Risk Management Plan (RMP) for NEMOLIZUMAB

Active substance(s) **(INN or common name)**	Nemolizumab
Pharmacotherapeutic group (ATC code)	D11AH12 (Agent for Dermatitis, excluding corticosteroids)
Company Name of Marketing Authorization Holder or Applicant	Galderma International La Défense 4 - Tour Europlaza, 20 avenue André Prothin 92927 Paris La Défense Cedex France
RMP version to be assessed as part of this application:	
RMP version number	2.0
Development International Birth Date	22 July 2011
Data Lock Point for this RMP	21 July 2023
Date of final sign-off	18 December 2024

SIGNATURES

The content of this RMP has been reviewed and approved by the marketing authorisation Galderma International's QPPV. The electronic signature is available on file

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LIST OF ABBREVIATIONS

Abbreviation	Term
ACT	Asthma Control Test
AD	Atopic Dermatitis
ADA	Anti-Drug Antibodies
ADCC	Antibody-Dependent Cell mediated Cytotoxicity
ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
AR	Adverse Reaction
AUC	Area Under the Curve
BMI	Body Mass Index
BW	Body Weight
CDC	Complement Dependent Cytotoxicity
CHO	Chinese Hamster Ovary (cell)
CI	Confidence interval
CKD-aP	Chronic kidney disease-associated pruritus
Cl/F	Apparent Clearance
Cmax	Maximum Concentration
COPD	Chronic Obstructive Pulmonary Disease
COVID	Coronavirus Disease
CPK	Creatine Phosphokinase
CRS	Cytokine Release Syndrome
C1q	Component 1q
CSR	Clinical Study Report
CVD	Cardiovascular Disease
DCC	Dual Chamber Cartridge
DCS	Dual Chamber Syringe
DCSI	Development Core Safety Information
DIBD	Development International Birth Date
DLP	Data Lock Point
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECLIA	Electrochemiluminescence Immunoassay
eGFR	Estimated Glomerular Filtration Rate
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ePPND	Enhanced Pre-And Postnatal Development Study
ESKD	End-stage Kidney Disease
FcγR	Fc gamma receptors
FDA	Food and Drug Administration
GVP	Good Pharmacovigilance Practice
HbsAb	Hepatitis B Core Antibody
HbsAg	Hepatitis B Surface Antigen
HC	Heavy chain
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form

Abbreviation	Term
ICH	International Council for Harmonization
ICSR	Individual Case Safety Reports
IGA	Investigator Global Assessment
IgG	Immunoglobulin G
IL- (6, 8, 31)	Interleukin- (6, 8, 31)
IL-31RA	Interleukin-31 Receptor A
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRR	Injection-Related Reaction
iSMP	Integrated Safety Management Plan
ITT	Intent-To-Treat
JAK	Janus Kinase
LD	Loading Dose
MAA	Marketing Authorization Application
MALT	Mucosa-Associated Lymphoid Tissue
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MP	Medicinal Product
mRNA	Messenger Ribonucleic Acid
Nab	Neutralizing Antibodies
NOAEL	No-observed-adverse-effect level
OR	Odd Ratio
OSMR	Oncostatin M Receptor
PCR	Polymerase Chain Reaction
PEF	Peak Expiratory Flow
PK	Pharmacokinetic
PIL	Patient Information Leaflet
PMDA	Pharmaceuticals and Medical Devices Agency
PN	Prurigo Nodularis
popPK	Population Pharmacokinetic
PT	Preferred Term
PY	Person years
Q4W	Every 4 Weeks
Q8W	Every 8 Weeks
QoL	Quality of Life
RMP	Risk Management Plan
RR	Relative Risk
SAE	Serious Adverse Event
SAF	Safety
SC	Subcutaneous
SHPT	Secondary Hyperparathyroidism
SmPC	Summary of Product Characteristics
SOC	System Organ Class
STAT	Signal Transducer and Activator of Transcription
SUSAR	Serious Unexpected Suspected Adverse Reaction
TB	Tuberculosis
TCI	Topical Calcineurin Inhibitor
TCS	Topical Corticosteroids
TEAE	Treatment-Emergent Adverse Event
TNF	Tumor Necrosis Factor
ULN	Upper Limit of Normal
UP	Uremic Pruritus

Abbreviation	Term
US	United States
UV	Ultraviolet
VAS	Visual Analog Scale
Vd/F	Apparent Volume of Distribution

INTRODUCTION

This Risk Management Plan (RMP) has been implemented for nemolizumab (CD14152), herein after nemolizumab. an investigational medicinal product (IMP) with Development International Birth Date (DIBD) of 22 July 2011, the approval date (i.e.: notification date) of the first interventional clinical study in Japan.

The RMP is a living document which is ideally written early in the drug development process and maintained throughout the product lifecycle. Its aim is to document the risk management system considered necessary to identify, characterize, and minimize the risks of a drug product.

This RMP lists important and non-important, identified and potential risks, as well as missing information, for nemolizumab, as of the above-mentioned cut-off date, and includes general recommendations for risk minimization. Specific risk minimization measures in the targeted indications, i.e. treatment of moderate-to-severe atopic dermatitis (AD) n patients aged 12 years and older who are candidates for systemic therapy and treatment of moderate-to-severe prurigo nodularis (PN) in adults who are candidates for systemic therapy will be provided within the individual clinical study protocols.

The cumulative exposure to nemolizumab presented in this document is based on the Data Lock Point (DLP) of most recently submitted Development Safety Update Report (DSUR) (i.e., 21 July 2023) from which it has been extracted.

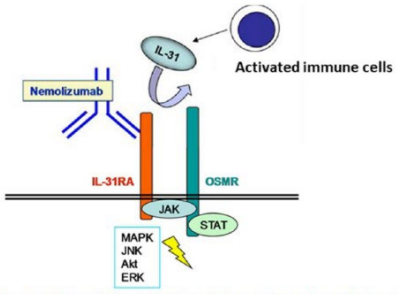
Galderma has a license agreement for nemolizumab with Chugai Pharmaceutical Co., Ltd., Japan (Chugai), a pharmaceutical development company. The clinical studies with nemolizumab conducted by Chugai are included with the Applicant studies. The cumulative exposure includes all subjects enrolled in clinical studies with nemolizumab that were conducted by the Applicant as well as the clinical studies with nemolizumab conducted by other applicants (i.e., Maruho).

As of 21st July 2023, a total of 4,093 subjects (patients and healthy volunteers) were enrolled and treated in the clinical trials sponsored by the Applicant, including 449 subjects in clinical trials sponsored by Chugai. Among the latter, 378 subjects have been exposed to nemolizumab, including 126 subjects exposed to doses <0.5 mg/kg, 79 subjects exposed to a dose of 0.5 mg/kg and 173 subjects exposed to doses > 0.5 mg/kg. In addition to the above, 689 subjects in the Maruho-sponsored studies.

Note: This RMP is prepared for the first marketing authorization application of nemolizumab for the treatment of moderate-to-severe AD in patients aged 12 years and older who are candidates for systemic therapy and for the treatment of moderate-to-severe prurigo nodularis in adults in Europe. Nemolizumab is also being investigated by the Applicant in the indication of chronic kidney disease-associated pruritus (CKD-aP), but this indication is not included in the current application (study still ongoing at the cut-off date of most recently submitted DSUR (i.e., 21 July 2023).

PART I: PRODUCT OVERVIEW

I.1 Description of the Medicinal Product

Active substance(s) (International Non-Proprietary Name (INN) or common name)	Nemolizumab
Pharmacotherapeutic group(s) (ATC Code)	D11AH12
Name of Marketing Authorisation Holder (MAH) or Applicant	Galderma International La Défense 4 - Tour Europlaza, 20 avenue André Prothin 92927 Paris La Défense Cedex France
Medicinal products to which this document refers	2
Invented names	NEMLUVIO
Marketing authorisation procedure	Centralised
Brief description of the product including:	
• Chemical class	Humanized Monoclonal Antibody Target: IL31RA
• Summary of mode of action	Nemolizumab is a humanized antibody targeting with high specificity and affinity an extracellular epitope (i.e., interleukin-31 receptor A; IL-31RA). After IL-31RA binds to its ligand, interleukin-31 (IL-31), IL-31RA forms a heterodimer with the oncostatin M receptor (OSMR), which activates the Janus kinase (JAK) Signal Transducer and Activator of Transcription (STAT) signalling pathway and transmits signals for cellular activity (Diveu C, 2004). By binding to IL-31RA, nemolizumab competitively blocks the binding of interleukin-31 (IL-31) to its receptor, thereby blocking subsequent transduction of the IL-31 signal into the cell (Figure 1). Interleukin-31 is a cytokine involved in pruritus of different conditions such as atopic dermatitis (AD), prurigo nodularis (PN), and patients with chronic kidney disease with associated pruritus (CKD-aP) (Dillon SR, 2004), (Ko MJ, 2014), (Arai I, 2013). IL- 31 also drives inflammatory processes (Yagi Y, 2007), (Singh B, 2016), (Nemmer JM, 2021), (Tsoi LC, 2022) and alters epidermal differentiation and skin barrier integrity (Cornelissen C, 2012), (Hänel KH, 2016), (Nemmer JM, 2021), (Tsoi LC, 2022). **Figure 1 Mechanism of action of nemolizumab**  Akt=protein kinase B; ERK=extracellular signal–regulated kinase; IL-31=interleukin-31; IL-31RA=interleukin-31 receptor A; JAK=Janus kinase; JNK=c-Jun N-terminal kinase; MAPK=Mitogen-activated protein kinase; OSMR=oncostatin M receptor; STAT=signal transducer and activator of transcription.

• Important information about its composition (e.g., origin of active substance of biological, relevant adjuvants or residues for vaccines	For the Drug Substance, the cell line used for cell culturing is generated from a Chinese Hamster Ovary cell line using recombinant deoxyribonucleic acid (DNA) technology. Drug product is provided as a lyophilized formulation, which upon reconstitution with water for injection, yields a solution containing 100 mg/mL nemolizumab, 20 mmol/L trometamol / tris hydrochloride, 250 mmol/L sucrose, 150 mmol/L L-arginine hydrochloride, and 0.5 mg/mL polyoxyethylene (160) polyoxypropylene (30) glycol, with a pH of 6.5 to 7.5.
Hyperlink to the product information	NEMLUVIO SmPC
Indication(s)	• Treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older who are candidates for systemic therapy. • Treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.
Dosage	**Atopic dermatitis (AD)** Adults and Adolescents (12 to 17 years of age) 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). NEMLUVIO can be used with or without topical corticosteroids (TCS). Topical calcineurin inhibitors (TCI) may be used, but 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. Some patients with initial partial response may further improve with continued treatment beyond 16 weeks. Once clinical response is achieved, the recommended maintenance dose of nemolizumab is 30 mg every 8 weeks. **Prurigo nodularis (PN)** The recommended dose of NEMLUVIO for patients aged 18 years and older 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 aged 18 years and older 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 on pruritus after 16 weeks of treatment for prurigo nodularis.
Pharmaceutical form(s) and strength(s)	1. NEMLUVIO 30 mg powder and solvent for solution for injection in pre-filled pen 2. NEMLUVIO 30 mg powder and solvent for solution for injection in pre-filled syringe
Is the product subject to additional monitoring?	Yes

PART II: SAFETY SPECIFICATION

PART II: MODULE SI EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

SI.1 Atopic dermatitis (AD)

Indication/target population	Atopic dermatitis
Disease	AD is a chronic disease of skin barrier dysfunction and immune responses to bacterial and environmental antigens and allergens, with principal features of eczematous lesions and pruritus characterized by recurring cycles of exacerbation and remission. The pathophysiology results from complex interactions of genetic and environmental factors (Rutkowski K, 2014) leading to the following 3 hallmarks of AD: skin barrier disruption (pillar 1), pruritus (pillar 2), and inflammation (pillar 3). The scratching associated with pruritus is also known to be a precipitating factor in the exacerbation of the skin eruptions. Scratching causes mechanical damage to the skin so that its barrier function is reduced. The penetration of foreign antigens into the epidermis increases the inflammatory response, and this leads to exacerbation of dermatitis and aggravation of the itching, which perpetuates more scratching. This vicious cycle is known as the "itch-scratch cycle" (Wahlgren, 1999) (Homey B, 2006). In many patients, AD starts during infancy/childhood and spontaneously resolves during the period from puberty to adulthood. However, for some it does not resolve, and for others, the disease begins in adulthood. The incidence of AD has increased 2- to 3-fold in industrialized countries in recent decades. The global prevalence rate of AD is estimated to be approximately 1 to 3% in adults and 15 to 30% in children (Nutten, 2015). Although AD is not a life-threatening disease, the signs and symptoms associated with AD, including pruritus and sleep disturbance, greatly affect quality-of-life (QOL) and activities of daily living. According to a survey in 2002 of AD patients and their caregivers in the United States and 7 European countries, patients with AD experience sleep disturbance due to itching on an average of 67 days per year, and patients with serious AD experience sleep disturbance due to itching on 162 days per year (Zuberbier T, 2006). For pediatric patients, there is considerable burden not only on the patients, but also on their caretakers. Parents of pediatric patients with moderate or severe AD spend an average of 2 to 3 hours every day administering therapeutic treatments and lose 1 to 2 hours of sleep every night (Su JC, 1997). As a result, maintenance of skin barrier function, treatment of inflammation, and control of itching are each very important for the improvement of dermatitis and QOL in AD.
Incidence and prevalence	AD is a common chronic inflammatory skin disease that affects up to 25% of children and 10% of adults around the world with great geographic differences. AD incidence and prevalence register a stable plateau in North America and Europe, while they are increased in other continents, such as Asia. Most cases (approx. 80%) AD onset occurs during the first years of life (Raimondo A, 2021). Incidence: Each year, up to 17.1% of adults and 22.6% of children were diagnosed with AD; with as many as 9.6% new cases of AD in children. The 1-year incidence ranged from 10.2 (95% CI 9.9-10.6) in Italy to 95.6 (95% CI 93.4-97.9) per 1,000 person-years in children in Scotland (Bylund S, 2020). Approximately, 80% of children with AD had disease onset during infancy (von Kobyletzki LB, 2014) and 66% had disease onset by the age of 7 years (Williams HC, 1998). In 1968, the incidence of AD in adults was 7.41 (95% CI 6.27–8.74) per 1,000 person years. The reported proportion of adult-onset AD was 8.0% in Germany at age 28–30 years (Burgess JA, 2008).

Indication/target population	Atopic dermatitis
	Prevalence: The prevalence of AD in the US childhood population is 17.2% (Laughter D, 2000) and it is similar to the 15.6% prevalence described in EU childhood population (Schultz Larsen F, 1996) and the 24% prevalence in 5- to 6-year-old children in Japan (Sugiura H, 1998). In the US and in Europe, recent data suggests that the prevalence of AD among children is approximately 20%. The 1-year US prevalence of AD was 12.98% in children in 2007-2008 and 7.2%-10.2% in adults in 2010-2012. In other regions, the 1-year prevalence among children in Asia is 0.96% to 22.6%. Studies of 21st century data for children showed that the point prevalence ranged from 0% in Nigeria (Ogunbiyi AO, 2005) to 18.2% in Turkey (Akcay A, 2014). The prevalence of AD among adults ranges between 7% and 14%, with substantial variation between countries. The 1-year prevalence of AD ranged from 7.2%-10.2% in the US in 2010-2012 and to 1.2% in Asia to 17.1% in Europe (Silverberg, 2017). The prevalence of AD was stable across age groups and across populations in 1958-2018. However, there was an increasing trend in Africa, and in some studies in Asia, especially in the 21st century, but the overall prevalence is usually lower than in Europe. The reported prevalence of AD was usually higher during the 21st century than the 20th century, especially in Africa and even in Europe. The data for Asia were more heterogeneous (Bylund S, 2020).
Demographic profile of target population – age, sex, race/ethnic origin	AD occurs in the early years of life. Some epidemiology studies have shown that 45% of affected children had the condition before 6 months of age, 60% before 1 year of age, and up to 85% before 5 years of age (Spergel, 2005), (Kay J, 1994). Some studies suggested a higher prevalence of AD for females than for males across all ages; however, there were conflicting results regarding sex differences.
Risk factors for the disease	The pathophysiology of AD is complex, encompassing both genetic and environmental risk factors.
Main treatment options	No treatment capable of completely curing the disease has been established. AD treatment guidelines established for the US (Eichenfield LF, 2014), Europe (Wollenberg A, 2018) and Japan (Saeki H, 2021) recommend TCSs of appropriate potency according to the severity of eruptions as first-line treatment. Topical calcineurin inhibitors (TCIs) are recommended as second-line therapy in patients who do not respond adequately to TCSs or in whom they are contraindicated. In particular, TCIs are commonly used to treat sensitive areas (e.g., face and neck), where TCS use is problematic. For pruritus alleviation, there are limited targeted antipruritic treatment options. Antihistamines are frequently used though their effect is limited (Pereira MP, 2018), (Matterne U, 2019). For patients who do not improve with these topical drugs or who have extensive and severe eruptions, phototherapy and immunomodulatory agents are considered. Systemic therapies such as oral corticosteroids, cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil are commonly used in severe AD. However, most of these treatments have not been approved in this indication and their use is limited by their side effects. Ultraviolet phototherapy is commonly used for AD treatment as well, although high-level evidence has not been obtained with phototherapy, and the burden for patients due to frequent clinic visits, limited access, and risk of skin cancers limits its utility. Several immunosuppressive (e.g., JAK inhibitors) and biological agents (e.g., anti- IL4 and/or IL-13 monoclonal antibodies) are currently being used or are in development for the treatment of AD.
Mortality and morbidity in target indication	All-cause mortality was found to be significantly increased in patients with AD, HR 1.27, (95% CI 1.11-1.45). Significant causes of death in this patient population were cardiovascular (HR 1.45; 95% CI 1.07-1.96), infectious (HR 3.71; 95% CI 1.43-9.60), and urogenital diseases (HR 5.51; 95% CI 1.54-19.80). No increased risk for death due to cancer, endocrine, neurologic, psychiatric, respiratory, or gastrointestinal disease was observed (Thyssen JP, 2018).

Indication/target population	Atopic dermatitis
Important comorbidities	AD comorbidities include food allergy, hay fever and asthma. Cross-sectional and longitudinal studies have suggested that allergic diseases occur following a time-based order: from AD and food allergy in infancy to gradual development into allergic asthma and allergic rhinitis in childhood (Yang L, 2020). Incidence of different types of atopies differs with age. AD peaks in the first years of life and declines after that time (Spergel JM, 2003). Asthma and allergic rhinitis increase in older ages, as sensitization develops. The atopic marsh is the natural history of the manifestations. In a recent meta-analysis, the overall pooled prevalence of asthma was 25.7% (95% CI 23.7-27.7) in AD patients and 8.1% (95% CI 7.0-9.4) among reference individuals (OR 3.03, 95% CI 2.64-3.47). Only few studies reported data on the severity of AD. Based on data from 10 and 15 studies, respectively, the pooled prevalence of asthma was 21.8% (95% CI 16.1-28.1) and 28.1% (95% CI 22.7-33.8) in 14,005 patients with mild AD and 6,453 patients with moderate-to-severe AD respectively (Ravnborg, et al., 2021). AD is associated with: - Sleep disturbances in 47% to 80% of children and 33% to 90% of adults (Bawany F, 2021). - Obesity (OR:1.47 (1.21-1.79) (Ali Z, 2018) - Cardiovascular diseases (CVD): AD was not associated with myocardial infarction (MI) in age- or multivariate-adjusted analyses in the nurses' Health Study 2, a cohort of US women. AD was significantly associated with stroke in the age- adjusted analysis (OR 1.38, 95% CI 1.03–1.85). This was no longer significant in multivariate models that adjusted for hypertension, hypercholesterolemia and diabetes (OR 1.31, 95% CI 0.98–1.76) and atopic comorbidities (OR 1.17, 95% CI 0.86–1.58). AD was not independently associated with nonfatal MI or stroke in this study (Drucker AM, 2016). However, the association between AD and CVD and type 2 diabetes mellitus have shown inconsistent results in a systematic review and meta-analysis. A positive association was observed with angina pectoris (OR 1·73; 95% CI 1·27–2·37), but no association was observed between AD and unspecified but suspected type 2 diabetes mellitus [pooled odds ratio (OR) 1·11; 95% CI: 0·87–1·42], hypertension (pooled OR 1·16; 95% CI 0·98–1·37), stroke (pooled OR 1·15; 95% CI 0·95–1·39) or MI (pooled OR 1·14; 95% CI 0·83–1·56) (Thyssen JP, 2018). - Psychiatric diseases: depression OR 3.27 (CI: 1.61-6.62), anxiety OR 2.01 (CI: 1.10-3.68), and suicidal ideation OR 2.03 (CI: 1.20-3.45 not adjusted, this decreased to OR 1.32 (CI: 0,75-2,33) in adjusted models (Drucker AM W. A., 2017). - Cancer: lymphoma (RR: 1.43 (95% CI: 1.12-1.81)) (Legendre L, 2015) . The risk can increase up to 6-fold with association with immunosuppression (OR: 6.18; 95% CI, 3.04-12.57) (Rafiq M, 2020). - Infections: AD found to be associated with a significantly increased risk of COVID-19 infection (OR: 1.48; P=0.020) (Patrick MT, 2021). - Conjunctivitis: compared to adults without AD, adults with AD had a fourfold higher risk of conjunctivitis (OR = 4.38; 95% CI, 1.39-13.79; p = .012) and specifically, an eight-fold higher risk of allergic conjunctivitis (OR = 8.03; 95% CI, 1.76-36.58; p = .007) (Wu KK, 2021).

SI.2 Prurigo nodularis (PN)

Indication/target population	Prurigo nodularis
Disease	PN is an under-recognized inflammatory skin condition characterized by intensely itchy nodules (Whang KA, 2020). This condition is characterized by the presence of multiple (up to hundreds), symmetrically distributed, highly pruritic, hyperkeratotic, erosive or crusted nodules and papules (Hyde JN, 1909). Chronic itching is believed to induce and maintain the characteristic PN skin lesions through an itch-scratch cycle (Bobko S, 2016). This leads to an impaired QOL due to severe itch and chronic skin lesions with a lack of treatment options (Warlich B, 2015). The physiopathology of PN is still not fully understood. Recent findings suggest that PN might be a consequence of chronic itch, which induces neural sensitization followed by lesion appearance and development of a chronic itch- scratch cycle. However, prurigo skin lesions are histo-pathologically characterized by peri-vascular infiltrates containing large numbers of lymphocytes, myeloid cells, and polynuclear cells (i.e., neutrophils, eosinophils, and basophils), (Weigelt N, 2010) (Ito Y, 2011), suggesting the involvement of immune cells that drive inflammation. Very recent studies have demonstrated mixed immune responses with both Type 2 and Type 17/22 involvement (Tsoi LC, 2022) (Sutaria N, 2022). In addition to cell infiltrate, histopathology of lesions of PN shows hyperplasia, with vertically arranged collagen fibers and increased number of fibroblasts in the dermis (Weigelt N, 2010), indicating dysregulated epidermal differentiation and major matrix remodeling. While PN pathophysiology remains yet to be fully elucidated, it is currently characterized by 4 hallmarks: pruritus, altered epidermal differentiation, inflammation, and skin fibrosis. A large spectrum of underlying conditions inducing chronic pruritus can be associated with PN, including dermatological (e.g., AD described also as “atopic prurigo”), systemic (e.g., chronic kidney failure), neurological (e.g., brachioradial pruritus), or psychiatric disorders (Ständer S, 2007). In some cases, the origin is unknown (idiopathic PN).
Incidence and prevalence	PN is relatively rare. The annual incidence of PN in Germany was 0.13% in 2011 (Augustin M, 2021). For the period 2016-2018, the prevalence of PN increased from 5.82 to 6.52 cases per 100,000 population in Poland (Ryczek et al., 2020). The prevalence of PN in the US was found to be 36.7-43.9 per 100,000 population based on the International Classification of Diseases (ICD)-10 coding using US claims database. (Ständer S A. M., 2021) (Whang KA, 2020). The prevalence found to be as high as 148.3 per 100,000 for the predominantly elderly Medicare population (Ständer S A. M., 2021).
Demographic profile of target population – age, sex, race/ethnic origin	PN primarily affects middle-aged females, although it can occur in patients of all ages and both sexes (Huang A, 2020). In a study of 909 adults with PN at a large US hospital network, the modal age group was 51 to 65 years of age and African American patients were 3.4 times more likely to have PN than white patients (OR: 3.4; 95% CI, 2.9–3.9; P .001) (Boozalis E, 2018).
Risk factors for the disease	Risk factors of PN include dermatoses (e.g. atopic dermatitis), systemic diseases (e.g. chronic kidney disease), infections (particularly chronic viral infections such as HIV and hepatitis C). (Huang A, 2020) Cancer treatment with pembrolizumab, paclitaxel, and carboplatin have been associated with the development of PN (Biswal SG, 2018, Fattore D, 2019). Psychogenic pruritus is thought to lead to PN (Kwon CD, 2019). Neuropathic itch might also cause PN.

Indication/target population	Prurigo nodularis
Main treatment options	The goal of PN treatment is to break the itch-scratch cycle to allow the skin to heal. There are limited disease management options for PN. The current international consensus treatment guideline (Ständer 2020a) advises following a multi-modal approach including general strategies to control pruritus, treatment of concomitant, potentially pruritogenic diseases and treatment of pruriginous lesions. The stepwise approach includes moisturizers, topical antipruritic topicals, topical corticosteroids and intralesional corticosteroids, topical calcineurin inhibitors as first steps (Weisshaar 2012). Second steps are mainly widespread skin-directed therapies like phototherapy, or systemic therapies targeting the immunologic (methotrexate or cyclosporine) (Berth- Jones J, 1995), and/or the neural (gabapentinoids, antidepressants) (Mazza M, 2013) components of the disease. Third steps include opioid-receptor antagonists, thalidomide (Andersen TP, 2011), and one biological treatment, dupilumab, approved in December 2022 in Europe. Other off- label therapeutic options for pruritus based on limited evidence include opioid receptor agonists (naltrexone) (Brune A, 2004), NK1-antagonists (aprepitant) (Ständer S S. D., 2010) and antibiotics (roxithromycin, erythromycin) (Horiuchi Y, 2006). However, given the high variability in response and the known adverse effects of these drugs, there is a need for new, well-tolerated drugs to better control the disease.
Mortality and morbidity in target indication	Over a 20-year observation period, patients with PN, overall, had higher all-cause mortality than controls (HR, 1.70; 95% CI, 1.51- 1.91) in an American study. subgroup analysis revealed that Black patients with PN had the highest mortality: (Sutaria N., 2022) - Black (HR, 2.07; 95% CI, 1.64-2.61), - White (HR, 1.74; 95% CI, 1.52-2.00), and - Hispanic (HR, 1.62; 95% CI, 1.03-2.54). The differences may be related to the existing racial disparities.
Important comorbidities	PN is associated with AD (up to 46%) (Kwon CD, 2019), as well as a variety of other dermatologic comorbidities, including xerosis cutis, excoriation disorder, cutaneous T-cell lymphoma, lichen planus, keratoacanthomas, and bullous pemphigoid (Iking, et al., 2013), (Whang, 2019), (Wu, 2013). A recent study demonstrated that PN has a significant effect on sleep in patients with PN (Gwillim EC, 2021), (Gwillim EC J. S., 2020) PN is significantly associated with a variety of systemic, cardiovascular (hypertension, congestive heart failure), metabolic (type II diabetes mellitus, obesity), renal (chronic kidney disease), psychiatric conditions (depression, substance-use disorders, mood disorder) comorbidities, liver disease (chronic hepatitis B, chronic hepatitis C, primary biliary cholangitis, chronic autoimmune cholestatic hepatitis), Human Immunodeficiency Virus infection, chronic obstructive pulmonary disease, and malignancies (specifically non-Hodgkin's lymphoma), (Boozalis E, 2018), (Kwon CD, 2019), (Williams KA, 2021). Rarer malignancies that have been associated with PN are metastatic transitional cell carcinoma of the bladder (Lin J.T., 2002) and Hodgkin's lymphoma (HL) (Dumont S, 2018), (Fina L., 1991). Case reports have noted an association between PN and malignancies, most notably hematologic malignancies such as non-HL (NHL) and HL for which the OR was reported to be 5.41 (95% CI 3.39- 8.64) (Larson VA, 2019). Similar results were found in to two US-based epidemiologic studies in which, compared to controls, patients with PN had 2 to 5 times increased odds of NHL (Huang AH, 2020). PN has also been linked to primary cutaneous lymphoma, mycosis fungoides, and multiple myeloma (Huang AH, 2020). Not only can PN be the presenting symptom of lymphoma, but the treatment of the underlying lymphoma can lead to improvement or resolution of PN lesions in some patients (Huang AH, 2020). An increased prevalence of PN has been observed in patients undergoing dialysis (Böhme T, 2014), (Hayani K, 2016). Non-dialysis CKD also has an impact on PN

Indication/target population	Prurigo nodularis
	according to a Korean population-based cohort study; eGFR was the strongest risk factor for PN, eGFR 15–29 (HR: 1.31, 95%CI: 1.05–1.62) and end-stage renal disease (HR: 1.46, 95%CF 1.25–1.69) (Kim HS, 2022).

PART II: MODULE SII NON-CLINICAL PART OF THE SAFETY SPECIFICATION

The nonclinical safety program for nemolizumab was designed to support the intended clinical indications.

Nemolizumab inhibited the IL-31-dependent proliferation of recombinant cells expressing human and monkey IL-31RA and OSMR in a concentration-dependent manner. It also inhibited IL-31-induced IL-6 production, MMP-1 production, MMP-3 production, and apoptosis in a human epidermal keratinocyte cell line (HaCaT cells) in a concentration-dependent manner.

Nemolizumab did not affect IL-6 dependent or oncostatin M (OSM)-dependent TF-1 cell proliferation.

The binding of nemolizumab to human FcγRs and human complement C1q was weak which was further confirmed by the reduced antibody-dependent cell-mediated cytotoxicity (ADCC) and complement dependent cytotoxicity activities observed. Therefore, the risk of constant region-mediated effector activity was considered to be low for nemolizumab.

The localization of IL-31RA was investigated immunohistochemically using skin tissue from AD patients, and the expression of IL-31RA at skin nerve endings was confirmed.

Nemolizumab showed cross-reactivity in cynomolgus monkeys only, no reactivity in mice, rats, or rabbits was observed. It showed high affinity for the soluble form of human and monkey IL-31RA inhibiting the binding of IL-31 to recombinant cells engineered to express human or monkey IL- 31RA in a concentration-dependent manner.

The itch-inhibiting effect of nemolizumab was tested by inducing systemic itching in cynomolgus monkeys by administration of IL-31 intravenously. In addition, efficacy was further tested in a mite antigen-induced AD mouse model using anti-mouse IL-31RA surrogate antibody.

In addition, the nemolizumab primary amino sequence was successfully engineered to minimize intrinsic immunogenic potential.

Expression in Chinese Hamster Ovary (CHO) cells precludes the presence of nonhuman glycans, and product- and process-related impurities are adequately controlled to exclude incremental risk. The selection of the human IgG2 heavy chain (HC) avoids Fc-mediated activities and reduces potential for binding to activating Fc receptors on innate immune effector cells.

A single CD4 T-cell epitope, located in the nemolizumab VH (variable domain) chain, was identified by in silico analysis. Thus, the possibility of a treatment-induced T-dependent humoral immune response cannot be excluded. However, the mode of action of nemolizumab to reduce levels of proinflammatory factors in the pruritic skin of subjects with AD or PN, including

downregulation of activated dendritic cells, may be anticipated to reduce probability of induction of an adaptive immune response to nemolizumab itself. Detection of mainly low-titer, treatment-emergent anti-drug antibody (ADA) in 11.2% and 12.8% of subjects treated in AD and PN Phase 3 clinical studies, respectively, is consistent with low intrinsic immunogenic potential and the mode of action of nemolizumab.

The most important potential risk was identified to be loss of efficacy during ongoing treatment in subjects who develop the highest ADA titers. Thus, sustainability of efficacy was assessed in relation to both ADA-positive status and ADA titer in the Phase 3 studies. Since it is uncertain whether the Th2 cytokine profile associated with AD and/or PN could increase risk of induction of antinemolizumab IgE antibodies with consequent impact on rate of occurrence of hypersensitivity reactions, the temporal relationship of the treatment-emergent ADA response to acute hypersensitivity reactions was also evaluated in the Phase 3 clinical studies. Because there was no association between detection of antinemolizumab IgE and hypersensitivity reactions in early clinical studies, monitoring of antinemolizumab IgE was not performed in the Phase 3 studies.

Based on the lack of effect of ADA observed on the PK, efficacy, and safety of nemolizumab in the Phase 3 studies for AD and PN, the risk of adverse events related to the immunogenic potential of nemolizumab is assessed as low. Therefore, no special warnings or precautions for immunogenicity-related risks are proposed for the prescribing information. Routine pharmacovigilance activities are considered adequate to detect any potential signal.

SII.1 Toxicity

The nonclinical safety evaluation was carried out in cynomolgus monkeys, in which the pharmacological activity of nemolizumab was demonstrated.

A summary of key nonclinical findings and their relevance to humans is outlined in Table 1.

Table 1 Key Nonclinical Safety Findings and Relevance to Human Use

Key Safety Finding (from nonclinical toxicity studies)	Relevance to Human Usage
Single dose toxicity studies	
There was no formal single-dose toxicity study performed. Evaluations related to the acute toxicity of nemolizumab were carried out as part of the repeated-dose toxicity study by monitoring cynomolgus monkeys up to 14 days after the first administration. No noteworthy toxicological changes were observed up to 25 mg/kg administered SC.	Results did not highlight systemic or local adverse effects or exaggerated/unexpected pharmacological activity after single dose.
Repeat-dose toxicity studies	
Nemolizumab was tested in cynomolgus monkey at doses up to 25 mg/kg once every 2 weeks in a 3- and 6-month intermittent SC dose-toxicity studies. No toxicological changes due to systemic exposure of nemolizumab were observed. No target organs were identified. The no-observed-adverse-effect level (NOAEL) related to systemic exposure for SC administration (the clinical route) was 25 mg/kg/2 weeks.	Results suggested neither systemic nor local or organ specific adverse effects or exaggerated/unexpected pharmacological activity after repeated administrations of nemolizumab.

Key Safety Finding (from nonclinical toxicity studies)	Relevance to Human Usage
Reproductive and developmental toxicity studies	
No toxicological changes on male or female reproductive organs were seen in the 3- and 6-month intermittent SC toxicity study using sexually mature cynomolgus monkeys. In addition, no toxicological changes attributable to nemolizumab to selected endpoints related to male and female fertility (menstrual cycle, sperm analysis, measurement of testicular size, and histological evaluation of reproductive organs) were noted in the 6-month toxicity study.	Nemolizumab did not exert toxicity or exaggerated/unexpected pharmacological activity on reproductive organs or fertility hallmarks.
Nemolizumab has been tested SC in pregnant female cynomolgus monkeys at doses up to 25 mg/kg/2-week from the beginning of the organogenesis to delivery (from Day 20 of gestation to late 3rd trimester, 9 to 12 times in total). In addition, the offspring were treated SC with nemolizumab for 26 weeks starting postnatal Day 35 with doses up to 25 mg/kg/2-week. There were no toxicological changes ascribable to nemolizumab. The NOAEL was 25 mg/kg/2-week for dams and offspring.	Results suggested neither toxicity nor exaggerated/unexpected pharmacological activity that could alter the course of pregnancy, the foetal and offspring development.
Genotoxicity	
No dedicated genotoxicity studies on nemolizumab were conducted. Considering the pharmacological activity of nemolizumab there is no scientific evidence to consider it as potential interacting with DNA or other chromosomal material.	Nemolizumab has no genotoxic potential.
Carcinogenicity	
No carcinogenicity studies have been conducted. Considering the pharmacological activity of nemolizumab there is no scientific evidence to consider it as potential interacting with DNA or other genetic material nor supporting or inducing clonal expansion or proliferation of cells or transformed cells.	Nemolizumab has no carcinogenic potential.
Local Tolerance studies In the evaluation of the local tolerance of nemolizumab in rabbits, the Phase I clinical formulation of nemolizumab did not elicit any irritant or other effects at the injection sites following single or repeated SC injection. Following an improvement in the formulation, local tolerance was evaluated again in the 6-month SC repeat dose toxicity study in cynomolgus monkeys. No macroscopic and histopathological treatment-related changes were observed in the injection sites in this study.	Results highlighted the satisfactory local tolerability of nemolizumab after repeated SC administrations.
Tissue cross-reactivity studies In the tissue cross-reactivity study using frozen tissue panels, the specific reactivity with nemolizumab was similar between humans and cynomolgus monkeys, and no staining suggestive of off-target binding was observed.	Staining pattern did not point out target organ(s) or recognition of off-target tissues.
In vitro risk estimation of cytokine release To estimate the risk of cytokine release syndrome at first-in-human administration, an *in vitro* study to detect cytokine release due to nemolizumab was conducted, using fresh whole blood obtained from 10 healthy adults. Nemolizumab induced increases in IL-6 or tumour necrosis factor, but the incidence and magnitude of the increases were substantially low when compared to that induced by high-risk comparator antibodies such as alemtuzumab.	*In vitro* nemolizumab did not induce cytokine release in whole blood, the risk of cytokine release syndrome is considered low.

SII.2 Safety Pharmacology

With reference to International Council for Harmonization, Preclinical safety evaluation of biotechnology-derived pharmaceuticals (S6[R1]), effects on the central nervous, respiratory, and cardiovascular systems were evaluated in 3- and 6-month intermittent SC toxicity studies in cynomolgus monkeys.

The repeated subcutaneous administration of nemolizumab did not exert effects on the functional observational battery, electrocardiography, blood pressure and respiratory rate. Pathological examinations (organ weight and histological examination of organs and tissues related to the central nervous, respiratory, and cardiovascular systems) did not highlight alterations attributable to nemolizumab exposure.

SII.3 Conclusion on Non-Clinical Data

Cynomolgus monkey was selected as the relevant animal species for the nonclinical program due to its cross-reactivity with nemolizumab.

The pharmacological characteristics of nemolizumab as an anti-IL-31RA neutralizing antibody were characterized in a battery of in vitro studies. The itch-inhibiting effect of nemolizumab was demonstrated in vivo in a monkey model where itching was systemically induced by intravenous administration of IL-31. In addition, efficacy was further demonstrated in a mite antigen-induced AD mouse model. The panel of in vitro and in vivo studies indicate the potential efficacy of nemolizumab in humans.

Neither systemic nor local toxicity were observed following intermittent SC administration of nemolizumab in cynomolgus monkeys for 3 and 6 months. Integrated safety pharmacology endpoints (i.e., functional observational battery, electrocardiography, blood pressure, respiratory rate or pathological examinations) in these studies showed no effects on the central nervous-, respiratory-, or cardiovascular system.

No effect on embryofoetal and juvenile development in monkey was observed following intermittent SC administration of nemolizumab in pregnant and offspring cynomolgus monkeys.

No immunological alterations were demonstrated after repeat dosing in the monkey.

In conclusion, no relevant safety potential risks have been identified in nonclinical studies.

PART II: MODULE SIII CLINICAL TRIAL EXPOSURE

SIII.1 Overview of Development

Nemolizumab was initially developed by Chugai Pharmaceutical Co., Ltd and licensed to the Applicant in 2016. On 28 March 2022, nemolizumab (60 mg) was approved under the commercial name of Mitchga® by the Pharmaceuticals and Medical Devices Agency (Japan) for the treatment of pruritus associated with AD (only when existing treatments are inadequate) in patients aged 13 years and older. Maruho is currently developing nemolizumab in PN, paediatric AD, and systemic sclerosis (SSc).

The list of clinical studies for AD is included in AD Module 5.2 and for PN is included in PN Module 5.2. It gives an overview of the clinical studies with nemolizumab that were conducted by Galderma as well as the clinical studies with nemolizumab conducted by another sponsor (i.e., Maruho). The clinical studies with nemolizumab conducted by Chugai are included with the Galderma studies.

SIII.1.1 Atopic dermatitis

The nemolizumab clinical development plan includes 17 clinical studies that support the safety of nemolizumab for the AD indication as of the 10 Mar 2023 cut-off date. This includes:

- 2 Phase 1 studies (RD.06.SPR.201590 [HV], CIM001JP [HV] and AD]);
- 3 Phase 2 clinical studies (RD.03.SPR.114322 [Phase 2b], RD.06.SPR.116912, and CIM003JG) in AD;
- 2 pivotal Phase 3 studies (RD.06.SPR.118161 and RD.06.SPR.118169) in AD;
- 10 ongoing studies (ongoing at the time of the BLA submission) including:
  - 1 Phase 3 long-term extension (LTE) study in AD (RD.06.SPR.118163);
  - 1 Phase 3b cyclosporin failure study (RD.06.SPR.201591) in AD.
  - 2 Phase 2 studies in AD: drug-drug interaction in adults (RD.06.SPR.201593), vaccine immunization response study in adults and adolescents (RD.06.SPR.118380). Note: results of the drug-drug interaction and vaccine immunization response studies will be submitted to the BLA as post-approval supplements as agreed with the Agency in the 24 Apr 2023 pre-BLA meeting.
  - 1 Phase 2 study (RD.06.SPR.118126) conducted in paediatric 2- to 11-year-old subjects (a different population from the intended indication in this submission) in AD; and
  - Studies conducted in another indication (CIM106JP [CKDaP], RD.06.SPR.115828 [PN], RD.06.SPR.203065 [PN], RD.06.SPR.202685 [PN], and RD.06.SPR.202699 [PN]).

In addition, although a different dose was investigated, the Applicant is also submitting summaries of the key outcomes for 7 clinical studies conducted by another sponsor (Maruho) in Japanese subjects for transparency:

- 4 AD studies (1 Phase 1 [M525101-05] and 3 Phase 3 [M525101-01, M525101-02, and M525101-04]);
- 2 Phase 1 studies in healthy volunteers (M525101-12 and M525101-13); and
- 1 ongoing Phase 2/3 PN study (M525101-11).

A description of the clinical studies to support the approval of nemolizumab in the treatment of moderate-to-severe AD in patients aged 12 years and older who are candidates for systemic therapy, is presented in AD Module 5.2.

SIII.1.2 Prurigo nodularis

The nemolizumab clinical development plan includes 19 clinical studies acquired or conducted by the Applicant or another sponsor (Maruho) to support the assessment of clinical pharmacology, efficacy, and safety of nemolizumab in PN indication as of the 10 Mar 2023 cut-off date. This includes:

- 5 studies in subjects with PN conducted by the Applicant:
  - 1 Phase 2 clinical study (RD.03.SPR.115828).
  - 2 Phase 3 clinical studies (RD.06.SPR.202685 and RD.06.SPR.203065).
  - 1 ongoing Phase 3 Long-term Extension (LTE) study (RD.06.SPR.202699).
  - 1 ongoing blinded Phase 3b durability of response study (RD.06.SPR.2038.90).
- 8 studies acquired or conducted by the Applicant in other indications or in healthy volunteers:
  - 2 completed Phase 1 studies (CIM001JP [healthy volunteers in Parts A and B; subjects with AD in Part C] and RD.06.SPR.201590) in healthy volunteers.
  - 5 completed studies (3 Phase 2 [CIM003JG; RD.03.SPR.114322 and RD.06.SPR.116912], and 2 Phase 3 studies [RD.06.SPR.118161 and RD.06.SPR.118169]) in subjects with AD;
  - 1 completed Phase 2 study in subjects with CKDaP (CIM106JP).

In addition, the Applicant is also submitting summaries of the key outcomes for 6 clinical studies conducted by another sponsor (Maruho) in Japanese subjects for transparency:

- 2 Phase 1 studies (M525101-12 and M525101-13) in healthy volunteers.
- 1 ongoing Phase 2/3 study (M525101-11) in subjects with PN; and
- 3 completed studies (1 Phase 1 [M525101-05] and 2 Phase 3 [M525101-01 and M525101-02]) in subjects with AD.

A description of the clinical studies to support the approval of nemolizumab in the treatment of PN is presented in PN Module 5.2.

SIII.2 Overall exposure by indication

As of 21st July 2023, a total of 4,093 subjects (patients and healthy volunteers) were enrolled and treated in the clinical trials sponsored by the Applicant, including 449 subjects in clinical trials sponsored by Chugai (Table 2). Among the latter, 378 subjects have been exposed to nemolizumab, including 126 subjects exposed to doses <0.5 mg/kg, 79 subjects exposed to a dose of 0.5 mg/kg and 173 subjects exposed to doses >0.5 mg/kg.

In addition to the above, 689 subjects in the Maruho-sponsored studies (Table 3).

Table 2 Cumulative subject exposure to nemolizumab (Galderma code: CD14152) in the Applicant's Clinical Development since DIBD up to 21 Jul 2023 (Applicant studies, including Chugai Studies)

	Healthy Volunteers N=272 n (%)	Subjects with AD N=2900 n (%)	Subjects with PN N=626 n (%)	Subjects with UPs N=295 n (%)	Total N=4093 n (%)
CD14152 < 0.5 mg/kg and 10mg	36 (13.24)	146 (5.03)	0	15 (5.08)	197 (4.81)
CD14152 0.003 mg/kg	6 (2.21)	0	0	0	6 (0.15)
CD14152 0.01 mg/kg	6 (2.21)	0	0	0	6 (0.15)
CD14152 0.03 mg/kg	6 (2.21)	0	0	0	6 (0.15)
CD14152 0.1 mg/kg	6 (2.21)	66 (2.28)	0	0	72 (1.76)
CD14152 0.125 mg/kg	0	0	0	15 (5.08)	15 (0.37)
CD14152 0.3 mg/kg	12 (4.41)	9 (0.31)	0	0	21 (0.51)
CD14152 10mg	0	71 (2.45)	0	0	71 (1.73)
CD14152 15mg	0	21 (0.72)	0	0	21 (0.51)
CD14152 15mg	0	21 (0.72)	0	0	21 (0.51)
CD14152 20mg	0	17 (0.59)	0	0	17 (0.42)
CD14152 20mg	0	17 (0.59)	0	0	17 (0.42)
CD14152 0.5 mg/kg and 30mg	0	2258 (77.86)	563 (89.94)	13 (4.41)	2834 (69.24)
CD14152 0.5 mg/kg	0	66 (2.28)	34*	13 (4.41)	79 (1.93)
CD14152 30mg	0	2192 (75.59)	563 (89.94)	0	2755 (67.31)
CD14152 60mg	192 (70.59)	0	124 (19.81)	0	316 (7.72)
CD14152 60mg	192 (70.59)	0	124 (19.81)	0	316 (7.72)
CD14152 > 0.5 mg/kg and 90mg	24 (8.82)	192 (6.62)	0	14 (4.75)	230 (5.62)
CD14152 1 mg/kg	12 (4.41)	9 (0.31)	0	0	21 (0.51)
CD14152 2 mg/kg	0	117 (4.03)	0	14 (4.75)	131 (3.20)
CD14152 3 mg/kg	12 (4.41)	9 (0.31)	0	0	21 (0.51)
CD14152 90mg	0	57 (1.97)	0	0	57 (1.39)
Active Comparator	0	0	0	13 (4.41)	13 (0.32)
Nalfurafine Hydrochloride	0	0	0	13 (4.41)	13 (0.32)
Placebo	20 (7.35)	870 (30.00)	222 (35.46)	14 (4.75)	1126 (27.51)
CD14152 Vehicle	20 (7.35)	870 (30.00)	222 (35.46)	14 (4.75)	1126 (27.51)
Blinded	0	508 (17.52)	34 (5.43)	226 (76.61)	768 (18.76)
Blinded	0	508 (17.52)	34 (5.43)	226 (76.61)	768 (18.76)

The safety population was defined as the ITT population who applied the study medication at least once
Number of subjects cannot be added because a subject may participate in more than one treatment group in crossover, intra-individual, and multiple phase studies
DIBD: Development International Birth Date
*reported as 0 in the DSUR. 34 subjects received at least one dose of Nemolizumab 0.5 mg/kg in Phase 2a in PN indication (RD.03.SPR.115828)

Source: DSUR No.10 (22 July 2022 to 21 July 2023)

Table 3 Cumulative subject exposure in the Partner Clinical Development since DIBD up to 21 Jul 2023 (Mahuro sponsored studies)

	Healthy Volunteers N=32	Subjects with AD N=425	Subjects with PN N=226
CD14152 30mg	0	46 (10.82%)	77 (34.07%)
CD14152 60mg	32 (100%)	256 (60.24%)	76 (33.63%)
CD14152 0.5 mg/kg	0	7 (1.65%)	0
CD14152 > 0.5 mg/kg	0	6 (1.41%)	0
Placebo - CD14152 30mg	0	43 (10.12%)	36 (15.93%)
Placebo - CD14152 60mg	0	67 (15.76%)	37 (16.37%)

The safety population was defined as the ITT population who applied the study medication at least once
Source: DSUR No. 10 (22 July 2022 to 21 July 2023)

SIII.3 Exposure to nemolizumab by Age-Group and Gender in all clinical studies

Table 4 Exposure to nemolizumab (Galderma code: CD14152) in the Applicant's Clinical Development since DIBD up to 21 Jul 2023 (Applicant studies, including Chugai Studies)

Population/Indication	CD14152 < 0.5 mg/kg and 10mg N=197				CD14152 15mg N=21				CD14152 20mg N=17				CD14152 0.5 mg/kg and 30mg N=2834			
Age Range	Male	Fem.	Miss.	Total	Male	Fem.	Miss.	Total	Male	Fem.	Miss.	Total	Male	Fem.	Miss.	Tota
Healthy Volunteers																
2-11 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-24 Years Old	22	0	0	22	0	0	0	0	0	0	0	0	0	0	0	0
25-34 Years Old	12	0	0	12	0	0	0	0	0	0	0	0	0	0	0	0
35-44 Years Old	2	0	0	2	0	0	0	0	0	0	0	0	0	0	0	0
45-54 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
55-64 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
>=65 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	36	0	0	36	0	0	0	0	0	0	0	0	0	0	0	0
Subjects with Atopic Dermatitis																
2-11 Years Old	8	8	0	16	11	10	0	21	9	8	0	17	10	9	0	19
12-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	153	154	0	307
18-24 Years Old	17	18	0	35	0	0	0	0	0	0	0	0	221	266	0	487
25-34 Years Old	28	19	0	47	0	0	0	0	0	0	0	0	298	239	0	537
35-44 Years Old	10	9	0	19	0	0	0	0	0	0	0	0	195	188	0	383
45-54 Years Old	12	7	0	19	0	0	0	0	0	0	0	0	142	168	0	310
55-64 Years Old	5	3	0	8	0	0	0	0	0	0	0	0	81	97	0	178
>=65 Years Old	1	1	0	2	0	0	0	0	0	0	0	0	63	55	0	118
Total	81	65	0	146	11	10	0	21	9	8	0	17	1131	1127	0	225
Subjects with Prurigo Nodularis																
2-11 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-24 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	3	9	0	12
25-34 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	17	25	0	42
35-44 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	22	43	0	65
45-54 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	46	83	0	129
55-64 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	63	86	0	149
>=65 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	74	101	0	175
Total	0	0	0	0	0	0	0	0	0	0	0	0	222	341	0	563

Population/Indication	CD14152 60mg N=316				CD14152 > 0.5 mg/kg and 90mg N=230				Blinded N=768				All Subjects N=3833			
Age Range	Male	Fem.	Miss.	Total	Male	Fem.	Miss.	Total	Male	Fem.	Miss.	Total	Male	Fem.	Miss.	Total
Healthy Volunteers																
2-11 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-24 Years Old	7	9	0	16	11	0	0	11	0	0	0	0	40	9	0	49
25-34 Years Old	19	27	0	46	9	0	0	9	0	0	0	0	40	27	0	67
35-44 Years Old	18	37	0	55	4	0	0	4	0	0	0	0	24	37	0	61
45-54 Years Old	14	25	0	39	0	0	0	0	0	0	0	0	14	25	0	39
55-64 Years Old	16	18	0	34	0	0	0	0	0	0	0	0	16	18	0	34
>=65 Years Old	1	1	0	2	0	0	0	0	0	0	0	0	1	1	0	2
Total	75	117	0	192	24	0	0	24	0	0	0	0	135	117	0	252
Subjects with Atopic Dermatitis																
2-11 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	38	35	0	73
12-17 Years Old	0	0	0	0	0	0	0	0	5	11	0	16	156	161	0	317
18-24 Years Old	0	0	0	0	27	21	0	48	43	60	0	103	277	318	0	595
25-34 Years Old	0	0	0	0	32	19	0	51	67	74	0	141	370	296	0	666
35-44 Years Old	0	0	0	0	23	18	0	41	51	67	0	118	237	235	0	472
45-54 Years Old	0	0	0	0	11	17	0	28	56	48	0	104	180	201	0	381
55-64 Years Old	0	0	0	0	9	8	0	17	8	9	0	17	96	109	0	205
>=65 Years Old	0	0	0	0	3	4	0	7	5	4	0	9	68	59	0	127
Total	0	0	0	0	105	87	0	192	235	273	0	508	1378	1357	0	2735
Subjects with Prurigo Nodularis																
2-11 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
12-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-24 Years Old	1	1	0	2	0	0	0	0	0	0	0	0	4	9	0	13
25-34 Years Old	2	4	0	6	0	0	0	0	0	1	0	1	17	26	0	43
35-44 Years Old	8	4	0	12	0	0	0	0	0	4	0	4	23	44	0	67
45-54 Years Old	13	15	0	28	0	0	0	0	2	7	0	9	47	87	0	134
55-64 Years Old	23	13	0	36	0	0	0	0	1	6	0	7	70	86	0	156
>=65 Years Old	27	13	0	40	0	0	0	0	4	9	0	13	78	103	0	181
Total	74	50	0	124	0	0	0	0	7	27	0	34	232	346	0	578

The safety population was defined as the ITT population who applied the study medication at least once
Number of subjects cannot be added because a subject may participate in more than one treatment group in crossover, intra-individual, and multiple phase studies
DIBD: Development International Birth Date Cut-off date: 21-Jul-2023
Source: DSUR No. 10 (22 July 2022 to 21 July 2023)

Table 5 Exposure to nemolizumab in the Partner Clinical Development since DIBD up to 21 Jul 2023 (Mahuro sponsored studies)

Population	CD14152 30 mg				CD14152 60 mg				CD14152 0.5 mg/kg				CD14152 > 0.5 mg/kg				Placebo-CD14152 30 mg				Placebo-CD14152 60 mg				All Patients			
Age Range	Male	Fem.	miss.	Tot.	Male	Fem.	miss.	Tot.	Male	Fem.	miss.	Tot.	Male	Fem.	miss.	Tot.	Male	Fem.	miss.	Tot.	Male	Fem.	miss.	Tot.	Male	Fem.	miss.	Tot.
Subjects with Atopic Dermatitis																												
6-12 Years Old	30	16	0	46	0	0	0	0	3	4	0	7	3	3	0	6	23	20	0	43	0	0	0	0	59	43	0	102
13-17 Years Old	0	0	0	0	8	2	0	10	0	0	0	0	0	0	0	0	0	0	0	0	3	0	0	3	11	2	0	13
18-24 Years Old	0	0	0	0	19	9	0	28	0	0	0	0	0	0	0	0	0	0	0	0	6	1	0	7	25	10	0	35
25-34 Years Old	0	0	0	0	40	15	0	55	0	0	0	0	0	0	0	0	0	0	0	0	8	4	0	12	48	19	0	67
35-44 Years Old	0	0	0	0	45	32	0	77	0	0	0	0	0	0	0	0	0	0	0	0	8	6	0	14	53	38	0	91
45-54 Years Old	0	0	0	0	36	24	0	60	0	0	0	0	0	0	0	0	0	0	0	0	12	9	0	21	48	33	0	81
55-64 Years Old	0	0	0	0	14	5	0	19	0	0	0	0	0	0	0	0	0	0	0	0	6	3	0	9	20	8	0	28
>=65 Years Old	0	0	0	0	6	1	0	7	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	1	7	1	0	8
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	30	16	0	46	168	88	0	256	3	4	0	7	3	3	0	6	23	20	0	43	44	23	0	67	271	154	0	425
Subjects with Prurigo Nodularis																												
6-12 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13-17 Years Old	2	1	0	3	2	1	0	3	0	0	0	0	0	0	0	0	0	1	0	1	1	0	0	1	5	3	0	8
18-24 Years Old	2	1	0	3	2	0	0	2	0	0	0	0	0	0	0	0	1	1	0	2	0	0	0	0	5	2	0	7
25-34 Years Old	1	4	0	5	6	2	0	8	0	0	0	0	0	0	0	0	1	0	0	1	0	1	0	1	8	7	0	15
35-44 Years Old	5	6	0	11	4	14	0	18	0	0	0	0	0	0	0	0	2	2	0	4	3	4	0	7	14	26	0	40
45-54 Years Old	8	17	0	25	3	15	0	18	0	0	0	0	0	0	0	0	2	6	0	8	4	11	0	15	17	49	0	66
55-64 Years Old	7	2	0	9	10	5	0	15	0	0	0	0	0	0	0	0	3	5	0	8	5	2	0	7	25	14	0	39
>=65 Years Old	12	9	0	21	7	5	0	12	0	0	0	0	0	0	0	0	9	3	0	12	3	3	0	6	31	20	0	51
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	37	40	0	77	34	42	0	76	0	0	0	0	0	0	0	0	18	18	0	36	16	21	0	37	105	121	0	226
Subjects with Systemic Sclerosis																												
6-12 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-24 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
25-34 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
35-44 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45-54 Years Old	0	0	0	0	0	3	0	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	3	0	3
55-64 Years Old	0	0	0	0	0	2	0	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	2	0	2
>=65 Years Old	0	0	0	0	0	1	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	1
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	0	6	0	6	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	0	6
Subjects with Healthy Volunteers																												
6-12 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13-17 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-24 Years Old	0	0	0	0	9	0	0	9	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	9	0	0	9
25-34 Years Old	0	0	0	0	14	0	0	14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	14	0	0	14
35-44 Years Old	0	0	0	0	5	0	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5	0	0	5
45-54 Years Old	0	0	0	0	4	0	0	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4	0	0	4
55-64 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
>=65 Years Old	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Unknown	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	0	0	0	0	32	0	0	32	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	32	0	0	32

The Safety population was defined as the ITT population who applied the study medication at least once.

Source: DSUR No. 10 (22 July 2022 to 21 July 2023)

SIII.4 Exposure to nemolizumab by Racial Group in all clinical studies

Table 6 Exposure to nemolizumab (Galderma code: CD14152) in the Applicant's Clinical Development since DIBD up to 21 Jul 2023 (Applicant studies, including Chugai Studies)

Population/Indication Racial Group	CD14152 < 0.5 mg/kg and 10mg N=197	CD14152 15mg N=21	CD14152 20mg N=17	CD14152 0.5 mg/kg and 30mg N=2834	CD14152 60mg N=316	CD14152 > 0.5 mg/kg and 90mg N=230	Blinded N=768	All Subject N=3833
Healthy Volunteers								
White	6	0	0	0	162	12	0	180
Black Or African American	0	0	0	0	17	0	0	17
Asian	30	0	0	0	2	12	0	44
American Indian Or Alaska Native	0	0	0	0	2	0	0	2
Native Hawaiian Or Other Pacific Islander	0	0	0	0	0	0	0	0
Other	0	0	0	0	9	0	0	9
Missing	0	0	0	0	0	0	0	0
Total	36	0	0	0	192	24	0	252
Subjects with Atopic Dermatitis								
White	90	21	17	1785	0	117	400	2092
Black Or African American	11	0	0	158	0	14	63	207
Asian	42	0	0	272	0	59	34	384
American Indian Or Alaska Native	1	0	0	6	0	1	2	8
Native Hawaiian Or Other Pacific Islander	0	0	0	4	0	0	2	4
Other	2	0	0	33	0	1	7	40
Missing	0	0	0	0	0	0	0	0
Total	146	21	17	2258	0	192	508	2735
Subjects with Prurigo Nodularis								
White	0	0	0	468	106	0	33	479
Black Or African American	0	0	0	34	12	0	0	37
Asian	0	0	0	47	3	0	1	48
American Indian Or Alaska Native	0	0	0	1	0	0	0	1
Native Hawaiian Or Other Pacific Islander	0	0	0	2	0	0	0	2
Other	0	0	0	11	3	0	0	11
Missing	0	0	0	0	0	0	0	0
Total	0	0	0	563	124	0	34	578
Subjects with Uremic Pruritus								
White	0	0	0	0	0	0	130	130

Source: DSUR No. 10 (22 July 2022 to 21 July 2023)

Table 7 Exposure to nemolizumab in the Partner Clinical Development since DIBD up to 21 Jul 2023 (Mahuro sponsored studies)

Population Race Group	CD14152 30 mg	CD14152 60 mg	CD14152 0.5 mg/kg	CD14152 > 0.5 mg/kg	Placebo-CD14152 30 mg	Placebo-CD14152 60 mg	All Patients
Subjects with Atopic Dermatitis							
White	0	0	0	0	0	0	0
Black Or African American	0	0	0	0	0	0	0
Asian	46	256	7	6	43	67	425
American Indian Or Alaska Native	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
missing	0	0	0	0	0	0	0
Total	46	256	7	6	43	67	425
Subjects with Prurigo Nodularis							
White	0	0	0	0	0	0	0
Black Or African American	0	0	0	0	0	0	0
Asian	77	76	0	0	36	37	226
American Indian Or Alaska Native	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
missing	0	0	0	0	0	0	0
Total	77	76	0	0	36	37	226
Subjects with Systemic Sclerosis							
White	0	0	0	0	0	0	0
Black Or African American	0	0	0	0	0	0	0
Asian	0	6	0	0	0	0	6
American Indian Or Alaska Native	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
missing	0	0	0	0	0	0	0
Total	0	6	0	0	0	0	6
Subjects with Healthy Volunteers							
White	0	0	0	0	0	0	0
Black Or African American	0	0	0	0	0	0	0
Asian	0	32	0	0	0	0	32
American Indian Or Alaska Native	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0
missing	0	0	0	0	0	0	0
Total	0	32	0	0	0	0	32

The Safety population was defined as the ITT population who applied the study medication at least once.

Source: DSUR No. 10 (22 July 2022 to 21 July 2023)

SIII.5 Exposure pools in Atopic Dermatitis and Prurigo Nodularis

SIII.5.1 Atopic dermatitis

The exposure pool population supporting the initial application for NEMLUVIO in AD indication includes the following studies:

- SPR118163 (Long Term Extension Study [LTE])
- SPR118161 (LTE Feeder Study)
- SPR118169 (LTE Feeder Study)
- SPR114322 (LTE Feeder Study)
- SPR116912 (LTE Feeder Study)
- SPR201593 (LTE Feeder Study)

The mean treatment duration for nemolizumab 30 mg subjects was 405.2 days (median of 424.0 days) (Table 8). Nemolizumab 30 mg subjects received a mean of 13.8 treatments (median of 15.0 treatments), with almost all (98.2%) nemolizumab 30 mg subjects receiving between 1 and 30 treatments. A total of 1148 (57.2%) subjects had ≥1 year of exposure to nemolizumab 30 mg. Results were generally similar in the all nemolizumab group.

Table 8 Extent of exposure (AD exposure pool population)

	Nemolizumab 10 mg N=55	Nemolizumab 30 mg N=2007	Nemolizumab 90 mg N=57	All nemolizumab N=2111
Treatment duration (days)				
Mean (SD)	153.8 (37.98)	405.2 (240.44)	152.7 (37.93)	393.4 (241.57)
Median	171.0	424.0	171.0	402.0
Q1, Q3	168.0, 174.0	176.0, 591.0	165.0, 172.0	171.0, 588.0
Minimum, maximum	59, 178	31, 1074	31, 181	31, 1074
Treatment duration (years)				
Mean (SD)	0.42 (0.104)	1.11 (0.658)	0.42 (0.104)	1.08 (0.661)
Median	0.47	1.16	0.47	1.10
Q1, Q3	0.46, 0.48	0.48, 1.62	0.45, 0.47	0.47, 1.61
Minimum, maximum	0.2, 0.5	0.1, 2.9	0.1, 0.5	0.1, 2.9
Number of treatments per subject				
Mean (SD)	5.3 (1.33)	13.8 (8.31)	5.3 (1.34)	13.4 (8.34)
Median	6.0	15.0	6.0	14.0
Q1, Q3	5.0, 6.0	6.0, 20.0	5.0, 6.0	6.0, 20.0
Minimum, maximum	2, 6	1, 38	1, 6	1, 38
Number of treatments per subject, n (%)				
1-5	14 (25.5)	444 (22.1)	15 (26.3)	472 (22.4)
6-10	41 (74.5)	304 (15.1)	42 (73.7)	380 (18.0)
11-15	0	351 (17.5)	0	351 (16.6)
16-20	0	438 (21.8)	0	436 (20.7)
21-25	0	318 (15.8)	0	315 (14.9)
26-30	0	115 (5.7)	0	120 (5.7)
31-35	0	32 (1.6)	0	31 (1.5)
36-40	0	5 (0.2)	0	6 (0.3)
Subjects with ≥6 months exposure to nemolizumab, n (%)	0	1497 (74.6)	0	1498 (71.0)
Subjects with ≥1 year exposure to nemolizumab, n (%)	0	1148 (57.2)	0	1148 (54.4)
Subjects with ≥1.5 years exposure to nemolizumab, n (%)	0	645 (32.1)	0	646 (30.6)
Subjects with ≥2 years exposure to nemolizumab, n (%)	0	171 (8.5)	0	176 (8.3)

AD=atopic dermatitis; ISS=Integrated Summary of Safety; N=number of subjects in the population; n=number of subjects with available data; Q1=first quartile; Q3=third quartile

Note: Exposure data from the long-term extension study (SPR.118163) were pooled with the exposure data from the relevant feeder studies, to give a total overall exposure for each subject. Total exposure to a given dose of nemolizumab was presented under the corresponding column. Feeder studies were SRE.118161, SRE.118169, SRE.114322, SRE.116912, and SPR.201593.

Source: AD ISS Table 14.3.4.5.14

SIII.5.2 Prurigo nodularis

The exposure pool population supporting the initial Application for NEMLUVIO in PN indication includes the following studies:

- SPR202699 (LTE)
- SPR202685 (LTE Feeder Study)
- SPR203065 (LTE Feeder Study)
- SPR115828 (LTE Feeder Study)

The mean treatment duration for nemolizumab (fixed dosing) subjects was 441.5 days (median of 479.0 days) (Table 9). Subjects in the All nemolizumab group received a mean of 15.1 treatments (median of 16.0 treatments), with almost all (99.8%) nemolizumab subjects receiving between 1 and 30 treatments. A total of 375 (64.9%) subjects in the All nemolizumab group had ≥1 year of exposure to nemolizumab. Exposure in the nemolizumab fixed dosing with body weight adjustment group was generally similar to those in the All nemolizumab group.

Table 9 Extent of exposure (PN exposure pool population)

	Nemolizumab 0.5 mg/kg N=34	Nemolizumab FDWBWA[a] N=555	All nemolizumab N=578
Treatment duration (days)			
Mean (SD)	84.9 (11.93)	454.6 (208.93)	441.5 (219.02)
Median	87.0	485.0	479.0
Q1, Q3	87.0, 88.0	308.0, 619.0	225.0, 619.0
Minimum, maximum	31, 95	31, 873	31, 874
Treatment duration (years)			
Mean (SD)	0.23 (0.033)	1.24 (0.572)	1.21 (0.600)
Median	0.24	1.33	1.31
Q1, Q3	0.24, 0.24	0.84, 1.69	0.70, 1.69
Minimum, maximum	0.1, 0.3	0.1, 2.4	0.1, 2.4
Number of treatments per subject			
Mean (SD)	2.9 (0.44)	15.5 (7.18)	15.1 (7.52)
Median	3.0	17.0	16.0
Q1, Q3	3.0, 3.0	10.0, 21.0	9.0, 21.0
Minimum, maximum	1, 3	1, 31	1, 31
Number of treatments per subject, n (%)			
1-5	34 (100)	65 (11.7)	87 (15.1)
6-10	0	74 (13.3)	75 (13.0)
11-15	0	110 (19.8)	110 (19.0)
16-20	0	155 (27.9)	153 (26.5)
21-25	0	112 (20.2)	110 (19.0)
26-30	0	38 (6.8)	42 (7.3)
31-35	0	1 (0.2)	1 (0.2)
Subjects with ≥6 months exposure to nemolizumab, n (%)	0	471 (84.9)	471 (81.5)
Subjects with ≥1 year exposure to nemolizumab, n (%)	0	375 (67.6)	375 (64.9)
Subjects with ≥1.5 years exposure to nemolizumab, n (%)	0	207 (37.3)	207 (35.8)
Subjects with ≥2 years exposure to nemolizumab, n (%)	0	51 (9.2)	54 (9.3)

FDWBWA=fixed dosing with body weight adjustment; ISS=Integrated Summary of Safety; N=number of subjects in the population; n=number of subjects with available data; PN=prurigo nodularis; Q1=first quartile; Q3=third quartile; Q4W=every 4 weeks

Note: Exposure data from the long-term extension study (SPR.202699) was pooled with the exposure data from the relevant feeder studies, to give a total overall exposure for each subject. Total exposure to a given dose of nemolizumab was presented under the corresponding column. Feeder studies were SPR.202685, SPR.203065, and SPR.115828. Treatment duration (days) = (date of last treatment + 30) – (date of first treatment) + 1. Treatment duration (years) = treatment duration (days) / 365.25. If the time between the last treatment in the feeder study and the first treatment in the long-term extension study was greater than 30 days, then the treatment duration was calculated separately for each study and summed to give an overall treatment duration.

a) Subject weight <90 kg at baseline: nemolizumab 30 mg Q4W, with a 60-mg loading dose at baseline. Subject weight ≥90kg at baseline: nemolizumab 60 mg Q4W.

Source: PN ISS Table 14.3.4.5.9

Part II: Module SIV Populations not Studied in Clinical Trials

SIV.1 Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

The following specific groups of subjects were excluded from the pivotal clinical trials conducted by the Applicant with nemolizumab in AD and PN (Table 10).

Table 10 Important Exclusion Criteria in Nemolizumab Clinical Studies

Indication	Key exclusion criteria	Reason for Exclusion	Is it considered to be included as Missing Information?
AD & PN	Body weight < 30 kg.	The PK of nemolizumab is shown to be mainly influenced by body weight (BW), as observed for many other monoclonal antibodies. Apparent Clearance (Cl/F) and apparent Volume of distribution (Vd/F) increase with increasing BW, leading to higher systemic exposures in subjects with lower BW. Hence, subjects with low body weight were excluded to avoid potential risks associated with a higher exposure to nemolizumab than investigated.	No
AD & PN	Subjects meeting ≥1 of the following criteria at screening or baseline: • Had an exacerbation of asthma requiring hospitalization in the preceding 12 months. • Reporting asthma that had not been well-controlled (i.e., symptoms occurring on > 2 days per week, night-time awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months. • ACT≤19 (only for subjects with a history of asthma) • PEF<80% of the predicted value.	Asthma was defined as a selected adverse event in Phase 2 AD study (CIM0003JG) based on the theoretical risk associated with IL-31 inhibition (note: the role of IL-31 and IL-31 receptor in asthma is not fully understood). It was also included as an adverse event of special interest (AESI) ("newly diagnosed asthma or worsening of asthma") in Phase 2 AD study (SPR114322). In this latter study, a dose-dependent increased in asthma flares with Nemolizumab was observed in subjects with AD with pre- existing asthma, hence justifying the exclusion criteria. This AESI was further characterized in 4 pivotal studies in AD and PN indications (SPR118161; SPR.118169; SPR.202685; SPR203965)	No
AD & PN	Current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.	Such subjects may have factors that could affect the safety and efficacy of nemolizumab, such as previous or current treatments, comorbidities, infections, or smoking history/status. Also, these subjects could have been at increased risk of adverse events when treated with nemolizumab if it worsened their respiratory function and exacerbated their symptoms	No

Indication	Key exclusion criteria	Reason for Exclusion	Is it considered to be included as Missing Information?
AD & PN	Cutaneous infection within 1 week of baseline, infection requiring treatment with oral or parenteral antibiotics, antiviral, antiparasitic, or antifungals within 2 weeks of baseline, or confirmed or suspected COVID-19 infection within 2 weeks of screening or baseline.	Excluding such subjects reduced the risk of unrelated adverse events associated with the concurrent conditions and treatments for same ('noise') and it also reduced potential confounding when assessing whether an adverse event should be attributed to the pre-existing condition or to nemolizumab. Therefore, this exclusion criterion enabled a more robust interpretation and analysis of the emerging clinical safety data and overall trial results.	No
AD	Required rescue therapy for AD during the Run-in period or expected to require rescue therapy within 2 weeks following baseline.	Such rescue therapy could have interfered with the assessment of efficacy of nemolizumab.	No
PN	Required rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following baseline.		
AD & PN	Positive serology results[a] at screening.	To avoid potential worsening of pre-existing infections and confounding in the assessment of efficacy and safety results of the trial.	No
AD & PN	Received a protocol-specified restricted treatment[b] within the specified timeframe before baseline.	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
AD & PN	Previous participation in a clinical study with Nemolizumab.	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
AD	After a 16-week treatment course of dupilumab, experienced AD worsening or failed to achieve minimal improvement (e.g., ≤10% reduction in EASI or no reduction in IGA).	To avoid confounding factors in the assessment of the efficacy of nemolizumab and to ensure the validity and reliability of the trial results.	No

Indication	Key exclusion criteria	Reason for Exclusion	Is it considered to be included as Missing Information?
AD & PN	Pregnant (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit) or breastfeeding women or women planning a pregnancy during the study.	Reproductive risk associated with nemolizumab has not been comprehensively evaluated in humans. No toxicological changes that could be attributed to nemolizumab have been observed in preclinical reproductive and developmental toxicity studies (pregnant female cynomolgus monkeys; and offspring) (see Section II.1.1). It is not known whether nemolizumab is excreted in human breast milk.	Yes. The current available data are not considered sufficient to inform about the pregnancy risks associated with nemolizumab exposure due to the limited number of pregnancies in exposed clinical trial subjects (N=11, as of cut-off date of10 March 2023)
AD & PN	History of lymphoproliferative disease or malignancy of any organ system within the last 5 years, except for: • Basal cell carcinoma, squamous cell carcinoma in situ, or carcinomas in situ of the cervix that had been treated and had no evidence of recurrence in the last 12 weeks before screening, or; • Actinic keratoses that had been treated	Subjects with lymphoproliferative disease or malignancy may have factors that could affect the safety and efficacy of nemolizumab, such as previous treatments, comorbidities, or genetic mutations. Also, the effect of IL-31 blockade on subjects with such history is unknown. Therefore, this exclusion criterion was intended to avoid potential risks and confounding factors, and to ensure the validity and reliability of the trial results.	No
AD & PN	History of hypersensitivity (including anaphylaxis) to an immunoglobulin product or to any of the study drug excipients.	Implemented for safety reasons given the risk of potentially life-threatening or fatal anaphylactic shock inherent to a severe hypersensitivity reaction. As per the proposed SmPC, nemolizumab will be contraindicated in individuals with known hypersensitivity to the active drug substance or to any of the drug excipients.	No
AD	History of intolerance to TCS or for whom TCS was not advisable (e.g., hypersensitivity, significant skin atrophy).	To avoid potential risks and confounding factors in the assessment of the efficacy and safety of nemolizumab, and to ensure the validity and reliability of the trial results.	No

Indication	Key exclusion criteria	Reason for Exclusion	Is it considered to be included as Missing Information?
AD & PN	Known active or untreated latent tuberculosis (TB) infection/ Current active or latent TB infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines	Such subjects may have factors that could affect the safety and efficacy of nemolizumab, such as previous or current treatments, comorbidities, drug interactions, or drug resistance. Also, Th2 lymphocyte response is considered to contribute to the pathogenesis of TB by inhibiting the function of Th1 cells and macrophages. By blocking IL-31 signalling, nemolizumab may theoretically reduce the activation and proliferation of Th2 cells, which could worsen the effect of TB. However, the exact effect of nemolizumab on Th1 and Th2 remains unknown and may depend on various factors (e.g., dose, duration, timing, underlying patient's characteristics).	No
AD & PN	Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections per investigator judgment.	To avoid potential risks and confounding factors in the assessment of the efficacy and safety of nemolizumab, and to ensure the validity and reliability of the trial results.	No
AD & PN	Presence of confounding skin condition that may have interfered with study assessments (e.g., Netherton syndrome, psoriasis, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis).	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
AD & PN	Any medical or psychological condition or any clinically relevant laboratory abnormalities during screening that may have put the subject at significant risk according to the Investigator's judgment, if he/she participated in the study, or may have interfered with study assessments.	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
AD & PN	Planned or expected major surgical procedure during the study.	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
AD & PN	Unwilling to refrain from using protocol-specified prohibited medications during the study.	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No

Indication	Key exclusion criteria	Reason for Exclusion	Is it considered to be included as Missing Information?
AD	Currently participating or participated in any other investigational drug or device study within the past 8 weeks (or 5 half-lives of the investigational drug, whichever was longer) before screening, or was in a verifiable exclusion period from a previous study.	Previous or concomitant exposure may have a potential impact on the efficacy and safety data.	No
AD & PN	History of alcohol or substance abuse within 6 months of screening.	Adherence to appropriate dosing and protocol requirements cannot be guaranteed. To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
PN	Chronic pruritus resulting from another active condition other than PN, such as but not limited to scabies, lichen simplex chronicus, psoriasis, atopic dermatitis, contact dermatitis, acne, folliculitis, lichen planus, habitual picking/excoriation disorders, sporotrichinosis, bullous autoimmune disease, end-stage renal disease, cholestatic liver disease (e.g., primary biliary cirrhosis), or diabetes mellitus or thyroid disease that is not adequately treated, as per standard of care.	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No
PN	Unilateral lesions of prurigo (e.g., only one arm affected)	PN is typically a symmetric disease. If a patient presents with unilateral lesions, a differential diagnosis should be considered. Therefore, this exclusion criterion was intended to reduce diagnostic ambiguity and to enhance enrolment of the appropriate patient population (i.e., only those patients with a 'genuine' diagnosis of PN).	No
PN	Neuropathic and psychologic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fibre neuropathy, skin picking syndrome or delusional parasitosis	To avoid confounding factors in the assessment of the efficacy and safety of nemolizumab and to ensure the validity and reliability of the trial results.	No

ACT= asthma control test; AD= atopic dermatitis; BSA= body surface area; EASI=Eczema Area and Severity Index; IGA=Investigator's Global Assessment; PEF=peak expiratory flow; PP NRS=peak pruritus numeric rating scale; TB=tuberculosis; TCI= topical calcineurin inhibitor; TCS=topical corticosteroid.

[a]Including hepatitis B surface antigen or hepatitis B core antibody; hepatitis C virus antibody with positive confirmatory test for HCV (e.g., polymerase chain reaction or human immunodeficiency virus antibody)

[b]As specified in Table 2 of SPR.118161 and SPR.118169

SIV.2 Limitations to Detect Adverse Reactions in Clinical Trial Development Program

The clinical development program for nemolizumab is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure (Table 11). Routine post-marketing safety surveillance will support the identification of these adverse reactions.

Pregnant and lactating women were excluded from all clinical trials with nemolizumab. In addition, no studies were specifically performed in patients with liver dysfunction or cardiac impairment; however, these subjects were not specifically excluded from the studies.

Table 11 Limitations of ADR detection of the development program for nemolizumab

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare (i.e., frequency ≥ 1 in 10,000 - < 1 in 1,000)	As of 21 July 2023, a total of 4,782 subjects have been enrolled in the clinical development program of nemolizumab conducted by the Applicant and Maruho (approximately 2,692 subjects received nemolizumab, 1,309 subjects received placebo, 13 received active comparator and 768 subjects are still blinded).	Only an ADR with a frequency greater than 1 in 1,594 ('rule of three') could be detected with 95% confidence if there were no background incidence in prior clinical trial. (No prior ADR observed). The development program may not have been able to detect rare (≥1/10,000 to <1/1,000) or very rare ADRs (<1/10,000).
Due to prolonged exposure	Two LTE studies in PN and AD indications respectively are ongoing. The safety profile observed in the LTE studies through week 52 (interim analysis) was generally consistent with the safety profile of nemolizumab observed in the controlled studies in AD and PN indications.	LTE studies (one for each indication) are ongoing and will provide additional information on the safety profile of nemolizumab associated with prolonged exposure (up to up to approximately 200 weeks in the AD study and 184 weeks in the PN study). In the current state of knowledge on nemolizumab, the Applicant proposes the following labelling regarding prolonged treatment with nemolizumab: AD indication: After 16 weeks of treatment, for patients who achieve clinical response, the recommended maintenance dose of Nemluvio is 30 mg every 8 weeks (Q8W).
Due to cumulative effects	None	No organ specific toxicity has been observed in preclinical and/or clinical studies with nemolizumab.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which have long latency	The safety profile observed in the long-term extension trials through week 52 (interim analysis) was generally consistent with the safety profile of nemolizumab observed in the controlled studies in AD and PN indications	Long term extension studies are ongoing, and these will provide additional information on any potential long latency adverse events associated with nemolizumab. The treatment duration in the AD and PN pivotal studies limits the opportunity to detect events with a long latency, such as malignancies. Although no carcinogenicity studies on nemolizumab were conducted, the carcinogenicity potential of nemolizumab was assessed by the Weight of Evidence approach. Based on available data, it is considered that the carcinogenicity risk potential of nemolizumab is low (source: carcinogenicity risk assessment document).
Pregnant and breastfeeding women	Subjects not included in the clinical development program.	*Pregnancy* There is a limited amount of data on the use of nemolizumab in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to fetal toxicity (see section 5.3). Nemolizumab should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus. *Breast-feeding* There are no data on the presence or transfer of nemolizumab 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 nemolizumab and any potential adverse effects on the breastfed child from nemolizumab or from the underlying maternal condition

SIV.3 Limitations in Respect to Populations Typically Under-Represented in Clinical Trial Development Program

Table 12 presents the exposure of special populations included or not included in the Clinical Development Program of nemolizumab.

Table 12 Exposure of special populations included or not in clinical trial development program of nemolizumab

Type of special population	Exposure
Pregnant women	There are no adequate and well-controlled studies to establish the safety of nemolizumab in pregnant women. Subjects who were pregnant or lactating were excluded from all studies and the use of adequate contraception was required in female study participants. Based on currently available data from the clinical studies with nemolizumab as of 10 Mar 2023, 11 subjects became pregnant during participation in the following studies: Study 114322 (1 subject), Study 118161 (4 subjects), Study 118163 (4 subjects), Study 203065 (1 subject), and CIM003JG (1 subject). The 11 female subjects ranged in age from 20 years to 33 years (10 subjects with AD who were receiving nemolizumab and 1 subject with PN who was receiving placebo). All 11 subjects prematurely discontinued study drug treatment as per the study protocol. Three subjects delivered a healthy infant/live birth with no congenital abnormalities or concerns reported. The outcomes of 4 pregnancies remain unknown (of these 4: 1 reported no AEs observed in the subject [mother] and foetus at early termination visit and 1 was not exposed to nemolizumab during pregnancy but to placebo). For the remaining 4: pregnancies, 2 were spontaneous abortions (2 of 11 [18%] consistent with the range of expected spontaneous abortions in the general population) and 2 were elective abortions (abortion induced) without complications. The investigator and the Sponsor assessed that there was no reasonable possibility of a relationship with the study drug for the pregnancy outcomes in 7 of the 11 subjects, 3 pregnancies were not assessed by the investigator, and one pregnancy was not applicable (Table 13). In the case of spontaneous abortion at 30 weeks of pregnancy, the subject was diagnosed pregnant (estimated gestational stage of 4 weeks based on last menstrual period) 7 months after the last dose of study drug. Exposure during pregnancy was highly unlikely considering the terminal elimination half-life of nemolizumab of 18.9 days, as the product should have been mostly eliminated (~99%) after approximately 3.1 months which represents 5 half-lives (18.9 days × 5 = 94.5 days = 3.1 months). Both the Investigator and the Sponsor assessed the event of abortion spontaneous as having no reasonable possibility of a relationship with the study drug. In the other case of spontaneous abortion, the causality was not assessable (no assessment was provided by the Investigator); the Sponsor conservatively assessed the event of abortion spontaneous as having a reasonable possibility of a relationship with the study drug.
Breastfeeding women	The safety of nemolizumab has not been established in nursing mothers. It is not known whether nemolizumab is excreted in human breast milk. In the enhanced pre-and postnatal development study (ePPND) using cynomolgus monkeys, maternal milk concentrations of nemolizumab were 0.2% to 0.5% of plasma levels, indicating that there was a limited excretion in milk.

Type of special population	Exposure
Elderly	Subjects >65 years old were not specifically excluded from the clinical development program. No clinically significant differences were observed in the pharmacokinetics of nemolizumab based on age (18 to 65 years compared to >65 years). In the Phase 2 study CIM106JP in haemodialysis patients with uremic pruritus (n = 69), which included elderly patients (i.e., > 65 years of age; 12 subjects in nemolizumab arm [2 at the dose of 0.125 mg/kg, 3 at the dose of 0.5 mg/kg and 7 at the dose of 2 mg/kg], 6 subjects in nalfurafine arm and 2 subjects in placebo arm), no age-related safety issues were observed. Overall, no major differences in the safety profile of nemolizumab across age groups were observed in the primary safety populations and LTE studies in AD and PN indications.
Children and adolescents	Nemolizumab clinical trial program for moderate-to-severe AD included children (age group 2-11 years old) (cohort 2 not yet initiated in SPR.118126) and adolescents (age group 12-<18 years old) (SPR.116912 & SPR.118126 [ongoing]). No clinically significant differences were observed in the pharmacokinetics of nemolizumab between 12–17-year-old adolescents and adults. Nemolizumab has not been studied in children or adolescents in PN by the Applicant.
Patients with relevant comorbidities	
Patients with renal or hepatic impairment	Subjects with renal or hepatic impairment were not specifically excluded from the clinical development program. However, subjects with positive serology results at screening (including hepatitis B surface antigen or hepatitis B core antibody; hepatitis C virus antibody with positive confirmatory test for HCV) and clinically relevant laboratory abnormalities during screening that may have put the subject at significant risk according to the Investigator's judgement were excluded. No clinically meaningful differences in the PK of nemolizumab were observed for subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. The effect of severe hepatic impairment on the PK of nemolizumab is unknown due to lack of data. No clinically meaningful differences in the PK of nemolizumab were observed for subjects with mild or moderate renal impairment compared to subjects with normal renal function. The effect of severe renal impairment on the PK on nemolizumab is unknown due to the limited number of subjects in this category. In the Phase 2 study CIM106JP in haemodialysis patients with uremic pruritus, there was no clear difference in AEs between the nemolizumab groups compared with the placebo group and no safety issues were observed. A study in subjects with CKD-aP is ongoing (SPR.204358).

Type of special population	Exposure
Patients with cardiovascular impairment	Subjects with cardiovascular impairment were not specifically excluded from the clinical development program. However, patients with a medical history (e.g. cardiac disease) during the screening period that may put the subject at significant risk according to the investigator's judgment, if he/she participates in the clinical study, or may interfere with study assessments (eg, poor venous access or needle-phobia). were excluded. No specific analyses have been conducted for subjects with cardiovascular impairment. No cardiac toxicity is anticipated from the mechanism of action and properties of nemolizumab (i.e., large therapeutic protein and monoclonal antibodies are not expected to have the ability to directly inhibit the function of ion channels responsible for the cardiac action potential molecule). No clinically relevant changes in ECG parameters were observed, based on the evaluation of mean values, potentially clinically significant values, and TEAEs. No cardiac safety concerns were observed based on the centralized ECG evaluation by external cardiac ECG experts. All data were reviewed by an external cardiac safety expert (Module 5.3.5.4 Expert Assessment Report); there was no evidence to suggest a cardiovascular safety concern associated with nemolizumab treatment in subjects with AD and PN. Mechanistic considerations or data from clinical or nonclinical studies did not evidence potential for proarrhythmic risk.
Immuno-compromised patients	Subjects with known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections (per Investigator Judgement) were excluded from the nemolizumab clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Subjects enrolled into the nemolizumab clinical program in both AD and PN indications were required to fulfil the inclusion criteria for moderate to severe disease at baseline (IGA score of 3 or 4]. Targeted indications for nemolizumab include: • Treatment of moderate-to-severe AD in patients aged 12 years and older who are candidates for systemic therapy . • Treatment of PN . The safety profile of nemolizumab is not anticipated to differ significantly in subjects with a disease severity different from that defined by the inclusion criteria of the trials conducted by the Applicant.
Population with relevant different ethnic origin	The subjects enrolled into the nemolizumab clinical development program were predominantly Caucasian/White. In the AD primary safety population, the following race distribution was observed in nemolizumab arms at baseline (source: AD ISS Table 14.1.3.1.1): • Initial Period (nemolizumab 30 mg Q4W, n=1192): White: 944 (79.2%); Asian: 156 (13.1%); Black or African American: 71 (6.0%); Others 21 (1.7%): • Maintenance Period (nemolizumab 30 mg Q4W to Q4W, n=170; nemolizumab 30 mg Q4W to Q8W, n=167; respectively): White: 146 (85.9%) and 141 (84.4%); Asian: 15 (8.8%) and 19 (11.4%); Black or African American: 8 (4.7%) and 6 (3.6%). In the PN primary safety population, the following race distribution was observed in nemolizumab arm at baseline (source: AD ISS Table 14.1.3.1.1): • Treatment Period: White: 305 (82.4%); Asian: 33 (8.9%), Black or African American: 22 (5.9%): Others: 10 (2.7%). PopPK analysis demonstrated that ethnicity, region and country, had no clinically relevant impact on nemolizumab PK profile.
Subpopulations carrying relevant genetic polymorphisms	No specific genetic testing was conducted during the nemolizumab clinical development program, as no specific genetic polymorphism was identified as being relevant with regards to the pharmacokinetic and pharmacodynamic characteristics of the compound.
Other	Not applicable.

Table 13 presents the cumulative pregnancies reported to the Applicant in the Clinical Setting with nemolizumab (as of 10 Mar 2023).

Table 13 Cumulative pregnancies reported in clinical setting with nemolizumab (cut- off date: 10 Mar 2023)

Study #	Age (years)/ Race	Study Drug Start/End	Treatment Allocation	Pregnancy Outcome	Causality per Investigator/Applicant
Atopic Dermatitis					
SPR114322		21 May 2018/ 31 May 2018	Nemolizumab 90°mg Q4W	Normal female child (weight 2600 g) with no malformation, no neonatal illness and no need to intensive care	No reasonable possibility of a relationship with the study drug.
SPR118161		16 Feb 2021/ 18 Feb 2021	Nemolizumab 30°mg Q4W / Initial period (received only the loading dose of 60 mg)	Unknown (lost to follow up) (gestational age 2.5 weeks at diagnosis /pregnancy. reportedly no observed adverse events in the mother or foetus at the early termination visit on 16 Mar 2021;	No reasonable possibility of a relationship with the study drug.
SPR118161		20 Sep 2021 07 Dec 2021	Placebo Maintenance period (from 06 Aug 2021) Prior allocation in the initial period Nemolizumab 30°mg Q4W	Unknown (subject refused to sign ICF pregnancy form; gestational age 4 weeks at diagnosis; no additional information)	No reasonable possibility of a relationship with the study drug.
SPR118161		11 Aug 2020/ 09 Sep 2020	Nemolizumab 30 mg Q4W	No additional information received as the subject declined to sign pregnancy ICF. At the time of follow- up information date 16 Oct 2020, no adverse event was observed in the subject (mother) and foetus.	Causality per investigator: not reported. Causality per Sponsor for the event: No reasonable possibility of a relationship with the study drug.
SPR118161/ SPR118163		21 Feb 2022/ 16 May 2022	Nemolizumab 30 mg Q4W SPR118163/LTE Prior allocation in SPR118161/initial period Nemolizumab 30°mg Q4W (up to	Unknown	No reasonable possibility of a relationship with the study drug.

Study #	Age (years)/ Race	Study Drug Start/End	Treatment Allocation	Pregnancy Outcome	Causality per Investigator/Applicant
			12 Jul 2021) Nemolizumab 30°mg Q8W/ Maintenance period		
SPR118161/ SPR118163		11 May 2021/ 04 Aug 2021	Nemolizumab 30 mg Q4W SPR118163/LTE Prior allocation in SPR118161 Placebo	Estimated date of delivery: 16Apr2022. Healthy male baby . No maternal complications. No neonatal illness.	Causality per Investigator: not reported. Causality per Sponsor for the event: Not assessable.
SPR118161/ SPR118163		29 Apr 2021/ 29 Apr 2021	Nemolizumab 30 mg Q4W SPR/118163/LTE Prior allocation in SPR118161 Nemolizumab 30 mg Q4W SPR118161/initial period Placebo/Maintenance Period (from 17 Sep 2020)	Spontaneous abortion (twin pregnancy) [no congenital malformation reported]	Causality per investigator and Sponsor for the event: no reasonable possibility of a relationship with the study drug.
SPR201591/ SPR118163		28 Jul 2022/ 15 Dec 2022	Nemolizumab 30 mg Q4W SPR118163/LTE Prior allocation in SPR201591/ Cyclosporin Placebo	Elective abortion (without complication)	No reasonable possibility of a relationship with the study drug.
SPR201591/ SPR118163		19 Sep 2022/ 05 Jan 2023	Nemolizumab 30 mg Q4W SPR118163/LTE Prior allocation in SPR201591/ Cyclosporin Nemolizumab 30°mg Q4W	Spontaneous abortion	Causality per investigator not reported. Considering that no assessment was provided by the investigator, the Sponsor conservatively assessed the event of abortion spontaneous as having a reasonable possibility of a relationship with the study drug
CIM003JG		07 Apr 2014/	Nemolizumab 2°mg/kg	Live birth (female) Reportedly "the subject had not had	Not applicable

Study #	Age (years)/ Race	Study Drug Start/End	Treatment Allocation	Pregnancy Outcome	Causality per Investigator/Applicant
		15 Dec 2014		any complications associated with this pregnancy".	
Prurigo Nodularis					
SPR203065		21 Jul 2021/ 21 Jul 2021	Placebo (Strata:<90 kg)	Elective abortion (Without complications)	No reasonable possibility of a relationship with the study drug.

PART II: MODULE SV POST-AUTHORIZATION EXPERIENCE

No marketing authorization for nemolizumab has been granted to the Applicant in any indication in any country at the data lock point of this RMP.

On 28 March 2022, nemolizumab (60 mg syringes for SC injection) was approved in Japan under the commercial name of Mitchga (Marketing Authorization Holder: Maruho Co. Ltd, the other licensing partner of Chugai) by the Pharmaceuticals and Medical Devices Agency for the treatment of pruritus associated with AD (only when existing treatments are inadequate) in patients over 13 years and older. The approved dosing regimen is 60 mg of nemolizumab administered subcutaneously once every 4 weeks. The product was launched in Japan on 08 Aug 2022.

As of 21 July 2023 (data cut-off of the most recent Development Safety Update Report for nemolizumab), no safety related-regulatory actions such as marketing authorization withdrawal, revocation or suspension, failure to obtain a marketing authorization renewal, restrictions on distribution, clinical trial suspension, dosage modification, changes in target population or indications, formulation changes, or urgent safety restrictions have taken place.

An estimated 4,000 patients had been treated with nemolizumab in Japan. A total of 676 adverse reactions from 474 patients were collected by Maruho. Over the same time period, 34 serious adverse reactions were reported in 27 patients and, of those serious adverse reactions, 30 events from 25 patients were assessed as unlisted adverse reactions, i.e., adverse reactions whose nature or severity were not consistent with the Japanese prescribing information for Mitchga®. No new risks were identified.

SV.1 Method to calculate exposure

Not applicable

SV.2 Exposure

Not applicable

PART II: MODULE SVI ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for Misuse for Illegal Purposes

The target population is not at an increased risk of intentional overdose. Misuse of nemolizumab is not expected.

SVI.2 Overdose

Study drug overdose is the accidental or intentional use of the drug in an amount higher than the dose being studied.

Nemolizumab will be commercially available as a single-use dual-chamber prefilled syringe designed to deliver a dose of 30 mg of nemolizumab upon reconstitution in a volume of 0.49 mg/mL and as an auto-injector designed with a dual-chamber cartridge. The single-dose delivery device will minimize the potential for an overdose. Multiple additional injections would be required for an overdose; therefore, the potential for an accidental overdose is not considered to be a significant risk.

There are only limited data at present on overdose in the clinical trial setting. However, doses of nemolizumab up to 90 mg (6 times at 4-week intervals) have been investigated in the late Phase2b study (SPR.114322) without evidence of clinically important risks for subjects.

An overdose of nemolizumab (vial presentation) occurred in the Phase 2a study CIM003JG in the AD indication. A subject accidentally received an injection of more than 2.0 mg/kg (i.e., 180 mg instead of 110 mg at Visit 12). No AEs were reported.

In the Phase 3 studies in AD, a total of 1192 subjects were randomized to receive at least 1 injection of nemolizumab 30 mg. In the Phase 3 studies in PN, a total of 370 subjects were randomized to receive at least 1 injection of nemolizumab. No overdose was reported.

Overall, the limited information available on overdose of nemolizumab in the clinical trial setting would indicate that a single overdose does not pose a clinically important risk to the patients.

SVI.3 Medication Errors

No medication errors were reported during the clinical development of nemolizumab.

There is no significant known potential for errors based on the product name, presentation, and instructions for use or labelling.

The risk of medication errors associated with Nemolizumab pre-filled DCS and pre-filled pen is assessed as low.

PART II: MODULE SVII IDENTIFIED AND POTENTIAL RISKS

The risks definitions have been used from Good Pharmacovigilance Practice [GVP] – Module Annex 1 & Module V – rev2) have been used.

SVII.1 Identification of Safety Concerns in the Initial RMP Submission

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

The risks not considered important for inclusion into the list of safety issues in this document are summarised in Table 14.

Table 14 Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP

Reason categorisation	Identified or Potential Risk
Risks with minimal clinical impact on patients (in relation to the severity of the indications treated).	**Eczematous reactions**
	Headache
	Urticaria (a type of hypersensitivity)

SVII.1.1.1 Eczematous reactions

Prurigo nodularis indication

Eczematous reactions representing a common pathophysiologic phenomenon (dermatitis atopic, eczema, eczema nummular) were reported during the Treatment Period at a higher frequency in the nemolizumab group compared to the placebo group (Primary Safety Population): dermatitis atopic (17 [4.6%] subjects versus 1 [0.5%] subject, respectively), eczema (14 [3.8%] subjects versus 4 [2.2%] subjects, respectively) and eczema nummular (13 [3.5%] subjects versus 0 subject, respectively). Most nemolizumab subjects had a relevant medical history of atopy. The eczematous reactions in the nemolizumab group were more frequently observed in male (31) than female (11) subjects although the subjects' disposition in this group showed more females (60.0%) than males (40.0%) at baseline. No other risk factors were identified. All events were non-serious and mild to moderate in severity. The incidence of study drug withdrawal due to the events was low (0.5% of nemolizumab subjects). When needed, the events were manageable with topical standard of care treatment (e.g., topical corticosteroids or topical calcineurin inhibitors). Most of the events (58%) resolved, with >60.0% of the events being assessed as related to nemolizumab.

Exposure-response analysis for safety did not show evidence for increased incidence of eczematous reactions with higher nemolizumab concentrations.

However, considering the magnitude of the difference with placebo, it is deemed that there is a reasonable possibility of a relationship between nemolizumab and eczematous reactions.

There is no evidence from available data that eczematous signs could have an impact on the benefit-risk balance of nemolizumab or on public health, which would qualify this risk as an important safety issue.

Atopic Dermatitis Indication

No imbalance between nemolizumab and placebo was observed in the AD Primary Safety Population: dermatitis atopic (124 [10.4%] subjects versus 66 [10.3%] subjects, respectively), eczema (1 [<0.1%] subjects versus 0 subject, respectively) and eczema nummular (1 [<0.1%] subjects versus 0 subject, respectively).

SVII.1.1.2 Headache

Prurigo Nodularis Indication

A total of 26 nemolizumab subjects experienced 32 events of headache and 1 event of tension headache. Twenty-two of the 26 (84.6%) subjects were female with a median age of 52.5 years (range: 20-79); most subjects were White (18 subjects), with the remaining subjects being Asian (3◦subjects) or native Hawaiian (1 subject).

None of the nemolizumab subjects had a medical history of headache but 1 subject had a medical history of migraine.

All events were non-serious and mostly mild (22/32 events; 68.8%) or moderate (9/32 events; 28.1%) in severity. One event was severe for one subject but the headache resolved the same day after treatment with a non-steroidal anti- inflammatory drug (ibuprofen). This subject had no medical history of headache or migraine.

The delay of onset from the first event was a median of 18 days (range: 1-174; N=25). Similarly the duration of the event varied largely: The duration of first events was a median of 7 days (range: 1-58; N=20).

A total of 4 out of 26 (15.4%) subjects presented with more than 1 event: one subject had 3 mild events (Day 20-20, Days 55-85, and Days 138-148); one subject had 2 mild events (Days 13-20 and Day 64- ongoing); one subject had 4 moderate events (Day 69-69, Day 71-71, Day 74-74, and Day 78-78); another subject had 2 moderate events (Day 106-106 and Day 109-109).

No confounders were identified for these subjects.

Six subjects had a concurrent TEAE that could explain the event: oropharyngeal pain (in one subject; mild back pain in one subject; moderate nasopharyngitis in one subject; moderate sinusitis in one subject; mild dyspnoea in one subject with a relevant medical history of sleep disorder). The other subjects had no concurrent TEAE that would provide a possible cause or trigger for the event of headache.

No action with nemolizumab was taken for all events. A total of 28/33 (84.8%) events resolved, either with treatment (22/28 [78.6%] events; metamizole [1 event], paracetamol [11 events], non-steroidal anti-inflammatory drug (naproxen or ibuprofen) [10 events]) or without treatment (6/28 [21.4%] events). Five of 33 (15.2%) events for which no treatment had been administered did not resolve. The duration of first events was a median of 7 days (range: 1-58; N=20). A total of 31 out of 33 (93.9%) events were considered study drug-related.

The exposure-response analysis for safety did not show evidence for higher incidence of headache with higher nemolizumab concentrations. However, considering the magnitude of the difference with placebo and the lack of confounders in most nemolizumab subjects, it was deemed that there is a reasonable possibility of a relationship.

There is no evidence from available data that headache could have an impact on the benefit-risk balance of nemolizumab or on public health, which would qualify this risk as an important safety issue.

Atopic Dermatitis Indication

No imbalance between nemolizumab and placebo was observed in the AD Primary Safety Population: 50 [4.2%] subjects versus 28 [4.4%] subjects, respectively).

Note regarding eczematous reactions and headache:

While an imbalance in the incidence of eczematous reactions and headache was observed only in the PN clinical program, the reason for the difference between the 2 indications has not been identified. The difference could be due to characteristic differences in the populations affected by the 2 indications, due to chance or other unknown factors at this time.

SVII.1.1.3 Urticaria

Prurigo Nodularis Indication

Urticaria (PTs: urticaria and urticaria papular) were reported as isolated events in nemolizumab arm: Urticaria (1 [0.3%] subject versus 0 subject, respectively), urticaria papular (1 [0.3%] subject versus 0 subject, respectively). Both events were nonserious and mild in severity and did not lead to discontinuation of nemolizumab. Urticaria papular and urticaria were assessed respectively as not related and related to nemolizumab.

Latency to the event was 56 days with most recent injection of nemolizumab on Day 29 in one subject who developed nonserious urticaria papular of mild intensity.

Latency to the event was 32 days with most recent injection of nemolizumab on Day 29 in another subject. Confounder was paracetamol (concomitant drug) for TEAE of musculoskeletal chest pain.

In both subjects, no action with nemolizumab was taken. The subjects recovered while on nemolizumab.

Based on the above, it is deemed that there is no evidence of a causal relationship between urticaria and nemolizumab in these subjects.

Atopic Dermatitis Indication

Urticaria was reported in 13 (1.1%) nemolizumab subjects versus 3 (0.5%) placebo subjects. Nonserious and mild urticaria was reported with a close temporal link after initial nemolizumab

injection in some cases (2 events) and after repeated injections in other cases (2 events). None of these events led to discontinuation of nemolizumab.

Based on the above, urticaria is considered an adverse reaction for Nemolizumab in the AD indication.

There is no evidence from available data that urticaria could have an impact on the benefit-risk balance of nemolizumab or on public health, which would qualify this risk as an important safety issue.

For both indications

Considering that any drug may cause hypersensitivity and that type 1 hypersensitivity reactions (Ig-E mediated reactions) were reported in subjects treated with nemolizumab, hypersensitivity is considered a risk for nemolizumab. There were no reports of anaphylactic shock or serum-sickness, and data suggest a low risk of serious and/or severe hypersensitivity reactions. Nevertheless, hypersensitivity reactions are unpredictable by their very nature and can be potentially life- threatening - especially in predisposed patients. Thus, if a clinically significant hypersensitivity reaction occurs, nemolizumab should be discontinued and appropriate therapy instituted. Also, the label will contraindicate the use of nemolizumab in patients with a known hypersensitivity to nemolizumab or to any of its excipients.

There is no evidence from available data that hypersensitivity could have an impact on the benefit-risk balance of nemolizumab or on public health, which would qualify this risk as an important safety issue.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Based on current state of knowledge, there is no identified or potential risks considered important for inclusion into the list of safety concerns for NEMLUVIO.

The risks considered important for inclusion into the list of safety concerns in the RMP are summarized in Table 15. The missing information for the purpose of the RMP for NEMLUVIO is summarized in Table 16 and Table 17 below:

Table 15 Reason for Including an Important Identified, Potential Risk or Missing information in the List of Safety Concerns in the RMP

	Risk-benefit impact
Important identified risk	Not applicable
Important potential risk	Not applicable
Missing information	**Use in pregnancy** Pregnant women were excluded from all clinical trials with nemolizumab. The limited available information on nemolizumab exposure during pregnancy is not sufficient to inform a drug-associated risk of major birth defects or miscarriage in humans. Therefore, further data collection is warranted to characterise the safety profile of nemolizumab in pregnancy. Further details of the safety concern are provided in Table 16. **Long-term safety beyond 1 year of treatment with nemolizumab** Data on long-term safety (beyond 1 year) of nemolizumab treatment are limited in both AD and PN indications. Further details of the safety concern are provided in Table 17.

SVII.2 New Safety Concerns and Reclassification with a Submission of an Updated RMP

Not applicable, as this is the initial RMP.

SVII.3 Details of Important Identified Risks, Important Potential Risks, and Missing Information from Clinical Development

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

SVII.3.1.1 Important identified risks

There are no important identified risks for nemolizumab.

SVII.3.1.2 Important potential risks

There are no important potential risks for nemolizumab.

SVII.3.2 Presentation of the Missing Information

SVII.3.2.1 Use in pregnancy

Table 16 Use in pregnancy

Missing Information: Use in pregnancy	
Evidence source(s) and strength of evidence	Population in need of further characterisation There are no adequate and well-controlled studies to establish the safety of nemolizumab in pregnant women. Administration of nemolizumab did not cause any toxicological changes in male or female reproductive organs in the 3- and 6-month intermittent SC dose toxicity studies using cynomolgus monkeys (TOX10-5016 and TOX12-0076). In the ePPND study (TOX14-0140) in cynomolgus monkeys, nemolizumab was administered SC in dams from the start of organogenesis to the delivery and in pups up to 7 months of age, no toxicological changes were observed in embryofetal development, prenatal or postnatal development, or maternal function. Subjects who were pregnant women were excluded from all clinical trials with nemolizumab and the use of adequate contraception was required in female study participants. However, based on currently available data from the clinical studies with Nemolizumab as of 10 Mar 2023, 11 subjects became pregnant during participation Study 114322 (1 subject), Study 118161 (4 subjects), Study 118163 (4 subjects), Study 203065 (1 subject), and CIM003JG (1 subject). The 11 female subjects ranged in age from 20 years to 33 years (10 subjects with AD [9 nemolizumab, 1 placebo] and 1 subject with PN who was receiving placebo). All 11 subjects prematurely discontinued study drug treatment as per the study protocol. Three subjects delivered a healthy infant/live birth with no congenital abnormalities or concerns reported. The outcomes of 4 pregnancies remain unknown (of these 4: 1 reported no AEs observed in the subject [mother] and fetus at early termination visit and 1 was not exposed to nemolizumab during pregnancy but to placebo). For the remaining 4 pregnancies, 2 were spontaneous abortions (2 of 11 [18%] consistent with the range of expected spontaneous abortions in the general population) and 2 were elective abortions (abortion induced) without complications. The Investigator and the Sponsor assessed that there was no reasonable possibility of a relationship with the study drug for the pregnancy outcomes in 7 of the 11 subjects; 3 pregnancies were not assessed by the Investigator, and the causality for 1 pregnancy was not applicable. Information regarding the use of nemolizumab during pregnancy is presented in SmPC (section 4.6) and Patient Information Leaflet (PIL) (Section 2). Preclinical data are presented in section 5.3 of the SmPC.

SVII.3.2.2 Long-term safety beyond 1 year of treatment with nemolizumab

Table 17 Long-term safety beyond 1 year of treatment with nemolizumab

Missing Information: Long-term safety beyond 1 year of treatment with nemolizumab	
Evidence source(s) and strength of evidence	Two prospective, multicenter, open-label, LTE studies respectively in adult and adolescent subjects with moderate-to-severe AD (Study RD.06.SPR.118163) and in adults with PN (Study RD.06.SPR.202699) who had been previously enrolled in nemolizumab AD or PN Phase 2 and Phase 3 studies are ongoing. Approximately 1700 (AD) and 500 (PN) total subjects are expected, including approximately 200 adolescents (AD only). Subjects will receive nemolizumab 30 mg Q4W in the AD study. PN subjects weighing <90 kg at baseline will receive open-label 30 mg nemolizumab (with 60 mg loading dose at baseline for those not exposed in feeder studies) every 4 weeks (Q4W). Subjects weighing ≥90 kg at baseline will receive 60 mg nemolizumab (two 30-mg injections; no loading dose) Q4W. Clinical assessments will occur according to the protocol-defined schedule (through up to approximately 200 weeks in the AD study and 184 weeks in the PN study), The safety profile of nemolizumab observed in the LTE studies through week 52 (interim analysis) was generally consistent with the safety profile of the product observed in placebo-controlled studies (primary safety populations) for both indications. Updated safety data from both LTE studies for long-term safety analyses are expected upon finalization of the study. Long-term safety beyond 1 year of treatment with nemolizumab30 mg Q4W in AD indication and Fixed dosing with body weight adjustment in PN indication is to be confirmed.

PART II: MODULE SVIII SUMMARY OF THE SAFETY CONCERNS

Table 18 Summary of Safety Concerns

Summary of Safety Concerns	
Important identified risks	None
Important potential risks	None
Missing information	• Use in pregnancy • Long-term safety beyond 1 year of treatment with nemolizumab

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION STUDIES)

III.1 Routine Pharmacovigilance Activities

Routine PV activities include individual case safety reports (ICSRs) management, signal management and continuous benefit-risk assessment, production of periodic reports responses to questions from competent authorities and label maintenance.

All required routine PV activities for all products are described in associated Standard Operating Procedures, Work Instructions and Guidelines. In addition, the company maintains a Pharmacovigilance System Master File describing the PV system for routine PV activities.

III.2 Additional Pharmacovigilance Activities

III.2.1 Pregnancy noninterventional (observational) study:

A Study of Pregnancy and Infant Outcomes in Patients Exposed to Nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Database(s)

Rationale and Study Objectives

There are limited data on nemolizumab use in pregnant individuals, and animal studies have not indicated direct or indirect harmful effects; however, as a precautionary measure, avoiding nemolizumab use during pregnancy is advisable (Galderma data on file, 2024). Women, particularly those of childbearing ages, are more frequently affected by AD, thus highlighting the importance of monitoring possible nemolizumab exposure in pregnancy (Valentini and Shahriari, 2024).

The Pregnancy PASS objectives are as follows:

- To estimate the frequency of select adverse pregnancy and birth outcomes (i.e., ectopic pregnancy, spontaneous abortion, foetal death/stillbirth, elective termination, and preterm birth) in pregnant patients exposed to nemolizumab and in disease-matched pregnant patients unexposed to nemolizumab.
- To estimate the frequency of select adverse foetal, neonatal, and infant outcomes (i.e., major congenital malformations [MCMs] and small for gestational age [SGA]) among infants from pregnancies in patients exposed to nemolizumab during the defined exposure window and from pregnancies in disease-matched patients unexposed to nemolizumab
- To estimate the adjusted relative risks (RRs) for the study outcomes in pregnant patients exposed to nemolizumab compared with disease-matched pregnant patients unexposed to nemolizumab, if study size permits.

Study Design

The design of the proposed noninterventional retrospective cohort study is consistent with relevant guidelines and recommendations (EMA, 2009; FDA, 2019).

This PASS will evaluate the safety of nemolizumab in pregnant patients and their infants. The comparison group will consist of disease-matched pregnant patients unexposed to nemolizumab, treated with other systemic therapies during pregnancy or untreated.

The study will be conducted in existing population-based healthcare databases. Pregnant individuals will be followed from the study entry date until the date of end of pregnancy; infants will be followed from the date of birth up to 1 year after birth.

The proposed study eligibility criteria are:

- Pregnancy identified with a recorded pregnancy outcome (i.e., live birth, stillbirth or foetal death, spontaneous abortion, or elective termination) during the study period
- Continuous health plan enrolment from 6 months prior to the LMP through delivery or end of pregnancy
- Complete medical and pharmacy benefit coverage from 6 months before LMP and through the end of pregnancy
- Women diagnosed with an approved indication for nemolizumab ascertained using appropriate algorithms; well-performing validated algorithms will be preferred (Chomistek et al., 2023)
- Individuals aged 16 to 49 years, inclusive, at their estimated LMP during the study period

Study Population

- Pregnant patients 16 to 49 years of age diagnosed with any approved indication for nemolizumab. Indications currently approved or under consideration are moderate to severe atopic dermatitis and prurigo nodularis; if other indications are approved in the future, they will be incorporated in the study
- Two cohorts will be identified prospectively: pregnant patients who use commercially available nemolizumab during pregnancy and disease-matched pregnant patients unexposed to nemolizumab.

Milestone

Protocol submission: within 3 months of the European Commission issuance of the marketing authorisation for nemolizumab.

Study start and relevant milestones depend on various factors, including drug approval by Health Authorities, local reimbursement, drug uptake, and administrative procedures. Contracts between the sponsor and research organization(s) and approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies and duration of contract reviews.

Further details are provided in the study synopsis Annex 3 - Pregnancy Protocol Synopsis

II.3 Summary Table of Additional Pharmacovigilance Activities

Table 19 Ongoing and planned additional Pharmacovigilance Activities

Study Status	Summary of objectives	Safety Concerns addressed	Milestones	Due dates
Category 3 - Required additional pharmacovigilance activities				
PASS *A Study of Pregnancy and Infant Outcomes in Patients Exposed to Nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Database(s)* *Planned*	To estimate the frequency of select adverse pregnancy and birth outcomes (i.e., ectopic pregnancy, spontaneous abortion, foetal death/stillbirth, elective termination, and preterm birth) in pregnant patients exposed to nemolizumab and in disease-matched pregnant patients unexposed to nemolizumab To estimate the frequency of select adverse foetal, neonatal, and infant outcomes (i.e., major congenital malformations [MCMs] and small for gestational age [SGA]) among infants from pregnancies in patients exposed to nemolizumab during the defined exposure window and from pregnancies in disease-matched patients unexposed to nemolizumab To estimate the adjusted relative risks (RRs) for the study outcomes in pregnant patients exposed to nemolizumab compared with disease-matched pregnant patients unexposed to nemolizumab, if study size permits.	*Missing information:* Use in pregnant women	*Protocol*	*Within 3 months of EC decision*
A Phase 3, Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis - ARCADIA LTE (RD.06.SPR.118163) *Ongoing*	To evaluate the long-term safety and efficacy of nemolizumab in subjects with moderate-to-severe AD	*Missing information:* Long term safety beyond 1 year	Final Study Report	Q1 2027

A Phase 3, Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects with Prurigo Nodularis – OLYMPIA LTE (RD.06.SPR.202699)*Ongoing*	To evaluate the long-term safety and efficacy of nemolizumab in subjects with moderate-to-severe PN	*Missing information:* Long term safety beyond 1 year	Final Study Report	Q3 2027

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

No post authorisation efficacy studies are ongoing or planned.

PART V: RISK MINIMISATION PLAN (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

The safety information in the proposed product information is aligned to the reference medicinal product.

V.1 Routine Risk Minimisation Measures

Details of the routine risk minimisation measures are summarised in Table 20.

Table 20 Description of Routine Risk Minimisation Measures by Safety Concern

Safety concern	Routine risk minimisation activities
Important identified risks	
	Not Applicable
Important potential risks	
	Not Applicable
Missing information	
Use in pregnancy	***Routine risk communication:*** Objective is to provide prescribers and patients information on the missing information. Information regarding the use of nemolizumab during pregnancy is presented in section 4.6 of the SmPC and in section 2 of the PIL. Preclinical data are presented in section 5.3 of the SmPC. Prescription only medicine. ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** N/A ***Other routine risk minimisation measures beyond the Product Information***: N/A
Long-term safety beyond 1 year of treatment with Nemolizumab	***Routine risk communication:*** No risk minimization measure is proposed as there is no evidence for a need at present.

	Prescription only medicine ***Routine risk minimisation activities recommending specific clinical measures to address the risk:*** N/A ***Other routine risk minimisation measures beyond the Product Information***: N/A

Table 21 Effectiveness of risk minimization measures

How effectiveness of risk minimization measures for the safety concern will be measured	Close monitoring and signal detection activities
Criteria for judging the success of the proposed risk minimization measures	No increase in reporting rate or increase in severity and/or seriousness over time
Planned dates for assessment	Each periodic report
Results of effectiveness measurement	No signal indicating changes of the aforementioned criterion over time
Impact of risk minimization	Awareness of the risk.

V.2 Additional Risk Minimisation Measures

Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product. There are no additional risk minimisation measures.

V.3 Summary of Risk Minimisation Measures

A summary of pharmacovigilance activities and risk minimisation activities is presented by safety concern in Table 22.

Table 22 Table of Pharmacovigilance Activities and Risk Minimisation Measures by Safety Concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important potential risks		
Not Applicable	Not Applicable	Not Applicable
Missing information		
Use in pregnancy	***Routine risk minimisation measures:*** Information regarding the use of nemolizumab during pregnancy is presented in section 4.6 of the SmPC and in section 2 of the PIL. Preclinical data are presented in section 5.3 of the SmPC. Prescription only medicine. ***Additional risk minimisation measures:*** There are no risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** continuous benefit-risk assessment, production of periodic reports responses to questions from competent authorities and label maintenance ***Additional pharmacovigilance activities***: Pregnancy non-interventional (observational) retrospective cohort study

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Long-term safety beyond 1 year of treatment with nemolizumab	***Routine risk minimisation measures:*** None ***Additional risk minimisation measures:*** There are no risk minimisation measures	***Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:*** continuous benefit-risk assessment, production of periodic reports responses to questions from competent authorities and label maintenance ***Additional pharmacovigilance activities***: A Phase 3, Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis -ARCADIA LTE (RD.06.SPR.118163) and A Phase 3, Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects with Prurigo Nodularis – OLYMPIA LTE (RD.06.SPR.202699)

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

This is a summary of the Risk Management Plan (RMP) for NEMLUVIO. The RMP details important risks of NEMLUVIO, how these risks can be minimised, and how more information will be obtained about NEMLUVIO's risks and uncertainties (missing information).

NEMLUVIO's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how NEMLUVIO should be used.

This summary of the RMP for NEMLUVIO should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of NEMLUVIO's RMP.

I. The Medicine and What it is used for

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.
- Treatment of adults with moderate-to-severe prurigo nodularis who are candidates for systemic therapy.

See SmPC for the full indications.

It contains nemolizumab as the active substance and it is given by subcutaneous (SC) injection.

Further information about the evaluation of NEMLUVIO's benefits can be found in NEMLUVIO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage.

link to the EPAR summary landing page.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of NEMLUVIO together with measures to minimise such risks and the proposed studies for learning more about NEMLUVIO's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimize its risks.

Together, these measures constitute routine Risk Minimisation Measures.

If important information that may affect the safe use of NEMLUVIO is not yet available, it is listed under 'missing information' below.

II.A List of Important Risks and Missing Information

Important risks of NEMLUVIO are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential:

- Identified risks are concerns for which there is sufficient proof of a link with the use of NEMLUVIO.
- Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.
- Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

Table 23 List of important risks and missing information

List of important risks and missing information	
Important identified risks	None
Important potential risks	None
Missing information	Use in pregnancy Long term safety beyond 1 year of treatment with nemolizumab

II.B Summary of Important Risks

The safety information in the proposed Product Information is aligned to the reference medicinal product.

Table 24 Missing information: Use in pregnancy

Missing information	
Risk Minimisation Measures	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3 PIL section 2 Prescription only medicine **Additional risk minimisation measures:** None
Additional Pharmacovigilance Activities	Additional Pharmacovigilance Activities: Observational PASS in Pregnancy: A Study of Pregnancy and Infant Outcomes in Patients Exposed to Nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Database(s) See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 25 Missing information: Long-term Safety beyond 1 year of treatment with nemolizumab

Missing information	
Risk Minimisation Measures	**Routine risk minimisation measures:** None **Additional risk minimisation measures:** None

Missing information	
Additional Pharmacovigilance Activities	**Additional Pharmacovigilance Activities**: A Phase 3, Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis – ARCADIA LTE (RD.06.SPR.118163) and A Phase 3, Prospective, Multicenter, Long-Term Study to Assess the Safety and Efficacy of Nemolizumab (CD14152) in Subjects with Prurigo Nodularis – OLYMPIA LTE (RD.06.SPR.202699)

II.C Post-authorisation Development Plan

II.C.1 Studies which are Conditions of the Marketing Authorisation

There are no studies which are Conditions of the Marketing Authorisation or Specific Obligation of NEMLUVIO.

II.C.2 Other Studies in the Post-Authorisation Development Plan

One PASS is currently planned. Its details are included below.

Planned PASS

Study short name:

Observational PASS of nemolizumab use in pregnancy.

A Study of Pregnancy and Infant Outcomes in Patients Exposed to nemolizumab During Pregnancy: A Retrospective Observational Study Based on Healthcare Database(s).

Purpose of the study:

No experimental data indicate reproductive toxicity of nemolizumab, but the available evidence is currently insufficient to draw conclusions about the safety of using nemolizumab during pregnancy.

The study will investigate whether maternal exposure to nemolizumab during pregnancy is associated with an increased risk of major congenital malformations, preterm births, infants born small for gestational age, spontaneous abortion, or stillbirths.

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PART IX ANNEXES

Annex 4 Protocols for Proposed and Ongoing Studies in RMP Part IV

None

Annex 6 Other Supporting Data other than References

Not Applicable