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Real-world 6 and 12-month Drug Retention, Remission and Response Rates of Secukinumab in 2,017 Psoriatic Arthritis patients in 13 European Countries

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ABSTRACT

Objective

There is a lack of real-life studies on IL-17 inhibition in psoriatic arthritis (PsA). We assessed real-life 6-/12-month effectiveness (i.e. retention, remission, low-disease-activity [LDA] and response rates) of the IL-17 inhibitor secukinumab in PsA patients overall, and across 1) number of prior biologic/targeted synthetic Disease-Modifying Anti-Rheumatic Drugs (b/tsDMARDs), 2) years since diagnosis, and 3) European registries.

Methods

Thirteen quality registries in rheumatology participating in the European Spondyloarthritis Research Collaboration Network provided longitudinal, observational data collected as part of

routine care, for secondary use. Data were pooled and analysed with Kaplan-Meier plots, log-rank tests, Cox regression, and multiple linear and logistic regression analyses.

Results

A total of 2,017 PsA patients started treatment with secukinumab between 2015 and 2018. Overall secukinumab retention rates were 86%/76% after 6/12 months. Crude (LUNDEX adjusted) 6-month remission/LDA (LDA including remission) rates for DAPSA28, DAS28-CRP and SDAI were 13%/46% (11%/39%), 36%/55% (30%/46%) and 13%/56% (11%/47%), and 12-month rates 11%/46% (7%/31%), 39%/56% (26%/38%) and 16%/62% (10%/41%), respectively. CDAI remission/LDA rates were similar to the SDAI rates. Six-month ACR20/50/70 responses were 34%/19%/11% (29%/16%/9%); 12-month: 37%/21%/11% (24%/14%/7%).

Secukinumab effectiveness was significantly better for b/tsDMARD naïve patients, similar across time since diagnosis (<2/2-4/>4 years) and varied significantly across the European registries.

Conclusion

In this large real-world study on secukinumab treatment in PsA, 6- and 12-month effectiveness was comparable to previous observational studies of TNFi. Retention, remission, LDA and response rates were significantly better for b/tsDMARD naïve patients, independent of time since diagnosis and varied significantly across the European countries.

SIGNIFICANCE AND INNOVATIONS

- Secukinumab retention, remission, LDA and response rates were significantly better for bionaïve patients after 6 as well as 12 months of treatment.
- Overall 6- and 12-month secukinumab retention rates were high, remission, LDA and response rates were good, and overall effectiveness comparable to previous observational studies of TNFi.
- This is to date the largest real-world study on secukinumab effectiveness in patients with psoriatic arthritis, including 2,017 patients from 13 European national registries.
- The study documents the effectiveness of secukinumab for treatment of psoriatic arthritis

in clinical practice and shows significantly better outcomes for bionaïve patients. This may be taken into consideration in treatment decisions in routine clinical care.

Psoriatic arthritis (PsA) is a heterogeneous inflammatory rheumatic disease affecting e.g. peripheral joints, axial spine, skin and entheses, with significant impact on health-related quality of life.[1-3] The treatment options for PsA have improved during the last few decades with the introduction of biologic Disease-Modifying Anti-Rheumatic Drugs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).[4] Nevertheless, a recent real-world study of >14,000 patients with PsA, who started treatment with a TNF inhibitor, showed that less than half of the patients had achieved clinical remission after 6 months.[5] Thus, there is an unmet need for other treatment options in patients with PsA.[2, 6]

The fully human IgG monoclonal IL-17A inhibitor secukinumab was approved for use in PsA patients in the European Union in 2015.[7] Secukinumab has demonstrated good efficacy and safety in randomized controlled trials (RCTs),[8-10] whereas large observational studies on its effectiveness in patients with PsA are lacking.

Hence, the main objective of this study was to assess the overall real-life 12-month retention rate of secukinumab in PsA patients in Europe. Secondary objectives were to assess the overall 6-month secukinumab retention rate, and 6- and 12-month remission, low-disease activity (LDA) and response rates. These aims were assessed overall, as well as compared across number of previous b/tsDMARD treatments, time since diagnosis and the European registries.

PATIENTS AND METHODS

The European Spondyloarthritis Research Collaboration Network

The European Spondyloarthritis Research Collaboration Network (EuroSpA RCN) currently includes 15 European quality registries of spondyloarthritis patients.[5, 11, 12] The collaboration was initiated in 2016, but data collection had started as early as 1999 in some of the registries. The main aim of the collaboration is to investigate clinically relevant research questions by secondary use of prospectively collected real-life data.[5, 11, 12] All data are anonymized in the different

registries before upload to a secured central server. The data are quality checked and pooled prior to statistical analyses.

Patients

The studies in the EuroSpA collaboration are based on secondary use of real-world data already collected in the different registries, i.e. independently of the current study. In this study we included data from PsA patients starting secukinumab for the first time between May 2015 and December 2018 in 13 countries in the EuroSpA RCN (ranked by number of patients): ARTIS (Sweden), DANBIO (Denmark), SCQM (Switzerland), GISEA (Italy), BIOBADASER (Spain), ATTRA (Czech Republic), biorx.si (Slovenia), Reuma.pt (Portugal), NOR-DMARD (Norway), ROB-FIN (Finland), ICEBIO (Iceland), RRBR (Romania) and TURKBIO (Turkey). Inclusion criteria for the current analyses were age ≥18 years at treatment initiation, a diagnosis of PsA as judged by the treating rheumatologist, and a registered start and, if relevant, stop date of secukinumab. Exclusion criterion was patients with no available clinical data.

Assessments

We included data on age, gender, time since diagnosis, current smoking status (yes/no), body mass index (BMI, kg/m^2), start and stop dates of secukinumab, previous b/tsDMARD treatment, evaluator's global assessment, patient's global assessment, pain and fatigue, C-reactive protein (CRP, mg/L), erythrocyte sedimentation rate (ESR, mm/h), 28-joint Disease Activity index for PSoriatic Arthritis (DAPSA28),[13] 28-joint Disease Activity Score with CRP (DAS28-CRP),[14] Clinical Disease Activity Index (CDAI)[15] and Simplified Disease Activity Index (SDAI).[15] The following remission/low-disease-activity (LDA) and response measures were calculated at 6 and 12 months treatment: DAPSA28 remission (≤4),[13] DAPSA28 LDA (≤14),[13] DAS28-CRP remission (<2.6),[16] DAS28-CRP LDA (≤3.2),[17] CDAI remission (≤2.8),[15] CDAI LDA (≤10),[15] SDAI remission (≤3.3),[15] SDAI LDA (≤11),[15] ACR/EULAR Boolean remission,[18] change in DAPSA28, DAS28-CRP, CDAI and SDAI, ACR 20/50/70 response[19] and EULAR response (moderate/good).[17]

Primary and secondary outcomes

Primary outcome was the overall 12-month secukinumab retention rate, and secondary outcomes were the overall 6-month secukinumab retention rate, and 6- and 12-month remission, LDA and response rates.

Statistical analyses

All statistical analyses were performed according to a predefined statistical analysis plan developed by the researchers in the EuroSpA collaboration. Descriptive statistics were performed for demographics and baseline disease activity measures. All effectiveness analyses were compared across a) the number of previous b/tsDMARDs (0/1/≥2), b) years since diagnosis (<2/2-4/>4) and c) the individual registries. Drug retention was explored by Kaplan-Meier analyses with log-rank test, and by Cox regression analyses adjusted for age, gender and time since diagnosis (comparisons a and c), or age and gender (comparison b). Remission, LDA, response rates and change measures were compared by Chi-Square test, Fisher's exact test and Kruskal-Wallis, as appropriate, as well as by multiple linear and logistic regression analyses adjusted for age, gender and time since diagnosis (comparisons a and c), or age and gender (comparison b), as appropriate. Multiple comparisons for a) were performed by log-rank test, Chi-Square test, Fisher's exact test and Kruskal-Wallis with post hoc Dunn test, as appropriate, where p-values were adjusted by applying the Holm's correction. Significance of relevant groups was tested through likelihood ratio test or Wald test, as appropriate, by comparing two nested models. A significance level of 0.05 was used for all statistical tests. In adjusted analyses Multivariate Imputation by Chained Equations (MICE, including 50 imputed datasets) was used for 463 patients with missing data for time since diagnosis (no missing data for age and gender). The variables used for imputing time since diagnosis were: age, gender, country and b/tsDMARD treatment series number. None of the other variables including outcome was imputed. To avoid inflating remission and response rates, these were provided both as crude values and with LUNDEX[20] adjustment, i.e. integrating clinical response and adherence to therapy in a composite value. In the Kaplan-Meier and Cox regression analyses observations were censored by first occurrence of one of the following: end of registry follow-up or date of data extraction. Patients who stopped treatment due to remission or other reasons (e.g. pregnancy) were censored at the

stop date to reflect that their withdrawal was not due to lack of effectiveness or adverse events. The baseline date was defined as the secukinumab treatment start date. To assess the robustness regarding the main outcomes, sensitivity analyses for patients 1) having ≥1 swollen joint out of 28 at baseline and 2) having date of data extraction at least 12 months after secukinumab treatment start were performed. Competing risk analysis was performed for a cumulative incidence curve showing withdrawal due to adverse events and lack of effectiveness. Numbers available for each of the analyses are shown in Supplementary Tables S1, S3 and S5-S9. Statistical analyses were performed with R version 3.6.1.

Ethics

Approval of the study was obtained from the respective national Data Protection Agencies and Research Ethical Committees according to the individual legal regulatory requirements in the different registries/countries. The study was performed in accordance with the Declaration of Helsinki and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[21]

RESULTS

We included a total of 2,017 PsA patients who started secukinumab for the first time (Table 1). The number of patients included from the different European registries varied from 30 (TURKBIO) to 657 (ARTIS). Significant heterogeneity in demographics and baseline disease activity across the European registries was found (Supplementary Table S1). Information on doses was not registered systematically. Of 745 patients in whom doses were registered, 42% of the patients initiated secukinumab 150 mg and 58% secukinumab 300 mg.

Secukinumab retention rates

Overall

The crude 95% CI secukinumab retention rates were overall 76% (74-78%) after 12 months and 86% (85-88%) after 6 months of treatment (Table 2).

Comparison across subgroups

Secukinumab retention rates after 6 as well as 12 months of treatment were significantly higher in bionaïve patients compared with patients previously treated with 2 or more b/tsDMARDs. (Table 2, Figure 1a). The findings were similar in 6 and 12-month adjusted Cox regression analyses (Supplementary Table S2a).

Secukinumab retention was not significantly associated with time since diagnosis, neither in unadjusted nor in adjusted analyses (Supplementary Table S2b and S3).

The number of included patients varied considerably across the European registries (from 30 to 657 patients). Significant differences in retention rates across the registries were observed with 6-month retention rates varying between 80% (DANBIO) and 97% (TURKBIO), and 12-month retention rates varying from 51% (ROB-FIN) to 92% (RRBR and ATTRA) (Table 3, Figure 2). Similar differences were found in adjusted analyses (Supplementary Table S2c).

Remission

Overall

Crude and LUNDEX adjusted proportions of patients achieving DAPSA28, DAS28-CRP, SDAI and CDAI remission after 6 and 12 months are presented in Table 2. DAPSA28, SDAI and CDAI remission rates were similar (approx. 10-15%), whereas approximately one third of the patients achieved DAS28-CRP remission.

Comparison across subgroups

The proportion of patients achieving remission were significantly higher in bionaïve patients than in patients previously treated with 1 and ≥2 b/tsDMARDs (Table 2, Figure 3 [12 months' results] and Supplementary Figure 1 [6 months' results]). Adjusted analyses gave similar results (Supplementary Table S4).

Crude and adjusted remission rates at 6 and 12 months of treatment were independent of time since diagnosis (Supplementary Tables S3 and S4).

Overall, heterogeneity in crude and adjusted remission rates across the European registries were found (Table 3 and Supplementary Table S9).

Low disease activity (including remission)

Overall

Crude and LUNDEX adjusted proportions of patients achieving DAPSA28, DAS28-CRP, SDAI and CDAI LDA after 6 and 12 months of treatment are presented in Table 2, Figure 3 (12 months' results) and Supplementary Figure 1 (6 months' results).

Comparison across subgroups

Overall, crude and LUNDEX adjusted LDA rates were significantly higher in bionaïve patients, also in adjusted analyses (Supplementary Table S4).

For all outcomes, achievement of LDA was independent of time since diagnosis (Supplementary Table S3), also after adjustment (Supplementary Table S4).

Significant heterogeneities in crude (Table 3) and adjusted (Supplementary Table S4) LDA rates were seen between the registries.

Response rates

Overall

ACR20/50/70 responses were achieved by 34%/19%/11% of the patients and EULAR moderate/good response by 59% of the patients after 6 months. After 12 months, numbers were largely the same (Table 2). Changes in outcome measures from baseline to 6 months (and 12 months, respectively) were: DAPSA28 -9.5 (-10.3), DAS28-CRP -0.9 (-1.1), SDAI -8.9 (-9.7) and CDAI -8.0 (-8.8).

Comparison across subgroups

Significantly better outcomes for ACR20/50/70 and EULAR moderate/good responses were observed for bionaïve patients (Table 2, Figure 3 [12 months' results] and Supplementary Figure 1 [6 months' results]), also after adjustment (Supplementary Table S4).

Response rates were independent of time since diagnosis (Supplementary Table S3), also in adjusted analyses (Supplementary Table S4).

Significant heterogeneity in response rates between the European registries were found in crude as well as adjusted analyses (Table 3 and Supplementary table S4).

Safety

Of the 2,017 patients starting secukinumab 1,543 patients started treatment at least 12 months before date of data extraction. Of these 1,543 patients 602 patients withdrew from secukinumab before 12 months, thereof 107 patients due to adverse events. Time in weeks to secukinumab withdrawal for these 107 patients was similar across number of previous b/tsDMARDs (0/1/≥2) (Table 2). More patients withdrew from secukinumab due to lack of effectiveness than due to adverse events (Table 2). The cumulative incidence curve, which estimates the cumulative probabilities of treatment withdrawal over time, shows that the cumulative probability of withdrawal due to lack of effectiveness is higher than adverse events after about 4 months of treatment (Figure 1b).

Sensitivity analyses

Sensitivity analyses of 976 patients with ≥1 swollen joint out of 28 at the start of secukinumab treatment showed largely similar results to the analyses in Table 2 (Supplementary Table S5). Sensitivity analyses of patients with secukinumab initiation at least 12 months before date of data extraction also showed largely similar results, but did not reach significance for the 6-month comparison of retention rates across number of previous b/tsDMARDs (b/tsDMARD naïve: 89% (86-93%), 1 prior b/tsDMARD: 85% (81-89%), ≥2 prior b/tsDMARDs: 85% (82-87%), p=0.107, Supplementary table S6).

DISCUSSION

This large real-life study of secukinumab effectiveness (i.e. drug retention, remission, LDA and response rates) included 2,017 patients with PsA treated as part of routine care in 13 countries across Europe. Overall, high 6-month (86%) and 12-month (76%) secukinumab retention rates were found. Secukinumab effectiveness was significantly better for bionaïve patients after 6 as well as 12 months of treatment, was independent of time since diagnosis and differed significantly across the European countries. Remission, LDA and response rates were overall comparable to previous real-life observations in patients treated with a TNFi.[5] Hence, this large observational study documents the effectiveness of secukinumab in the treatment of PsA patients.

Secukinumab effectiveness has previously been reported in one observational study of 76 Spanish PsA patients, in which 12-month retention rates were somewhat higher than in our study; for bionaïve patients it was 91% and for non-naïve patients 82%.[22] Good 1-year secukinumab effectiveness has also been reported in an Italian observational study of 130 PsA patients.[23] In the FUTURE 1 RCT 89% of the patients in the 150 mg secukinumab group reached 52 weeks, and ACR20/50 responses at week 24 and 52 were achieved by 50%/35% and 60%/43% of the patients, respectively.[24] In our observational study ACR20/50 responses at week 26 and 52 were lower than in FUTURE 1 (34%/19% and 37%/21%), probably reflecting that the study designs differed substantially (longitudinal observational study with 22% bionaïve patients vs. RCT with 71% bionaïve patients). In the FUTURE 5 RCT, 91% of the patients treated with 150 mg secukinumab completed 52 weeks of treatment, with ACR20/50/70 responses of 64%/41%/26%, thus substantially higher than in our study.[10]

Interestingly, the overall secukinumab retention rates in this real-life study were similar to the retention rates of TNFi in a recently published observational study of 14,261 European bionaïve PsA patients (86% vs. 86% at 6 months; 76% vs. 77% at 12 months, respectively), and numerically slightly higher for bionaïve secukinumab than TNFi starters (90% vs. 86% at 6 months and 82% vs. 77% at 12 months, respectively).[5] Overall, remission and response rates for patients treated with secukinumab were fairly similar to what was reported for TNFi,[5] as well as to the effectiveness of TNFi reported in other, smaller observational studies.[25-28]

Similar to findings in observational studies on TNFi, and in the FUTURE 2 and 5 trials, the current study demonstrated that effectiveness of secukinumab declines with increasing previous use of b/tsDMARDs, possibly reflecting confounding by indication.[9, 27, 29, 30] The similar secukinumab effectiveness for patients with different disease durations found in this study is also in accordance with previous findings for TNFi in patients with PsA.[31-33]

In the 2017 updated treat-to-target recommendations for PsA, DAPSA and MDA are the preferred measures to define treatment target in PsA patients.[34] In our study, DAPSA (including a 66/68 joint count)[35] was only available in a minority of patients. Instead we used DAPSA28, which only requires a 28 joint count.[13] DAPSA28 has shown good criterion, correlational and construct validity, as well as sensitivity to change, although the original DAPSA should be preferred when

available.[13] MDA was not assessed in the study due to lack of data on enthesitis and psoriasis in the majority of registries.

We chose DAS28-CRP over DAS28-ESR, due to less missing data for DAS28-CRP. Overall, DAS28-CRP was a more liberal remission criterion than SDAI, CDAI and DAPSA28 in our study, which is consistent with previous reports.[5, 12, 36, 37] In the DAPSA28, SDAI and CDAI LDA measures we chose to include remission, in accordance with the DAS28 LDA - as we believe rheumatologists will be mainly interested in knowing how many patients that at least were in LDA (i.e. in LDA or remission).

The major strength of the study is the 12-month longitudinal, observational study design with inclusion of a high number of PsA patients from 13 different countries. Furthermore, the data included in the study is collected independently of commercial interests as part of standard care. Hence, although Novartis supports the EuroSpA collaboration, Novartis had no influence on data collection, statistical analyses, manuscript preparation, or the decision to submit. Major limitations of the study include lack of data on extra-articular inflammatory involvement and that data on the optimal number of joints (66/68) were generally not available, which may have led to underestimation of disease activity. Furthermore, DAS28, CDAI and SDAI are composite scores originally developed for RA and not PsA.

Heterogeneity in baseline characteristics and secukinumab effectiveness across the registries was found. Importantly, the number of included patients (from 30 to 657) and proportions of bionaïve patients (from 5% to 97%) varied considerably across the registries and may explain some of the heterogeneity in effectiveness measures, e.g. a higher proportion of bionaïve patients may positively impact upon treatment outcomes. Moreover, low patient numbers in some registries will lead to more uncertain estimates, i.e. single patients will have a higher influence on outcomes. Also, the influence of different treatment guidelines and access to treatment in the different European countries were not accounted for in this study. Hence, interpretation of the pooled analyses should be done with caution. Of note, however, consistent results in prespecified unadjusted and adjusted analyses were found.

Furthermore, as often the case in observational studies, some missing data on disease states and response rates were observed, challenging the generalizability of the findings. However, the

study is by far the largest real-life study to date on secukinumab effectiveness in patients with PsA.

In conclusion, in this longitudinal observational study of more than 2000 patients with PsA treated with secukinumab we found high retention rates after 6 and 12 months of treatment, and good remission, LDA and response rates. Secukinumab effectiveness was significantly better for bionaïve patients, was independent of time since diagnosis and varied across European registries.

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Table 1 Demographics and baseline disease activity measures

	All patients (n=2,017)	b/tsDMARD naïve (n=441)	1 prior b/tsDMARD (n=461)	≥2 prior b/tsDMARDs (n=1,115)	p-value*
Age (years)	52 (44-60)	50 (41-58)	51 (44-59)	53 (45-60)	<0.001
Men	43%	51%	46%	39%	<0.001
Years since diagnosis	7 (3-13)	4 (1-10)	6 (2-12)	8 (5-14)	<0.001
Current smokers	19%	18%	22%	18%	0.356
Body mass index (kg/m²)	27.5 (24.3-31.2)	28.1 (24.1-31.8)	27.3 (24.1-30.1)	27.3 (24.5-31.6)	0.309
First (*last previous*) b/tsDMARD treatment,					
Adalimumab	29% (*21%*)	-	30% (*30%*)	28% (*18%*)	<0.001 (*<0.001*)
Certolizumab	5% (*8%*)	-	5% (*5%*)	5% (*10%*)	
Etanercept	28% (*22%*)	-	25% (*25%*)	29% (*20%*)	
Golimumab	10% (*12%*)	-	9% (*9%*)	10% (*13%*)	
Infliximab	22% (*13%*)	-	15% (*15%*)	25% (*12%*)	
Other**	7% (*24%*)	-	15% (*15%*)	3% (*27%*)	
CRP	5 (2-12)	7 (2-19)	4 (2-9)	5 (2-12)	<0.001
ESR	16 (7-31)	20 (8-36)	13 (6-27)	16 (7-30)	0.002
28 tender joint count	4 (1-9)	5 (1-10)	3 (1-8)	4 (1-9)	<0.001
28 swollen joint count	1 (0-4)	2 (0-6)	1 (0-3)	2 (0-4)	<0.001
Patient's global	70 (50-83)	70 (51-84)	67 (42-80)	70 (50-85)	<0.001
Pain	66 (46-80)	65 (45-78)	62 (40-78)	68 (48-81)	<0.001
Fatigue	70 (50-85)	65 (50-80)	65 (41-80)	73 (55-87)	<0.001

Evaluator's global	40 (20-60)	57 (30-75)	35 (20-50)	35 (20-50)	<0.001
HAQ	1.1 (0.6-1.6)	1.0 (0.5-1.5)	1.0 (0.5-1.4)	1.2 (0.8-1.8)	<0.001
DAPSA28	25.9 (17.4-37.6)	29.1 (19.1-41.9)	22.3 (13.5-32.4)	26.2 (18.0-37.6)	<0.001
DAS28-CRP	4.2 (3.2-5.0)	4.5 (3.6-5.4)	3.8 (2.7-4.6)	4.2 (3.3-5.0)	<0.001
SDAI	19.5 (12.9-28.9)	24.4 (15.3-35.4)	16.9 (10.0-24.3)	18.9 (13.0-27.5)	<0.001
CDAI	18.0 (12.0-26.7)	22.6 (14.3-33.9)	16.0 (8.9-23.6)	17.5 (12.0-25.4)	<0.001

*Comparisons between b/tsDMARD naïve, 1 prior and ≥2 prior b/tsDMARD treated patients were performed with Kruskal-Wallis or Chi-square test, as appropriate. ** "Other previous b/tsDMARDs" include ustekinumab, rituximab, abatacept, tocilizumab, apremilast, anakinra, and additionally (never as first b/tsDMARD) baricitinib and tofacitinib. Patients were included between May 2015 and December 2018. Shown are median (IQR) unless otherwise indicated (%). *Number available for each of the analyses are shown in Supplementary Table S7.* CDAI, Clinical Disease Activity Index; CRP, C-reactive protein, mg/L; DAPSA28, 28-joint Disease Activity index for PSoriatic Arthritis; DAS28-CRP, 28-joint Disease Activity Score with CRP; b/tsDMARD, biologic/targeted synthetic Disease-Modifying Anti-Rheumatic Drug; ESR, erythrocyte sedimentation rate, mm/h; HAQ, Health Assessment Questionnaire; IQR, interquartile range; SDAI, Simplified Disease Activity Index

Table 2 Treatment effectiveness after 6 and 12 months of secukinumab treatment (unadjusted analyses)

		All patients (n=2,017)	b/tsDMARD naïve (n=441)	1 prior b/tsDMARD (n=461)	≥2 prior b/tsDMARDs (n=1,115)	p-value*
Secukinumab drug retention rate, % (95% CI)	**6 months**	86% (85-88%)	90% (87-93%)	86% (83-90%)	85% (83-87%)	0.045[b]
	12 months	76% (74-78%)	82% (78-86%)	78% (74-82%)	72% (70-75%)	0.001[b]
Time in weeks to secukinumab withdrawal before 12 months, median (IQR), due to:**						
Primary and secondary lack of effectiveness		24 (17-33)	24 (17-35)	24 (17-30)	24 (17-34)	0.691
Adverse events		14 (6-28)	22 (13-28)	15 (7-25)	12 (5-29)	0.395
Remission		21 (20-43)	20 (19-20)	-	43 (32-43)	0.236
Other reasons		21 (12-32)	27 (15-40)	10 (4-36)	21 (15-27)	0.161
DAPSA28	**6 months**	15.1 (8.2-25.0)	10.1 (5.2-17.5)	15.7 (9.0-22.0)	16.9 (9.6-27.1)	<0.001 [a,b]
	12 months	14.9 (8.1-24.8)	10.2 (4.1-16.3)	15.2 (8.4-23.6)	16.3 (10.0-26.0)	<0.001 [a,b]
DAS28-CRP	**6 months**	3.0 (2.2-4.0)	2.5 (1.9-3.3)	3.1 (2.2-3.9)	3.2 (2.4-4.2)	<0.001 [a,b,c]
	12 months	3.0 (2.2-4.0)	2.5 (1.7-3.3)	3.0 (2.1-3.9)	3.2 (2.4-4.2)	<0.001 [a,b]
SDAI	**6 months**	10.2 (5.4-16.7)	6.9 (3.5-11.0)	10.4 (6.3-15.3)	11.4 (6.6-18.5)	<0.001 [a,b]
	12 months	9.2 (5.2-15.2)	5.7 (2.5-9.5)	9.3 (5.8-16.2)	10.5 (6.8-16)	<0.001 [a,b]
CDAI	**6 months**	9.3 (4.9-15.9)	6.2 (3.4-10.5)	9.4 (5.5-14.4)	10.9 (6.0-17.8)	<0.001 [a,b,c]
	12 months	8.5 (4.4-14.2)	5.1 (2.1-9.3)	8.7 (5.2-14.6)	9.8 (5.8-14.9)	<0.001 [a,b]
Change in DAPSA28 from baseline	**6 months**	-9.5 (-20.7,-0.2)	-17.2 (-27.5,-8.3)	-8.5 (-17.6,-0.1)	-6.6 (-18.3,0.3)	<0.001 [a,b]
	12 months	-10.3 (-21.9,-1.3)	-16.2 (-28.0,-8.3)	-5.0 (-10.6,1.0)	-10.3 (-21.9,-0.2)	<0.001 [a,b,c]

Change in DAS28-CRP from baseline		**6 months**	-0.9 (-1.9,-0.1)	-2.0 (-3.0,-1.1)	-0.8 (-1.7,0.1)	-0.6 (-1.6,0.01)	<0.001 [a,b]
		12 months	-1.1 (-2.0,-0.1)	-1.9 (-3.1,-1.0)	-0.5 (-1.3,0.03)	-1.0 (-1.9,-0.02)	<0.001 [a,b,c]
Change in SDAI from baseline		**6 months**	-8.9 (-17.4,-2.0)	-16.9 (-26.1,-9.3)	-7.5 (-13.5,-1.1)	-6.0 (-13.4,-0.2)	<0.001 [a,b]
		12 months	-9.7 (-18.6,-2.4)	-15.0 (-24.2,-7.5)	-4.9 (-10.4,1.3)	-9.6 (-17.9,-2.2)	<0.001 [a,b,c]
Change in CDAI from baseline		**6 months**	-8.0 (-16.1,-1.6)	-15.1 (-24.6,-8.0)	-6.0 (-13.1,-1.4)	-5.3 (-12.2,-0.1)	<0.001 [a,b]
		12 months	-8.8 (-16.0,-2.0)	-13.9 (-21.5,-7.3)	-5.0 (-10.4,0.8)	-8.1 (-15.9,-1.5)	<0.001 [a,b,c]
DAPSA28 ≤4	**6 months**	**Crude**	13%	23%	13%	10%	<0.001 [b]
		LUNDEX adjusted**	11%	20%	11%	8%	<0.001 [a,b]
	12 months	**Crude**	11%	22%	11%	8%	<0.001 [a,b]
		LUNDEX adjusted**	7%	17%	7%	5%	<0.001 [b]
DAPSA28 ≤14	**6 months**	**Crude**	46%	64%	45%	41%	<0.001 [a,b]
		LUNDEX adjusted**	39%	57%	37%	34%	<0.001 [a,b]
	12 months	**Crude**	46%	70%	46%	40%	<0.001 [a,b]
		LUNDEX adjusted**	31%	52%	30%	26%	<0.001 [a,b]
DAS28-CRP <2.6	**6 months**	**Crude**	36%	53%	35%	30%	<0.001 [a,b]
		LUNDEX adjusted**	30%	47%	29%	25%	<0.001 [a,b]
	12 months	**Crude**	39%	55%	41%	34%	<0.001 [a,b]
		LUNDEX adjusted**	26%	41%	27%	21%	<0.001 [a,b]
DAS28-CRP ≤3.2	**6 months**	**Crude**	55%	71%	57%	49%	<0.001 [a,b]
		LUNDEX adjusted**	46%	63%	47%	40%	<0.001 [a,b]
	12 months	**Crude**	56%	72%	55%	51%	<0.001 [a,b]
		LUNDEX adjusted**	38%	54%	37%	33%	<0.001 [a,b]

SDAI ≤3.3	**6 months**	**Crude**	13%	24%	13%	9%	<0.001 [a,b]
		LUNDEX adjusted**	11%	21%	11%	8%	<0.001 [a,b]
	12 months	**Crude**	16%	32%	11%	11%	<0.001 [a,b]
		LUNDEX adjusted**	10%	24%	8%	7%	<0.001 [a,b]
SDAI ≤11	**6 months**	**Crude**	56%	75%	56%	48%	<0.001 [a,b]
		LUNDEX adjusted**	47%	66%	47%	39%	<0.001 [a,b]
	12 months	**Crude**	62%	81%	58%	56%	<0.001 [a,b]
		LUNDEX adjusted**	41%	61%	39%	36%	<0.001 [a,b]
CDAI ≤2.8	**6 months**	**Crude**	13%	19%	12%	10%	0.004 [b]
		LUNDEX adjusted**	10%	17%	10%	8%	0.002 [b]
	12 months	**Crude**	16%	32%	14%	11%	<0.001 [a,b]
		LUNDEX adjusted**	11%	24%	10%	7%	<0.001 [a,b]
CDAI ≤10	**6 months**	**Crude**	55%	74%	58%	46%	<0.001 [a,b]
		LUNDEX adjusted**	46%	66%	48%	38%	<0.001 [a,b]
	12 months	**Crude**	59%	79%	58%	53%	<0.001 [a,b]
		LUNDEX adjusted**	40%	59%	39%	34%	<0.001 [a,b]
ACR/EULAR Boolean remission	**6 months**	**Crude**	9%	20%	8%	6%	<0.001 [a,b]
		LUNDEX adjusted**	8%	18%	6%	5%	<0.001 [a,b]
	12 months	**Crude**	9%	17%	9%	6%	<0.001 [b]
		LUNDEX adjusted**	6%	12%	6%	4%	<0.001 [b]
ACR20 response	**6 months**	**Crude**	34%	59%	26%	27%	<0.001 [a,b]
		LUNDEX adjusted**	29%	52%	22%	22%	<0.001 [a,b]
	12 months	**Crude**	37%	63%	16%	33%	<0.001 [a,b]
		LUNDEX adjusted**	24%	47%	10%	21%	<0.001 [a,b]

ACR50 response	**6 months**	**Crude**	19%	41%	11%	13%	<0.001 [a,b]
		LUNDEX adjusted**	16%	36%	9%	11%	<0.001 [a,b]
	12 months	**Crude**	21%	45%	4%	16%	<0.001 [a,b]
		LUNDEX adjusted**	14%	34%	3%	10%	<0.001 [a,b]
ACR70 response	**6 months**	**Crude**	11%	26%	7%	6%	<0.001 [a,b]
		LUNDEX adjusted**	9%	23%	6%	5%	<0.001 [a,b]
	12 months	**Crude**	11%	28%	4%	6%	<0.001 [a,b]
		LUNDEX adjusted**	7%	21%	3%	4%	<0.001 [a,b]
EULAR good/moderate response	**6 months**	**Crude**	59%	83%	57%	50%	<0.001 [a,b]
		LUNDEX adjusted**	49%	74%	48%	41%	<0.001 [a,b]
	12 months	**Crude**	60%	79%	44%	59%	<0.001 [a,b]
		LUNDEX adjusted**	40%	59%	30%	38%	<0.001 [a,b]

*Drug retention rates were compared across the three groups with Kaplan-Meier with log-rank test, continuous measures by Kruskal-Wallis and proportions by Chi-square test or Fisher's exact test, as appropriate. Multiple comparisons between groups were conducted by log-rank test, Kruskal-Wallis with post hoc Dunn test, Chi-square test or Fisher's exact test, as appropriate, with p-values to be adjusted by applying the Holm's correction; [a] Statistically significant difference between b/tsDMARD naïve patients and patients treated with 1 prior b/tsDMARD; [b] Statistically significant difference between b/tsDMARD naïve patients and patients treated with ≥2 prior b/tsDMARDs; [c] Statistically significant difference between patients treated with 1 prior b/tsDMARD and ≥2 prior b/tsDMARDs. Significance level for all tests is 0.05 **Patients with at least 12 months from secukinumab start to date of data extraction. *Patients who stopped treatment due to remission or other reasons (e.g. pregnancy) were censored at the stop date to reflect that their withdrawal was not due to lack of effectiveness or adverse events*; Shown are median (IQR) unless otherwise indicated. *Number available for each of the analyses are shown in Supplementary Table S8.* ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAPSA28, 28-joint Disease Activity index for PSoriatic Arthritis; DAS28-CRP, 28-joint Disease Activity Score with CRP; b/tsDMARD, biologic/targeted synthetic Disease Modifying Anti-Rheumatic Drug; IQR, interquartile range; EULAR, European League Against Rheumatism; SD, standard deviation; SDAI, Simplified Disease Activity Index

Table 3 Retention, remission, LDA (including remission) and response rates after 6 and 12 months of secukinumab treatment across European observational registries (unadjusted analyses)

	Months		ARTIS (n=657)	ATTRA (n=151)	BIO-BADASER (n= 154)	biorx.si (n=79)	DANBIO (n=313)	GISEA (n=180)	ICEBIO (n=38)	NOR-DMARD (n=60)	Reuma.pt (n=68)	ROB-FIN (n=47)	RRBR (n=37)	SCQM (n=203)	TURKBIO (n=30)	p-value*
Drug retention rate, % (95% CI)	**6**		82% (79-85%)	94% (90-98%)	93% (89-97%)	92% (87-98%)	80% (75-84%)	96% (93-99%)	87% (77-98%)	83% (74-94%)	91% (84-98%)	83% (73-94%)	92% (83-100%)	90% (85-94%)	97% (90-100%)	<0.001
	12		66% (62-70%)	92% (88-97%)	84% (78-91%)	89% (82-96%)	70% (65-76%)	88% (82-93%)	77% (64-93%)	72% (61-86%)	86% (78-96%)	51% (39-68%)	92% (83-100%)	82% (77-88%)	-	<0.001
DAPSA28 ≤4	**6**	**Crude**	8%	22%	-	11%	12%	-	0%	14%	14%	19%	-	35%	21%	<0.001
		Lundex	6%	21%	-	10%	9%	-	0%	12%	13%	16%	-	31%	-	<0.001
	12	**Crude**	6%	23%	-	10%	14%	-	NC	16%	16%	NC	-	15%	NC	0.004
		Lundex	3%	20%	-	9%	9%	-	NC	11%	14%	NC	-	12%	-	0.002
DAPSA28 ≤14	**6**	**Crude**	37%	61%	-	53%	44%	-	42%	61%	54%	54%	-	58%	74%	<0.001
		Lundex	30%	58%	-	49%	33%	-	35%	50%	49%	45%	-	51%	-	<0.001
	12	**Crude**	35%	79%	-	48%	46%	-	NC	68%	63%	NC	-	59%	NC	<0.001
		Lundex	19%	67%	-	42%	29%	-	NC	49%	55%	NC	-	47%	-	<0.001
DAS28-CRP <2.6	**6**	**Crude**	27%	46%	50%	40%	33%	-	29%	54%	45%	42%	60%	49%	63%	<0.001
		Lundex	21%	44%	44%	37%	25%	-	24%	44%	41%	35%	52%	43%	-	<0.001
	12	**Crude**	25%	62%	49%	46%	41%	-	50%	63%	50%	NC	NC	41%	NC	<0.001
		Lundex	14%	53%	36%	41%	26%	-	37%	45%	44%	NC	NC	33%	-	<0.001

DAS28-CRP ≤3.2	**6**	**Crude**	45%	62%	69%	64%	53%	-	64%	79%	64%	73%	73%	60%	74%	<0.001
		Lundex	36%	58%	60%	59%	40%	-	54%	64%	58%	61%	64%	53%	-	<0.001
	12	**Crude**	43%	80%	73%	60%	54%	-	75%	68%	80%	NC	NC	76%	NC	<0.001
		Lundex	23%	69%	54%	52%	34%	-	55%	49%	70%	NC	NC	61%	-	<0.001
SDAI ≤3.3	**6**	**Crude**	6%	21%	-	16%	12%	-	0%	10%	18%	21%	24%	21%	21%	0.003
		Lundex	5%	20%	-	15%	9%	-	0%	8%	16%	17%	21%	18%	-	0.003
	12	**Crude**	8%	32%	-	23%	14%	-	NC	25%	5%	NC	NC	15%	NC	0.002
		Lundex	4%	27%	-	20%	8%	-	NC	18%	4%	NC	NC	12%	-	<0.001
SDAI ≤11	**6**	**Crude**	42%	68%	-	58%	54%	-	46%	67%	64%	67%	76%	65%	74%	<0.001
		Lundex	33%	64%	-	53 %	41%	-	39%	54%	58%	55%	66%	57%	-	<0.001
	12	**Crude**	50%	88%	-	56%	55%	-	NC	83%	85%	NC	NC	67%	NC	<0.001
		Lundex	27%	75%	-	49%	35%	-	NC	59%	74%	NC	NC	53%	-	<0.001
CDAI ≤2.8	**6**	**Crude**	6%	18%	-	12%	14%	-	0%	9%	11%	12%	20%	23%	21%	0.007
		Lundex	5%	17%	-	11%	10%	-	0%	7%	10%	10%	17%	21%	-	0.008
	12	**Crude**	8%	31%	-	19%	14%	-	14%	25%	10%	NC	NC	23%	NC	0.003
		Lundex	4%	27%	-	17%	9%	-	10%	18%	9%	NC	NC	18%	-	<0.001
CDAI ≤10	**6**	**Crude**	41%	68%	-	60%	53%	-	41%	59%	64%	62%	76%	64%	74%	<0.001
		Lundex	33%	64%	-	55%	40%	-	35%	48%	58%	52%	66%	56%	-	<0.001
	12	**Crude**	44%	88%	-	58%	56%	-	57%	83%	80%	NC	NC	63%	NC	<0.001
		Lundex	24%	75%	-	51%	35%	-	42%	59%	70%	NC	NC	50%	-	<0.001

ACR/EULAR Boolean remission	**6**	**Crude**	5%	22%	18%	9%	9%	0%	0%	8%	6%	12%	23%	15%	16%	<0.001
		Lundex	4%	21%	15%	8%	7%	0%	0%	7%	6%	10%	20%	13%	-	<0.001
	12	**Crude**	5%	24%	15%	7%	9%	0%	5%	10%	8%	15%	NC	7%	NC	<0.001
		Lundex	3%	21%	11%	7%	6%	0%	4%	7%	7%	8%	NC	5%	-	<0.001
ACR20 response	**6**	**Crude**	24%	55%	-	59%	25%	-	NC	NC	56%	-	-	NC	22%	<0.001
		Lundex	20%	51%	-	54%	19%	-	NC	NC	51%	-	-	18%	-	<0.001
	12	**Crude**	27%	67%	-	50%	24%	-	NC	NC	NC	-	-	NC	NC	<0.001
		Lundex	14%	58%	-	44%	15%	-	NC	NC	NC	-	-	24%	-	<0.001
ACR50 response	**6**	**Crude**	11%	36%	-	38%	12%	-	NC	NC	31%	-	-	NC	11%	<0.001
		Lundex	9%	34%	-	35%	9%	-	NC	NC	28%	-	-	NC	-	<0.001
	12	**Crude**	15%	45%	-	35%	11%	-	NC	NC	NC	-	-	NC	NC	<0.001
		Lundex	8%	39%	-	30%	7%	-	NC	NC	NC	-	-	NC	-	<0.001
ACR70 response	**6**	**Crude**	6%	21%	-	21%	7%	-	NC	NC	19%	-	-	NC	11%	0.010
		Lundex	4%	20%	-	19%	6%	-	NC	NC	17%	-	-	NC	-	0.001
	12	**Crude**	5%	24%	-	31%	5%	-	NC	NC	NC	-	-	NC	NC	0.002
		Lundex	3%	20%	-	27%	3%	-	NC	NC	NC	-	-	NC	-	0.001
EULAR good/ moderate response	**6**	**Crude**	50%	88%	69%	83%	50%	-	NC	55%	62%	47%	93%	NC	39%	<0.001
		Lundex	40%	82%	61%	76%	38%	-	NC	45%	56%	39%	81%	NC	-	<0.001
	12	**Crude**	48%	93%	63%	77%	60%	-	NC	43%	83%	NC	NC	64%	NC	<0.001
		Lundex	26%	79%	47%	68%	37%	-	NC	30%	73%	NC	NC	50%	-	<0.001

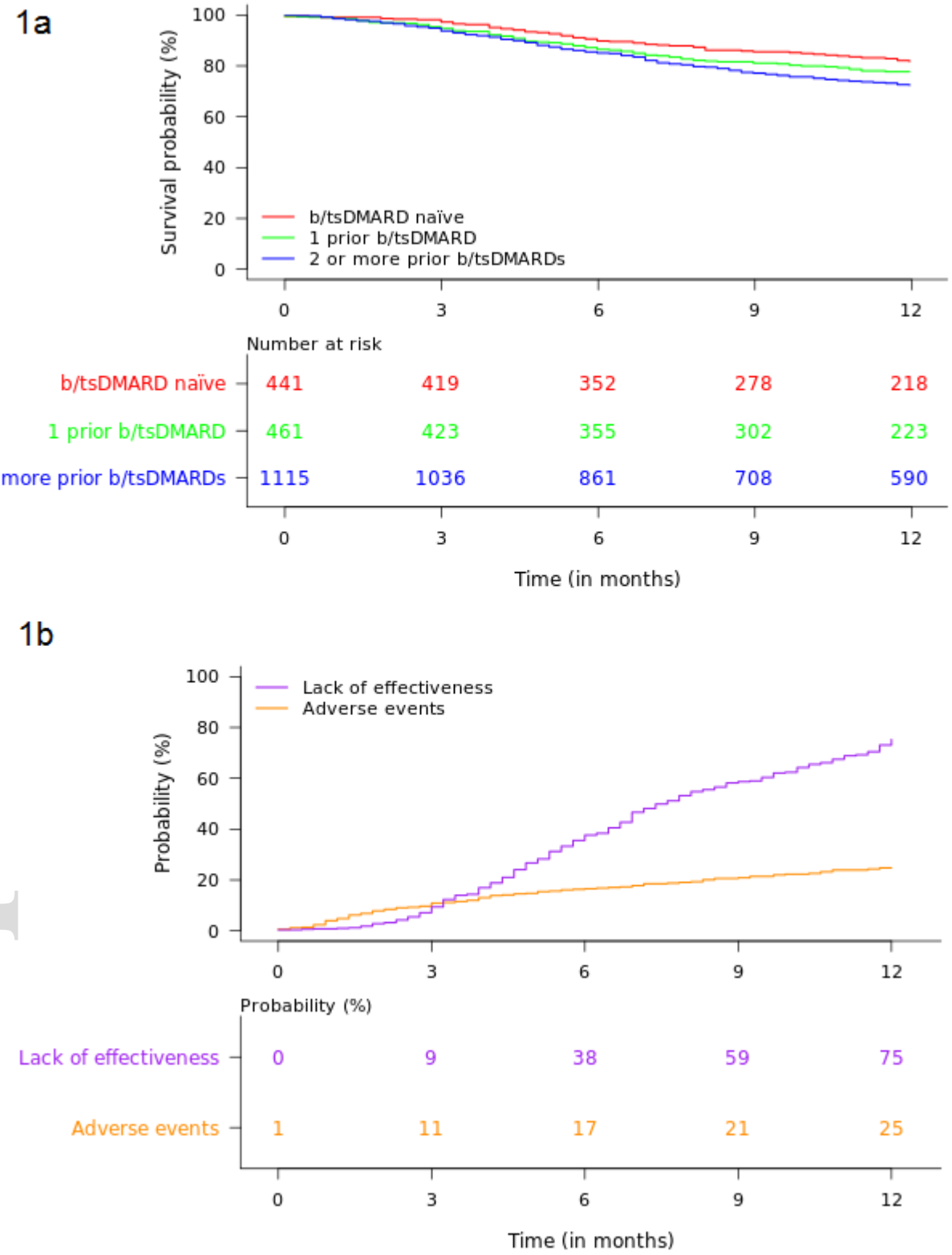
*Comparisons between the registries were performed with Kaplan-Meier with log rank test for retention rates and Chi-Square test or Fisher's exact test for remission and response rates, as appropriate. -, not collected/no available data; NC: Not calculated, due to data from <10 patients available; Number *available for each of the analyses are shown in Supplementary Table S9.* ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; DAPSA28, Disease Activity index for PSoriasis arthritis; DAS28-CRP, 28-joint Disease Activity Score with CRP; b/tsDMARD, biologic/targeted synthetic Disease Modifying Anti-Rheumatic Drug; EULAR, European League Against Rheumatism; IQR, interquartile range; SDAI, Simplified Disease Activity Index

Figure legends

Figure 1a Pooled 12-month secukinumab retention rates stratified by number of previous b/tsDMARDs (Kaplan-Meier with log-rank test, p=0.001); **Figure 1b** Cumulative incidence curve for withdrawal of secukinumab due to adverse events and lack of effectiveness

Figure 2 Twelve-month secukinumab retention rates compared across the European registries (Kaplan-Meier with log-rank test, p<0.001)

Figure 3 Bar charts of crude proportions of patients achieving remission, LDA (including remission) and response rates after 12 months of secukinumab treatment compared across number of previous b/tsDMARDs



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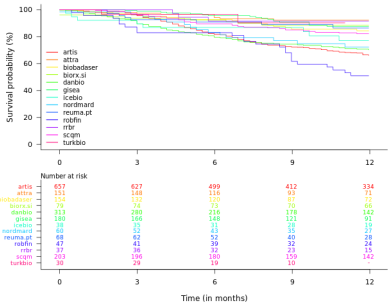

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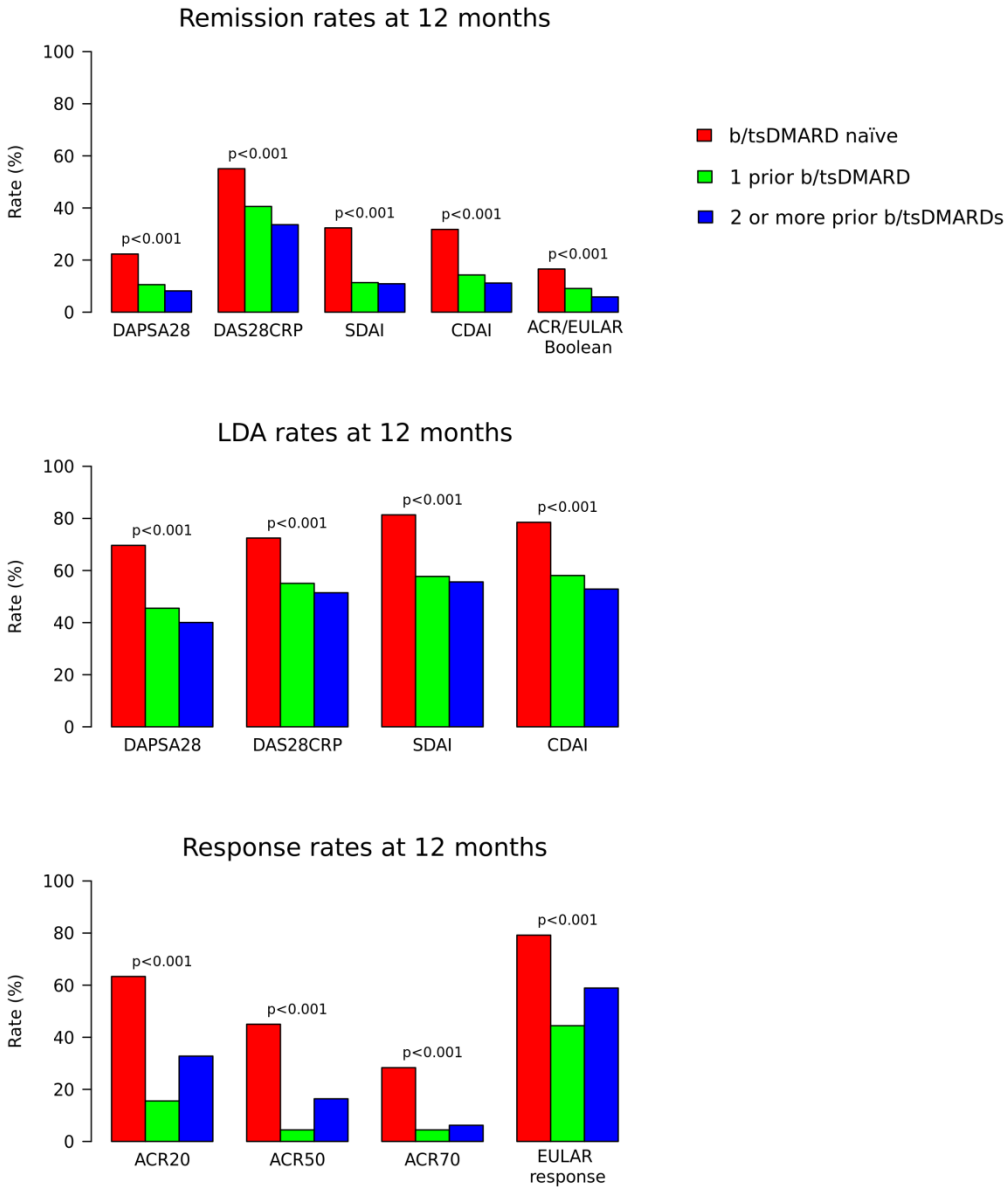

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