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ORIGINAL RESEARCH

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Treatment-emergent Candida infections in patients with psoriasis, psoriatic arthritis, and axial spondyloarthritis treated with ixekizumab: an integrated safety analysis of 25 clinical studies

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ABSTRACT

Background: This safety analysis investigates treatment-emergent mucosal/cutaneous Candida infections in patients treated with ixekizumab (IXE), an anti-interleukin-17A monoclonal antibody, across the approved indications: psoriasis (PsO), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA).
Research design and methods: Safety data were pooled from 25 clinical studies. Incidence rates (IRs) are expressed as per 100 patient-years (PY), using the entire duration of exposure.
Results: Candida infections had an IR of 1.9 per 100 PY in patients with PsO ($N = 6892$; total PY = 18025.7), 2.0 per 100 PY in patients with PsA ($N = 1401$; total PY = 2247.7), and 1.2 per 100 PY in patients with axSpA ($N = 932$; total PY = 2097.7). The majority of treatment-emergent Candida infections were: (i) experienced only once by patients (IR = 1.3;IR = 1.6;IR = 1.0), (ii) mild/moderate in severity (IR = 0.8/0.9;IR = 1.5/0.4;IR = 0.8/0.5) as opposed to severe (IR = 0.0; IR = 0.0; IR = 0.0), (iii) oral Candida or genital Candida (IR = 0.9/0.6;IR = 1.0/0.7;IR = 0.4/0.6), (iv) marked as recovered/resolved during the studies (89.3%;93.8%;90.3%), (v) not leading to IXE discontinuation (0.0%;0.0%;0.1% discontinued), (vi) managed with topical (34.7%;22.2%;11.5%) or no anti-fungal medications (63.5%;77.8%;80.8%) as opposed to systemic therapies (1.5%;0.0%;7.7%), (vii) typically resolved before next visit.
Conclusions: This integrated safety analysis shows that the risk of developing Candida infections is low with IXE, and the severity is mild-to-moderate in most instances across the approved IXE indications.
Trial registration: A comprehensive list of the clinical trials and their registration numbers is reported in Table S1 of the supplemental material.

PLAIN LANGUAGE SUMMARY

Ixekizumab (IXE) is a drug approved for the treatment of psoriasis, psoriatic arthritis, and axial spondyloarthritis. IXE belongs to the class of molecules that blocks a protein called interleukin-17A. Since interleukin-17A is involved in the defense against fungi, the clinical use of this class of drug has the potential to increase the risk of developing fungal infections, such as Candida infections.
Therefore, researchers collected safety data from 25 clinical studies comprising 9225 adult patients treated with IXE: 6892 with psoriasis, 1401 with psoriatic arthritis, and 932 with axial spondyloarthritis. Researchers looked at the rate of new cases of Candida infections, the so-called incidence rate, and found that 1.9 per 100 patient-years experienced at least 1 Candida infection in the psoriasis group, 2.0 per 100 patient-years in the psoriatic arthritis group, and 1.2 per 100 patient-years in the axial spondyloarthritis group.
Across indications, the majority of Candida infections (*i*) were experienced only once by patients, (*ii*) were mild or moderate in severity, (*iii*) involved infections caused by superficial skin fungus in the mouth or genitals, (*iv*) were considered recovered/resolved during the studies, (*v*) did not lead to IXE discontinuation, (*vi*) were managed with topical anti-fungal medications or no medications, and (*vii*) were typically resolved before next visit.
In conclusion, this safety analysis shows that the risk of developing Candida infections is low with IXE, and the severity is mild-to-moderate in most instances across the approved IXE indications.

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1. Introduction

1.1. Background

Interleukin (IL)-17 is a cytokine that plays a critical role in host defense against common extracellular pathogens, including fungi [1–3]. The IL-17 cytokine family, which includes 6 members (IL-17A through IL-17F) produced by T helper 17 cells and other cell types, plays important roles in the development of autoimmunity, inflammation, tumors, host defenses against bacterial and fungal infections, mucosal host defense mechanisms and other lesser-known functions [4]. Deficiency in IL-17 signaling makes mice more susceptible to systemic candidiasis and mucosal candidiasis [5,6], and chronic mucocutaneous candidiasis was observed in humans with inborn errors in IL-17 immunity, specifically deficiency in the IL-17 receptor A which abolishes cellular responses to IL-17A and IL-17F homo- and heterodimers [7]. Since mice with a deficiency in IL-17A were observed to have an increased intestinal permeability after gut injury, it was hypothesized that IL-17A might have a role in ensuring the intestinal barrier integrity by regulating the cellular localization of the epithelial tight junction protein occludin [8]. IL-17 is also essential in the defense against dermatophytoses, also known as ringworms or *tinea*, partially by enhancing epithelial barrier function and by preventing uncontrolled fungal growth [9].

Consequently, treatment with IL-17 inhibitors has been associated with a risk of developing fungal infections [10–12]. In a real-world observational study of multiple independent sources, including the World Health Organization (WHO) and the European Medicines Agency's (EMA) adverse drug reaction databases, Davidson et al. found a strong association between the use of IL-17 inhibitors and the risk of candidiasis, particularly for cutaneous, oropharyngeal, and esophageal candidiasis [13]. In a systematic analysis and review of the literature, Yamanaka et al. analyzed the clinical use of anti-IL-17 medications. While the incidence of Candida infections varies within the IL-17 class (ixekizumab [IXE, 0–3.5%], brodalumab [0.3–7%], secukinumab [1.4–13.5%], bimekizumab [1.9–21.2%]), with early and accurate diagnosis and appropriate treatment, these infections can be managed without drug discontinuation [14].

IXE is an anti-IL-17A monoclonal antibody [15] approved for the treatment of psoriasis (PsO), psoriatic arthritis (PsA), and axial spondyloarthritis (axSpA). IXE demonstrated efficacy in patients with PsO enrolled in the UNCOVER-1, −2, and −3 clinical trials [16], in patients with PsA enrolled in the SPIRIT-P1, -P2, and -H2H clinical trials [17,18], and in patients with axSpA participating in the COAST-V, -W, -X, and -Y clinical trials [19]. Regarding IXE safety, Deodhar et al. analyzed final safety data from 25 randomized clinical trials, consisting of over 22,000 patient-years (PY) of exposure, and confirmed the long-term safety profile of IXE in adult patients with PsO, PsA, and axSpA, reporting Candida infections at a rate of 1.9 per 100 PY, 2.0 per 100 PY, and 1.2 per 100 PY, respectively [20]. Additionally, Blauvelt et al. published data on treatment-emergent fungal infections in patients with PsO treated with IXE from 16 clinical studies, consisting of 6645 patients and 17,902 PY of exposure, and reported Candida infections at a rate of 2.0 per 100 PY [21].

Here, we expand the integrated safety analysis to include adult patients from 25 clinical studies across all the IXE-approved indications: PsO, PsA, and axSpA (including ankylosing spondylitis [AS] and non-radiographic axial spondyloarthritis [nr-axSpA]). We describe treatment-emergent mucosal/cutaneous Candida infections, hereafter referred to as Candida infections, in terms of frequency/incidence rates (IRs), severity, types/subtypes, recovery/resolution, management, duration, time between infections, and, for the first time, we present data on recurrence of treatment-emergent Candida infections.

1.2. Objective

The objective of this integrated safety analysis of 25 clinical studies was to investigate treatment-emergent Candida infections in adult patients treated with IXE across the approved indications: PsO, PsA, and axSpA.

2. Patients and methods

2.1. Clinical studies and patient population

This *post-hoc* safety analysis of treatment-emergent Candida infections pooled data from the IXE adult clinical trial programs, comprising 25 clinical studies: 17 for PsO, 4 for PsA, and 4 for axSpA (Table S1). Study designs and eligibility criteria for these clinical studies were previously described [22–35]. Each clinical study was approved by the local Ethics Committee or Institutional Review Board and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Each patient signed an informed consent form before entering the respective clinical study. Demographics and baseline characteristics of the integrated patient population including patients with PsO, PsA, and axSpA (including patients with AS and nr-axSpA) who received at least 1 dose of IXE are presented. Further descriptive statistical analyses were performed on the patient subpopulation who experienced at least 1 event of treatment-emergent Candida infection.

2.2. Integrated safety analysis

Treatment-emergent adverse events (TEAEs) were reported using the Medical Dictionary for Regulatory Activities (MedDRA) Version 24.1 or higher; the high-level group term 'fungal infectious disorders' was used and reviewed based on the available data (*e.g.*, infectious agent, bodily location, and reported terms data). These were reported at the investigator's discretion and not adjudicated. The severity of Candida infections (mild, moderate, severe) was also defined at the investigator's discretion. In patients with multiple occurrences of fungal events, they were counted under the highest severity of any of the occurrences. Recurrence of Candida infections was defined by at least 2 separate events in a given patient, irrespective of location, and at different visits. IRs are reported with 95% confidence intervals and expressed as the number of individual patients with ≥ 1 event in a particular category of TEAE per 100 PY, using the entire duration of exposure. The median duration of treatment-emergent Candida infections is expressed as the median number of weeks, with the lower quartile (Q1) having the 25% of duration

lower than this value and the upper quartile (Q3) having the 75% of duration lower than this value. Patients with predisposing risk factors to fungal infections were defined as the patients whose medical history reported (*i*) diabetes (broad definition), (*ii*) use of hormonal medications (both oral and injectable contraceptives), and/or (*iii*) use of steroids and/or systemic therapies (including corticosteroids, cortisone injections, prednisone, prednisolone tablets, triamcinolone, triamcinolone injections, azathioprine, cyclosporine, leflunomide, etanercept, and tofacitinib) [36].

3. Results

3.1. Patients

A total of 9225 adult patients received at least 1 dose of IXE and were included in this integrated safety analysis: 6892 with PsO, 1401 with PsA, and 932 with axSpA (including patients with AS and nr-axSpA) (Table 1). The cumulative IXE exposure was 22,371.1 PY: 18025.7 PY for PsO, 2247.7 PY for PsA, and 2097.7 for axSpA. The mean PY was 2.6 for PsO, 1.6 for PsA, and 2.3 for axSpA.

3.2. Demographics and baseline characteristics of the integrated patient population

At baseline, the integrated patient population had a mean (± standard deviation [SD]) age of 45.7 ± 13.2 in the PsO cohort, 49.1 ± 11.9 in the PsA cohort, and 42.8 ± 12.6 in the axSpA cohort. Most patients were male in the PsO (68.1%) and axSpA (69.7%) cohorts, while in the PsA cohort, the proportion of male patients (48.5%) was balanced with female patients (51.5%). Across the indications, over 70% of patients were White. The mean (± SD) body mass index (BMI) was numerically lower in the axSpA cohort (27.5 ± 5.7 kg/m^2) as compared to the PsO (30.4 ± 7.3 kg/m^2) and PsA (30.0 ± 6.9 kg/m^2) cohorts. The proportion of patients who were naïve to systemic therapy was highest in the PsO cohort (35.9%), followed by the PsA cohort (20.7%), and lowest in the axSpA cohort (0.6%). Among patients who previously used systemic therapies, most were biologic-naïve (PsO = 35.1%; PsA = 55.2%; axSpA = 66.6%) as opposed to biologic-experienced (PsO = 12.0%; PsA = 5.1%; axSpA = 0.1%) and biologic and non-biologic-experienced (PsO = 17.0%; PsA = 19.1%; axSpA = 32.6%). Patients with PsO had the longest average duration of symptoms (18.7 years), followed by patients with axSpA (15.2 years) and patients with PsA (9.4 years). Pre-existing or historical PsO was observed in 99.9% of patients with PsA and 8.8% of patients with axSpA (Table 1).

3.3. Frequency/rates, recurrence, and severity of treatment-emergent candida infections

Among the integrated patient population, the number of patients (frequency/IR per 100 PY) who experienced at least

Table 1. Demographics and baseline characteristics of the integrated patient population treated with IXE across the approved indications.

	PsO (*N* = 6892)	PsA (*N* = 1401)	axSpA (*N* = 932)
Age, years, mean ±SD	45.7 ± 13.2	49.1 ± 11.9	42.8 ± 12.6
Sex, n (%)			
Male	4696 (68.1)	679 (48.5)	650 (69.7)
Female	2196 (31.9)	722 (51.5)	282 (30.3)
Race, n (%)			
White	5612 (81.5)	1278 (91.3)	689 (74.1)
Other	914 (13.3)	68 (4.9)	181 (19.5)
Asian	359 (5.2)	54 (3.9)	60 (6.4)
Weight, kg, mean ±SD	90.3 ± 23.6	86.1 ± 20.3	79.6 ± 17.3
BMI, kg/m^2, mean ±SD	30.4 ± 7.3	30.0 ± 6.9	27.5 ± 5.7
Previous use of systemic therapy, n (%)			
No prior treatment[a]	2474 (35.9)	290 (20.7)	6 (0.6)
Non-biologic only[b]	2418 (35.1)	773 (55.2)	621 (66.6)
Biologic only[c]	826 (12.0)	71 (5.1)	1 (0.1)
Biologic and non-biologic	1174 (17.0)	267 (19.1)	304 (32.6)
Concomitant medications, n (%)			
Methotrexate	60 (0.9)	349 (24.9)	116 (12.4)
Sulfasalazine	7 (0.1)	34 (2.4)	210 (22.5)
Hydroxychloroquine	2 (0.0)	5 (0.4)	3 (0.3)
Duration of symptoms,[d] years, mean ±SD	18.7 ± 12.2	9.4 ± 8.6	15.2 ± 10.9
Pre-existing or historical PsO, n (%)	n/a	1400 (99.9)	82 (8.8)

Data are presented as mean ±SD unless stated otherwise.
Percentage is calculated by n/Nx * 100%.
[a]No prior treatment with systemic therapy might include the use of glucocorticoids, and other non-biologic non-systemic agents.
[b]Non-biologic systemic therapies include 6mercaptopurine, azathioprine, corticosteroids, cyclooxygenase-2 inhibitors, cyclosporine, hydroxychloroquine, leflunomide, methotrexate, opiate analgesics, sulfasalazine, and other systemic agents.
[c]Biologic systemic therapies include adalimumab, alefacept, alefacept, briakinumab, brodalumab, certolizumab pegol, efalizumab, etanercept, golimumab, infliximab, secukinumab, ustekinumab.
[d]Duration of symptoms of PsO, PsA, and axSpA, respectively, is calculated as: (date of informed consent – date of onset of symptoms)/365.25.
Abbreviations: axSpA, axial spondyloarthritis. BMI, body mass index. IXE, ixekizumab. N, number of patients in the analysis population. Nx, number of patients with non-missing values. n, number of patients with at least 1 treatment-emergent Candida infection in the specified category. n/a, not applicable. PsA, psoriatic arthritis. PsO, psoriasis. SD, standard deviation.

Table 2. Clinical spectrum (types and subtypes) of treatment-emergent Candida infections in the integrated patient population treated with IXE across the approved indications.

	PsO ($N = 6892$; total PY = 18025.7) n (%) [IR] (95% CI)	PsA ($N = 1401$; total PY = 2247.7) n (%) [IR] (95% CI)	axSpA ($N = 932$; total PY = 2097.7) n (%) [IR] (95% CI)
Patients with ≥ 1 TEAE of Candida infections	337 (4.9%) [1.9] (1.7-2.1)	45 (3.2%) [2.0] (1.5-2.7)	26 (2.8%) [1.2] (0.8-1.8)
Oral Candida	160 (2.3%) [0.9] (0.8-1.0)	22 (1.6%) [1.0] (0.6-1.5)	8 (0.9%) [0.4] (0.2-0.8)
Oral candidiasis	144 (2.1%) [0.8] (0.7-0.9)	16 (1.1%) [0.7] (0.4-1.2)	5 (0.5%) [0.2] (0.1-0.6)
Oral fungal infection	11 (0.2%) [0.1] (0.0-0.1)	6 (0.4%) [0.3] (0.1-0.6)	3 (0.3%) [0.1] (0.0-0.4)
Oropharyngeal candidiasis	8 (0.1%) [0.0] (0.0-0.1)	0	0
Genital Candida	112 (1.6%) [0.6] (0.5-0.7)	16 (1.1%) [0.7] (0.4-1.2)	12 (1.3%) [0.6] (0.3-1.0)
Genital candidiasis	9 (0.1%) [0.0] (0.0-0.1)	3 (0.2%) [0.1] (0.0-0.4)	1 (0.1%) [0.0] (0.0-0.3)
Genital infection fungal	0	0	1 (0.1%) [0.0] (0.0-0.3)
Vulvovaginal candidiasis[a]	53 (2.4%) [0.9] (0.7-1.2)	6 (0.8%) [0.5] (0.2-1.2)	7 (2.5%) [1.2] (0.6-2.5)
Vulvovaginal mycotic infection[a]	48 (2.2%) [0.9] (0.6-1.1)	9 (1.2%) [0.8] (0.4-1.5)	2 (0.7%) [0.3] (0.1-1.3)
Candida balanitis[b]	6 (0.1%) [0.0] (0.0-0.1)	0	0
Fungal balanitis[b]	0	0	1 (0.2%) [0.1] (0.0-0.5)
Skin Candida	46 (0.7%) [0.3] (0.2-0.3)	5 (0.4%) [0.2] (0.1-0.5)	2 (0.2%) [0.1] (0.0-0.4)
Skin Candida	45 (0.7%) [0.2] (0.2-0.3)	5 (0.4%) [0.2] (0.1-0.5)	2 (0.2%) [0.1] (0.0-0.4)
Otitis externa Candida	1 (0.0%) [0.0] (0.0-0.0)	0	0
Oesophageal candidiasis	16 (0.2%) [0.1] (0.1-0.1)	2 (0.1%) [0.1] (0.0-0.4)	5 (0.5%) [0.2] (0.1-0.6)
Nail Candida	2 (0.0%) [0.0] (0.0-0.0)	1 (0.1%) [0.0] (0.0-0.3)	0
Other mucosal/cutaneous Candida	1 (0.0%) [0.0] (0.0-0.0)	0	0
Mucosal/cutaneous candidiasis	1 (0.0%) [0.0] (0.0-0.0)	0	0
Unspecified Candida	32 (0.5%) [0.2] (0.1-0.3)	0	0
Candida infection	32 (0.5%) [0.2] (0.1-0.3)	0	0
Other Candida infections	3 (0.0%) [0.0] (0.0-0.1)	0	0
Gastrointestinal candidiasis	3 (0.0%) [0.0] (0.0-0.1)	0	0
Systemic candidiasis	0	0	0

The number of patients, percentage (relative to the total study population, N), incidence rates per 100 PY, and 95% CIs are reported.
Percentage is calculated by n/N * 100%.
[a]Denominator adjusted because gender-specific event for females: $N = 2196$ (PY = 5580.5) in the PsO cohort, $N = 722$ (PY = 1142.2) in the PsA cohort, and $N = 282$ (PY = 592.8) in the axSpA cohort.
[b]Denominator adjusted because gender-specific event for males: $N = 4696$ (PY = 12445.3) in the PsO cohort and $N = 650$ (PY = 1504.9) in the axSpA cohort.
Adverse event is considered TEAE if it first occurs or worsens following the start of treatment during a study period.
Patients with multiple occurrences of these categories are counted once for each category. Patients may be counted in more than one category.
Adverse event is coded using MedDRA Version 24.1.
Abbreviations: axSpA, axial spondyloarthritis. CI, confidence interval. IR, incidence rate per 100 patient-years. IXE, ixekizumab. MedDRA, Medical Dictionary for Regulatory Activities. N, number of patients in the analysis population. n, number of patients with at least 1 treatment-emergent Candida infection in the specified category. PsA, psoriatic arthritis. PsO, psoriasis. PY, patient-years. TEAE, treatment-emergent adverse events. Total PY, total time patients were in the treatment period.

1 event of treatment-emergent Candida infection was 337 (4.9%; IR = 1.9 per 100 PY) in the PsO cohort, 45 (3.2%; IR = 2.0 per 100 PY) in the PsA cohort, and 26 (2.8%; IR = 1.2 per 100 PY) in the axSpA cohort (Table 2).

Across indications, most patients experienced a single event of Candida infection as opposed to recurrent Candida infections. Specifically, the number of patients experiencing 1 event of Candida infections was 243 (3.5%; IR = 1.3 per 100 PY) in the PsO cohort, 36 (2.6%; IR = 1.6 per 100 PY) in the PsA cohort, and 22 (2.4%; IR = 1.0 per 100 PY) in the axSpA cohort. Conversely, the number of patients experiencing 2 events or ≥ 3 events of Candida infections was 51 (0.7%; IR = 0.3 per 100 PY) and 43 (0.6%; IR = 0.2 per 100 PY) in the PsO cohort, 6 (0.4%; IR = 0.3 per 100 PY) and 3 (0.2%; IR = 0.1 per 100 PY) in the PsA cohort, and 3 (0.3%; IR = 0.1 per 100 PY) and 1 (0.1%; IR = 0.0 per 100 PY) in the axSpA cohort (Figure 1).

Across indications, the majority of Candida infections experienced by patients were mild or moderate in severity as opposed to severe (based on the investigator's judgment). Specifically, mild

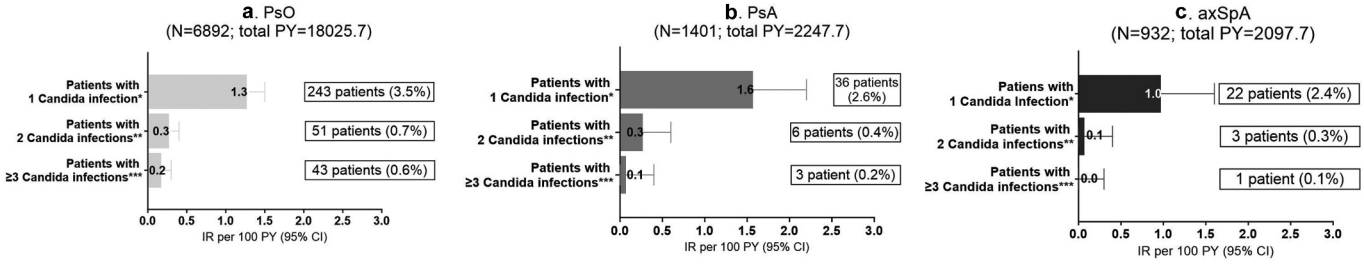

Figure 1. Recurrence of treatment-emergent Candida infections in the integrated patient population treated with IXE across the approved indications: A. PsO, B. PsA, and C. axSpA.

*Patients with 1 Candida infection; **Patients with 2 Candida infections (not inclusive of patients with 1 Candida infection); ***Patients with 3 or more Candida infections (not inclusive of patients with 1 or 2 Candida infections).

Abbreviations: axSpA, axial spondyloarthritis. CI, confidence interval. IR, incidence rate per 100 patient years. IXE, ixekizumab. N, number of patients in the analysis population. PsA, psoriatic arthritis. PsO, psoriasis. PY, patient-years. Total PY, total time patients were in the treatment period.

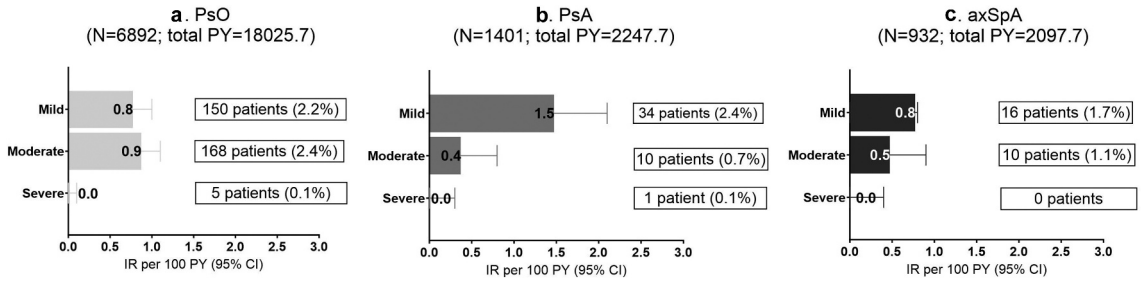

Figure 2. Severity of treatment-emergent Candida infections in the integrated patient population treated with IXE across the approved indications: A. PsO, B. PsA, and C. axSpA.

Severity was defined at the investigator's discretion. Patients with multiple occurrences of the same event are counted under the highest severity.

Abbreviations: axSpA, axial spondyloarthritis. CI, confidence interval. IR, incidence rate per 100 patient years. IXE, ixekizumab. N, number of patients in the analysis population. PsA, psoriatic arthritis. PsO, psoriasis. PY, patient-years. Total PY, total time patients were in the treatment period.

Table 3. Patients who experienced severe Candida infections in the integrated patient population treated with IXE across the approved indications.

	Age (years)	Sex	Race	Predisposing factors	Type of Candida infection	Drug-related adverse event	Anti-fungal medications used	Recovered/ resolved
PsO cohort								
Patient 1	48	Female	White	Diabetes	Severe Esophageal candidiasis (thrush esophagitis)	No	Pantoprazole, amoxicillin, clarithromycin, fluconazole	Yes
Patient 2	51	Female	White	None	Oral candidiasis (Candida albicans infecting oral cavity and throat)	No	Nystatin, moisturizing mouth spray, fluconazole	Yes
Patient 3	45	Male	White	Concomitant use of steroids[a]	Severe oral candidiasis (oral thrush), followed by a second and third event of oral candidiasis of mild and moderate severity	Yes (all 3 events)	n/a	Yes (all 3 events)
Patient 4	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Patient 5	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
PsA cohort								
Patient 1	65	Female	White	Concomitant use of steroids[b]	Severe esophageal candidiasis	n/a	Fluconazole	Yes

In the axSpA cohort, no patients experienced severe Candida infections.
[a]The type of steroids used is not specified in the patient narrative.
[b]Steroids used included: fluticasone/salmeterol and prednisone.
The relationship between the adverse event and the study drug is as per the investigator's judgment.
Abbreviations: axSpA, axial spondyloarthritis. IXE, ixekizumab. n/a, not available. PsA, psoriatic arthritis. PsO, psoriasis.

and moderate Candida infections were experienced by 150 (2.2%; IR = 0.8 per 100 PY) and 168 (2.4%; IR = 0.9 per 100 PY) patients with PsO, 34 (2.4%; IR = 1.5 per 100 PY) and 10 (0.7%; IR = 0.4 per 100 PY) patients with PsA, and 16 (1.7%; IR = 0.8 per 100 PY) and 10 (1.1%; IR = 0.5 per 100 PY) patients with axSpA. Conversely, severe Candida infections were experienced by 5 (0.1%; IR = 0.0 per 100 PY) patients with PsO, 1 (0.1%; IR = 0.0 per 100 PY) patient with PsA, and 0 (0.0%; IR = 0.0 per 100 PY) patient with axSpA (Figure 2). Information about patients who experienced severe Candida infections is reported in Table 3.

3.4. Clinical spectrum of treatment-emergent candida infections

Across indications, the most common Candida infections were oral Candida or genital Candida. Specifically, oral Candida was experienced by 160 (2.3%; IR = 0.9 per 100 PY) patients in the PsO cohort, 22 (1.6%; IR = 1.0 per 100 PY) patients in the PsA cohort, and 8 (0.9%; IR = 0.4 per 100 PY) patients in the axSpA cohort, with oral candidiasis being the most prevalent infection across indications. Genital Candida was experienced by 112 (1.6%; IR = 0.6 per 100 PY) patients in the PsO cohort, 16 (1.1%; IR = 0.7 per 100 PY) patients in the PsA cohort, and 12 (1.3%; IR = 0.6 per 100 PY) patients in the axSpA cohort, with vulvovaginal candidiasis and vulvovaginal mycotic infection being the most prevalent infections across indications. Less common Candida infections (≤0.7%; IR ≤ 0.3 per 100 PY) were skin Candida, nail Candida, other mucosal/cutaneous Candida, and unspecified Candida. Candida infections involving internal organs were reported in 3 patients with PsO and were classified as gastrointestinal candidiasis. No cases of subcutaneous or systemic mycosis infections were reported (Table 2).

3.5. Recovery/resolution of treatment-emergent candida infections and events leading to drug discontinuation

Across indications, approximately 90% of Candida infection events were marked as recovered/resolved by the end of the study, specifically, 89.3% in the PsO cohort, 93.8% in the PsA

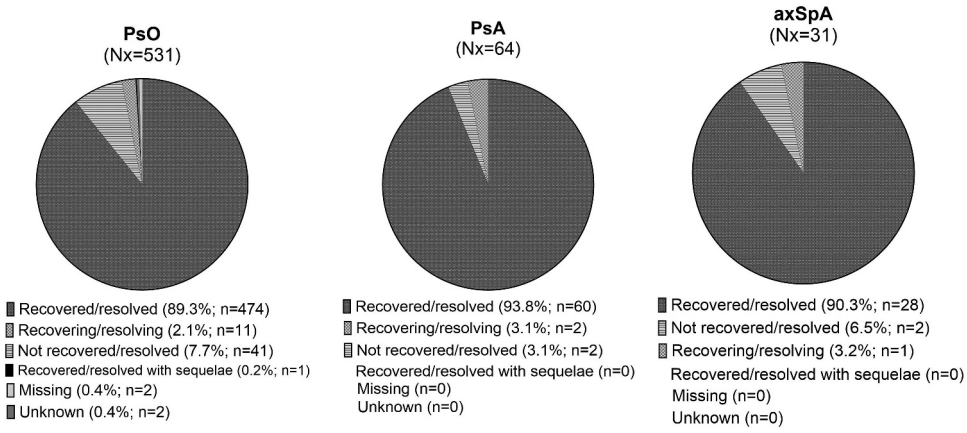

Figure 3. Recovery/resolution of treatment-emergent Candida infections in the integrated patient population treated with IXE across the approved indications.

Percentage is calculated by n/Nx*100%.

Among the patients with a treatment-emergent Candida infections marked as not recovered/resolved, systemic therapies were used by 1 patient with PsO, topical therapies were used by 15 patients with PsO and 1 patient with PsA, and no anti-fungal medications were used by 22 patients with PsO, 1 patient with PsA, and 2 patients with axSpA.

Abbreviations: axSpA, axial spondyloarthritis. IXE, ixekizumab. Nx, number of events. n, number of events in the specified category. PsA, psoriatic arthritis. PsO, psoriasis.

cohort, and 90.3% in the axSpA cohort. Less than 10% of Candida infection events were marked as not recovered/resolved by the end of the study, specifically, 7.7% in the PsO cohort, 3.1% in the PsA cohort, and 6.5% in the axSpA cohort (Figure 3). No further information is available for the patients whose Candida infections were marked as not recovered/resolved since the study was completed.

Across indications, drug discontinuation caused by Candida infections was low. Specifically, 2 patients experienced Candida infection events that were marked as the cause of IXE discontinuation: 1 in the PsO cohort (0.0%; IR = 0.0 per 100 PY) and 1 in the axSpA cohort (0.1%; IR = 0.0 per 100 PY). In the PsO cohort, a 28-year-old White male discontinued due to moderate esophageal candidiasis, which was marked as recovered/resolved by the end of the study. In the axSpA cohort, a 35-year-old Asian female discontinued due to a non-serious esophageal candidiasis, thought to be due to study drug and marked as recovering/resolving by the end of the study.

3.6. Management of treatment-emergent Candida infections

Across indications, most patients who experienced at least 1 event of treatment-emergent Candida infection did not use any anti-fungal medication (63.5% in the PsO cohort, 77.8% in the PsA cohort, and 80.8% in the axSpA cohort). Among the patients who reported the specific anti-fungal medication used, the majority used topical anti-fungal medications as opposed to systemic therapies. Specifically, the proportions of patients who received topical anti-fungal medications and systemic anti-fungal therapies were 34.7% and 1.5% in the PsO cohort, 22.2% and 0.0% in the PsA cohort, and 11.5% and 7.7% in the axSpA cohort (Figure 4).

In the PsO cohort, 5 patients used systemic therapy to manage Candida infections: 3 patients experienced non-serious fungal infections (Candida infection, oral candidiasis, and oral fungal infection, respectively), which were considered non-drug-related, moderate in severity, and were marked as recovered/resolved by the end of the study; systemic therapy used included metronidazole, chlorquinaldol, fluconazole, clotrimazole, and nystatin; no information is available for the other 2 patients. In the PsA cohort, no patients used systemic therapy to manage Candida infections. In the axSpA cohort, 2 patients used systemic therapy to manage Candida infections: a 35-year-old Asian female experienced a non-serious esophageal candidiasis, which was considered moderate in severity, drug-related, and led to IXE discontinuation; systemic therapy used was fluconazole; no information is available for the other patient.

3.7. Duration and time between treatment-emergent Candida infections

Across indications, the majority of treatment-emergent Candida infections were typically resolved before next visit. Specifically, the median (Q1-Q3) duration was 4.6 (1.6–14.3) weeks in the PsO cohort, 3.4 (1.3–10.1) weeks in the PsA cohort, and 3.1 (1.1–8.6) weeks in the axSpA cohort. In the PsO cohort, nail Candida and other mucosal/cutaneous candidiasis had a median duration of over 1 year (102.7 and 61.3 weeks, respectively), while the other Candida infections had a median duration lower than 3 months. Specifically, oral fungal infections, vulvovaginal candidiasis, vulvovaginal mycotic infection, Candida balanitis, and gastrointestinal candidiasis had a median duration lower than 1 month. In the PsA cohort, except for vulvovaginal candidiasis (9.7 weeks), all the other Candida infections had a median duration lower than 2 months. In the axSpA cohort, skin Candida had a median duration of over 1 year (73.8 weeks), while the other Candida infections had a median duration lower than 3 months. Specifically, genital candidiasis, genital infection fungal, vulvovaginal candidiasis, vulvovaginal mycotic infection, and fungal balanitis had a median duration lower than 1 month (Table 4).

Among the minority of patients who experienced more than 1 Candida infection, the median (Q1-Q3) time between infections was 20.8 (5.9–47.1) weeks in the PsO cohort, 7.4 (3.7–18.0) weeks in the PsA cohort, and 33.0 (20.9–49.0) weeks in the axSpA cohort.

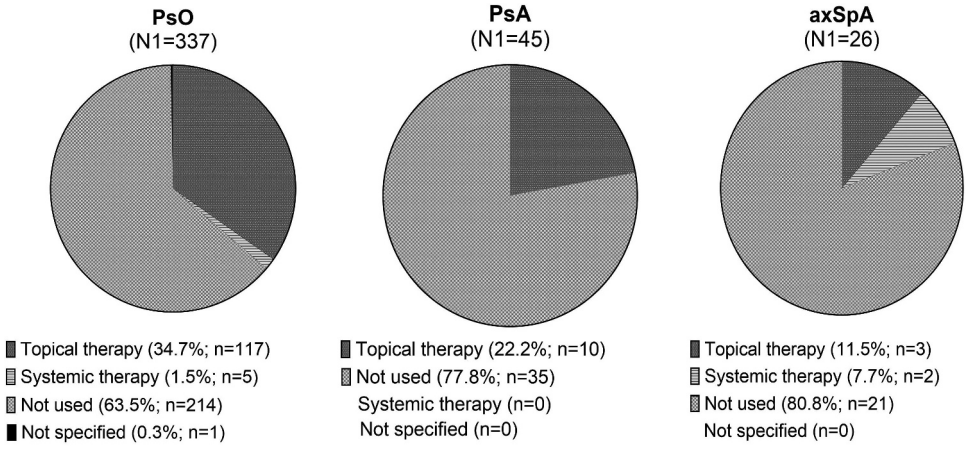

Figure 4. Anti-fungal medications used to manage treatment-emergent Candida infections in patients who experience at least 1 Candida infection and who were treated with IXE across the approved indications.

Percentage is calculated by n/N1*100%.

Patients treated with multiple different medications were counted in more than 1 medication category.

Abbreviations: axSpA, axial spondyloarthritis. IXE, ixekizumab. N1, number of patients in the analysis population who experienced at least 1 event of treatment-emergent Candida infection. n, number of patients in the specified category. PsA, psoriatic arthritis. PsO, psoriasis.

Table 4. Duration of treatment-emergent Candida infections in the integrated patient population treated with IXE across the approved indications.

	PsO ($N = 6892$) Duration in weeks Median [Q1-Q3] (n)	PsA ($N = 1401$) Duration in weeks Median [Q1-Q3] (n)	axSpA ($N = 932$) Duration in weeks Median [Q1-Q3] (n)
Patients with ≥ 1 TEAE of Candida infections	4.6 [1.6-14.3] (337)	3.4 [1.3-10.1] (45)	3.1 [1.1-8.6] (26)
Oral Candida	n/a	n/a	n/a
Oral candidiasis	6.4 [2.4-17.1] (144)	7.1 [1.9-13.1] (16)	5.7 [4.6-8.7] (5)
Oral fungal infection	2.3 [1.7-7.9] (11)	4.6 [2.1-6.1] (6)	8.1 [1.4-21.7] (3)
Oropharyngeal candidiasis	6.6 [2.7-22.4] (8)	n/a	n/a
Genital Candida	n/a	n/a	n/a
Genital candidiasis	6.1 [4.3-11.1] (9)	2.1 [1.6-3.4] (3)	1.6 [1.6-1.6] (1)
Genital infection fungal	n/a	n/a	0.9 [0.9-0.9] (1)
Vulvovaginal candidiasis[a]	1.4 [1.0-5.9] (53)	9.7 [0.7-24.1] (6)	1.1 [0.6-1.3] (7)
Vulvovaginal mycotic infection[a]	1.1 [0.8-1.9] (48)	1.3 [0.6-1.7] (9)	1.6 [1.0-2.1] (2)
Candida balanitis[b]	3.1 [1.9-4.6] (6)	n/a	n/a
Fungal balanitis[b]	n/a	n/a	2.3 [2.3-2.3] (1)
Skin Candida	n/a	n/a	n/a
Skin Candida	9.7 [4.1-30.7] (45)	2.9 [1.3-4.4] (5)	73.8 [4.4-143.1] (2)
Otitis externa Candida	6.4 [6.4-6.4] (1)	n/a	n/a
Oesophageal candidiasis	6.0 [1.3-38.5] (16)	2.4 [0.9-3.9] (2)	8.6 [5.4-21.3] (5)
Nail Candida	102.7 [20.9-184.6] (2)	5.0 [5.0-5.0] (1)	n/a
Other mucosal/cutaneous Candida	n/a	n/a	n/a
Mucosal/cutaneous candidiasis	61.3 [61.3-61.3] (1)	n/a	n/a
Unspecified Candida	n/a	n/a	n/a
Candida infection	7.3 [2.5-24.6] (32)	n/a	n/a
Other Candida infections	n/a	n/a	n/a
Gastrointestinal candidiasis	2.7 [1.7-8.6] (3)	n/a	n/a
Systemic candidiasis	n/a	n/a	n/a

Data are presented as median with Q1 and Q3.

[a]Denominator adjusted because gender-specific event for females: $N = 2196$ in the PsO cohort, $N = 722$ in the PsA cohort, and $N = 282$ in the axSpA cohort.

[b]Denominator adjusted because gender-specific event for males: $N = 4696$ in the PsO cohort and $N = 650$ in the axSpA cohort.

Duration of TEAE of Candida infections was calculated as = (End date of adverse event − Start date of adverse event + 1)/7.

If an adverse event has not ended by the date of completion from the treatment period, or date of early discontinuation, it is censored as of that date (last visit within the treatment period, or date of early discontinuation). If a patient has multiple episodes of the same TEAE, the episode with the most severity is used for the duration of event calculation. If a patient has more than one TEAE with the same severity, the event with the longest duration will be used.

Adverse event is coded using MedDRA Version 24.1.

Abbreviations: axSpA, axial spondyloarthritis. IXE, ixekizumab. MedDRA, Medical Dictionary for Regulatory Activities. N, number of patients in the analysis population. n, number of patients with at least 1 treatment-emergent of Candida infection in the specified category. n/a, not applicable. PsA, psoriatic arthritis. PsO, psoriasis. Q1, lower quartile. Q3, upper quartile. TEAE, treatment-emergent adverse event.

3.8. Frequency/rates of treatment-emergent Candida infections in patients with predisposing risk factors to fungal infections

Among the integrated patient population, the proportion of patients with predisposing risk factors to fungal infections was 16.6% ($n = 1145$) in the PsO cohort, 43.2% ($n = 605$) in the PsA cohort, and 18.7% ($n = 174$) in the axSpA cohort. Diabetes was the prevalent risk factor for patients with PsO ($n = 751$), while the use of steroids and/or systemic therapies was the prevalent risk factor for patients with PsA ($n = 488$) and axSpA ($n = 127$). The use of hormonal medications was observed in a few patients with PsO ($n = 7$), PsA ($n = 11$), and axSpA ($n = 7$).

Among this subpopulation of patients with predisposing risk factors to fungal infections, the IRs of treatment-emergent Candida infection were numerically higher than the overall analyzed patient population: 4.5 per 100 PY in the PsO cohort (*vs*. 1.9 per 100 PY in the overall PsO population), 4.9 per 100 PY in the PsA cohort (*vs*. 2.0 per 100 PY in the overall PsO population), and 4.9 per 100 PY in the axSpA cohort (*vs*. 1.2 per 100 PY in the overall PsO population). Specifically, treatment-emergent Candida infections were experienced at an IR of 4.5, 4.9, and 4.9 in patients with diabetes in the PsO, PsA, and axSpA cohorts, respectively, at an IR of 0.0, 0.0, and 7.0 in patients using hormonal medications, and 6.8, 5.0, and 4.7 in patients using steroids and/or systemic therapies (Table 5).

4. Discussion

The efficacy of IXE has been previously established across the approved indications in clinical trials [17,19,37], and in real-world settings [38–40]. The safety profile of IXE has been established from data for up to 6 years, including 9225 patients and 22,371.1 PY total exposure, across PsO, PsA, and axSpA [20]. However, the use of this class of medications (IL-17 inhibitors) may be associated with an increased risk of developing fungal infections [10–12]. Therefore, long-term analyses of fungal infections in clinical trial data are important in informing clinical decisions. Here, we have reported analyses of Candida infections for the total IXE clinical trial program.

This integrated safety analysis of treatment-emergent Candida infections in patients with PsO, PsA, or axSpA treated with IXE showed that the risk of developing Candida infection is low with IXE, and the severity is mild-to-moderate in most instances across the approved IXE indications. Our integrated safety analysis supersedes previously published data about rates of Candida infections in patients treated with IXE in clinical trials [22,23,35].

Treatment-emergent fungal infections have been observed in patients treated with other IL-17 inhibitors as well. For instance, PsO-treatment with brodalumab, an IgG2 antibody that selectively binds human IL-17RA, thereby inhibiting interaction with IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer, showed fungal infections (primarily driven by skin and mucosal Candida infections) at a numerically higher IR than IXE: 5.0 per 100 PY for the 140 mg dose and 11.9 per 100 PY for the 210 mg [41]. Treatment with secukinumab (150 mg and/or 300 mg for at least 16 weeks), an IL-17A inhibitor, showed Candida infections at exposure-adjusted IR comparable to IXE: 2.7 per 100 PY in patients with PsO, 1.7 per 100 PY in patients with PsA, and 1.0 per 100 PY in patients with axSpA [42]. Treatment with bimekizumab, an IL-17A and IL-17F inhibitor, showed Candida infections at a numerically higher exposure-adjusted IR than IXE: 11.5 per 100 PY (6.1 times higher than IXE) in patients with PsO treated with 320 mg every 4 weeks or every 8 weeks [43], 4.6 per 100 PY (2.3 times higher than IXE) in patients with PsA treated with 160 mg or 320 mg every 4 weeks [44], and 12.8 per 100 PY (10.7 times higher than IXE) in patients with non-radiographic axSpA treated with 160 mg every 4 weeks and 8.3 per 100 PY (6.9 times higher than IXE) in patients with radiographic axSpA treated with 160 mg every 4 weeks [45]. The high rates of Candida infections observed with bimekizumab might be related to the mechanism of action of this molecule, which inhibits both IL-17A and IL-17F. Identification of the reason remains to be elucidated. It is also important to note that the risk of Candida infections might vary among the IL-17 inhibitors based on the dose used, with higher doses generally leading to a higher risk of infections [46].

Table 5. Treatment-emergent Candida infections in patients with predisposing risk factors to fungal infections and treated with IXE across the approved indications.

	PsO ($N = 6892$; total PY = 18025.7) n (%) [IR] (95% CI)	PsA ($N = 1401$; total PY = 2248) n (%) [IR] (95% CI)	axSpA ($N = 932$; total PY = 2098) n (%) [IR] (95% CI)
Patients with predisposing risk factors to fungal infections[a]	1145 (16.6%) [5.2] (4.5-6.1)	605 (43.2%) [4.9] (3.7-6.6)	174 (18.7%) [4.9] (3.1-7.6)
Diabetes	751 (10.9%) [4.5] (3.6-5.6)	169 (12.1%) [4.9] (2.8-8.6)	50 (5.4%) [7.9] (4.0-15.9)
Use of hormonal medications[b]	7 (0.1%) [0.0] (0.0-0.0)	11 (0.8%) [0.0] (0.0-0.0)	7 (0.8%) [7.0] (1.0-49.9)
Use of steroids and/or systemic therapies[c]	435 (6.3%) [6.8] (5.5-8.4)	488 (34.8%) [5.0] (3.7-6.8)	127 (13.6%) [4.7] (2.8-7.9)

The number of patients, percentage (relative to the total study population, N), incidence rates per 100 PY, and 95% CIs are reported.
Percentage is calculated by n/N * 100%.
[a]Patients who are in more than 1 category (diabetes, use of hormonal medications, or use of steroids and/or systemic therapies) are counted once in patients with predisposing risk factors to fungal infections.
[b]Hormonal medications include both oral and injectable contraceptives. A comprehensive list of the hormonal medications is reported in Table S2 of the supplemental material.
[c]Steroids and/or systemic therapies include corticosteroids, cortisone injections, prednisone, prednisolone tablets, triamcinolone, triamcinolone injections, azathioprine, cyclosporine, leflunomide, etanercept, and tofacitinib for patients with PsA; corticosteroids, azathioprine, cyclosporine, and leflunomide for patients with axSpA.
IR is the incidence rate of Candida infections among patients with predisposing risk factors to fungal infections.
Predisposing risk factors to fungal infections is coded using MedDRA Version 26.0.
Abbreviations: axSpA, axial spondyloarthritis. CI, confidence interval. IR, incidence rate per 100 patient-years. IXE, ixekizumab. MedDRA, Medical Dictionary for Regulatory Activities. N, number of patients in the analysis population. n, number of patients with condition in the specified category. n/a, not applicable. PsA, psoriatic arthritis. PsO, psoriasis. PY, patient-years. TEAE, treatment-emergent adverse events. Total PY, total time patients were in the treatment period.

Candida infections have been reported in real-world studies analyzing the use of IL-17 inhibitors in patients with PsO, PsA, and axSpA [13,40,47,48]. However, comparison with real-world data is not advisable because there are important differences between clinical trials and routine care settings that limit comparability (*e.g.*, time periods and treatment paradigms, patient populations, outcome collection, treatment strategies) [49].

In terms of Candida infections duration, the longest Candida infections (over 1 year) were nail Candida (experienced by 2 patients in the PsO cohort), other mucosal/cutaneous candidiasis (experienced by 1 patient in the PsO cohort), and skin Candida (experienced by 2 patients in the PsA cohort). Nail Candida represents a challenging anatomical area that normally requires many weeks to be treated. Other factors that have contributed to the long duration of the analyzed Candida infections were (*i*) most patients used either topical anti-fungal therapies or no medications as opposed to systemic therapies to manage their fungal infections, (*ii*) Candida infections were marked as ended at the time of the follow-up visit as opposed to the actual date in which they ended, and (*iii*) the analysis were performed using the Candida infections with the highest severity in case a patient had multiple episodes of the same TEAE and with the longest duration in case a patient had more than 1 episode with the same severity.

Limitations of this integrated safety analysis of treatment-emergent Candida infections were (*i*) lack of microbial culture results in some patients to confirm clinical diagnoses, (*ii*) disparity of experience between dermatologists and rheumatologists in the diagnosis of cutaneous fungal infections, (*iii*) inclusion of data from all IXE dosing regimens, (*iv*) non-inclusion of control groups, (*iv*) non-inclusion of real-world data, and (*vi*) inability to take into account preexposure risk factors such as previous Candida infections.

Although safety analyses of treatment-emergent fungal infections associated with IXE have been previously published [21], this analysis is the first comprising the full clinical trial program: 25 clinical studies, which included 9225 adult patients across the approved IXE indications. Furthermore, this study provides a complete picture of treatment-emergent Candida infections in terms of frequency/IRs, severity, types/subtypes, recovery/resolution, management, duration, time between infections, and it is the first study presenting data on recurrence of treatment-emergent Candida infections in patients treated with IXE.

5. Conclusions

In this integrated safety analysis of 25 clinical studies, we found that the majority of treatment-emergent Candida infections observed in patients treated with IXE across the approved indications (PsO, PsA, and axSpA) were (*i*) experienced only once by patients, (*ii*) mild or moderate in severity, (*iii*) oral Candida or genital Candida, (*iv*) marked as recovered/resolved during the studies, (*v*) not leading to IXE discontinuation, (*vi*) managed with topical or no anti-fungal medications, and (*vii*) typically resolved before next visit.

In conclusion, this integrated safety analysis of treatment-emergent Candida infections in patients with PsO, PsA, or axSpA treated with IXE supersedes previously reported IXE safety data and shows that the risk of developing Candida infection is low with IXE, and the severity is mild-to-moderate in most instances across the approved IXE indications, which confirms the benefit/risk profile of IXE.

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Declaration of interests

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Author contribution statement

All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, had full access to all the data in this study, take responsibility for the integrity of data and accuracy of the data analysis, and have given their approval for this version to be published. Specifically, Carlos Diaz, Alyssa Garrelts, Nadezhda Eberhart, Areti Eleftheriadi, Nithi Tangsirisap, and Christopher Schuster contributed to the conception and design of the study, to the interpretation of the data and to the drafting of the manuscript. Marcus Ngantcha performed the statistical analysis and contributed to the interpretation of the data and to the drafting of the manuscript. Sergio

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Ethical approval and patient consent

Each clinical study was approved by the local Ethics Committee or Institutional Review Board and was conducted in accordance with the ethical principles of the Declaration of Helsinki. Each patient signed an informed consent form before entering the respective clinical study.

Data availability statement

Eli Lilly and Company provides access to all individual participant data collected during the trial and after anonymization, except for pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and 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, 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 www.vivli.org.

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