Summary Report of Benefit-Risk Assessment

NEMLUVIO POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PRE-FILLED PEN 30MG
NEMLUVIO POWDER AND SOLVENT FOR SOLUTION FOR INJECTION IN PRE-FILLED SYRINGE 30MG

NEW DRUG APPLICATION

Active Ingredient(s)	Nemolizumab
Product Registrant	Galderma Singapore Private Limited
Product Registration Number	SIN17206P, SIN17207P
Application Route	Full evaluation
Date of Approval	17 March 2025

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A INTRODUCTION

Nemluvio is indicated for the following:

- Treatment of moderate-to-severe atopic dermatitis (AD) in combination with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI) in adult and adolescent patients ≥12 years old with body weight of at least 30 kg, who are inadequately controlled by topical therapies and are candidates for systemic therapy; and
- Treatment of adults with moderate-to-severe prurigo nodularis (PN) who are candidates for systemic therapy.

The active substance, nemolizumab, is a humanised monoclonal antibody of the immunoglobulin G2 (IgG2) subclass that inhibits interleukin-31 (IL-31) signalling by binding selectively to interleukin-31 receptor A (IL-31RA). IL-31 is a neuroimmune cytokine that drives pruritus and the inflammation process, which are important pathophysiological components of AD and PN. IL-31 has additional barrier dysfunction effects in AD, and epidermal differentiation and profibrotic effects in PN. Multiple cell types express IL-31RA and are activated by IL-31. Those involved in the pathophysiology of AD and PN include immune cells (e.g., mononuclear phagocytes, granulocytes) and structural cells (e.g., neurons, fibroblasts, keratinocytes). Blocking IL-31RA with nemolizumab ameliorates pruritus and inhibits inflammatory responses in both AD and PN. Additionally, nemolizumab restores barrier integrity in AD and normalises epidermal differentiation by blocking profibrotic processes in PN. The mechanism of action of nemolizumab has not been definitively established.

Nemluvio is available as powder and solvent for solution for injection containing 30 mg of nemolizumab in a dual chamber glass barrel assembled into an autoinjector (prefilled pen) or dual chamber prefilled syringe. The lyophilised drug product, with L-arginine hydrochloride, poloxamer 188, sucrose, trometamol and trometamol hydrochloride, is in chamber 1. The solvent, water for injection, is in chamber 2.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, nemolizumab, is manufactured at [redacted]. The drug product in the dual chamber glass barrel for the prefilled pen is manufactured at [redacted]. The drug product in the dual chamber prefilled syringe is manufactured at [redacted].

Drug substance:

Adequate controls have been presented for the starting materials, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of the drug substance and its impurities have been appropriately performed. Potential and actual impurities are adequately controlled in the manufacturing process and specifications.

The drug substance specifications were established in accordance with ICH Q6B guideline and the impurity limits were appropriately qualified. The analytical procedures used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference materials used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substance at ≤-[redacted]°C with a shelf life of [redacted] months. The packaging is [redacted].

Drug product:

[redacted] For the prefilled pen, the filled dual chamber glass barrel is assembled into an autoinjector.

The manufacturing sites are compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B guideline and impurity limits were adequately qualified. The analytical procedures used were adequately described and non-compendial methods have been validated in accordance with ICH Q2 guideline, with information on the reference materials used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf life of 24 months for the drug product in the prefilled pen, or 36 months for the prefilled syringe, when stored between 2°C and 8°C. The in-use period after reconstitution is 4 hours when stored at up to 30°C. The primary container closure system is a dual chamber Type 1 glass barrel.

C ASSESSMENT OF CLINICAL EFFICACY

Atopic dermatitis

The clinical efficacy of nemolizumab in combination with TCS and/or TCI in the treatment of moderate-to-severe AD was based on two pivotal Phase 3 studies, RD.06.SPR.118161 (ARCADIA 1) and RD.06.SPR.118169 (ARCADIA 2). These were identical, randomised, double-blind, placebo-controlled, multicentre, parallel-group studies designed to assess the efficacy and safety of nemolizumab in adult and adolescent patients aged 12 years and older with moderate-to-severe AD and a documented history of inadequate response to topical AD medications.

Key inclusion criteria included male or female patients aged ≥12 years with chronic AD according to American Academy of Dermatology Consensus Criteria for ≥2 years, Eczema Area and Severity Index (EASI) score ≥16, Investigator's Global Assessment (IGA) score ≥3, AD involvement ≥10% of body surface area (BSA), Peak Pruritus Numerical Rating Scale (PP NRS) score ≥4.0 at both screening and baseline visits, and documented history of inadequate

response to topical medications (TCS ± TCI). Key exclusion criteria included body weight <30 kg and uncontrolled asthma.

Each study consisted of 4 periods: 4-week screening period (including a run-in of at least 14 days), 16-week Initial Treatment Period, Maintenance Period (Week 16 to Week 48), and 8-week follow-up period.

Patients were randomised in a 2:1 ratio to receive subcutaneous (SC) nemolizumab 30 mg (with a 60-mg loading dose) or placebo every 4 weeks (Q4W) for 16 weeks (last dose at Week 12). Randomisation was stratified by disease severity (IGA=3 [moderate], IGA=4 [severe]) and pruritus severity (PP NRS ≥7, PP NRS <7).

During the ≥14-day run-in period and throughout each study, patients applied a moisturiser at least once daily and were allowed to use a background topical therapy (including a medium-potency TCS for the body and a low-potency TCS or a TCI for sensitive areas such as the face, neck, and intertriginous areas). The background therapy was adjusted during the study based on the investigator's clinical judgement according to the disease activity and tolerability of the patient.

All nemolizumab-treated patients who were clinical responders at Week 16 were re-randomised in a 1:1:1 ratio to nemolizumab 30 mg Q4W, nemolizumab 30 mg Q8W, or placebo Q4W for an additional 32 weeks in the Maintenance Period. A clinical responder was defined as a patient at Week 16 with an IGA of 0 (clear) or 1 (almost clear) or EASI-75. All placebo-treated patients who responded to placebo during the Initial Treatment Period continued to receive placebo Q4W in the Maintenance Period.

The co-primary efficacy endpoints were the proportion of patients with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-point reduction from baseline) and the proportion of patients with EASI-75 (≥75% improvement in EASI from baseline) at Week 16.

The key secondary efficacy endpoints were as follows:

- Proportion of patients with an improvement of PP NRS ≥4 at Week 16
- Proportion of patients with PP NRS <2 at Week 16
- Proportion of patients with an improvement of Sleep Disturbance NRS (SD NRS) ≥4 at Week 16
- Proportion of patients with an improvement of PP NRS ≥4 at Week 4
- Proportion of patients with PP NRS <2 at Week 4
- Proportion of patients with an improvement of PP NRS ≥4 at Week 2
- Proportion of patients with an improvement of PP NRS ≥4 at Week 1
- Proportion of patients with EASI-75 and improvement of PP NRS ≥4 at Week 16
- Proportion of patients with IGA success and improvement of PP NRS ≥4 at Week 16

The co-primary and key secondary endpoints of the Initial Treatment Period were analysed for all patients in the intent-to-treat (ITT) population and patients with baseline PP NRS ≥7 (severe pruritus population). To control the type I error at 5% significance level, a serial gatekeeping approach was implemented. The co-primary endpoints were tested first at the 2.5% significance level for each population. If both co-primary endpoints were statistically significant at the 2.5% significance level, the key secondary endpoints were tested sequentially following a hierarchical testing procedure using the pre-specified order of endpoints (as above) for each population. The subsequent tests were to be stopped when no statistical difference was found.

If p<2.5% for all co-primary and key secondary endpoints in at least one population, then 2.5% was recycled to test the other population at the 5% level of significance.

In ARCADIA 1, a total of 941 patients (620 nemolizumab, 321 placebo) were randomised in the Initial Treatment Period and included in the ITT population. At Week 16, 272 nemolizumab-treated patients who were clinical responders were re-randomised to receive nemolizumab Q4W (N=90), Q8W (N=91), or placebo (N=91) during the Maintenance Period. One hundred placebo-treated patients responded to placebo at Week 16 and continued to receive placebo Q4W in the Maintenance Period.

In ARCADIA 2, a total of 787 patients (522 nemolizumab, 265 placebo) were randomised in the Initial Treatment Period and included in the ITT population. At Week 16, 235 nemolizumab-treated patients who were clinical responders were re-randomised to receive nemolizumab Q4W (N=79), Q8W (N=78), or placebo (N=78) during the Maintenance Period. Eighty-five placebo-treated patients responded to placebo at Week 16 and continued to receive placebo Q4W in the Maintenance Period.

Patient demographics and baseline disease characteristics were generally well-balanced between treatment groups in both studies. The majority of patients were White (79.9%) and the ARCADIA 1 study had a higher proportion of Asian patients than the ARCADIA 2 study (17.9% vs 6.7%). Slightly more than half of the patients were male (51.0%). The mean age across both studies was 34.1 years, and 15.4% of patients were adolescents aged 12 to 17 years. The study population was representative of patients with moderate-to-severe AD as measured by the baseline IGA scores (70.1% had an IGA score of 3 and 29.9% had an IGA score of 4) and EASI scores (mean baseline 27.51). Patients reported moderate-to-severe itching, with a mean weekly average PP NRS at baseline of 7.126. More than half of the patients (57.6%) had baseline PP NRS ≥7. Overall, 63.3% of patients received any previous systemic treatment for AD. Almost all patients (99.0%) reported at least one background topical therapy, including TCS and TCI. The most frequently reported background topical therapy was mometasone furoate, a potent TCS (ARCADIA 1: 51.8% nemolizumab vs 52.0% placebo; ARCADIA 2: 56.9% nemolizumab vs 59.6% placebo). The majority of patients (ARCADIA 1: 68.1% nemolizumab vs 70.4% placebo; ARCADIA 2: 75.7% nemolizumab vs 78.5% placebo) received background potent corticosteroids.

Both studies met the co-primary endpoints in both the ITT and severe pruritus populations. In the ITT population, the proportion of patients with IGA success was statistically significantly greater with nemolizumab compared with placebo at Week 16 [ARCADIA 1: 35.6% vs 24.6%; proportion difference: 11.5% (97.5% CI: 4.7, 18.3); p=0.0003; ARCADIA 2: 37.7% vs 26.0%; proportion difference: 12.2% (97.5% CI: 4.6, 19.8); p=0.0006]. The proportion of patients with EASI-75 was also statistically significantly greater with nemolizumab compared with placebo at Week 16 [ARCADIA 1: 43.5% vs 29.0%; proportion difference: 14.9% (97.5% CI: 7.8, 22.0); p<0.0001; ARCADIA 2: 42.1% vs 30.2%; proportion difference: 12.5% (97.5% CI: 4.6, 20.3); p=0.0006].

Results for both co-primary endpoints were generally consistent in the severe pruritus population (baseline PP NRS ≥7) as well as across sensitivity analyses. The treatment effects in subgroups (age, sex, race, ethnicity, region, baseline IGA, baseline PP NRS, and previous use of systemic therapy for AD) were also consistent with the results in the overall population, except for a numerically lower proportion of responders with nemolizumab compared with placebo in the subgroup of patients aged >65 years [IGA success: 38.8% vs 41.7%; proportion difference: -2.0% (95% CI: -25.4, 21.4); EASI-75: 47.8% vs 50.0%; proportion difference: -3.8% (95% CI: -27.0, 19.5)]. However, limited conclusions could be drawn in view of the small

sample size for this subgroup (n=91 across both studies) as reflected by the wide 95% CIs. Furthermore, there were no clinically meaningful differences in the pharmacokinetics of nemolizumab in the elderly (>65 years) compared to adults or adolescents, and age was not a significant covariate in the pharmacokinetic/pharmacodynamic (PK/PD) models for AD.

Both studies also met all the key secondary endpoints. Nemolizumab demonstrated statistically significantly greater proportion of patients with an improvement of ≥4 from baseline in weekly average PP NRS compared with placebo at Week 1 (ARCADIA 1: 4.7% vs 1.2%; p=0.0064; ARCADIA 2: 6.7% vs 0.4%; p<0.0001), Week 2 (ARCADIA 1: 17.7% vs 3.1%; p<0.0001; ARCADIA 2: 16.9% vs 1.9%; p<0.0001), Week 4 (ARCADIA 1: 27.4% vs 6.5%; p<0.0001; ARCADIA 2: 26.1% vs 5.3%; p<0.0001), and Week 16 (ARCADIA 1: 42.7% vs 17.8%; p<0.0001; ARCADIA 2: 41.0% vs 18.1%; p<0.0001).

The proportion of patients with a weekly average PP NRS <2 was statistically significantly (p<0.0001) greater with nemolizumab compared with placebo at Week 4 (ARCADIA 1: 16.0% vs 3.7%; ARCADIA 2: 15.9% vs 2.6%) and at Week 16 (ARCADIA 1: 30.6% vs 11.2%; ARCADIA 2: 28.4% vs 11.3%).

For sleep disturbance outcomes, a statistically significantly (p<0.0001) greater proportion of patients with an improvement of ≥4 from baseline in weekly average SD NRS was observed with nemolizumab compared with placebo at Week 16 (ARCADIA 1: 37.9% vs 19.9%; ARCADIA 2: 33.5% vs 16.2%).

The proportion of patients with both EASI-75 and an improvement of ≥4 from baseline in weekly average PP NRS was statistically significantly (p<0.0001) greater with nemolizumab compared with placebo at Week 16 (ARCADIA 1: 23.7% vs 11.2%; ARCADIA 2: 23.0% vs 9.8%).

Similarly, the proportion of patients with both IGA success and an improvement of ≥4 from baseline in weekly average PP NRS was statistically significantly (p<0.0001) greater with nemolizumab compared with placebo at Week 16 (ARCADIA 1: 19.7% vs 9.3%; ARCADIA 2: 20.5% vs 8.7%).

Results for the key secondary efficacy endpoints were consistent in the severe pruritus population (baseline PP NRS ≥7).

Summary of key efficacy results in ITT population (ARCADIA 1, ARCADIA 2)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	**Placebo (N=321)**	**Nemolizumab (N=522)**	**Placebo (N=265)**
Co-primary endpoints				
IGA success at Week 16				
n (%)	221 (35.6)	79 (24.6)	197 (37.7)	69 (26.0)
Proportion difference (97.5% CI)[a]	11.5 (4.7, 18.3)		12.2 (4.6, 19.8)	
p-value[a]	0.0003		0.0006	
EASI-75 at Week 16				
n (%)	270 (43.5)	93 (29.0)	220 (42.1)	80 (30.2)
Proportion difference (97.5% CI)[a]	14.9 (7.8, 22.0)		12.5 (4.6, 20.3)	
p-value[a]	<0.0001		0.0006	
Key secondary endpoints				
Improvement of ≥4 from baseline in PP NRS				
Week 1, n (%)	29 (4.7)	4 (1.2)	35 (6.7)	1 (0.4)

Proportion difference (97.5% CI)[a]	3.4 (1.1, 5.8)		6.4 (3.8, 9.1)	
p-value[a]	0.0064		<0.0001	
Week 2, n (%)	110 (17.7)	10 (3.1)	88 (16.9)	5 (1.9)
Proportion difference (97.5% CI)[a]	14.6 (10.6, 18.7)		15.1 (11.0, 19.2)	
p-value[a]	<0.0001		<0.0001	
Week 4, n (%)	170 (27.4)	21 (6.5)	136 (26.1)	14 (5.3)
Proportion difference (97.5% CI)[a]	20.9 (15.8, 26.0)		20.9 (15.6, 26.1)	
p-value[a]	<0.0001		<0.0001	
Week 16, n (%)	265 (42.7)	57 (17.8)	214 (41.0)	48 (18.1)
Proportion difference (97.5% CI)[a]	24.9 (18.4, 31.5)		23.2 (15.7, 30.1)	
p-value[a]	<0.0001		<0.0001	
PP NRS <2				
Week 4, n (%)	99 (16.0)	12 (3.7)	83 (15.9)	7 (2.6)
Proportion difference (97.5% CI)[a]	12.2 (8.2, 16.3)		13.2 (9.0, 17.4)	
p-value[a]	<0.0001		<0.0001	
Week 16, n (%)	190 (30.6)	36 (11.2)	148 (28.4)	30 (11.3)
Proportion difference (97.5% CI)[a]	19.5 (13.7, 25.2)		17.1 (10.9, 23.3)	
p-value[a]	<0.0001		<0.0001	
Improvement of ≥4 from baseline in SD NRS at Week 16				
n (%)	235 (37.9)	64 (19.9)	175 (33.5)	43 (16.2)
Proportion difference (97.5% CI)[a]	17.9 (11.3, 24.5)		17.5 (10.8, 24.3)	
p-value[a]	<0.0001		<0.0001	
EASI-75 improvement and improvement of ≥4 from baseline in PP NRS at Week 16				
n (%)	147 (23.7)	36 (11.2)	120 (23.0)	26 (9.8)
Proportion difference (97.5% CI)[a]	12.6 (7.1, 18.1)		13.4 (7.6, 19.2)	
p-value[a]	<0.0001		<0.0001	
IGA success and improvement of ≥4 from baseline in PP NRS at Week 16				
n (%)	122 (19.7)	30 (9.3)	107 (20.5)	23 (8.7)
Proportion difference (97.5% CI)[a]	10.5 (5.4, 15.6)		12.1 (6.6, 17.6)	
p-value[a]	<0.0001		<0.0001	

[a] The proportion differences and the corresponding p-values were based on the Cochran-Mantel-Haenszel test adjusted for the randomisation stratification factors (IGA severity and PP NRS).

At Week 16, clinical responders (IGA 0/1 or EASI-75) from the nemolizumab group were re-randomised to nemolizumab Q4W, nemolizumab Q8W, or placebo up to Week 48. The efficacy data from the re-randomised arms in the Maintenance Period were pooled as the 2 pivotal studies had identical study designs and assessment procedures. At Week 48, the percentage of patients with IGA response was statistically significantly higher in the nemolizumab Q4W to Q4W and nemolizumab Q4W to Q8W groups (61.5% and 60.4%, respectively) compared with the nemolizumab Q4W to placebo group (49.7%). Similarly, the percentage of patients with EASI-75 at Week 48 was statistically significantly higher in the Q4W and Q8W groups (76.3% and 75.7%, respectively) compared with the placebo group (63.9%). The maintenance of clinical response with the Q8W dosing regimen was similar to the Q4W dosing regimen.

Overall, the ARCADIA 1 and ARCADIA 2 studies met the co-primary and key secondary endpoints, demonstrating a statistically significant and clinically meaningful treatment effect of nemolizumab in combination with TCS and/or TCI in adult and adolescent patients ≥12 years old with body weight ≥30 kg, who are inadequately controlled by topical therapies and are candidates for systemic therapy. As the 30 mg Q8W maintenance dosing regimen showed similar efficacy to the Q4W dosing regimen, the requested maintenance dose of 30 mg Q8W was considered appropriate.

Prurigo nodularis

The clinical efficacy of nemolizumab in the treatment of adults with moderate-to-severe PN was based primarily on two pivotal Phase 3 studies, RD.06.SPR.202685 (OLYMPIA 1) and RD.06.SPR.203065 (OLYMPIA 2), and supported by a Phase 3 long-term extension (LTE) study RD.06.SPR.202699.

OLYMPIA 1 and OLYMPIA 2 were randomised, double-blind, placebo-controlled, multicentre, parallel-group studies designed to evaluate the safety and efficacy of nemolizumab in patients with PN. The studies were similarly designed except for the treatment duration (24 weeks in OLYMPIA 1 and 16 weeks in OLYMPIA 2).

Key inclusion criteria included male or female patients ≥18 years of age with a clinical diagnosis of PN for at least 6 months, with PN lesions on upper limbs, trunk, and/or lower limbs, at least 20 nodules on the entire body with a bilateral distribution, an IGA score ≥3, and severe pruritus based on the PP NRS of ≥7.0. Key exclusion criteria included body weight <30 kg, chronic pruritus resulting from another active condition other than PN, unilateral lesions of prurigo, history of or current confounding skin condition, chronic obstructive pulmonary disease and/or chronic bronchitis, and uncontrolled asthma.

Each study consisted of 3 periods: screening (up to 4 weeks), a 16-week (OLYMPIA 2) or 24-week (OLYMPIA 1) treatment period, and an 8-week follow-up period.

Patients were randomised in a 2:1 ratio to receive either nemolizumab or placebo. Randomisation was stratified by study site and baseline body weight (<90 kg and ≥90 kg). Patients weighing <90 kg at baseline received either 30 mg nemolizumab (with a 60 mg loading dose at baseline) or placebo Q4W. Patients weighing ≥90 kg at baseline received either 60 mg nemolizumab (no loading dose) or placebo Q4W. Concomitant use of TCS or TCI was not allowed.

The primary efficacy endpoints were the proportion of patients with an improvement of ≥4 from baseline in PP NRS and the proportion of patients with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-grade improvement from baseline), each assessed at Week 16.

The key secondary efficacy endpoints were as follows:
- Proportion of patients with an improvement of PP NRS ≥4 at Week 4
- Proportion of patients with PP NRS <2 at Week 16
- Proportion of patients with an improvement of SD NRS ≥4 at Week 16
- Proportion of patients with an improvement of SD NRS ≥4 at Week 4
- Proportion of patients with PP NRS <2 at Week 4

To control the type I error at 5%, a fixed sequential testing approach was implemented. The 2 primary endpoints were tested first in a predefined order at a 5% significance level, and testing of key secondary endpoints started only if both primary endpoints were successful at a 5% level of significance. The key secondary endpoints were tested in the predefined order, stopping when a non-significant (p>0.05) result occurred.

A total of 286 patients (190 nemolizumab, 96 placebo) and 274 patients (183 nemolizumab, 91 placebo) were randomised in the OLYMPIA 1 and OLYMPIA 2 studies, respectively, and included in the ITT population. Patient demographics and baseline disease characteristics were generally well-balanced between treatment groups in both studies. The majority of patients were White (81.4%) and 8.8% (4.2% in OLYMPIA 1 and 13.5% in OLYMPIA 2) were Asian. More than half of the patients were female (59.6%). The mean age was 55.2 years, and 25.4% of patients were aged >65 years. Patients had moderate-to-severe skin disease based on baseline IGA scores (58.0% had an IGA score of 3 and 42.0% had an IGA score of 4) and baseline weekly average PP NRS (mean 8.4580). The percentage of patients with severe IGA at baseline was higher in the nemolizumab group compared with the placebo group (43.7% vs 35.4%) in OLYMPIA 1 and similar between the nemolizumab and placebo groups (41.0% vs 47.3%) in OLYMPIA 2.

Both studies met the primary endpoints. Nemolizumab was statistically significantly superior to placebo with respect to improvement of ≥4 from baseline in weekly average PP NRS [OLYMPIA 1: 58.4% vs 16.7%; proportion difference: 40.1% (95% CI: 29.4, 50.8); p<0.0001; OLYMPIA 2: 56.3% vs 20.9%; proportion difference: 37.4% (95% CI: 26.3, 48.5); p<0.0001] and IGA success [OLYMPIA 1: 26.3% vs 7.3%; proportion difference: 14.6% (95% CI: 6.7, 22.6); p=0.0025; OLYMPIA 2: 37.7% vs 11.0%; proportion difference: 28.5% (95% CI: 18.8, 38.2); p<0.0001] at Week 16. The treatment effects in subgroups (age, sex, race, ethnicity, region, country, baseline weight, baseline IGA score, history of atopy, and prior systemic treatment for PN) were generally consistent with the results in the overall population.

Both studies also met all the key secondary endpoints (p<0.0001). The proportion of patients with an improvement of ≥4 from baseline in weekly average PP NRS was statistically significantly greater with nemolizumab compared with placebo at Week 4 (OLYMPIA 1: 41.1% vs 6.3%; OLYMPIA 2: 41.0% vs 7.7%). The proportion of patients with a weekly average PP NRS <2 was statistically significantly greater with nemolizumab compared with placebo at Week 4 (OLYMPIA 1: 21.6% vs 1.0%; OLYMPIA 2: 19.7% vs 2.2%) and at Week 16 (OLYMPIA 1: 34.2% vs 4.2%; OLYMPIA 2: 35.0% vs 7.7%). A statistically significantly greater proportion of patients with an improvement of ≥4 from baseline in weekly average SD NRS was observed with nemolizumab compared with placebo at Week 4 (OLYMPIA 1: 31.1% vs 5.2%; OLYMPIA 2: 37.2% vs 9.9%) and at Week 16 (OLYMPIA 1: 50.0% vs 11.5%; OLYMPIA 2: 51.9% vs 20.9%).

Summary of key efficacy results in ITT population (OLYMPIA 1, OLYMPIA 2)

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab (N=190)	**Placebo (N=96)**	**Nemolizumab (N=183)**	**Placebo (N=91)**
Primary endpoints				
Improvement of ≥4 from baseline in PP NRS at Week 16				
n (%)	111 (58.4)	16 (16.7)	103 (56.3)	19 (20.9)
Proportion difference (95% CI)[a]	40.1 (29.4, 50.8)		37.4 (26.3, 48.5)	
p-value[a]	<0.0001		<0.0001	
IGA success at Week 16				
n (%)	50 (26.3)	7 (7.3)	69 (37.7)	10 (11.0)

Proportion difference (95% CI)[a]	14.6 (6.7, 22.6)		28.5 (18.8, 38.2)	
p-value[a]	0.0025		<0.0001	
Key secondary endpoints				
Improvement of ≥4 from baseline in PP NRS at Week 4				
n (%)	78 (41.1)	6 (6.3)	75 (41.0)	7 (7.7)
Proportion difference (95% CI)[a]	31.7 (23.0, 40.4)		33.4 (24.3, 42.4)	
p-value[a]	<0.0001		<0.0001	
PP NRS <2				
Week 4, n (%)	41 (21.6)	1 (1.0)	36 (19.7)	2 (2.2)
Proportion difference (95% CI)[a]	18.7 (12.3, 25.0)		18.8 (12.0, 25.7)	
p-value[a]	<0.0001		<0.0001	
Week 16, n (%)	65 (34.2)	4 (4.2)	64 (35.0)	7 (7.7)
Proportion difference (95% CI)[a]	30.5 (22.3, 38.7)		30.0 (21.3, 38.6)	
p-value[a]	<0.0001		<0.0001	
Improvement of ≥4 from baseline in SD NRS				
Week 4, n (%)	59 (31.1)	5 (5.2)	68 (37.2)	9 (9.9)
Proportion difference (95% CI)[a]	22.7 (14.7, 30.7)		27.9 (18.4, 37.5)	
p-value[a]	<0.0001		<0.0001	
Week 16, n (%)	95 (50.0)	11 (11.5)	95 (51.9)	19 (20.9)
Proportion difference (95% CI)[a]	38.0 (27.8, 48.2)		31.9 (20.7, 43.2)	
p-value[a]	<0.0001		<0.0001	

[a] The proportion differences and the corresponding p-values were based on the Cochran-Mantel-Haenszel test adjusted for the randomisation stratification factors (analysis centre and body weight at randomisation).

The LTE study RD.06.SPR.202699 was an ongoing Phase 3, open-label, multicentre study in patients who had been enrolled in a prior Phase 2a study SPR.115828 or prior Phase 3 pivotal studies (OLYMPIA 1 or OLYMPIA 2). The primary objective was to assess the long-term safety of nemolizumab in patients with PN, with long-term efficacy as the secondary objective.

Based on the available data (N=508), the proportion of patients with an IGA score of 0 or 1 at LTE baseline was 29.3% and further increased to 68.1% at Week 52. The proportion of patients with an improvement of ≥4 in weekly average PP NRS from the baseline of the prior studies was 52.5% at LTE baseline and further increased to 85.5% at Week 52. The proportion of patients with weekly average PP NRS <2 at LTE baseline was 28.3% and further increased to 66.0% at Week 52.

Overall, the OLYMPIA 1 and OLYMPIA 2 studies met the primary and key secondary endpoints, demonstrating a statistically significant and clinically meaningful treatment effect in patients with PN. The LTE study demonstrated continued improvements through Week 52, but the results should be interpreted with caution in the context of an open-label study. Taken together, the results adequately supported the efficacy of nemolizumab in the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy.

D ASSESSMENT OF CLINICAL SAFETY

Atopic dermatitis

The safety data supporting the use of nemolizumab in moderate-to-severe AD were based on the primary safety population, defined as all randomised or enrolled patients who received at least one dose of study drug in the two pivotal Phase 3 studies (ARCADIA 1 and ARCADIA 2) and in the Phase 2 dose-ranging study RD.03.SPR.114322. The primary safety population included 55 patients in the nemolizumab 10 mg Q4W group, 1,192 patients in the nemolizumab 30 mg Q4W group, 57 patients in the nemolizumab 90 mg Q4W group, and 640 patients in the placebo group. This primary safety population included all 176 adolescents 12 to 17 years of age who received nemolizumab 30 mg Q4W in the Initial Period.

The median treatment duration in the Initial Period was 115.0 days for nemolizumab 30 mg Q4W patients and 115.0 days for placebo patients. The median treatment duration in the Maintenance Period was 226.0 days in the nemolizumab 30 mg Q4W to Q4W and nemolizumab 30 mg Q4W to placebo groups, 226.5 days in the placebo group, and 227.0 days in the nemolizumab 30 mg Q4W to Q8W group.

Overview of safety profile (AD)

	Initial Period			Maintenance Period			
	Nemo 30 mg Q4W (N=1,192)	**All nemo (N=1,304)**	**Placebo (N=640)**	**Nemo 30 mg Q4W to Q4W (N=170)**	**Nemo 30 mg Q4W to Q8W (N=167)**	**Nemo 30 mg Q4W to placebo (N=168)**	**Placebo (N=184)**
Treatment-emergent adverse event (TEAE)	566 (47.5%)	660 (50.6%)	306 (47.8%)	91 (53.5%)	90 (53.9%)	98 (58.3%)	92 (50.0%)
Drug-related TEAE	207 (17.4%)	241 (18.5%)	91 (14.2%)	18 (10.6%)	20 (12.0%)	18 (10.7%)	14 (7.6%)
Serious adverse event (SAE)	21 (1.8%)	24 (1.8%)	8 (1.3%)	10 (5.9%)	3 (1.8%)	4 (2.4%)	2 (1.1%)
Drug-related SAE	6 (0.5%)	8 (0.6%)	0	1 (0.6%)	0	1 (0.6%)	0
TEAE leading to study drug withdrawal	31 (2.6%)	41 (3.1%)	20 (3.1%)	4 (2.4%)	5 (3.0%)	5 (3.0%)	4 (2.2%)
TEAE leading to death	0	0	0	0	0	0	0

Nemo=nemolizumab

A total of 566 (47.5%) nemolizumab 30 mg Q4W patients and 306 (47.8%) placebo patients experienced at least one TEAE during the Initial Period. The majority of the TEAEs were mild or moderate in severity. The most common TEAEs occurring with a higher frequency (≥0.5% difference) with nemolizumab compared to placebo were asthma (4.0% vs 3.3%), arthralgia (1.3% vs 0.5%), urticaria (1.1% vs 0.5%), and fatigue (1.0% vs 0.5%). The most common drug-related TEAEs were dermatitis atopic (3.7% vs 2.3%), asthma (1.7% vs 1.7%) and headache (1.3% vs 1.1%).

During the Maintenance Period, the percentage of patients who experienced at least one TEAE ranged from 50.0% (placebo) to 58.3% (nemolizumab Q4W to placebo). The majority of the TEAEs were mild or moderate in severity. The most common TEAEs across treatment groups were COVID-19 (7.6% to 11.3%), dermatitis atopic (6.6% to 10.7%), nasopharyngitis (4.8% to 8.2%), upper respiratory tract infection (2.4% to 6.0%), asthma (2.7% to 3.6%), headache (1.8% to 4.2%), diarrhoea (1.1% to 3.6%), asymptomatic COVID-19 (1.1% to 2.4%), sinusitis

(0% to 2.4%), dyspnoea (0% to 2.4%), and viral upper respiratory tract infection (0.6% to 2.2%). The most common drug-related TEAEs were dermatitis atopic (1.6% to 2.9%) and asthma (1.1% to 1.8%).

A total of 21 (1.8%) nemolizumab 30 mg Q4W patients and 8 (1.3%) placebo patients experienced treatment-emergent SAEs during the Initial Period. The only treatment-emergent SAEs experienced by >1 patient in either group were dermatitis atopic (6 [0.5%] in nemolizumab Q4W vs 3 [0.5%] in placebo) and intervertebral disc protrusion (2 [0.2%] vs 0 [0%]). During the Maintenance Period, no treatment-emergent SAE was experienced by >1 patient in any group.

TEAEs leading to study drug withdrawal were experienced by 31 (2.6%) nemolizumab 30 mg Q4W patients and 20 (3.1%) placebo patients during the Initial Period. TEAEs leading to study drug withdrawal in >1 patient in either group were dermatitis atopic (20 [1.7%] in nemolizumab Q4W vs 19 [3.0%] in placebo) and lymphadenopathy and oedema peripheral (2 [0.2%] nemolizumab Q4W patients each). During the Maintenance Period, the only TEAE leading to study drug withdrawal in >1 patient in any group was dermatitis atopic (2 [1.2%] in nemolizumab Q4W to Q4W, 4 [2.4%] in nemolizumab Q4W to Q8W, 3 [1.8%] in nemolizumab Q4W to placebo, and 4 [2.2%] in placebo).

There were no deaths during the Treatment Period. One (1.8%) nemolizumab 10 mg Q4W patient experienced TEAEs leading to death during the Follow-up Period. The patient experienced pneumonia aspiration on Day 70 and cardio-respiratory arrest on Day 83. The death was not considered related to study drug by the investigator.

The adverse events of special interest (AESIs) included injection-related reactions (IRRs), newly diagnosed asthma or worsening of asthma, infections, and peripheral and facial oedema.

Summary of AESIs (AD)

	Initial Period			Maintenance Period			
	Nemo 30 mg Q4W (N=1,192)	**All nemo (N=1,304)**	**Placebo (N=640)**	**Nemo 30 mg Q4W to Q4W (N=170)**	**Nemo 30 mg Q4W to Q8W (N=167)**	**Nemo 30 mg Q4W to placebo (N=168)**	**Placebo (N=184)**
Any AESI	107 (9.0%)	118 (9.0%)	42 (6.6%)	24 (14.1%)	25 (15.0%)	31 (18.5%)	24 (13.0%)
IRRs	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0
Newly diagnosed asthma or worsening of asthma	51 (4.3%)	62 (4.8%)	20 (3.1%)	7 (4.1%)	6 (3.6%)	4 (2.4%)	5 (2.7%)
Infections	40 (3.4%)	40 (3.1%)	22 (3.4%)	16 (9.4%)	17 (10.2%)	25 (14.9%)	21 (11.4%)
Peripheral and facial oedema	19 (1.6%)	19 (1.5%)	2 (0.3%)	1 (0.6%)	2 (1.2%)	3 (1.8%)	0

Nemo=nemolizumab

IRRs, which included anaphylactic reactions, acute allergic reactions requiring treatment, and severe injection site reactions with a duration >24 hours, were considered AESIs. One (<0.1%) nemolizumab 30 mg Q4W patient experienced an IRR (severe injection site pain which lasted

>24 hours) during the Initial Period. No patient experienced an IRR during the Maintenance Period.

In the Initial Period, 4.3% of nemolizumab Q4W patients and 3.1% of placebo patients experienced an AESI meeting the protocol definition of newly diagnosed asthma or worsening of asthma[1]. Study drug-related AESIs of newly diagnosed asthma or worsening of asthma were reported in 1.6% of nemolizumab Q4W patients and 1.9% of placebo patients. There were no serious AESIs of newly diagnosed asthma or worsening of asthma in the nemolizumab Q4W group. During the Maintenance Period, 4.1% of nemolizumab Q4W to Q4W patients, 3.6% of nemolizumab Q4W to Q8W patients, 2.4% of nemolizumab Q4W to placebo patients, and 2.7% of placebo patients experienced an AESI of newly diagnosed asthma or worsening of asthma. There was 1 (0.6%) nemolizumab Q4W to Q4W patient who experienced a serious AESI of newly diagnosed asthma or worsening of asthma. The available data, as supported by the exposure-safety analysis, did not suggest an increased risk of asthma associated with nemolizumab use.

During the Initial Period, 3.4% of nemolizumab Q4W patients and 3.4% of placebo patients had at least one event that qualified as an AESI of infection[2]. During the Maintenance Period, AESIs of infection were reported in 9.4% of nemolizumab Q4W to Q4W patients, 10.2% of nemolizumab Q4W to Q8W patients, 14.9% of nemolizumab Q4W to placebo patients and 11.4% of placebo patients. Most of the AESIs of infection were COVID-19 related. Infections other than COVID-19 that met the AESI criteria were not common and were mostly non-serious. Thus, there was no evidence of increased risk of serious or severe infections or infections requiring prolonged treatment in association with the use of nemolizumab.

In the Initial Period, 19 (1.6%) nemolizumab Q4W patients and 2 (0.3%) placebo patients experienced AESIs of peripheral and facial oedema. Approximately half had events that were considered drug-related (0.8% vs 0.3%). The majority of drug-related AESIs of peripheral and facial oedema were non-serious, considered mild or moderate in severity, and did not lead to study drug withdrawal or study discontinuation; all events resolved. In the Maintenance Period, AESIs of peripheral and facial oedema were reported in 1 (0.6%) nemolizumab Q4W to Q4W patient, 2 (1.2%) nemolizumab Q4W to Q8W patients, and 3 (1.8%) nemolizumab Q4W to placebo patients. No patient experienced a serious AESI of peripheral and facial oedema. The incidence of this adverse event (AE) has been included in the package insert.

In the analysis by age group, adolescents 12 to 17 years of age treated with nemolizumab had similar or lower frequencies of TEAEs (36.4% vs 50.3%), SAEs (1.7% vs 1.8%) and TEAEs leading to study drug withdrawal (1.1% vs 3.0%) during the Initial Period compared with patients 18 to 65 years of age. Among the common TEAEs, only nasopharyngitis (5.1% vs 3.4%) and upper respiratory tract infection (2.8% vs 1.5%) occurred with higher frequencies in adolescents than in patients 18 to 65 years of age.

In terms of immunogenicity, the incidence of treatment-emergent anti-drug antibodies (ADAs) in the pivotal and LTE studies up to 128 weeks was 11.2%. Of these patients, 6.6% had persistent ADAs, 4.3% had transient ADAs and 0.3% had treatment-boosted ADAs.

[1] Newly diagnosed or worsening of asthma AESIs were reported when: (a) patients with a medical history of asthma had an asthma control test (ACT) score ≤19, peak expiratory flow (PEF) <80% of the predicted value, or unexpected worsening of asthma was observed or reported, or (b) patients without a medical history of asthma had signs and/or symptoms suggestive of asthma observed or reported or respiratory assessments (e.g., examination, PEF) suggested a decline in the patient's respiratory health.
[2] AESIs of infections included any severe infection, any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for >2 weeks, and any confirmed or suspected COVID-19 infection.

Neutralising ADAs were observed in 0.5% of the patients. ADA status had no significant impact on the PK, efficacy and safety of nemolizumab.

Overall, the most common TEAEs occurring with higher frequency with nemolizumab compared to placebo were asthma, arthralgia, urticaria, and fatigue. Among AESIs, peripheral and facial oedema occurred more frequently with nemolizumab; however, these events were generally mild to moderate in severity. IRRs were rare, with only one patient experiencing such an event. The safety profile of nemolizumab was considered acceptable for the intended population with moderate-to-severe AD.

Prurigo nodularis

The safety data supporting the use of nemolizumab in moderate-to-severe PN were based on the primary safety population, defined as all randomised or enrolled patients who received at least one dose of study drug in the two pivotal Phase 3 studies (OLYMPIA 1 and OLYMPIA 2). The primary safety population included 370 patients in the nemolizumab group and 186 patients in the placebo group. The median treatment duration was 120.0 days for nemolizumab patients and 117.5 days for placebo patients.

Overview of safety profile (PN)

	Nemolizumab (N=370)	**Placebo (N=186)**
TEAE	246 (66.5%)	111 (59.7%)
Drug-related TEAE	92 (24.9%)	34 (18.3%)
SAE	25 (6.8%)	16 (8.6%)
Drug-related SAE	3 (0.8%)	2 (1.1%)
TEAE leading to study drug withdrawal	15 (4.1%)	5 (2.7%)
TEAE leading to death	0	1 (0.5%)

A total of 246 (66.5%) nemolizumab patients and 111 (59.7%) placebo patients experienced at least one TEAE. The majority of the TEAEs were mild or moderate in severity. The most common TEAEs occurring with a higher frequency (≥0.5% difference) with nemolizumab compared to placebo were headache (6.8% vs 3.2%), dermatitis atopic (4.6% vs 0.5%), eczema (3.8% vs 2.2%), fatigue (3.8% vs 2.7%), eczema nummular (3.5% vs 0), and back pain (2.2% vs 1.1%). The most common drug-related TEAEs were neurodermatitis (1.1% vs 2.7%), dyspnoea (1.4% vs 2.2%), dermatitis atopic (3.0% vs 0.5%), headache (2.7% vs 0.5%), asthma (0.8% vs 2.2%) and eczema nummular (2.7% vs 0%).

Treatment-emergent SAEs were experienced by 25 (6.8%) nemolizumab patients and 16 (8.6%) placebo patients. Treatment-emergent SAEs experienced by >1 patient in either group were neurodermatitis (4 [1.1%] vs 2 [1.1%]), pemphigoid (3 [0.8%] vs 0), osteoarthritis (2 [0.5%] vs 1 [0.5%]), and acarodermatitis (2 [0.5%] vs 0). There were no deaths reported in the nemolizumab group.

TEAEs leading to study drug withdrawal were experienced by 15 (4.1%) nemolizumab patients and 5 (2.7%) placebo patients. TEAEs leading to study drug withdrawal in >1 patient in either group were pemphigoid (3 [0.8%] vs 0) and dermatitis atopic (2 [0.5%] vs 1 [0.5%]).

Summary of AESIs (PN)

	Nemolizumab (N=370)	**Placebo (N=186)**
Any AESI	53 (14.3%)	28 (15.1%)
IRRs	2 (0.5%)	0
Newly diagnosed asthma or worsening	12 (3.2%)	5 (2.7%)

of asthma		
Infections	31 (8.4%)	22 (11.8%)
Peripheral and facial oedema	11 (3.0%)	3 (1.6%)

In terms of AESIs, two (0.5%) nemolizumab patients experienced an IRR. One patient experienced an IRR of dermatitis allergic while the other patient experienced an IRR of drug eruption.

Twelve (3.2%) nemolizumab patients and 5 (2.7%) placebo patients experienced an AESI meeting the protocol definition of newly diagnosed asthma or worsening of asthma. Events were considered study drug-related in 4 (1.1%) nemolizumab patients and 4 (2.2%) placebo patients. All study drug-related AESIs of newly diagnosed asthma or worsening of asthma were non-serious, considered mild or moderate in severity, and did not result in study drug withdrawal or study discontinuation. The available data did not indicate an increased risk of asthma with nemolizumab use.

A total of 31 (8.4%) nemolizumab patients and 22 (11.8%) placebo patients had at least one event that qualified as an AESI of infection. Most of the AESIs of infection were COVID-19-related. There were no non-COVID-19 related events occurring in >1 patient. Serious AESIs of infection were reported in 3 (0.8%) nemolizumab patients and 3 (1.6%) placebo patients. The events in the nemolizumab group included severe campylobacter colitis in 1 patient, severe pneumonia and severe pneumococcal sepsis in 1 patient, and mild urinary tract infection in 1 patient. The data did not suggest an increased risk of serious or severe infections or infections requiring prolonged treatment.

Eleven (3.0%) nemolizumab patients and 3 (1.6%) placebo patients experienced AESIs of peripheral and facial oedema. All events were non-serious and either mild or moderate in severity. This AE has been reflected in the package insert.

With regard to immunogenicity, the incidence of treatment-emergent ADAs across the pivotal and LTE studies up to 116 weeks was 12.8%. Of these, 8.9% had persistent ADAs, 3.4% had transient ADAs and 2 (0.6%) patients had treatment-boosted ADAs. Neutralising ADAs were detected in 3.4% of the patients. ADA presence was not associated with significant impact on the PK, efficacy and safety of nemolizumab.

Overall, the majority of TEAEs were mild to moderate in severity. The most common TEAEs occurring at a higher frequency with nemolizumab compared to placebo were headache, dermatitis atopic, eczema, fatigue, eczema nummular, and back pain. Among AESIs, peripheral and facial oedema occurred more frequently with nemolizumab compared to placebo, while injection-related reactions were uncommon. The safety profile of nemolizumab was considered acceptable for patients with moderate-to-severe PN.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Atopic dermatitis

AD is a chronic, relapsing inflammatory skin disease characterised by intense pruritus and eczematous lesions. For moderate-to-severe AD not adequately controlled with topical therapies, options include phototherapy and systemic treatments such as biologics (e.g., dupilumab) and JAK inhibitors.

The efficacy of nemolizumab in moderate-to-severe AD has been adequately demonstrated in two pivotal Phase 3 studies (ARCADIA 1 and ARCADIA 2) in patients aged 12 years and older with inadequate response to topical therapies. Both studies met the co-primary endpoints, demonstrating statistically significant and clinically meaningful improvements in IGA and EASI-75 response rates at Week 16 for nemolizumab compared to placebo (treatment differences of 11.5%–12.2% and 12.5%–14.9%, respectively). Nemolizumab also showed significant improvements in pruritus, with significantly greater proportions of patients achieving an improvement of PP NRS ≥4 starting at Week 1. Other key secondary endpoints were also met, including significant improvements in sleep disturbance (SD NRS improvement ≥4), proportion of patients achieving PP NRS <2, and combined endpoints of IGA success or EASI-75 with pruritus improvement. Efficacy was maintained through 48 weeks with both Q4W and Q8W maintenance dosing regimens. The requested maintenance dose of 30 mg Q8W was supported as both Q4W and Q8W regimens showed similar efficacy.

The safety profile of nemolizumab was considered acceptable with predominantly mild to moderate TEAEs. TEAEs reported more commonly with nemolizumab compared to placebo included asthma, arthralgia, urticaria, and fatigue.

Overall, the benefit-risk profile of nemolizumab in combination with TCS and/or TCI was considered favourable for the treatment of moderate-to-severe AD in adult and adolescent patients ≥12 years old with body weight ≥30 kg, who are inadequately controlled by topical therapies and are candidates for systemic therapy.

Prurigo nodularis

PN is a chronic, inflammatory skin condition characterised by severely pruritic nodules. Treatment options for PN are limited, with current available systemic therapy primarily based on dupilumab.

The efficacy of nemolizumab in moderate-to-severe PN was demonstrated in two pivotal Phase 3 studies (OLYMPIA 1 and OLYMPIA 2) in adult patients. Both studies met the co-primary endpoints, demonstrating statistically significant and clinically meaningful improvements in the proportion of patients with an improvement of ≥4 from baseline in PP NRS and IGA success at Week 16 for nemolizumab compared to placebo (treatment differences of 37.4%–40.1% and 14.6%–28.5%, respectively). Nemolizumab showed significant improvements in pruritus, with significantly greater proportions of patients achieving an improvement of PP NRS ≥4 starting at Week 4. The studies also met the key secondary endpoints, including significant improvements in sleep disturbance (SD NRS improvement ≥4) and proportion of patients achieving PP NRS <2. Efficacy was maintained through 52 weeks in the long-term extension study, with continued improvements observed in IGA scores and pruritus measures.

Nemolizumab demonstrated an acceptable safety profile with most TEAEs being mild to moderate in severity. Common TEAEs reported more frequently with nemolizumab than placebo were headache, dermatitis atopic, eczema, fatigue, eczema nummular, and back pain.

Overall, the benefit-risk profile of nemolizumab was considered favourable for the treatment of adults with moderate-to-severe PN who are candidates for systemic therapy.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Nemluvio for the following indications was deemed favourable and approval of the product registration was granted on 17 March 2025:

- Treatment of moderate-to-severe AD in combination with TCS and/or TCI in adult and adolescent patients ≥12 years old with body weight of at least 30 kg, who are inadequately controlled by topical therapies and are candidates for systemic therapy; and
- Treatment of adults with moderate-to-severe PN who are candidates for systemic therapy.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
Nemluvio 30 mg powder and solvent for solution for injection in pre-filled syringe

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
Each single-use pre-filled pen contains 30 mg of nemolizumab per 0.49 ml dose following reconstitution.

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled syringe
Each single-use pre-filled syringe contains 30 mg of nemolizumab per 0.49 ml dose following reconstitution.

Nemolizumab, an interleukin-31 receptor alpha (IL-31RA) antagonist, is a humanized monoclonal modified immunoglobulin G (IgG) antibody targeting IL-31RA. Nemolizumab has a molecular weight of 144.153 kDa. Nemolizumab is produced by recombinant DNA technology in Chinese Hamster Ovary cells.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection

Powder: lyophilised white powder.
Solvent: A clear, colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Atopic dermatitis (AD)

Nemluvio is indicated for the treatment of moderate-to-severe atopic dermatitis in combination with topical corticosteroids (TCS) and/or topical calcineurin inhibitors (TCI) in adult and adolescent patients ≥ 12 years old with body weight of at least 30 kg, who are inadequately controlled by topical therapies and are candidates for systemic therapy.

Prurigo nodularis (PN)

Nemluvio is indicated for the treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

4.2 Posology and method of administration

Posology

Atopic dermatitis (AD)

The recommended dosage of Nemluvio is:
- An initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W)
- After 16 weeks of treatment, for patients who achieve clinical response, the recommended maintenance dose of Nemluvio is 30 mg every 8 weeks (Q8W).

Concomitant Topical Therapies:

Use Nemluvio with TCS and/or TCI. TCI should be reserved for problem areas only, such as the face, neck, intertriginous and genital areas. Any use of topical therapies should be tapered and subsequently discontinued when the disease has sufficiently improved.

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for atopic dermatitis.

Prurigo nodularis (PN)

The recommended dose of Nemluvio for patients weighing < 90 kg is an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W).

The recommended dose of Nemluvio for patients weighing ≥ 90 kg is an initial dose of 60 mg dose (two 30 mg injections), followed by 60 mg given every 4 weeks (Q4W).

Consideration should be given to discontinuing treatment in patients who have shown no response after 16 weeks of treatment for prurigo nodularis.

Missed dose

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Special populations

Elderly (≥ 65 years)
No dose adjustment is recommended for elderly patients (see section 5.2).

Hepatic and Renal impairment
No dose adjustment is needed in patients with mild to moderate hepatic or renal impairment (see section 5.2). No recommendation can be made in patients with severe hepatic or renal impairment due to lack of data.

Body weight
No dose adjustment for body weight is recommended for patients 12 years of age and older with atopic dermatitis (see section 5.2).

For patients with prurigo nodularis and with body weight ≥ 90 kg, the 60 mg dose (two 30 mg injections) is recommended (see section 5.2).

Paediatric population
The safety and efficacy of Nemluvio in children with moderate-to-severe atopic dermatitis younger than 12 years old have not yet been established.

The safety and efficacy of Nemluvio have not been established in paediatric patients below the age of 18 years with prurigo nodularis.

Method of administration

Subcutaneous use.

Administer subcutaneous injection into the front upper thighs or abdomen avoiding the 5 cm area around the navel. Injection into the upper arm should only be performed by a caregiver or healthcare professional.

For subsequent doses, it is recommended to rotate the injection site with each dose. Nemluvio should not be injected into skin that is tender, inflamed, swollen, damaged or has bruises, scars or open wounds.

Nemluvio is intended for use under the guidance of a healthcare professional. A patient may self-inject Nemluvio or the patient's caregiver may administer Nemluvio if their healthcare professional determines that this is appropriate. Prior to first injection, patients and/or caregivers should be given proper instructions for preparation and administration of Nemluvio according to the instructions for use at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance(s) or to any of the excipients listed in section 6.1

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
If a systemic hypersensitivity reaction (immediate or delayed) occurs, administration of Nemluvio should be discontinued and appropriate therapy initiated.

Vaccinations
Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines prior to initiating treatment with Nemluvio. Avoid use of live vaccines in patients treated with Nemluvio. It is unknown if administration of live vaccines during Nemluvio treatment will impact the safety or efficacy of these vaccines. No data are available on the response to non-live vaccines.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There is a limited amount of data on the use of Nemluvio in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to fetal toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of nemolizumab during pregnancy.

Breast-feeding

There are no data on the presence or transfer of Nemluvio in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Nemluvio and any potential adverse effects on the breastfed child from Nemluvio or from the underlying maternal condition.

Fertility

Animal studies showed no impairment of fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Nemluvio has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reaction in patients with atopic dermatitis is urticaria. The most common adverse reactions in patients with prurigo nodularis are headache, dermatitis atopic, eczema and eczema nummular.
Uncommon cases of hypersensitivity reactions were reported in both indications (see section 4.4).

Tabulated list of adverse reactions

The Nemluvio safety data presented in Table 1 were evaluated in a pool of three randomized, placebo-controlled trials in subjects with atopic dermatitis (1192 patients receiving Nemluvio and 640 patients receiving placebo), and two randomized, placebo-controlled trials in subjects with prurigo nodularis (370 patients receiving Nemluvio and 186 patients receiving placebo).

Listed in Table 1 are adverse reactions observed in clinical trials presented by system organ class and frequency, using the following categories: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 1: List of adverse reactions

MedDRA System Organ Class	Frequency	Adverse reactions
Nervous system disorders	Common	Headache (incl. tension headache)*
Skin and subcutaneous tissue disorders	Common	Urticaria† Dermatitis atopic*, Eczema*, Eczema nummular*
	Uncommon	Angioedema*
General disorders and administration site conditions	Uncommon	Injection site reactions (includes erythema, pruritus, pain†, irritation†, bruising*)
	Rare	Injection site oedema†

†Occurred in atopic dermatitis studies
*Occurred in prurigo nodularis studies

In atopic dermatitis, the safety profile of Nemluvio through Week 52 in the open-label trial (ARCADIA LTE) was generally consistent with the safety profile observed at Week 16.

In prurigo nodularis, the safety profile of Nemluvio through Week 52 in the open-label trial (OLYMPIA LTE) was generally consistent with the safety profile observed at Week 16 and at Week 24.

Description of selected adverse reactions

Hypersensitivity
Type 1 hypersensitivity reactions (Ig-E mediated reactions) were reported in patients treated with Nemluvio in atopic dermatitis and prurigo nodularis. These included mild urticaria and one report of mild facial (peri-ocular) angioedema (0.3%) that did not lead to discontinuation of treatment. There were no reports of anaphylactic shock or serum-sickness.

Injections site reactions
The incidence of injection site reactions during the initial period was low in patients with atopic dermatitis treated either with Nemluvio (1.3% subjects) or placebo (1.1% subjects); during the maintenance period, the incidence remained low with Nemluvio Q4W (0.6%), Nemluvio Q8W (0%) and placebo (0.5%).

In patients with prurigo nodularis, the incidence of injection site reactions was low when treated either with Nemluvio (1.1%) or placebo (1.6%). There were no severe injection site reactions.

For both indications, none of the reactions led to discontinuation of treatment.

Peripheral and facial oedema
In patients with atopic dermatitis and prurigo nodularis, peripheral and facial oedema were reported more frequently in patients treated with Nemluvio (1.6% and 3.0%) than in patients treated with placebo (0.3% and 1.6%). The information currently available on peripheral and facial oedema is insufficient to establish a causal relationship with Nemluvio.

Headache
In patients with prurigo nodularis, headache was more frequently reported in Nemluvio-treated patients (7.0%) compared to patients treated with placebo (3.6%). Headache was more frequently observed in female patients in both groups. In the Nemluvio group, headache was mostly mild or moderate in severity and did not lead to discontinuation of treatment.

Eczematous reactions
In patients with prurigo nodularis, eczematous reactions such as dermatitis atopic, eczema nummular or eczema were more frequently reported in Nemluvio-treated patients compared to patients treated with placebo: dermatitis atopic (4.6% subjects versus 0.5% subject respectively), eczema (3.8% subjects versus 2.2% subjects respectively) and eczema nummular (3.5% subjects versus 0% subjects respectively). These eczematous reactions were mild or moderate in severity. Dermatitis atopic led to Nemluvio discontinuation in 2 (0.5%) patients. No event of eczema nummular or eczema led to study discontinuation.

Immunogenicity
As with all therapeutic proteins, there is a potential for immunogenicity with Nemluvio.

The observed incidence of anti-drug antibodies is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the trials described below with the incidence of anti-drug antibodies in other trials, including those of nemolizumab.

Anti-Drug-Antibodies (ADA) responses were not generally associated with impact on nemolizumab exposure, safety, or efficacy.

In the Phase 3 AD pivotal trials (ARCADIA 1, ARCADIA 2) and ARCADIA LTE trial up to 128 weeks, the incidence of treatment-emergent ADAs was 11.2%; neutralizing antibodies were seen in 0.5% of subjects.

In the Phase 3 PN pivotal trials (OLYMPIA 1, OLYMPIA 2) and OLYMPIA LTE trial up to 116 weeks, the incidence of treatment-emergent ADAs was 12.8%; neutralizing antibodies were seen in 3.5% of subjects.

Paediatric population

Atopic dermatitis

Adolescents (12 to 17 years of age)
The safety of Nemluvio was assessed in 176 paediatric subjects 12 to 17 years of age with moderate-to-severe atopic dermatitis enrolled in the ARCADIA 1 and ARCADIA 2 trials. The safety profile of Nemluvio in these subjects through Week 16 was similar to the safety profile seen in adults with atopic dermatitis.

The safety profile of Nemluvio in paediatric subjects followed through Week 48 was similar to the safety profile observed at Week 16. The long-term safety profile of Nemluvio in paediatric subjects 12 to 17 years of age was consistent with that seen in adults with atopic dermatitis (ARCADIA LTE).

4.9 Overdose

There is no specific treatment for Nemluvio overdose. In the event of overdosage, monitor the patient for any signs or symptoms of adverse reactions and institute appropriate symptomatic treatment immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other dermatological preparations, agents for dermatitis, excluding corticosteroids, ATC code: D11AH12

Mechanism of action

Nemolizumab is a humanized monoclonal antibody of the IgG2 subclass that inhibits IL-31 signaling by binding selectively to IL-31RA. IL-31 is a neuroimmune cytokine that drives pruritus and inflammation, which are important pathophysiological components of AD and PN. IL-31 has an additional barrier dysfunction effect in AD, and epidermal differentiation and profibrotic effect in PN. Multiple cell types express IL-31RA and are activated by IL-31. Those involved in the pathophysiology of AD and PN include immune cells (e.g., mononuclear phagocytes, granulocytes) and structural cells (e.g., neurons, fibroblasts, keratinocytes). Blocking IL-31RA with nemolizumab ameliorates pruritus and inhibits inflammatory responses in both AD and PN. Additionally, nemolizumab restores barrier integrity in AD and normalizes epidermal differentiation by blocking profibrotic processes in PN. The mechanism of action of nemolizumab has not been definitively established.

Pharmacodynamic effects

In exploratory biomarker studies conducted in the Phase 3 program, nemolizumab was found to modulate gene expression related to the pathophysiology of atopic dermatitis, with a primary impact on immune system processes, by decreasing the inflammatory and proliferative profile of specific immune cells (T-cells and monocytes/macrophages) without leading to immunosuppression.

In prurigo nodularis, nemolizumab was found to modulate molecular processes related to the pathophysiology of prurigo nodularis, with impact on pruritus, inflammation, epidermal differentiation and fibrosis.

Clinical efficacy and safety in atopic dermatitis

Adults and adolescents with atopic dermatitis

The efficacy and safety of Nemluvio with concomitant topical background therapy was evaluated in two randomized, double-blind, placebo-controlled pivotal studies (ARCADIA 1 and ARCADIA 2) that enrolled a total of 1728 subjects 12 years of age and older with moderate-to-severe atopic dermatitis not adequately controlled by topical treatments. Patients with uncontrolled asthma were excluded from the studies and no data with Nemluvio are available in this population. Disease severity was defined by an Investigator's Global Assessment (IGA) score of 3 (moderate) and 4 (severe) in the overall assessment of atopic dermatitis, an Eczema Area and Severity Index (EASI) score of ≥16, a minimum body surface area (BSA) involvement of ≥10%, and a Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥ 4.

Subjects in the studies received initial subcutaneous injections of either Nemluvio 60 mg, followed by 30 mg injections every 4 weeks (Q4W), or matching placebo. Concomitant low and/ or medium potency TCS and/or TCI were administered both in Nemluvio and placebo groups for at least 14 days prior to baseline and continued during the trial. Based on disease activity, these concomitant therapies could be tapered and/or discontinued at investigator discretion.

After 16 weeks, subjects achieving either EASI-75 or IGA success continued into the trial maintenance period for another 32 weeks to evaluate the maintenance of response achieved at Week 16. Nemluvio responders were re-randomized to either Nemluvio 30 mg every 4 weeks, Nemluvio 30 mg every 8 weeks or placebo every 4 weeks (all groups continued background TCS/TCI). Subjects randomized to placebo in the initial treatment period who achieved the same clinical response at Week 16 continued to receive placebo every 4 weeks. Non-responders at Week 16, subjects who lost clinical response during the maintenance period and subjects who completed maintenance period had the opportunity to enrol into the open-label trial (ARCADIA LTE) and receive treatment with Nemluvio 30 mg every 4 weeks up to 200 weeks.

Endpoints

Both ARCADIA 1 and ARCADIA 2 assessed the primary endpoints of:

- Proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-point reduction from baseline) at Week 16
- Proportion of subjects with EASI-75 (≥75% improvement in EASI from baseline) at Week 16

Key secondary endpoints included PP NRS improvement ≥4 from baseline at Weeks 1, 2, 4 and 16, PP NRS <2 at Week 4 and Week 16, Sleep Disturbance Numeric Rating Scale (SD NRS) improvement ≥4 from baseline at Week 16, subjects with both EASI-75 and PP NRS improvement ≥4 from baseline at Week 16, and subjects with both IGA success and PP NRS improvement ≥4 from baseline at Week 16. Other secondary endpoints included change from baseline to week 16 in PP NRS, SD NRS, AD-associated pain frequency and intensity and Dermatology Life Quality Index (DLQI).

Baseline characteristics

In these studies, at baseline, 51.0% of subjects were male, 79.9% were White, and 15.4% of subjects were 12-17 years of age. 70% of subjects had a baseline IGA score of 3 (moderate AD), and 30% of subjects had a baseline IGA score of 4 (severe AD). The mean baseline EASI score was 27.5, the baseline weekly average PP NRS was 7.1 (severe itch), baseline weekly average SD NRS was 5.8 and the mean baseline DLQI was 15.0. Overall, 63.3% of patients received other previous systemic treatments for atopic dermatitis.

Clinical Response

ARCADIA 1 and ARCADIA 2 – Adults and Adolescents - induction period, week 0 to week 16

Nemluvio was statistically significantly superior to placebo with respect to skin-related co-primary endpoints IGA success and EASI-75 over 16 weeks (Table 2).

Table 2 – Efficacy Results of Nemluvio (30 mg Q4W) with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16

	ARCADIA 1		ARCADIA 2	
	Nemluvio + TCS/ TCI	Placebo + TCS/ TCI	Nemluvio + TCS/ TCI	Placebo + TCS/ TCI
Number of subjects randomized and dosed (Baseline PP NRS ≥4)	620	321	522	265

% of subjects with IGA 0 or 1[a]	35.6[#]	24.6	37.7[#]	26.0
% of subjects with EASI-75[a]	43.5*	29.0	42.1[#]	30.2
Number of subjects with severe pruritus (Baseline PP NRS≥7)	406	210	316	164
% of subjects with IGA 0 or 1[a]	35.5[#]	21.4	36.7[#]	22.0
% of subjects with EASI-75[a]	41.6*	23.8	41.1[#]	25.0

[a] Subjects who received rescue treatment or with missing data were considered as non-responders

*p-value <0.0001, [#]p-value <0.001

Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Figure 1 and Figure 2 represent the proportion of subjects with IGA success and EASI-75 from baseline to Week 16 in ARCADIA 1 and ARCADIA 2.

Figure 1 – Proportion of subjects with IGA success from baseline to Week 16 in ARCADIA 1 and ARCADIA 2

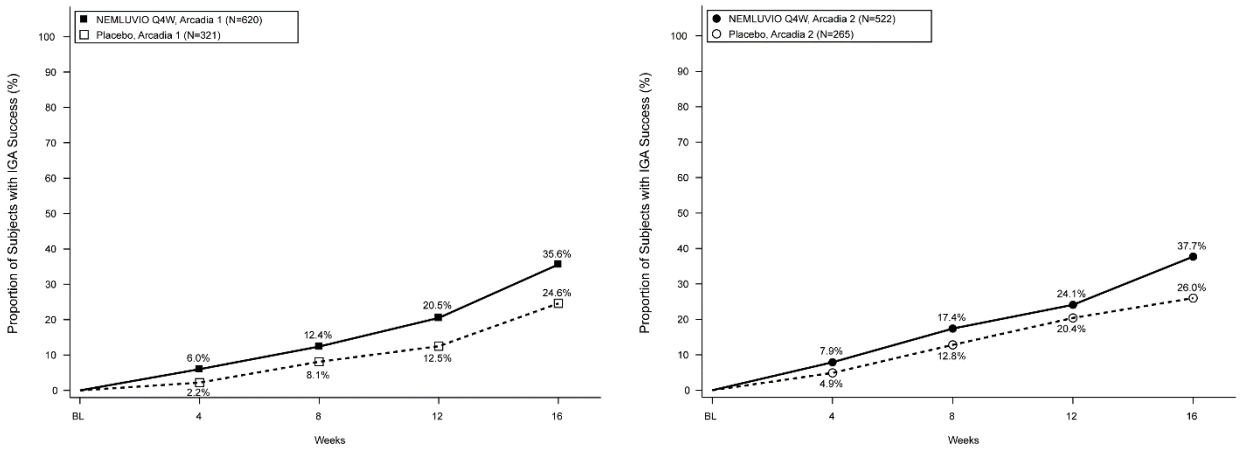
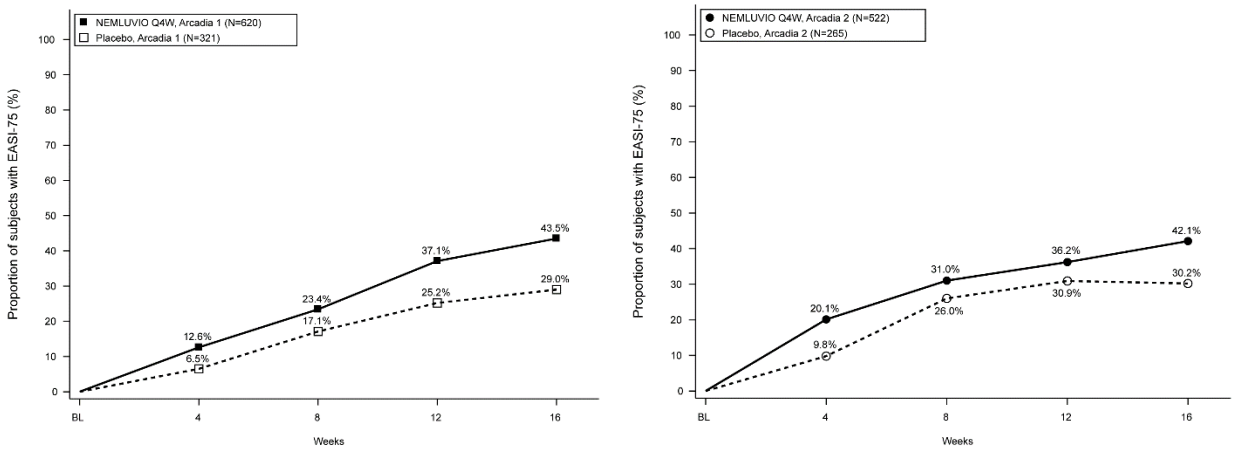


Figure 2 – Proportion of subjects with EASI-75 from baseline to week 16 in ARCADIA 1 and ARCADIA 2



Significant improvement in pruritus for patients treated with Nemluvio in ARCADIA 1 and ARCADIA 2 compared to placebo based on PP NRS improvements ≥4 and PP NRS percent change from baseline was observed starting at Week 1 and was maintained up to Week 16 (Table 3, Figure 3a-3b and Figure 4a-4b).

Table 3 – Efficacy results on Itch for Nemluvio with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 up to Week 16

	ARCADIA 1		ARCADIA 2	
	Nemluvio + TCS/TCI	Placebo + TCS/TCI	Nemluvio + TCS/ TCI	Placebo + TCS/ TCI
Number of subjects randomized and dosed (Baseline PP NRS ≥4)[a]	620	321	522	265
% of subjects with PP NRS improvement ≥4[a]				
At Week 1	4.7[§]	1.2	6.7*	0.4
At Week 2	17.7*	3.1	16.9*	1.9
At Week 4	27.4*	6.5	26.1*	5.3
At Week 16	42.7*	17.8	41.0*	18.1
% of subjects with PP NRS <2[a]				
At Week 4	16.0*	3.7	15.9*	2.6
At Week 16	30.6*	11.2	28.4*	11.3
Mean change from baseline (%) in PP NRS				
At Week 16	-56.1*	-30.6	-55.6*	-30.3
Number of subjects with severe pruritus (Baseline PP NRS≥7)	406	210	316	164
% of subjects with PP NRS improvement ≥4[a]				
At Week 1	6.2[§]	1.9	8.5[#]	0.6
At Week 2	20.7*	3.8	19.3*	3.0
At Week 4	28.3*	7.1	30.4*	7.9
At Week 16	46.1*	18.6	48.4*	21.3
% of subjects with PP NRS <2[a]				
At Week 4	12.6*	2.9	11.1*	1.2
At Week 16	27.8*	7.6	26.9*	8.5
Mean change from baseline (%) in PP NRS				
At Week 16	-55.5*	-27.9	-57.0*	-30.2

[a] Subjects who received rescue treatment or with missing data were considered as non-responders

*p-value <0.0001, [#]p-value <0.001, [§]p-value <0.05

Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Figure 3a –Proportion of subject with PP NRS improvement of ≥4 from baseline up to Week 16 in ARCADIA 1

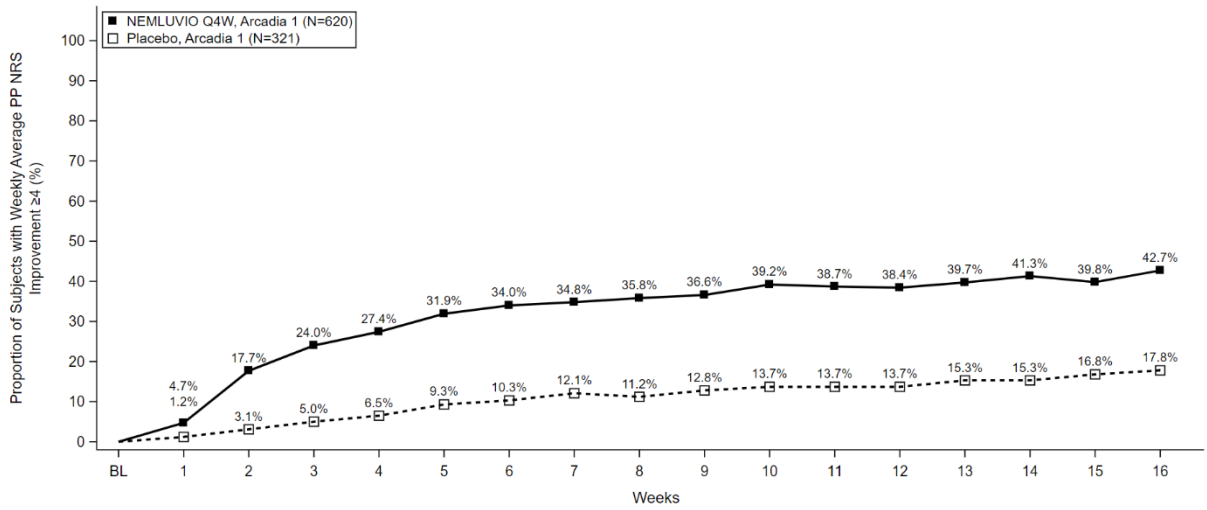


Figure 3b – Proportion of subject with PP NRS improvement of ≥4 from baseline up to Week 16 in ARCADIA 2

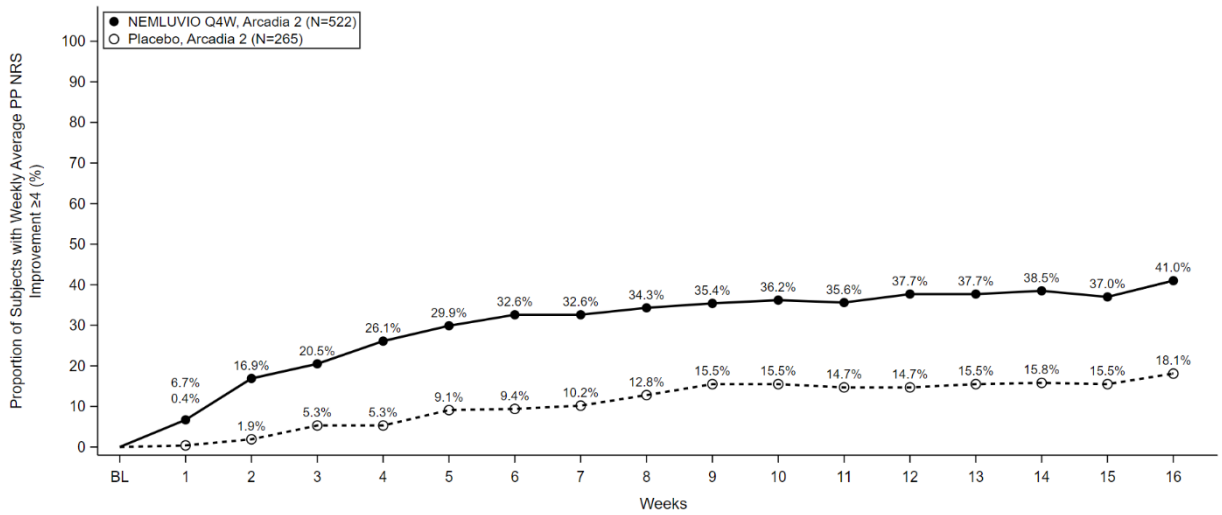


Figure 4a – Mean percent change from baseline in PP NRS up to Week 16 in ARCADIA 1

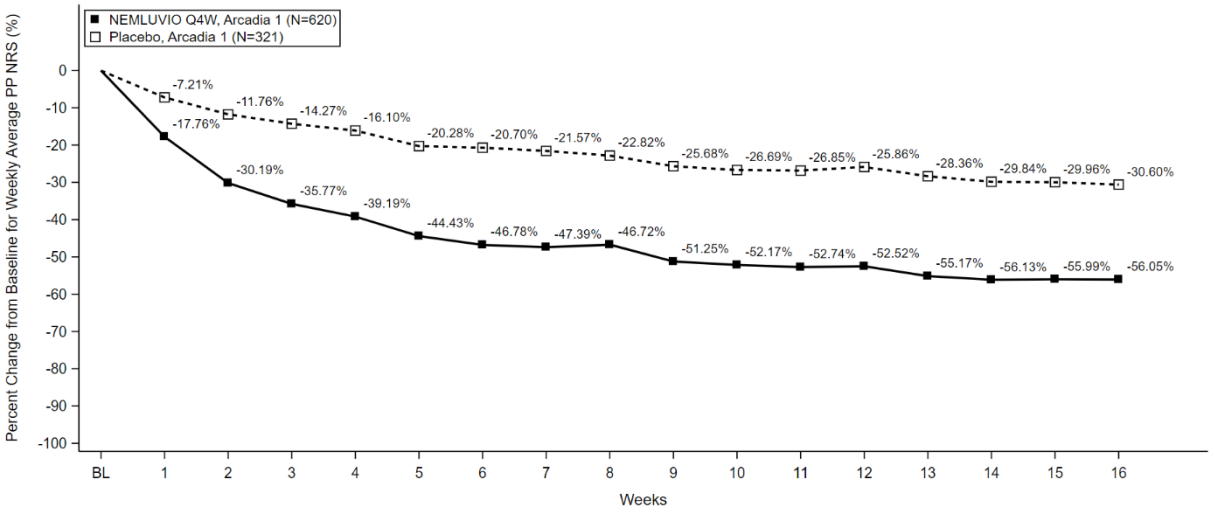
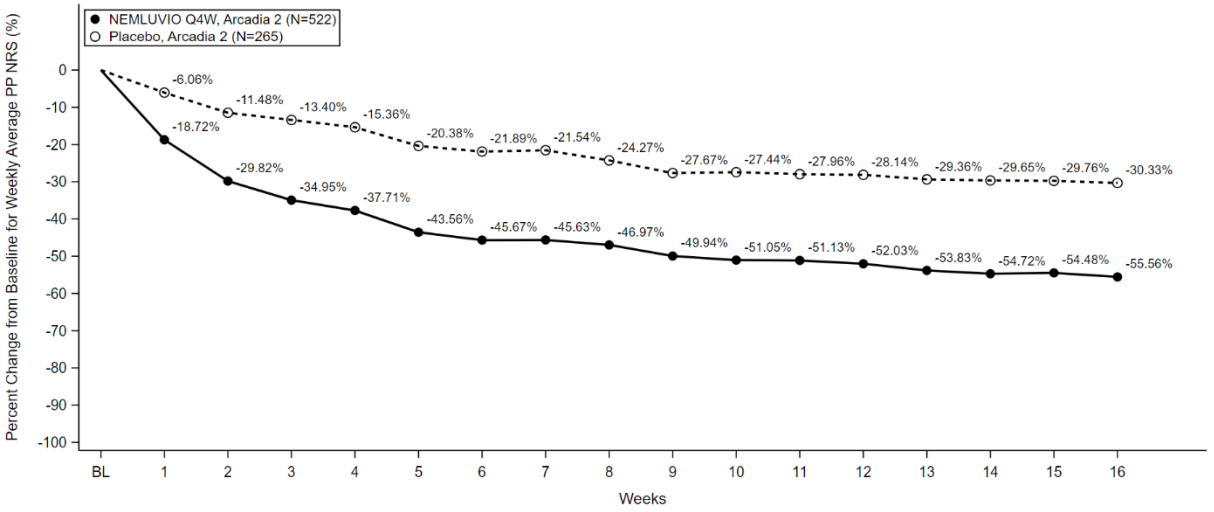


Figure 4b – Mean percent change from baseline in PP NRS up to Week 16 in ARCADIA 2



The SD NRS is a daily scale used by the subjects to report the degree of their sleep loss related to atopic dermatitis. A significant improvement in sleep disturbance was observed at Week 16 when compared to placebo (Table 4).

Table 4 – Efficacy on Sleep Disturbance for Nemluvio with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16

	ARCADIA 1		ARCADIA 2	
	Nemluvio + TCS/TCI	Placebo + TCS/TCI	Nemluvio + TCS/ TCI	Placebo + TCS/ TCI
Number of subjects randomized and dosed (Baseline PP NRS ≥4)[a]	620	321	522	265

% of subjects with SD NRS improvement ≥4[a]	37.9%*	19.9%	33.5%*	16.2%
Mean change from baseline (%) in SD NRS	-64.6	-38.1	-59.7	-35.4
Number of subjects with severe pruritus (Baseline PP NRS≥7)	406	210	316	164
% of subjects with SD NRS improvement ≥4[a]	42.1%*	22.4%	42.7%*	20.7%
Mean change from baseline (%) in SD NRS	-62.6	-37.0	-60.7	-42.0

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
*p-value <0.0001
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

ARCADIA 1 and ARCADIA 2 – Adults and Adolescents – maintenance period, week 16 to week 48

The clinical response in Nemluvio responders (IGA 0/1 or EASI-75 at Week 16) was evaluated between Week 16 and Week 48 in ARCADIA 1 and ARCADIA 2 studies. For the maintenance treatment period, 507 Nemluvio responders were re-randomized to Nemluvio 30 mg Q4W, Nemluvio 30 mg Q8W or placebo Q4W (Nemluvio withdrawal) with concomitant TCS/TCI. The pooled efficacy results for this period in the pivotal studies (ARCADIA 1 and ARCADIA 2) with Nemluvio at Week 48 are presented in Table 5.

Table 5 –Maintenance Period Pooled Efficacy Results for Nemluvio with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 48

	Nemluvio + TCS/TCI Q4W N=169	**Nemluvio + TCS/TCI Q8W N=169**	**Placebo + TCS/TCI Q4W (Nemluvio withdrawal) N=169**
% of subjects with IGA 0 or 1[a]			
Week 16 (maintenance baseline)	84.0	84.0	77.5
Week 48	61.5*	60.4*	49.7
% of subjects with EASI-75[a]			
Week 16 (maintenance/baseline)	96.4	96.4	92.9
Week 48	76.3*	75.7*	63.9

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
*p-value <0.05
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Treatment effects in subgroups (weight, age, gender race, and prior treatment, including immunosuppressants) in ARCADIA 1 and ARCADIA 2 were generally consistent with the results in the overall study population.

Other patient-reported outcomes

In both studies (ARACADIA 1 and ARCADIA 2), Nemluvio improved patient-reported symptoms and the impact of AD on health-related quality of life as measured by DLQI total score, at week 8 and week 16 compared to placebo (Table 6).

Table 6 –Efficacy results on DLQI for Nemluvio with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 up to week 16

	ARCADIA 1		ARCADIA 2	
	Nemluvio + TCS/TCI N=620	Placebo + TCS/TCI N=321	Nemluvio + TCS/ TCI N=522	Placebo + TCS/ TCI N=265
Mean change in DLQI from baseline				
At Week 8	-6.9	-4.7	-6.1	-4.6
At Week 16	-7.8	-5.3	-7.0	-4.5

In assessments of other patient reported outcomes, improvements in signs and symptoms related to pain frequency and intensity were observed at Week 16 when compared to placebo.

Adolescents with atopic dermatitis (12 to 17 years of age)

The efficacy results of the ARCADIA 1, ARCADIA 2 studies at Week 16 for paediatric patients 12 to 17 years of age are presented in Table 7 and Table 8, respectively. The results in the paediatric patient population were generally consistent with the results in the adult patient population.

Table 7 – Efficacy Results for Nemluvio (30 mg Q4W) with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16 in paediatric patients 12 to 17 years of age

	ARCADIA 1 AND ARCADIA 2	
	Nemluvio + TCS/TCI	Placebo + TCS/TCI
Number of subjects randomized and dosed (Baseline PP NRS ≥4)	179	90
% of subjects with IGA 0 or 1 [a]	48.9*	34.4
% of subjects with EASI-75 [a]	53.4[§]	43.3
Number of subjects with severe pruritus (Baseline PP NRS≥7)	120	61
% of subjects with IGA 0 or 1 [a]	54.2*	32.8
% of subjects with EASI-75 [a]	57.5[#]	42.6

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
*p-value <0.05, [#]p-value =0.1025, [§]p-value =0.1824
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Table 8 – Efficacy results on Itch and Sleep Disturbance for Nemluvio (30mg Q4W) with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16 for paediatric patients 12 to 17 years of age

	ARCADIA 1 and ARCADIA 2	
	Nemluvio + TCS/TCI	Placebo + TCS/TCI
Number of subjects randomized and dosed (Baseline PP NRS ≥4)	176	90
% of subjects with PP-NRS improvement ≥4[a]	40.9[#]	17.8
% of subjects with PP NRS <2 [a]	30.1*	6.7
% of subjects with SD NRS improvement ≥4 [a]	31.8[§]	20.0

Number of subjects with severe pruritus (Baseline PP NRS≥7)	120	61
% of subjects with PP-NRS improvement ≥4 [a]	48.3[#]	21.3
% of subjects with PP NRS <2 [a]	30.0[#]	4.9
% of subjects with SD NRS improvement ≥4 [a]	35.8[∞]	21.3

[a] Subjects who received rescue treatment or with missing data were considered as non-responders
*p-value <0.0001, [#]p-value <0.001, [§]p-value =0.0591, [∞]p-value =0.0606
Strata adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline

Clinical efficacy and safety in adults with prurigo nodularis

The efficacy and safety of Nemluvio as monotherapy was evaluated in two randomized, double-blind, placebo-controlled pivotal studies (OLYMPIA 1 and OLYMPIA 2) that enrolled a total of 560 subjects 18 years of age and older with prurigo nodularis. Patients with uncontrolled asthma were excluded from the studies and no data with Nemluvio are available in this population. Disease severity was defined using an Investigator's Global Assessment (IGA) in the overall assessment of prurigo nodularis nodules on a severity scale of 0 to 4. Subjects enrolled in these two studies had an IGA score ≥ 3, severe pruritus as defined by a weekly average of the peak pruritus numeric rating scale (PP-NRS) score of ≥7 on a scale of 0 to 10, and greater than or equal to 20 nodular lesions.
OLYMPIA 1 and OLYMPIA 2 assessed the effect of Nemluvio monotherapy on the signs and symptoms of prurigo nodularis, targeting improvement in skin lesions and pruritus over 16 weeks. OLYMPIA 1 had a 24-week treatment period and OLYMPIA 2 a 16-week treatment period.
Subjects completing OLYMPIA 1 and OLYMPIA 2 had the opportunity to enrol into the open-label trial (OLYMPIA LTE) and receive treatment with Nemluvio every 4 weeks up to 184 weeks.
Subjects weighing less than 90 kg in the Nemluvio monotherapy group received subcutaneous injections of Nemluvio 60 mg (2 injections of 30 mg) at Week 0, followed by 30 mg injections every 4 weeks.
Subjects weighing 90 kg or more in the Nemluvio monotherapy group received subcutaneous injections of Nemluvio 60 mg (2 injections of 30 mg) at Week 0 and every 4 weeks.

Endpoints

Both OLYMPIA 1 and OLYMPIA 2 assessed the same two primary endpoints:
- Proportion of subjects with an improvement of ≥4 from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16
- Proportion of subjects with an IGA success (defined as an IGA of 0 [Clear] or 1 [Almost Clear], and a ≥2-point improvement from baseline) at Week 16

Key secondary endpoints included PP NRS improvement ≥4 from baseline at Week 4, PP NRS <2 at Week 4 and Week 16, SD NRS improvement ≥4 from baseline at Week 4 and 16. Other secondary endpoints included the change from baseline to week 16 in PP NRS, SD NRS, PN-associated pain frequency and intensity and the Dermatology Life Quality Index (DLQI).

Baseline characteristics

In these studies, at baseline, 59.6% of subjects were female, 81.4% were white, 25.4% of subjects were older than 65 years of age. The baseline weekly average PP NRS score was a mean (SD) of 8.4 (0.9).

Fifty-eight (58)% of subjects had a baseline IGA score of 3 (moderate PN), 42% of subjects had a baseline IGA of 4 (severe PN) and the mean baseline DLQI was 16.9.

Clinical Response

Monotherapy studies (OLYMPIA 1 and OLYMPIA 2) – week 0 to week 16

Results of the pivotal studies evaluating treatment of Nemluvio in OLYMPIA 1 and OLYMPIA 2 are presented in Table 9 and show significant improvement in Nemluvio treated subjects, compared to placebo for both primary endpoints (Figure 5 and Figure 6) and key secondary endpoints (Figure 7).

Table 9 - Efficacy Results for Nemluvio monotherapy (Q4W) in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemluvio	**Placebo**	**Nemluvio**	**Placebo**
Number of subjects randomized	190	96	183	91
% of subjects with improvement of PP NRS ≥4 from baseline[a]				
Week 4	41.1*	6.3	41.0*	7.7
Week 16	58.4*	16.7	56.3*	20.9
% of subjects with PP NRS <2 [a]				
Week 4	21.6*	1.0	19.7*	2.2
Week 16	34.2*	4.2	35.0*	7.7
Mean change from baseline (%) in PP NRS at Week 16[b]	-54.7§	-18.7	-56.2§	-18.9
% of subjects with IGA 0 or 1 at Week 16[a]	26.3#	7.3	37.7*	11
% of subjects with improvement of SD NRS ≥4 from baseline[a]				
Week 4	31.1*	5.2	37.2*	9.9
Week 16	50.0*	11.5	51.9*	20.9
Mean change from baseline (%) in SD NRS at Week 16 [b]	-52.5§	-18.8	-53.1§	-9.6

[a] If a subject received any rescue therapy, composite variable strategy is applied, the underlying data at/after receipt of rescue therapy is set as worst possible value, and the response is derived from underlying data value. Subjects with missing results are considered as non-responders.

[b] Not adjusted for multiplicity

*p-value <0.0001, #p-value =0.0025 Strata adjusted using the randomized stratification variables (analysis centre and baseline body weight (<90 kg, ≥90 kg)

§p-value <0.0001 Strata-adjusted vs placebo (ANCOVA MI-MAR)

Figure 5 – Proportion of Subjects with PP-NRS Improvement ≥4 from baseline to Week 16

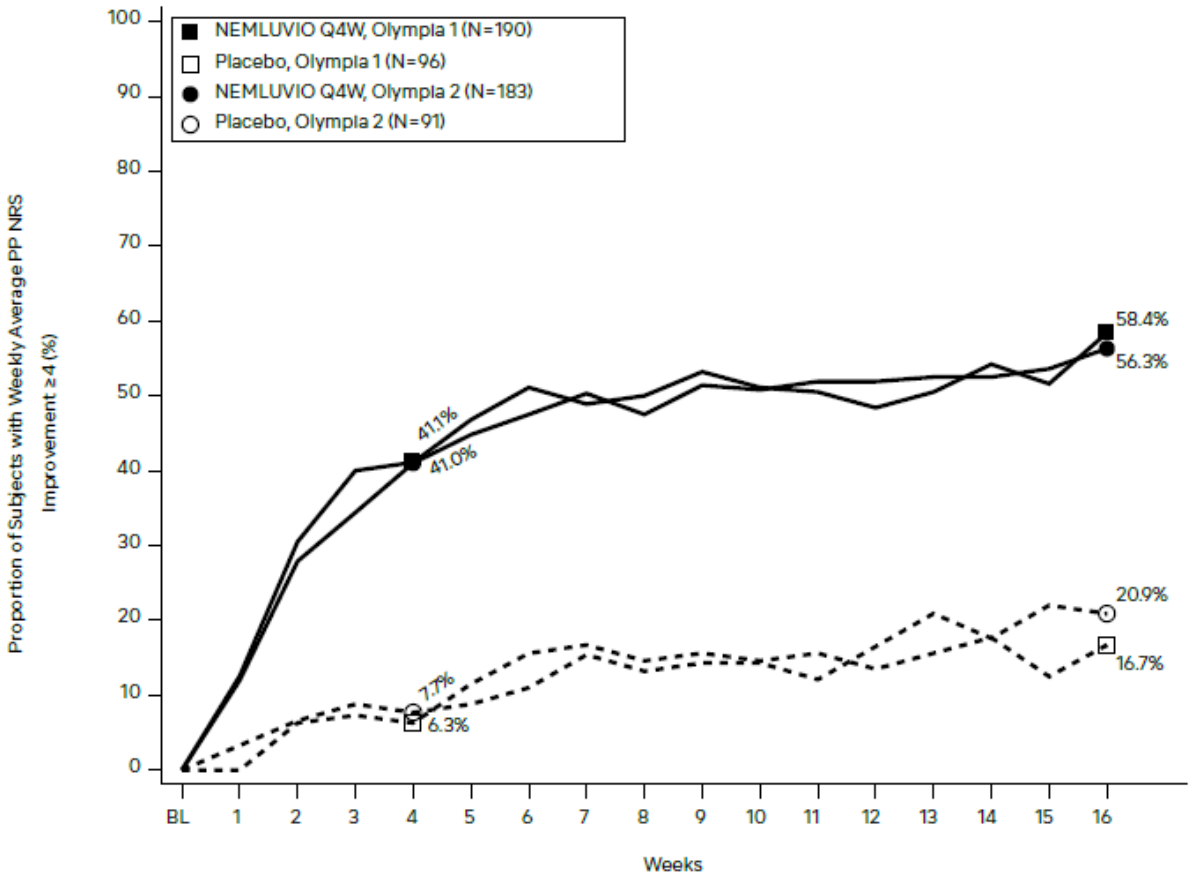


Figure 6 – Proportion of IGA responders from baseline to Week 16

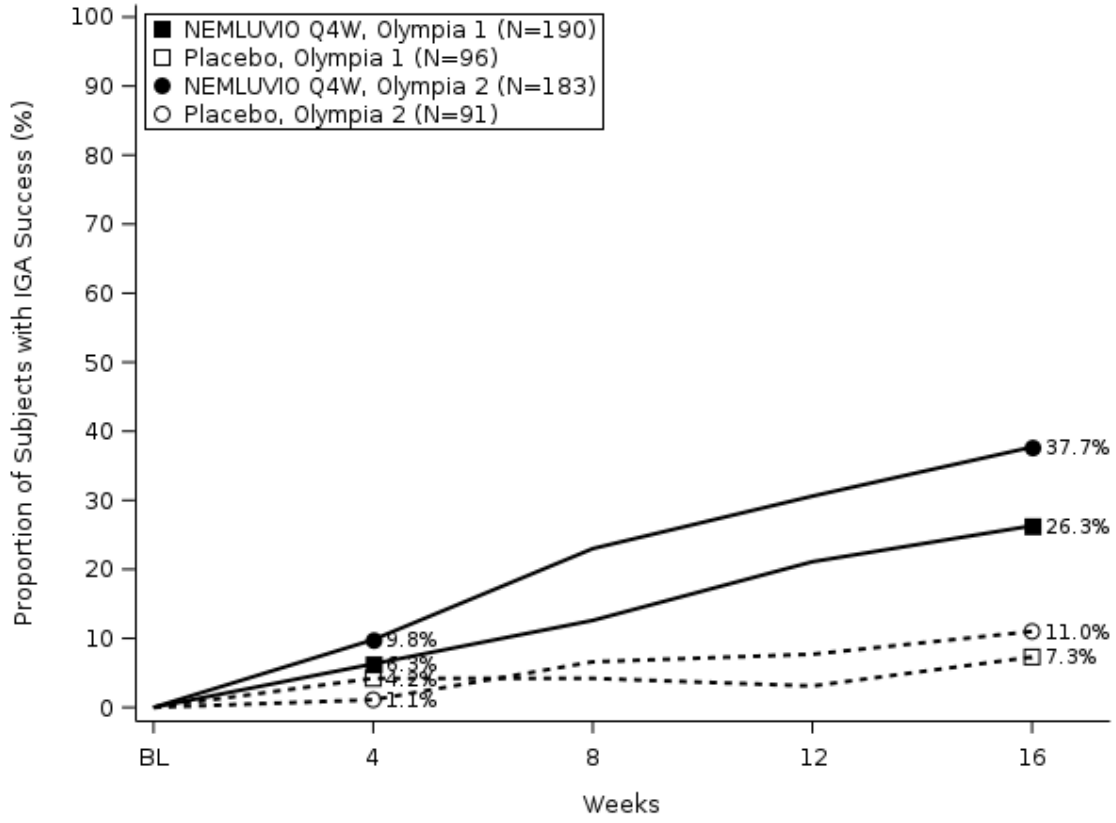
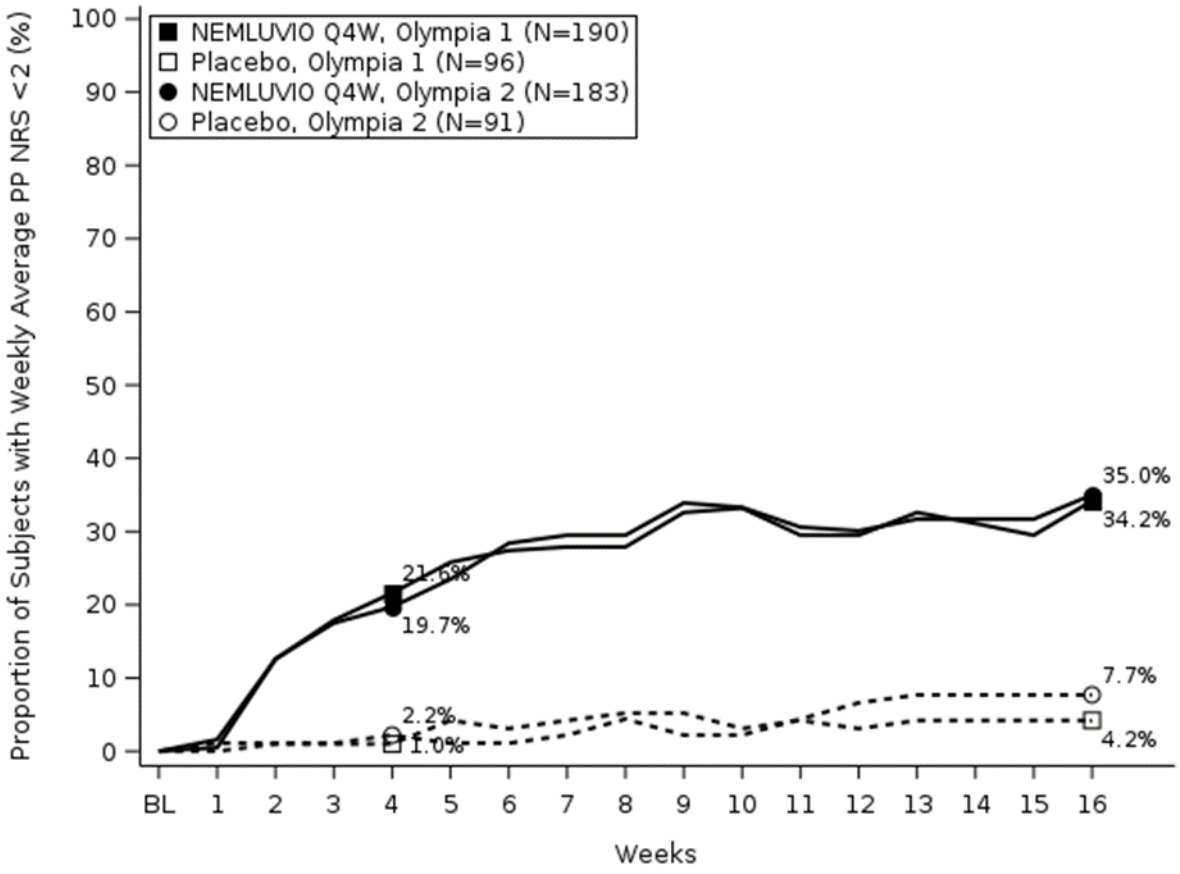


Figure 7 – Proportion of Subjects achieving PP-NRS <2 at Week 4 and Week 16



Treatment effects in subgroups (weight, age, gender, race, history of atopy, and prior treatment, including immunosuppressants) in OLYMPIA 1 and OLYMPIA 2 were generally consistent with the results in the overall study population.

Other Patient-reported outcomes

In both monotherapy studies (OLYMPIA 1 and OLYMPIA 2), Nemluvio improved patient-reported symptoms of PN-associated pain frequency and intensity, and health-related quality of life as measured by DLQI total score (Table 10), at 16 weeks compared to placebo.

Table 10 –Efficacy results on DLQI of Nemluvio Monotherapy (Q4W) in OLYMPIA 1 and OLYMPIA 2 up to week 16

	OLYMPIA 1		OLYMPIA 2	
	Nemluvio N=190	Placebo N=96	Nemluvio N=183	Placebo N=91
Mean change in DLQI from baseline				
At Week 4	-7.8	-3.0	-8.0	-1.9
At Week 16	-8.6	-2.2	-8.9	-0.8

% of subjects with improvement of DLQI ≥4 from baseline				
At Week 4	70.0	42.7	68.9	39.6
At Week 16	70.5	42.7	74.9	39.6

5.2 Pharmacokinetic properties

Absorption

Following an initial subcutaneous dose of 60 mg in a phase1 trial (96 subjects per arm), nemolizumab reached peak mean (SD) concentrations (Cmax) of 7.5 (2.31) µg/mL by approximately 6 days post dose.

Following multiple doses of Nemluvio in subjects with atopic dermatitis, the population PK estimated mean (SD) steady-state trough concentrations of nemolizumab were 2.63 (1.27) µg/mL for 30 mg administered Q4W and 0.74 (0.44) µg/mL for 30 mg administered Q8W.

Following multiple doses of Nemluvio in subjects with prurigo nodularis, the population PK estimated mean (SD) steady-state trough concentrations of nemolizumab 3.04 (1.23) µg/mL in patients with body weight <90 kg for 30 mg administered Q4W; and 3.66 (1.63) µg/mL in patients with body weight ≥90 kg for 60 mg administered Q4W.

In both atopic dermatitis and prurigo nodularis population, steady state concentrations of nemolizumab were achieved by week 4 after a 60 mg loading dose and by week 12 without a loading dose.

Distribution

Based on a population PK analysis, the volume of distribution was 7.67 L.

Biotransformation

Specific metabolism studies were not conducted because nemolizumab is a protein. Nemolizumab is expected to be metabolized into small peptides by catabolic pathways.

Elimination

Nemolizumab is expected to be degraded in the same manner as endogenous IgG. In the population PK analysis, the terminal elimination half-life (SD) of nemolizumab was estimated to be 18.9 (4.96) days and systemic clearance was estimated to be 0.263 L/day.

Linearity/non-linearity

After a single dose, nemolizumab exhibited linear pharmacokinetics with exposures increasing in dose-proportional manner between 0.03 and 3 mg/kg.

After multiple doses, nemolizumab systemic exposure increased in an approximately dose-proportional manner across the SC dose range up to 30 mg. There was a slight decrease in bioavailability by 9% with the 60 mg SC dose and by 15% with the 90 mg SC dose.

Special populations

Gender, age and race
Gender, age, and race did not have a significant effect on the pharmacokinetics of nemolizumab.

Hepatic impairment
Nemolizumab, as a monoclonal antibody, is not expected to undergo significant hepatic elimination. No clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of nemolizumab. Mild to moderate hepatic impairment was not found to affect the PK of nemolizumab determined by population PK analysis. No data are available in patients with severe hepatic impairment.

Renal impairment
Nemolizumab, as a monoclonal antibody, is not expected to undergo significant renal elimination. No clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of nemolizumab. Population PK analysis did not identify mild or moderate renal impairment as having a clinically meaningful influence on the systemic exposure of nemolizumab. Very limited data are available in patients with severe renal impairment.

Body weight
Nemolizumab exposure was lower in subjects with higher body weight.

Table 11 – PK parameters by weight quartile

Body weight (kg)	1st Quartile [30.8 to 62.0]	2nd Quartile [62.0 to 74.0]	3rd Quartile [74.0 to 87.1]	4th Quartile [87.1 to 181]
$C_{max,ss}$ (µg/mL)	6.64	5.48	4.86	3.99
$C_{trough,ss}$ (µg/mL)	2.92	2.39	2.18	1.72
$AUC_{\tau,ss}$ (µg•day/mL)	137	113	101	81.6

$AUC_{t,ss}$ Area under the concentration-time curve during a dosing interval (τ) at steady state; $C_{max,ss}$ Maximum concentration at steady state; $C_{trough,ss}$ Predose concentration at steady state
PK parameters calculated with population PK model (N=1952)

Atopic Dermatitis
The difference in systemic exposure due to body weight had no clinically meaningful impact on efficacy. Dose adjustment based on body weight is not needed (see section 4.2).

Prurigo Nodularis
The variability in systemic exposure due to body weight had a clinically meaningful impact on skin lesion efficacy as assessed by IGA response but not on pruritus improvement and does require dose adjustment in subjects with prurigo nodularis (see section 4.2).

Paediatric population
Atopic dermatitis
In the population PK analysis, no clinically significant difference in the pharmacokinetics of nemolizumab was estimated in 12-17 years paediatric subjects compared to adults. Dose adjustment in this population is not recommended.

5.3 Preclinical safety data

Dedicated animal studies have not been conducted to evaluate the carcinogenic or mutagenic potential of Nemluvio.

Due to its nature and pharmacological properties, direct DNA or other genetic material interaction is not expected for a recombinant humanized monoclonal immunoglobulin such as nemolizumab. Nemluvio and its metabolites (oligo peptides and amino acids) are not deemed to have an intrinsic carcinogenic potential or to be tumor initiators/promotors.

No effects on fertility parameters such as reproductive organs morphology, menstrual cycle length, or sperm/testicular analysis were observed in sexually mature cynomolgus monkey that were chronically administered by the subcutaneous route at doses up to 25 mg/kg/2-week (AUC exposure 43-fold or 34-fold higher than in AD or PN patients respectively, at the 60 mg Maximum Recommended Human Dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder for solution for injection:
Sucrose
Trometamol
Trometamol hydrochloride (for pH-adjustment)
L-arginine hydrochloride
Poloxamer 188

Solvent:
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen

24 months

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled syringe

36 months

If necessary, the carton containing the pre-filled pen or pre-filled syringe can be removed from the refrigerator at room temperature (up to 30°C) for a single period up to 90 days. Write the date first removed from the refrigerator in the space provided on the outer carton for the pen or the syringe. Do not

use Nemluvio beyond the expiration date or 90 days after the date it was first removed from the refrigerator (whichever is earlier).

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

Once reconstitution steps are completed, Nemluvio must be held below 30 ºC and used within 4 hours.

6.5 Nature and contents of container

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled pen
Single-use dual-chamber borosilicate glass type 1 cartridge in an auto-injector, with a stainless steel staked needle.

Pack size:
• 1 pre-filled pen
• Multipack containing 2 (2 packs of 1) pre-filled pens

Nemluvio 30 mg powder and solvent for solution for injection in pre-filled syringe
Single-use dual-chamber pre-filled syringe in a borosilicate glass type 1, co-packaged with a 27G needle (stainless steel) with safety shield.

Pack size:
• 1 pre-filled syringe

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Comprehensive instructions for the administration of Nemluvio in a pre-filled pen or in a pre-filled syringe are given at the end of the package leaflet.

Nemluvio must be removed from the refrigerator for 30-45 min before reconstitution. Once reconstitution steps are completed, Nemluvio must be held below 30ºC or discarded.

Inspect Nemluvio visually prior to reconstitution. Nemluvio consists of a white powder and a clear liquid. Do not use if powder is not white, or if liquid is cloudy, or particulate matter is visible. Prior to administration, check that Nemluvio is clear and colourless to slightly yellow and does not contain particles.

The pre-filled pen or the pre-filled syringe should not be exposed to heat or direct sunlight and should not be shaken.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. Product owner

Galderma SA,
Zählerweg 10,
6300 Zug,
Switzerland

8. DATE OF REVISION OF THE TEXT

March 2025