swissmedic

Date: 11 April 2025
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Nemluvio

International non-proprietary name: nemolizumab

Pharmaceutical form:	powder and solvent for solution for injection in pre-filled pen
Dosage strength(s):	30 mg
Route(s) of administration:	subcutaneous
Marketing authorisation holder:	Galderma SA
Marketing authorisation no.:	69707
Decision and decision date:	approved on 17 February 2025

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical classification system
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
TQT	Thorough QT

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for nemolizumab in the above-mentioned medicinal product.

Work-sharing procedure
The applicant requested a work-sharing procedure with Australia, Singapore and the United Kingdom (UK).
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

2.2 Indication and dosage

2.2.1 Requested indication

Atopic dermatitis (AD)
Nemluvio is indicated for the treatment of moderate to severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy.

Prurigo nodularis (PN)
Nemluvio is indicated for the treatment of prurigo nodularis.

2.2.2 Approved indication

Atopic Dermatitis (AD)
Nemluvio is indicated for the treatment of adults and adolescents 12 years of age and older weighing at least 30 kg with moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical medicinal products alone (see "Dosage/Administration" and "Clinical efficacy").

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

2.2.3 Requested dosage

Summary of the requested standard dosage:

Nemluvio is applied by subcutaneous injection.

Atopic dermatitis:
- Loading dose of 60 mg (two 30 mg injections), followed by 30 mg every 4 weeks (Q4W) for 16 weeks
- After 16 weeks of treatment: 30 mg every 8 weeks (Q8W), if a clinical response was achieved

Prurigo nodularis:
- Patients < 90 kg: loading dose of 60 mg (two 30 mg injections), followed by 30 mg every 4 weeks (Q4W)
- Patients ≥ 90 kg: loading dose of 60 mg (two 30 mg injections), followed by 60 mg every 4 weeks (Q4W)

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	19 March 2024
Formal objection	26 March 2024
Response to formal objection	2 April 2024
Formal control completed	3 May 2024
List of Questions (LoQ)	30 August 2024
Response to LoQ	30 October 2024
Preliminary decision	13 December 2024
Response to preliminary decision	29 December 2024
Labelling corrections and/or other aspects	16 January 2025
Response to labelling corrections and/or other aspects	30 January 2025
Final decision	17 February 2025
Decision	approval

3 Medical context

Atopic dermatitis
Atopic dermatitis (AD) is a chronic, pruritic, inflammatory skin disease. It is often associated with a personal or family history of atopy. A multiplicity of mechanisms are involved in the pathogenesis of AD, including epidermal barrier dysfunction, genetic factors, T helper type 2 (Th2) cell-skewed immune dysregulation, altered skin microbiome, and environmental triggers of inflammation.

AD affects between 5 and over 20 percent of children and approximately 10 percent of adults worldwide. In most cases, AD presents before the age of 5 years and persists beyond infancy in approximately 50 percent of patients. However, 1 in 4 adults with AD report adult onset of the disease.

Dry skin and severe pruritus are the cardinal signs of AD. Acute AD presents with erythematous papules and vesicles with exudation and crusting, while subacute and chronic AD is characterised by dry, scaly, or excoriated papules or skin thickening (lichenification) from chronic scratching. However, the clinical presentation is highly variable, depending upon the patient's age, ethnicity, and disease activity. Atopic dermatitis follows a chronic, relapsing course over months to years. The diagnosis of atopic dermatitis is clinical, based upon history, morphology, and distribution of skin lesions, and associated clinical signs.

The most commonly used disease severity scales used in clinical trials for AD are IGA (Investigator Global Assessment) and EASI (Eczema Area and Severity Index). The IGA is a five-point scale that provides a global clinical assessment of AD severity ranging from 0 to 4, where 0 indicates clear, 2 is mild, 3 is moderate, and 4 indicates severe AD. The EASI is a tool used to measure the extent (area) and severity of atopic eczema and ranges from 0 (clear) to 72 (very severe).

The goals of treatment of atopic dermatitis are to reduce symptoms (pruritus and dermatitis), prevent exacerbations, and minimise therapeutic risks. Management involves elimination of exacerbating factors, restoration of the skin barrier function and hydration of the skin, patient education, and pharmacological treatment of skin inflammation.
Patients with mild to moderate symptoms are generally managed with topical therapies. For patients with moderate to severe disease who have an inadequate response to topical therapies, biologics or JAK inhibitors are recommended.

Prurigo nodularis
Prurigo nodularis (PN) is a chronic, inflammatory skin condition characterised by severely pruritic nodules that cause a profound negative impact on quality of life. The pathogenesis of PN is thought to be a cutaneous reaction pattern caused by vicious cycles of chronic itch followed by repeated scratching. However, the exact pathogenesis of PN remains unknown.

PN is a relatively rare condition, with an estimated prevalence of 72 per 100,000 individuals in an epidemiological study of US adults 18 to 64 years of age who have health care insurance. While clinical experience has shown that PN affects both genders, there is some evidence that PN is slightly more common in females

PN typically presents with firm, dome-shaped, itchy nodules ranging in size from a few millimetres to several centimetres and often symmetrically distributed on the extensor surfaces of the arms and legs and on the trunk. Nodules can be flesh-coloured, erythematous, or brown/black and range in number from few to hundreds.
Pruritus is always severe and distressing; it can be paroxysmal, sporadic, or continuous and is worsened by heat, sweating, or irritation from clothing. In many cases, the cause of pruritus is unknown.

The most commonly used disease severity scales used in clinical trials for PN are PP NRS (Peak Pruritus Numerical Rating Scale) and IGA (Investigator Global Assessment). The PP NRS assesses the severity of itch, ranging from 0 (no itch) to 10 (worst itch imaginable). The IGA is a five-point scale that provides a global clinical assessment of PN severity ranging from 0 to 4, where 0 indicates clear, 2 is mild, 3 is moderate, and 4 indicates severe PN.

Treatment of PN is difficult and requires a multifaceted approach, involving patient education to adopt skin care measures to reduce skin irritation and scratching, symptomatic treatment of pruritus, and topical or systemic therapies aimed at interrupting the itch-scratch cycle and flattening the skin lesions. In Switzerland, only dupilumab is approved for the systemic treatment of PN.

4 Quality aspects

Swissmedic has not assessed the primary data relating to quality aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

5 Nonclinical aspects

Swissmedic has not assessed the primary data relating to nonclinical aspects submitted with this application and is adopting the results of the assessment of the foreign reference authority (see section 2.1 Applicant's request / Work-sharing procedure).

6 Clinical aspects

6.1 Clinical pharmacology

Biopharmaceutical development
During the entire clinical development program, two formulations of nemolizumab were used: a lyophilized and a solution formulation. They were either presented in a vial, a dual-chamber cartridge assembled with an autoinjector (DCC-AI), or a dual-chamber syringe (DCS).
Following subcutaneous (SC) administration of a single 60 mg dose of nemolizumab, bioequivalence between DCC-AI and DCS was demonstrated in healthy adult subjects. Different injection sites (arm, abdomen, and thigh) did not have an impact on the bioavailability of nemolizumab. Furthermore, nemolizumab formulation (liquid versus lyophilised powder) or device (vial versus DCS) were not identified as significant covariates in the population PK analysis.
The final drug product to be marketed is a sterile, white lyophilised powder for solution for subcutaneous injection. It will be provided either in a single-use, single-dose DCS or DCC-AI containing 30 mg nemolizumab and water for injection. After reconstitution, the drug product is formulated as 61.5 mg/mL nemolizumab.

Pharmacokinetics
The PK profiles of nemolizumab in healthy subjects as well as patients with AD and PN were evaluated in 2 Phase 1 studies, 4 Phase 2, and 6 Phase 3 studies. Single nemolizumab doses from 0.003 mg/kg to 3 mg/kg and 60 mg, as well as multiple nemolizumab doses including 0.1 mg/kg Q4W, 0.5 mg/kg Q4W, 2 mg/kg Q4W/Q8W, 10 mg Q4W (LD 20 mg), 30 mg Q4W/Q8W (LD 60 mg), 60 mg Q4W, 90 mg Q4W, were administered.

Absorption
Based on simulations in AD patients using the population PK model for nemolizumab, there was a large overlap between the concentrations following the body weight-based dose of 0.5 mg/kg and the flat dose of 30 mg (with 60 mg LD) Q4W, particularly between 50 kg to 80 kg. As expected, exposures were higher for subjects weighing less than 50 kg following the administration of the flat dose, whereas they were lower for subjects heavier than 80 kg. However, both dosing regimens led to concentrations that were within the observed range for the 30 mg dose (with 60 mg LD).
Following the SC administration of 60 mg nemolizumab in healthy subjects, the maximum concentrations were reached within 4 to 6 days.
Based on simulations using the population PK model for nemolizumab, steady state concentrations were reached after the loading dose of 60 mg. Without loading dose, steady state concentrations were achieved by week 12, and the accumulation ratio was estimated at 1.6.
In the maintenance period, steady state exposure in AD patients was approximately 3.6 times lower with the Q8W dosing interval.
Comparable steady state exposure was reached following the administration of 30 mg nemolizumab Q4W in PN patients weighing <90 kg and 60 mg Q4W in PN patients weighing ≥90 kg.
Following single dose administration, nemolizumab exposure increased dose-proportionally between 0.03 mg/kg and 3 mg/kg. Less than dose-proportional increases were observed following the administration of multiple doses between 10 mg and 90 mg. Based on the population PK analysis, there was an effect of the 60 mg and 90 mg doses on the bioavailability, characterised by slight decreases by 9.49% and 14.6%, respectively.
Based on the population PK analyses, the PK of nemolizumab was comparable between patients with AD and PN. In healthy subjects, the apparent clearance (CL/F) and volume of distribution (V/F) were decreased by approximately 22% and 15%, respectively.

Distribution
Based on the population PK analyses, the mean estimate of the apparent volume of distribution V/F was 7.67 L.

Metabolism and Elimination
No studies regarding the metabolism of nemolizumab have been conducted, considering the biological nature of the molecule.
Based on the PopPK analysis, the CL/F was estimated at 0.263 L/day, and the mean $t_{1/2}$ was approximately 18.9±4.96 days.

Special populations / Intrinsic factors
Since renal and hepatic impairment is not expected to have an impact on the PK of monoclonal antibodies, no dedicated studies in these populations were conducted. Based on the population PK analysis, mild or moderate hepatic and mild or moderate renal impairment have no impact on the PK of nemolizumab.
In the first-in-human study, the PK of nemolizumab was comparable in healthy Japanese adult males and healthy White adult males. The exposure appeared to be lower and the half-lives shorter in Japanese AD patients. In the population PK analysis, race, ethnicity, and region were not identified as statistically significant covariates.
The PK and safety of nemolizumab in adolescent subjects with moderate-to-severe AD and associated pruritus were investigated in a Phase 2 study. Following the administration of a 30 mg Q4W dose (with a 60 mg LD) of nemolizumab, trough concentrations were comparable to those observed in adult AD patients. In the population PK analysis, age (12 to 82 years) was not identified as a statistically significant covariate.

At different stages during clinical development, population PK analyses were conducted to guide dose selection. Using PK data from two Phase 1 studies, four Phase 2 studies, and four Phase 3 studies, the final population PK model was developed to identify factors that account for variability of the nemolizumab PK. The PK of nemolizumab was well described with a 1-compartment model with first order absorption and linear elimination, with a dose effect on the relative bioavailability for 60 mg and 90 mg. An absorption lag time was added to better describe the absorption phase. As expected for mABs, body weight had a significant impact on both nemolizumab CL/F and V/F. The final population PK model also included these additional covariates: albumin, CRCL, ethnicity, race, sex on CL/F and albumin on V/F. Overall, no dose adjustments are required based on any of the investigated covariates apart from body weight.

Interactions
No *in vitro* or clinical interaction studies were conducted. A direct interaction of nemolizumab with CYPs, UGTs or transporters by its metabolism, chemical properties or mechanism of action is unlikely.
However, cytokine levels may have an impact on CYP expression. Considering the ability of nemolizumab to modulate interferon/cytokine levels, an impact on the PK of CYP450 substrates is theoretically possible.
In a clinical DDI study in patients with moderate-to-severe AD, the impact of nemolizumab on the PK of midazolam (CYP3A4/5 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate), and caffeine (CYP1A2 substrate) were investigated. The 90% confidence intervals (CIs) were within bioequivalence acceptance criteria for midazolam and S-warfarin. For (baseline-corrected) caffeine, the majority of lower limits of the 90% CIs were slightly below 80%, indicating a borderline weak interaction of nemolizumab with CYP1A2. The lower limit of the 90% CI was slightly below 80% for C_{max} of metoprolol. The lower limit of the 90% CIs was slightly below 80% for C_{max} and $AUC_{0\text{-last}}$ of omeprazole. Overall, these effects are not deemed clinically significant.

Pharmacodynamics

Mechanism of action and primary pharmacology

Nemolizumab is a humanised anti-human interleukin-31 receptor A (IL-31RA) monoclonal antibody. Upon binding to IL-31RA, nemolizumab competitively blocks the binding of IL-31 to its receptor, thereby inhibiting the subsequent transduction of the IL-31 signal. Interleukin-31 is a cytokine involved in pruritus of different conditions such as AD and PN.

Secondary pharmacology (safety)

No tQT study was conducted. Generally, monoclonal antibodies harbour a low risk of prolonging the QT interval. No correlation between nemolizumab concentrations and QTc (C-QT) values was observed in an exposure-safety analysis assessing the correlation between nemolizumab concentrations and QTc (C-QT) values from 263 AD patients.

Exposure efficacy/safety relationship

At different stages during clinical development, exposure-efficacy analyses were conducted to guide the selection of the Phase 3 dosing regimen. The dose adjustment for PN patients with a body weight ≥90 kg was based on the exposure-response relationship for IGA. Overall, the models remained consistent throughout the analyses.

Using data from one Phase 1, three Phase 2, and two Phase 3 studies, the exposure-efficacy and -safety relationships in patients with AD were investigated.
During the exploratory data analysis, no clear dose-response relationship was observed for EASI scores, IGA, or weekly average PP NRS. The exposure-response relationships for EASI scores and weekly average PP NRS were well described, with a turnover model with an inhibiting concentration effect of nemolizumab (described by an I_{max} model) and a constant placebo effect. No statistically significant covariates were identified. Overall, EASI scores and weekly average PP NRS decreased with higher nemolizumab concentrations. The exposure-response relationship for IGA was well described with a 4-compartment continuous time Markov model with a linear nemolizumab effect on descending transition rate constants (λ_{desc}) for all descending transitions (E_{desc}). Baseline IGA score and sex were significant covariates. Overall, higher nemolizumab concentrations led to faster transitions towards lower IGA scores. A decrease towards lower IGA scores was less likely for patients with a higher baseline IGA score, whereas female patients showed a better response to nemolizumab treatment.
Exposure-efficacy simulations using the final PK/PD models demonstrated that the Phase 3 study dosing regimen was adequate for low and high body weight AD patients.
In the context of the exposure-safety analysis, no correlation was detected between exposure and the incidence of dermatitis atopic flares, newly diagnosed asthma or worsening of asthma, as well as facial and peripheral oedema.

Using data from one Phase 2 and two Phase 3 studies, the exposure-efficacy and -safety relationships in patients with PN were investigated.
During the exploratory data analysis, no clear dose-response relationship was observed for IGA and weekly average PP NRS. The exposure-response relationship for weekly average PP NRS was well described with a turnover model with an inhibiting concentration effect of nemolizumab (described by an I_{max} model) and a constant placebo effect. Although age, sex, and body weight were identified as statistically significant covariates, they were not included in the final model. Overall, weekly average PP NRS decreased with higher nemolizumab concentrations. The exposure-response relationship for IGA was well described with a 4-compartment continuous time Markov model with a linear nemolizumab effect on descending transition rate constants (λ_{desc}) and a linear nemolizumab effect on ascending transition rate constants (λ_{asc}). Baseline IGA score was a significant covariate. Overall, higher nemolizumab concentrations were associated with faster transitions towards lower IGA scores and reduced transitions towards higher IGA scores. Subjects with a severe IGA score at baseline showed a worse response to nemolizumab treatment.

Exposure-efficacy simulations using the final PK/PD models demonstrated that the Phase 3 study dosing regimen was adequate for low and high body weight PN patients.
In the context of the exposure-safety analysis, no correlation was detected between exposure and the incidence of eczematous reactions and headache, newly diagnosed asthma or worsening of asthma, as well as facial and peripheral oedema.

6.2 Dose finding and dose recommendation

Atopic dermatitis
The Phase 2 Study RD.06.SRE.114322 demonstrated that, of three evaluated nemolizumab doses (10 mg, 30 mg, and 90 mg), nemolizumab 30 mg (with a 60 mg loading dose) showed the highest percent change from baseline in EASI at Week 24.
Therefore, the 30 mg dose (with a 60 mg loading dose) was chosen for the pivotal phase 3 studies for the initial treatment period. However, no formal dose finding was carried out for the maintenance treatment period.

Prurigo nodularis
There was a supportive Phase 2a study RD.06.SRE.115828 evaluating the dose of 0.5 mg/kg nemolizumab or matching placebo every 4 weeks in PN patients (at Baseline, Week 4 and Week 8). Nemolizumab was superior to placebo in reducing the weekly average PP NRS score at Week 4. There was, however, no specific dose-finding study in PN, and the chosen dosage for the pivotal studies was justified with PK/PD modelling and simulations.

6.3 Efficacy

Atopic dermatitis
Two pivotal studies (RD.06.SPR.118161 and RD.06.SPR.118169) in AD patients were submitted. Both studies had the same design, endpoints and inclusion/exclusion criteria. Both were Phase 3, randomised, double-blind, placebo-controlled, multicentre, parallel-group studies and patients were randomised 2:1 to receive either nemolizumab 30 mg Q4W (with a loading dose of 60 mg at baseline) or placebo until week 16. Afterwards, nemolizumab-treated subjects who were clinical responders at week 16 (IGA of 0 or 1 or EASI-75) were re-randomised (1:1:1) to different treatment regimens (nemolizumab injections Q4W or Q8W or placebo Q4W) for the maintenance treatment up to week 48.
Beginning at screening, subjects applied a moisturiser at least once daily and a topical background therapy (a medium- or low-potency TCS or TCI), which could be adjusted according to the disease activity and tolerability.
The co-primary efficacy endpoints were the 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 and the proportion of subjects with EASI-75 (≥75% improvement in EASI from baseline) at week 16. The study design and the endpoints are considered acceptable to evaluate the efficacy of nemolizumab in combination with topical therapies. However, no monotherapy studies of nemolizumab in AD patients were submitted to assess the effect of a nemolizumab monotherapy in AD patients.
Included were patients ≥12 years of age with chronic, moderate to severe AD (defined by an EASI score ≥16, an IGA score ≥3, a PP NRS score of at least 4.0 and an AD involvement ≥10% of BSA), and a recent history of inadequate response to topical medications.
Main exclusion criteria were a body weight <30 kg, patients with a recent asthma exacerbation requiring hospitalisation in the preceding 12 months, poorly controlled asthma, and patients with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.
Overall, the demographic and disease baseline characteristics were similar between the two groups and represented the intended target population well.

Both studies met both co-primary endpoints and the key secondary efficacy endpoints, with a statistically significant higher effect of nemolizumab compared to placebo. For details regarding the endpoints, please refer to the attached Information for healthcare professionals. The percentage of patients achieving both co-primary endpoints in the nemolizumab group is also considered clinically relevant.
The results of the maintenance treatment period demonstrated that a percentage of 60.4% had IGA success and 75.7% had EASI-75 at Week 48 in the nemolizumab 30 mg Q4W to Q8W group. This is considered a relevant clinical effect after approx. one year.
Therefore, the clinical benefit of nemolizumab in combination with topical therapy in AD patients for the initial treatment period and the maintenance period has been demonstrated.

In total, 266 adolescents (15.4%) were included in both pivotal studies with 176 adolescents receiving nemolizumab and 90 adolescents receiving placebo. Comparing the pooled results for the co-primary endpoints for adolescents and adults side-by-side, the results were even slightly better for the co-primary endpoints in adolescents compared to adults for the induction and the maintenance period. Therefore, the clinical benefit for nemolizumab in combination with topical therapy is also demonstrated for adolescent AD patients.

Prurigo nodularis
There were two pivotal PN studies, SPR.203065 and SPR.202685. Both studies had the same design, endpoints and study population. Both were Phase 3, randomised, double-blind, placebo-controlled, multicentre, parallel-group trials. Subjects were randomised 2:1 to receive either nemolizumab, with subjects weighing <90 kg at baseline receiving either 30 mg nemolizumab (with 60 mg loading dose at baseline) or placebo Q4W and subjects weighing ≥90 kg at baseline receiving either 60 mg nemolizumab (no loading dose) or placebo Q4W. No concomitant use of TCS or TCI was allowed in either study.
The co-primary efficacy endpoints were the proportion of subjects with an improvement of ≥4 from baseline in PP NRS and the 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. Both studies had the same objectives and primary endpoints at week 16; however, the treatment duration of SPR.202685 was extended by 8 weeks (i.e. 24-week Treatment Period).
Included were adult patients with a clinical diagnosis of PN for at least 6 months with at least 20 nodules on the entire body with a bilateral distribution, and an IGA score ≥3 and PP NRS score ≥7.0. Main exclusion criteria were a body weight <30 kg, chronic pruritus resulting from an active condition other than PN, unilateral lesions of prurigo (e.g. only 1 arm affected) and a history of, or current, confounding skin condition. In addition, patients with an exacerbation of asthma requiring hospitalisation in the preceding 12 months, patients with poorly controlled asthma during the preceding 3 months, and patients with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis were excluded.
Overall, the demographic and disease baseline characteristics were similar between the two groups and represented the intended target population well.
The co-primary endpoints and also the key secondary endpoints were all met, and the results with nemolizumab are also considered clinically relevant. For details regarding the endpoints, please refer to the attached Information for healthcare professionals.
Therefore, the clinical benefit of nemolizumab in adult PN patients has been demonstrated.

The results of the LTE study D.06.SPR.202699 demonstrated an increase in efficacy over the period of 52 weeks, although this has to be interpreted with caution as these were open-label data.

6.4 Safety

Atopic dermatitis

The primary safety population was defined as all randomised subjects who received at least 1 dose of study drug in the 2 pivotal Phase 3 studies (SPR.118161 and SPR.118169) and in the Phase 2 Study SPR.114322.
The primary safety population included 1192 subjects in the nemolizumab 30 mg Q4W group and 640 subjects in the placebo group.
The mean treatment duration was 112.5 days for nemolizumab 30 mg Q4W subjects and 114.1 days for placebo subjects during the initial treatment period. The mean treatment duration in the maintenance period ranged from 204.0 days (nemolizumab 30 mg Q4W to placebo) to 211.4 days (nemolizumab 30 mg Q4W to Q8W).

The most common TEAEs in the initial period (reported by ≥2.0% of subjects in either the nemolizumab 30 mg Q4W or placebo groups) were AD, headache, nasopharyngitis, asthma, COVID-19, and upper respiratory tract infection.

There were no deaths during the treatment period. One nemolizumab 10 mg Q4W subject died during the follow-up period (pneumonia aspiration and cardio-respiratory arrest). This death is not considered related to the study drug.

The only treatment-emergent SAEs experienced by >1 subject in the initial period in either group were AD and intervertebral disc protrusion.

From the AESIs, there was a numerical imbalance in peripheral and facial oedema in the nemolizumab compared to the placebo group during the initial treatment period. However, due to confounding factors and the time connections, no firm conclusion about a relationship between peripheral and facial oedema and nemolizumab can be drawn. However, information about this observed imbalance was included in the Information for healthcare professionals.

During the initial treatment period, the percentage of adolescents with TEAEs, severe TEAEs, and SAEs was similar or even lower compared to adults. Only nasopharyngitis and upper respiratory tract infection occurred in a higher percentage in adolescents.

Prurigo nodularis
The primary safety population was defined as all randomised or enrolled subjects who received at least 1 dose of study drug in the 2 pivotal Phase 3 studies (SPR.202685 and SPR.203065). The primary safety population included 370 subjects in the nemolizumab group and 186 subjects in the placebo group. The mean treatment duration in the primary safety population was 137.1 days (median of 120.0 days) for nemolizumab subjects and 138.2 days (median of 117.5 days) for placebo subjects.

The most common TEAEs (reported by ≥5.0% of subjects in either the nemolizumab or placebo group) were worsening of PN, COVID-19, nasopharyngitis, and headache.

There was one death during the Overall Period in a placebo subject (fatal cardiogenic shock).

Treatment-emergent SAEs experienced by >1 subject in either group were worsening of PN, pemphigoid, osteoarthritis, and acarodermatitis.

From the AESIs, a higher percentage had AESIs of peripheral and facial oedema. However, due to confounding factors and the time connections, no firm conclusion about a relationship between peripheral and facial oedema and nemolizumab can be drawn. However, information about this observed imbalance was included in the Information for healthcare professionals.

6.5 Final clinical benefit risk assessment

An adequate clinical pharmacology programme was conducted. The PK of nemolizumab was comparable between patients with AD and PN. Based on the population PK analysis, no dose adjustments are required based on any of the investigated covariates apart from body weight. Exposure-efficacy simulations using the final PK/PD models demonstrated that the proposed dosing regimens are adequate for low and high body weight AD and PN patients.For both indications the pivotal studies demonstrated a clinically relevant effect of nemolizumab. Nemolizumab in combination with topical therapy can be concluded to be efficacious in adult and adolescent AD patients. Since no monotherapy studies for nemolizumab in AD patients were conducted, no conclusions for nemolizumab monotherapy in AD patients can be drawn.
Nemolizumab as monotherapy can be concluded to be efficacious in adult PN patients.

Although rare AEs may not have been covered and longer-term data are sparse, the overall safety database is considered adequate to assess the safety profile of nemolizumab. No major safety concerns were observed in the safety database.

The benefit/risk ratio is therefore considered positive for adolescent and adult patients with moderate to severe AD in combination with topical therapy when the disease is not adequately controlled with topical medicinal products alone and as monotherapy in adult PN patients who are candidates for a systemic therapy.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Nemluvio was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the “Undesirable effects” section for advice on the reporting of adverse reactions.

Nemluvio®

Composition

Active substances

Nemolizumab, produced by recombinant DNA technology in Chinese Hamster Ovary cells.

Excipients

Powder: sucrose, trometamol, trometamol hydrochloride (for pH adjustment), arginine hydrochloride, poloxamer 188
Solvent: water for injections

Pharmaceutical form and active substance quantity per unit

Powder and solvent for solution for injection in pre-filled pen:

- Following reconstitution, each single-use pre-filled pen contains 30 mg nemolizumab per 0.49 mL dose administered.

Powder and solvent for solution for injection in pre-filled syringe:

- Following reconstitution, each single-use pre-filled syringe contains 30 mg nemolizumab per 0.49 mL dose administered.

Indications/Uses

Atopic dermatitis (AD)

Nemluvio is indicated for the treatment of adults and adolescents 12 years of age and older weighing at least 30 kg with moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical medicinal products alone (see “Dosage/Administration” and “Clinical efficacy”).

Prurigo nodularis (PN)

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

Dosage/Administration

Atopic dermatitis (AD)

The recommended dosage of Nemluvio in adults and adolescents 12 years of age and older 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:
Nemluvio is used with low or medium potency topical corticosteroids and/or topical calcineurin inhibitors. Topical calcineurin inhibitors should be reserved for problem areas only, such as the face and neck, as well as the 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.

Prurigo nodularis (PN)

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

The recommended Nemluvio dose for patients weighing 90 kg or more is an initial dose of 60 mg (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 of prurigo nodularis after 16 weeks of treatment.

Traceability

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Missed dose (for all indications)

If a dose is missed, it should be administered as soon as possible. Thereafter, dosing should be resumed at the regular scheduled time.

Special dosage instructions

Elderly patients (≥65 years)

No dose adjustment is needed for elderly patients (see “Pharmacokinetics” section).

Patients with impaired hepatic or renal function

No dose adjustment is needed for patients with mild or moderate hepatic or renal impairment. Very limited data are available for patients with severe hepatic or renal insufficiency (see “Pharmacokinetics” section).

Children and adolescents

The safety and efficacy of Nemluvio in children less than 12 years of age with moderate-to-severe atopic dermatitis have not yet been established.
The safety and efficacy of Nemluvio in children and adolescents less than 18 years of age with prurigo nodularis have not been established. No data are available.

Body weight

No dose adjustment based on body weight is recommended for patients 12 years of age and older with atopic dermatitis (see “Pharmacokinetics” section).
A dose of 60 mg (two 30 mg injections) is recommended for prurigo nodularis patients weighing 90 kg or more (see “Pharmacokinetics” section).

Mode of administration

Treatment should be initiated by healthcare professionals experienced in the diagnosis and treatment of conditions for which Nemluvio is indicated (see “Indications/Uses” section). A patient may self-inject Nemluvio or a patient’s caregiver may inject Nemluvio if their healthcare professional determines that this is appropriate. Prior to use, the patient and/or their caregivers should be given training on the preparation and administration of Nemluvio according to the instructions for use provided in the package leaflet.

Subcutaneous use

Nemluvio should be subcutaneously injected into the front upper thigh or the abdomen except for the 5 cm area around the navel. Injection into the upper arm is also an option if performed by a person other than the patient themselves.
The injection site must be alternated with each injection. Nemluvio should not be injected into skin areas that are tender, inflamed, swollen, damaged or have bruises, scars or open wounds.
Refer to the “Instructions for handling” section for more information about administration of this medicinal product.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in the “Composition” section.

Warnings and precautions

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

Uncontrolled asthma
Patients with uncontrolled asthma were excluded from studies and no data are available on Nemluvio in this population.

Vaccinations

It is recommended that patients be brought up to date with all vaccinations in line with current immunisation recommendations prior to initiating treatment with Nemluvio. Use of live vaccines in patients treated with Nemluvio should be avoided. It is unknown whether administration of live vaccines during treatment with Nemluvio will impact the safety or efficacy of these vaccines. No data are available on the response to non-live vaccines.

Interactions with cytochrome P450

The effects of nemolizumab on the pharmacokinetics of midazolam (CYP3A4/5 substrate), warfarin (CYP2C9 substrate), omeprazole (CYP2C19 substrate), metoprolol (CYP2D6 substrate) and caffeine (CYP1A2 substrate) were evaluated in a study (SPR.201593) in 14 subjects with moderate-to-severe AD receiving an initial subcutaneous dose of 60 mg followed by 30 mg subcutaneously every 4 weeks for 12 weeks. No clinically significant changes in the exposure of CYP450 substrates before and after multiple nemolizumab injections were observed, with Cmax and AUC ratios ranging from 88.24% to 107.81%. Nemolizumab is not expected to impact the pharmacokinetics of co-administered medicinal products.

Pregnancy, lactation

Pregnancy

There is a very limited amount of data on the use of nemolizumab in pregnant women to date. Animal studies have not revealed any evidence of direct or indirect harmful effects with respect to reproductive toxicity (see “Preclinical data”). As a precautionary measure, the use of nemolizumab should be avoided during pregnancy.

Lactation

It is unknown whether Nemluvio is excreted in human milk or whether it has any effects on the breastfed infant or any effects on milk production. No data are available on the excretion of nemolizumab in human milk. In humans, excretion of IgG antibodies in milk occurs during the first few days after birth, which is decreasing to low concentrations soon afterwards. Consequently, transfer of IgG antibodies to the newborn through milk may happen during the first few days. In this short period, a risk to the breastfed child cannot be excluded.

Fertility

Animal studies demonstrated no impairment of fertility (see “Preclinical data”).

Effects on ability to drive and use machines

The effects of Nemluvio on the ability to drive or use machines have not been investigated in dedicated studies.

Undesirable effects

Summary of the safety profile

The most common adverse reactions in atopic dermatitis and prurigo nodularis are type I hypersensitivity reactions (1.1%; includes urticaria 1.0% and angioedema 0.1%) and injection site reactions (1.2%). Additional adverse reactions such as headache (7.0%), atopic dermatitis (4.6%), eczema (3.8%) and eczema nummular (3.5%) were reported in prurigo nodularis (see “Warnings and precautions” section).

List of undesirable effects

The safety of Nemluvio was evaluated in a pool of three randomised, placebo-controlled studies in patients with atopic dermatitis (1192 patients who received Nemluvio and 640 patients who received placebo) and two randomised, placebo-controlled studies in patients with prurigo nodularis (370 patients who received Nemluvio and 186 patients who received placebo).

Table 1 lists undesirable effects observed in clinical studies, presented by MedDRA system organ class and frequency, using the following categories: very common (≥1/10), common (≥1/100, <1/10), uncommon (≥1/1000, <1/100), rare (≥1/10,000, <1/1000), and very rare (<1/10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 1: List of undesirable effects

MedDRA system organ class	Frequency	Undesirable effects
Nervous system disorders	Common	Headache (incl. tension headache)*
Skin and subcutaneous tissue disorders	Common	Urticaria† Atopic dermatitis*, eczema*, eczema nummular*
	Uncommon	Angioedema*
General disorders and administration site conditions	Uncommon	Injection site reactions (including erythema, pruritus, pain†, irritation†, haematoma*)
	Rare	Injection site oedema†

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

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

Description of specific adverse reactions and additional information

Hypersensitivity

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

Injection site reactions

The incidence of injection site reactions during the initial period was low in patients with atopic dermatitis treated with either Nemluvio (1.3% of patients) or placebo (1.1% of patients). During the maintenance period, the incidence remained low with Nemluvio Q8W (0%) and placebo (0.5%).
In patients with prurigo nodularis, the incidence of injection site reactions was low, both with treatment with Nemluvio (1.1%) and with placebo (1.6%). There were no severe injection site reactions.
There were no reactions leading to treatment discontinuation in either indication.

Headache

In patients with prurigo nodularis, headache was more frequently reported in patients treated with Nemluvio (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 atopic dermatitis, eczema nummular or eczema were more frequently reported in Nemluvio-treated patients compared to patients treated with placebo: atopic dermatitis (4.6% of patients compared to 0.5% of patients), eczema (3.8% of patients compared to 2.2% of patients) and eczema nummular (3.5% of patients compared to 0% of patients). These eczematous reactions were mild or moderate in severity. Atopic dermatitis led to discontinuation of Nemluvio in two patients (0.5%). There were no events of eczema nummular or eczema that led to discontinuation of the study.

Peripheral and facial oedema

In patients with atopic dermatitis and prurigo nodularis, peripheral and facial oedema was more frequently reported in patients treated with Nemluvio (1.6% and 3.0%) compared to patients treated with placebo (0.3% and 1.6%).

Currently available information about peripheral and facial oedema is not sufficient to establish a causal relationship with Nemluvio.

Immunogenicity

Like all therapeutic proteins, Nemluvio has the potential for immunogenicity.
The observed incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the assay. Differences in assay procedures preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of nemolizumab.

In the AD phase 3 pivotal studies (ARCADIA 1, ARCADIA 2) and the ARCADIA LTE study over up to 128 weeks, the incidence of treatment-emergent ADAs was 11.2%. Neutralising antibodies were observed in 0.5% of patients.
In the PN phase 3 pivotal studies (OLYMPIA 1, OLYMPIA 2) and the OLYMPIA LTE study over up to 116 weeks, the incidence of treatment-emergent ADAs was 12.8%. Neutralising antibodies were observed in 3.5% of patients.

Paediatric population

Atopic dermatitis (AD) – Adolescents (12 to 17 years of age)

The safety of Nemluvio was assessed in 176 paediatric patients 12 to 17 years of age with moderate-to-severe atopic dermatitis enrolled in the ARCADIA 1 and ARCADIA 2 studies. The safety profile of

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

Statement on the reporting of adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or serious adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There is no specific treatment for Nemluvio overdose. In the event of overdose, the patient should be monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment should be instituted immediately if necessary.

Properties/Effects

ATC code

D11AH12

Mechanism of action

Nemolizumab is a humanised IgG2 monoclonal antibody that inhibits interleukin-31 (IL-31) signalling by binding selectively to interleukin-31 receptor alpha (IL-31 RA). IL-31 is a naturally occurring cytokine that is involved in pruritus, inflammation, epidermal dysregulation and fibrosis. Nemolizumab inhibits IL-31-induced responses including the release of proinflammatory cytokines and chemokines.

Pharmacodynamics

Clinical efficacy

1) Clinical efficacy and safety in adults and adolescents with atopic dermatitis

The efficacy and safety of Nemluvio with concomitant topical background therapy was evaluated in two randomised, 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. 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.

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

After 16 weeks, patients achieving either EASI-75 or IGA success continued into the study maintenance period for another 32 weeks to evaluate the maintenance of response achieved at Week 16. Nemluvio responders were re-randomised to receive either Nemluvio 30 mg every 8 weeks or placebo every 4 weeks (all groups continued treatment with TCS/TCI). Patients randomised 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, patients who lost clinical response during the maintenance period and patients who completed the maintenance period had the opportunity to enrol into the open-label study (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 patients 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 patients 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, patients with both EASI-75 and PP NRS improvement ≥4

from baseline at Week 16, and patients with both IGA success and PP NRS improvement ≥4 from baseline at Week 16.

Baseline characteristics

In these studies, at baseline, 51.0% of patients were male, 79.9% were White and 15.4% were 12 to 17 years of age. 70% of patients had a baseline IGA score of 3 (moderate AD), and 30% of patients 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) and baseline weekly average SD NRS was 5.8. Overall, 63.3% of patients had received other previous systemic treatments for atopic dermatitis.

Clinical efficacy – 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). Results for both co-primary endpoints were consistent in the severe pruritus population (baseline PP NRS ≥7).

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 patients randomised and dosed (baseline PP NRS ≥4)	620	321	522	265
% of patients with IGA 0 or 1[a]	35.6[#]	24.6	37.7[#]	26.0
% of patients with EASI-75[a]	43.5*	29.0	42.1[#]	30.2

[a] Patients 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 – Proportion of patients with IGA success and EASI-75 from baseline to Week 16 in ARCADIA 1 and ARCADIA 2

Fig. 1a: IGA success

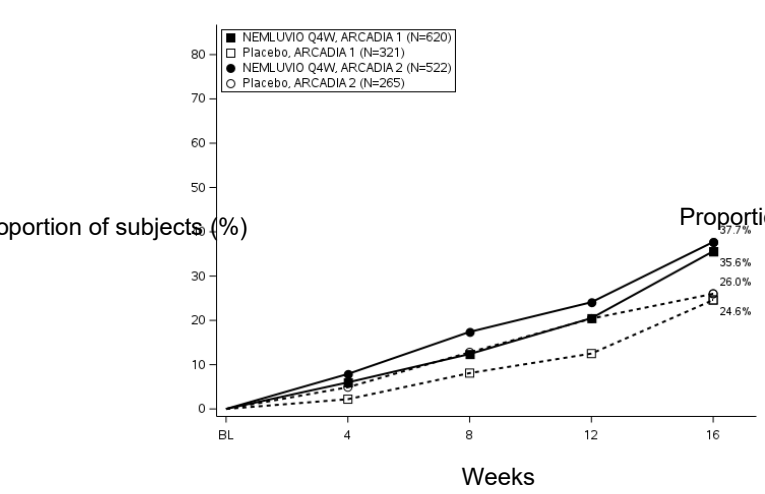
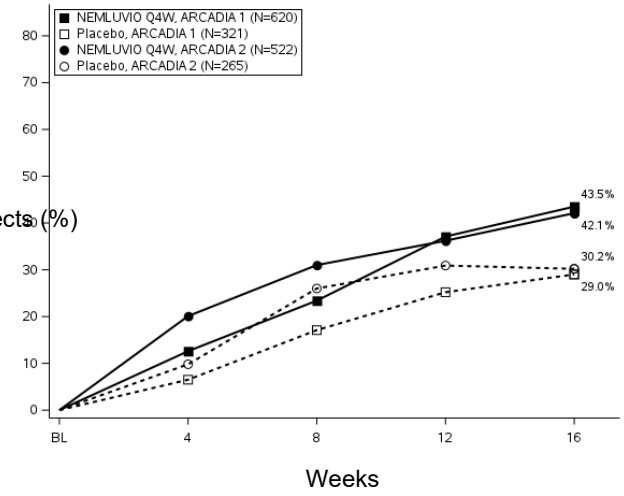


Fig. 1b: EASI-75



Significant improvement in pruritus for patients treated with Nemluvio in ARCADIA 1 and ARCADIA 2, compared to placebo, based on PP NRS improvements ≥4 from baseline was observed starting at Week 1 and was maintained through Week 16 (Table 3). Results were consistent in the severe pruritus population (baseline PP NRS ≥7).

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

	ARCADIA 1		**ARCADIA 2**	
	Nemluvio + TCS/TCI	**Placebo + TCS/TCI**	**Nemluvio + TCS/TCI**	**Placebo + TCS/ TCI**
Number of patients randomised and dosed (baseline PP NRS ≥4)[a]	620	321	522	265
% of patients 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 patients 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

[a] Patients 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.

The Sleep Disturbance Numeric Rating Scale (SD NRS) is a daily scale used by 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). Results were consistent in the severe pruritus population (baseline PP NRS ≥7).

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 patients randomised and dosed (baseline PP NRS ≥4)[a]	620	321	522	265
% of patients with SD NRS improvement ≥4[a]	37.9*	19.9	33.5*	16.2
Mean change from baseline (%)	-64.6	-38.1	-59.7	-35.4

[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

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

The efficacy results of the ARCADIA 1 and ARCADIA 2 studies at Week 16 for paediatric subjects 12 to 17 years of age are presented in Table 5. The results in the paediatric subject population were generally consistent with the results in the adult subject population. Results in co-primary and key secondary endpoints were consistent in the severe pruritus population (baseline PP NRS ≥7).

Table 5 – Efficacy results for nemolizumab (30 mg Q4W) with concomitant TCS/TCI in ARCADIA 1 and ARCADIA 2 at Week 16 in paediatric subjects 12 to 17 years of age

	ARCADIA 1 AND ARCADIA 2	
	Nemluvio + TCS/TCI	**Nemluvio + TCS/TCI**
Number of patients randomised and dosed (baseline PP NRS ≥4)	179	90
% of patients with IGA 0 or 1[a]	48.9*	34.4
% of patients with EASI-75[a]	53.4[§]	43.3

[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 <0.05, [∞]p-value =0.0591, [§]p-value =0.1824
Strata-adjusted p-value is based on the CMH test stratified by PP NRS and IGA score at baseline.

Clinical efficacy – ARCADIA 1 and ARCADIA 2 – Adults and adolescents – Maintenance period, Week 16 to Week 48

The clinical response in nemolizumab responders (IGA 0/1 or EASI-75 at Week 16) was analysed between Week 16 and Week 48 in ARCADIA 1 and ARCADIA 2 studies. For the maintenance treatment period, 338 nemolizumab responders were re-randomised to receive either nemolizumab 30 mg Q8W or placebo Q4W (nemolizumab withdrawal) with concomitant TCS/TCI. At Week 48, in the nemolizumab 30 mg + TCS/TCI Q8W group, 60.4% of patients achieved IGA 0/1 and 75.7% achieved EASI-75, compared to 49.7% of patients who achieved IGA 0/1 and 63.9% who achieved EASI-75 in the placebo + TCS/TCI Q4W group.

2) Clinical efficacy and safety in adults with prurigo nodularis

The efficacy and safety of Nemluvio as monotherapy was evaluated in two randomised, 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. 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. Patients 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 had a 16-week treatment period.

Subjects who completed OLYMPIA 1 or OLYMPIA 2 had the opportunity to enrol into the open-label study (OLYMPIA LTE) and receive treatment with Nemluvio every 4 weeks up to 184 weeks.

In the Nemluvio monotherapy group, subjects weighing less than 90 kg received a subcutaneous injection of Nemluvio 60 mg (2 injections of 30 mg) at Week 0, followed by 30 mg injections every 4 weeks. In the Nemluvio monotherapy group, subjects weighing 90 kg or more 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 patients with an improvement of ≥4 from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16
- Proportion of patients 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 Weeks 4 and 16.

Baseline characteristics

In these studies, at baseline, 59.6% of patients were female, 81.4% were White and 25.4% were older than 65 years of age. The baseline weekly average PP NRS score was a mean (SD) of 8.4 (0.9). 58% of patients had a baseline IGA score of 3 (moderate PN), and 42% of patients had a baseline IGA score of 4 (severe PN).

Clinical efficacy

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

The results of the pivotal studies evaluating treatment with Nemluvio in OLYMPIA 1 and OLYMPIA 2 are presented in Table 6 and show significant improvement in Nemluvio-treated patients, compared to placebo for both primary endpoints (Figure 2 and Figure 3) and key secondary endpoints.

Table 6 – Efficacy results for Nemluvio monotherapy (Q4W) in OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		**OLYMPIA 2**	
	Nemluvio	**Placebo**	**Nemluvio**	**Placebo**
Number of patients randomised	190	96	183	91
% of patients with PP NRS improvement ≥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 patients with IGA 0 or 1 at Week 16[a]	26.3[#]	7.3	37.7*	11
% of patients 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
% of patients with SD NRS improvement ≥4 from baseline[a]				
Week 4	31.1*	5.2	37.2*	9.9
Week 16	50.0*	11.5	51.9*	20.9

[a] If subjects received any rescue therapy, a 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 the 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 randomised stratification variables (analysis centre and baseline body weight (<90 kg, ≥90 kg))
[§] p-value <0.0001 Strata-adjusted vs. placebo (ANCOVA MI-MAR)

Figure 2 – Proportion of patients with PP NRS improvement ≥4 from baseline to Week 16

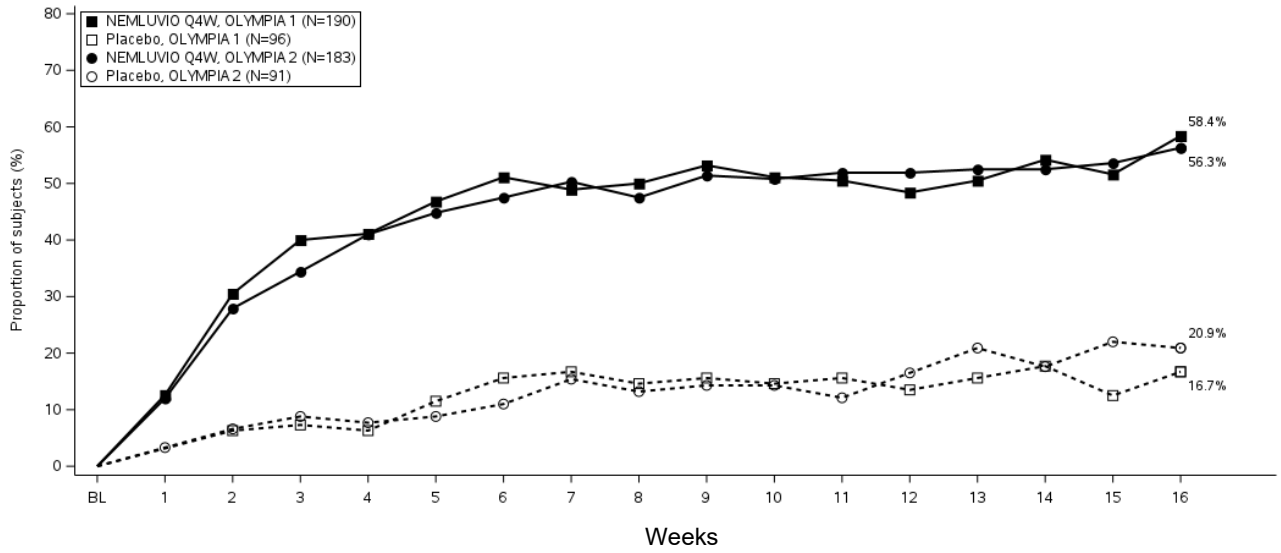
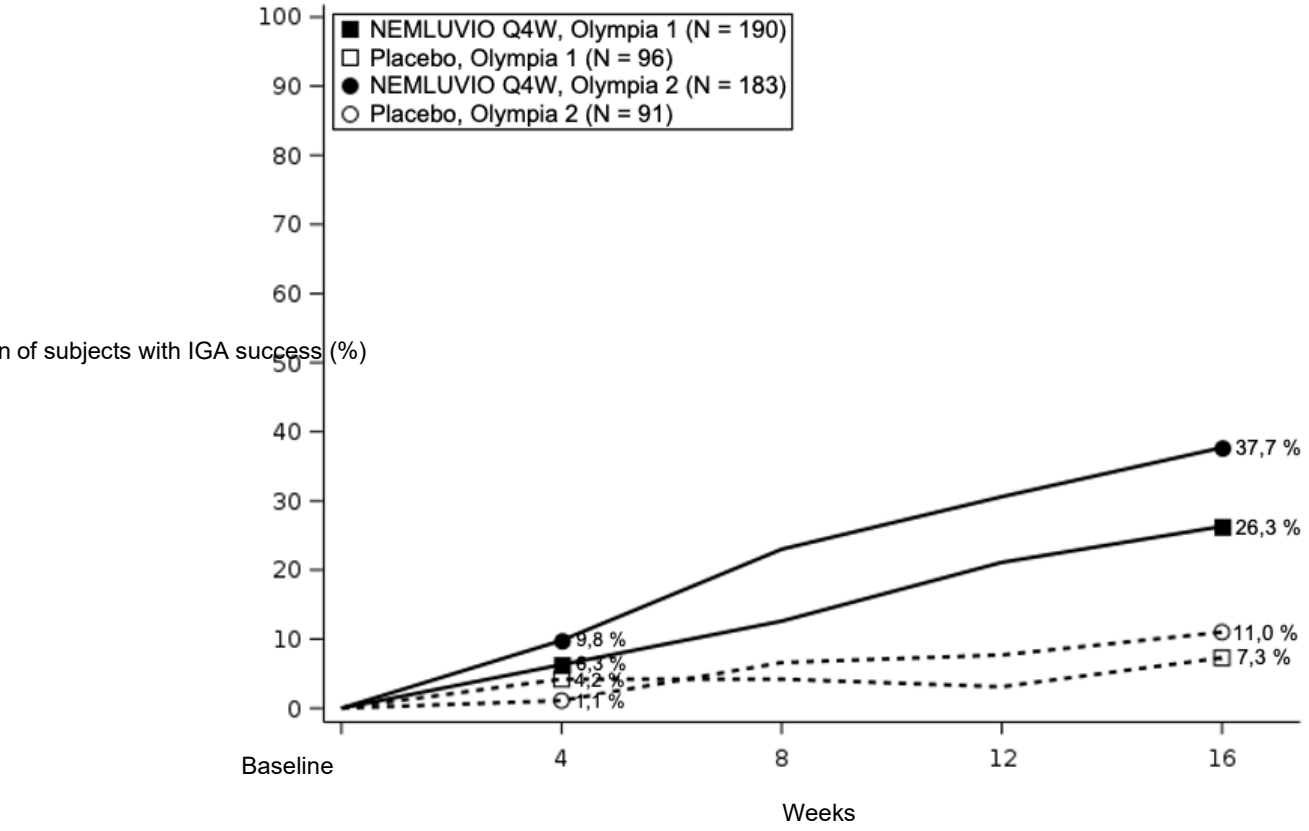


Figure 3 – Proportion of IGA responders from baseline to Week 16



Pharmacokinetics

Absorption

Following an initial subcutaneous dose of 60 mg in a phase 1 study (96 patients per arm), nemolizumab reached peak mean (SD) concentrations (Cmax) of 7.5 (2.31) µg/mL by approximately 6 days post dose.
After multiple doses of Nemluvio administered to patients with atopic dermatitis, the 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.
After multiple doses of Nemluvio administered to patients with prurigo nodularis, the estimated mean (SD) steady-state trough concentrations of nemolizumab were 3.04 (1.23) µg/mL in patients weighing <90 kg for 30 mg administered Q4W and 3.66 (1.63) µg/mL in patients weighing ≥90 kg for 60 mg administered Q4W.
In both the atopic dermatitis population and the 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 pharmacokinetic analysis, the volume of distribution was 7.67 L.

Metabolism

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

Elimination

Nemolizumab is expected to be degraded in the same manner as endogenous IgG. In the population pharmacokinetic 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 showed linear pharmacokinetics with exposures increasing in a 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 subcutaneous dose range up to 30 mg. There was a slight decrease in bioavailability by 9% with the 60 mg subcutaneous dose and by 15% with the 90 mg subcutaneous dose.

Kinetics in specific patient groups

Gender, age and ethnicity

Based on a population pharmacokinetic analysis, gender, age (12 to 85 years for atopic dermatitis and 18 to 84 years for prurigo nodularis) and ethnicity 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 pharmacokinetics of nemolizumab determined by population pharmacokinetic analysis. No data are available for 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 pharmacokinetic analysis did not identify mild or moderate renal impairment as having a clinically significant influence on nemolizumab systemic exposure. Very limited data are available for patients with severe renal impairment.

Body weight

Nemolizumab exposure was lower in patients with higher body weight.

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 “Dosage/Administration”).

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 patients with prurigo nodularis (see “Dosage/Administration”).

Paediatric population

Atopic dermatitis

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

Preclinical data

Mutagenicity and carcinogenicity

The mutagenic potential of nemolizumab has not been evaluated. However, monoclonal antibodies are not expected to alter DNA or chromosomes.
Carcinogenicity studies have not been conducted with nemolizumab. The results of the animal studies and the available evidence related to IL-31 inhibition do not suggest carcinogenic potential for nemolizumab.

Reproductive toxicity

No effects on fertility parameters were observed in sexually mature cynomolgus monkeys after long-term subcutaneous treatment with nemolizumab. No direct or indirect harmful effects on pregnancy, embryonic and foetal development, or postnatal development were observed during subcutaneous treatment of dams with nemolizumab from early organogenesis to delivery and during direct administration to the offspring over a period of 26 weeks starting on day 35 after birth. However, at high exposures (43- or 34-fold higher than human exposure at the maximum recommended human dose in AD or PN patients, respectively) in the group of dams treated with 25 mg/kg of nemolizumab every two weeks, a slight increase in the incidence of offspring death was observed during the early postnatal period. Although unlikely, a relationship between this finding and nemolizumab cannot be completely excluded.

Other information

The information provided below applies to all available dosage forms.

Incompatibilities

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

Effects on diagnostic methods

No data are available.

Shelf life

Do not use this medicine after the expiry date (“EXP”) stated on the package. If necessary, the carton containing the pre-filled pen or pre-filled syringe can be removed from the refrigerator and kept at room temperature (up to 25°C) for a single period up to 90 days. The date of first removal from the refrigerator should be recorded in the space provided for this purpose on the outer carton of the pre-filled pen or pre-filled syringe. Nemluvio must not be used after the expiry date or 90 days after the date it was first removed from the refrigerator (whichever is earlier).

Special precautions for storage

Keep out of the sight and reach of children.
Keep the pre-filled syringe or pre-filled pen in the original package in order to protect the contents from light.
Store in the refrigerator (2-8°C). Do not freeze or expose this medicinal product to heat.
For storage conditions after reconstitution of the medicinal product, see Instructions for handling section.

Instructions for handling

For comprehensive instructions for the administration of Nemluvio in a pre-filled pen or in a pre-filled syringe, see the end of the package leaflet.
Nemluvio must be removed from the refrigerator 30-45 minutes before reconstitution. Once the reconstitution steps are completed, Nemluvio must be used within 4 hours or discarded.
Nemluvio must be inspected visually prior to reconstitution. Nemluvio consists of a white powder and a clear liquid. Nemluvio must not be used if the powder is not white or if the liquid is cloudy or has visible particles in it. Prior to administration, it must be checked that Nemluvio is clear and colourless to slightly yellow and does not contain any particles.
The pre-filled pen or pre-filled syringe must not be exposed to heat or direct sunlight, and it must not be shaken.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

Nemluvio, powder and solvent for solution for injection in pre-filled pen: 69707 (Swissmedic)
Nemluvio, powder and solvent for solution for injection in pre-filled syringe: 69818 (Swissmedic)

Packs

Nemluvio, 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 sizes:
• 1 pre-filled pen [B]
• Multipack containing 2 (2 packs of 1) pre-filled pens [B]

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

Single-use dual-chamber borosilicate glass type 1 pre-filled syringe, co-packaged with a 27G needle (stainless steel) with safety shield.
Pack size:

• 1 pre-filled syringe [B]

Marketing authorisation holder

Galderma Ltd

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