ORIGINAL REPORT

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A Real-world Meta-analysis Study of Disease Severity in European Patients Who Received Baricitinib for Atopic Dermatitis: Data from BioDay, SCRATCH and TREATgermany

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Clinical trials have demonstrated the effectiveness of baricitinib, an oral selective Janus kinase 1/2 inhibitor, for patients with moderate-severe atopic dermatitis, but data from real-world practice are limited. This non-interventional cohort study evaluated clinician- and patient-reported disease severity over 16 weeks using 3 national atopic dermatitis registries: BioDay (Netherlands), SCRATCH (Denmark) and TREATgermany (Germany). Absolute scores for Eczema Area and Severity Index (EASI) and itch Numerical Rating Scale (Itch-NRS) were assessed at baseline and follow-up (Week 13/16) for each registry and for the overall pooled cohort. Descriptive analyses, generalized linear mixed modelling and meta-analysis approaches were applied to complete-case and multiply-imputed datasets. In total, 264 patients (89 BioDay, 117 SCRATCH, 58 TREATgermany) were included. Results showed improvements in EASI, with 58%, 68% and 62% achieving EASI≤7 at Week 13/16 in BioDay, SCRATCH and TREATgermany, respectively. In the pooled cohort, the proportion was 62% (95% CI: 50–73%). The pooled mean EASI change was -7.8 [14.4,–1.1]. Effectiveness was generally observed in both biologic-naïve and -experienced patients. Notable heterogeneity was observed, particularly for Itch-NRS, with the proportion achieving NRS≤4 ranging from 20% (BioDay) to 71% (TREATgermany). These real-world findings support the effectiveness of baricitinib while also highlighting variability in patient outcomes.

Key words: Atopic Dermatitis; Baricitinib; EASI; Registry.

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SIGNIFICANCE

This real-world study used data from 3 European registries to investigate the effectiveness of baricitinib for improving atopic dermatitis over 16 weeks. Overall, we found baricitinib to be effective in improving clinician-assessed severity scores, even in patients who had previously used biologics. Nevertheless, there was some variability in the observed effectiveness, especially in terms of patient-reported itch severity, highlighting the challenges in treating this population. Further research into the longer-term effectiveness of baricitinib would be beneficial, alongside an improved understanding of the patient populations deriving the greatest benefit from treatment.

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Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by severe itch and typically presents with erythematous, infiltrated and excoriated lesions, imposing a substantial burden on patients' quality of life (1).

Historically, broad-acting immunosuppressants were the only systemic options for AD not controlled by topical therapies, but recent developments include the approval of more targeted therapies including Janus kinase (JAK) inhibitors such as baricitinib, upadacitinib and abrocitinib, and the interleukin-4/13/31 inhibitors such as dupilumab, tralokinumab, lebrikizumab and nemolizumab (2).

Baricitinib was the first European Medicine Agency (EMA)-approved oral JAK inhibitor for

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treatment of adult patients with moderate-to-severe AD who are candidates for systemic therapy (3). Phase III monotherapy (BREEZE-AD1 and BREEZE-AD2) and combined therapy trials (baricitinib with topical corticosteroids [TCS]; BREEZE-AD7) have demonstrated baricitinib's efficacy in moderate-to-severe AD patients who had inadequate response to topical therapies, improving clinical signs and symptoms in patients within 16 weeks of treatment and inducing rapid reduction of itch (4, 5). Post-hoc analyses also revealed rapid onset of itch improvement, often within a day of the first dose (6). Furthermore, recent data indicate that patients with an Itch Numerical Rating Scale (Itch-NRS)≥7 and<40% affected Body Surface Area (BSA), "itch-dominant" patients, are most likely to see Eczema Area and Severity Index (EASI) improvement or benefit most from combination (baricitinib and TCS) therapy (7, 8).

Since 2016, several national prospective treatment registries for AD have been established to assess the long-term effectiveness and safety of systemic treatments for AD (9, 10). These include the Dutch BioDay (established in 2018 with>2000 patients from 23 centres) (11), Danish SCRATCH (established in 2017 with ~1200 patients from 6 centres) (12) and German TREATgermany (established in 2016, with>2,500 adult AD patients across 66 centres (13)) registries; all include patients who received systemic treatments for moderate-to-severe AD and represent a rich data source of real-world baricitinib-treated patients.

Existing real-world research in systemic treatment of AD patients is fragmented, with separate observational studies from BioDay, SCRATCH and TREATgermany corroborating the effectiveness of baricitinib (9, 14, 15). Initial data from BioDay (N=51) and SCRATCH (N=44) registries showed significant improvements in clinician-assessed and patient-reported outcomes within the first 16 weeks of treatment, with a higher discontinuation rate due to ineffectiveness in BioDay (33.3%) compared to SCRATCH (7%) (14, 16).

This study aimed to demonstrate the real-world clinical effectiveness of baricitinib in AD patients by combining data from 3 European registries and to describe the characteristics of specific subgroups of interest including: patients with and without exposure to biologic treatment prior to baricitinib initiation and patients with a baseline BSA≤40% AND Itch-NRS≥7 (Itch-dominant phenotype).

MATERIALS AND METHODS

Study design and registry populations

This study combined data from BioDay, SCRATCH and TREATgermany; each registry's patient inclusion criteria is described in Table SI. For this study, each registry aligned patient selection and outcome measurements at different time-points to ensure consistency.

Patient selection

The study population included adults (≥18 years) participating in BioDay, SCRATCH and TREATgermany who were treated with baricitinib for AD within routine clinical practice prior to August 2023 and were baricitinib-naïve prior to registry entry. Patients initiated on another non-baricitinib systemic therapy on the same day as initiation of baricitinib (index date, Day 0) were excluded from the study.

Time periods, variables and outcomes

Patient characteristics, treatment patterns, EASI scores and Itch-NRS scores were extracted from each registry for the period prior to the index date (baseline) until 125 days (16 weeks) post-index date (unless the patient was lost to follow-up, or otherwise censored).

Primary outcomes were EASI (to evaluate clinician-assessed severity) and Itch-NRS (patient-reported severity) and were described for Week 0 (i.e. baseline; includes data documented 14 days prior to and up to 2 days post initiation of baricitinib [Day: -14 to Day 2]) and Week 13/16 (Day 70 to Day 125]. In TREATgermany, patient visits typically occurred closer to Week 13 than Week 16, and therefore, our analysis window was expanded (Table SI). Where a patient had>1 baricitinib visit within a time window, data from the most recent visit were analysed.

The proportion of patients achieving specified clinical outcome thresholds (EASI≤7, Itch-NRS≤4 and EASI≤7 and/or Itch NRS≤4) were assessed at Week 13/16.

Key analyses were conducted for the overall cohort and for cohorts of interest. Biologic-experienced and biologic-naïve patients were defined as patients who did, and did not, receive a prescription of dupilumab and/or tralokinumab prior to initiation of baricitinib, respectively and "Itch-dominant" patients had BSA≤40% AND Itch NRS≥7 at baseline.

Statistical methods

Descriptive statistics for complete cases (patients with non-missing EASI / Itch-NRS scores at baseline and Week 13/16 only) were reported for absolute EASI and Itch-NRS scores (as continuous outcomes). Generalised Linear Mixed Models (GLMM) for normal and binomial distributions were fitted for continuous outcomes (absolute EASI & Itch NRS score) and binary outcomes (EASI≤7, Itch NRS≤4, EASI≤7 and/or Itch NRS≤4), respectively. As a sensitivity analysis, multiple

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imputation with chained equations (MICE) was applied for missing outcomes to avoid bias due to selection and to optimise statistical power. Imputation models included outcomes (EASI, Itch-NRS) at each available time-point, with predictive mean matching or linear regression (in the case of high proportion of missing data) for continuous variables, and (polytomous) logistic regression methods for imputation for dichotomous or categorical outcomes.

Meta-analytic approaches were used to pool the per-registry results for primary outcomes, with random effects (RE) modelling with inverse variance weighting for meta-analyses of means and regression coefficients. GLMM approaches for meta-analysis were used to pool proportions (17). Results were reported as pooled effects (means, proportions and regression coefficients), 95% confidence interval (CI) with Hartung-Knapp adjustment (where applicable) of the pooled effect size and associated *p*-values, as well as appropriate heterogeneity measures (e.g. I-Square, Tau^2, prediction intervals [PI]). Pooled results were presented with and without data imputation for missing data, except for pooled proportions, where only non-imputed results are described due nonconvergence of models for imputed data.

Descriptive analyses were conducted using R Statistical Software® version 4.2.0 or later (18). The meta-analyses were performed by BioDay using the Statistical Software v4.3.0 (or later) adapted package (metafor) (19).

RESULTS

In total, 264 patients (89 patients from BioDay, 117 from SCRATCH and 58 from TREATgermany) were included (**Fig. 1**). Overall, 60% (BioDay), 28% (SCRATCH) and 31% (TREATgermany) of patients were biologic-experienced at baseline (**Table I**).

Patient demographics, clinical characteristics and treatment history were broadly similar across registries (Table I). Baseline EASI [mean (SD)] was 16.8 (13.6) for BioDay, 15.1 (10.8) for SCRATCH and 19.5 (12.8) for TREATgermany. Mean [SD] Itch-NRS at baseline was broadly similar across registries (6.3 [2.5] for BioDay, 6.7 [2.7] for SCRATCH and 6.6 [2.3] for TREATgermany).

The proportions of patients with the Itch-dominant phenotype (BSA≤40% AND Itch-NRS≥7) at baseline per registry were 22% (BioDay), 17% (SCRATCH) and 21% (TREATgermany); patient characteristics were generally similar to the overall cohort (Table SII).

Effectiveness

The proportions of patients who achieved EASI≤7 at Week 13/16 were 58% (25/43) in BioDay, 68% (25/37) in SCRATCH and 62% (24/39) in TREATgermany, respectively. Of biologic-naïve/experienced patients, 65%/54% (BioDay), 65%/83% (SCRATCH) and 59%/70% (TREATgermany) achieved EASI≤7 at follow-up (**Fig. 2**).

Overall, 20% (6/30), 49% (19/39) and 71% (25/35) of the patients reached Itch-NRS≤4 at Week 13/16 in BioDay, SCRATCH and TREATgermany, respectively; when considering prior biologic exposure, 20%/20% (BioDay), 50%/43% (SCRATCH) and 78%/50% (TREATgermany) of biologic naïve/experienced patients reached Itch-NRS≤4 (Fig. 2).

Of patients with the Itch-dominant phenotype at baseline, the proportions who achieved EASI≤7 were 70% (7/10), 67% (6/9) and 67% (8/12) for BioDay, SCRATCH and TREATgermany, respectively (Fig. S1).

Absolute and change scores at baseline and follow-up are shown in Table SIII; general improvements were observed on average for descriptive (non-imputed) EASI and Itch-NRS at follow-up.

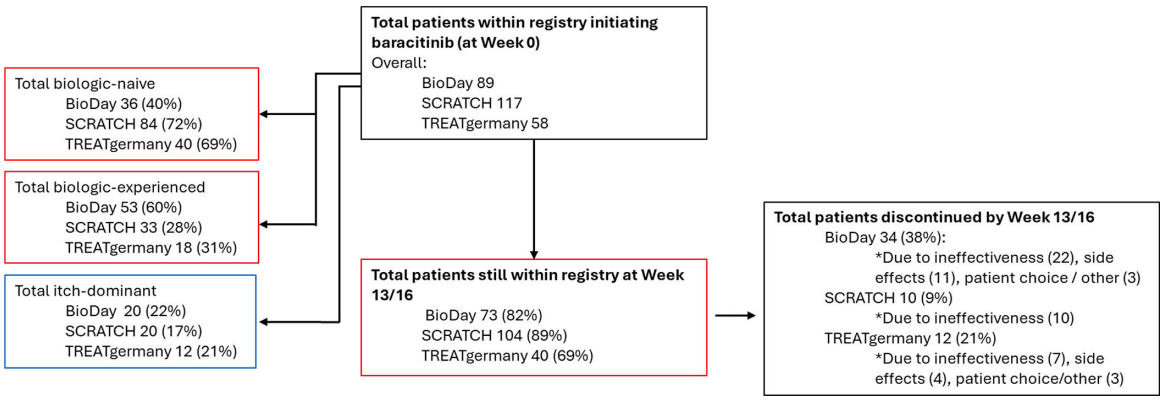

Fig. 1. Total number of patients included in key study cohorts per registry. Red boxes indicate cohort for key effectiveness analyses (primary outcomes); additional sub-analyses were conducted for the cohorts in blue. *Ineffectiveness was a documented reason for all 10 discontinuations in SCRATCH, 22 of 34 in BioDay [11/34 due to side-effects and 3/34 due to patient choice), and 7 of 12 in TREATgermany [4/12 side-effects, 3/12 patient choice or other]).

Table I. Patient demographics, clinical characteristics and treatment history per registry (as observed at baseline/Week 0)

	BioDay N=89	SCRATCH N=117	TREATgermany N=58
Age, index date, years, mean (SD)	44.0 (18.5)	39.0 (14.3)	41.5 (14.6)
Gender, N (%)			
Male	54 (61%)	41 (35%)	42 (72%)
Female	35 (39%)	76 (65%)	16 (28%)
Baseline EASI[a], N (%)	81 (91%)	75 (68%)	57 (98%)
Mean (SD)	16.8 (13.6)	15.1 (10.8)	19.5 (12.8)
Median (IQR)	13.0 (14.6)	13.2 (14.2)	18 (16.0)
Baseline itch NRS[b], N (%)	66 (74%)	72 (62%)	55 (95%)
Mean (SD)	6.3 (2.5)	6.7 (2.7)	6.6 (2.3)
Median (IQR)	7.0 (3.0)	7.0 (3.5)	7 (3.0)
Itch-dominant phenotype, N (%)	20 (22%)	20 (17%)	12 (21%)
Prior treatment history			
Biologic-experienced, N (%)	53 (60%)	33 (28%)	18 (31%)
Previous systemic therapy, N (%)*	85 (96%)	107 (91%)	22 (38%)

Note: Baseline EASI/Itch NRS scores are 'as observed' for all patients in overall cohort who had a score recorded at Week 0.
*The most frequent treatments in BIODAY were cyclosporin (79%), dupilumab (61%) and methotrexate (51%); in SCRATCH were methotrexate (75%), azathioprine (50%) and prednisolone (35%) and in TREATgermany was dupilumab (68%).
[a]EASI scores range from 0 to 72, with higher scores indicating worse AD severity. [b]Itch NRS scores range from 0 (no itch) to 10 (worst itch imaginable). [c]In patients with systemic treatment recorded post or on registry entry date and prior to index date.
EASI: Eczema Area and Severity Index; IQR: Interquartile range; Itch-NRS: itch Numerical Rating Scale; SD: standard deviation.

Results from the adjusted analysis (GLMM) for continuous outcomes are shown in Table SIV.

Pooled meta-analysis

Meta analysis of EASI in all patients showed a pooled mean reduction of -7.8 (95% CI: -14.4; -1.1; p=0.04) points at Week 13/16 and a reduction in Itch-NRS of -2.2 (95% CI: -4.6; 0.2; p=0.06). (**Fig. 3**). Heterogeneity was observed, especially in the results of the overall pooled cohort, with I^2 values of up to 76.55%: patients in the TREATgermany registry generally showed better improvement in EASI and Itch-NRS compared to the patients in BioDay and SCRATCH (Fig. 3). Similar results were observed when using the descriptive (non-imputed) approach (Fig. S2). The pooled mean (95% CI) reduction from baseline at follow-up for EASI (with

Fig. 2. Percentage (number) of patients achieving specified outcome thresholds at Week 13/16 per registry, overall and by prior biologic exposure. Total sample size excluding missing data, (i.e.) total patients with complete Week 0 and Week 13/16 information for the specified variable; Abbreviations: EASI: Eczema Area and Severity Index, Itch-NRS: itch Numerical Rating Scale.

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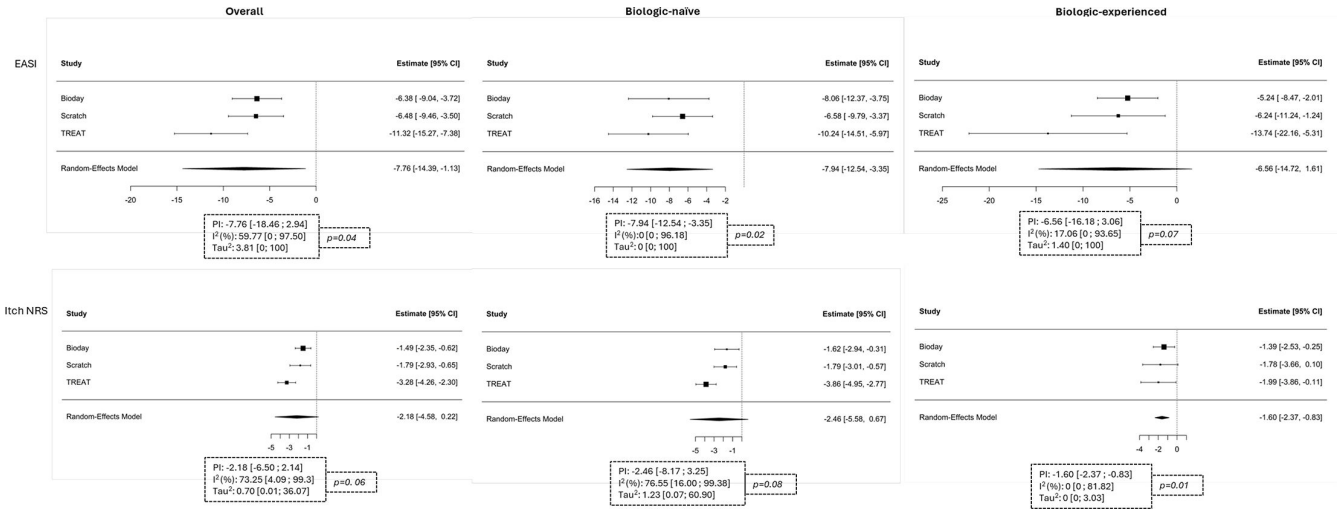

Fig. 3. Meta analyses depicting pooled change in EASI and Itch NRS scores at follow-up for overall cohort and by prior biologic exposure (multiple imputation approach). Results shown include mean change (95% CI) for each registry and the pooled cohort (as per random effects modelling), and associated *p*-values, prediction intervals (PI), Tau^2 and I^2 percentage with 95% CI.

data-imputation) was -6.6 points (-14.7; 1.6; *p*=0.07) in biologic-experienced and 7.9 points (-12.5; -3.4; *p*=0.02) in biologic-naive patients, respectively (Fig. 3; see Fig. S1 for non-imputed results).

For the overall cohort, the pooled proportions of patients meeting the thresholds at follow-up were 0.62 (95% CI: 0.50; 0.73) for EASI≤7, 0.46 (95% CI: 0.05; 0.94) for Itch NRS≤4, and 0.78 (95% CI: 0.63; 0.88) for EASI≤7 and/or Itch-NRS≤4, respectively; broadly similar results were observed when stratifying by prior biologic exposure. Heterogeneity was mostly observed for NRS≤4, with I^2 values up to 88.71%, whereas heterogeneity for other proportions was generally low (**Fig. 4**).

There were 52 (mean age 42 years; 56% male) patients included in the pooled Itch-Dominant cohorts. The pooled mean change [95% CI] estimates (imputed) for EASI and Itch-NRS were -5.03 [-10.70; 0.65]; *p*=0.06 and -3.94 [-6.*78*; -1.09]; *p*=0.03, respectively (Fig. S3).

Treatment discontinuation

Overall, 38%, 9% and 21% of patients in BioDay, SCRATCH and TREATgermany, respectively, discontinued baricitinib treatment by Week 13/16. Ineffectiveness was the most frequently reported reason for discontinuation in all registries (Fig. 1).

DISCUSSION

Main findings

This study provides an updated assessment of the real-world effectiveness of baricitinib in AD for patients treated in the Netherlands, Denmark and Germany.

General improvements based on meta-analyses in absolute EASI scores were observed at follow-up in all patients, with a mean reduction of almost 8 points for the overall pooled cohort. Clinical response was somewhat better in biologic-naïve patients and slightly lower in those with prior biologic exposure. Improvements were also observed for Itch-NRS, with a mean reduction of more than 2 points at Week 13/16.

The descriptive (non-imputed) results showed that 62% of patients in the overall pooled cohort achieved EASI≤7 at follow-up. There was broad consistency across registries, while prediction intervals (indicative of the range into which we can expect the effects of future studies to fall (20)) were moderately supportive of a beneficial effect for EASI.

Interpretation

Moderate-to-high levels of heterogeneity were observed for both EASI and Itch-NRS outcomes. This led to the observation that the improvement over time was statistically significant in each registry separately, but the corresponding *p*-value of, for example, the pooled Itch-NRS was slightly higher than the traditional threshold of 0.05. Heterogeneity was observed in pooled results of both EASI and Itch-NRS for all patients and in some subgroups of biologic-naïve and biologic-experienced patients. In the meta-analyses of proportions, heterogeneity was mainly observed for NRS≤4. In all results, the heterogeneity estimates (i.e. CIs of I^2 and tau^2 values) were uncertain with a wide confidence interval, likely related to the low number of studies in this meta analyses (21). Heterogeneity appears to be caused by a more pronounced improvement in patients in the TREATgermany registry. Notably, in Germany, baricitinib is used as a first-line systemic treatment,

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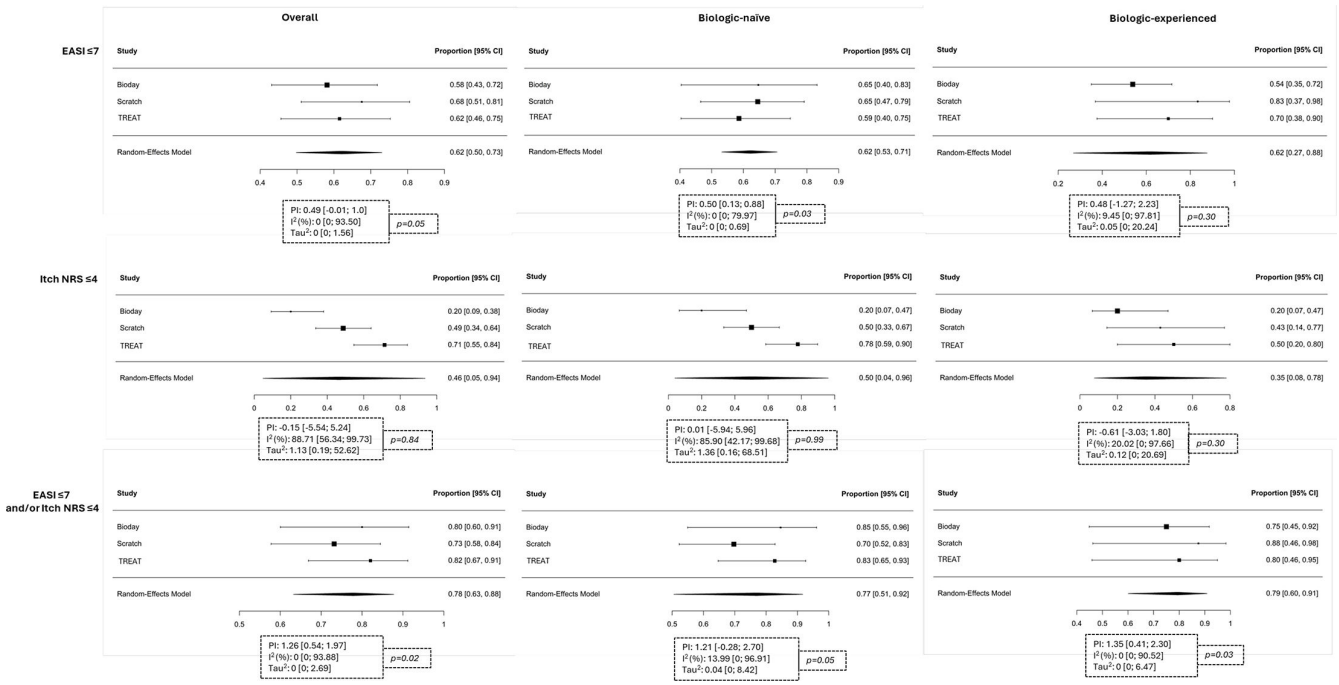

Fig. 4. Results from meta-analysis of the proportion of patients meeting specified thresholds at Week 13/16 for overall cohort and by prior biologic exposure (no imputation).

while in the Netherlands and Denmark, it is prescribed after the failure of conventional treatments (12, 22). Patients in BioDay may also be more difficult to treat overall (due to higher proportion of biologic experienced patients). Differences in descriptive results between registries may also be influenced by the number of patients in washout of other systemic medications and the need for alignment of definitions and timepoints, which also contributes to variation when comparing with other publications.

When considering data from each registry separately, mean EASI ranged from 15.1 (SCRATCH) to 19.5 (TREATgermany) at baseline, aligning with baseline scores in prior real-world studies for patients with moderate-to-severe AD who had previously had an inadequate response to biologic therapy (14, 15, 23). At follow-up, mean EASI ranged from 7.2 (SCRATCH) to 10.1 (BioDay) in the current study while the proportions of patients reaching EASI≤7 ranged from 58% (25/43) to 68% (25/37). Real-world data on the 16 week effectiveness of baricitinib are somewhat limited, with existing publications primarily based on single-country registries. In a previous BioDay study of moderate-severe patients undergoing baricitinib treatment, the mean EASI was 11.1 at Week 16, with a probability of achieving EASI≤7 of 29.4% (95% CI 13.1–53.5) (14), likely reflective of the more complex, elderly or refractory patient characteristics under study. Similarly, a TREATgermany study found a substantial decrease in EASI at 3 months (mean±SD 21.5 ± 13.2 vs. 9.3 ± 9.0), with a slightly higher proportion of patients (44%) achieving EASI-75 at follow up (15) as baseline EASI were also higher. These results may have been influenced by differences in baseline characteristics, including the distribution of prior systemic therapies, age and EASI baseline. It is however notable that improvements in EASI were observed in this study despite a lower baseline EASI than observed in the clinical trials for baricitinib (4, 5) and for other real-world studies involving other treatments (24–26): this may indicate that there is a place for oral and more targeted therapies in populations with more moderate disease (e.g. pre-biologic or following biologic-failure).

In this study, results regarding the effectiveness of baricitinib were however particularly mixed when considering the impact on Itch-NRS relative to other RCTs and single-country RWE studies (4, 5, 14). In general, the most favourable results were observed for TREATgermany, although results were less consistent for Itch-NRS compared with EASI. Overall mean reductions in Itch-NRS from baseline to follow-up ranged from 1.2 to 3.2 points while the percentage of patients achieving Itch-NRS≤4 ranged from 20% (BioDay) to 71% (TREATgermany), indicating wide variability across settings; this notion was also reflected in some of the pooled data and wider heterogeneity measures (e.g. relatively high I^2/ Tau^2 and wide CIs). Variability in patient-reported measures such as Itch-NRS has been reported in other AD studies and may be driven by wider factors such as age, gender and race

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(27, 28). Further research regarding what constitutes a meaningful change in AD severity for patients within real-world vs trial settings may be beneficial. Ultimately, these findings highlight the inherent challenges of treating this population and indicate that treatment effectiveness, particularly in terms of reducing itch severity, can be highly variable. This factor may also have contributed to the relatively high discontinuation rate observed in the current study, and in previous work (14).

In addition, our study provides insights into the effectiveness of baricitinib for specific patient subgroups. In general, EASI results for patients who were biologic-naïve at baseline were consistent with those observed in the overall cohort, supporting the clinical effectiveness of baricitinib for these patients. Although heterogeneity was observed in the results, there was some indication that baricitinib can be effective for patients who had switched from another advanced systemic treatment, both within individual registries and in the pooled cohort. These findings generally align with previous research which showed no significant differences in effectiveness for those with a prior lack of response to biologic treatment ("dupilumab non-responders") vs those who switched to baricitinib for other reasons (14).

Our study also supports earlier findings that patients with the Itch-dominant phenotype may show greater regional improvements in disease severity (8). Despite small sample sizes, a slightly higher proportion of these patients met study thresholds at follow-up vs the overall cohort, despite the benchmark for improvement arguably being more challenging to reach in these patients (due to lower or more moderate baseline scores vs overall cohort). While real-world data are limited, patients with a more moderate BSA score (<40) yet higher perceived itch may represent a sizeable proportion of the population receiving baricitinib in routine clinical practice (29). These findings may indicate that this is a particular group that could benefit from baricitinib in the real-world, warranting further investigation.

Limitations

Our findings differed somewhat from the BREEZE-AD clinical trials (4, 5), likely due to baseline population differences and the smaller magnitude of change observed in the real-world settings, where patients had more moderate EASI scores (4, 5). Comparisons with trial data are limited by stricter trial inclusion criteria (e.g. worse baseline severity and requirement for treatment wash-out periods) unlike the broader, more flexible registry criteria. This reduces the potential for improvement in the real-world registries and also limits the usability of outcome measures based on relative or percentage change (including EASI-75) typically used in trial settings, prompting our focus on absolute outcomes. Additional factors that may explain differences in results include country-level discrepancies in treatment algorithms, the timing of approvals for relevant treatments (including dupilumab and JAK inhibitors), inter-rater variability, discontinuation rates and broader factors related to finances and access to treatment (12, 22), reflecting real-world complexity. Missing data, partially addressed via multiple imputation, and wider observational study limitations (e.g. unmeasured confounding, model assumptions), may have also introduced bias. Differences in registry definitions of "biologic-experienced" may also affect comparability.

Finally, assessing heterogeneity in meta-analyses is often debated, with no single gold-standard measure (20, 30, 31). We reported several measures (I^2, Tau^2, prediction intervals) to address limitations of individual metrics (20). While prediction intervals were broad and sometimes overlapped zero, they generally supported baricitinib's effectiveness across real-world contexts (20).

Conclusions

Based on data to week 16 from 3 European registries, baricitinib appears effective in reducing clinically-assessed AD severity in a real-world population with relatively moderate - but still impactful - baseline severity, likely partially influenced by bridging therapies. Most patients were refractory to other systemic or biologic treatments. Improvements in EASI appeared to be broadly reflected not only in biologic-naïve patients, but also in those with prior biologic exposure and those with BSA≤40 but NRS≥7 (Itch-Dominant). Nevertheless, the real-world effectiveness of baricitinib appears to be heterogenous, particularly regarding its impact on patient-reported itch severity. Although these data reinforce previously published data, further research into the longer-term effectiveness of baricitinib would be valuable, alongside further evidence derived from moderate patients with predominant itch, to improve understanding of the patient populations likely to derive the greatest benefit from AD treatments.

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Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics committee: No formal ethics approval process was required for this study. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki, consistent with Good Pharmacoepidemiology Practices (GPP), and applicable laws and regulations of the country or countries where the study was conducted. The BIODAY

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study protocol was approved by the Medical Ethics Committee of the University Medical Centre Utrecht and followed Good Clinical Practice guidelines. The BioDay registry was registered with ClinicalTrials.gov (NCT03549416). The SCRATCH registry project was approved by the Danish Data Protection Agency (P-2019-746). The TREATgermany protocol was submitted to all responsible ethics committees and received a positive vote (No. EK TUD 118032016). TREATgermany was registered in the clinicaltrials.gov database (NCT03057860) and the ENCePP Resource Database (EMA).

Conflict of interest: MdB-W: Consultant, advisory board member, and/or speaker for AbbVie, Almirall, Amgen, Aslan, Eli Lilly, Galderma, Leo Pharma, Pfizer, Regeneron, and Sanofi-Genzyme. IH: Received nonfinancial support from Eli Lilly and Company, Sanofi Genzyme, LEO Pharma, and AbbVie during the conduct of the study. M-LS: Received grants from Sanofi Genzyme/Regeneron during the conduct of the study as well as grants from Pfizer, support from Amgen and LEO Pharma, and serving on the advisory boards for Eli Lilly and Company, Galderma, and AbbVie outside the submitted work.SFT: Research support from AbbVie, Almirall, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi and UCB, and speaker/consultant for Abbvie, Almirall, Boehringer, CSL, Dr. August Wolff, Eir Ventures, Eli Lilly, Galderma, Incyte, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, Servier, Symphogen, UCB, and Union Therapeutics. JS: Co-principal investigator of the German Atopic Eczema Registry TREATgermany. Unrelated to this study, He reports institutional grants for investigator-initiated research from the German Federal Joint Committee, German Ministry of Health, German Ministry of Research, European Union, German Federal State of Saxony, Novartis, Sanofi, ALK, and Pfizer. He participated in advisory board meetings as a paid consultant for Sanofi, Lilly, and ALK. He serves the German Ministry of Health as a member of the German National Council for Health and Care. SW: received research grants from Leo Pharma, Pfizer and Sanofi, and consulting and/or lecture fees from Abbvie, Almirall, Boehringer, Eli Lilly, Galderma SA, GSK, Kymab, LEO Pharma, Pfizer, Sanofi, Regeneron. TW: is a co-principal investigator of the German Atopic Eczema Registry TREATgermany. He received honoraria for talks and/or scientific advice and/or grants from AbbVie, Almirall, Eli Lilly, Galderma, Janssen/JNJ, Leo Pharma, Novartis, Pfizer, Regeneron/Sanofi. CB, SeB, MK, NZ, LLT, ND, AA, ICN, TB, LH have no conflicts of interest to declare.

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