Cutaneous safety profile of nemolizumab in moderate-to-severe atopic dermatitis and prurigo nodularis: pooled analysis of phase 3 trials (ARCADIA 1&2 and OLYMPIA 1&2)

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OBJECTIVE

- The objective of this analysis was to characterize the safety profile associated with nemolizumab, particularly cutaneous adverse events (CAEs), using safety data from the four phase 3 trials in AD and PN pooled by indication

CONCLUSION

- This exploratory post hoc safety analysis of 2275 patients from pivotal AD and PN trials demonstrates that overall AE and SAE rates were similar with nemolizumab versus placebo
- Cutaneous adverse events, specifically eczema-like events, were the most common adverse event category
  - Eczema-like events were generally mild/moderate in severity, transient, resolved with topical corticosteroids and rarely required study-drug discontinuation
- These findings support clinicians in anticipating and managing eczema-like events associated with nemolizumab

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INTRODUCTION

- Nemolizumab, the first health-authority-approved IL-31 receptor alpha antagonist, is available in multiple countries for the treatment of both adult and adolescent patients with moderate-to-severe atopic dermatitis (AD) and adult patients with prurigo nodularis (PN)[1,2]
- Eczematous events (AD, eczema, nummular eczema) were common adverse events (AEs) in pivotal PN trials (OLYMPIA 1 [NCT04501666] and OLYMPIA 2 [NCT04501679]), while no imbalance in AD events was observed in pivotal AD trials (ARCADIA 1 [NCT03985943] and ARCADIA 2 [NCT03989349])[3–5]

METHODS

- This exploratory post-hoc safety analysis included four randomized, double-blind, placebo-controlled trials: ARCADIA 1&2 (AD; initial 16-week treatment period) and OLYMPIA 1&2 (PN; 24-week treatment period for OLYMPIA 1 and 16-week treatment period for OLYMPIA 2), pooled by indication
- AEs were grouped into defined safety areas of interest based on the known safety profile of nemolizumab and other biologics in the field. Incidence rates, exposure-adjusted incidence rates (EAIRs)/100 patient-years (PY) and rate ratios (RRs) with 95% confidence intervals (CIs) were calculated
- AEs were investigator-reported and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 25.0
- To identify potential risk factors for eczema-like CAEs, a Cox proportional hazards model analysis was conducted

RESULTS

BASELINE CHARACTERISTICS

- Overall, 1135 patients received nemolizumab and 584 received placebo in the AD phase 3 trials while in the PN phase 3 trials 370 patients received nemolizumab and 186 received placebo (**Table 1**)
- Baseline characteristics were generally balanced between the nemolizumab and placebo arms in both AD and PN pools

Table 1. Baseline characteristics of patients with AD and PN from pooled phase 3 trials of nemolizumab

	AD pool			PN pool		
	Nemolizumab N=1135	Placebo N=584	Total N=1719	Nemolizumab N=370	Placebo N=186	Total N=556
Demographics						
Age (years), mean (SD)	34.1 (16.7)	34.2 (16.3)	34.1 (16.6)	55.6 (13.7)	54.2 (14.5)	55.1 (14.0)
Age group, n (%)						
12–17	176 (15.5)	89 (15.2)	265 (15.4)	NA	NA	NA
18–65	893 (78.7)	471 (80.7)	1364 (79.3)	271 (73.2)	145 (78.0)	416 (74.8)
>65	66 (5.8)	24 (4.1)	90 (5.2)	99 (26.8)	41 (22.0)	140 (25.2)
Sex, n (%)						
Male	570 (50.2)	304 (52.1)	874 (50.8)	148 (40.0)	76 (40.9)	224 (40.3)
Female	565 (49.8)	280 (47.9)	845 (49.2)	222 (60.0)	110 (59.1)	332 (59.7)
Weight (kg), mean (SD)	74.8 (18.0)	75.3 (19.3)	75.0 (18.5)	83.5 (20.3)	81.0 (20.0)	82.7 (20.2)
BMI (kg/m^2), mean (SD)	25.9 (5.5)	26.1 (6.1)	26.0 (5.7)	29.1 (6.0)	28.4 (5.5)	28.9 (5.8)
Race, n (%)						
White	904 (79.6)	470 (80.5)	1374 (79.9)	305 (82.4)	148 (79.6)	453 (81.5)
Black or African American	61 (5.4)	38 (6.5)	99 (5.8)	22 (5.9)	17 (9.1)	39 (7.0)
Asian	150 (13.2)	68 (11.6)	218 (12.7)	33 (8.9)	16 (8.6)	49 (8.8)
Other races	20 (1.8)	8 (1.4)	28 (1.6)	10 (2.7)	5 (2.7)	15 (2.7)
Cardiovascular, metabolic, and musculoskeletal comorbidities						
Cardiac disorders[a]	49 (4.3)	22 (3.8)	71 (4.1)	71 (19.2)	31 (16.7)	102 (18.3)
Endocrine disorders[a]	63 (5.6)	39 (6.7)	102 (5.9)	62 (16.8)	25 (13.4)	87 (15.6)
Metabolism and nutrition disorders[a]	194 (17.1)	99 (17.0)	293 (17.0)	141 (38.1)	61 (32.8)	202 (36.3)
Hypertension[b]	144 (12.7)	72 (12.3)	216 (12.6)	139 (37.6)	58 (31.2)	197 (35.4)
Musculoskeletal and connective tissue disorders[a]	127 (11.2)	65 (11.1)	192 (11.2)	113 (30.5)	57 (30.6)	170 (30.6)
Allergic/atopic comorbidities						
Dermatitis atopic	1135 (100)	584 (100)	1719 (100)	22 (5.9)	12 (6.5)	34 (6.1)
Asthma	364 (32.1)	182 (31.2)	546 (31.8)	48 (13.0)	26 (14.0)	74 (13.3)
Seasonal allergy	250 (22.0)	126 (21.6)	376 (21.9)	41 (11.1)	23 (12.4)	64 (11.5)
Rhinitis allergic	198 (17.4)	112 (19.2)	310 (18.0)	19 (5.1)	15 (8.1)	34 (6.1)
Conjunctivitis allergic	127 (11.2)	67 (11.5)	194 (11.3)	10 (2.7)	8 (4.3)	18 (3.2)
Food allergy	170 (15.0)	104 (17.8)	274 (15.9)	7 (1.9)	7 (3.8)	14 (2.5)
Allergy to animal	110 (9.7)	40 (6.8)	150 (8.7)	8 (2.2)	4 (2.2)	12 (2.2)
Multiple allergies	105 (9.3)	48 (8.2)	153 (8.9)	6 (1.6)	3 (1.6)	9 (1.6)
Mite allergy	104 (9.2)	40 (6.8)	144 (8.4)	10 (2.7)	6 (3.2)	16 (2.9)

[a]SOC; [b]PT. AD, atopic dermatitis; BMI, body mass index; N, number of patients in the population; n, number of patients with available data; NA, not applicable; PN, prurigo nodularis; PT, preferred term; SD, standard deviation; SOC, system organ class

SAFETY SUMMARY OVERVIEW OF NEMOLIZUMAB IN AD AND PN

- There was a similar incidence of any treatment-emergent adverse events (TEAEs) between study arms, with 45.9% vs 45.0% of patients (nemolizumab vs placebo) reporting such events in the AD pool and 66.5% vs 59.1% of patients reporting such events in the PN pool (**Table 2**)
- Most patients had events rated as mild or moderate in terms of maximum severity (<6% of patients had severe TEAEs in any treatment arm)
- A low incidence of serious AEs (SAEs) was reported; SAEs related to the study drug were infrequent in all study arms
- Rates of study drug discontinuation due to AEs were low and comparable between treatment arms in both AD and PN pools. No deaths occurred in the nemolizumab arms; however, one death (deemed unrelated to the study drug) was reported in the placebo arm of the PN trials

Table 2. Overall safety summary: patients with TEAEs in the AD and PN studies (pooled data)

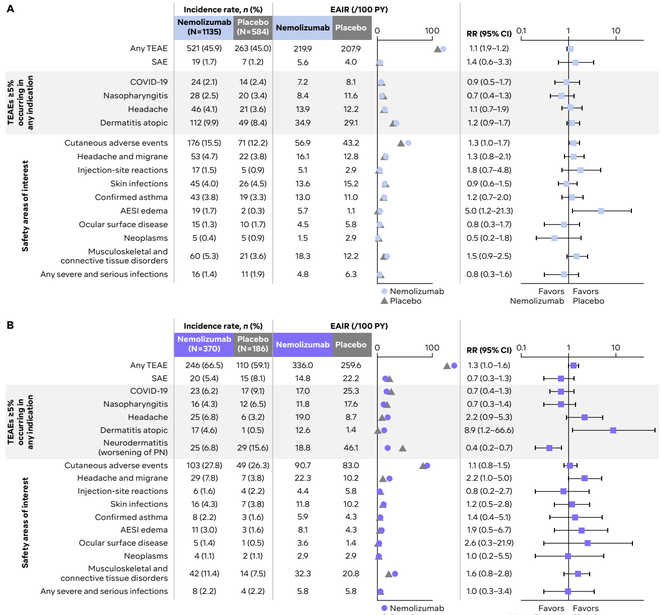
	AD pool			PN pool		
	Nemolizumab N=1135 n (%)	Placebo N=584 n (%)	Total N=1719 n (%)	Nemolizumab N=370 n (%)	Placebo N=186 n (%)	Total N=556 n (%)
Any TEAE	521 (45.9)	263 (45.0)	784 (45.6)	246 (66.5)	110 (59.1)	356 (64.0)
Any TEAE related to study drug	190 (16.7)	71 (12.2)	261 (15.2)	92 (24.9)	34 (18.3)	126 (22.7)
Any serious TEAE	19 (1.7)	7 (1.2)	26 (1.5)	20 (5.4)	15 (8.1)	35 (6.3)
Any serious TEAE related to study drug	5 (0.4)	0	5 (0.3)	2 (0.5)	2 (1.1)	4 (0.7)
Any death	0	0	0	0	1 (0.5)	1 (0.2)
Any TEAE by maximum severity						
Mild	281 (24.8)	155 (26.5)	436 (25.4)	130 (35.1)	62 (33.3)	192 (34.5)
Moderate	201 (17.7)	93 (15.9)	294 (17.1)	104 (28.1)	37 (19.9)	141 (25.4)
Severe	39 (3.4)	15 (2.6)	54 (3.1)	12 (3.2)	11 (5.9)	23 (4.1)
Action to study drug and study discontinuations						
Any TEAE leading to study drug interruption	32 (2.8)	9 (1.5)	41 (2.4)	14 (3.8)	9 (4.8)	23 (4.1)
Any TEAE leading to study drug discontinuation	29 (2.6)	16 (2.7)	45 (2.6)	14 (3.8)	5 (2.7)	19 (3.4)
Any TEAE leading to study discontinuation	24 (2.1)	6 (1.0)	30 (1.7)	13 (3.5)	6 (3.2)	19 (3.4)

AD, atopic dermatitis; N, number of patients in the population; n, number of patients with available data; PN, prurigo nodularis; TEAE, treatment-emergent adverse event

SAFETY AREAS OF INTEREST CATEGORIES

- The most frequent safety area of interest category in both AD and PN cohorts was cutaneous AEs (CAEs)
  - AD pool: CAEs reported in 15.5% (nemolizumab) vs 12.2% (placebo) of patients with AD (56.9 vs 43.2 events per 100 PY; RR 1.3, 95% CI 1.0–1.7) (**Figure 1A**)
  - PN pool: CAEs reported in 27.8% vs 26.3% of patients with PN (90.7 vs 83.0 events per 100 PY; RR 1.1, 95% CI 0.8–1.5) (**Figure 1B**)
- Safety area of interest categories with a RR>2.5 for nemolizumab were AESI edema in the AD pool (**Figure 1A**) and ocular surface disease in the PN pool (**Figure 1B**)
  - However, the low incidence and wide CIs indicate uncertainty in these estimates

Figure 1. Safety areas of interest categories profile for the AD pool (A) and the PN pool (B)



AD, atopic dermatitis; AESI, adverse event of special interest; CI, confidence interval; COVID-19, coronavirus disease 2019; EAIR, exposure-adjusted incidence rate; PN, prurigo nodularis; PY, patient-year; RR, rate ratio; SAE, serious adverse event; TEAE, treatment-emergent adverse event

SAFETY AREAS OF INTEREST - CUTANEOUS AES SUBCATEGORIES PROFILE

- Among patients who experienced CAEs, the majority experienced an eczema-like CAE; this was the only subcategory, in the PN pool, where the RR 95% CIs did not overlap 1 (**Table 3**)
  - Dermatitis atopic was the most common TEAE (at preferred term [PT] level) reported in this subcategory across indications (data not shown)
    - In the AD pool, this TEAE primarily represented worsening of underlying AD and accounted for most eczema-like events
    - In the PN pool, other TEAEs (PTs) with incidence >1% included eczema nummular and eczema

Table 3. Safety areas of interest: cutaneous AE subcategories profile for the AD and PN pooled data

Event category	AD pool			PN pool		
	Nemolizumab N=1135	Placebo N=584	RR (95% CI)	Nemolizumab N=370	Placebo N=186	RR (95% CI)
CAEs						
Eczema-like CAEs						
n (%) E	120 (10.6) 153	52 (8.9) 60		49 (13.2) 64	9 (4.8) 9	
EAIR (/100 PY)	37.5	31.0	1.2 (0.9–1.7)	38.8	13.1	3 (1.5–6.0)
Autoimmune CAEs						
n (%) E	1 (<0.1) 1	3 (0.5) 4		3 (0.8) 3	0 (0.0) 0	
EAIR (/100 PY)	0.3	1.7	0.2 (0.0–1.7)	2.2	0.0	NC
Psoriasiform CAEs						
n (%) E	1 (0.1) 1	0 (0.0) 0		2 (0.5) 2	1 (0.5) 1	
EAIR (/100 PY)	0.3	0.0	NC	1.4	1.4	1 (0.1–11.2)
SCARs						
n (%) E	0 (0.0) 0	0 (0.0) 0		0 (0.0) 0	0 (0.0) 0	
EAIR (/100 PY)	0.0	0.0	NC	0.0	0.0	NC
Exfoliative reactions						
n (%) E	4 (0.4) 4	1 (0.2) 1		1 (0.3) 1	1 (0.5) 1	
EAIR (/100 PY)	1.2	0.6	2.1 (0.2–18.6)	0.7	1.4	0.5 (0.0–8.1)

AD, atopic dermatitis; AE, adverse event; CAE, cutaneous adverse event; CI, confidence interval; E, event; EAIR, exposure-adjusted incidence rate; NC, not calculated; PN, prurigo nodularis; PY, patient-year; RR, rate ratio; SCAR, severe cutaneous adverse reaction

CHARACTERIZATION OF ECZEMA-LIKE EVENTS IN AD AND PN

- Eczema-like CAEs were mostly rated as mild and moderate in severity (**Table 4**)
- Median latency of the first event in the AD pool was 43.5 days (nemolizumab) vs 42.0 days (placebo) and 30.0 days vs 52.0 days in the PN pool
- Median duration of the first event was 22.0 days vs 28.0 days in the AD pool and 38.0 days vs 28.0 days in the PN pool
- Most patients continued with the study drug and most events resolved by the end of the study
- In all groups, the most common treatment for eczema-like CAEs was topical corticosteroids: (AD: 31.4% [nemolizumab] vs 46.7% [placebo]; PN: 57.8% vs 44.4%)
- The results of risk factor analyses for eczema-like CAEs showed:
  - AD pool:
    - Race other than White, Black or African American, or Asian and severe disease markers (prior systemic therapy, IGA of 4 [severe], high eosinophils, asthma) were potential risk factors
    - There was no statistically reliable association between nemolizumab treatment and the risk of eczema-like CAEs
  - PN pool:
    - Older age, male, atopy background and nemolizumab use were associated with increased risk for eczema-like CAEs

Table 4. Characterization of eczema-like cutaneous AEs during treatment period for the AD and PN pooled data

	AD pool		PN pool	
	Nemolizumab N=120 (Nev=153)	Placebo N=52 (Nev=60)	Nemolizumab N=49 (Nev=64)	Placebo N=9 (Nev=9)
Severity, E (%)				
Mild	55 (35.9)	18 (30.0)	42 (65.6)	5 (55.6)
Moderate	73 (47.7)	34 (56.7)	22 (34.4)	3 (33.3)
Severe	25 (16.3)	8 (13.3)	0	1 (11.1)
Event outcomes, E (%)				
Not recovered/not resolved	55 (35.9)	17 (28.3)	25 (39.1)	4 (44.4)
Recovered/resolved	92 (60.1)	41 (68.3)	37 (57.8)	5 (55.6)
Recovered/resolved with sequelae	5 (3.3)	1 (1.7)	2 (3.1)	0
Unknown	1 (0.7)	1 (1.7)	0	0
Types of medication taken, E (%)				
Overall	79 (51.6)	47 (78.3)	47 (73.4)	5 (55.6)
Local (topical)	51 (33.3)	30 (50.0)	46 (71.9)	4 (44.4)
Systemic oral	39 (25.5)	24 (40.0)	6 (9.4)	0
Study treatment action, E (%)				
Dose not changed[a,b]	128 (83.7)	45 (75.0)	58 (90.6)	7 (77.8)
Drug interrupted	5 (3.3)	0	1 (1.6)	0
Drug withdrawn	20 (13.1)	15 (25.0)	3 (4.7)	1 (11.1)
Not applicable[b]	-	-	2 (3.1)	1 (11.1)
Study drug related, E (%)	50 (32.7)	14 (23.3)	41 (64.1)	7 (77.8)
Events leading to study discontinuation, E (%)	15 (9.8)	5 (8.3)	3 (4.7)	1 (11.1)
Event duration (days)[c] of the first event				
n	69	37	26	5
Mean (SD)	28.5 (24.0)	29.0 (21.3)	47.0 (44.4)	38.2 (23.1)
Median	22.0	28.0	38.0	28.0
Latency (days)[d] of the first event				
n	120	52	49	9
Mean (SD)	45.2 (29.7)	45.7 (25.4)	44.6 (39.3)	64.0 (50.3)
Median	43.5	42.0	30.0	52.0
Number of events per patient, n (%)[e]				
Patients with only 1 event	102 (85.0)	45 (86.5)	35 (71.4)	9 (100.0)
Patients with ≥2 events	18 (15.0)	7 (13.5)	14 (28.6)	0

[a]In the AD pool, patients with this outcome were active in the study but the AE had no impact on study drug administration; [b]In the PN pool the outcome was 'dose not changed' if there was no change to the dose of the study drug in relation to the AE, or the drug was already temporarily interrupted due to another AE and/or this AE did not contribute to or extend the interruption; the outcome was 'not applicable' when a patient was not actively taking the study drug (prior to the initial dose or after the last dose). [c]The event duration was not calculated if the event start/end date was incomplete or an ongoing event; [d]Latency was calculated as event onset date of the first event to the date of first dosing in the study; [e]n is the number of patients and percentage (%) is based on N. AD, atopic dermatitis; AE, adverse event; CAE, cutaneous adverse event; E, event; Nev, number of events; N, number of patients in the population; n, number of patients with available data; PN, prurigo nodularis; SD, standard deviation