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Twice-daily versus Once-daily Applications of Pimecrolimus Cream 1% for the Prevention of Disease Relapse in Pediatric Patients with Atopic Dermatitis

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Abstract: **The aim of this study is to compare twice-daily and once-daily applications of pimecrolimus cream 1% for prevention of atopic dermatitis relapses in pediatric patients. This multicenter trial enrolled 300 outpatients aged 2 to 17 years, with mild-to-severe atopic dermatitis. The patients were initially treated with twice-daily topical pimecrolimus until complete clearance or for up to 6 weeks (open-label period). Those who achieved a decrease of at least 1 point in the Investigator's Global Assessment score were then randomized to double-blind treatment with pimecrolimus cream 1% either twice daily or once daily for up to 16 weeks. Study medication was discontinued during periods of disease remission (Investigator's Global Assessment = 0). The primary efficacy end point of the double-blind phase was disease relapse (worsening requiring topical corticosteroids or additional/alternative therapy and confirmed by Investigator's Global Assessment score ≥ 3 and pruritus score ≥ 2). Of the 300 patients enrolled in the study, 268 were randomized to treatment with pimecrolimus cream 1% either twice daily or once daily (*n* = 134 in each group). The relapse rate was lower in the twice-daily dose group (9.9%) than that in the once-daily dose group (14.7%), but analysis of the time to disease relapse, using a Cox proportional model to adjust for confounding variables, did not show a statistically significant difference between treatment arms (hazard ratio: 0.64; 95% CI: 0.31–1.30). Treatment of active atopic dermatitis lesions with pimecrolimus cream 1% twice daily, followed by the once-daily dosing regimen, was sufficient to prevent subsequent atopic dermatitis relapses over 16 weeks in pediatric patients.**

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Atopic dermatitis (AD) is an inflammatory disease with a chronically relapsing course (1–3). It is, therefore, important to identify safe and effective regimens of care to treat areas of disease persistence or frequent recurrence of inflammatory eczema, to prevent progression to major flares and to prolong remission periods of AD over time (4). Pimecrolimus cream 1% (Novartis Pharma AG, Basel, Switzerland) is a topical, noncorticosteroid, anti-inflammatory agent that may be used to prevent AD relapses (4). It combines a more selective mode of action than topical corticosteroids (TCS) (5) and a favorable safety profile (5–7), as established in numerous long-term clinical trials (8–14) and confirmed in postmarketing surveillance (15,16). Moreover, it may enhance the ability of keratinocytes to kill bacteria and produce antimicrobial peptides (17). Previous randomized controlled studies in pediatric patients (10,11,18) have demonstrated that treatment with pimecrolimus cream 1% twice daily (bid) induces rapid and sustained AD improvement and also reduces the incidence of major flares requiring TCS use in the long-term. While less frequent applications of pimecrolimus cream 1% are much less effective than the bid regimen at treating active skin lesions (19), it is possible that they are sufficient to prevent subsequent relapses once an initial exacerbation has been adequately controlled. This study was designed to test this hypothesis by evaluating the relative efficacy of pimecrolimus cream 1% when applied bid or once daily (od) to prevent relapses after resolution of active AD in pediatric patients.

METHODS

Patients and Study Design

This 22-week trial was conducted in 34 centers (5 in Austria, 5 in Belgium, 4 in Finland, 5 in France, 4 in Spain, 4 in Switzerland, and 7 in the UK). All study sites received protocol approval from the appropriate institutional review board and written informed consent was obtained from all patients or their legal guardians. Eligible participants were pediatric outpatients aged ≥2 and ≤17 years, with mild-to-severe AD affecting ≥5% of their total body surface area. The severity of AD was to be confirmed at the screening visit by an Investigator's Global Assessment (IGA) score ≥2 (Tables 1 and 2). The main exclusion criteria at screening are listed in Table 2. During an initial open-label (OL) period, patients applied pimecrolimus cream 1% bid to lesional areas until disease remission (see Table 3 for definition) or for up to 6 weeks. Patients who achieved disease remission and those who demonstrated a decrease in IGA scores of at least 1 point by the end of the OL period, without experiencing a disease relapse (see Table 3 for definition), were randomized to double-blind (DB) treatment with pimecrolimus cream 1% either bid (pimecrolimus cream 1% in the morning and in the evening) or od (pimecrolimus cream 1% in the morning and vehicle cream in the evening) for up to 16 weeks (Fig. 1). The criteria for excluding patients from the DB phase before randomization are listed in Table 2. DB study medication was discontinued during periods of disease remission and resumed during periods of disease recurrence (see Table 3 for definition). A bland emollient was applied daily throughout the study as a standard care for dry skin. Scheduled visits were the screening visit 1, the randomization visit 2 at the time of disease remission or at the end of the OL period (whichever occurred first), visit 3 at week 14, and visit 4 at week 22. Unscheduled visits were performed whenever there was a suspect disease relapse prior to initiation of TCS or an additional/alternative therapy.

Efficacy was evaluated using the IGA (Table 1) at each scheduled and unscheduled visit, and the primary end point of the DB phase was disease relapse (see Table 3 for definition). The intensity of pruritus over the 24 hours preceding an unscheduled visit for a disease relapse was assessed by the pruritus score (Table 1). The main secondary efficacy parameter was the time to first disease recurrence (see Table 3 for definition). Other secondary efficacy outcome measures included the IGA at each scheduled visit and the Eczema Area and Severity Index (EASI) (20), which was assessed at the screening visit and at visit 4. Safety and tolerability were evaluated by physical examination and monitoring of adverse events (AEs) throughout the study.

Statistical Analysis

The primary efficacy analysis was based on the modified intention-to-treat (mITT) population, which included all randomized patients (ITT population) who applied study medication at least once during the DB phase. All the other efficacy analyzes were based on the ITT population. The differences between treatment groups in terms of time to disease relapse were analyzed using the Cox proportional-hazard model (21). The hazard function was the probability that a patient will have a relapse in the next interval time given that he had experienced no relapse until the beginning of the interval (visit 2). The model included country, EASI score at visit 2, IGA score at visit 2, age, and treatment as explanatory variables to take into account the independent variables that could have a multiplicative, or proportional, effect on the probability of having a relapse. The Kaplan–Meier analysis was used to estimate the time to first disease

TABLE 1. *Investigator's Global Assessment (IGA) and Pruritus Score*

	Definition (morphologic description)	Score
IGA		
Clear	No inflammatory signs of AD	0
Almost clear	Skin generally clear with sparse areas of just perceptible erythema, rarely associated with just perceptible population/infiltration	1
Mild disease	Mild erythema (faintly detectable erythema, very light pink) and mild population/infiltration (barely perceptible elevation)	2
Moderate disease	Moderate erythema (dull red, clearly distinguishable) and moderate papulation/infiltration (clearly perceptible but not extensive elevation)	3
Severe disease	Severe erythema (deep/dark red) and severe papulation/infiltration (marked and extensive elevation)	4
Very severe disease	Severe erythema (deep/dark red) and severe papulation/infiltration with oozing/crusting (marked and extensive elevation with erosive or crusty lesions)	5
Pruritus		
None		0
Mild	Occasional, slight itching/scratching	1
Moderate	Constant or intermittent itching/scratching, which is not disturbing night sleep	2
Severe	Bothersome itching/scratching, which is disturbing night sleep	3

TABLE 2. *Inclusion and Exclusion Criteria*

OL period (at screening)	
Inclusion criteria	Male or female pediatric outpatients aged ≥2 and ≤17 yrs
	Mild-to-severe AD affecting ≥5% of the total body surface area
	Severity of AD confirmed at the screening visit by an IGA score ≥ 2
Exclusion criteria	Topical therapy (e.g., tar, TCS, pimecrolimus, or tacrolimus) during the preceding 4 wks
	Treatment with systemic immunosuppressants, including systemic corticosteroids, during the preceding 4 wk
	History of altered immune competence or malignancy
	Active skin infections at the sites to be treated
	Head lice or scabies
	Clinical conditions other than AD that may interfere with AD evaluation (e.g., generalized erythroderma, acne, Netherton syndrome, psoriasis)
	AD requiring systemic therapy
	History of inadequate response to treatment with calcineurin inhibitors
	Known hypersensitivity to pimecrolimus cream 1% or related drugs
	Use of any experimental or investigational drug or therapy within the previous 6 wks
DB phase (before randomization)	
Inclusion criteria	Disease remission (IGA = 0) by the end of the 6-wk OL period or earlier
	or
	Decrease in IGA scores of at least 1 point by the end of the OL period, without experiencing a disease relapse
Exclusion criteria	Disease relapse during the OL period
	Use of TCS or any additional/alternative therapy during the OL period
	Active skin infections at the application site
	Failure to record use (or nonuse) of study medication and dosing regimen during the OL period
	Failure to apply open-label study drug bid until disease remission or until the end of the 6-wk OL period (whichever occurred first)
	Failure to record concomitant medications during the OL period
	Failure to return OL study drug (used, partially used, and unused tubes) at the time DB study drug was dispensed

TABLE 3. *Definition of Disease Remission, Recurrence, and Relapse*

Disease stage	Definition
Disease remission	No signs and/or symptoms of active AD (IGA score = 0)
Disease recurrence	Presence of early signs or symptoms of an acute exacerbation (increased skin dryness, itching, rash, redness, bumps, tingling, warmth, localized erythema, and skin thickening) after a period of complete remission
Time to disease recurrence	Time elapsed from the randomization visit 2 to the first day of study drug resumption during the DB phase, after a period of complete disease remission (IGA = 0)
Disease relapse	Worsening of AD to a level where the use of TCS or alternative/additional therapy was needed To be confirmed by the investigator during an unscheduled visit as it follows: IGA score ≥3 Pruritus score ≥2
Time to disease relapse	Time elapsed from the randomization visit 2 to the time of confirmed relapse by the investigator (IGA score ≥3 and pruritus score ≥2) during an unscheduled visit

recurrence and the effect of treatments was analyzed for statistical significance with the Log-rank test. The other secondary efficacy outcome measures were analyzed using the Cochran-Mantel-Haenszel test (with country as stratification factor) or the Fisher exact test, as appropriate. The incidence of each AE is presented in terms of crude incidence rate and incidence density (ID) rate. The ID for a given event is defined as the number of occurrences of that event in a treatment group divided by the total person-time at risk accumulated during the study in that group, as described elsewhere (16).

On the basis of previous studies (10,11,18), it was estimated that about 60% of patients on a bid regimen would not experience any disease relapse by the end of the DB phase. To detect a 20% difference between the bid and the od regimens, with a power of 90% and a significance level of 0.05, 131 patients per arm were required to enter the DB phase and receive at least one application of DB study medication.

RESULTS

Patients and Treatment

A total of 300 patients were enrolled and treated with pimecrolimus cream 1% bid during the OL period and 268 were then randomized to DB treatment with pimecrolimus cream 1% bid or od (134 patients per arm) (Fig. 1). The drop-out rates during the DB phase were 16.4% in the bid-regimen group and 21.6% in the od-regimen group. In both groups, the most common reason for discontinuation was unsatisfactory therapeutic effect (Fig. 1). At the screening visit, the demographic and clinical characteristics of patients randomized in the DB phase were well-matched in the two treatment groups (Table 4). The mean DB treatment days were 60.4 days in the bid-regimen group and 58.6 days in the od-regimen group.

Disease Recurrence and Disease Relapse

During the OL period, 50.0% of the patients subsequently randomized to the bid regimen and 51.5% of those subsequently randomized to the od regimen achieved disease remission (IGA = 0) (Table 5). The vast majority of these patients experienced at least one episode of disease recurrence during the DB phase, because the recurrence rate was 97.0% in the bid-regimen group and 97.1% in the od-regimen group. The median time to first disease recurrence was 5 days in the bid-regimen group and 6 days in the od-regimen group, without statistically significant differences between treatment arms (Table 5).

The incidence rate of disease relapse was 9.7% in the bid-regimen group and 14.7% in the od-regimen group (Table 5). Analysis of the time to disease relapse (Cox proportional-hazard model) showed that the adjusted relative risk of experiencing a disease relapse during the 16-week DB phase was lower for a patient on the bid-regimen than that for a patient on the od-regimen (hazard ratio: 0.64), but the difference between treatment arms did not reach statistical significance (Table 5). In the patients who had a disease relapse during the DB phase, the time to relapse ranged from 15 to 78 days in the bid-regimen group and from 7 to 83 days in the od-regimen group.

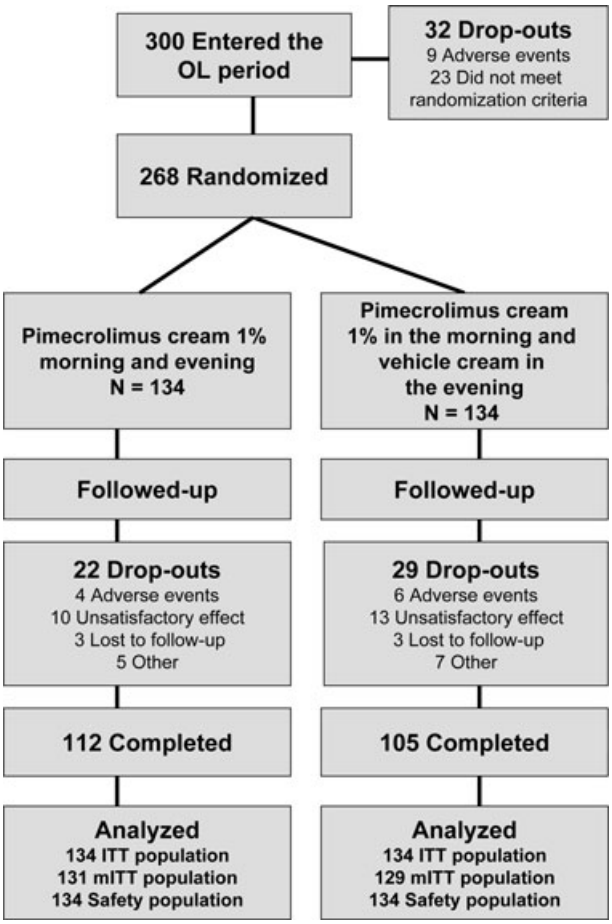


Figure 1. Patient disposition and the flow of participants through each stage of the study. Randomization was performed using a validated system that automates the random assignment of treatment groups to randomization numbers. During the DB phase, the identity of treatments was concealed by the use of study drugs (tubes of pimecrolimus cream 1% and vehicle cream, color-coded for use in the morning and in the evening) that were identical in packaging, labeling, schedule of administration, appearance, taste, and color.

TABLE 4. *Demographic and Clinical Characteristics at Screening by Treatment Received in the Double-blind Phase (Intention-to-Treat Population)*

	Pimecrolimus cream 1% bid, $N = 134$	Pimecrolimus cream 1% od, $N = 134$
Age (years)		
Mean (range)	6.9 (2–17)	7.0 (2–17)
Age groups [*n* (%)]		
2 to <8 yrs	86 (64.2)	81 (60.4)
8 to <12 yrs	25 (18.7)	31 (23.1)
12 to 17 yrs	23 (17.2)	22 (16.4)
Gender [*n* (%)]		
Male	74 (55.2)	70 (52.2)
Female	60 (44.8)	64 (47.8)
Race [*n* (%)]		
Caucasian	125 (93.3)	127 (94.8)
Black	0 (0.0)	1 (0.7)
Oriental	5 (3.7)	0 (0.0)
Other	4 (3.0)	5 (3.7)
Hispanic	0 (0.0)	1 (0.7)
IGA [*n* (%)]		
1 = Mild	54 (40.3)	58 (43.3)
2 = Moderate	71 (53.0)	64 (47.8)
3 = Severe	9 (6.7)	12 (9.0)
%TBSA involved [*n* (%)]		
<10	55 (41.0)	61 (45.5)
10–29	54 (40.3)	60 (44.8)
30–49	16 (11.9)	6 (4.5)
50–69	8 (6.0)	6 (4.5)
70–89	1 (0.7)	1 (0.7)
90–100	0 (0.0)	0 (0.0)
EASI		
Mean (SE)	10.4 (0.78)	9.1 (0.67)
Median	7.8	7.2

TABLE 5. *Disease Recurrence and Disease Relapse*

	Pimecrolimus cream 1% bid	Pimecrolimus cream 1% od
Disease recurrence (ITT population)		
N	134	134
Disease remission in OL period [*n*/*N* (%)]	67/134 (50.0)	69/134 (51.5)
Disease recurrence rate [*n*/*n* (%)]	65/67 (97.0)	67/69 (97.1)
Time to first disease recurrence (Kaplan–Meier estimates) [days]		
Median	5.0	6.0
95% CI	(4.00–7.00)	(4.00–9.00)
Interquartile range (Q25–Q75)	2.0–11.0	2.0–14.0
p-value*	0.420	
Disease relapse (mITT population)		
N	131	129
Disease relapse rate [*n* (%)]	13 (9.9)	19 (14.7)
Time to disease relapse† (Cox proportional-hazard model)		
Hazard ratio	0.64	
95% CI	0.31–1.30	
p-value	0.216	

*Effect of treatment analyzed by the Log-rank test.
†As low number of patients experienced disease relapse in both treatment groups, the Kaplan–Meier estimates of time to disease relapse for the modified intention-to-treat (mITT) population could not be obtained. The Cox proportional-hazard model included country, EASI score at visit 2, IGA score at visit 2, age, and treatment as explanatory variables. The variable country did not have a significant effect on the probability of having a relapse.

Other Efficacy Outcome Measures

Whereas all patients had an IGA score ≥2 at visit 1, 83.2% of those who were randomized reported an IGA score of 0 (clear) or 1 (almost clear) at the end of the OL period (randomization visit 2) (Fig. 2). At visit 4, the percentage of patients with an IGA score of 0 or 1 was 62.1% in the bid-regimen group and 59.5% in the od-regimen group (Fig. 2). The mean EASI scores at visit 4 were comparable in the two treatment groups (Fig. 2).

Safety and Tolerability

During the OL period, nine patients discontinued because of the following AEs: application site reactions (four patients), AD exacerbation (one patient), exfoliative dermatitis (one patient), eczema (one patient), application site infection (one patient), and varicella (one patient). The application site reactions (irritation, erythema, pruritus, and edema) and exfoliative dermatitis were considered treatment related. Serious AEs were reported in three patients and included one case each of exfoliative dermatitis mentioned above, hematuria, and bronchitis. The latter two events were not considered treatment related.

The most frequently reported AEs during the DB phase are listed by treatment group in Table 6. No major differences were observed in the crude incidence rate of AEs between treatment groups, but the percentage of patients who experienced nasopharyngitis tended to be higher in the bid-regimen group than that in the od-regimen group (Table 6). The ID analysis gave ID rates for this event of 1.7 and 1.0 per 1000 patient-days in the study, respectively (Table 6). Therefore, the estimated difference in the number of case of nasopharyngitis between treatment arms would be less than 1 (0.7) per 1000 patient-days. Other frequently reported AEs were disorders commonly observed in pediatric individuals or in patients with AD, such as cough, pyrexia, minor infection, and allergic rhinitis. Most AEs were mild or moderate and were not considered treatment related. Two serious AEs were reported in the od-regimen group (application site dermatitis and asthma) and none in the bid-regimen group. Discontinuations because of AEs occurred less frequently in the bid-regimen group (3.0% of patients) than that in the od-regimen group (4.5% of patients). Only 2 of these discontinuations were because of treatment-related AEs: one case of serious application site dermatitis in the od-regimen group and one case of

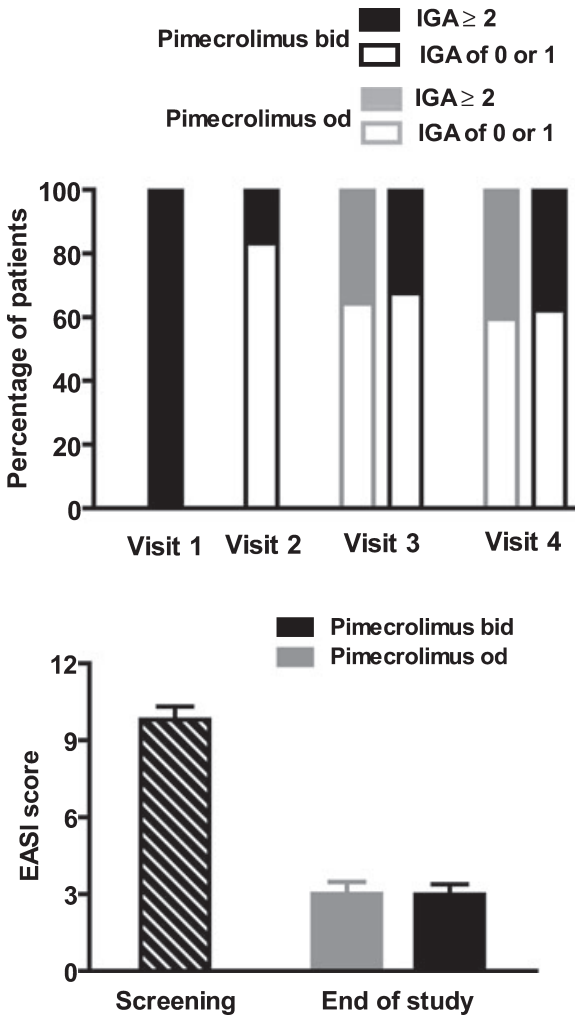


Figure 2. Upper panel: Percentage of patients with IGA scores ≤1 or ≥2 by visit and treatment received during the OL period (from visits 1–2) and the DB phase (visits 2–4). Comparison of the data by the Fisher's exact test did not reveal statistically significant differences between DB treatment arms at any time of the study. Lower panel: EASI scores at screening and by treatment group at the end of the DB phase (visit 4). The EASI was not assessed at visits 2 and 3. The data are reported as the mean values and standard errors. The mean (SE) percent change in EASI score from screening was −67.7% (5.12%) in the bid-regimen group and −60.6% (5.32%) in the od-regimen group.

nonserious application site pruritus in the bid-regimen group.

DISCUSSION

In this study, initial treatment of active skin lesions with pimecrolimus cream 1% bid was very effective at inducing a substantial improvement of AD, with more than 89% of the treated patients achieving at least a disease control sufficient to allow entry into the DB phase of the study. In over 83% of these patients, the initial treatment induced complete or almost complete resolution of signs of AD. Virtually all patients who experienced disease remission during the OL period had at least one episode of disease recurrence during the DB phase. Nonetheless, only a minority of the patients in both treatment groups showed progression of the early signs or symptoms of an acute exacerbation or mild AD to moderate or severe flares, requiring TCS or an additional/alternative therapy. It is worth noting that the percentage of patients with a disease relapse in both treatment groups was much lower (9.9% in the bid-regimen group and 14.7% in the od-regimen group) than that expected (40%) on the basis of previous studies, (10,11,18) which included a control group receiving only vehicle cream bid. However, as this study did not include a placebo or a vehicle cream control group, it is difficult to interpret this finding.

Intervention with pimecrolimus cream 1% during the DB phase tended to be more effective at preventing disease relapse when the cream containing the active ingredient was applied bid rather than od, but the differences between treatment groups, in terms of adjusted relative risk of experiencing a disease relapse over 16 weeks, did not reach statistical significance. Therefore, our data indicate that, once an initial exacerbation of AD has been effectively treated with the use of pimecrolimus cream 1% bid, the od regimen may be sufficient to prevent subsequent escalations from residual lesions or early signs of recurrence to more severe disease.

In this study, the safety and tolerability profile of the two dosing regimens was comparable. These results confirm the ample safety margin of pimecrolimus cream 1% demonstrated in a previous study (22), where topical pimecrolimus was applied either bid or four times daily in adolescents and adults with moderate-to-severe AD for up to 3 weeks, without significant differences between treatment groups in terms of systemic absorption of the active ingredient and in terms of safety profile. However, the finding that the od regimen was sufficient to prevent disease relapses is important because less frequent applications of the product result in reduced exposure to the active ingredient, with a consequent reduction in the risk of side-effects in the intermittent long-term use.

Because AD is a chronic disease that requires chronic treatment, the perception of patients, being an important aspect of adherence to treatment, greatly affects the success of AD management in daily practice (23). Many patients and their families are not satisfied with current therapeutic options and would need drugs that offer less frequent applications, fewer adverse effects, and greater effectiveness in the long-term (24,25). The intermittent use of pimecrolimus cream 1% od when needed to

TABLE 6. *Crude Incidence Rate and ID of the Most Common AE during the Double-blind Phase (Safety Population)*

	Pimecrolimus cream 1% bid, $N = 134$		Pimecrolimus cream 1% od, $N = 134$	
	Crude incidence rate (%)	ID rate* (No. events per 1000 patient-days)	Crude incidence rate (%)	ID rate† (No. events per 1000 patient-days)
Nasopharyngitis	14.9	1.7	8.2	1.0
Cough	9.7	1.3	7.5	0.8
Pyrexia	9.0	1.0	6.0	1.1
Bronchitis	4.5	0.6	6.0	0.6
Gastroenteritis	3.0	0.4	5.2	0.6
Otitis media	2.2	0.2	6.0	0.6
Pharyngolaryngeal pain	3.0	0.3	5.2	0.5
Allergic rhinitis	4.5	0.6	3.0	0.4
Asthma	1.5	0.2	3.7	0.4
Headache	3.7	0.4	1.5	0.1
Varicella	2.2	0.2	3.0	0.3
Conjunctivitis	3.7	0.4	0.7	0.1
Pharyngitis	0.7	0.1	3.7	0.4
Rhinitis	3.0	0.3	1.5	0.1
Upper respiratory tract infection	0.7	0.1	3.7	0.4
External otitis	2.2	0.2	1.5	0.1
Tonsillitis	1.5	0.1	2.2	0.2
Food allergy	0.7	0.3	2.2	0.2
Laryngitis	0.7	0.1	2.2	0.2
Impetigo	2.2	0.3	0.0	NE
Influenza	0.0	NE	2.2	0.2
Molluscum contagiosum	0.0	NE	2.2	0.3
Urinary tract infection	0.0	NE	2.2	0.2

Most common AE are events reported by ≥2% of patients in any group. The ID of an AE per 1000 patient-days was calculated as the number of occurrences (k) of that AE in a treatment group divided by the total number of days patients were followed during the DB phase of the study in that group, multiplied by 1000 according to the following formula: [(k/days) × 1000] (16).
AE, adverse event; ID, incidence density; NE, not estimable.
*Total follow-up: 14,237 days.
†Total follow-up: 13,803 days.

prevent progression of AD recurrences to more severe flare-ups may be particularly useful for those patients who are bothered by applying medications bid, as this therapeutic regimen is still effective at keeping AD under control. In such cases, increased patients' acceptance may lead to increased compliance with treatment.

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CONFLICTS OF INTEREST

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