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BRIEF REPORT

# No Increased Risk of Overall Infection in Adults with Moderate-to-Severe Atopic Dermatitis Treated for up to 4 Years with Dupilumab

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## ABSTRACT

***Introduction***: Patients with atopic dermatitis (AD) have an increased risk for infections. This open-label extension study, LIBERTY AD OLE, reports the incidence of infections in adults with moderate-to-severe AD treated with dupilumab for up to 4 years.

***Methods***: We evaluated infections in adults with moderate-to-severe AD treated with dupilumab 300 mg weekly (qw) or every 2 weeks (q2w; approved regimen) for up to 4 years. Topical corticosteroids (TCS) and calcineurin inhibitors (TCI) were permitted. Exposure-adjusted incidence rates (number of patients with at least one event per 100 patient-years [nP/100 PY]) are reported.

***Results***: Overall, 2677 patients were enrolled and treated with dupilumab: 352 (13.1%) completed up to week 204; 226 patients (8.4%) switched from qw to q2w during the trial. Rates of overall infections (71.27 nP/100 PY), serious and/or severe infections (1.39 nP/100 PY), and infections leading to discontinuation (0.34 nP/100 PY) were consistent with a previous 3-year analysis of this study and low compared with 1-year results in adults with AD treated with placebo + TCS. The cumulative number of patients with treatment-emergent serious or severe infections, non-herpetic or herpetic

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infections, and total skin infections decreased year-over-year. Limitations included open-label study design with no placebo arm; decreasing sample size at later time points due to sponsor decision to close sites following regulatory approval; qw dosing differs from approved q2w dosing; and patients could use TCS/TCI throughout the study, which may have impacted infection rates.

***Conclusions***: Continuous long-term dupilumab treatment in adults with moderate-to-severe AD is not associated with an increased risk of overall systemic or cutaneous infections.

***Trial Registration***: ClinicalTrials.gov Identifier: NCT01949311.

***Infographic***:

## PLAIN LANGUAGE SUMMARY

Atopic dermatitis is a chronic disease that causes dry skin, skin inflammation, and itching. Patients with atopic dermatitis have an increased risk of bacterial or viral skin infections, which can cause further serious infections in the entire body. This study investigated the rates of infections in adults with moderate-to-severe atopic dermatitis after 204 weeks (almost 4 years) of dupilumab treatment. The patients received 300 mg of dupilumab every week, and a subset of patients switched to the approved dose of 300 mg of dupilumab every 2 weeks. Patients were allowed the use of topical corticosteroids. Among the patients receiving dupilumab for up to 4 years, rates of total infections, serious and severe infections, and infections leading to treatment discontinuation were consistent with a previously published 3-year evaluation. The infection rates in the 4-year study were lower than those in a previous 1-year study in adults with atopic dermatitis treated with placebo and topical corticosteroids. Importantly, our results showed that the cumulative number of patients with total skin infections decreased over 4 years of dupilumab treatment. The number of patients with severe infections appearing after the start of treatment, herpes viral infections, and infections not involving herpes virus also decreased yearly during the 4-year study. The safety data presented here show that long-term dupilumab treatment does not increase the overall risk of skin infections, and provides important evidence related to continuous use of dupilumab treatment in adults with moderate-to-severe atopic dermatitis.

**Keywords:** Adults; Atopic dermatitis; Clinical trials; Dupilumab; Infections; Long-term; Safety

**Key Summary Points**

In adults with moderate-to-severe atopic dermatitis (AD) treated with dupilumab for up to 4 years, rates of overall infections, herpetic and non-herpetic infections, serious and/or severe infections, and infections leading to discontinuation were consistent with a previously published 3-year analysis of this study and low compared with adults with AD treated with placebo plus topical corticosteroids for 1 year

Over 4 years of dupilumab treatment, yearly reductions were observed in the cumulative number of patients with treatment-emergent serious or severe infections, non-herpetic or herpetic infections, and total skin infections

Continuous long-term treatment with dupilumab in adults with moderate-to-severe AD is not associated with an increased risk of overall systemic or cutaneous infections

## DIGITAL FEATURES

This article is published with digital features, including a video abstract and infographic, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.21106339.

## INTRODUCTION

Patients with atopic dermatitis (AD) are at risk for bacterial and/or viral cutaneous infections, which can predispose them to serious and systemic infections [1–4]. Traditional immuno-

suppressants (including corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil) and several recently approved treatments for AD can increase infection risk [5–9]. Given that AD is a chronic, relapsing disease, it is important to consider long-term safety, including risk of serious and/or severe infections, when making treatment decisions.

Dupilumab is a fully human VelocImmune®-derived [10, 11] monoclonal antibody that blocks the shared receptor subunit for interleukin (IL)-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases. Dupilumab is approved for the treatment of moderate-to-severe AD in adults, adolescents, and children aged 6 years and older [12, 13]. Multiple placebo-controlled phase 3 clinical trials of dupilumab treatment with or without concomitant topical corticosteroids (TCS) demonstrated rapid, significant, and sustained improvements in AD signs/symptoms and quality of life, with an acceptable safety profile including no evidence of increased overall infection rates [14–18]. Moreover, previous analyses of long-term treatment with dupilumab in an open-label extension (OLE) study, LIBERTY AD OLE, revealed acceptable overall safety and sustained efficacy in adults with moderate-to-severe AD for up to 4 years [19–21]. Here, we present a comprehensive analysis of infection data from the LIBERTY AD OLE study.

# METHODS

## Study Design, Patients, and Treatment

The study design of LIBERTY AD OLE (NCT01949311) has been fully described elsewhere [19–21]. Briefly, the OLE is an ongoing, multicenter, phase 3 trial designed to assess the long-term safety and efficacy of dupilumab in adults with moderate-to-severe AD. The OLE enrolled adult patients who previously participated in phase 1 through 3 dupilumab AD trials. Patients who had an adverse event (AE) related to dupilumab leading to treatment discontinuation or a serious AE related to dupilumab in the parent study, which in the opinion of the investigator or medical monitor could indicate that continued treatment with dupilumab may present an unreasonable risk for the patient, were ineligible. In this analysis, we report results with a cutoff date of March 19, 2021 (database lock April 28, 2021), including patients from approximately 550 sites in 28 countries in North America, Europe, and Asia–Pacific.

Patients enrolled from the start of the study (October 2013) subcutaneously received dupilumab 200 mg weekly (qw; with a 400 mg loading dose). On June 12, 2014, the protocol was amended and patients began receiving a dose regimen of 300 mg qw based on results from a dose-ranging study (NCT01859988). The protocol was again amended on November 12, 2019, at which point patients began receiving a dose regimen of 300 mg every 2 weeks (q2w) to align with the regimen approved by regulatory agencies [12, 13]. Topical corticosteroids (TCS) and calcineurin inhibitors (TCI) were permitted.

## Ethics

This study was conducted in accordance with ethical standards of the responsible committees and the Declaration of Helsinki and with the International Council for Harmonisation guidelines for Good Clinical Practice. The trial was overseen by an independent data and safety monitoring board. The protocol was reviewed and approved by institutional review boards/ethics committees at all centers. All patients provided written informed consent before any study procedures began.

## Safety Data

Safety data are reported according to the system organ class (SOC), high level term (HLT), high level group term (HLGT), and preferred term (PT) of the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1. All AEs are reported on the basis of the primary MedDRA SOC axis. The following data are included in this analysis: number of patients per 100 patient-years (nP/100 PY) with treatment-emergent infections (≥ 2% incidence) by PT (≥ 1 nP/

100 PY in OLE), including overall infections, serious or severe infections, and infections leading to treatment discontinuation reported under the SOC "Infections and Infestations"; non-herpetic skin infections (adjudicated PTs reported under the SOC "Infections and Infestations"; herpes viral infections (HLT including the PTs: eczema herpeticum, herpes simplex, and herpes zoster), total skin infection (herpes viral infections and non-herpetic skin infections), and helminth infections (HLGT). A serious adverse event is defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is an important medical event. A severe adverse event is one that produces significant impairment of functioning or incapacitation and is a definite hazard to the patient's health. Treatment for symptom may be given and/or patient hospitalized.

### Statistical Analysis

This analysis included all patients who received one or more dose of dupilumab or placebo (safety analysis set). Exposure-adjusted incidence rates (number of patients with at least one event per 100 patient years [nP/100 PY]) were calculated for the duration of study participation. As a result of the absence of a control arm in LIBERTY AD OLE, safety results from LIBERTY AD CHRONOS (NCT02260986) are provided for comparison [15]. The CHRONOS trial was selected for comparison because of its large sample size, 52-week duration, and required use of concomitant TCS.

## RESULTS

### Patients

This analysis included 2677 patients. As of the cutoff date, 2207 (82.4%) patients completed up to week 52, 1065 (39.8%) completed up to week 100, 557 (20.8%) completed up to week 148, and 352 (13.1%) completed up to week 204. During the trial, 226 (8.4%) patients switched from qw to q2w dosing. A total of 1362 (50.9%) patients withdrew from the study; the primary reason for withdrawal was sponsor decision to close study sites following regulatory approval and subsequent commercialization of dupilumab (810 [30.3%] patients). Few patients withdrew because of lack of efficacy (58 [2.2%]) or AEs (114 [4.3%]). Treatment discontinuation due to AEs was also uncommon (99 [3.7%] patients). Baseline demographics and disease characteristics as well as the duration of dupilumab exposure among this group of patients have been reported previously [20, 21].

### Exposure-Adjusted Infection Rates

Overall, 1765 patients experienced at least one treatment-emergent infection in the OLE, with an exposure-adjusted infection rate of 71.27 nP/100 PY. Most infections were mild to moderate in severity, with 77 patients (1.39 nP/100 PY) experiencing at least one serious or severe infection. Infections leading to treatment discontinuation were uncommon (19 patients [0.34 nP/100 PY); conjunctivitis was the most common MedDRA PT leading to treatment discontinuation in the "Infections and Infestations" SOC (10 patients [0.18 nP/100 PY]). Of note, the PT "conjunctivitis" is in the "Infections and Infestations" SOC, but represents conjunctivitis of unspecified or undetermined etiology, including non-infectious cases [22]. Indeed, rates of bacterial and/or viral conjunctivitis leading to treatment discontinuation were low, with only one patient experiencing bacterial conjunctivitis leading to treatment discontinuation and no patients experiencing viral conjunctivitis leading to treatment discontinuation. Other infections leading to treatment discontinuation in the OLE included two cases of bronchitis and one case each of coronavirus infection, eczema herpeticum, influenza, ophthalmic herpes simplex, pharyngitis streptococcal, staphylococcal skin infection, superinfection bacterial, and urosepsis. These findings are consistent with a previous 3-year analysis of this study [20].

**Table 1** Exposure-adjusted numbers of patients with treatment-emergent infections

| Event (patients with ≥ 1 event in OLE) | OLE (up to 4 years) | CHRONOS (1-year placebo-controlled trial) | |
|---|---|---|---|
| | Dupilumab 300 mg qw/q2w (*N* = 2677) nP (nP/100 PY) | Placebo qw + TCS (*n* = 315) nP (nP/100 PY) | Dupilumab 300 mg qw + TCS (*n* = 315) nP (nP/100 PY) |
| Overall[a] | 1765 (71.27) | 182 (106.98) | 167 (93.66) |
| Serious or severe infections[a] | 77 (1.39) | 6 (2.12) | 1 (0.34) |
| Infections leading to treatment discontinuation[a] | 19 (0.34) | 3 (0.92) | 0 (0) |
| Non-herpetic skin infections[b] | 248 (4.69) | 57 (20.21) | 26 (7.87) |
| Herpes viral infections (HLT) | | | |
| Total | 343 (6.78) | 25 (9.17) | 22 (7.72) |
| Eczema herpeticum (PT)[c] | 13 (0.23) | 6 (2.13) | 0 (0) |
| Herpes simplex (PT) | 95 (1.72) | 2 (0.70) | 5 (1.70) |
| Herpes zoster (PT) | 54 (0.97) | 5 (1.77) | 1 (0.34) |
| Total skin infections (herpes viral infections + non-herpetic skin infections) | 534 (11.24) | 71 (29.53) | 47 (17.57) |
| Helminth infections (HLGT)[d] | 1 (0.02) | 0 | 0 |

OLE data presented up to 4 years, CHRONOS data presented up to 52 weeks

*HLGT* high level group term, *HLT* high level term, *MedDRA* Medical Dictionary for Regulatory Activities, *nP* number of patients with an event, *nP/100 PY* number of patients with ≥ 1 event per 100 PY, *OLE* open-label extension, *PT* preferred term, *PY* patient-years, *q2w* every 2 weeks, *qw* weekly, *SOC* system organ class, *TCS* topical corticosteroid

[a]Reported under the SOC "Infections and Infestations"

[b]Adjudicated PTs reported under the SOC "Infections and Infestations"

[c]Eczema herpeticum infections in OLE were classified as serious/severe in 2 patients, and 1 patient required treatment discontinuation

[d]Includes HLTs: cestode infections, helminthic infections, nematode infections, trematode infections. The 1 case of helminth infection in OLE was a mild case of ascariasis that resolved within 1 month

Overall infections were lower in patients receiving up to 4 years of dupilumab qw/q2w in the OLE (71.27) compared with patients receiving up to 1 year of placebo + TCS in CHRONOS (106.98; Table 1). The same trend was observed for serious or severe infections (1.39 vs. 2.12), infections leading to treatment discontinuation (0.34 vs. 0.92), non-herpetic skin infections (4.69 vs. 20.21), and total skin infections (including herpes viral infections and non-herpetic skin infections; 11.24 vs. 29.53). Among herpes viral infections, rates of total herpes viral infections, eczema herpeticum, and herpes zoster were numerically lower in the OLE compared with placebo + TCS in CHRONOS (6.78 vs. 9.17; 0.23 vs. 2.13; 0.97 vs. 1.77). Exposure-adjusted infection rates were also lower in the dupilumab 300 mg qw + TCS arm compared with placebo in CHRONOS, with the exception of herpes simplex (Table 1).

Of the 13 patients in the OLE who experienced treatment-emergent eczema herpeticum infections over the course of 4 years, six had a history of eczema herpeticum, five had no

history, and two had an unknown history. Of the 13 cases of eczema herpeticum, 11 were not serious, and of these five were of mild severity and six were of moderate severity. Of the two serious cases, one patient had no history of eczema herpeticum, developed a moderate case, and recovered/resolved; the other patient had a history of eczema herpeticum, developed a severe case that was not related to treatment, and also recovered/resolved. In both cases dupilumab treatment was not withdrawn. Overall, four of 13 patients experienced eczema herpeticum cases that were considered related to treatment, and one of 13 patients (case unrelated to treatment) had dupilumab withdrawn. One patient with eczema herpeticum had more than one case (of the patient's three cases, all were not serious, of moderate severity, and recovered/resolved; dose was not changed). In comparison, over the course of 1 year, six patients in the CHRONOS placebo group had eczema herpeticum infections, of which two were considered related to treatment: one was serious (not related to treatment), one was severe (not related to treatment), all recovered/resolved, and none required treatment discontinuation. One patient in the CHRONOS 300 mg q2w dupilumab treatment arm had a non-serious, mild case of eczema herpeticum which was not related to treatment and recovered/resolved. One patient in the OLE experienced a helminth infection (a mild case of ascariasis in a Polish patient that resolved within 1 month and did not result in change to dupilumab treatment), while no patients in CHRONOS experienced helminth infections.

Exposure-adjusted infection rates for most common infections (MedDRA PTs; ≥ 1% incidence) were numerically less frequent in the OLE compared with patients receiving placebo + TCS or dupilumab 300 mg qw + TCS in CHRONOS. These included nasopharyngitis, upper respiratory tract infection (URTI), influenza, sinusitis, gastroenteritis (CHRONOS placebo + TCS group only), bacterial conjunctivitis, urinary tract infection, viral URTI, pharyngitis, rhinitis, and folliculitis; exceptions were conjunctivitis (5.33 vs. 1.77), oral herpes (3.77 vs. 3.20), bronchitis (2.17 vs. 1.76), and herpes simplex (1.72 vs. 0.70) (Table 2). The rate of oral herpes was lower in the OLE compared with patients receiving dupilumab 300 mg qw + TCS in CHRONOS, and the rates of herpes simplex were comparable.

Over the course of dupilumab treatment in the OLE, consistent reductions were observed over time (at 16 weeks, 1 year, 2 years, 3 years, and 4 years) in the cumulative number of patients with treatment-emergent serious or severe infections, non-herpetic or herpetic infections, and total skin infections (Fig. 1a–d).

## DISCUSSION

In this analysis of infection data from adults with moderate-to-severe AD treated with dupilumab 300 mg qw or q2w for up to 4 years, exposure adjusted rates of overall infections, serious and/or severe infections, and infections leading to discontinuation were similar to a previous 3-year analysis of the same study and low compared with previously published results in patients with AD treated with placebo + TCS for 1 year (CHRONOS trial) [15, 20]. The cumulative number of patients with infections decreased over time, as did the rate of serious or severe infections, herpetic and non-herpetic infections, and overall skin infections. Rates of common infections (incidence ≥ 2%) were generally less frequent in the OLE compared with patients receiving placebo + TCS or dupilumab 300 mg qw + TCS in CHRONOS. Exposure adjusted rates of herpes zoster and eczema herpeticum were also numerically lower in the OLE compared with the placebo + TCS arm in CHRONOS, and even lower in the dupilumab + TCS arm in CHRONOS; at the HLT level, exposure adjusted rates of total herpes viral infections were numerically lower in the OLE compared with both the placebo + TCS arm and dupilumab + TCS arm in CHRONOS.

As new therapies become available to treat moderate-to-severe AD, it is important to consider long-term safety, including infection risk. In a previous analysis of pooled data from seven short-term phase 3 trials of dupilumab, dupilumab treatment was associated with a reduced risk of serious and/or severe infections and non-herpetic skin infections, and no increase in

**Table 2** Exposure-adjusted treatment-emergent infections by PT

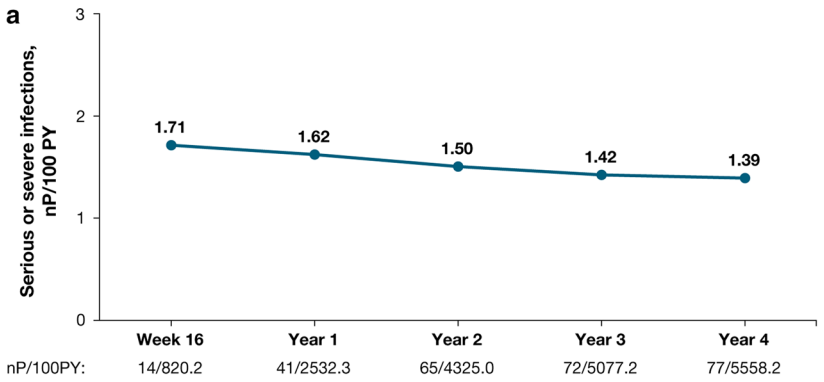
| Most common TEAEs by PT[a] (≥ 1 nP/100 PY in OLE) MedDRA version 18.0 | OLE (up to 4 years) | CHRONOS (1-year placebo-controlled trial) | |
|---|---|---|---|
| | Dupilumab 300 mg qw/q2w (*N* = 2677) nP (nP/100 PY) | Placebo qw + TCS (*n* = 315) nP (nP/100 PY) | Dupilumab 300 mg qw + TCS (*n* = 315) nP (nP/100 PY) |
| Nasopharyngitis | 773 (17.95) | 62 (24.93) | 62 (24.16) |
| Upper respiratory tract infection | 362 (7.15) | 32 (12.03) | 43 (15.85) |
| Conjunctivitis | 276 (5.33) | 5 (1.77) | 8 (2.73) |
| Oral herpes | 199 (3.77) | 9 (3.20) | 15 (5.21) |
| Bronchitis | 119 (2.17) | 5 (1.76) | 4 (1.35) |
| Influenza | 119 (2.16) | 16 (5.76) | 9 (3.07) |
| Sinusitis | 100 (1.82) | 9 (3.19) | 18 (6.31) |
| Herpes simplex | 95 (1.72) | 2 (0.70) | 5 (1.70) |
| Gastroenteritis | 92 (1.66) | 9 (3.22) | 4 (1.36) |
| Conjunctivitis bacterial | 90 (1.63) | 5 (1.77) | 9 (3.09) |
| Urinary tract infection | 80 (1.44) | 13 (4.64) | 13 (4.45) |
| Viral upper respiratory tract infection | 79 (1.43) | 9 (3.21) | 9 (3.10) |
| Pharyngitis | 70 (1.27) | 8 (2.83) | 5 (1.70) |
| Rhinitis | 61 (1.10) | 4 (1.41) | 7 (2.39) |
| Folliculitis | 57 (1.02) | 7 (2.49) | 4 (1.36) |

OLE data presented up to 4 years, CHRONOS data presented up to 52 weeks. The more common bacterial skin infections in patients with AD, e.g., impetigo and cellulitis, were observed at levels below those reported here

*MedDRA* Medical Dictionary for Regulatory Activities, *nP* number of patients with an event, *nP/100 PY* number of patients with ≥ 1 event per 100 PY, *OLE* open-label extension, *PT* preferred term, *PY* patient-years, *q2w* every 2 weeks, *qw* weekly, *TCS* topical corticosteroid, *TEAE* treatment-emergent adverse event

[a]Treatment-emergent infections with ≥ 2% incidence (from SOC "Infections and infestations")

overall infections in adults with moderate-to-severe AD [18]. Moreover, a previous 16-week trial that directly compared safety outcomes in adults with moderate-to-severe AD receiving dupilumab (300 mg q2w) or upadacitinib revealed higher rates of serious infection, eczema herpeticum, and herpes zoster among patients receiving upadacitinib compared with dupilumab; patients receiving dupilumab experienced higher rates of conjunctivitis [23]. However, it is important to note that although the PT "conjunctivitis" is included in the "Infections and Infestations" SOC, it represents conjunctivitis of unspecified or undetermined etiology, and cases of conjunctivitis are often non-infectious [22]. Consistent with 16-week data, rates of serious infections and eczema herpeticum were also higher in two 52-week trials of upadacitinib compared with the rates reported here for the dupilumab OLE [24], although there are limitations of such indirect treatment comparisons. In a 16-week trial that directly compared safety outcomes between adults with moderate-to-severe AD receiving dupilumab (300 mg q2w) or abrocitinib, the rate of overall infections was numerically


a
Serious or severe infections, nP/100 PY
3
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1
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1.62
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1.42
1.39
Week 16
Year 1
Year 2
Year 3
Year 4
nP/100PY:
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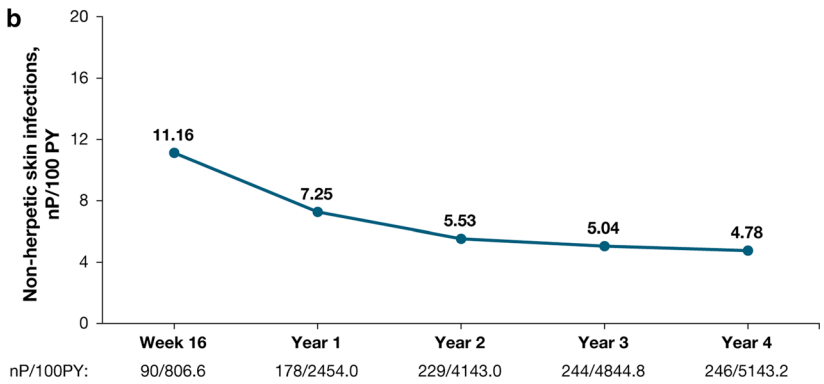
41/2532.3
65/4325.0
72/5077.2
77/5558.2


b
Non-herpetic skin infections, nP/100 PY
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90/806.6
178/2454.0
229/4143.0
244/4844.8
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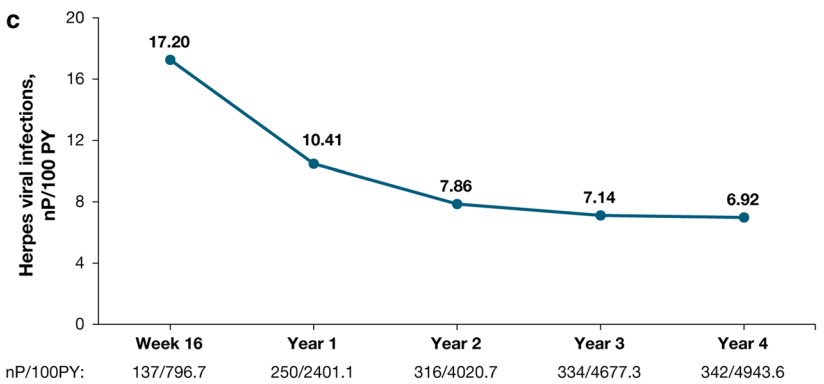
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Herpes viral infections, nP/100 PY
20
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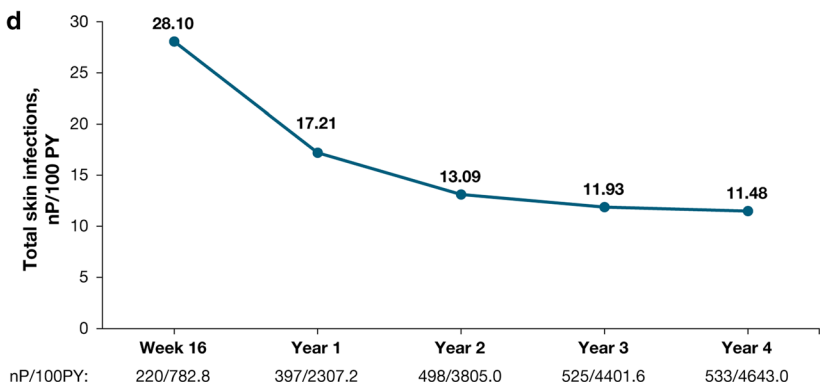
17.20
10.41
7.86
7.14
6.92
Week 16
Year 1
Year 2
Year 3
Year 4
nP/100PY:
137/796.7
250/2401.1
316/4020.7
334/4677.3
342/4943.6


d
Total skin infections, nP/100 PY
30
25
20
15
10
5
0
28.10
17.21
13.09
11.93
11.48
Week 16
Year 1
Year 2
Year 3
Year 4
nP/100PY:
220/782.8
397/2307.2
498/3805.0
525/4401.6
533/4643.0

◀**Fig. 1** **a** Cumulative number of patients with treatment-emergent serious or severe infections per 100 PY through each time point. Data presented are reported under the SOC "Infections and Infestations." **b** Cumulative number of patients with treatment-emergent non-herpetic skin infections per 100 PY through each time point. Data presented are reported under the SOC "Infections and Infestations." **c** Cumulative number of patients with treatment-emergent herpes viral infections per 100 PY through each time point. Data presented are reported under the MedDRA HLT "Herpes viral infections." **d** Cumulative number of patients with treatment-emergent skin infections (herpes viral infections + non-herpetic skin infections) per 100 PY through each time point. Data presented are herpes viral infections (reported under the MedDRA HLT "Herpes viral infections") + non-herpetic skin infections (adjudicated PTs reported under the SOC "Infections and Infestations"). *HLT* high level term, *MedDRA* Medical Dictionary for Regulatory Activities, *nP* number of patients with an event, *nP/100 PY* number of patients with ≥ 1 event per 100 PY, *PT* preferred term, *PY* patient-years, *qw* weekly, *SOC* system organ class

greater in the abrocitinib group [25]. While the rate of serious infections was low with both treatments, three serious infections were reported in two patients in the abrocitinib group, while no serious infections were reported in the dupilumab group. An integrated safety analysis of 200 mg and 100 mg abrocitinib treatment up to 108 weeks also revealed numerically higher rates of serious infections (2.33 and 2.65 nP/100 PY, respectively) compared with the rates observed here for serious or severe infections in the dupilumab OLE (1.39 nP/100 PY) [26]. Consistent with these findings, our analysis of infection data from the OLE revealed yearly reductions in overall infections, serious and/or severe infections, and infections leading to discontinuation over 4 years of dupilumab treatment. These findings suggest that unlike traditional immunosuppressants and JAK inhibitors (recently approved treatments for AD), which are known to interfere with both the type I interferon and type 2 pathways [27], dupilumab acts as a narrowly targeted immunomodulator of the type 2 pathway and does not increase risk of infection. Similar infection data have recently been published for pediatric patients treated with dupilumab [28]. In contrast, a concern regarding adverse effects from JAK inhibitors is the increased risk of infection [27]. Additional studies are needed to directly compare long-term safety outcomes between dupilumab and other AD treatments.

Recent studies demonstrate that dupilumab treatment reduces *Staphylococcus aureus* bacterial colonization in lesional and non-lesional skin and increases microbial diversity on the skin of patients with AD [29, 30]. Given that a disrupted skin barrier due to underlying type 2 inflammation favors dysbiosis, and *S. aureus* colonization is associated with reduced skin barrier integrity, one mechanism by which dupilumab might reduce skin infections is by improving skin barrier integrity and reducing *S. aureus* colonization. Moreover, recent studies suggest that dupilumab treatment normalizes epidermal barrier function, as demonstrated by reduction of transepidermal water loss and normalization of lipids and natural moisturizing factor composition in patients treated for 16 weeks with dupilumab compared with healthy volunteers [31]. Future studies are needed to further investigate the mechanism underlying the reduced infection risk seen in patients taking dupilumab.

Strengths of this study include the treatment duration and overall sample size. Limitations include the open-label design, the absence of a placebo arm, the smaller number of patients at later time points (primarily due to sponsor decision to close sites following regulatory approval of dupilumab), the fact that qw dosing differs from approved q2w dosing, and that patients were allowed to use TCS/TCI throughout the study, which may have impacted infection rates.

## CONCLUSIONS

Continuous long-term dupilumab treatment in adults with moderate-to-severe AD is not associated with an increased risk of overall systemic or cutaneous infections.

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***Compliance with Ethics Guidelines.*** This study was conducted in accordance with ethical standards of the responsible committees and the Declaration of Helsinki and with the International Council for Harmonisation guidelines for Good Clinical Practice. The trial was overseen by an independent data and safety monitoring board. The protocol was reviewed and approved by institutional review boards/ethics committees at all centers. All patients provided written informed consent before any study procedures began.

***Consent to Participate.*** Written informed consent was obtained from all patients or their proxies.

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***Data Availability.*** Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, and statistical analysis plan) that support the

methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA), if there is legal authority to share the data and there is not a reasonable likelihood of participant re-identification. Submit requests to https://vivli.org/.



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