *VAS* visual analogue scale

groups A–C at month 12. No results were analysed for patients in group D due to the low number of patients (Supplementary Tables 4, 5, 6).

Safety

A total of 774 patients (52.8%) reported at least one AE and 374 patients (25.5%) reported at least one ADR during SDZ ETN treatment. The overall summary of AEs by treatment group during SDZ ETN treatment is presented in Table 3. The most commonly (> 5% patients) reported AEs by system organ class were general disorders and administration-site conditions (22.4%), infections and infestations (16.7%), musculoskeletal and connective tissue disorders (11.1%), and investigations (6.1%).

Approximately, 123 patients (8.4%) reported at least one serious AE and 96 patients (6.5%) reported discontinuation due to an AE. Overall, 6 deaths (0.4%) were reported [2 (0.3%) in group A and 4 (0.6%) in group C]. Overall, injection-site reactions were reported in 43 patients (2.9%) (19 [3.3%] in group A, 5 [2.9%] in group B, 19 [2.7%] in group C). COVID-19 infection was reported in 1.4% (n = 21) of patients.

DISCUSSION

COMPACT, a multi-country, non-interventional study designed to ensure systematic and consistent real-world data collection, evaluated the persistence, effectiveness, PROs and safety of SDZ ETN in a broad spectrum of patients with RA, axSpA, or PsA to whom SDZ ETN was recommended by the treating physician in line with the prescribing recommendations in each country. The distribution of the patients in different groups aimed to present the results according to previous therapy and its impact on the treatment response.

Patients who were on previous iETN treatment and who had stable disease presented the best drug survival rates, similar to the previously observed switches between ref-ETN and other biosimilars [21–23]. The high treatment persistence rates with reported discontinuation rates of 8.8% observed at 12 months after SDZ ETN treatment start in group A patients are fully in line with other published data such as those reported by Di Giuseppe et al. [24], who compared treatment retention rates between biosimilars and their reference products based on data from the Swedish Rheumatology Quality Register. The study reported that the 1-year retention rate among patients who switched from ref-ETN to SB4 was 90% (95% CI 89–92). Our results are numerically higher when compared with the data in other real-life cohorts, such as the DANBIO registry [22]; the 1-year adjusted retention rate was 83% in patients who switched from ref-ETN to SB4.

Patients who started SDZ ETN as the first ETN also presented survival rates similar to those previously observed with ref-ETN or other ETN biosimilars [24]. Disease activity, as measured by DAS28, ASDAS and BASDAI, indicated comparable disease activity scores between patients who were switched from iETN, patients switched from other targeted therapies or patients switched after conventional therapy failure after 12 months of treatment with SDZ ETN. Our data confirm no impact on effectiveness and retention after switch from iETN to SDZ ETN. Overall, no major differences in the effectiveness and PROs were observed between baseline and month 12. This could be due to the ongoing SDZ ETN treatment at the time of enrolment for an observed average of 138 days (median [88 days], range 1–841).

Among patients with RA who discontinued due to lack of efficacy, moderate disease activity remained unchanged, therefore showing no improvement. Owing to only a limited number of patients with PsA and low number of patients with axSpA, no meaningful conclusions could be made regarding disease activities in the continued versus discontinued treatment groups. No new safety signals were observed for SDZ ETN, compared to the ref-ETN or other ETN biosimilars [25, 26]. The number of patients with COVID-19-related AEs and injection site-related AEs during the study was low. Injection-site reactions were low across the treatment groups.

A limitation of the study was the descriptive nature of the analyses. Another potential

Table 3 Overall safety profile during SDZ ETN treatment

Category, *n* (%)	Group A *N* = 572	Group B *N* = 171	Group C *N* = 713	Group D *N* = 10	Total A–D *N* = 1466
At least one AE	272 (47.6)	97 (56.7)	399 (56.0)	6 (60.0)	774 (52.8)
At least one ADR	110 (19.2)	53 (31.0)	207 (29.0)	4 (40.0)	374 (25.5)
At least one severe AE	22 (3.8)	10 (5.8)	26 (3.6)	0	58 (4.0)
AEs leading to discontinuation	21 (3.7)	14 (8.2)	59 (8.3)	2 (20.0)	96 (6.5)
At least one ISR	19 (3.3)	5 (2.9)	19 (2.7)	0	43 (2.9)
Deaths	2 (0.3)	0	4 (0.6)	0	6 (0.4)
Most frequent AEs (> 5% of patients in the total group by SOC)					
General disorders and administration-site conditions	95 (16.6)	49 (28.7)	180 (25.2)	4 (40.0)	328 (22.4)
Infections and infestations	94 (16.4)	21 (12.3)	129 (18.1)	1 (10.0)	245 (16.7)
Musculoskeletal and connective tissue disorders	84 (14.7)	12 (7.0)	67 (9.4)	0	163 (11.1)
Investigations	48 (8.4)	5 (2.9)	36 (5.0)	0	89 (6.1)
AEs of special interest	24 (4.2)	7 (4.1)	32 (4.5)	1 (10.0)	64 (4.4)
Most frequent AEs of special interest (> 1% patients in the total group by SOC)					
Infections and infestations	22 (3.8)	4 (2.3)	23 (3.2)	1 (10.0)	50 (3.4)
COVID-19	9 (1.6)	1 (0.6)	10 (1.4)	1 (10.0)	21 (1.4)

ADR adverse drug reaction, *AE* adverse event, *COVID* Coronavirus disease, *ISR* injection-site reaction, *N* number of patients in the treatment group, *n* number of patients with available assessments, *SDZ ETN* Sandoz etanercept, *SOC* system organ class

limitation of the current study design was that the primary endpoint used drug survival rates from study enrolment instead of considering from the start of SDZ ETN treatment, and baseline was considered the day patients had been enrolled in the study instead of the day SDZ ETN treatment was started. Moreover, disease activity measures from when patients started SDZ ETN treatment were not available, and this impacted the results of patients from groups B, C and D. A separate assessment of drug persistence from treatment start date and analysis of discontinuation due to the lack of efficacy and AEs were performed to mitigate this limitation as much as possible.

CONCLUSION

To date, this is the first multi-country real-world study that confirms to have safely and effectively treated a very large set of patients with RA, PsA and axSpA (over 1300) with SDZ ETN under various biosimilar use patterns (groups A–D) in Europe and Canada. The observed high treatment persistence rates and very low discontinuation rates are fully consistent with previously published reports of patients treated with reference or other ETN biosimilars. In addition, PRO data further confirmed the effectiveness of SDZ ETN across these indications. The safety profile of SDZ ETN was consistent with literature on ref-ETN and other ETN biosimilars, with no new safety signals identified through switching. These results may help both patients and healthcare providers with the application of routine-based SDZ ETN.

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Data Availability. The datasets generated and/or analysed during the current study are available upon reasonable request. Anonymised datasets and related documents, such as the statistical analysis plan, protocol, and amendments, can be shared upon reasonable request through a data sharing agreement.

Declarations

Conflict of Interest. Marc Schmalzing: Compensation for consultancies: Chugai/Roche, Hexal/Sandoz, Gilead, AbbVie, Janssen-Cilag, Boehringer/Ingelheim, onkowissen.de, EUSA-Pharma, Novartis, AstraZeneca, Amgen, medac, Lilly, Galapagos, UCB; Speaker's fees: Novartis, AbbVie, AstraZeneca, Chugai/Roche, Janssen-Cilag, Gilead, Boehringer/Ingelheim, Mylan, Galapagos, EUSA-Pharma; Travel grants: Chugai/Roche, Boehringer/Ingelheim, Celgene,

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Ethical Approval. The study was approved for each participating site according to the local regulations. All patients signed an informed consent form that was reviewed and approved by an independent ethics committee or institutional review board. The study design was reviewed by the ethics committees or institutional review boards, and the study was conducted in accordance with the principle of the Declaration of Helsinki. Details of the institutional review boards and ethics committees can be found in Supplementary Table 7.

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