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ORIGINAL ARTICLE

An integrated analysis of herpes virus infections from eight randomized clinical studies of baricitinib in adults with moderate-to-severe atopic dermatitis

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Abstract

Background Atopic dermatitis (AD) is associated with an increased risk for viral infections including those caused by herpes simplex virus and varicella zoster virus.

Objectives This study examined treatment-emergent (TE) herpes simplex infection including eczema herpeticum (EH), and herpes zoster (HZ), in adult patients with AD receiving ≥1 dose of baricitinib (BARI), an oral selective inhibitor of Janus kinase 1/2.

Methods We evaluated data from six double-blinded, randomized, placebo-controlled (PC) trials and two long-term extension studies, within three analysis sets: PC, 2–4-mg BARI extended and All-BARI-AD. Frequency, incidence rate (IR)/100 person-years (PYs) and clinical characteristics of TE-herpes simplex, EH and HZ were reported.

Results In the All-BARI-AD dataset (n = 2531; 2247 PYs), herpes simplex was reported in 8.9% of patients (n = 224; IR = 10.3). Most herpes simplex events were rated as mild or moderate (93.3%), rarely led to permanent discontinuation (2.2%) and presented mostly as oral/perioral herpes simplex (51.3%). TE-EH occurred at a low frequency (All-BARI-AD 1.7% n = 43; IR = 2.0) and were reported in 0.5%, 0.2% and 1.4% of patients receiving placebo, 2-mg or 4-mg BARI respectively. In the All-BARI-AD dataset, most events were investigator-rated as mild/moderate (79.1%), affected ≤2% of the body surface area (74.2%) and occurred as single events (88.4%). Serious TE-EH (n = 11) occurred exclusively in patients with poor disease control (vIGA-AD™ score ≥3) at infection onset. TE-HZ was reported in 2.1% of BARI patients (n = 53; IR = 2.3), without a dose relationship during the PC period (IR = 2.7 and IR = 0.0) or the extended dataset (IR = 3.7 and IR = 1.7) for 2- or 4-mg BARI respectively.

Conclusions TE-herpes simplex was common, while occurrence of EH was uncommon. Most events of EH were localized with involvement of a small BSA and were linked to poor disease control. Events of HZ were rare in the PC dataset and without a dose dependent increase in frequency.

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Conflicts of interest

TW has received personal fees from AbbVie, Almirall, Eli Lilly, Galderma, Janssen/JNJ, Leo Pharma, Novartis, Pfizer, Regeneron/Sanofi for lectures or advisory boards. AI has served as a scientific adviser for Eli Lilly and Company, Abbvie, Sanofi, Regeneron, Pfizer, Leo and Almirall. CB has received personal fees for lectures or advisory boards from AbbVie, Bayer, Eli Lilly, LEO Pharma, Mylan, Novartis, Pfizer, and Sanofi Genzyme. JS has received personal fees from Abbvie,

Clinicaltrials.gov: NCT02576938 (JAHG, Phase 2), NCT03334396 (JAHL; BREEZE-AD1), NCT03334422 (JAHM; BREEZE-AD2), NCT03334435 (JAHN; BREEZE-AD3), NCT03428100 (JAIN; BREEZE-AD4), NCT03435081 (JAIW; BREEZE-AD5), NCT03559270 (JAIX; BREEZE-AD6), NCT03733301 (JAIY; BREEZE-AD7).

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Introduction

Patients with atopic dermatitis (AD) exhibit an increased susceptibility to cutaneous and systemic bacterial and viral infections, including those caused by herpes simplex virus (HSV) and varicella zoster virus (VZV).[1–4] Among the first line of defence against viral infections are interferons (IFNs). Patients with AD and especially those with a history of eczema herpeticum (EH) have reduced levels of IFN-γ, reduced production of its receptor and express receptor variants which confer increased risk to EH, compared to AD patients without a history of EH.[5,6] Considering that IFNs signal *via* Janus kinase (JAK)1/JAK2, events of EH are of special interest in patients with AD treated with BARI.

Baricitinib (BARI), an oral selective JAK1/JAK2 inhibitor, has recently been approved in Europe, Australia and Japan among other countries for the treatment of moderate-to-severe AD in adults and is also indicated for the treatment of adults with moderate-to-severe active rheumatoid arthritis (RA).[7] The safety profile of BARI has been well established in RA, with 3770 patients being exposed over 14774 patient years in clinical trials.[8] Similar to other JAK inhibitors, BARI is associated with increased rates of treatment-emergent (TE) HZ in RA patients. In contrast, HZ rates were low in a recent integrated safety analysis of 2531 patients treated with BARI in the AD clinical trial programme.[9] These findings underline the need for disease-specific characterization of the BARI safety profile, and more specifically of herpetic infections.

This analysis therefore aims to further evaluate the risk and clinical characteristics of herpetic infections, specifically herpes simplex with focus on EH and HZ, among patients who have received BARI in the AD clinical trial programme, with exposure up to 2 years.

Methods

Study designs and patients

We present safety data from six double-blinded, randomized, placebo-controlled clinical studies which included phase 2 (NCT02576938), phase 3 (NCT03334396 (BREEZE-AD1), NCT03334422 (BREEZE-AD2), NCT03428100 (BREEZE-AD4), NCT03435081 (BREEZE-AD5), NCT03733301 (BREEZE-AD7)), and two long-term extension (LTE) studies (NCT03334435 (BREEZE-AD3)) and open-label LTE (NCT03559270 (BREEZE-AD6)) with data cut-off for all studies of December 2019.[9] Study design and eligibility criteria are included in Table S1 and Appendix S1, with important exclusion criteria related to herpes infections including history of EH within 12 months prior to screening or ≥2 episodes of EH at any time previously, HZ within 12 weeks of screening and symptomatic herpes simplex at randomization. All patients provided written informed consent. Studies were conducted in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki and approved by individual institutional review boards at each participating study centre.

Analysis sets

1 Placebo-controlled dataset (PC dataset):
assessed the safety profile of 2-mg and 4-mg BARI vs. placebo in five 16-week, placebo-controlled studies (Phase 2 study, BREEZE-AD1, -AD2, -AD4 and -AD7).

2 2–4-mg extended dataset (extended dataset):
provided the long-term safety profile for BARI 2-mg and BARI 4-mg including data from the 16-week PC trials (phase 2 study and patients in BREEZE-AD1, BREEZE-AD2, BREEZE-AD4, BREEZE-AD7) and the long-term extension (LTE) study BREEZE-AD3, yielding a total exposure up to 105 weeks of treatment.

3 All-BARI AD dataset (All-BARI-AD dataset):
included data for all patients who received ≥1 dose (1-mg, 2-mg or 4-mg) of BARI from any of the eight clinical trials at any time.

Safety outcomes

A treatment-emergent adverse event (TEAE) was defined as an event that first occurred/worsened in severity after the first dose of study treatment and on or prior to the last visit date during the analysis (Table S2). TE and serious adverse events (SAEs) are shown along with those leading to permanent discontinuation and temporary interruption of study drug. If a TEAE occurred multiple times for a patient, the event was counted once in the incidence rate (IR). AE(s) analysed were those coded to Medical Dictionary for Regulatory Activities (MedDRA Version 22.1 preferred terms (PTs)).

Statistical analysis

Adjusted percentages and adjusted incidence rates were calculated to allow for direct comparison across treatment groups. Adjusted percentages are shown for both the placebo-controlled and the extended 2–4-mg dataset and were derived using study weights based on total sample size per study. Adjusted IRs are shown for both the placebo-controlled and the extended 2–4-mg dataset. Adjusted IRs per 100 patient-years at risk (PYR) of observation time, censored at event, were derived using study weights based on total patient-years of exposure per study. For All-BARI-AD, IRs were calculated as the number of patients with an event per 100 PYR of observation time with observation time censored at event date. Confidence intervals (95%) for IRs are based on the Poisson distribution. A multivariable Cox regression analysis was carried out to evaluate potential risk factors for TE-herpes simplex and TE-herpes zoster using the all-BARI-AD dataset. Covariates with a significant association ($P < 0.05$) from the univariable model were selected for a multi-variable Cox regression model based on the first event. For herpes simplex, the covariates in the logistic model included history of HSV (yes vs. no), baseline vIGA-AD™ scale (4 vs. 3), a medical history of allergic diseases (yes vs. no) and sex (male vs. female). For HZ, no factors were identified as significant in the univariable model.

Results

This integrated safety analysis included 2531 patients, totalling 2247.4 PYs exposure to BARI with 1060 patients treated with BARI for ≥52 weeks and a median duration of exposure of 310 days. The baseline characteristics of patients within this population have been previously published, with ~47% of patients presenting with severe AD (vIGA-AD score of 4) across different treatment arms and datasets.[9]

Herpes simplex

Around half of patients with TE-herpes simplex were male (51.8%), with a mean (±SD) age of 36.5 (±12.9) years and a disease duration of 27.4 (±14.7) years (Table S3). A previous history of herpes simplex (almost 1 in 5), female sex (48.2%), a vIGA-AD of 4 at baseline (54.7%) and a history of allergic disease (>80%) were identified as factors which attributed to a higher incidence of TE-herpes simplex, in the All-BARI-AD dataset (Fig. 1). All other factors examined were not associated with increased risk.

During the first 16 weeks (PC dataset), the IR for herpes simplex was higher in the 2-mg (IR = 12.4) and 4-mg (IR = 21.3) vs. the placebo (IR = 9.4) group (Fig. 2a). The number of herpes simplex events remained higher in the 4-mg (IR = 14.5) vs. 2-mg (IR = 9.6) group in the extended dataset but were overall lower compared to the PC dataset. In the All-BARI-AD dataset, the IR for herpes simplex events was 10.3 ($n = 224$). In the All-BARI-AD dataset, the IR peaked during the first 16 weeks of treatment and decreased thereafter, levelling off between weeks 32 and 52 (Fig. 2b).

Most herpes simplex events in the All-BARI-AD dataset were investigator-rated mild or moderate (93.3%, $n = 209$) in severity (Table 1) and rarely led to permanent treatment discontinuation (2.2%, $n = 5$), with no discontinuation related to herpes simplex events during the PC period. Overall, 58.5% ($n = 131$) of patients with an event of herpes simplex received systemic antiviral treatment, with the majority receiving oral therapy ($n = 119/130$). In >95% of events, outcomes were reported as recovered or resolved with or without treatment at the time of the database lock.

About half of the patients with TE-herpes simplex (51.3%, $n = 115/224$) presented with oral/perioral herpes simplex (IR = 5.3); and in 88 patients (39.3%, IR = 4.1), the herpes simplex events were unclassified (IR = 4.1). EH was reported in 43 patients (19.2%, IR = 2.0), genital herpes simplex in eight patients (3.6%, IR = 0.4) and ophthalmic herpes simplex in seven patients (3.1%, IR = 0.3; Table 1). Of cases with ophthalmic herpes simplex, all reported as peri-orbital, three were classified as severe ($n = 3/7$, 42.9%). For both genital herpes simplex and herpes simplex events unclassified, all events were rated as mild or moderate. Similarly, most oral/perioral herpes simplex events were rated as either mild or moderate (96.5%).

Most patients with any TE-herpes simplex experienced a single event (66.1%, $n = 148$), recurrence was highest with oral/perioral herpes simplex, with 27.8% ($n = 32$) of patients experiencing ≥2 events (Fig. 3a, Table S4). The time from first dose to first onset of a herpes simplex event varied with a median range of 93 days for genital to 178 days for ophthalmic herpes simplex. Median duration for herpes simplex events was 14 days and median time from first dose to first TE-herpes simplex was 146 days.

Eczema herpeticum

The proportion of patients with EH in the PC dataset was 0.2% for 2-mg and 1.4% for 4-mg vs. 0.4% on placebo (Table 2). In the extended dataset, the IR was 1.2 in the 2-mg and 2.8 in the 4-mg group. One patient with EH had a prior history of EH, whereas six had a prior history of any HSV infection. Overall, 86.0% ($n = 37$) of patients with an EH event had a medical history of allergic disease (vs. 74.0% in patients without TE-herpes simplex). Most patients experienced only a single event ($n = 38$, 88.4%), while 11.6% ($n = 5$) of patients had recurrent EH, and the median duration of a TE-EH was 11.5 days. All patients recovered from or resolved ($n = 43$, 100.0%) their EH event.

Of all TE-EH, 55.8% ($n = 24$) were reported as related to study drug. The majority of EH events were rated as mild or moderate (79.1%) as evaluated by the investigator. In line with reported severity, the percentage of EH body surface area (BSA) involvement did not exceed 2% in most patients. Of patients with known EH BSA involvement ($n = 31$), 74.2% ($n = 23/31$)

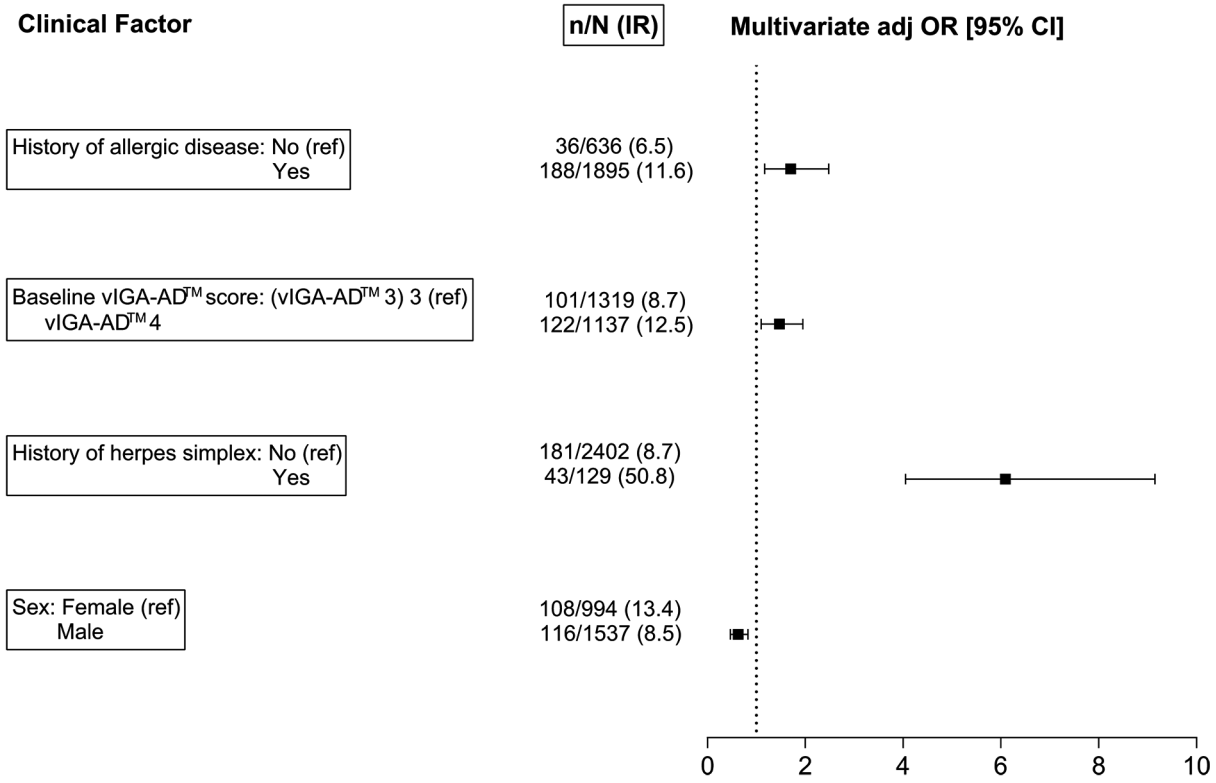

Figure 1 Multi-variable risk factor analysis for herpes simplex events in the All-BARI-AD dataset (adjusted odds ratio; 95% CI). Potential risk factors were evaluated in a univariable model, including history of herpes simplex, vIGA-AD at baseline (does not include phase 2 study), EASI at baseline, BSA at baseline, presence of allergic diseases in medical history, IgE, age at baseline, age at diagnosis, duration since AD diagnosis, and race. Covariates with a significant association ($P < 0.05$) were selected for a multivariable Cox regression model. AD, atopic dermatitis; BSA, body surface area; EASI, Eczema Area and Severity Index.

did not exceed 2% of BSA on any BARI dose. In 48.4% of events (n = 15/31), ≤1% BSA was affected (Fig. 3b). Systemic antivirals were used in most events (79.2%) and in about half of the events concomitant antibiotic therapy was initiated (48.8%, n = 21). Only a minor proportion of patients used pain medication (9.3%, n = 4) and none of the patients reported pyrexia at the time of the event. Discontinuation of study drug due to EH occurred in two patients (4.7%).

Of note, in most patients with EH in the All-BARI-AD dataset, the event was linked to poor disease control (vIGA-AD 3 or 4) preceding the infection onset (n = 29, 67.4%) (Fig. 3c). For comparison, this correlation is less clear for events of oral/perioral herpes simplex, where only 52.2% (n = 60/115) of events occurred in patients with vIGA-AD 3 or 4 prior to the event.

In total, 11 events of herpes simplex were reported as SAEs (IR = 0.5), all of them being classified as EH with six events occurring in patients on 4-mg, three events on 2-mg and two events on 1-mg. All events were linked to poor disease control (vIGA-AD 3 or 4) at time of EH onset (9 had a vIGA-AD of 3, while 2 had a vIGA-AD of 4). All were categorized as SAE due to hospitalization and were treated with acyclovir, the majority intravenously (90.9%, n = 10) and one orally (9.1%, n = 1).

Herpes zoster

Baseline characteristics were similar across patients with or without an event of HZ during treatment with BARI (Table S5). The mean age of patients with reported HZ was 39.6 (±14.3) years. A history of HZ was reported in 11.3% of patients with TE-HZ compared to 4.4% of study patients without TE-HZ. HZ vaccination status was known for 69.8% (n = 37/53) of patients with a TE-HZ, of these only 5.4% (n = 2/37) were vaccinated for HZ (vs. 6.4%, n = 113/1760 in patients without TE-HZ). A multivariable Cox regression analysis identified no specific risk factors for patients developing a TE-HZ event within the All-BARI-AD dataset.

In the PC dataset (Table 3), TE-HZ was only reported for 2-mg (n = 6) and PBO (n = 3), while no events occurred in the 4-mg group (n = 0; Fig. 4a). HZ events were independent of the BARI dose in the extended analysis set, and occurred in 2.7%, (n = 16, IR = 3.8) and 1.6% (n = 8, IR = 1.8) in the 2-mg and

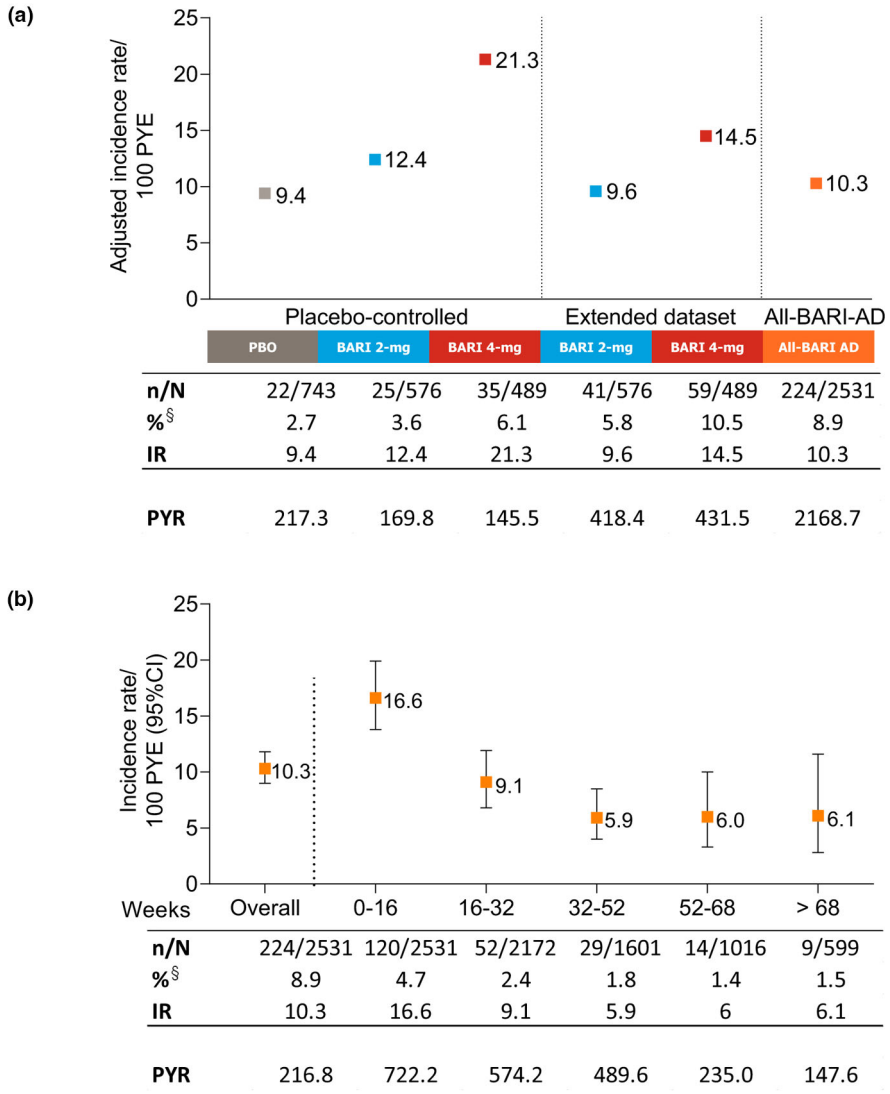

Figure 2 Frequency of TE-herpes simplex. (a) The frequency of TE-herpes simplex is shown for placebo (PBO; grey), BARI 2-mg (blue), BARI 4-mg (red) in the placebo-controlled and the extended analysis datasets and for the All-BARI-AD dataset (orange). §Percentages and IRs (per 100 PYE) for the placebo-controlled datasets (to week 16) and the 2–4-mg extended dataset (to week 105) are study-size adjusted rates; percentages and IRs are not adjusted for the All-BARI-AD dataset. (b) The frequency (IR) of TE-herpes simplex over 16-week intervals through 68 weeks are shown in the All-BARI-AD dataset. The All-BARI-AD dataset includes 1-mg, 2-mg and 4-mg BARI doses. CI, confidence interval; IR, incidence rate; *n*, number; PYE, patient years of exposure.

4-mg groups respectively. In the All-BARI-AD dataset (Table 3), the IR for events of HZ was 2.3 (n = 53). Most HZ infections were single events (94.3%, n = 50) and only three patients had two events (Table S4). The median duration of an event was 14.0 days and most occurred within the first year (77.4%, n = 41) of treatment. When examining HZ IR over time, long-term exposure to BARI did not lead to an increase in incidence of HZ (Fig. 4b).

HZ events were mostly mild or moderate (96.2%, n = 51) in severity and none were deemed serious (Table 3). Except for two events (one multidermatomal and one disseminated), TE-HZ were limited to one dermatome (All-BARI-AD dataset). Study drug was interrupted in 27 patients (50.9%) with TE-HZ and discontinued in one patient in the All-BARI-AD dataset. Most patients received antiviral medication (81.1%, n = 43) and in 94.3% (n = 50) outcomes were reported as recovered.

Table 1 Summary of treatment emergent herpes simplex infections

	Placebo-controlled (to Week 16)			Extended analysis		All-BARI-AD
	PBO (*N* = 743) PYE = 211.8	BARI 2-mg (*N* = 576) PYE = 169.1	BARI 4-mg (*N* = 489) PYE = 147.1	BARI 2-mg (*N* = 576) PYE = 425.5	BARI 4-mg (*N* = 489) PYE = 459.4	All-BARI-AD‡ (*N* = 2531) PYE = 2247.4
Adverse events						
TE-herpes simplex, *n*, (adj %) [adj IR]†,‡	22 (2.7) [9.4]	25 (3.6) [12.4]	35 (6.1) [21.3]	41 (5.8) [9.6]	59 (10.5) [14.5]	224 (8.9) [10.3]
Herpes simplex sub-type, *n* (adj %), [adj IR]†,‡,§						
Oral/perioral herpes simplex	9 (1.2)	11 (1.4)	14 (2.4)	19 [4.6]	30 [7.4]	115 [5.3]
Herpes simplex unclassified	8 (0.9)	12 (1.9)	15 (2.6)	17 [4.2]	28 [6.5]	88 [4.1]
Periorbital	0 (0.0)	2 (0.2)	3 (0.5)	3 [0.7]	7 [1.5]	24 [1.1]
Head/neck not further specified	5 (0.6)	4 (0.5)	3 (0.5)	10 [2.4]	10 [2.6]	39 [1.8]
Location unspecified	4 (0.4)	8 (1.4)	10 (1.7)	8 [2.1]	13 [2.8]	33 [1.5]
Eczema herpeticum	4 (0.4)	1 (0.2)	7 (1.4)	5 [1.2]	12 [2.8]	43 [2.0]
Genital herpes simplex	1 (0.2)	1 (0.1)	2 (0.4)	2 [0.3]	2 [0.7]	8 [0.4]
Ophthalmic herpes simplex	0 (0.0)	0 (0.0)	1 (0.2)	2 [0.3]	3 [0.6]	7 [0.3]
Severity, *n* (*n*/*n* %)¶						
Mild	14 (63.6)	14 (56.0)	21 (60.0)	23 (56.1)	35 (59.3)	134 (59.8)
Moderate	8 (36.4)	11 (44.0)	14 (40.0)	16 (39.0)	21 (35.6)	75 (33.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.9)	3 (5.1)	15 (6.7)
SAE, *n* (*n*/*n* %)	2 (9.1)	0 (0.0)	0 (0.0)	1 (2.4)	3 (5.1)	11 (4.9)
Treatment discontinuation/ interruption, *n* (*n*/*n* %)						
Leading to permanent discontinuation from the study drug	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.8)	2 (3.4)	5 (2.2)
Temporary interruption from the study drug	2 (9.1)	3 (12.0)	7 (20.0)	6 (14.6)	11 (18.6)	39 (17.4)
Antiviral treatment, *n* (*n*/*n* %)						
Treated with antiviral medication	12 (54.5)	14 (56.0)	16 (45.7)	27 (65.9)	31 (52.5)	131 (58.5)
Topical	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Topical and Systemic	3 (13.6)	4 (16.0)	3 (8.6)	5 (12.2)	4 (6.8)	23 (10.3)
Systemic	9 (40.9)	10 (40.0)	13 (37.1)	22 (53.7)	26 (44.1)	108 (48.2)
Route of administration for systemic antivirals, *n* (*n*/*n* %)††						
Oral	11 (50.0)	13 (48.0)	14 (40.0)	25 (61.0)	26 (44.1)	119 (53.1)
Intravenous	1 (4.5)	0 (0.0)	1 (2.9)	0 (0.0)	3 (5.1)	5 (2.2)
Oral and Intravenous	0 (0.0)	0 (0.0)	1 (2.9)	1 (2.4)	2 (3.4)	6 (2.7)
Recovered/Resolved, *n* (*n*/*n* %)	20 (90.9)	24 (96.0)	33 (94.3)	38 (92.7)	55 (93.2)	213 (95.1)

†Percentages and IRs (per 100 PYE) for the placebo-controlled datasets (to week 16) and the 2–4-mg extended dataset (to week 105) are study-size adjusted rates.

‡Percentages and IRs are not adjusted for the All-BARI-AD dataset which includes BARI 1-mg, 2-mg and 4-mg doses.

§Herpes simplex included the preferred terms (PTs) herpes simplex, oral herpes, eczema herpeticum, Kaposi's varicelliform eruption, ophthalmic herpes simplex, genital herpes and genital herpes simplex. Subclassification of herpes simplex was based on PTs taking into account reported terms. Clusters of PTs of herpes ophthalmic and ophthalmic herpes simplex are further reported as ophthalmic herpes simplex. The cluster of PTs eczema herpeticum and Kaposi's varicelliform eruption were reported as eczema herpeticum. The PT genital herpes and genital herpes simplex were reported as cluster genital herpes simplex. Patients with events of PT herpes simplex, further categorized as herpes simplex unclassified, have been subcategorized by location based on their reported term into perioral, head/neck not further specified and location unspecified. Oral/perioral herpes simplex consist of events reported with PT oral herpes and those with oral/perioral herpes based on reported term in PT herpes simplex.

¶Severity was investigator rated as mild, moderate or severe.

††One patient on 2-mg BARI took tablet Valacyclovir but was recorded as topical in the database; therefore, this patient was excluded. AD, atopic dermatitis; BARI, baricitinib; EH, eczema herpeticum; IR, incidence rate; *n*, number; PBO, placebo; PYE, patient years exposure; SAE, serious adverse event; TE, treatment emergent.

Discussion

This integrated safety analysis of 2531 patients, totalling 2247.4 PYs, reports and characterizes TE-herpes simplex, EH and HZ infections in BARI-treated AD patients. Adults with moderate-to-severe AD are prone to infections due to disruption of their skin barrier function and defects in their immune response increase the risk for bacterial as well as viral infections, including those caused by HSV and VZV.[2,10]

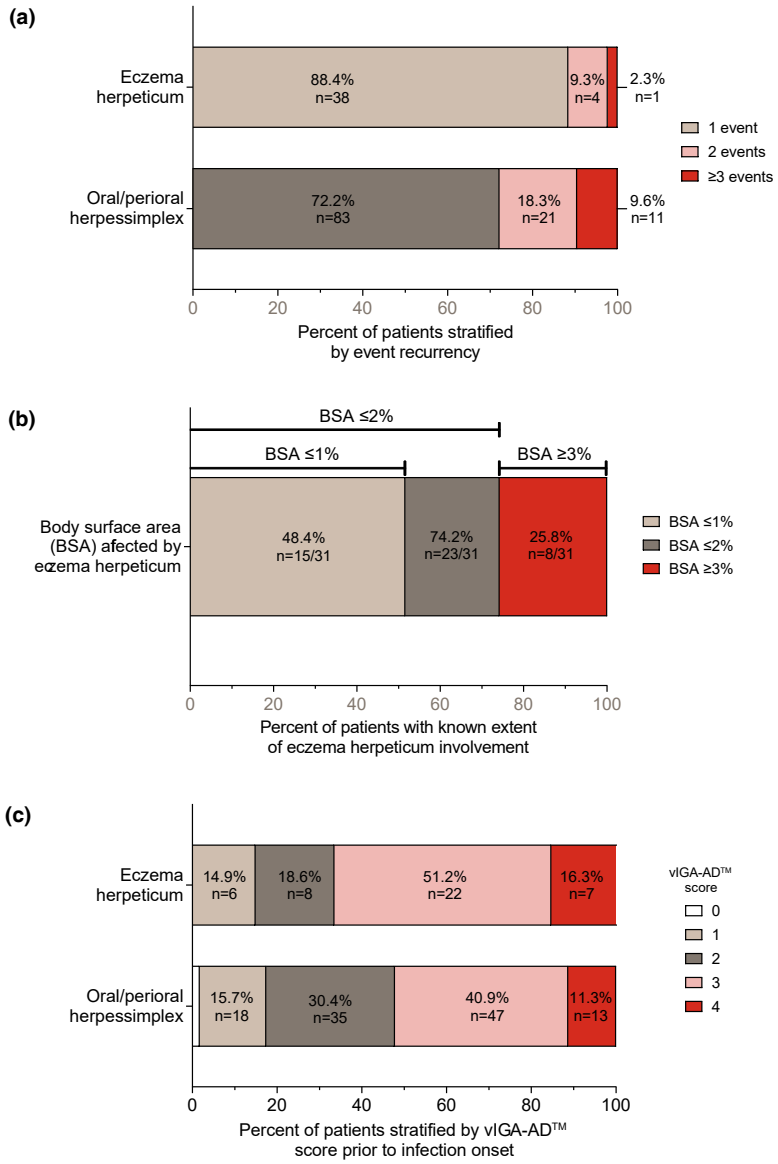

Figure 3 Overview of recurrency, extent of eczema herpeticum (EH) body surface area (BSA) involvement and disease severity (vIGA-AD score) prior to infection onset of herpes simplex subtypes of oral/perioral herpes simplex or EH in the All-BARI-AD dataset. (a) Recurrency is shown as the percent of patients that experienced a TE-herpes simplex, specifically oral/perioral herpes simplex (N = 115) or EH (N = 43). (b) The extent of BSA affected by EH is shown for patients with known BSA involvement (N = 31). (c) Disease severity is shown as the percent of patients with the respective vIGA-AD score prior to event onset in the All-BARI-AD dataset. BSA, body surface area; EH, eczema herpeticum; *n*, number.

In the current study, herpes simplex was more frequent in the BARI group within the first weeks of treatment. However, after week 16, the IR decreased and remained stable. This suggests that prolonged treatment with BARI does not increase the susceptibility for herpes simplex, perhaps as a result of improved disease control in those who remain on therapy beyond 16 weeks. Most events occurred in typical locations (orally or periorally) were rated as mild or moderate and rarely led to discontinuation.

The frequency of EH was 1.7% among patients treated with any dose of BARI, which was lower than previously reported.[2] It

Table 2 Summary of treatment emergent eczema herpeticum

	Placebo-controlled (to Week 16)			Extended analysis		All-BARI-AD
	PBO (*N* = 743) PYE = 211.8	BARI 2-mg (*N* = 576) PYE = 169.1	BARI 4-mg (*N* = 489) PYE = 147.1	BARI 2-mg (*N* = 576) PYE = 425.5	BARI 4-mg (*N* = 489) PYE = 459.4	All-BARI-AD[‡] (*N* = 2531) PYE = 2247.4
Adverse events						
Patients with ≥1 TE-eczema herpeticum event, *n* (adj %) [adj IR][†]	4 (0.4)	1 (0.2)	7 (1.4)	5 (0.6) [1.2]	12 (2.3) [2.8]	43 (1.7) [2.0]
Severity, *n* (*n*/*n* %)[§]						
Mild	2 (50.0)	1 (100.0)	4 (57.1)	3 (60.0)	4 (33.3)	15 (34.9)
Moderate	2 (50.0)	0 (0.0)	3 (42.9)	1 (20.0)	6 (50.0)	19 (44.2)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (20.0)	2 (16.7)	9 (20.9)
SAE, *n* (*n*/*n* %)	2 (50.0)	0 (0.0)	0 (0.0)	1 (20.0)	3 (25.0)	11 (26.5)
Treatment discontinuation/ interruption, *n* (*n*/*n* %)						
Leading to permanent discontinuation from the study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (16.7)	2 (4.7)
Temporary interruption from the study drug	1 (25.0)	0 (0.0)	3 (42.9)	1 (20.0)	5 (41.7)	15 (34.9)
Events related to study drug, *n* (*n*/*n* %)	2 (50.0)	0 (0.0)	3 (42.9)	1 (20.0)	8 (66.7)	24 (55.8)
Treated with antiviral medication, *n* (*n*/*n* %)						
Topical	—	—	—	0 (0.0)	0 (0.0)	0 (0.0)
Topical and systemic	—	—	—	1 (20.0)	2 (16.7)	7 (16.3)
Systemic	—	—	—	4 (80.0)	9 (75.0)	34 (79.2)
Recovered/Resolved, *n* (*n*/*n* %)	3 (75.0)	1 (100.0)	7 (100.0)	5 (100.0)	12 (100.0)	43 (100.0)
TE specific information at time of EH event, *n* (*n*/*n* %)						
Infection requiring concomitant antibiotic therapy	—	—	—	3 (60.0)	3 (25.0)	21 (48.8)
Pain medication usage for EH event	—	—	—	0 (0.0)	1 (8.3)	3 (7.0)
Pyrexia at time of EH event	—	—	—	0 (0.0)	0 (0.0)	0 (0.0)
TE specific patient information, *n* (*n*/*n* %)						
Prior history of EH	—	—	—	0 (0.0)	0 (0.0)	1 (2.3)
Presence of allergic disease in history	—	—	—	5 (100.0)	9 (75.0)	37 (86)

[†]IRs (per 100 PY) for the placebo-controlled datasets and the extended analysis dataset are study-size adjusted rates; adjusted percentages are only shown for the placebo-controlled dataset.
[‡]All-BARI-AD includes BARI 1-mg, 2-mg and 4-mg doses.
[§]Severity was investigator rated as mild, moderate or severe. Analysis was carried out for extended and All-BARI-AD datasets only. AD, atopic dermatitis; BARI, baricitinib; EH, eczema herpeticum; IR, incidence rate; *n*, number; PBO, placebo; PY, patient years; SAE, serious adverse event; TE, treatment emergent.

should be noted that a history of recurrent EH or a recent episode of EH were exclusion criteria from the BREEZE trial programme, which may explain the lower frequency of EH. Most events of EH were rated mild/moderate in severity, affected an area of 2% or less, did not lead to study drug discontinuation and required hospitalization in only ~25% of cases. A recent retrospective European study assessing the clinical characteristics of EH in AD patients found that recurrence of EH occurred in 26.5% of AD patients and identified extrinsic AD, early disease onset, and severe AD as risk factors for developing EH.[11] In our current study, recurrence of EH was less than half of that reported in Seegräber *et al.* 2020, with only 11.6% of patients having 2 or more events of EH. This finding indicates that prolonged exposure to BARI does not increase EH recurrency. In contrast, our data support the concept that better skin disease control decreases the risk to develop skin infections, including EH.[11–14]

Indeed, more patients with EH had a vIGA-AD 3 or 4 preceding the infection onset as compared to those with oral/perioral herpes simplex. These findings are in line with previous reports that linked AD severity and BSA involvement to a higher risk of developing EH.[2,12,13] In addition, data from this clinical trial programme observed less skin infections requiring antibiotics in people treated with BARI 4-mg relative to 2-mg and placebo which underlines the concept that improvements in skin integrity in patients with AD reduce the risk for skin infections.[9,15] Similarly, treatment of AD with dupilumab led to a decrease in *S. aureus* colonization and improvements in EH as compared to placebo.[16,17] Thus, data from both the BARI and dupilumab clinical development programmes suggest that better control of skin disease reduces the frequency of skin infections, including EH.[15]

In the BARI-AD programme,[9] TE-herpes simplex was reported more frequently compared to the BARI-RA[8]

Table 3 Summary of treatment emergent herpes zoster.

	Placebo-controlled (to Week 16)			Extended analysis		All-BARI-AD
	PBO (*N* = 743) PYE = 211.8	BARI 2-mg (*N* = 576) PYE = 169.1	BARI 4-mg (*N* = 489) PYE = 147.1	BARI 2-mg (*N* = 576) PYE = 425.5	BARI 4-mg (*N* = 489) PYE = 459.4	All-BARI-AD (*N* = 2531) PYE = 2247.4
Adverse events						
Patients with ≥1 TE-HZ event, *n*, (adj %) [adj IR][†,‡]	3 (0.3) [1.0]	6 (0.8) [2.7]	0 (0.0) [0.0]	16 (2.5) [3.8]	8 (1.5) [1.8]	53 (2.1) [2.3]
Severity, *n* (*n*/*n* %)[§]						
Mild	1 (33.3)	2 (33.3)	0 (0.0)	4 (25)	3 (37.5)	19 (35.8)
Moderate	2 (66.7)	4 (66.7)	0 (0.0)	11 (68.8)	5 (62.5)	32 (60.4)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (3.8)
SAE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Treatment interruption/ discontinuation, *n* (*n*/*n* %)						
Leading to permanent discontinuation from the study drug	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Temporary interruption from the study drug	1 (33.3)	5 (83.3)	0 (0.0)	8 (50)	5 (62.5)	27 (50.9)
Treated with antiviral medication, *n* (*n*/*n* %)	2 (66.7)	4 (66.7)	0 (0.0)	13 (81.3)	8 (100)	43 (81.1)
Recovered/Resolved, *n* (*n*/*n* %)	2 (66.7)	5 (83.3)	0 (0.0)	15 (93.8)	7 (87.5)	50 (94.3)
Extent						
Localized or non-multidermatomal	3 (0.3)	5 (0.7)	0 (0.0)	15 (93.8)	8 (100)	51 (96.2)
Multidermatomal	0 (0.0)	1 (0.1)	0 (0.0)	1 (6.3)	0 (0.0)	1 (1.9)
Disseminated	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.9)
Motor nerve involvement	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	2 (3.8)
Vaccination status & prior HZ history, *n* (adj %)						
Prior herpes zoster vaccination	25 (2.6)	13 (2.0)	9 (1.5)	13 (2.0)	9 (1.5)	122 (4.8)
Prior herpes zoster in history	43 (4.5)	28 (4.2)	26 (4.2)	31 (4.7)	26 (4.2)	116 (4.6)

[†]Percentages and IRs (per 100 PYE) for the placebo-controlled datasets (to week 16) and the 2–4-mg extended dataset (to week 105) are study-size adjusted rates.
[‡]Percentages and IRs are not adjusted for the All-BARI-AD dataset which includes BARI 1-mg, 2-mg and 4-mg doses.
[§]Severity was investigator rated as mild, moderate or severe. AD, atopic dermatitis; BARI, baricitinib; HZ, herpes zoster; IR, incidence rate; PBO, placebo; PY, patient years; TE, treatment emergent.

programme underscoring the importance of considering the underlying disease when assessing safety profiles.[18] Patients in the AD programme were younger (36.4 years) than those in the RA clinical programme (52.7 years) and the risk for herpes simplex virus has been shown to be 50% higher in those with AD compared to those without.[19] In addition, plasmacytoid dendritic cell numbers are low in AD lesions, thus adding a risk factor for EH.[20] Characteristics including allergic disease, severe AD, and a history of herpes simplex were found to be risk factors for developing a TE-herpes simplex and all have been previously described as risk factors for developing EH.[11] A previous history of herpes simplex has also been established as a risk factor with another oral JAK inhibitor.[21]

AD is a recognized risk factor for developing an event of HZ and associated with increased hospitalization.[1,22] In this study, TE-HZ occurred less frequently with 4-mg than 2-mg BARI in the PC and extended datasets, indicating no dose-dependent impact of BARI treatment, and no events were reported for 4-mg during the PC period making it a very rare event over the first 16 weeks of treatment.[23] The frequency of HZ did not increase with prolonged exposure and no SAEs of HZ were reported. Upon commencement of this study a very small proportion (4.8%) of patients were vaccinated against HZ and despite this, the frequency of HZ during the AD clinical programme was lower compared to the RA programme.[8,24] In the RA programme, advancing age and region (South Korea, Taiwan and Japan) were independent risk factors for developing a TE-HZ.[24] This discrepancy may arise from population demographics, with age identified as a risk factor for developing HZV.[8,9] In this current study, no risk factors were identified for patients developing HZ.

Limitations

There was a lack of a control group beyond week 16. There was not a universal standard data collection tool specific for herpes simplex events and thus some sub-classification was reliant on investigator reported terms and data clarification queries to sites. Potential differences in exclusion criteria, clinical characteristics and other patient- and disease-dependent factors limit the comparability with previously published trials.

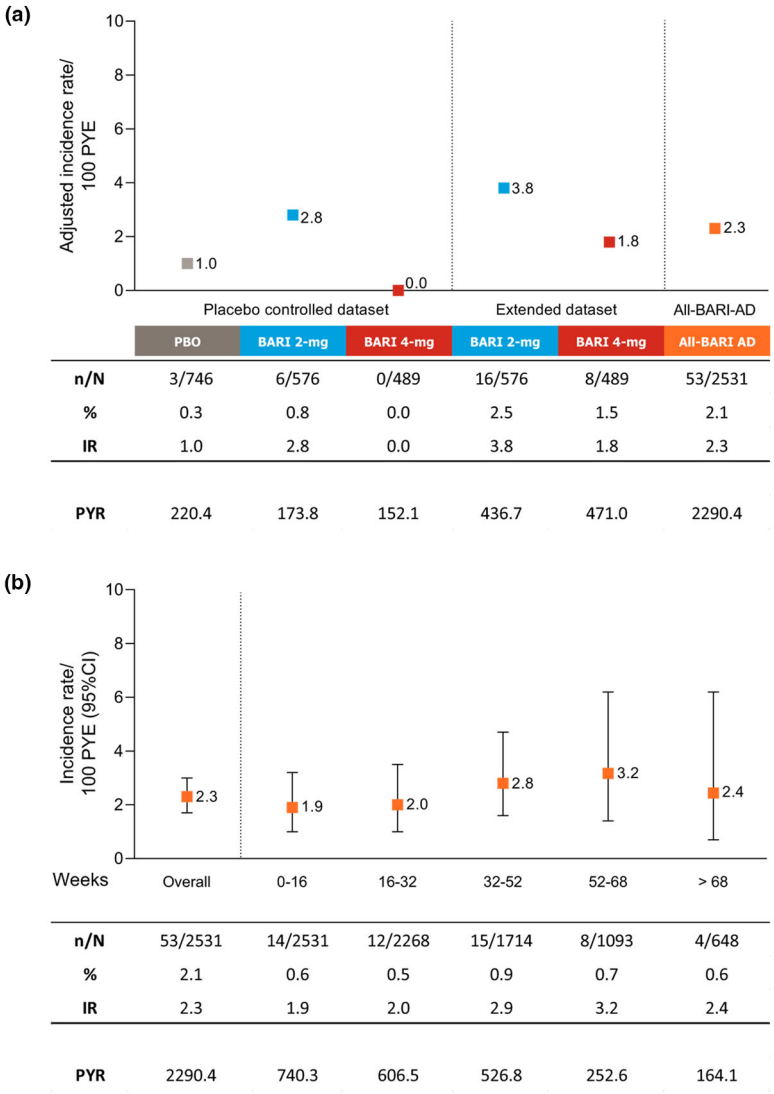

Figure 4 Frequency of TE-herpes zoster. (a) The frequency of TE-herpes zoster is shown for placebo (PBO; grey), BARI 2-mg (blue), BARI 4-mg (red) in the placebo-controlled and the extended analysis datasets and for the All-BARI-AD dataset (orange). Percentages and IRs (per 100 PYE) for the placebo-controlled datasets (to week 16) and the 2–4-mg extended dataset (to week 105) are study-size adjusted rates; percentages and IRs are not adjusted for the All-BARI-AD. (b) The frequency (IR) of TE-herpes zoster over 16-week intervals through 68 weeks are shown in the All-BARI-AD dataset. The All-BARI-AD dataset includes 1-mg, 2-mg and 4-mg BARI doses. BARI, baricitinib; CI, confidence interval; IR, incidence rate; *n*, number; PYE, patient years of exposure.

Conclusion

Results from this integrated safety analysis suggest an increased risk for uncomplicated herpes simplex in BARI-treated AD patients. These events were mostly mild-to-moderate, presented as localized oral/perioral herpes simplex and rarely led to discontinuation. EH was infrequent (1.7%) and occurred mostly in conjunction with poor disease control, strengthening the link between AD disease severity and EH onset. TE-HZ was rare (<1%), mostly rated as mild-to-moderate, and lacking a dose dependent relationship with BARI treatment in the AD clinical programme.

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Prior presentations

These data previously presented in part at the 50th European Society for Dermatological Research (ESDR) Virtual Congress; 22–25th September 2021 (Werfel *et al.*, ESDR 2021. Virtual Meeting. P084).

Data availability statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and the European Union and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report and blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at https://www.vivli.org.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Key inclusion criteria.

Table S1. Baricitinib trials included in the integrated analysis.

Table S2. Safety outcomes definitions.

Table S3. Baseline Characteristics of patients with and without TE-herpes simplex events in the All-BARI-AD dataset.

Table S4. Recurrency and duration of TE-herpes simplex and herpes zoster in the All-BARI-AD dataset.

Table S5. Baseline characteristics of patients with and without TE-herpes zoster events in the All-BARI-AD dataset. Data reported as *n*, (%) unless otherwise stated. [a]JAHG not included. AE, adverse event, AD, atopic dermatitis, DLQI, Dermatology Life Quality Index, EASI, Eczema Area and Severity Index, KU/L, kilounits per litre, N, number, TCS, topical corticosteroids, TCNI, Topical calcineurin inhibitors, vIGA-AD, validated Investigator Global Assessment for Atopic Dermatitis.