CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761390Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761390
Priority or standard	PRIORITY
Submit date(s)	12/12/2023
Received date(s)	12/12/2023
PDUFA goal date	8/12/2024
Division/office	Division of Dermatology and Dentistry (DDD)
Review completion date	8/8/2024
Established/proper name	Nemolizumab-ilto
(Proposed) proprietary name	NEMLUVIO
Pharmacologic class	Interleukin-31 receptor antagonist
Other product name(s)	CIM331/CD14152
Applicant	Galderma Laboratories, L.P.
Dosage form(s)/formulation(s)	Injection, Powder, Lyophilized, for Solution
Dosing regimen	Patients weighing less than 90 kg: an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks Patients weighing 90 kg or more: an initial dose of 60 mg (two 30 mg injections), followed by 60 mg given every 4 weeks
Applicant-proposed indication(s)/ population(s)	Treatment of adults with prurigo nodularis
SNOMED CT code for proposed indication disease term(s)[1]	63501000 |Prurigo nodularis (disorder)|
Regulatory action	Approval
Approved dosage (if applicable)	Not applicable
Approved indication(s)/ population(s) (if applicable)	Not applicable
SNOMED CT code for approved indication disease term(s)[1]	Not applicable

[1] For internal tracking purposes only.
Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Population	Dose mg/kg	n	$AUC_{0\text{-}inf}$ (day•µg/mL)	C_{max} (µg/mL)	T_{max} (day)	$t_{1/2}$ (day)	CL/F (mL/day)	V/F (mL)
Healthy Japanese subjects (Part A)	0.03	6	7.01 (1.20)[a]	0.315 (0.0352)	6.50 (4.00, 11.0)	12.7 (3.38)[a]	274 (35.1)[a]	4960 (1150)[a]
	0.1	6	19.7 (5.16)	0.782 (0.143)	7.00 (6.00, 10.0)	14.5 (4.22)	331 (122)	6510 (1620)
	0.3	5	75.7 (12.0)	2.33 (0.486)	10.00 (4.00, 10.0)	15.1 (1.71)	264 (37.3)	5690 (697)
	1.0	6	226 (24.5)	8.82 (1.23)	4.00 (4.00, 7.00)	15.2 (1.81)	269 (47.7)	5840 (842)
	3.0	6	634 (199)	23.9 (3.40)	5.00 (4.00, 6.00)	16.4 (3.92)	319 (75.9)	7250 (1200)
Healthy White subjects (Part B)	0.3	6	79.7 (19.5)	2.28 (0.535)	8.51 (7.00, 14.0)	16.0 (2.87)	300 (117)	6590 (1470)
	1.0	6	272 (103)	8.33 (1.57)	6.50 (3.00, 7.00)	16.3 (7.20)	321 (110)	6760 (1150)
	3.0	6	777 (236)	26.0 (8.01)	6.00 (2.00, 10.0)	16.5 (3.01)	337 (119)	7700 (1850)
Japanese subjects with AD (Part C)	0.3	9	49.2 (14.3)	2.20 (0.689)	5.00 (2.00, 14.0)	12.6 (4.01)	408 (141)	7320 (3150)
	1.0	9	161 (25.1)	6.50 (1.57)	4.24 (2.00, 7.23)	13.2 (3.44)	368 (56.8)	6990 (2160)
	3.0	9	489 (196)	19.4 (5.85)	3.99 (3.01, 7.03)	14.6 (6.18)	459 (207)	8510 (2050)

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Glossary

ADA	antidrug antibody
AE	adverse event
AELD	adverse event leading to discontinuation of treatment
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC_{ss}	area under the concentration-time curve at steady state
BCC	basal cell carcinoma
BLA	biologics license application
CL/F	apparent clearance
C_{max}	maximum plasma concentration
$C_{max,ss}$	maximum plasma concentration at steady state
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	Clinical Outcome Assessment
DCC	dual chamber cartridge
DCC-AI	dual chamber cartridge assembled with an autoinjector
DCS	dual chamber syringe
DDI	drug-drug interaction
ECG	electrocardiogram
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
GCP	good clinical practice
ICE	intercurrent event
ICH	International Council for Harmonization
IGA	Investigator's Global Assessment
IIV	interindividual variability
IL	Interleukin
IND	investigational new drug application
ITT	intent-to-treat
LD	loading dose
LTE	long term extension
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
NOAEL	no-observed-adverse-effect level
OPQ	Office of Pharmaceutical Quality
OSMR	oncostatin M receptor
PD	pharmacodynamic
PI	prescribing information
PK	pharmacokinetic

PN	prurigo nodularis
PND	postnatal day
PP	per protocol
PP-NRS	Peak Pruritus Numeric Rating Scale
PRO	patient-reported outcome
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SCC	squamous cell carcinoma
SD-NRS	Sleep Disturbance Numeric Rating Scale
SEE	substantial evidence of effectiveness
SSD	Subject Sleep Diary
TEAE	treatment-emergent adverse event
T_{max}	time to maximum concentration
ULN	upper limit of normal
WGT	body weight

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Galderma (Applicant) submitted this biologics license application (BLA) for nemolizumab-ilto (tradename NEMLUVIO), seeking approval of this interleukin (IL)-31 receptor antagonist for prurigo nodularis, an uncommon chronic skin disorder (Stander et al. 2021). Patients with prurigo nodularis present with severe pruritis due to firm, itchy nodules on the trunk and extensor surfaces of the arms and legs. The pathophysiology is not fully understood, but emerging data implicate Th2 cytokines, including IL-31, which binds to the IL-31 receptor expressed on small C-fiber sensory neurons in the skin that mediate pruritis.

The BLA was reviewed by a multidisciplinary review team. Each discipline recommends approval for the single-dose prefilled dual chamber pen dosage form, and the signatory authority for this application concurs with this recommendation. (b) (4)

Substantial evidence of effectiveness for nemolizumab was established using data from two adequate and well-controlled trials. OLYMPIA 1 and 2 enrolled 560 adult subjects with prurigo nodularis and randomized them (2:1) to nemolizumab or placebo. Nemolizumab was administered via subcutaneous injection, beginning with a 60 mg loading dose and followed every four weeks with a maintenance dose of either 30 or 60 mg depending on weight (<90kg or ≥90 kg, respectively). Subjects were followed for 16 weeks and asked to rate their worst itch intensity over the past 24 hours from 0 (no itch) to 10 (worst itch imaginable); investigators were asked to assess nodule severity on a five point scale ranging from clear (no nodules) to severe (abundant nodules). Compared to placebo, a higher proportion of patients randomized to nemolizumab achieved an improvement of four our more points on the peak pruritis scale and improvement in severity to clear or almost clear (22% vs. 2% in OLYMPIA 1, and 25% vs. 4% in OLYMPIA 2). These results were statistically significant (treatment difference of 15% (95%CI 8% to 21%) for OLYMPIA 1 and 22% (95%CI 14 to 30%) for OLYMPIA 2).

The available safety data show that nemolizumab is safe for its intended use as labeled. The safety concerns identified for nemolizumab can be adequately managed through labeling and further evaluated during routine pharmacovigilance. No deaths were reported in subjects treated with nemolizumab during the phase 3 trials. Serious adverse events were more common in the placebo treated patients. Hypersensitivity reactions, including facial angioedema, were reported with the use of nemolizumab and will be included in the label with a Warning & Precaution. This section will also include class labeling for avoidance of live vaccines during treatment with nemolizumab. Adverse reactions that occurred more frequently in the nemolizumab treated patients included headache, atopic dermatitis, eczema, and numular eczema. Treatment with nemolizumab may modulate serum levels of some cytokines that influence the formation of

CYP450 enzymes, so labeling advises prescribers to consider monitoring concomitant administration of CYP450 substrates with narrow therapeutic indices, such as warfarin or cyclosporin.

The BLA included appropriate preapproval nonclinical and clinical pharmacology studies. No additional studies will be conducted as postmarketing requirements.

The review team concludes that the improvement in pruritis and nodule severity observed with nemolizumab treatment compared to placebo outweighs the risks when nemolizumab is used as recommended in the approved labeling. There are no outstanding issues from any review discipline. I concur with the content of the various discipline assessments and their recommendation for approval of the pen dosage form. The Agency and the Applicant have agreed upon the final labeling language. The submitted clinical program is adequate to support the efficacy and safety of nemolizumab in the pen dosage form for the treatment of adults with prurigo nodularis.

The action for the pen dosage form will be **Approval**. (b) (4)

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

Trials OLYMPIA 1 and OLYMPIA 2 were randomized, multicenter, double-blind, placebo-controlled, parallel-group, phase 3 trials to evaluate the safety and efficacy of nemolizumab compared to placebo for the treatment of adult patients with prurigo nodularis (PN).

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	Prurigo nodularis (PN) is a chronic skin disorder characterized by multiple firm dome-shaped, severely pruritic nodules, symmetrically distributed, and typically localized to the extensor surface of the extremities and certain areas of the trunk with sparing of the face, palms, soles and upper midback (Elmariah et al. 2021). Nodules can vary in size, color, and number. The itching of PN is typically episodic, severe, disruptive and can precede typical PN lesions by at least six weeks (Zeidler et al. 2018). PN may be associated with a variety of diseases, such as atopic dermatitis, chronic renal failure, hyperthyroidism, iron-deficiency anemia, gastric malignancy, lymphoma, and leukemia. PN may be the presenting symptom of infections with human immunodeficiency virus (HIV), hepatitis B and C, mycobacteria, and parasitic infestations (Pereira et al. 2018). PN is often associated with significant physical and psychological morbidity, including sleep disruption, anxiety, and depression. The diagnosis of PN is clinical, based upon a history of chronic, severe pruritus and the clinical finding of characteristic nodular lesions symmetrically distributed (Stander et al. 2020).	While PN is not a life-threatening condition, it may be serious and can have significant impact on the quality of life. Due to scratching caused by intense pruritus, the skin barrier may become compromised predisposing patients to secondary infections. Additionally, the primary and secondary disease-related skin changes (lichenification, scaring, post-inflammatory pigmentary changes) may affect the appearance of the skin. PN is associated with significant physical and psychological morbidity, including sleep disruption, anxiety, and depression.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	Dupilumab is the only FDA-approved therapy indicated for the treatment of adult patients with prurigo nodularis (PN). Treatment of PN is difficult and requires a multifaceted approach to interrupt the itch-scratch cycle and flatten the skin lesions. Although not approved for the treatment of PN, in clinical practice super-potent topical corticosteroids and intralesional corticosteroids are used off-label and considered first-line therapy for those patients with a limited number of PN lesions (Elmariah et al. 2021). The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions (Qureshi et al. 2019).[1] Other off-label topical treatments reported as efficacious include topical capsaicin (Stander et al. 2001), tacrolimus, topical pimecrolimus, topical vitamin D analogues (e.g., calcipotriol, tacalcitol), and a compounded mixture of topical ketamine, amitriptyline, and lidocaine (Lee et al. 2017). These topical therapies are often limited in use due to time-intensive treatment schedules and risk of recurrence upon discontinuation (Williams et al. 2020). Phototherapy is used in patients who do not respond to treatment with topical or intralesional corticosteroids or for those with widespread disease (Bruni et al. 2010). Oral antihistamines, the tricyclic antidepressants doxepin or amitriptyline, or gabapentin/pregabalin have been used as adjunctive treatments to control pruritus. Patients with widespread or recalcitrant disease often rely on systemic therapies. Systemic products that are used off-label to treat moderate-to-severe PN include cyclosporine, methotrexate, and thalidomide, each with varying degrees of efficacy (Qureshi et al. 2019).	In the opinion of this reviewer, approval for licensure of nemolizumab for the treatment of adult patients with PN would represent an important addition to the treatment options for a patient population for whom the only FDA- approved product is limited to dupilumab. Nemolizumab would be the second systemic product (following the licensure of dupilumab in September 2022 for the treatment of PN) to be licensed for this indication and would represent an alternative for patients with PN for whom treatment with dupilumab may not be available or advisable. The medical needs of such patients are not currently being met as the only other available treatment option would be the (off-label) use of immunomodulating products with their potential risks for adverse reactions.

[1] www.aad.org American Academy of Dermatology, statement released October 18, 2021

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	The efficacy of nemolizumab was demonstrated in two Randomized, Double-Blind, Placebo-Controlled trials, OLYMPIA 1 and OLYMPIA 2. Nemolizumab was statistically superior to placebo for the two primary efficacy endpoints of the proportion of subjects with IGA success (defined as IGA score of 0 [clear] or 1 [almost clear] with at least a 2-grade improvement from baseline) at Week 16 and the proportion of subjects with an improvement (reduction) of ≥4 from baseline in PP-NRS at Week 16, as well as for the (multi-component) secondary efficacy endpoint of "Proportion of subjects with both an improvement (reduction) of ≥4 from baseline in PP-NRS and IGA 0 or 1" (not adjusted for multiplicity) at Week 16 (this endpoint is currently the FDA-recommended primary endpoint for PN trials).	Nemolizumab demonstrated efficacy in patients with PN in adequate and well-controlled trials. The clinical trial design and endpoints were appropriate for the PN population, for which there are limited treatment options.
Risk and risk management	The overall assessment of safety of nemolizumab is informed by a variety of sources, including nonclinical toxicology, safety pharmacology studies, and early-phase clinical studies. The safety assessment for the intended population of PN patients is based primarily on the phase 3 PN trials OLYMPIA 1 and OLYMPIA 2 and included the following results: • No deaths were reported in any subject treated with nemolizumab during phase 3 trials. The safety database was adequate to assess risks and outcomes. The two phase 3 trials included 370 subjects in the nemolizumab group and 186 subjects in the placebo group. The PN exposure pool (including two phase 3 trials, a phase 2 trial, and a long-term phase 3 trial) included a total of 555 subjects who received treatment with the same dose of nemolizumab, including 471 subjects treated for ≥6 months, 375 subjects treated for ≥1 year, 207 subjects treated for ≥18 months, and 51 subjects treated for ≥2 years. The most common adverse reactions reported at a frequency of ≥1% in the nemolizumab group through Week 16 (and more frequently than in the placebo group) included headache (6% vs. 3%), dermatitis atopic (4% vs. 0.5%), eczema (4% vs. 2%), and eczema nummular (3% vs. 0%). Immunogenicity had no significant impact on the PK, efficacy, or safety of nemolizumab in the phase 3 PN trials.	Based on the available data, nemolizumab has a reasonable safety profile and would be acceptable for approval for licensure based on this application. The safety database was adequate for comprehensive safety assessment of nemolizumab for the proposed indication, patient population, dosage regimen, and duration of treatment. Safety risks have not been identified that require risk management beyond standard pharmacovigilance. A REMS is not recommended for this application. Due to the low prevalence of PN in the population and limited incidence of pregnancies expected in this patient population, pregnancy registries for nemolizumab may not have utility and will not be recommended by the review team as postmarketing requirements.

Abbreviations: HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; PK, pharmacokinetic; PP-NRS, Peak Pruritus Numeric Rating Scale; PN, prurigo nodularis; REMS, risk evaluation and mitigation strategy

2.2. Conclusions Regarding Benefit-Risk

Review of the application supports an approval recommendation for BLA 761390 licensure from the nonclinical, clinical pharmacology, clinical, and statistical review teams. Based upon review of all available efficacy and safety data, the benefits of nemolizumab clearly outweigh the risks for treatment of prurigo nodularis in adult patients.

The Applicant conducted two phase 3, randomized, double-blind, placebo-controlled trials (OLYMPIA 1 and OLYMPIA 2) which enrolled 560 adult subjects with (moderate to severe) PN with baseline Investigator's Global Assessment (IGA) scores ≥ 3, ≥20 PN nodules, and a weekly average peak pruritus numeric rating scale (PP-NRS) score of ≥7.

The results of trials OLYMPIA 1 and OLYMPIA 2 showed statistically significant improvements for the primary efficacy endpoints ("the proportion of subjects with an IGA score of 0 [clear] or 1 [almost clear]" at Week 16 and "the proportion of subjects with at least 4-point improvement (reduction) from baseline in PP-NRS" at Week 16). Additionally, statistically significant improvements were demonstrated for the efficacy endpoints of "the proportion of subjects with both an improvement (reduction) of ≥4 from baseline in PP-NRS and an IGA 0 or 1" at week 16 (multi-component endpoint, not controlled for multiplicity), and the proportion of subjects with PP-NRS <2 at week 16.

The safety results of trials OLYMPIA 1 and OLYMPIA 2 demonstrated a reasonable safety profile. Adverse events reported for ≥1% of subjects treated with nemolizumab compared to the vehicle group (and at a greater frequency than vehicle) during 16 weeks of treatment included headache (6% vs. 3%), dermatitis atopic (4% vs. 0.5%), eczema (4% vs. 2%), and eczema nummular (3% vs. 0%). The WARNINGS AND PRECAUTIONS section of the label will include subsections for hypersensitivity (5.1) and vaccinations (5.2).

No PREA PMRs will be issued because studies in pediatric subjects with PN is impossible or highly impracticable due to small number of pediatric subjects with PN. Additionally, no PMRs for pregnancy or lactation studies will be issued because of the small number of pregnancies expected in the PN patient population.

No REMS is recommended by the review team, as routine pharmacovigilance and labeling should be adequate to communicate risks to prescribers and patients.

An Active Risk Identification and Analysis System (ARIA) [a component of FDA's Sentinel System] memorandum (for a known serious risk, signals of a serious risk or to identify an unexpected serious risk related to the use of a drug) was not requested by the review team from DEPI because the review of safety data reported during the clinical trials did not identify any serious safety concerns that would warrant assessment by ARIA; and routine pharmacovigilance appears adequate for postmarketing surveillance.

The review team recommends an Approval action for this BLA only for the prefilled dual-chamber pen (Autoinjector) presentation (b) (4) .

II. Interdisciplinary Assessment

3. Introduction

The Applicant, Galderma Laboratories L.P., seeks approval for licensure of NEMLUVIO (nemolizumab-ilto) 30 mg/0.49 mL for the treatment of prurigo nodularis (PN). Nemolizumab would be the second drug product, after dupilumab, to be approved by the US Food and Drug Administration (FDA) for the treatment of PN. The Applicant conducted 5 studies in subjects with PN:

- One phase 2 clinical study (RD.03.SPR.115828)
- Two (pivotal) phase 3 clinical studies (RD.06.SPR.203065 [OLYMPIA 2] and RD.06.SPR.202685 [OLYMPIA 1])
- One (ongoing) phase 3 long-term extension (LTE) study (RD.06.SPR.202699)
- One (ongoing) blinded phase 3b durability of response study (RD.06.SPR.203890)

The two phase 3 trials (OLYMPIA 1 and OLYMPIA 2) were used to demonstrate the safety and superior efficacy of nemolizumab compared to placebo.
Nemolizumab is a humanized anti-human interleukin-31 receptor A (IL-31RA) monoclonal antibody which competitively blocks the binding of IL-31 to its receptor and subsequent activation of JAK/STAT pathway and transduction of the IL-31 signal into the cell.
Nemolizumab is proposed to be administered by subcutaneous (SC) injection at the recommended initial dose of 60 mg followed by SC injections every 4 weeks of:

- 30 mg for patients weighing <90 kg
- 60 mg for patients weighing ≥90 kg

The review issues with potential impact on the approvability of nemolizumab identified by the review team are summarized in Section 3.1 of this review.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. (b) (4)

3.1.1.2. (b) (4)

3.1.2. Key Safety Review Issues

No Critical Safety Concerns Identified.

3.2. Approach to the Clinical Review

The following Table 3 provides an overview of the clinical studies (listed in Section 3 of this review) conducted by the Applicant and submitted to biologics license application (BLA) 761390 to support the benefit-risk assessment of nemolizumab for the treatment of PN.

Table 3. Clinical Trials Submitted[1] in Support of Efficacy and Safety Determinations for Nemolizumab

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Randomized	Number of Centers and Countries
SPR202685 OLYMPIA 1 (phase 3)	Male or female subjects at least 18 years of age with a clinical diagnosis of prurigo nodularis (PN) for at least six months	Control type: Placebo-controlled Randomization: Randomized 2:1 Intervention: Parallel-group study Stratification: By study center and baseline body weight (<90 kg and ≥90 kg) Blinding: Double blind Biomarkers: None Innovative design features: None	Nemolizumab 60 mg On Day 1, followed by 30 mg Q4W (for subjects with baseline weight < 90 kg) or 60 mg Q4W (for subjects with baseline weight ≥90 kg) at Weeks 4, 8, 12, 16, and 20) Duration: 24 weeks Number treated: 187 Placebo number treated: 95	Primary: An improvement of ≥4 from baseline in PP-NRS at Week 16. An IGA success at Week 16 Secondary: improvement of ≥4 from baseline in PP-NRS at Week 4 PP-NRS <2 at Week 16 Improvement of ≥4 from baseline in SD-NRS at Week 16 Improvement of ≥4 from baseline in SD-NRS at Week 4 PP-NRS <2 at Week 4	Planned: (b) (4) Randomized: 286	Centers: 77 Countries: 10

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Randomized	Number of Centers and Countries
SPR203065 OLYMPIA 2 (phase 3)	Male or female subjects at least 18 years of age with a clinical diagnosis of prurigo nodularis (PN) for at least six months	Control type: Placebo controlled Randomization: Randomized 2:1 Intervention: Parallel-group study Stratification: By study center and baseline body weight (<90 kg and ≥90 kg) Blinding: Trial blinding schema – double blind Biomarkers: None Innovative design features: None	Nemolizumab 60 mg On Day 1, followed by 30 mg Q4W (for subjects with baseline weight < 90 kg) or 60 mg Q4W (for subjects with baseline weight ≥90 kg) at Weeks 4, 8, and 12) Duration: 16 weeks number treated: 183 Placebo number treated: 91	Primary: An improvement of ≥4 from baseline in PP-NRS at Week 16 An IGA success at Week 16 Secondary: Improvement of ≥4 from baseline in PP-NRS at Week 4 PP-NRS <2 at Week 16 Improvement of ≥4 from baseline in SD-NRS at Week 16 Improvement of ≥4 from baseline in SD-NRS at Week 4 PP-NRS <2 at Week 4	Planned: (b) (4) Actual: 274	Centers: 55 Countries: 9

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Randomized	Number of Centers and Countries
RD.06.SPR.202699 (phase 3 LTE) (ongoing)	Male or female subjects at least 18 years of age with a clinical diagnosis of prurigo nodularis (PN) for at least six months who had been enrolled in prior phase 2a or phase 3 trial of nemolizumab for PN	A prospective, multicenter, open-label, long-term study to assess the safety and efficacy of nemolizumab in subjects with prurigo nodularis	Nemolizumab 30 mg Q4W for baseline body weight <90 kg Nemolizumab 60 mg Q4W for baseline body weight ≥90 kg Treatment duration: 184 weeks	Primary (safety): TEAE, SAE, AESI, severe AEs Secondary (efficacy): An IGA success at each visit up to Week 184 IGA ≤2 at each visit up to Week 184 Improvement of ≥4 from baseline in PP-NRS at each visit up to Week 184 PP-NRS <2 at each visit up to Week 184	Planned: (b) (4) Enrolled: 508	Centers: 120 Countries: 16

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Patients Planned; Actual Randomized	Number of Centers and Countries
RD.03.SRE.115828 (phase 2a)	Male or female subjects at least 18 years of age with a clinical diagnosis of prurigo nodularis (PN) for at least six months	Control type: Placebo- controlled Randomization: Randomized 1:1 Intervention: Parallel-group study Blinding: Double blind	Nemolizumab 0.5 mg/kg Q4W X3 (at Weeks 0, 4, 8) Number treated: 35 Placebo number treated: 35 Duration: 12 weeks	Primary: Percent change from baseline in pruritus NRS to Week 4 (weekly average of the peak) Secondary: Absolute and percent change from baseline in weekly average of the peak and average pruritus NRS to each visit The proportion of subjects achieving a 50%, 75% and 90% reduction from baseline in weekly average of the peak pruritus An IGA success at Week 12 IGA at each visit	Planned: 70 Randomized: 70	Centers: 16 Countries: 4

Source: Clinical Study Reports and adsl.xpt
Note: An IGA success was defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥2-grade improvement from baseline.
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
Abbreviations: AE, adverse event; AESI, adverse event of special interest; IGA, Investigator's Global Assessment; LTE, long-term extension; NRS, numeric rating scale; PN, prurigo nodularis; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, every four weeks; SAE, serious adverse event; SD-NRS, Sleep Disturbance Numeric Rating Scale; TEAE, treatment-emergent adverse event

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response):

   Treatment of adults with prurigo nodularis.

2. SEE was established [for the dual-chamber prefilled autoinjector (AI) presentation] with *(check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE)*

   a. Adequate and well-controlled clinical investigation(s):

      i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
      ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

      OR

   b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence[2,3,4]

      OR

   c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)[2]

3. Complete response, if applicable

   a. ☐ SEE was established
   b. ☐ SEE was not established *(if checked, omit item 2)*

2 FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (2019)*

3 FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

4 FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (2023)

4. Patient Experience Data

Table 4. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcomes (PROs): • Peak Pruritus Numeric Rating Scale (PP-NRS; primary endpoint) • Sleep Disturbance Numeric Rating Scale (SD-NRS; key secondary endpoint) • Average Pruritus Numeric Rating Scale (secondary endpoint) • Subject Sleep Diary (secondary endpoint) • Pain Frequency Numeric Rating Scale (secondary endpoint) • Patient Global Assessment of Disease (secondary endpoint) • Dermatology Life Quality Index (secondary endpoint) • Hospital Anxiety and Depression Scale (secondary endpoint) • EuroQoL 5-Dimension (secondary endpoint)	The PP-NRS is discussed in Section 6.2.4. The SD-NRS is discussed in Sections 6.2.5 and 6.3.2.
☐	Observer-reported outcome	
☒	Clinician-reported outcome • Investigator's Global Assessment (IGA; primary endpoint) • Prurigo Activity Score (secondary endpoint)	The IGA is discussed in Section 6.2.4.
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel) • Study EVM-25950-01 (individual patient interviews)	See DCOA review for a summary of Study EVM-25950-01.
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

The nonclinical data support the potential effectiveness of nemolizumab based on the following findings (see Section 2.1 for detailed information).

- Nemolizumab is a humanized monoclonal IgG2 antibody recognizing the interleukin-31 receptor alpha chain (IL-31RA) and blocking binding of IL-31. IL-31, a cytokine secreted by activated T cells, induces itch, barrier disruption, skin inflammation, and fibrosis.
- Nemolizumab binds to human and cynomolgus monkey IL-31RA with high affinity.
- Nemolizumab inhibited human IL-31-dependent proliferation of recombinant cells engineered to express human and monkey IL-31RA.
- Nemolizumab inhibited IL-31-induced STAT3 phosphorylation in an IL-31RA-expressing human cell line.
- Nemolizumab inhibited IL-31-induced IL-6, MMP-1, and MMP-3 production and apoptosis in a human epidermal keratinocyte cell line.
- In an IL-31-induced itch model in cynomolgus monkeys, nemolizumab administered via intravenous (IV) or subcutaneous (SC) routes inhibited itching behavior.
- In a mite antigen-induced mouse atopic dermatitis model, treatment with BM095 (a mouse IL-31RA neutralizing antibody) showed reduction in ear thickness, pinna dermatitis score and number of scratching movements.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic activity
Established pharmacologic class (EPC)	Interleukin (IL)-31 receptor antagonist.
Mechanism of action	Nemolizumab-ilto is a humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by binding selectively to IL-31 RA. IL-31 is a naturally occurring cytokine that is involved in pruritus, inflammation, epidermal dysregulation, and fibrosis. Nemolizumab-ilto inhibited IL-31-induced responses including the release of proinflammatory cytokines and chemokines.
Active moieties	Nemolizumab is the active moiety.
QT prolongation	In the clinical development program of nemolizumab, there was no evidence to suggest a cardiovascular safety concern associated with nemolizumab treatment in subjects with PN. No clinically relevant changes of ECG parameters have been observed, based on the evaluation of mean values, potentially clinically significant values, and AEs. No cardiac safety concerns have been observed, based on the centralized ECG evaluation. Overall, the cardiovascular safety profile of nemolizumab has been adequately characterized and that additional designated studies, including a thorough QT study, are generally not needed for monoclonal antibodies due to its large molecular size.
	General information
Bioanalysis	Nemolizumab serum concentrations were measured using validated enzyme-linked immunosorbent assay (ELISA) methods.
Healthy subjects versus patients	PK was similar between healthy subjects and subjects with PN.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Parameter Mean ± SD $AUC_{T,ss}$ 130±42.0 µg•day/mL for subjects with body weight <90 kg; and 160 ± 57.7 µg•day/mL for subjects with body weight ≥90 kg. C_{max} 6.05 ± 1.70 µg/mL for subjects with body weight <90 kg; and 7.55 ± 2.37 µg/mL for subjects with body weight ≥90 kg. C_{24} 3.04 ± 1.23 µg/mL for nemolizumab 30 mg Q4W in subjects with body weight <90 kg; and 3.66 ± 1.63 µg/mL for 60 mg Q4W in subjects with body weight ≥90 kg.

Characteristic	Drug Information
Range of effective dose(s) or exposure	In the phase 2a study (Study 115828), a 0.5 mg/kg weight-based dose administered Q4W for 12 weeks showed efficacy in subjects with PN. Nemolizumab was clinically and statistically significantly superior to placebo in reducing the weekly average PP NRS scores at Week 4. The proportion of subjects with IGA success was numerically higher in the nemolizumab group compared with the placebo group at Weeks 4 and 8 and statistically significantly higher in the nemolizumab group compared with the placebo group at Weeks 12 and 18. In the pivotal phase 3 trials (Studies 202685 and 203065), an initial dose of 60 mg followed by 30 mg given Q4W for patients <90 kg and an initial dose of 60 mg followed by 60 mg given Q4W for patients weighing ≥90 kg, nemolizumab was superior to placebo with respect to the primary endpoints of weekly average PP NRS improvement of ≥4 from baseline and IGA success (0 or 1 and a ≥2-grade improvement from baseline.
Maximally tolerated dose or exposure	The highest studied single dose was 3 mg/kg in the FIH Study CIM001JP. The highest-studied multiple dose was 60 mg Q4W using the to-be-marketed formulation.
Dose proportionality	After a single dose, nemolizumab exposure increased dose proportionally over a dose range between 0.03 and 3 mg/kg following subcutaneous administration. After multiple doses, nemolizumab systemic exposure increased in an approximately dose-proportional manner across the subcutaneous dose range up to 30 mg. There was a slight decrease in bioavailability by 9% with the 60 mg subcutaneous dose and by 15% with the 90 mg subcutaneous dose.
Accumulation	The accumulation index (Rac) of nemolizumab following multiple-dose administration was 1.6, calculated using Population PK analysis.
Time to achieve steady-state	For subjects with body weight <90 kg, receiving nemolizumab 30 mg SC Q4W with a 60 mg SC loading dose, steady-state was reached by Week 4. No loading dose is proposed for subjects with bodyweight ≥90 kg because the 60 mg dose was sufficient to achieve similar steady-state nemolizumab concentrations to the 30 mg dose (with 60-mg loading dose) after the second dose, i.e., Week 8.
Bridge between to-be-marketed and clinical trial/study formulations	In the phase 3 trials in subjects with PN (Studies 202685, 203065, and 202699), nemolizumab was supplied as a lyophilized powder in a dual chamber syringe (DCS) for solution for injection, which held the lyophilized nemolizumab or placebo and the sWFI separately. The Applicant intends to register (b) (4) the drug product (dual-chamber cartridge assembled with an autoinjector (DCC-AI) (b) (4) A relative bioavailability study comparing nemolizumab PK after administration using the DCC-AI and the DCS has been conducted. Results from Study 201590 provide support for the DCC-AI as (b) (4) commercial drug product presentation. An OSIS inspection request was submitted for Study 201590 and OSIS determined not to inspect the sites and all of the sites will be issued a Decline to Inspect memo. For further details, see OSIS Inspection report in DARRTS dated July 12, 2024.

Characteristic	Drug Information
	Absorption
Bioavailability	Absolute BA was not assessed.
T_{max}	Following an initial subcutaneous dose of 60 mg, nemolizumab reached peak mean (SD) concentrations (C_{max}) of 7.5 (2.31) µg/mL by approximately six days post dose.
Food effect (fed/fasted) geometric least square mean and 90% CI	NA since SC administration.
	Distribution
Volume of distribution	7.67 L
Plasma protein binding	NA as this is a monoclonal antibody
Drug as substrate of transporters	NA as this is a monoclonal antibody
	Elimination
Mass balance results	NA as this is a monoclonal antibody
Clearance	0.263 L/day
Half-life	18.9 days
Metabolic pathway(s)	The metabolic pathway of nemolizumab has not been characterized. Nemolizumab is expected to be degraded into small peptides by catabolic pathways.
Primary excretion pathways (% dose)	The drug is catabolized into small peptides.
	Intrinsic factors and specific populations
Body weight	Body weight was identified as a significant covariate on nemolizumab exposure. The exposure of nemolizumab decreases with increasing body weight with a flat dosing regimen. With a flat dosing regimen of 30 mg Q4W, steady-state systemic C_{trough} exposure was predicted to be 1.7-fold lower between the upper body weight quartile (87 to 181 kg: 1.72 µg/mL) and the lower body weight quartile (31 to 62 kg: 2.92 µg/mL). The PK/PD simulations also predicted that for subjects with body weight ≥90 kg, the same flat dose (30 mg Q4W regimen with 60-mg loading dose) would lead to lower efficacy as measured by IGA success compared to patients with body weight <90 kg. Based on the above considerations, a body weight tiered dosing regimen was studied in the pivotal phase 3 studies, with a 60-mg loading dose followed by 30 mg Q4W for subjects with body weight <90 kg and a 60-mg dose administered Q4W for subjects with body weight ≥90 kg, to achieve matching systemic exposure and similar efficacy response (IGA) in subjects with body weight <90 kg and ≥90 kg. The proposed dosing regimen was the same dosing regimen as studied in the pivotal phase 3 studies.
Age	Age did not impact nemolizumab exposures.
Renal impairment	Nemolizumab is not expected to undergo renal elimination. Therefore, no dedicated studies were conducted to evaluate nemolizumab PK in patients with renal impairment. Based on population PK analyses, no impact of mild or moderate renal impairment was observed on nemolizumab PK. However, due to limited data, the impact of severe renal impairment on the PK of nemolizumab is unknown.

Characteristic	Drug Information
Hepatic impairment	Nemolizumab is not expected to undergo metabolism by hepatic metabolic enzymes. Therefore, no dedicated studies were conducted to evaluate nemolizumab PK in patients with hepatic impairment. Based on population PK analyses, no impact of mild or moderate hepatic impairment was observed on nemolizumab PK. However, due to limited data, the impact of severe hepatic impairment on the PK of nemolizumab is unknown.
	Drug interaction liability (drug as perpetrator)
Inhibition/induction of metabolism	No dedicated drug-drug interaction studies in subjects with PN have been conducted. However, the formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Treatment with nemolizumab may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes. Therefore, upon initiation or discontinuation of nemolizumab in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.
Inhibition/induction of transporter systems	NA
	Immunogenicity (if applicable)
Bioanalysis	A validated anti-drug antibody (ADA) assay method using a homogeneous electrochemiluminescence (ECL) format with the MesoScale Discovery (MSD) platform was applied for testing of antibody testing in all clinical studies.
Incidence	In the pivotal trials in subjects with PN (Studies 202685 and 203065) and the long-term extension (LTE) study in subjects with PN (Study 202699) up to 116 weeks, the incidence of treatment-emergent ADAs was 12.8% (46 out of 358 subjects).
Clinical impact	ADA had no apparent impact on nemolizumab PK, efficacy, or safety.

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; $AUC_{t\text{-}ss}$, area under the concentration-time curve from time, t to steady state; BA, bioavailability; C, plasma concentration; CI, confidence interval; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; DCC-AI, dual-chamber cartridge assembled with an autoinjector; DCS, dual chamber syringe; ECG, electrocardiogram; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; EPC, established pharmacologic class; FIH, first-in-human; IGA, Investigator's Global Assessment; IgG2, immunoglobulin G 2; IL, interleukin; LTE, long-term extension; MSD, MesoScale Discovery; OSIS, Office of Study Integrity and Surveillance; PD, pharmacodynamic; PK, pharmacokinetic; PN, prurigo nodularis; PP-NRS, Peak Pruritus Numeric Rating Scale; QT, qualification threshold; Q4W, every 4 weeks; Rac, accumulation index; SC, subcutaneous; sWFI, sterile water for injection; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant conducted two phase 3 trials (OLYMPIA 1 [RD.06.SPR.202685] and OLYMPIA 2 [RD.06.SPR.203065]). The proposed dose was determined to be acceptable for approval.

The selection of the dosing regimen used in the phase 3 trials was based on the results of the phase 2a study conducted in 70 subjects with PN (Study 115828) along with modeling and simulation analyses. Subjects enrolled in the phase 2a study received a 0.5-mg/kg weight-based dose administered Q4W for 12 weeks. This 0.5-mg/kg dose successfully demonstrated efficacy in the treatment of PN with an acceptable safety profile. Data from the phase 2a study were used to refine population pharmacokinetic (PK) and pharmacokinetics/pharmacodynamics (PK/PD) models. Population PK simulations showed that the 30-mg dose (60-mg loading dose) was expected to achieve similar steady state systemic exposure and efficacy as the 0.5-mg/kg dose and was therefore selected for the pivotal phase 3 trials. However, a significant impact of body weight was predicted on the nemolizumab PK profile, with increasing body weight resulting in a decrease in the nemolizumab systemic exposure for subjects receiving a flat dose. As the population PK analysis showed an impact of body weight on nemolizumab PK profile, the effect of body weight on efficacy was further assessed using PK/PD simulations. The PK/PD model for (Peak Pruritus Numeric Rating Scale) PP-NRS predicted that the lower systemic exposure in higher body weight subjects would not impact efficacy as measured by the PP-NRS responder rate. Conversely, the PK/PD model for Investigator's Global Assessment (IGA) score suggested that lower systemic exposure may result in lower efficacy as measured by the IGA success. Based on the above considerations, a body weight tiered dose adjustment was selected in the pivotal phase 3 trials, with a 60-mg loading dose followed by 30 mg Q4W for subjects with body weight <90 kg and a 60-mg dose administered Q4W for subjects with body weight ≥90 kg.

The proposed dose for patients with PN is an initial loading dose of 60 mg, followed by 30 mg given SC Q4W for patients with a body weight <90 kg or nemolizumab 60 mg SC Q4W (no loading dose) for patients with body weight ≥90 kg. The efficacy of nemolizumab for the treatment of PN following this dosing regimen was established in 2 pivotal phase 3 trials (Studies 202685 and 203065).

After the completion of the phase 3 studies, the initial population PK model was refined based on pooled data from the PN and the atopic dermatitis (AD) clinical development programs. The PK/PD models for IGA and weekly average PP-NRS were developed based only on data from subjects with PN enrolled in phase 2a and pivotal phase 3 trials. The exposure of nemolizumab decreased with increasing body weight with a flat dose. With a flat dose of 30 mg Q4W, steady-state systemic C_{trough} exposure was predicted to be 1.7-fold lower between the upper body weight quartile (87 to 181 kg: 1.72 μg/mL) and the lower body weight quartile (31 to 62 kg: 2.92 μg/mL). As the population PK analysis showed an impact of body weight on nemolizumab PK profile, the effect of body weight on efficacy was further assessed using the PK/PD simulations. PK/PD simulations based on the 2 clinical primary endpoints of the phase 3

studies (IGA success and weekly average PP-NRS responders at Week 16) demonstrated that the variability in systemic exposure due to body weight had no clinically meaningful impact on weekly average PP-NRS responders at Week 16. However, a lower IGA success was predicted for subjects with body weight ≥90 kg when treated with a non-adjusted dose (30 mg Q4W regimen with 60 mg loading dose). Therefore, the proposed dosing regimens were selected to achieve matching systemic exposure and similar efficacy response in subjects with body weight <90 kg and ≥90 kg.

The population PK analysis also confirmed the adequacy of the 60-mg loading dose to rapidly reach the desired steady-state concentrations in subjects with PN with body weight <90 kg. Steady-state was reached by Week 4 with a loading dose and by Week 12 without a loading dose. Without a loading dose, accumulation of nemolizumab following multiple dosing was predicted to be 1.6-fold to reach the desired steady-state conditions. No loading dose is proposed for patients with PN and a body weight ≥90 kg, as the 60 mg dose was sufficient to achieve similar steady-state nemolizumab concentrations to the 30 mg dose (with 60 mg loading dose) after the second dose, i.e., Week 8.

At steady state, the population PK mean (± SD) nemolizumab C_{trough} was 3.04 ± 1.23 μg/mL for nemolizumab 30 mg Q4W in subjects with body weight <90 kg; and 3.66 ± 1.63 μg/mL for 60 mg Q4W in subjects with body weight ≥90 kg.

In addition, the analyses of exposure-safety relationships did not show evidence for any increased safety events with higher nemolizumab concentrations. Anti-drug antibodies to nemolizumab were not associated with clinically relevant changes in serum nemolizumab concentrations, reduced efficacy, or any safety findings. Overall, the clinical efficacy and safety results from the 2 pivotal phase 3 trials, PK results, PK/PD, and exposure-safety outcomes provided supportive evidence for the effectiveness and safety of the selected doses and the proposed dosing regimens in subjects with PN. The proposed dose adjustment based on body weight was adequate to achieve therapeutic exposure and clinical benefit in the overall population.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Trial Design, Trials OLYMPIA 1 and OLYMPIA 2

OLYMPIA 1 and OLYMPIA 2 were randomized, multicenter, double-blind, placebo-controlled, parallel-group, phase 3 trials to evaluate the safety and efficacy of nemolizumab compared to placebo for the treatment of PN.

Figure 1 presents the study design schematics for both trials. The treatment duration was 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2. Each trial was designed to enroll and randomize approximately 270 subjects from about 70 centers (Europe, North America, and Asia Pacific) in a 2:1 ratio to receive either nemolizumab or placebo. The protocols specified stratifying the randomization by center and baseline body weight (<90 kg and ≥90 kg). For nemolizumab, subjects weighing <90 kg at baseline received 60 mg at baseline (loading dose)

followed by 30 mg every 4 weeks (Q4W), and subjects weighing ≥ 90 kg at baseline received 60 mg at baseline and Q4W.

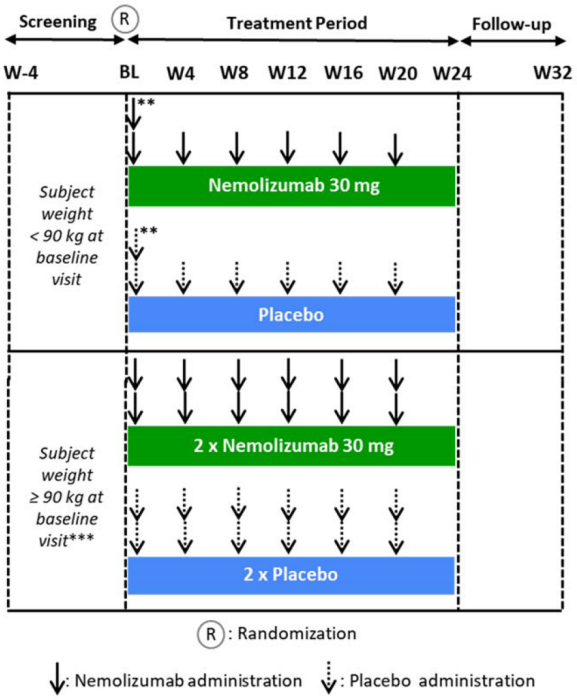
For OLYMPIA 1, subjects were scheduled to have the following site visits: Screening (Day -28 to -8), Baseline (Day 1), Weeks 4, 8, 12, 16, 20, and 24. For OLYMPIA 2, subjects were scheduled to have the following site visits: Screening (Day -28 to -8), Baseline (Day 1), Weeks 4, 8, 12, and 16. The protocols specified that the end of the treatment period, consenting subjects may be eligible to enter a long-term extension (LTE) study (SPR.202699). Subjects who opted not to participate in the LTE study were scheduled to return for a follow-up visit (Week 32 for OLYMPIA 1 and Week 24 for OLYMPIA 2).

The protocols specified that if deemed to be medically necessary by the investigator (e.g., to control intolerable PN signs/symptoms), rescue therapies can be prescribed to the subjects. The protocols specified that rescue therapy must not be prescribed during the screening period and should not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure. The protocols specified the following as rescue therapies: topical corticosteroids, topical calcineurin inhibitors, oral antihistamines, systemic or intralesional corticosteroids, biologics (including their biosimilars), systemic nonsteroidal immunosuppressants/immunomodulators, and phototherapy. The protocols stated:

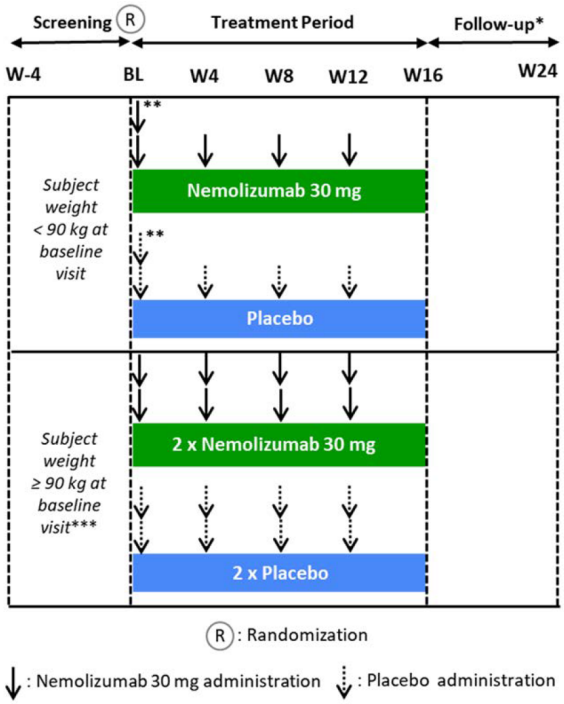
“For the purpose of efficacy analysis, subjects receiving any rescue therapies will be considered as treatment failures. Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy. Further, the use of any rescue therapies should be documented in the eCRF.”

Figure 1. Trial Design Schematics for OLYMPIA 1 and OLYMPIA 2

OLYMPIA 1



OLYMPIA 2



Source: page 53 of the protocols (Version 5.0) for OLYMPIA 1 and OLYMPIA 2.
* Applicable for subjects who do not participate in the LTE study only
** Loading dose (two injections) administered at baseline visit for subjects weighing <90 kg
*** Two injections administered at all applicable visits for subjects weighing ≥ 90 kg at the baseline visit
Abbreviations: BL, baseline; R, randomization; W4, week 4; W8, week 8; W12, week 12; W16, week 16; W20, week 20; W24, week 24; W32, week 32

6.2.2. Eligibility Criteria, Trials OLYMPIA 1 and OLYMPIA 2

Key eligibility criteria for both trials are summarized in this section and the full criteria are available in Table 60 in Section 15.2 and Table 62 in Section 15.3.

Inclusion Criteria

- Male or female and aged ≥18 years at the time of screening
- Clinical diagnosis of prurigo nodularis for at least 6 months with:
  - Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs
  - At least 20 nodules on the entire body with a bilateral distribution
  - IGA score ≥3 (moderate) at both the Screening and Baseline visits
- Severe pruritus defined as follows on the Peak Pruritus Numeric Rating Scale (PP-NRS):
  - Screening visit: PP-NRS score is ≥7.0 for the 24-hour period immediately preceding the Screening visit.
  - Baseline visit: Mean of the daily intensity of the PP-NRS score is ≥7.0 over the previous week. The protocols specified that the PP-NRS score be measured on at least 4 days

during the week preceding the baseline visit. In addition, the protocols specified that rounding of the mean PP-NRS score is not permitted.

Exclusion Criteria

- Body weight <30 kg
- 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 disorder, sporotrichosis, 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
- Unilateral lesions of prurigo (e.g., only one arm affected)
- History of or current confounding skin condition (e.g., Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis)
- Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months

6.2.3. Clinical Endpoints, Trials OLYMPIA 1 and OLYMPIA 2

The protocols specified the following two primary efficacy endpoints:

- Proportion of subjects with a ≥4-point improvement on the PP-NRS from Baseline to Week 16
- Proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) and a ≥2-point improvement from baseline at Week 16

The protocols specified the following key secondary efficacy endpoints:

- Proportion of subjects with a ≥4-point improvement on the PP-NRS from Baseline to Week 4
- Proportion of subjects with PP-NRS score <2 at Week 16
- Proportion of subjects with a ≥4-point improvement on the Sleep Disturbance Numeric Rating Scale (SD-NRS) from baseline to Week 16
- Proportion of subjects with a ≥4-point improvement on the SD-NRS from Baseline to Week 4
- Proportion of subjects with PP-NRS score <2 at Week 4

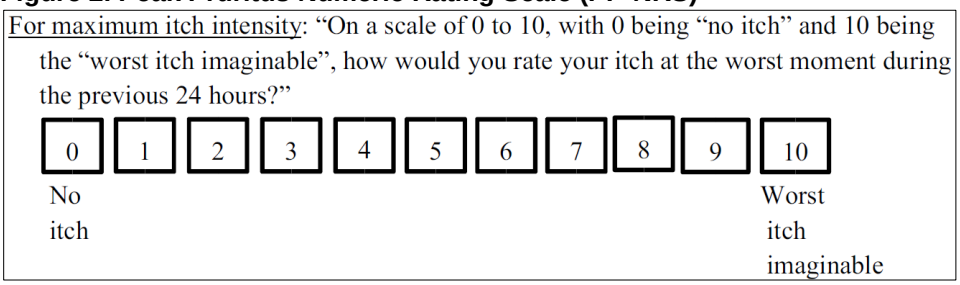
6.2.4. Clinical Outcome Assessment Instruments Used to Assess the Primary Endpoints, Trials OLYMPIA 1 and OLYMPIA 2

The PP-NRS and IGA were analyzed separately as primary efficacy endpoints. A description of the instruments used to collect the data for these endpoints is summarized below.

6.2.4.1. Peak Pruritus Numeric Rating Scale

The PP-NRS (Figure 2) is a single-item patient reported outcome PRO instrument designed to assess itch intensity using an 11-point scale NRS ranging from 0 ("No itch") to 10 ("Worst itch imaginable"). The recall period is the previous 24 hours. The PP-NRS was administered electronically daily from Screening (Visit 1; Day -28 to -8) to Week 24 for OLYMPIA 1 and from Screening (Visit 1; Day -28 to -8) to Week 16 for OLYMPIA 2.

Figure 2. Peak Pruritus Numeric Rating Scale (PP-NRS)



Source: page 164 of the protocols (Version 5.0) for OLYMPIA 1 and OLYMPIA 2.

The PP-NRS generated a weekly score that ranged from 0 to 10, with higher scores indicating greater itch intensity. The baseline weekly PP-NRS score was determined based on the average of the PP-NRS (score ranging from 0 to 10) during the seven days immediately preceding Baseline (rounding to nearest whole number is not permitted). See Section 6.2.6 for details on the calculation of the weekly scores based on the daily diary data.

6.2.4.2. Investigator's Global Assessment

The Investigator's Global Assessment (IGA) (Table 6) is a single-item clinician-reported outcome (ClinRO) instrument designed to assess PN severity using a 5-point scale verbal rating scale ranging from 0 ("Clear") to 4 ("Severe"). The recall period is current state. In OLYMPIA 1 and OLYMPIA 2, the IGA was administered at Screening (Day -28 to -8), Baseline (Day 1), and Weeks 4, 8, 12, 16, 20 (only OLYMPIA 1), and 24 (only OLYMPIA 1).

Table 6. Investigator's Global Assessment (IGA) Scale

Score	Category	Description
0	Clear	No nodules
1	Almost clear	Rare palpable pruriginous nodules
2	Mild	Few palpable pruriginous nodules
3	Moderate	Many palpable pruriginous nodules
4	Severe	Abundant palpable pruriginous nodules

Source: page 159 of the protocols (Version 5.0) for OLYMPIA 1 and OLYMPIA 2.

The IGA generated a single item score that ranged from 0 to 4, with higher scores indicating greater PN severity.

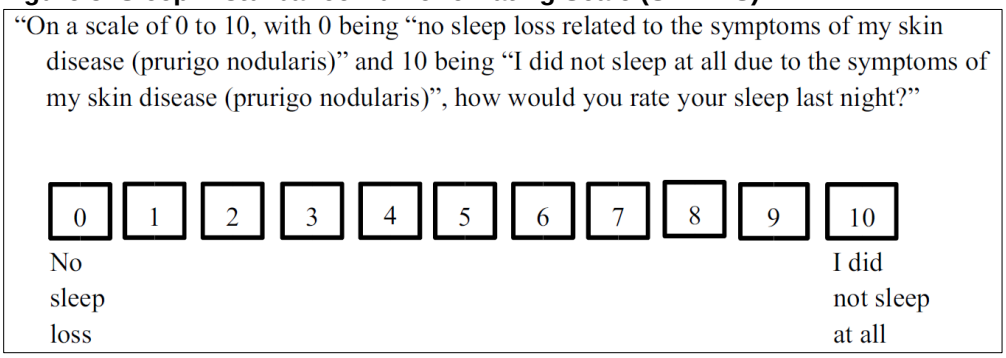
6.2.5. Patient-Reported Outcome Instrument Used to Assess the Key Secondary Endpoint, Trials OLYMPIA 1 and OLYMPIA 2

The SD-NRS was used to assess the ranked secondary efficacy endpoints #3 and #4 in OLYMPIA 1 and OLYMPIA 2. The instrument is described briefly below. Refer to Section 6.3.2 and the Clinical Outcome Assessment (COA) memo by the Division of Clinical Outcome Assessment for the evaluation of the adequacy of the instrument.

6.2.5.1. Sleep Disturbance Numeric Rating Scale

The SD-NRS (Figure 3) is a single-item PRO instrument designed to assess sleep loss related to symptoms of PN using an 11-point scale NRS ranging from 0 ("No sleep loss") to 10 ("I did not sleep at all"). The recall period is the previous 24 hours. The SD-NRS was administered electronically daily from Screening (Visit 1; Day -28 to -8) to Week 24 for OLYMPIA 1 and from Screening (Visit 1; Day -28 to -8) to Week 16 for OLYMPIA 2.

Figure 3. Sleep Disturbance Numeric Rating Scale (SD-NRS)



Source: page 165 of the protocols (Version 5.0) for OLYMPIA 1 and OLYMPIA 2.

The SD-NRS generated a weekly score that ranged from 0 to 10, with higher scores indicating greater sleep loss. The baseline weekly SD-NRS score was determined based on the average of the SD-NRS (score ranging from 0 to 10) during the seven days immediately preceding baseline (rounding to nearest whole number is not permitted). See Section 6.2.6 for details on the calculation of the weekly scores based on the daily diary data.

6.2.6. Statistical Analysis Plan, Trials OLYMPIA 1 and OLYMPIA 2

Analysis Populations

The specified primary analysis population for efficacy was the intent-to-treat (ITT) population, defined as all randomized subjects. The protocols and the statistical analysis plans (SAPs)

specified conducting supportive analyses using a per-protocol (PP) population. The PP population was defined as all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. The protocols listed the following as major protocol deviations:

- Eligibility deviations (inclusion/exclusion criteria)
- Improper reconstitution and administration of study drug
- Noncompliance with study drug per the investigator's discretion
- Noncompliance with study procedures if the consequence of noncompliance would compromise either the subject's safety and/or the study integrity, primary endpoint(s), and/or is not in line with Good Clinical Practice (GCP)/International Council for Harmonisation (ICH) guidelines
- Use of prohibited concomitant therapies
- Visit/treatment windows (i.e., if a study visit occurs outside the visit window defined in the Schedule of Assessments

Estimands

The protocol and statistical analysis plan (SAP) specified the following as the main estimand for the primary and key secondary efficacy endpoints (all binary endpoints):

- **Treatments**: nemolizumab and placebo
- **Population**: ITT Population
- **Endpoint**: a binary response at a specified timepoint
- **Intercurrent Events (ICEs) and Strategy for Handling**:
  - *Rescue Therapy*: subjects who use rescue therapy on or prior to the specified timepoint for the endpoint are considered as non-responder (composite variable strategy)
  - *Treatment Discontinuation*: observed data after treatment discontinuation will be used (treatment policy strategy)
- **Population-level Summary Measure**: difference in proportions between nemolizumab and placebo

Analysis Methods

The protocols and SAP specified analyzing the primary and key secondary efficacy endpoints (all binary endpoints) using the Cochran-Mantel-Haenszel (CMH) test stratified by analysis center and baseline body weight (90 kg and ≥90 kg). The SAP specified calculating the adjusted treatment difference in proportions using the weighted average of the treatment differences across the strata with the CMH weights, along with the associated two-sided 95% confidence intervals (CIs) using a normal approximation to the weighted average. Missing data was specified to be imputed using the non-responder imputation approach.

Multiplicity Adjustment Plan

The protocols and SAPs specified using a fixed sequential testing approach to control the Type I error rate at the two-sided 0.05 level. The primary and key secondary efficacy endpoints were specified to be tested in the order listed below, and testing would stop if an endpoint was not significant at the two-sided 0.05 level.

1. Proportion of subjects with a ≥4-point improvement on the PP-NRS from Baseline to Week 16
2. Proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) and a ≥2-point improvement from Baseline at Week 16
3. Proportion of subjects with a ≥4-point improvement on the PP-NRS from Baseline to Week 4
4. Proportion of subjects with PP-NRS score <2 at Week 16
5. Proportion of subjects with a ≥4-point improvement on the SD-NRS from Baseline to Week 16
6. Proportion of subjects with a ≥4-point improvement on the SD-NRS from Baseline to Week 4
7. Proportion of subjects with PP-NRS score <2 at Week 4

Sensitivity and Supplementary Analyses

The SAP specified the following sensitivity analyses of the primary efficacy endpoints for the handling of missing data:

- **Tipping Point Analysis:** To assess the robustness of non-responder analysis, a tipping point analysis will be performed by converting non-responders due to missing data to responders in successive increments (Δ) for both treatment groups. The value of Δ that overturns (i.e., non-significant) the primary results will represent the tipping point. A graphic display of all possible combinations of the number of responders among both treatment groups will be presented.
- **Multiple Imputation – Missing at Random (MI-MAR):** The non-monotone missing data will be first imputed 50 times using the Markov-Chain-Monte-Carlo (MCMC) method. The monotone missing data will be then imputed using the regression method (ordinal logistic regression for IGA and linear regression for PP-NRS). The model will include treatment, randomization strata, and assessments from earlier timepoints.
- **Multiple Imputation – Missing Not at Random (MI-MNAR):** A controlled based pattern imputation method where only observations in the placebo group will be used to impute the missing data in both treatment groups.
- **Last Observation Carried Forward (LOCF):** Subjects who use rescue medication will have the value prior to start of the medication carried forwarded. The SAP specifies that missing post-baseline values will be carried forward from the last non-missing post-baseline value.
- **Observed Case (OC):** Missing data will not be imputed. For subjects that use rescue medication, data post-rescue will be analyzed as observed (i.e., not set to missing) by ignoring the use of rescue medication.

For the above sensitivity analyses, the SAP specified that except for the OC analyses, assessments on or after rescue therapy will be considered as non-responders (i.e., use the composite variable strategy).

Calculation of the Weekly Scores for Daily Diary Data (PP-NRS and SD-NRS)

On November 24, 2021, the Applicant submitted the SAPs ("Stable Version 0.1") for OLYMPIA 1 and OLYMPIA 2 to the investigational new drug (IND) application. In this version of the SAP, a minimum of 4 daily scores out of the 7 days was specified to be required to calculate the weekly prorated average score.

According to the Applicant (submission dated June 11, 2024), a blinded data review meeting for OLYMPIA 2 occurred on May 10, 2022. The Applicant stated that during this meeting, a high proportion of protocol deviations due to missing diary data was observed, and the Applicant evaluated alternative approaches to handle the missing data. The Applicant decided to extend the analysis window at baseline and Week 16 for the PP-NRS and the SD-NRS. The SAP ("Final Version 1.0") for OLYMPIA 2 was finalized with the following extensions on May 20, 2022:

- Baseline: "If there are less than 4 non-missing assessments within last 7 days prior to the first dose, the interval lower bound will be extended up to 7 additional days, one day at a time, to obtain the most recent 4 non-missing values. The extention [sic] will not be applied for the sensitivity analysis by using a minimum of 2 (or 3) daily scores out of the 7 days."
- Week 16: "If there are less than 4 assessments during Week 16 visit window, upper bound of the visit window (106 - 112) or (107 - 113) will be extended for 5 additional days. If there are still less than 4 assessments after extending upper bound of the visit window, lower bound of the visit window will be extended for another 5 days until 4 assessments are reached."

In addition, the Applicant added sensitivity analyses using a minimum of 2 daily scores out of 7 days and a minimum of 3 daily scores out of 7 days for calculating the weekly scores.

The database lock for OLYMPIA 2 occurred on May 26, 2022. The SAP ("Final Version 1.0") for OLYMPIA 1 was finalized with the extensions on March 3, 2023, and the database lock for OLYMPIA 1 occurred on April 11, 2023. The finalized SAPs for OLYMPIA 1 and OLYMPIA 2 were not submitted to the IND.

On March 13, 2024, the Agency sent an IR to the Applicant and requested the Applicant submit results for the primary and key secondary efficacy endpoints based on the PP-NRS and the SD-NRS without the extensions to the analysis window for baseline and Week 16. The Applicant submitted the requested results on March 27, 2024.

6.2.7. Results of Analyses, Trials OLYMPIA 1 and OLYMPIA 2

Subject Disposition, Demographics and Baseline Disease Characteristics

OLYMPIA 1 enrolled and randomized a total of 286 subjects (190 to nemolizumab and 96 to placebo) from 77 centers. OLYMPIA 2 enrolled and randomized a total of 274 subjects (183 to nemolizumab and 91 to placebo) from 55 centers. Table 7 presents the subject disposition for the placebo-controlled phase of the trials. The trial discontinuation rate was higher in OLYMPIA 1

compared to OLYMPIA 2; however, it should be noted that the trial duration was longer in OLYMPIA 1 compared to OLYMPIA 2 (i.e., 24 weeks versus. 16 weeks). The demographics and baseline disease characteristics were generally balanced across the two treatment groups and are presented in Table 8.

Table 7. Subject Disposition, OLYMPIA 1 and OLYMPIA 2

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab	**Placebo**	**Nemolizumab**	**Placebo**
Randomized subjects	190	96	183	91
Treated subjects, n (%)[1]	187 (98)	95 (99)	183 (100)	91 (100)
Discontinued from trial, n (%)[1]	24 (13)	13 (14)	9 (5)	3 (3)
Adverse events	12 (6)	4 (4)	4 (2)	2 (2)
Subject's request	10 (5)	6 (6)	2 (1)	0
Protocol deviation	2 (1)	1 (1)	0	0
Lost to follow-up	0	0	2 (1)	0
Physician decision	0	1 (1)	1 (<1)	0
Pregnancy	0	0	0	1 (1)
Other	0	1 (1)	0	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] The percentages were calculated based on the number of subjects that were randomized.
Abbreviations: n, number of patients meeting criteria

Table 8. Demographics and Baseline Disease Characteristics, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1		OLYMPIA 2	
Demographics/Characteristic	**Nemolizumab (N=190)**	**Placebo (N=96)**	**Nemolizumab (N=183)**	**Placebo (N=91)**
Age (years)				
Mean (SD)	57.5 (12.8)	57.6 (13.4)	53.7 (14.4)	50.8 (15.0)
Median	58.0	59.0	55.0	53.0
Min, max	24, 82	23, 84	20, 81	18, 78
Categories, n (%)				
<65	136 (72)	68 (71)	137 (75)	77 (85)
≥65	54 (28)	28 (29)	46 (25)	14 (15)
Sex, n (%)				
Male	80 (42)	40 (42)	70 (38)	36 (40)
Female	110 (58)	56 (58)	113 (62)	55 (60)
Race, n (%)				
White	160 (84)	81 (84)	147 (80)	68 (75)
Black or African American	18 (9)	10 (10)	5 (3)	7 (8)
Asian	10 (5)	2 (2)	23 (13)	14 (15)
Other	2 (1)	3 (3)	8 (4)	2 (2)
Ethnicity, n (%)				
Hispanic or Latino	4 (2)	5 (5)	5 (3)	7 (8)
Not Hispanic or Latino	184 (97)	88 (92)	173 (95)	79 (87)
Unknown or not reported	2 (1)	3 (3)	5 (3)	5 (5)
Weight (kg)				
Mean (SD)	87.1 (21.8)	80.8 (17.8)	79.7 (17.8)	80.8 (22.3)
Median	84.1	80.5	79.0	74.0
Min, max	39.1, 180.5	43.5, 129.0	38.7, 137.0	42.5, 160.0
Categories, n (%)				
<90	117 (62)	67 (70)	132 (72)	67 (74)
≥90	73 (38)	29 (30)	51 (28)	24 (26)

Demographics/Characteristic	OLYMPIA 1 Nemolizumab (N=190)	OLYMPIA 1 Placebo (N=96)	OLYMPIA 2 Nemolizumab (N=183)	OLYMPIA 2 Placebo (N=91)
Country, n (%)				
United States	44 (23)	23 (24)	23 (13)	9 (10)
Outside United States	146 (77)	73 (76)	160 (87)	82 (90)
History of atopy, n (%)				
Yes	60 (32)	33 (34)	57 (31)	31 (34)
No	130 (68)	63 (66)	126 (69)	60 (66)
Prior systemic therapy for PN, n (%)				
Yes	79 (42)	33 (34)	104 (57)	57 (63)
No	111 (58)	63 (66)	79 (43)	34 (37)
IGA score, n (%)				
3 – moderate	107 (56)	62 (65)	108 (59)	48 (53)
4 – severe	83 (44)	34 (35)	75 (41)	43 (47)
PP-NRS score				
n	184	96	183	91
Mean (SD)	8.5 (0.9)	8.4 (1.0)	8.5 (0.9)	8.4 (1.0)
Median	8.4	8.4	8.4	8.4
Min, max	5.9, 10.0	6.5, 10.0	5.1, 10.0	4.6, 10.0
Categories, n (%)				
<7	2 (1)	4 (4)	4 (2)	3 (3)
≥7	182 (96)	92 (96)	179 (98)	88 (97)
Missing	6 (3)	0	0	0
SD-NRS score				
n	190	96	182	91
Mean (SD)	7.0 (2.4)	6.9 (2.3)	7.2 (2.2)	7.3 (2.2)
Median	7.9	7.4	7.9	8.0
Min, max	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0
Categories, n (%)				
<4	22 (12)	11 (11)	15 (8)	9 (10)
≥4	168 (88)	85 (89)	167 (91)	82 (90)
Missing	0	0	1 (1)	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects.
Abbreviations: IGA, Investigator's Global Assessment; N, number of patients in treatment arm; n, number of patients meeting criteria; PN, prurigo nodularis; PP-NRS, Peak Pruritus Numeric Rating Scale; SD-NRS, Sleep Disturbance Numeric Rating Scale

Rescue Therapy Use

The use of rescue therapy is summarized in Table 9. A greater proportion of subjects in the placebo group (20% in OLYMPIA 1 and 15% in OLYMPIA 2) used rescue medication than in the nemolizumab group (6% in OLYMPIA 1 and 5% in OLYMPIA 2). In both trials, a higher proportion of subjects used topical rescue medications than systemic rescue medications.

Table 9. Rescue Therapy Use, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1 Nemolizumab (N=190)	OLYMPIA 1 Placebo (N=96)	OLYMPIA 2 Nemolizumab (N=183)	OLYMPIA 2 Placebo (N=91)
Any rescue therapy	12 (6%)	19 (20%)	9 (5%)	14 (15%)
Topical medication	11 (6%)	16 (17%)	9 (5%)	11 (12%)
Systemic medication	2 (1%)	7 (7%)	3 (2%)	7 (8%)

Source: page 183 of clinical study report for OLYMPIA 1 (RD.06.SRE.202685) and page 185 of clinical study report for OLYMPIA 2 (RD.06.SRE.203065).
[1] Intent-to-treat (ITT) population: all randomized subjects.
Abbreviations: N, number of patients in treatment arm

Results for the Primary Efficacy Endpoints

Table 10 presents the results for the primary efficacy endpoint of the proportion of subjects with a ≥4-point improvement on the PP-NRS from Baseline to Week 16 for the ITT population in both trials. The table presents the results with and without the extended bounds for calculating the weekly scores (i.e., Baseline and Week 16), see Section 6.2.6 for details on the extended bounds. For both trials, nemolizumab was statistically superior to placebo (p-values <0.0001) regardless of the bounds. The treatment effect was slightly smaller without the extended bounds (38% in OLYMPIA 1 and 34% in OLYMPIA 2) than with the extended bounds (40% in OLYMPIA 1 and 37% in OLYMPIA 2). The results for the PP population (not shown) were generally similar to the results for the ITT population.

Table 10. Results for the Primary Efficacy Endpoint of ≥4-Point Improvement on the PP-NRS From Baseline to Week 16, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1		OLYMPIA 2	
Endpoint	**Nemolizumab (N=190)**	**Placebo (N=96)**	**Nemolizumab (N=183)**	**Placebo (N=91)**
With extended bounds[2]				
≥4-point improvement on the PP-NRS	111 (58%)	16 (17%)	103 (56%)	19 (21%)
Unadjusted difference (95% CI)		42% (32%, 52%)		35% (24%, 46%)
Adjusted difference (95% CI)[4]		40% (29%, 51%)		37% (26%, 48%)
p-value[4]		<0.0001		<0.0001
Without extended bounds[3]				
≥4-point improvement on the PP-NRS	106 (56%)	15 (16%)	89 (49%)	15 (16%)
Unadjusted difference (95% CI)		40% (30%, 50%)		32% (22%, 43%)
Adjusted difference (95% CI)[4]		38% (27%, 48%)		34% (23%, 45%)
p-value[4]		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
[2] The Applicant's original analysis allowed for extensions to the bounds of the 7-day period for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[3] This analysis does not include the extensions to the bounds for calculating the weekly average for the PP-NRS.
[4] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 11 presents the results for the primary efficacy endpoint of the proportion of subjects with an IGA score of 0 (clear) or 1 (almost clear) and a ≥2-point improvement from Baseline at Week 16 for the ITT population in both trials. For both trials, nemolizumab was statistically superior to placebo (p-values ≤0.0025). The treatment effect was smaller in OLYMPIA 1 than in OLYMPIA 2 (15% versus 29%). The results for the PP population (not shown) were generally similar to the results for the ITT population.

Table 11. Results for the Primary Efficacy Endpoint of IGA Score of 0 or 1 at Week 16, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1		OLYMPIA 2	
Endpoint	**Nemolizumab (N=190)**	**Placebo (N=96)**	**Nemolizumab (N=183)**	**Placebo (N=91)**
IGA score of 0 or 1	50 (26%)	7 (7%)	69 (38%)	10 (11%)
Unadjusted difference (95% CI)		19% (11%, 27%)		27% (17%, 36%)
Adjusted difference (95% CI)[2]		15% (7%, 23%)		29% (19%, 38%)
p-value[2]		0.0025		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
[2] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm

For the treatment of PN, the Division recommends a multi-component primary efficacy endpoint defined as the proportion of subjects that achieve BOTH a ≥4-point improvement on the PP-NRS from Baseline and an IGA score of 0 (clear) or 1 (almost clear) with a ≥2-point improvement from Baseline. Table 12 presents the results for this multi-component endpoint at Week 16 with and without the extended bounds for the PP-NRS component. This multi-component endpoint was specified as secondary efficacy endpoint in the protocol and SAP; however, it was not included in the multiplicity adjustment plan.

Table 12. Results for the FDA Recommended Primary Efficacy Endpoint of Achieving Both ≥4-Point Improvement on the PP-NRS From Baseline and an IGA Score of 0 or 1 at Week 16, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1		OLYMPIA 2	
Endpoint	**Nemolizumab (N=190)**	**Placebo (N=96)**	**Nemolizumab (N=183)**	**Placebo (N=91)**
With extended bounds[2]				
Both ≥4-point improvement on the PP-NRS and IGA score of 0 or 1	43 (23%)	2 (2%)	54 (30%)	5 (5%)
Unadjusted difference (95% CI)		21% (14%, 27%)		24% (16%, 32%)
Adjusted difference (95% CI)[3]		16% (9%, 23%)		26% (17%, 35%)
p-value[3]		0.0002 (nominal[4])		<0.0001 (nominal[4])
Without extended bounds[3]				
Both ≥4-point improvement on the PP-NRS and IGA score of 0 or 1	41 (22%)	2 (2%)	46 (25%)	4 (4%)
Unadjusted difference (95% CI)		20% (13%, 26%)		21% (13%, 28%)
Adjusted difference (95% CI)[4]		15% (8%, 21%)		22% (14%, 30%)
p-value[3]		0.0005 (nominal[5])		<0.0001 (nominal[5])

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
[2] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[3] This analysis does not include the extensions to the bounds for calculating the weekly average for the PP-NRS.
[4] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
[5] This endpoint was not included in the multiplicity adjustment plan, see Section 6.2.6.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 13 present the number and percentage of subjects who had missing data Baseline and Week 16. Subjects with an ICE (i.e., use of rescue therapy before Week 16) are not included in the Week 16 values as these subjects are automatically imputed as non-responders (i.e., composite variable strategy). The proportion of subjects with missing data was greater in OLYMPIA 2 than in OLYMPIA 1. Table 69 and Table 70 in Section 16.1 present the results for the primary efficacy endpoints by the various imputation methods specified as sensitivity analyses for the handling of missing data in OLYMPIA 1 and OLYMPIA 2, respectively. The results for both endpoints were generally similar across the primary analysis and the sensitivity analyses in both trials.

The Applicant also conducted tipping point analyses for the primary efficacy endpoints. For OLYMPIA 1, the results for the primary endpoint of ≥4-point improvement on the PP-NRS from baseline to Week 16 with and without the extended bounds remained statistically significant (i.e., p-value < 0.05) even under the worst-scenario (i.e., subjects with missing data in the nemolizumab group are imputed as non-responders and subjects with missing data in the placebo group are imputed as responders), and the results for the primary endpoint of IGA score of 0 or 1 at Week 16 tip (i.e., no longer significant at the 0.05 level) when a high proportion of the missing data in the nemolizumab group is imputed as non-responders and a high proportion of subjects in the placebo group is imputed as responders, see Figure 33 in Section 16.1. For OLYMPIA 2, the results for the primary endpoint of ≥4-point improvement on the PP-NRS from Baseline to Week 16 with the extended bounds and the results for the primary endpoint of IGA score of 0 or 1 at Week 16 remained statistically significant even under the worst-scenario; the results for the primary endpoint of ≥4-point improvement on the PP-NRS from Baseline to Week 16 without the extended bounds tip only under the worst-case scenario, see Figure 34 in Section 16.1.

Table 13. Missing Data at Baseline and Week 16, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab (N=190)	Placebo (N=96)	Nemolizumab (N=183)	Placebo (N=91)
Missing data at baseline				
IGA	0	0	0	0
PP-NRS (with extended bounds[2])	6 (3%)	0	0	0
PP-NRS (without extended bounds[2])	6 (3%)	1 (1%)	1 (1%)	2 (2%)
SD-NRS (with extended bounds[2])	0	0	1 (1%)	0
SD-NRS (without extended bounds)	0	1 (1%)	3 (2%)	1 (1%)
Missing data at Week 16 (excluding subjects with ICE)				
IGA	17 (9%)	7 (7%)	7 (4%)	3 (3%)
PP-NRS (with extended bounds[2])	15 (8%)	9 (9%)	16 (9%)	8 (9%)
PP-NRS (without extended bounds[2])	25 (13%)	12 (13%)	37 (20%)	18 (20%)
SD-NRS (with extended bounds[2])	13 (7%)	7 (7%)	17 (9%)	7 (8%)
SD-NRS (without extended bounds[2])	20 (11%)	10 (10%)	31 (17%)	17 (19%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects.
[2] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
Abbreviations: ICE, intercurrent event; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale; SD-NRS, Sleep Disturbance Numeric Rating Scale

Results for the Key Secondary Efficacy Endpoints

The protocol-specified key secondary efficacy endpoints were either based on the PP-NRS or the SD-NRS. Table 14 and Table 15 present the results for the key secondary efficacy endpoints in the ITT population with and without the extended bounds, respectively. For both trials, nemolizumab was statistically superior to placebo (p-values <0.0001) regardless of the bounds. The treatment effect without the extended bounds was either the same or slightly smaller than the treatment effect with the extended bounds. The results for the PP population (not shown) were generally similar to the results for the ITT population.

Table 14. Results for the Key Secondary Efficacy Endpoints With Extended Bounds[1], OLYMPIA 1 and OLYMPIA 2 (ITT[2])

	OLYMPIA 1		OLYMPIA 2	
Endpoint	Nemolizumab (N=190)	Placebo (N=96)	Nemolizumab (N=183)	Placebo (N=91)
≥4-point improvement on the PP-NRS at Week 4	78 (41%)	6 (6%)	75 (41%)	7 (8%)
Unadjusted difference (95% CI)	35% (26%, 43%)		33% (24%, 42%)	
Adjusted difference (95% CI)[3]	32% (23%, 40%)		33% (24%, 42%)	
p-value[3]	<0.0001		<0.0001	
PP-NRS score <2 at Week 16	65 (34%)	4 (4%)	64 (35%)	7 (8%)
Unadjusted difference (95% CI)	30% (22%, 38%)		27% (18%, 36%)	
Adjusted difference (95% CI)[3]	30% (22%, 39%)		30% (21%, 39%)	
p-value[3]	<0.0001		<0.0001	
≥4-point improvement on the SD-NRS at Week 16	95 (50%)	11 (11%)	95 (52%)	19 (21%)
Unadjusted difference (95% CI)	39% (29%, 48%)		31% (20%, 42%)	
Adjusted difference (95% CI)[3]	38% (28%, 48%)		32% (21%, 43%)	
p-value[3]	<0.0001		<0.0001	
≥4-point improvement on the SD-NRS at Week 4	59 (31%)	5 (5%)	68 (37%)	9 (10%)
Unadjusted difference (95% CI)	26% (18%, 34%)		27% (18%, 37%)	
Adjusted difference (95% CI)[3]	23% (15%, 31%)		28% (18%, 37%)	
p-value[3]	<0.0001		<0.0001	
PP-NRS score <2 at Week 4	41 (22%)	1 (1%)	36 (20%)	2 (2%)
Unadjusted difference (95% CI)	21% (14%, 27%)		17% (11%, 24%)	
Adjusted difference (95% CI)[3]	19% (12%, 25%)		19% (12%, 26%)	
p-value[3]	<0.0001		<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADSDNRS.xpt
[1] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[2] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
[3] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale; SD-NRS, Sleep Disturbance Numeric Rating Scale

Table 15. Results for the Key Secondary Efficacy Endpoints Without Extended Bounds[1], OLYMPIA 1 and OLYMPIA 2 (ITT[2])

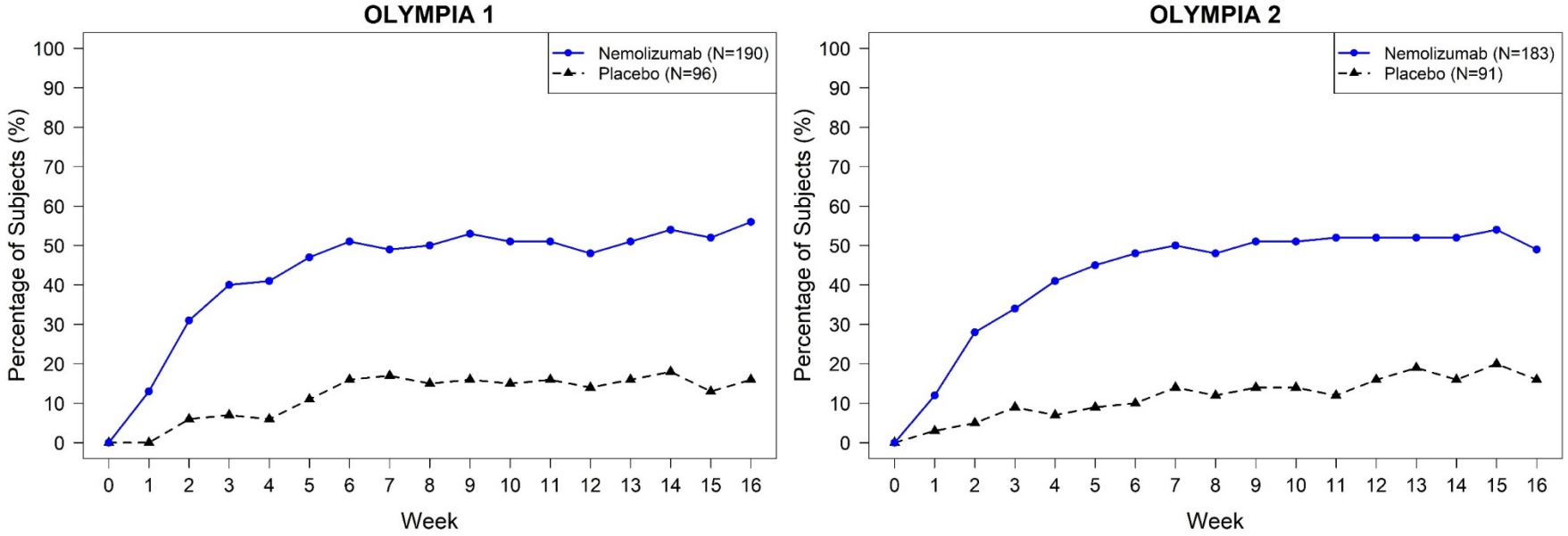
	OLYMPIA 1		OLYMPIA 2	
Endpoint	**Nemolizumab (N=190)**	**Placebo (N=96)**	**Nemolizumab (N=183)**	**Placebo (N=91)**
≥4-point improvement on the PP-NRS at Week 4	78 (41%)	6 (6%)	75 (41%)	6 (7%)
Unadjusted difference (95% CI)	35% (26%, 43%)		34% (26%, 43%)	
Adjusted difference (95% CI)[3]	32% (23%, 40%)		34% (25%, 43%)	
p-value[3]	<0.0001		<0.0001	
PP-NRS score <2 at Week 16	61 (32%)	4 (4%)	56 (31%)	6 (7%)
Unadjusted difference (95% CI)	28% (20%, 36%)		24% (16%, 32%)	
Adjusted difference (95% CI)[3]	28% (20%, 36%)		26% (18%, 34%)	
p-value[3]	<0.0001		<0.0001	
≥4-point improvement on the SD-NRS at Week 16	92 (48%)	10 (10%)	83 (45%)	16 (18%)
Unadjusted difference (95% CI)	38% (29%, 47%)		28% (17%, 38%)	
Adjusted difference (95% CI)[3]	37% (27%, 47%)		30% (19%, 40%)	
p-value[3]	<0.0001		<0.0001	
≥4-point improvement on the SD-NRS at Week 4	59 (31%)	5 (5%)	68 (37%)	9 (10%)
Unadjusted difference (95% CI)	26% (18%, 34%)		27% (18%, 37%)	
Adjusted difference (95% CI)[3]	23% (15%, 31%)		28% (18%, 37%)	
p-value[3]	<0.0001		<0.0001	
PP-NRS score <2 at Week 4	41 (22%)	1 (1%)	36 (20%)	2 (2%)
Unadjusted difference (95% CI)	21% (14%, 27%)		17% (11%, 24%)	
Adjusted difference (95% CI)[3]	19% (12%, 25%)		19% (12%, 26%)	
p-value[3]	<0.0001		<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF2.xpt, ADSDNRS2.xpt
[1] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[2] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
[3] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale; SD-NRS, Sleep Disturbance Numeric Rating Scale

Efficacy Over Time

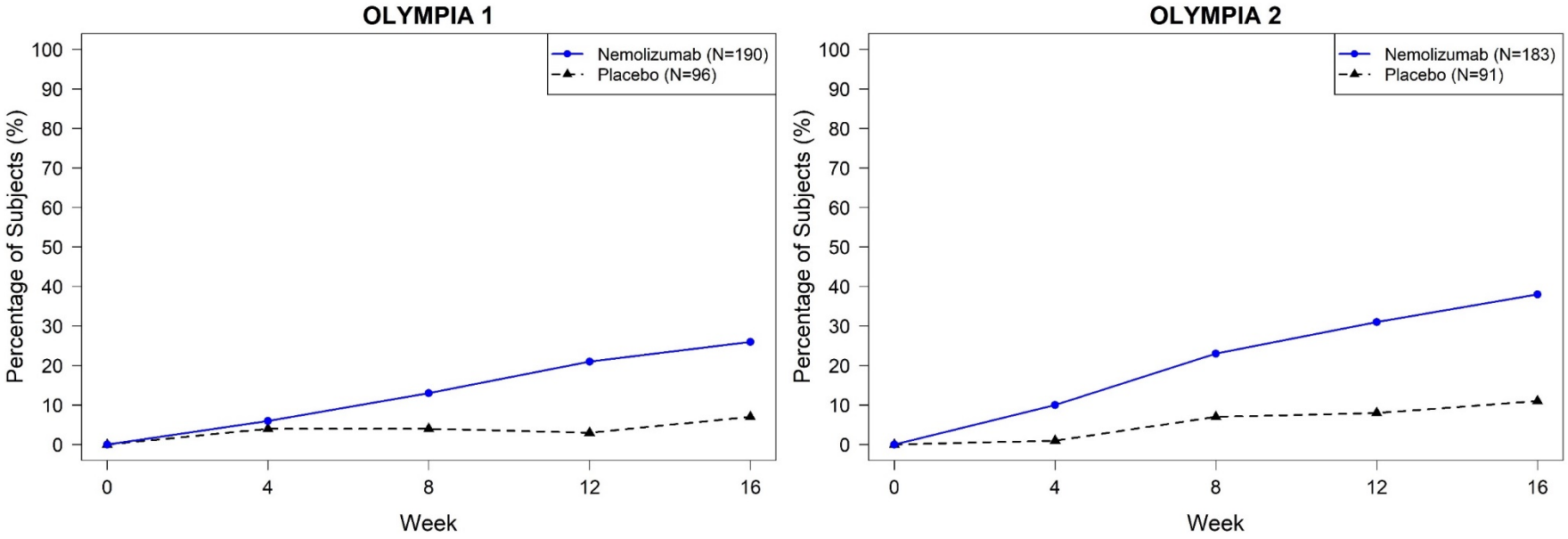
Figure 4 and Figure 5 present the results over time for the two primary efficacy endpoints in both trials. Figure 6 presents the results over time for the recommended multi-componenet efficacy endpoint. Figure 7 presents the results for the secondary efficacy endpoint of proportion of subjects with PP-NRS <2. The figures based on the PP-NRS were generated without the extended bounds for Baseline and Week 16. The results over time with the extended bounds (not shown) were similar to those without the extended bounds as only Baseline and Week 16 had extended bounds and a small number of subjects were affected with the extensions for Baseline, see Table 13.

Figure 4. Proportion of Subjects With ≥4-Point Improvement From Baseline on the PP-NRS Over Time [Without Extended Bounds[1]], OLYMPIA 1 and OLYMPIA 2 (ITT[2])



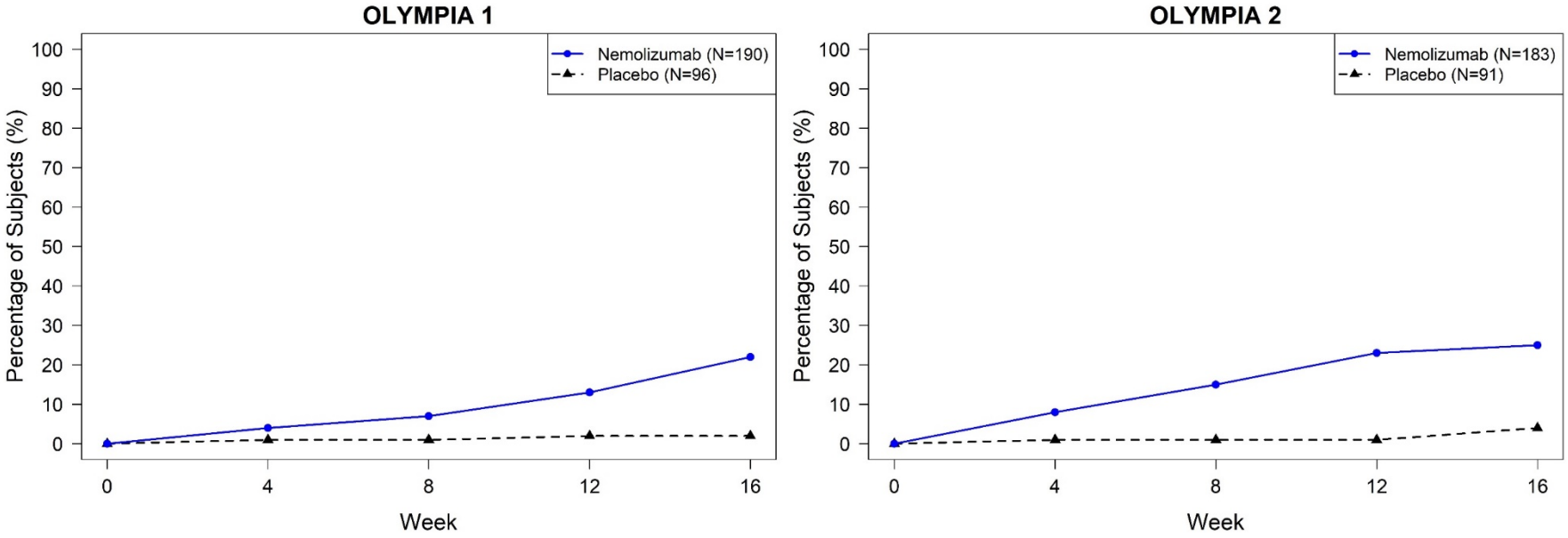
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF2.xpt
[1] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[2] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Figure 5. Proportion of Subjects With IGA Score of 0 or 1 Over Time, OLYMPIA 1 and OLYMPIA 2 (ITT[1])



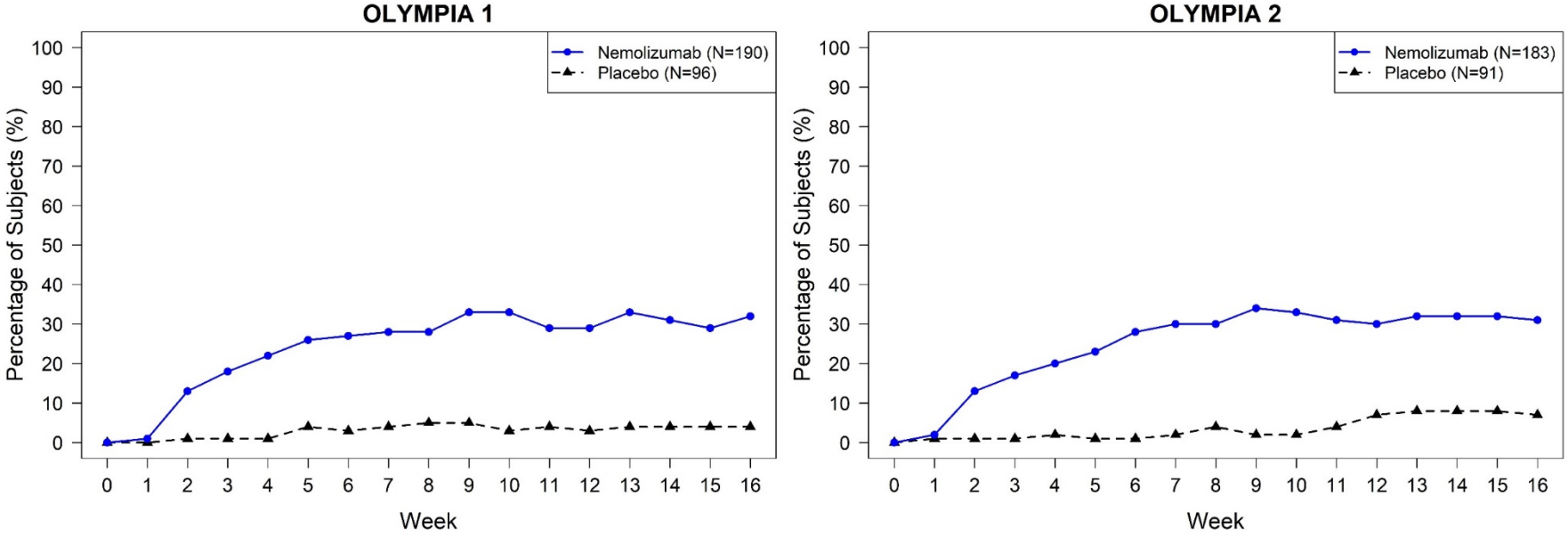
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: IGA, Investigator's Global Assessment; N, number of patients in treatment arm

Figure 6. Proportion of Subjects With Both ≥4-Point Improvement on the PP-NRS From Baseline [Without Extended Bounds[1]] and an IGA Score of 0 or 1 at Week 16, OLYMPIA 1 and OLYMPIA 2 (ITT[2])



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFF2.xpt
[1] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[2] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Figure 7. Proportion of Subjects With PP-NRS <2 Over Time [Without Extended Bounds[1]], OLYMPIA 1 and OLYMPIA 2 (ITT[2])



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFF2.xpt
[1] The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[2] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Subgroup Analyses

Results for subgroup analyses by age (<65 and ≥65 years), sex, race, ethnicity, weight (<90 and ≥90 kg), country (United States and outside United States), history of atopy, previous systemic treatment for PN, and baseline IGA score are presented in Table 72 to Table 77 in Section 16.2. The treatment effect was generally consistent across these subgroups. For race, the sample sizes for some of the subgroups were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

6.3. Key Efficacy Review Issues

There were no efficacy review issues affecting the approvability of nemolizumab for the treatment adults with prurigo nodularis.

6.3.1. (b) (4)

(b) (4)

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7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The toxicity profile of nemolizumab has been adequately evaluated in repeat-dose subcutaneous toxicity studies with treatment durations up to 6 months and an enhanced pre- and postnatal development (ePPND) study in cynomolgus monkeys. Safety pharmacology endpoints and fertility assessment were incorporated into the 6-month repeat-dose toxicity study. Embryofetal development, pre- and postnatal development, and juvenile toxicity were evaluated in the ePPND study. A carcinogenicity risk assessment for nemolizumab was also provided (see Section 13.1.4 for detailed information).

Nemolizumab was well tolerated in the 6-month toxicity study. No significant toxicity was noted, and the no-observed-adverse-effect level (NOAEL) was identified as the high dose, 25 mg/kg, once every two weeks. In the ePPND study, no significant maternal toxicity, embryofetal toxicity, or juvenile toxicity were noted, and the NOAEL for these endpoints was identified as the high dose, 25 mg/kg, once every two weeks. An increase in early postnatal death was seen at the high dose (3/14 versus 1/14 in control), and its relation to treatment was unclear. The clinical significance of this nonclinical finding is unknown. A NOAEL for pre- and postnatal development was conservatively identified as the low dose, 1 mg/kg, once every two weeks.

Overall, the nonclinical safety assessment was considered acceptable to support the licensing of this biologic product. NEMLUVIO is approvable from a Pharmacology/Toxicology perspective.

The multiples of human exposure based on area under the concentration-time curve (AUC) comparison between the NOAELs identified in pivotal toxicology studies and the maximum recommended human dose (MRHD, 60 mg every 4 weeks) are shown in Table 16 below.

Table 16. Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies

Study	Route	NOAEL (mg/kg)	$AUC_{0-14\ day}$ (µg·hr/ml)	Multiples of Human Exposure** (Based on AUC Comparison)
26-week toxicity study in monkeys	Subcutaneous	25	86800*	53
Enhanced pre- and postnatal development study in monkeys	Subcutaneous	Maternal: 25	59900	36
		Embryofetal: 25	59900	36
		Pre- and postnatal: 1	3310	2
		Juvenile: 25	201000	122

Source: Nonclinical reviewer's analysis
*The lower mean AUC value between males and females was used for the calculation.
**The average human $AUC_{0-28\ day}$ value in the phase 3 clinical trial in subjects with prurigo nodularis (SPR.203065) exposed to 60 mg loading dose was 137 µg·day/ml (3288 µg·hr/ml). A factor of 2 was used to convert it to the $AUC_{0-14\ day}$ value (1644 µg·hr/ml), which was used for the multiple calculation.
Abbreviations: AUC, area under the concentration-time curve; NOAEL, no-observed-adverse-effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Similar to other therapeutic proteins, there is a potential for immunogenicity with nemolizumab. However, no clinically meaningful differences in the PK, safety, or efficacy of nemolizumab-ilto were reported in patients who tested positive for anti-nemolizumab-ilto antibody (including neutralizing antibodies).

Hypersensitivity reactions, including facial angioedema, have been reported with the use of nemolizumab-ilto and will be included in the label.

Due to the low prevalence of PN in the US population, the age distribution of PN patients which is principally in older subjects, and limited incidence of pregnancies expected in the PN patient population, the review team (in consultation with the Division of Pediatric and Maternal Health) concluded that pregnancy registries for nemolizumab may not have utility and will not be recommended by the review team as postmarketing requirements.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

No marketing authorization for nemolizumab has been granted to the Applicant in any country to date. However, there is limited postmarketing safety data available for nemolizumab from Japan. Nemolizumab was approved on March 28, 2022, and launched on August 8, 2022, for marketing in Japan (under the commercial name of Mitchga®) for the treatment of patients 13 years of age and older with “pruritus associated with atopic dermatitis (AD), only when existing treatments are inadequate”.

7.3.1. Adverse Events Identified in Postmarket Experiences

As of the data cut-off date of the most recent DSUR on 21 Jul 2023, of an estimated 4,000 patients treated with nemolizumab in Japan, 474 patients were reported with 676 AEs including 27 patients with 34 serious adverse events (SAEs) (25 patients with 30 SAEs unlisted as adverse reactions in the Japanese prescribing information for Mitchga®). However, no new risks for nemolizumab were identified from the postmarketing safety data.

7.3.2. Expectations on Safety

N/A

7.3.3. Additional Safety Issues From Other Disciplines

None.

7.4. FDA Approach to the Safety Review

The Applicant submitted safety data from four clinical studies for nemolizumab in patients with moderate-to-severe PN:

- Two phase 3 trials (OLYMPIA 1 (SPR.202685) (N = 286) (treatment period of 24 weeks) and OLYMPIA 2 (SPR.203065) (N = 274) (treatment period of 16 weeks)). Each trial had a 4-week screening period and an 8-week follow-up period.
- One phase 3, long-term extension (LTE) study (SPR.202699) of 184 weeks duration (N = 450)
- One phase 2 study (SPR.115828) (N = 70)

The main safety data pools, as described in the statistical analysis plan (SAP) for the integrated summary of safety, include the following:

- The primary safety population (OLYMPIA 1 and OLYMPIA 2) includes 370 subjects in the nemolizumab group and 186 subjects in the placebo group.
- The PN Exposure pool (used only for the summary of exposure data) includes 578 subjects in the "All nemolizumab group" pooled exposure data from the phase 2 study SPR.115828, the phase 3 trials (OLYMPIA 1 and OLYMPIA 2), and the phase 3 LTE study SPR.202699. Of these subjects, 555 were included in the "fixed dosing with body weight adjustment" (FDWBWA) who received treatment with the same dose/dosing regimen as in the phase 3 trials.

Safety data summarized for the primary safety population included the following parameters:

1. Exposure to study drug
2. Adverse events (AEs), including Adverse events of special interest (AESIs)
3. Laboratory results
4. Vital signs
5. Electrocardiograms (ECGs)
6. Peak expiratory flow (PEF)
7. Asthma control test (ACT)

Adverse Events of Special Interest (AESI)s included the following 6 categories of AEs:

1. Injection-related reactions (IRRs), including anaphylactic reactions, acute allergic reactions requiring treatment, and severe injection site reactions lasting >24 hours.
2. Newly diagnosed asthma or worsening of asthma.
3. Infections, including any severe infection, any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for >2 weeks, and any confirmed or suspected COVID-19 infection.
4. Peripheral edema- limbs, bilateral
5. Facial edema
6. Elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>3 × the upper limit of normal [ULN]) in combination with elevated bilirubin (>2 × ULN).

In addition, the Applicant conducted analyses of safety data for subgroups based on age groups (18-65 years or >65 years of age at baseline of the parent trials), sex (male, female), race (White,

Black or African American, Asian, Other Race), region (North America, Europe, Asia Pacific), country, and weight at randomization (<90 kg, ≥90 kg).

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v. 25.0). The Clinical Data Scientist team for BLA 761390 conducted safety analyses and provided standard safety tables and figures to the clinical review team. The Clinical Data Scientist team, in cooperation with the clinical and statistical review teams, performed data fitness assessments which did not identify any major data quality or integrity issues that would preclude conducting a safety review of BLA 761390.

There were no major issues identified with respect to recording, coding, and categorizing AEs. The Applicant's translations of verbatim terms to MedDRA PTs for the events reported in OLYMPIA 1 and OLYMPIA 2 trials were reviewed and found to be acceptable.

Treatment-emergent adverse event (TEAEs) were protocol-defined as "any untoward medical occurrence in a clinical study subject administered a medicinal product which does not necessarily have a causal relationship with this treatment". All AEs in the reviewed studies were classified by severity (mild, moderate, or severe), causality (reasonable possibility, no reasonable possibility), action taken (none, study drug stopped, study drug temporarily interrupted, concomitant medication [any additions or discontinuations], other), and outcome (unknown, recovered, not yet recovered, recovered with sequelae, death [with date and cause reported]) which was reviewed and found to be acceptable.

A serious adverse event (SAE) was defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/ incapacity, a congenital anomaly/ birth defect, or is a medically important condition (e.g., events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition of SAE).

AESIs were predefined in the study protocols based on the potential risks of nemolizumab and the risks associated with biologics or biosimilars (class effects), and included injection-related reactions, newly diagnosed asthma or worsening of asthma, infections, peripheral edema (limbs, bilateral), facial edema, and elevated ALT or AST (>3 × ULN) in combination with elevated bilirubin (>2 × ULN).

Laboratory parameters for hematology and clinical chemistry were classified as low, normal, or high, depending on their value relative to their reference range, with shift tables to compare their values at the end of treatment with their baseline values. Any laboratory abnormality assessed as clinically significant by the investigator was recorded as an adverse event (AE).

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate for comprehensive safety assessment of nemolizumab for the proposed indication, patient population, dosage regimen, and duration. The number of subjects exposed and duration of exposure are adequate to satisfy the recommendations of the ICH E1A guidelines.

In the PN exposure pool, 555 subjects received treatment with nemolizumab per the FDWBWA regimen for a mean (SD) of 454.6 (208.9) days [a median of 485 days, a minimum 31 days to a

maximum of 873 days], including 471 subjects treated for ≥6 months, 375 subjects treated for ≥1 year, 207 subjects treated for ≥18 months, and 51 subjects treated for ≥2 years.

Duration of exposure for the primary safety pool is summarized in Table 17.

Table 17. Duration of Exposure, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks		Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)	
Parameter	Nemolizumab Q4W N=370	Placebo N=186	Nemolizumab Q4W N=370	Placebo N=186
Duration of treatment, weeks				
Mean (SD)	13.5 (3.4)	13.5 (3.1)	19.6 (5.1)	19.7 (5)
Median (Q1, Q3)	12.9 (12.1, 16.1)	12.5 (12.1, 16.1)	17.1 (16.4, 24.4)	16.8 (16.4, 24.4)
Min, max	0.1, 16.1	0.1, 16.1	4.4, 27.3	4.4, 27.4
Total exposure (person years)	96	48	139	70
Patients treated, by duration, n (%)				
<4 weeks	12 (3.2)	4 (2.2)	12 (3.2)	4 (2.2)
≥4 to <8 weeks	6 (1.6)	4 (2.2)	6 (1.6)	4 (2.2)
≥8 to <12 weeks	19 (5.1)	17 (9.1)	19 (5.1)	17 (9.1)
≥12 to <16 weeks	164 (44.3)	74 (39.8)	164 (44.3)	74 (39.8)
≥16 to <24 weeks	343 (92.7)	166 (89.2)	202 (54.6)	88 (47.3)
≥24 weeks*	0	0	141 (38.1)	78 (41.9)

Source: Clinical Data Scientist Reviewer, adex.xpt and adsl.xpt; Software: R
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
* 0 to 16 weeks columns were limited to first 16 weeks of the study. Sponsor's definition for treatment duration: treatment duration +30 days.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; Q4W, every four weeks

The mean treatment duration (up to Week 16) for the primary safety pool was 13.5 weeks (median of 12.9 weeks) for subjects in the nemolizumab group and 13.5 weeks (median of 12.5 weeks) for subjects in the placebo group.

7.6. Safety Results

7.6.1. Safety Results, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

The primary safety pool included 370 subjects in the nemolizumab group and 186 subjects in the placebo group. Of these subjects, 343/370 (92.7%) in the nemolizumab group and 172/186 (92.5%) in the placebo group completed treatment; 340/370 (91.9%) in the nemolizumab group and 171/186 (91.9%) in the placebo group completed the trials.

Table 18. Overview of Adverse Events, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Event Category	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W Vs. Placebo Risk Difference % (95% CI)**
SAE	15 (4.1)	14 (7.5)	-3.5 (-8.5, 0.4)	25 (6.8)	16 (8.6)	-1.8 (-7.2, 2.6)
SAEs with fatal outcome	0	0	0.0 (-2.0, 1.0)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Life-threatening SAEs	0	0	0.0 (-2.0, 1.0)	0	0	0.0 (-2.0, 1.0)
SAEs requiring hospitalization	14 (3.8)	9 (4.8)	-1.1 (-5.4, 2.3)	23 (6.2)	11 (5.9)	0.3 (-4.5, 4.3)
AE leading to permanent discontinuation of study drug	14 (3.8)	5 (2.7)	1.1 (-2.6, 4.1)	15 (4.1)	5 (2.7)	1.4 (-2.4, 4.4)
AE leading to dose modification of study drug	13 (3.5)	9 (4.8)	-1.3 (-5.7, 2.0)	14 (3.8)	9 (4.8)	-1.1 (-5.4, 2.3)
AE leading to interruption of study drug	13 (3.5)	9 (4.8)	-1.3 (-5.7, 2.0)	14 (3.8)	9 (4.8)	-1.1 (-5.4, 2.3)
AE leading to reduction of study drug	0	0	0.0 (-2.0, 1.0)	0	0	0.0 (-2.0, 1.0)
AE leading to dose delay of study drug	0	0	0.0 (-2.0, 1.0)	0	0	0.0 (-2.0, 1.0)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Event Category	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W Vs. Placebo Risk Difference % (95% CI)**
Any AE	228 (61.6)	102 (54.8)	6.8 (-1.9, 15.5)	246 (66.5)	111 (59.7)	6.8 (-1.6, 15.4)
Severe and worse	11 (3.0)	11 (5.9)	-2.9 (-7.5, 0.5)	13 (3.5)	12 (6.5)	-2.9 (-7.7, 0.7)
Moderate	92 (24.9)	32 (17.2)	7.7 (0.3, 14.4) *	105 (28.4)	38 (20.4)	7.9 (0.3, 15.1) *
Mild	125 (33.8)	59 (31.7)	2.1 (-6.3, 10.1)	128 (34.6)	61 (32.8)	1.8 (-6.7, 9.9)

Source: Clinical Data Scientist Reviewer, adae.xpt; Software: R. Consistent with Applicant's Table 7 in the SCS (M 2.7.4).
Treatment-emergent adverse events defined as those AEs occurring after the first administration of study treatment until the last study visit.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
Severity as assessed by the investigator.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; Q4W, every four weeks; SAE, serious adverse event

7.6.1.2. Deaths, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

One subject (b) (6)) randomized to the placebo group of trial OLYMPIA 1 died during the trial. This subject was a 57-year-old African American/Hispanic male with history of diabetes mellitus, hypertension, congestive heart failure, malignant ventricular arrhythmia, implantable cardioverter defibrillator, mitral valve repair, hypercholesterolemia, and depression who was hospitalized for the SAE of cardiogenic shock on Study Day 128 and died from an unknown cause on Study Day 132. No autopsy was performed, and causality was assessed as unrelated to the study drug or study procedures by the Investigator and the Applicant.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

SAEs were reported with a similar or lower frequency for the nemolizumab group compared to the placebo group during Weeks 0-16 and the overall treatment periods. SAEs (reported in >1 subject in the nemolizumab group) included the following:

For subjects in the nemolizumab group compared to the placebo group, respectively:

- Neurodermatitis (4 [1.1%] versus 2 [1.1%])
- Pemphigoid (3 [0.8%] versus 0)
- Osteoarthritis (2 [0.5%] versus 1 [0.5%])
- Acrodermatitis (2 [0.5%] versus 0)

The results are consistent with the SAEs reported by the Food and Drug Administration Medical Dictionary for Regulatory Activities Query (FMQ) and are summarized in Table 19.

Table 19. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
System Organ Class Preferred Term	Nemolizumab Q4W N=370 n (%)	Placebo N=186 n (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Nemolizumab Q4W N=370 n (%)	Placebo N=186 n (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Any SAE	15 (4.1)	14 (7.5)	-3.5 (-8.5, 0.4)	25 (6.8)	16 (8.6)	-1.8 (-7.2, 2.6)
Cardiac disorders (SOC)	3 (0.8)	3 (1.6)	-0.8 (-3.9, 1.0)	3 (0.8)	4 (2.2)	-1.3 (-4.7, 0.6)
Acute myocardial infarction	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Coronary artery disease	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Supraventricular tachycardia	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Cardiogenic shock	0	0	0.0 (-2.0, 1.0)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Atrial flutter	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Cardiac sarcoidosis	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Coronary artery occlusion	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Myocardial infarction	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Gastrointestinal disorders (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Gastritis	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Pancreatitis	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
General disorders and administration site conditions (SOC)	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Oedema peripheral	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Hepatobiliary disorders (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Cholecystitis acute	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Infections and infestations (SOC)	3 (0.8)	3 (1.6)	-0.8 (-3.9, 1.0)	6 (1.6)	3 (1.6)	0.0 (-3.1, 2.2)
Campylobacter colitis	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Pneumococcal sepsis	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Pneumonia	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Acrodermatitis	0	0	0.0 (-2.0, 1.0)	2 (0.5)	0	0.5 (-1.5, 2.0)
Urinary tract infection	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Cellulitis	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)
Appendicitis	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
COVID-19 pneumonia	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Postoperative wound infection	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Injury, poisoning and procedural complications (SOC)	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)
Subdural haemorrhage	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Fall	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)

System Organ Class Preferred Term	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W N=370 n (%)	 Placebo N=186 n (%)	 Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W N=370 n (%)	 Placebo N=186 n (%)	 Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Metabolism and nutrition disorders (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Type 2 diabetes mellitus	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.5)	-0.5 (-3.0, 0.5)	3 (0.8)	1 (0.5)	0.3 (-2.2, 1.9)
Intervertebral disc protrusion	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Osteoarthritis	0	1 (0.5)	-0.5 (-3.0, 0.5)	2 (0.5)	1 (0.5)	0.0 (-2.5, 1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	0.0 (-2.0, 1.0)	2 (0.5)	0	0.5 (-1.5, 2.0)
Basal cell carcinoma	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Bladder neoplasm	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Squamous cell carcinoma of skin	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Nervous system disorders (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	2 (0.5)	0	0.5 (-1.5, 2.0)
Tension headache	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Arachnoid cyst	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Psychiatric disorders (SOC)	0	1 (0.5)	-0.5 (-3.0, 0.5)	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)
Depressed mood	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Panic disorder	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	0.0 (-2.0, 1.0)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Vocal cord polyp	0	0	0.0 (-2.0, 1.0)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Skin and subcutaneous tissue disorders (SOC)	5 (1.4)	3 (1.6)	-0.3 (-3.4, 1.8)	8 (2.2)	3 (1.6)	0.5 (-2.6, 2.9)
Pemphigoid	3 (0.8)	0	0.8 (-1.2, 2.4)	3 (0.8)	0	0.8 (-1.2, 2.4)
Dermatitis contact	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Dermatitis exfoliative generalized	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Neurodermatitis	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)	4 (1.1)	2 (1.1)	0.0 (-2.8, 1.9)
Surgical and medical procedures (SOC)	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Abortion induced	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)

Source: Clinical Data Scientist Reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs occurring after the first administration of study treatment until the last study visit.
Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
Abbreviations: CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every four weeks; SAE, serious adverse event; SOC, system organ class

Narratives for SAEs are summarized in Table 20.

Table 20. SAE Narratives for OLYMPIA 1 and OLYMPIA 2 for Overall Treatment Periods (Safety Population)

USUBJID	Age (Years)	Sex	PT	Severity	Action Taken	AESI	Causality	Outcome	Comments
OLYMPIA 1 (Weeks 0-24)									
(b) (6)	48	F	Intervertebral disc protrusion	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, history of cervical disc herniation
	65	F	Osteoarthritis	Moderate	None	No	Not related	Recovered/resolved with sequalae	Hospitalized, history of osteoarthritis
	68	F	Pemphigoid (bullous)	Severe	Drug withdrawn	No	Not related	Not recovered/not resolved	Biopsy confirmed BP. Possible unmasking of coexisting BP off corticosteroids
	55	M	Campylobacter colitis	Severe	None	Yes	Possibly related	Recovered/resolved	Hospitalized, (+) stool culture, ileo-colitis by colonoscopy and CT scan/US
	59	M	Gastritis	Mild	None	No	Not related	Recovered/resolved with sequalae	Hospitalized, endoscopy
			Pemphigoid (bullous)	Moderate	Drug withdrawn	No	Possibly related	Recovered/resolved with sequalae	Hospitalized, skin biopsy: BP, (+) anti-BP180/-230. possible unmasking of preexisting subclinical BP off immuno-suppressants
			Pancreatitis	Moderate	None	No	Not related	Recovered/resolved with sequalae	Hospitalized, CT/US and treated with antibiotics
	65	F	Acrodermatitis (scabies)	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, third AE of scabies with generalized eczema
	71	F	Neurodermatitis	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, treated with balneotherapy (sulfur bath)
	53	F	Acrodermatitis (scabies)	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, treated with permethrin
			Neurodermatitis	Moderate	Drug withdrawn for AELD (before SAE)	No	Not related	Recovered/resolved	Hospitalized, treated with naloxone
	64	M	Neurodermatitis	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, treated with balneotherapy
	79	F	Tension headache	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, EEG, treated with metamizole
	58	M	Neurodermatitis	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, treated with balneotherapy (sulfur bath)

USUBJID	Age (Years)	Sex	PT	Severity	Action Taken	AESI	Causality	Outcome	Comments
(b) (6)	68	M	Bladder neoplasm	Severe	None. Discontinued from trial in follow-up period	No	Not related	Not recovered/not resolved	History of smoking for 40 years. Hospitalized for surgery, after US/ cystoscopy
	82	M	Coronary artery disease	Moderate	None	No	Not related	Recovered/resolved	Hospitalized, coronary angiography/ stent
			Squamous cell carcinoma of skin	Moderate	None	No	Not related	Recovered/resolved	SCC of R. temple excision
			Basal cell carcinoma	Moderate	None	No	Not related	Recovered/resolved	BCC of L. temple excision
	46	F	Depressed mood	Severe	None	No	Not related	Not recovered/not resolved	History of depressed mood, hospitalized
	46	F	Type 2 diabetes mellitus	Mild	None	No	Not related	Not recovered/not resolved	Hospitalized, hyperglycemia treatment with insulin
			Arachnoid cyst	Mild	None	No	Not related	Not recovered/not resolved	Hospitalized, excision of benign cyst on MRI
	78	F	Urinary tract infection	Mild	None	No	Not related	Not recovered/not resolved	Asymptomatic UTI while hospitalized for mild unrelated chest pain
	58	M	Cholecystitis acute	Severe	None	No	Not related	Recovered/resolved	Hospitalized, US, laparoscopic cholecystectomy
	63	M	Cellulitis	Moderate	None	No	Not related	Recovered/resolved	History of obesity and lower abdominal cellulitis, hospitalized- (+) culture groin fungal w/ bacterial infection (skin friction)
	60	F	Acute myocardial infarction (NSTEMI)	Severe	None	No	Not related	Recovered/resolved	Hospitalized, echocardiogram.
	44	M	Osteoarthritis	Moderate	None	No	Not related	Not recovered/not resolved	History of osteoarthritis. Hospitalized for right hip arthroplasty
	80	M	Subdural haemorrhage (due to head trauma)	Severe	None	No	Not related	Recovered/resolved	Hospitalized. Head CT (+)

USUBJID	Age (Years)	Sex	PT	Severity	Action Taken	AESI	Causality	Outcome	Comments
OLYMPIA 2 (Weeks 0-16)									
(b) (6)	69	F	Pemphigoid (bullous)	Severe	Drug Withdrawn	No	Possibly related	Not recovered/not resolved	History of BP suspect with (-) biopsy. Hospitalized, (+) skin Biopsy. No other etiology for BP identified
	38	F	Pneumonia, Pneumococcal sepsis	Severe	Drug interrupted	Yes	Not related	Recovered/resolved	(+) blood culture, chest XR, CT
	57	F	Dermatitis Contact (due to essential oil allergen)	Severe	Drug withdrawn	No	Not related	Recovered/resolved with sequelae	History of AD and lichenified eczema. Hospitalized for eczema flare. Skin biopsy. TCS treatment.
	67	M	Supraventricular tachycardia	Moderate	None	No	Not related	Recovered/resolved	History of atrial fibrillation. Hospitalized for SVT, outpatient electrophysiology tests.60

Source: Clinical Reviewer Table compiled from Narratives in OLYMPIA 1 and OLYMPIA 2 Clinical Study Reports.
Abbreviations: AD, atopic dermatitis; AE, adverse event; AELD, adverse events leading to discontinuation from treatment; AESI, adverse event of special interest; BCC, basal cell carcinoma; BP, blood pressure; CT, computed tomography; EEG, electroencephalogram; F, female; M, male; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; PT, preferred term; SAE, serious adverse event; SCC, squamous cell carcinoma; SVT, supraventricular tachycardia; TCS, Treacher Collins Syndrome; US, ultra-sound; UTI, urinary tract infection; XR, extended release

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

Adverse events leading to discontinuation from treatment (AELDs) were reported at a greater overall frequency for the nemolizumab group compared to the placebo groups during Weeks 0-16 and the overall treatment periods. AELDs reported in >1 subject in the nemolizumab group included pemphigoid (3 [0.8%] versus 0) and dermatitis atopic (2 [0.5%] versus 1 [0.5%]) for subject in the nemolizumab group compared to the placebo group, respectively.

The results are consistent with the AELDs reported by the FMQ and are as summarized in Table 21.

Table 21. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
System Organ Class Preferred Term	Nemolizumab Q4W N=370 n (%)	Placebo N=186 n (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Nemolizumab Q4W N=370 n (%)	Placebo N=186 n (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Any AE leading to discontinuation	14 (3.8)	5 (2.7)	1.1 (-2.6, 4.1)	15 (4.1)	5 (2.7)	1.4 (-2.4, 4.4)
Cardiac disorders (SOC)	0	2 (1.1)	-1.1 (-3.8, -0.0) *	0	2 (1.1)	-1.1 (-3.8, -0.0) *
Atrial flutter	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Cardiac sarcoidosis	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Myocardial infarction	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)
Ear and labyrinth disorders (SOC)	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
Vertigo positional	0	0	0.0 (-2.0, 1.0)	1 (0.3)	0	0.3 (-1.8, 1.5)
General disorders and administration site conditions (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Face oedema	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Oedema peripheral	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Infections and infestations (SOC)	3 (0.8)	0	0.8 (-1.2, 2.4)	3 (0.8)	0	0.8 (-1.2, 2.4)
COVID-19	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Nasopharyngitis	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Staphylococcal skin infection	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Myalgia	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Squamous cell carcinoma	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Skin and subcutaneous tissue disorders (SOC)	9 (2.4)	3 (1.6)	0.8 (-2.4, 3.3)	9 (2.4)	3 (1.6)	0.8 (-2.4, 3.3)
Pemphigoid	3 (0.8)	0	0.8 (-1.2, 2.4)	3 (0.8)	0	0.8 (-1.2, 2.4)
Dermatitis allergic	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Dermatitis contact	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Drug eruption	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	0	0.3 (-1.8, 1.5)
Dermatitis atopic	2 (0.5)	1 (0.5)	0.0 (-2.5, 1.5)	2 (0.5)	1 (0.5)	0.0 (-2.5, 1.5)
Neurodermatitis	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)	1 (0.3)	1 (0.5)	-0.3 (-2.7, 1.0)

System Organ Class Preferred Term	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W N=370 n (%)	 Placebo N=186 n (%)	 Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W N=370 n (%)	 Placebo N=186 n (%)	 Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Dermatitis exfoliative generalized	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	1 (0.5)	-0.5 (-3.0, 0.5)

Source: Clinical Data Scientist Reviewer, adae.xpt; Software: R. Consistent with Applicant's Table 13 in the SCS (M 2.7.4).
Treatment-emergent adverse events defined as those AEs occurring after the first administration of study treatment until the last study visit.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every four weeks; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

Treatment Emergent Adverse Events (TEAEs) reported by ≥1% of subjects in the nemolizumab group (and at a greater frequency than the placebo group) during weeks 0 to 16 treatment periods included:

- Headache (6.2% versus 3.2%)
- Dermatitis atopic (4.3% versus 0.5%)
- Eczema (3.8% versus 1.6%)
- Fatigue (3.5% versus 2.7%)
- Cough (3.2% versus 2.7%)
- Eczema nummular (3.0% versus 0%)
- Pain in extremity (1.9% versus 0%)
- Back pain (1.9% versus 1.1%)
- Peripheral edema (1.9% versus 1.1%)
- Sinusitis (1.6% versus 0.5%)
- Upper respiratory tract infection (1.6% versus 0.5%)
- Arthralgia, (1.6% versus 1.1%)
- Dermatitis contact (1.4% versus 0%)
- Peak expiratory flow reduced (1.4% versus 0%)
- Pyrexia (1.4% versus 0%)
- Folliculitis (1.1% versus 0%)
- Pneumonia (1.1% versus 0%),
- Stasis dermatitis (1.1% versus 0%)
- Rash (1.1% versus 0.5%)
- Urinary tract infection (1.1% versus 0.5%)

TEAEs are summarized in Table 22.

Table 22. Patients With Common Adverse Events Occurring at ≥1% Frequency, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Preferred Term	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**
Any AE	228 (61.6)	102 (54.8)	6.8 (-1.9, 15.5)	246 (66.5)	111 (59.7)	6.8 (-1.6, 15.4)
Dermatitis atopic	16 (4.3)	1 (0.5)	3.8 (1.1, 6.5) *	17 (4.6)	1 (0.5)	4.1 (1.3, 6.8) *
Headache	23 (6.2)	6 (3.2)	3.0 (-1.1, 6.5)	25 (6.8)	6 (3.2)	3.5 (-0.6, 7.1)
Eczema nummular	11 (3.0)	0	3.0 (0.9, 5.2) *	13 (3.5)	0	3.5 (1.5, 5.9) *
Eczema	14 (3.8)	3 (1.6)	2.2 (-1.1, 4.9)	14 (3.8)	4 (2.2)	1.6 (-1.9, 4.5)
Pain in extremity	7 (1.9)	0	1.9 (-0.1, 3.9)	7 (1.9)	1 (0.5)	1.4 (-1.2, 3.4)
Dermatitis contact	5 (1.4)	0	1.4 (-0.7, 3.1)	5 (1.4)	0	1.4 (-0.7, 3.1)
Peak expiratory flow rate decreased	5 (1.4)	0	1.4 (-0.7, 3.1)	7 (1.9)	0	1.9 (-0.1, 3.9)
Pyrexia	5 (1.4)	0	1.4 (-0.7, 3.1)	5 (1.4)	0	1.4 (-0.7, 3.1)
Sinusitis	6 (1.6)	1 (0.5)	1.1 (-1.5, 3.1)	6 (1.6)	1 (0.5)	1.1 (-1.5, 3.1)
Upper respiratory tract infection	6 (1.6)	1 (0.5)	1.1 (-1.5, 3.1)	7 (1.9)	4 (2.2)	-0.3 (-3.7, 2.1)
Folliculitis	4 (1.1)	0	1.1 (-1.0, 2.7)	4 (1.1)	0	1.1 (-1.0, 2.7)
Pneumonia	4 (1.1)	0	1.1 (-1.0, 2.7)	4 (1.1)	0	1.1 (-1.0, 2.7)
Stasis dermatitis	4 (1.1)	0	1.1 (-1.0, 2.7)	4 (1.1)	0	1.1 (-1.0, 2.7)
Fatigue	13 (3.5)	5 (2.7)	0.8 (-2.9, 3.7)	14 (3.8)	5 (2.7)	1.1 (-2.6, 4.1)
Back pain	7 (1.9)	2 (1.1)	0.8 (-2.1, 3.0)	8 (2.2)	2 (1.1)	1.1 (-1.8, 3.3)
Oedema peripheral	7 (1.9)	2 (1.1)	0.8 (-2.1, 3.0)	7 (1.9)	2 (1.1)	0.8 (-2.1, 3.0)
Cough	12 (3.2)	5 (2.7)	0.6 (-3.1, 3.4)	14 (3.8)	7 (3.8)	0.0 (-4.1, 3.2)
Arthralgia	6 (1.6)	2 (1.1)	0.5 (-2.3, 2.6)	7 (1.9)	2 (1.1)	0.8 (-2.1, 3.0)
Rash	4 (1.1)	1 (0.5)	0.5 (-2.0, 2.3)	4 (1.1)	1 (0.5)	0.5 (-2.0, 2.3)
Urinary tract infection	4 (1.1)	1 (0.5)	0.5 (-2.0, 2.3)	7 (1.9)	2 (1.1)	0.8 (-2.1, 3.0)
Cystitis	3 (0.8)	1 (0.5)	0.3 (-2.2, 1.9)	4 (1.1)	1 (0.5)	0.5 (-2.0, 2.3)
Oral herpes	3 (0.8)	1 (0.5)	0.3 (-2.2, 1.9)	3 (0.8)	3 (1.6)	-0.8 (-3.9, 1.0)
Osteoarthritis	3 (0.8)	1 (0.5)	0.3 (-2.2, 1.9)	7 (1.9)	1 (0.5)	1.4 (-1.2, 3.4)
Proteinuria	1 (0.3)	0	0.3 (-1.8, 1.5)	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)
Asthma	6 (1.6)	3 (1.6)	0.0 (-3.1, 2.2)	6 (1.6)	5 (2.7)	-1.1 (-4.6, 1.3)
Diarrhoea	6 (1.6)	3 (1.6)	0.0 (-3.1, 2.2)	6 (1.6)	3 (1.6)	0.0 (-3.1, 2.2)
Dry skin	4 (1.1)	2 (1.1)	0.0 (-2.8, 1.9)	4 (1.1)	2 (1.1)	0.0 (-2.8, 1.9)
Dyshidrotic eczema	2 (0.5)	1 (0.5)	0.0 (-2.5, 1.5)	2 (0.5)	2 (1.1)	-0.5 (-3.3, 1.1)
Hypertension	7 (1.9)	4 (2.2)	-0.3 (-3.7, 2.1)	9 (2.4)	4 (2.2)	0.3 (-3.2, 2.8)
Pharyngitis	3 (0.8)	2 (1.1)	-0.3 (-3.1, 1.5)	4 (1.1)	2 (1.1)	0.0 (-2.8, 1.9)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Preferred Term	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n (%)**	**Placebo N=186 n (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**
Seasonal allergy	3 (0.8)	2 (1.1)	-0.3 (-3.1, 1.5)	3 (0.8)	2 (1.1)	-0.3 (-3.1, 1.5)
Dyspnoea	8 (2.2)	5 (2.7)	-0.5 (-4.1, 2.0)	9 (2.4)	6 (3.2)	-0.8 (-4.6, 2.0)
Dizziness	4 (1.1)	3 (1.6)	-0.5 (-3.6, 1.4)	4 (1.1)	3 (1.6)	-0.5 (-3.6, 1.4)
Aspartate aminotransferase increased	2 (0.5)	2 (1.1)	-0.5 (-3.3, 1.1)	2 (0.5)	2 (1.1)	-0.5 (-3.3, 1.1)
Rhinitis	2 (0.5)	2 (1.1)	-0.5 (-3.3, 1.1)	3 (0.8)	2 (1.1)	-0.3 (-3.1, 1.5)
Polyneuropathy	0	1 (0.5)	-0.5 (-3.0, 0.5)	0	2 (1.1)	-1.1 (-3.8, -0.0) *
Myalgia	5 (1.4)	4 (2.2)	-0.8 (-4.2, 1.4)	5 (1.4)	4 (2.2)	-0.8 (-4.2, 1.4)
Alanine aminotransferase increased	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)
Blood lactate dehydrogenase increased	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)
Cellulitis	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)
Depression	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)
Gout	1 (0.3)	2 (1.1)	-0.8 (-3.6, 0.6)	2 (0.5)	2 (1.1)	-0.5 (-3.3, 1.1)
Pruritus	2 (0.5)	3 (1.6)	-1.1 (-4.1, 0.6)	2 (0.5)	3 (1.6)	-1.1 (-4.1, 0.6)
Presyncope	0	2 (1.1)	-1.1 (-3.8, -0.0) *	0	2 (1.1)	-1.1 (-3.8, -0.0) *
Skin infection	0	2 (1.1)	-1.1 (-3.8, -0.0) *	0	2 (1.1)	-1.1 (-3.8, -0.0) *
Gastritis	1 (0.3)	3 (1.6)	-1.3 (-4.4, 0.2)	1 (0.3)	3 (1.6)	-1.3 (-4.4, 0.2)
Injection site erythema	1 (0.3)	3 (1.6)	-1.3 (-4.4, 0.2)	1 (0.3)	3 (1.6)	-1.3 (-4.4, 0.2)
Blood creatine phosphokinase increased	2 (0.5)	4 (2.2)	-1.6 (-4.9, 0.2)	2 (0.5)	4 (2.2)	-1.6 (-4.9, 0.2)
Nasopharyngitis	11 (3.0)	9 (4.8)	-1.9 (-6.2, 1.3)	17 (4.6)	12 (6.5)	-1.9 (-6.7, 1.9)
COVID-19	17 (4.6)	13 (7.0)	-2.4 (-7.3, 1.5)	24 (6.5)	17 (9.1)	-2.7 (-8.1, 1.8)
Neurodermatitis	21 (5.7)	27 (14.5)	-8.8 (-15.0, -3.7) *	25 (6.8)	29 (15.6)	-8.8 (-15.2, -3.4) *

Source: Clinical Data Scientist Reviewer, adae.xpt; Software: R. Consistent with Applicant's Table 3 in the SCS (M 2.7.4).
Treatment-emergent adverse events defined as those AEs occurring after the first administration of study treatment until the last study visit.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
Coded as MedDRA preferred terms.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; Q4W, every four weeks

TEAEs reported with a frequency of ≥2% by Narrow FMQ during weeks 0 to 16 were consistent with those reported for the common TEAEs (≥1%), as summarized in Table 23.

Table 23. Patients With Treatment-Emergent Adverse Events by PT and FDA Medical Query (Narrow) Occurring at ≥2% Frequency (Weeks 0-16) and Greater Than Placebo, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

Preferred Term	Nemolizumab Q4W N=370 n (%)	Placebo N=186	Risk Difference (%) (95% CI)[3]
Bacterial infection	31 (8.4%)	11(5.9%)	2.5 (-2.5, 6.7)
Headache	27 (7.3%)	7 (3.8%)	3.5 (-0.8, 7.3)
Rash	20 (5.4%)	5 (2.7%)	2.7 (-1.1, 6)
Fatigue	15 (4.1%)	6 (3.2%)	0.8 (-3.1,4)
Cough	12 (3.2%)	5 (2.7%)	0.6 (-3.1,3.4)
Dyspnea	11 (3%)	5 (2.7%)	0.3 (-3.4, 3.1)
Fungal infection	9 (2.4%)	0	2.4 (0.4, 4.6)
Back pain	8 (2.2%)	2 (1.1%)	1.1 (-1.8, 3.3)
Peripheral edema	8 (2.2%)	2 (1.1%)	1.1 (-1.8, 3.3)

Source: Clinical Data Scientist Reviewer, OLYMPIA pooled- Summary Table AE nFMQ.xlsx
Note: TEAEs reported with Broad FMQ during weeks 0 to 16 were consistent with those reported for the common TEAEs and Narrow FMQ. In the SOC of Immune System Disorders, Broad FMQ for subjects in the nemolizumab group compared to the vehicle group, respectively, Broad FMQ of Angioedema was reported for 4 (1.1%) versus 0%; and Hypersensitivity was reported for 61 (16.5%) versus 36 (19.4%) subjects.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; Q4W, every 4 weeks

AESIs

1. Injection-related reactions (IRRs)
   Injection site reactions were reported with similar frequency for the nemolizumab group in 4 (1.1%) subjects and for the placebo group in 3 (1.6%) subjects. IRRs (including anaphylactic reactions, acute allergic reactions requiring treatment, and severe injection site reactions lasting >24 hours) were reported for the following 2 (0.5%) subjects treated with nemolizumab:
   - Subject (b) (6) was reported with moderate severity, drug-related, AE of dermatitis allergic on Day 90; was discontinued from treatment and the AE outcome was reported as ongoing.
   - Subject (b) (6) was reported with moderate severity, drug-related, AE of drug eruption on Day 32; was discontinued from treatment and the AE outcome was reported as resolved on Day 88.
2. Newly diagnosed asthma or worsening of asthma. This AESI was adjudicated by an Independent Adjudication Committee and was reported for 12 (3.2%) nemolizumab-treated subjects and 5 (2.7%) placebo-treated subjects during the overall treatment period. Of the 12 nemolizumab-treated subjects, 4 were considered related to study drug, non-serious, mild to moderate in severity, did not result in treatment discontinuation, and were reported as resolved in 2/4 subjects.
   Of the 48 (13.0%) nemolizumab-treated subjects and 26 (14.0%) placebo-treated subjects with a medical history of asthma at baseline, 8 (2.2%) and 1 (0.5%) subjects, respectively, had a confirmed worsening of asthma during the overall treatment period.

3. Infections, including any severe infection, any infection requiring treatment with parenteral antibiotics or with oral antibiotics/antivirals/antifungals for >2 weeks, and any confirmed or suspected COVID-19 infection.
   During the overall treatment period, 98 (26.5%) nemolizumab-treated subjects and 47 (25.3%) placebo-treated subjects were reported with a treatment-emergent adverse event (TEAE) in the system organ class of "Infections and Infestations", including the AESI of infections for 31 (8.4%) [26/31 related to COVID-19] and 22 (11.8%) subjects [18/22 related to COVID-19], respectively.
   The following AESIs of infections (not related to COVID-19) were reported for nemolizumab-treated subjects: Campylobacter colitis (1), eczema impetiginous (1), Lyme disease (1), pneumococcal sepsis (1), pneumonia (1), staphylococcal skin infection (1), and urinary tract infection (1); none were SAEs, severe AEs, or AELDs.

4. Peripheral edema- limbs, bilateral
   AESIs of peripheral edema were reported for 8 (2.2%) nemolizumab-treated subjects compared to 3 (1.6%) placebo-treated subjects. Peripheral edema in 5/8 nemolizumab-treated subjects were considered as related to the study drug; included no SAEs or severe AEs, 1 AELD, and recovered/resolved in 3/5 subjects. Concurrent or a history of Hashimoto's thyroiditis, stasis dermatitis (varicose veins), AD, or eczema were reported for some subjects and may have been contributing factors to peripheral edema.

5. Facial edema
   AESI of facial edema was reported for 4 (1.1%) nemolizumab-treated subjects (including 1 AE of [periocular] angioedema) compared to no placebo-treated subjects. None were reported as SAEs or severe AEs. One of the 4 subjects was reported with an AELD (AE of mild AD and peripheral edema that led to treatment discontinuation). One AE of (periocular) angioedema was reported for the following subject:
   Subject ([redacted]^(b) (6) in trial OLYMPIA 2) was a 54-year-old female with history of angioedema since 2004. She was reported on Day 48 with a non-serious AESI of discrete periocular angioedema of mild severity which resolved on the same day without treatment and did not lead to discontinuation from the trial. The Investigator and the Applicant both considered causality as having a reasonable possibility of being related to the study drug.

6. Elevated ALT or AST (>3 × ULN) in combination with elevated bilirubin (>2 × ULN). No subject was reported with elevated ALT or AST >3×ULN in combination with elevated bilirubin >2×ULN during the overall treatment period.

Other Safety Topics

Malignancy

During the overall treatment period, 2 (0.6%) subjects in the nemolizumab group (listed below), compared to 1 (0.5%) subject in the placebo group were reported with nonmelanoma skin cancers.

- Subject [redacted]^(b) (6): An 82-year-old White male with history of actinic keratosis and basal cell carcinoma (BCC) was reported with both a BCC and a squamous cell carcinoma (SCC) of

moderate severity on Day 145 and underwent surgical excisions. No action with study drug was taken and the outcome of AEs were reported as resolved.

- Subject (b) (6): A 66-year-old White male with history of actinic keratosis and BCC was reported with an SCC of moderate severity on Day 35 and underwent surgical excision on Day 80. This AE led to study drug discontinuation (AELD) and withdrawal from trial, with the outcome of AE reported as resolved.

Malignancies reported for nemolizumab-treated subjects during the PN long-term extension study SPR.202699 (up to the data cut-off point for interim analysis) included BCC (1), Hodgkin's disease stage IV (1), rectal adenocarcinoma (1), SCC (1), and uterine cancer (1). The potential relationship of the reported malignancies to the study drug is unknown.

Pregnancy

No pregnancy was reported for any subject treated with nemolizumab during PN trials compared to one subject treated with placebo.

LTE Phase 3 Study RD.06.SPR.202699- Interim Safety Data

As of the data cut-off date (March10, 2023) for interim analysis, 407/508 (80.1%) subjects enrolled in this study were reported with a TEAE. Most AEs were mild or moderate in severity. TEAEs reported with a frequency (≥10.0%) included COVID-19 (22.2%), nasopharyngitis (13.8%), and neurodermatitis (preferred term [PT] for worsening of PN) (10.8%). A comparable incidence of TEAEs over time was reported by time of occurrence (<3 months, 3 to <6 months, 6 to <12 months, and ≥12 months).

Deaths were reported for 2 subjects from SAEs of myocardial infarction (1) and end stage renal disease (1); both SAEs were considered as not related to the study drug.

SAEs were reported for 54/508 (10.6%) subjects, including the following SAEs reported for >1 subject: neurodermatitis (4), myocardial infarction (3), angina pectoris (2), cardiac failure congestive (2), cholelithiasis (2), pneumonia (2), osteoarthritis (2), and carotid artery stenosis (2).

AEs that led to study drug discontinuation (AELD) were reported for 29/508 (5.7%) subjects; most were mild to moderate in severity and the outcomes were reported as ongoing. AELDs were considered as related to the study drug for 18 (3.5%) subjects, including the following AELDs reported for >1 subject: eczema nummular (3), dermatitis atopic (2), and neurodermatitis (2).

TEAEs considered as related to study drug (Adverse Reactions) were reported for 136/508 (26.8%) subjects. Most frequently reported (for ≥2.0% of subjects) ARs were eczema nummular (4.3%) and neurodermatitis (3.7%).

AESIs were reported for 161/508 (31.7%) subjects, including the following:

- IRR of hypersensitivity (1) of moderate severity, not related to study drug (but related to study procedure) with the outcome as resolved.
- Infections were reported for 133 (26.2%) subjects, including the following 4 AESIs of infection considered as related to study drug and outcomes reported as resolved: COVID-19 (2), eczema herpeticum (1), and pneumonia bacterial (1).
- Peripheral edema (limbs, bilateral) and facial edema were reported for 15 (3.0%) subjects. AEs considered as related to study drug included peripheral edema (5), face edema (1), and angioedema (1); were non- serious, mild or moderate in severity, were not AELDs, and the outcomes for most were reported as resolved.
- No subject was reported with an ALT or AST >3×ULN and bilirubin >2×ULN.
- Newly diagnosed asthma or worsening of asthma was reported for 22 (4.3%) subjects, most were considered as not related to the study drug and their outcomes as resolved.

7.6.1.6. Laboratory Findings, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

No trends over time were reported for shifts from baseline in clinical chemistry laboratory parameters, lipids, liver function, kidney function, or urinalysis; and no clinically significant imbalances were reported for the proportion of subjects with laboratory parameters values greater than or less than their corresponding reference range of normal.

For hematology parameters other than eosinophils, no trends for the shifts from baseline were reported. For eosinophils, a higher proportion of subjects were reported with elevated eosinophil levels in the nemolizumab group (5.5%) compared to the placebo group (2.7%). Eosinophil levels at Weeks 16 and 24 returned to near-baseline values. One subject (0.3%) in the nemolizumab group was reported with a non-serious TEAE of mild eosinophilia and an TEAE of acrodermatitis (related to scabies) which did not lead to study drug discontinuation. No eosinophilic disorders were reported with elevated eosinophil measurements. The proportion of subjects with laboratory values reported as out of normal range are summarized in the following tables.

Table 24. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Laboratory Parameter	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Sodium, low (mEq/L)						
Level 1 (<132)	4/365 (1.1)	0/186 (0)	1.1 (-0.9, 2.8)	4/365 (1.1)	1/186 (0.5)	0.6 (-1.9, 2.3)
Level 2 (<130)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Level 3 (<125)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Sodium, high (mEq/L)						
Level 1 (>150)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 2 (>155)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 3 (>160)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Potassium, low (mEq/L)						
Level 1 (<3.6)	4/365 (1.1)	3/186 (1.6)	-0.5 (-3.6, 1.5)	5/365 (1.4)	3/186 (1.6)	-0.2 (-3.4, 1.9)
Level 2 (<3.4)	0/365 (0)	3/186 (1.6)	-1.6 (-4.6, -0.5) *	1/365 (0.3)	3/186 (1.6)	-1.3 (-4.4, 0.2)
Level 3 (<3)	0/365 (0)	1/186 (0.5)	-0.5 (-3.0, 0.5)	0/365 (0)	1/186 (0.5)	-0.5 (-3.0, 0.5)
Potassium, high (mEq/L)						
Level 1 (>5.5)	3/365 (0.8)	2/186 (1.1)	-0.3 (-3.1, 1.5)	3/365 (0.8)	2/186 (1.1)	-0.3 (-3.1, 1.5)
Level 2 (>6)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Level 3 (>6.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Chloride, low (mEq/L)						
Level 1 (<95)	8/365 (2.2)	1/186 (0.5)	1.7 (-0.9, 3.8)	9/365 (2.5)	2/186 (1.1)	1.4 (-1.5, 3.7)
Level 2 (<88)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 3 (<80)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Chloride, high (mEq/L)						
Level 1 (>108)	6/365 (1.6)	3/186 (1.6)	0.0 (-3.1, 2.2)	12/365 (3.3)	7/186 (3.8)	-0.5 (-4.5, 2.6)
Level 2 (>112)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Level 3 (>115)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Bicarbonate, low (mEq/L)						
Missing	NA	NA	NA	NA	NA	NA
Bicarbonate, high (mEq/L)						
Missing	NA	NA	NA	NA	NA	NA

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Laboratory Parameter	**Nemolizumab Q4W N=370 n/N_w (%)**	**Placebo N=186 n/N_w (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n/N_w (%)**	**Placebo N=186 n/N_w (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**
Glucose, low (mg/dL)						
Level 1 (<70)	4/365 (1.1)	5/186 (2.7)	-1.6 (-5.1, 0.6)	6/365 (1.6)	7/186 (3.8)	-2.1 (-6.0, 0.5)
Level 2 (<54)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 3 (<40)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Glucose, fasting, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Glucose, random, high (mg/dL)						
Level 2 (>=200)	9/365 (2.5)	8/186 (4.3)	-1.8 (-6.0, 1.2)	10/365 (2.7)	11/186 (5.9)	-3.2 (-7.7, 0.2)
Level 3 (>250)	3/365 (0.8)	2/186 (1.1)	-0.3 (-3.1, 1.5)	4/365 (1.1)	5/186 (2.7)	-1.6 (-5.1, 0.6)
Calcium, low (mg/dL)						
Level 1 (<8.4)	3/365 (0.8)	0/186 (0)	0.8 (-1.2, 2.4)	3/365 (0.8)	1/186 (0.5)	0.3 (-2.2, 1.9)
Level 2 (<8)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Level 3 (<7.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Calcium, high (mg/dL)						
Level 1 (>10.5)	7/365 (1.9)	7/186 (3.8)	-1.8 (-5.8, 0.9)	11/365 (3.0)	8/186 (4.3)	-1.3 (-5.5, 1.8)
Level 2 (>11)	1/365 (0.3)	1/186 (0.5)	-0.3 (-2.7, 1.1)	2/365 (0.5)	1/186 (0.5)	0.0 (-2.5, 1.5)
Level 3 (>12)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Magnesium, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)						
Missing	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)						
Level 1 (<6)	4/365 (1.1)	2/186 (1.1)	0.0 (-2.8, 1.9)	4/365 (1.1)	5/186 (2.7)	-1.6 (-5.1, 0.6)
Level 2 (<5.4)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Level 3 (<5)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Albumin, low (g/dL)						
Level 1 (<3.1)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	1/186 (0.5)	-0.5 (-3.0, 0.5)
Level 2 (<2.5)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 3 (<2)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
CPK, high (U/L)						
Level 1 (>3X ULN)	4/365 (1.1)	2/186 (1.1)	0.0 (-2.8, 1.9)	4/365 (1.1)	4/186 (2.2)	-1.1 (-4.4, 1.1)
Level 2 (>5X ULN)	1/365 (0.3)	1/186 (0.5)	-0.3 (-2.7, 1.1)	1/365 (0.3)	1/186 (0.5)	-0.3 (-2.7, 1.1)
Level 3 (>10X ULN)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Amylase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)						
Missing	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)						
Level 1 (>23)	31/365 (8.5)	16/186 (8.6)	-0.1 (-5.6, 4.6)	39/365 (10.7)	19/186 (10.2)	0.5 (-5.4, 5.6)
Level 2 (>27)	14/365 (3.8)	8/186 (4.3)	-0.5 (-4.7, 2.8)	18/365 (4.9)	10/186 (5.4)	-0.4 (-5.0, 3.2)
Level 3 (>31)	9/365 (2.5)	1/186 (0.5)	1.9 (-0.7, 4.2)	11/365 (3.0)	3/186 (1.6)	1.4 (-1.8, 4.0)

Source: Clinical Data Scientist Reviewer, adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; Q4W, every four weeks; ULN, upper limit of normal

Table 25. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. placebo risk difference % (95% CI)	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. placebo risk difference % (95% CI)
Creatinine, high (mg/dL)						
Level 1 (≥1.5X baseline)	2/365 (0.5)	0/186 (0)	0.5 (-1.5, 2.0)	5/365 (1.4)	1/186 (0.5)	0.8 (-1.7, 2.7)
Level 2 (≥2X baseline)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)
Level 3 (≥3X baseline)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Laboratory Parameter	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. placebo risk difference % (95% CI)	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. placebo risk difference % (95% CI)
eGFR, low (ml/min/1.73 m2)						
Level 1 (≥25% decrease)	12/358 (3.4)	2/181 (1.1)	2.2 (-0.8, 4.9)	20/358 (5.6)	4/181 (2.2)	3.4 (-0.4, 6.7)
Level 2 (≥50% decrease)	0/358 (0)	0/181 (0)	0.0 (-2.1, 1.1)	1/358 (0.3)	0/181 (0)	0.3 (-1.8, 1.6)
Level 3 (≥75% decrease)	0/358 (0)	0/181 (0)	0.0 (-2.1, 1.1)	0/358 (0)	0/181 (0)	0.0 (-2.1, 1.1)

Source: Clinical Data Scientist Reviewer, adlb.xpt; Software: R
Notes: Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; Q4W, every four weeks

Table 26. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Laboratory Parameter	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5X ULN)	8/365 (2.2)	2/186 (1.1)	1.1 (-1.8, 3.4)	8/365 (2.2)	2/186 (1.1)	1.1 (-1.8, 3.4)
Level 2 (>2X ULN)	3/365 (0.8)	1/186 (0.5)	0.3 (-2.2, 1.9)	3/365 (0.8)	2/186 (1.1)	-0.3 (-3.1, 1.5)
Level 3 (>3X ULN)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Alanine aminotransferase, high (U/L)						
Level 1 (>3X ULN)	1/365 (0.3)	0/186 (0)	0.3 (-1.8, 1.5)	2/365 (0.5)	0/186 (0)	0.5 (-1.5, 2.0)
Level 2 (>5X ULN)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 3 (>10X ULN)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3X ULN)	0/364 (0)	1/186 (0.5)	-0.5 (-3.0, 0.5)	0/365 (0)	1/186 (0.5)	-0.5 (-3.0, 0.5)
Level 2 (>5X ULN)	0/364 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	1/186 (0.5)	-0.5 (-3.0, 0.5)
Level 3 (>10X ULN)	0/364 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W N=370 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks Placebo N=186 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W N=370 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Placebo N=186 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5X ULN)	1/365 (0.3)	1/186 (0.5)	-0.3 (-2.7, 1.1)	2/365 (0.5)	3/186 (1.6)	-1.1 (-4.1, 0.7)
Level 2 (>2X ULN)	1/365 (0.3)	1/186 (0.5)	-0.3 (-2.7, 1.1)	1/365 (0.3)	2/186 (1.1)	-0.8 (-3.6, 0.6)
Level 3 (>3X ULN)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)

Source: Clinical Data Scientist Reviewer, adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot...” and “Cholestatic Drug-Induced Liver Injury Screening Plot...” and the tables “Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot...” and “Patients in Each Quadrant for Cholestatic DILI Screening Plot…”
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; Q4W, every four weeks; ULN, upper limit of normal

Table 27. Patients With One or More Lipids Analyte Values Exceeding Specified Levels, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W N=370 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks Placebo N=186 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W N=370 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Placebo N=186 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)						
Level 1 (>200)	218/365 (59.7)	115/186 (61.8)	-2.1 (-10.6, 6.6)	235/365 (64.4)	116/186 (62.4)	2.0 (-6.4, 10.6)
Level 2 (>210)	182/365 (49.9)	93/186 (50.0)	-0.1 (-8.9, 8.7)	197/365 (54.0)	98/186 (52.7)	1.3 (-7.5, 10.1)
Level 3 (>225)	134/365 (36.7)	69/186 (37.1)	-0.4 (-9.0, 8.0)	149/365 (40.8)	79/186 (42.5)	-1.7 (-10.4, 7.0)
HDL, males, low (mg/dL)						
Level 1 (<40)	53/145 (36.6)	29/76 (38.2)	-1.6 (-15.2, 11.5)	57/145 (39.3)	33/76 (43.4)	-4.1 (-17.8, 9.3)
Level 2 (<30)	7/145 (4.8)	3/76 (3.9)	0.9 (-6.6, 6.5)	8/145 (5.5)	3/76 (3.9)	1.6 (-5.9, 7.3)
Level 3 (<20)	0/145 (0)	0/76 (0)	0.0 (-4.8, 2.6)	0/145 (0)	0/76 (0)	0.0 (-4.8, 2.6)
HDL, females, low (mg/dL)						
Level 1 (<50)	81/220 (36.8)	35/110 (31.8)	5.0 (-6.1, 15.4)	86/220 (39.1)	40/110 (36.4)	2.7 (-8.5, 13.5)
Level 2 (<40)	24/220 (10.9)	14/110 (12.7)	-1.8 (-10.1, 5.2)	29/220 (13.2)	15/110 (13.6)	-0.5 (-9.0, 6.9)
Level 3 (<20)	0/220 (0)	0/110 (0)	0.0 (-3.4, 1.7)	0/220 (0)	0/110 (0)	0.0 (-3.4, 1.7)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks: Nemolizumab Q4W N=370 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks: Placebo N=186 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks: Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks): Nemolizumab Q4W N=370 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks): Placebo N=186 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks): Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
LDL, high (mg/dL)						
Level 1 (>130)	164/363 (45.2)	84/185 (45.4)	-0.2 (-9.0, 8.5)	179/363 (49.3)	90/185 (48.6)	0.7 (-8.2, 9.5)
Level 2 (>160)	67/363 (18.5)	37/185 (20.0)	-1.5 (-8.9, 5.2)	74/363 (20.4)	44/185 (23.8)	-3.4 (-11.1, 3.8)
Level 3 (>190)	24/363 (6.6)	15/185 (8.1)	-1.5 (-6.8, 2.9)	27/363 (7.4)	20/185 (10.8)	-3.4 (-9.2, 1.5)
Triglycerides, high (mg/dL)						
Level 1 (>150)	161/365 (44.1)	83/186 (44.6)	-0.5 (-9.3, 8.2)	177/365 (48.5)	89/186 (47.8)	0.6 (-8.2, 9.4)
Level 2 (>300)	30/365 (8.2)	18/186 (9.7)	-1.5 (-7.1, 3.3)	33/365 (9.0)	21/186 (11.3)	-2.2 (-8.2, 2.9)
Level 3 (>500)	3/365 (0.8)	2/186 (1.1)	-0.3 (-3.1, 1.5)	4/365 (1.1)	4/186 (2.2)	-1.1 (-4.4, 1.1)

Source: Clinical Data Scientist Reviewer, adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; Q4W, every four weeks

Table 28. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks: Nemolizumab Q4W N=370 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks: Placebo N=186 n/N_w (%)	OLYMPIA 1 & 2 0 to 16 Weeks: Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks): Nemolizumab Q4W N=370 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks): Placebo N=186 n/N_w (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks): Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Complete blood count						
WBC, low (10^3 cells/uL)						
Level 1 (<3.5)	12/365 (3.3)	3/186 (1.6)	1.7 (-1.6, 4.3)	13/365 (3.6)	4/186 (2.2)	1.4 (-2.1, 4.2)
Level 2 (<3)	5/365 (1.4)	0/186 (0)	1.4 (-0.7, 3.2)	6/365 (1.6)	0/186 (0)	1.6 (-0.4, 3.5)
Level 3 (<1)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
WBC, high (10^3 cells/uL)						
Level 1 (>10.8)	21/365 (5.8)	11/186 (5.9)	-0.2 (-4.9, 3.7)	25/365 (6.8)	12/186 (6.5)	0.4 (-4.6, 4.5)
Level 2 (>13)	6/365 (1.6)	4/186 (2.2)	-0.5 (-3.9, 1.8)	8/365 (2.2)	4/186 (2.2)	0.0 (-3.4, 2.5)
Level 3 (>15)	2/365 (0.5)	1/186 (0.5)	0.0 (-2.5, 1.5)	3/365 (0.8)	1/186 (0.5)	0.3 (-2.2, 1.9)

Laboratory Parameter	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W N=370 n/N$_w$ (%)	OLYMPIA 1 & 2 0 to 16 Weeks Placebo N=186 n/N$_w$ (%)	OLYMPIA 1 & 2 0 to 16 Weeks Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W N=370 n/N$_w$ (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Placebo N=186 n/N$_w$ (%)	Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks) Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 g/dL dec. from baseline)	6/365 (1.6)	4/186 (2.2)	-0.5 (-3.9, 1.8)	10/365 (2.7)	6/186 (3.2)	-0.5 (-4.3, 2.4)
Level 3 (>2 g/dL dec. from baseline)	2/365 (0.5)	3/186 (1.6)	-1.1 (-4.1, 0.7)	3/365 (0.8)	3/186 (1.6)	-0.8 (-3.9, 1.1)
Hemoglobin, high (g/dL)						
Level 2 (>2 g/dL inc. from baseline)	6/365 (1.6)	1/186 (0.5)	1.1 (-1.4, 3.1)	8/365 (2.2)	3/186 (1.6)	0.6 (-2.6, 3.0)
Level 3 (>3 g/dL inc. from baseline)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	1/365 (0.3)	1/186 (0.5)	-0.3 (-2.7, 1.1)
Platelets, low (10^3 cells/uL)						
Level 1 (<140)	7/363 (1.9)	7/184 (3.8)	-1.9 (-5.9, 0.9)	7/363 (1.9)	7/185 (3.8)	-1.9 (-5.8, 0.9)
Level 2 (<125)	2/363 (0.6)	4/184 (2.2)	-1.6 (-4.9, 0.2)	2/363 (0.6)	4/185 (2.2)	-1.6 (-4.9, 0.2)
Level 3 (<100)	0/363 (0)	1/184 (0.5)	-0.5 (-3.0, 0.5)	0/363 (0)	1/185 (0.5)	-0.5 (-3.0, 0.5)
WBC differential						
Lymphocytes, low (10^3 cells/uL)						
Level 1 (<1)	44/365 (12.1)	25/186 (13.4)	-1.4 (-7.8, 4.2)	51/365 (14.0)	29/186 (15.6)	-1.6 (-8.3, 4.4)
Level 2 (<0.75)	7/365 (1.9)	3/186 (1.6)	0.3 (-2.9, 2.6)	10/365 (2.7)	5/186 (2.7)	0.1 (-3.6, 2.8)
Level 3 (<0.5)	2/365 (0.5)	1/186 (0.5)	0.0 (-2.5, 1.5)	2/365 (0.5)	1/186 (0.5)	0.0 (-2.5, 1.5)
Lymphocytes, high (10^3 cells/uL)						
Level 1 (>4)	2/365 (0.5)	0/186 (0)	0.5 (-1.5, 2.0)	2/365 (0.5)	0/186 (0)	0.5 (-1.5, 2.0)
Level 2 (>10)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Level 3 (>20)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Neutrophils, low (10^3 cells/uL)						
Level 1 (<2)	28/365 (7.7)	5/186 (2.7)	5.0 (0.9, 8.6) *	29/365 (7.9)	6/186 (3.2)	4.7 (0.5, 8.5) *
Level 2 (<1)	3/365 (0.8)	0/186 (0)	0.8 (-1.2, 2.4)	4/365 (1.1)	0/186 (0)	1.1 (-0.9, 2.8)
Level 3 (<0.5)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Eosinophils, high (10^3 cells/uL)						
Level 1 (>0.65)	35/365 (9.6)	11/186 (5.9)	3.7 (-1.4, 8.1)	39/365 (10.7)	12/186 (6.5)	4.2 (-1.0, 8.8)
Level 2 (>1.5)	4/365 (1.1)	1/186 (0.5)	0.6 (-1.9, 2.3)	5/365 (1.4)	1/186 (0.5)	0.8 (-1.7, 2.7)
Level 3 (>5)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)	0/365 (0)	0/186 (0)	0.0 (-2.0, 1.0)
Coagulation Studies						
PT, high (sec)						
Missing	NA	NA	NA	NA	NA	NA

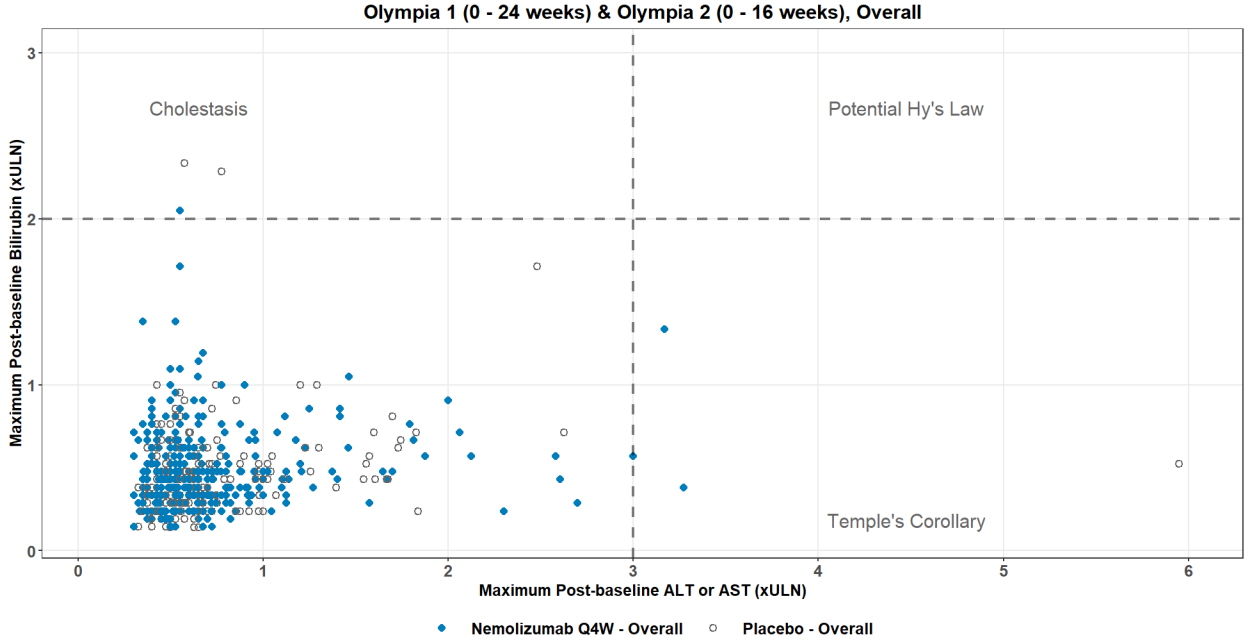
	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Laboratory Parameter	**Nemolizumab Q4W N=370 n/N_w (%)**	**Placebo N=186 n/N_w (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n/N_w (%)**	**Placebo N=186 n/N_w (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**
PTT, high (sec)						
Missing	NA	NA	NA	NA	NA	NA

Source: Clinical Data Scientist Reviewer, adlb.xpt; Software: R
Notes: Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; Q4W, every four weeks; WBC, white blood cells

7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

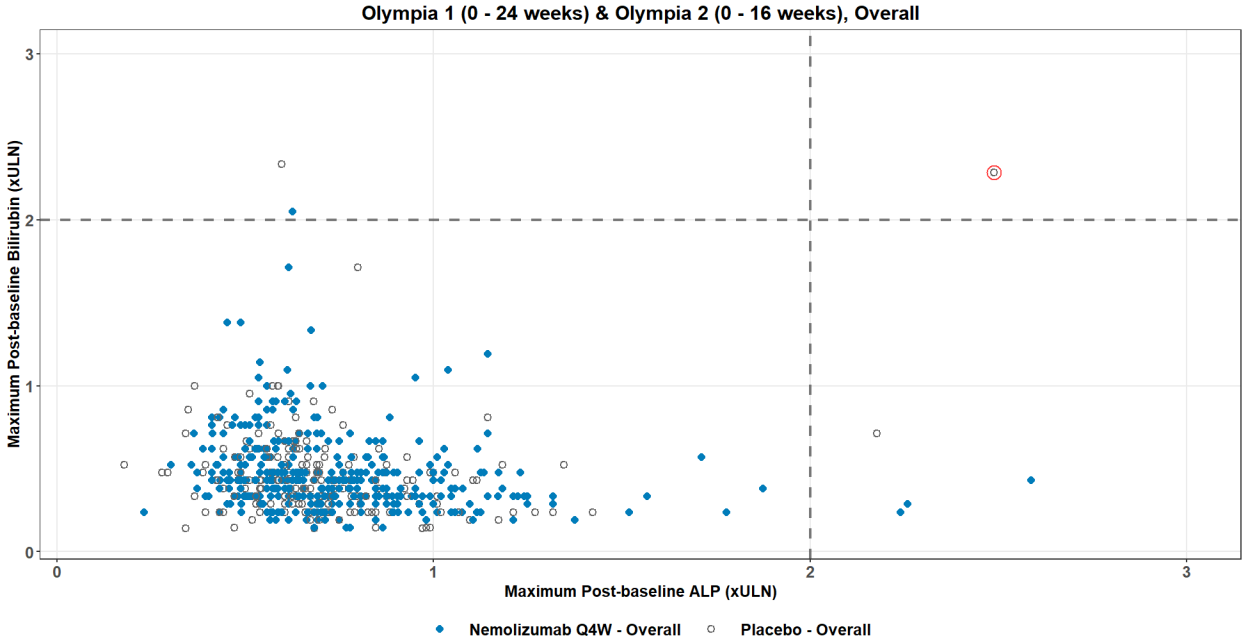
No subject was reported with concomitantly elevated transaminase and bilirubin levels in the nemolizumab group which would be consistent with an increased risk of drug-induced liver injury or a potential case of Hy's law. A 55-year-old white female subject ([redacted] (b) (6)) in trial OLYMPIA 2 (depicted in the left upper [cholestasis] quadrant of Figures 8 and 9) received treatment with nemolizumab 30 mg Q4W and was reported with elevated bilirubin > x2 ULN at Week 16 (end of trial) visit. This subject's ALT, AST, and ALP measurements were within normal range and her bilirubin measurements were elevated >ULN, starting on Day 1 and continuing to Week 16 visit. This subject's pattern of liver enzymes elevation does not appear to be consistent with DILI. DILI screening plots are depicted in the following Figures and table (Figure 8, Figure 9and Table 29).

Figure 8. Hepatocellular Drug-Induced Liver Injury Screening Plot, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)



Source: Clinical Data Scientist Reviewer. adlb.xpt; Software: R
Notes: Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).
All patients with at least one post-baseline ALT or AST and bilirubin are plotted. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; Q4W, every four weeks; ULN, upper limit of normal

Figure 9. Cholestatic Drug-Induced Liver Injury Screening Plot, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)



Source: Clinical Data Scientist Reviewer. adlb.xpt; Software: R
Notes: Each data point represents a patient plotted by their maximum ALP versus their maximum total bilirubin values in the post-baseline period.
A potential cholestatic DILI case (red circled) was defined as having a maximum post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after post-baseline ALP became equal to or exceeding 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALP, alkaline phosphatase; Q4W, every four weeks; ULN, upper limit of normal

Table 29. Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks		Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)	
Quadrant	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)	Nemolizumab Q4W N=370 n/N_w (%)	Placebo N=186 n/N_w (%)
Potential Hy's Law (right upper)	0/365 (0)	0/186 (0)	0/365 (0)	0/186 (0)
Cholestasis (left upper)	1/365 (0.3)	1/186 (0.5)	1/365 (0.3)	2/186 (1.1)
Temple's corollary (right lower)	1/365 (0.3)	0/186 (0)	3/365 (0.8)	1/186 (0.5)
Total	2/365 (0.5)	1/186 (0.5)	4/365 (1.1)	3/186 (1.6)

Source: Clinical Data Scientist Reviewer. adlb.xpt; Software: R
A potential Hy's Law case was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data; Q4W, every four weeks

7.6.1.8. Vital Signs, Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

A weight gain of ≥5% of baseline weight was reported in a higher proportion of subjects in the nemolizumab group compared to the placebo group, respectively, at week 12 (3.6% versus 2.2%), week 16 (5.1% versus 1.1%), and week 24 (8.9% versus 5.9%) with a trend towards a return to their baseline weights at the end of study. No TEAEs of weight increased considered as related to nemolizumab was reported in any subject. No trends for changes over time in the systolic or diastolic blood pressures, heart rate, temperature, or ECGs were reported for subjects in the nemolizumab or placebo groups.

7.6.1.9. Subgroups, Pooled Analyses, Studies/Trials A and B

The Applicant conducted safety analyses based on demographic subgroups for age category, sex, and race. The Applicant did not submit analysis based on ethnicity subgroups because only a total of 21 subjects of Hispanic or Latino ethnicity were enrolled in the OLYMPIA 1 and OLYMPIA 2 trials (including 9/370 in the nemolizumab group and 12/186 subjects in the placebo groups).

The results for the subgroup analysis by the Applicant and by the Clinical Data Scientist Reviewer for BLA 761390 indicated that there were no substantial differences in the risk of TEAEs in any subgroup. However, because the trials were not powered for these analyses, the data must be interpreted with caution. An overview of TEAEs by demographic subgroups are presented below and summarized in Table 30.

TEAEs by Age Group

The proportion of subjects reported with AEs during the overall period was higher among subjects >65 years of age in the nemolizumab group (74.7%) compared to subjects >65 years of age in the placebo group (56.1%) and compared to subjects between 18 to 65 years of age in the nemolizumab group (63.5%) or the placebo group (60.7%). The most frequently reported TEAEs in subjects >65 years of age in the nemolizumab group were neurodermatitis, eczema, and eczema nummular (7.1% each).

TEAEs by Sex

A similar proportion of male (67.6%) and female (65.8%) subjects were reported with TEAEs during the overall period in the nemolizumab group, compared to the corresponding male (57.9%) and female (60.9%) subjects in the placebo group, respectively. A trend towards a higher frequency of TEAEs were reported for the preferred terms (PT)s of dermatitis atopic (8.1%), eczema (6.8%), and nummular eczema (6.8%) for male subjects in the nemolizumab group, compared to male subjects in the placebo group and compared to female subjects.

TEAEs by Race and Ethnicity

No clinically significant differences in the frequency of TEAEs by racial or ethnic subgroups were reported during Weeks 0-16 and during the overall period.

Table 30. Overview of Adverse Events by Demographic Subgroup, Trials OLYMPIA 1 and OLYMPIA 2, Safety Population

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Characteristic	**Nemolizumab Q4W N=370 n/N_s (%)**	**Placebo N=186 n/N_s (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**	**Nemolizumab Q4W N=370 n/N_s (%)**	**Placebo N=186 n/N_s (%)**	**Nemolizumab Q4W vs. Placebo Risk Difference % (95% CI)**
Sex						
Female	146/222 (65.8)	67/110 (60.9)	4.9 (-6.0, 16.0)	146/222 (65.8)	67/110 (60.9)	4.9 (-6.0, 16.0)
Male	100/148 (67.6)	44/76 (57.9)	9.7 (-3.5, 23.1)	100/148 (67.6)	44/76 (57.9)	9.7 (-3.5, 23.1)
Age group, years						
>65	74/99 (74.7)	23/41 (56.1)	18.6 (1.7, 35.9) *	74/99 (74.7)	23/41 (56.1)	18.6 (1.7, 35.9) *
18 to 65	172/271 (63.5)	88/145 (60.7)	2.8 (-6.9, 12.7)	172/271 (63.5)	88/145 (60.7)	2.8 (-6.9, 12.7)
Age group ≥65, years						
≥65	85/114 (74.6)	24/45 (53.3)	21.2 (4.9, 37.5) *	85/114 (74.6)	24/45 (53.3)	21.2 (4.9, 37.5) *
Age group ≥75, years						
≥75	18/21 (85.7)	7/12 (58.3)	27.4 (-3.4, 57.3)	18/21 (85.7)	7/12 (58.3)	27.4 (-3.4, 57.3)
Race						
American Indian or Alaska Native	1/1 (100)	0/0 (NA)	NA	1/1 (100)	0/0 (NA)	NA
Asian	17/33 (51.5)	7/16 (43.8)	7.8 (-21.5, 35.3)	17/33 (51.5)	7/16 (43.8)	7.8 (-21.5, 35.3)
Black or African American	10/22 (45.5)	11/17 (64.7)	-19.3 (-47.1, 12.5)	10/22 (45.5)	11/17 (64.7)	-19.3 (-47.1, 12.5)
Native Hawaiian or other Pacific Islander	1/2 (50.0)	0/0 (NA)	NA	1/2 (50.0)	0/0 (NA)	NA
Other	4/7 (57.1)	5/5 (100)	-42.9 (-75.9, 11.7)	4/7 (57.1)	5/5 (100)	-42.9 (-75.9, 11.7)
White	213/305 (69.8)	88/148 (59.5)	10.4 (1.1, 19.9) *	213/305 (69.8)	88/148 (59.5)	10.4 (1.1, 19.9) *
Ethnicity, n (%)						
Hispanic or Latino	5/9 (55.6)	7/12 (58.3)	-2.8 (-42.9, 37.4)	5/9 (55.6)	7/12 (58.3)	-2.8 (-42.9, 37.4)
Not Hispanic or Latino	236/355 (66.5)	101/166 (60.8)	5.6 (-3.1, 14.6)	236/355 (66.5)	101/166 (60.8)	5.6 (-3.1, 14.6)
Not reported	5/6 (83.3)	3/8 (37.5)	45.8 (-8.6, 78.4)	5/6 (83.3)	3/8 (37.5)	45.8 (-8.6, 78.4)
Is in USA, n (%)						
USA	29/67 (43.3)	15/32 (46.9)	-3.6 (-24.2, 16.8)	29/67 (43.3)	15/32 (46.9)	-3.6 (-24.2, 16.8)
Non-USA	217/303 (71.6)	96/154 (62.3)	9.3 (0.3, 18.6) *	217/303 (71.6)	96/154 (62.3)	9.3 (0.3, 18.6) *

Source: Clinical Data Scientist Reviewer, adae.xpt; Software: R.
* indicates that 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm; Q4W, every four weeks

7.6.1.10. Exposure-Adjusted Pooled Analyses, Trials OLYMPIA 1 and OLYMPIA 2

An overview of the TEAEs for phase 3 trials based on the exposure-adjusted incidence rates per person-years (at risk) was consistent between Weeks 0-16 and the overall treatment period as summarized in Table 31.

Table 31. Overview of Adverse Events, Trials OLYMPIA 1 and OLYMPIA 2 (Safety Population)

	OLYMPIA 1 & 2 0 to 16 Weeks			Overall OLYMPIA 1 (24 Weeks) & OLYMPIA 2 (16 Weeks)		
Event Category	Nemolizumab Q4W PY=95.6 N=370 n/py (EAIR)	Placebo PY=48.2 N=186 n/py (EAIR)	Nemolizumab Q4W vs. Placebo EAIR Difference (95% CI)	Nemolizumab Q4W PY=108.4 N=370 n/py (EAIR)	Placebo PY=55.1 N=186 n/py (EAIR)	Nemolizumab Q4W vs. Placebo EAIR Difference (95% CI)
SAE	15/95.3 (15.7)	14/47.8 (29.3)	-13.5 (-34.4, 2.0)	25/112 (22.3)	16/55 (29.1)	-6.8 (-26.3, 8.7)
SAEs with fatal outcome	0/95.6 (0)	0/48.2 (0)	0.0 (-8.0, 4.0)	0/108.4 (0)	1/55.5 (1.8)	-1.8 (-10.2, 1.7)
Life-threatening SAEs	0/95.6 (0)	0/48.2 (0)	0.0 (-8.0, 4.0)	0/108.4 (0)	0/55.1 (0)	0.0 (-7.0, 3.5)
SAEs requiring hospitalization	14/95.3 (14.7)	9/47.8 (18.8)	-4.1 (-22.1, 9.3)	23/111.3 (20.7)	11/54.9 (20.0)	0.6 (-16.6, 14.3)
AE leading to permanent discontinuation of study drug	14/95.8 (14.6)	5/48.4 (10.3)	4.3 (-10.6, 16.0)	15/108.8 (13.8)	5/55.3 (9.0)	4.7 (-8.4, 15.3)
AE leading to dose modification of study drug	13/96 (13.5)	9/47.9 (18.8)	-5.3 (-23.1, 7.8)	14/108.5 (12.9)	9/54.5 (16.5)	-3.6 (-19.4, 8.1)
AE leading to interruption of study drug	13/96 (13.5)	9/47.9 (18.8)	-5.3 (-23.1, 7.8)	14/108.5 (12.9)	9/54.5 (16.5)	-3.6 (-19.4, 8.1)
AE leading to reduction of study drug	0/95.6 (0)	0/48.2 (0)	0.0 (-8.0, 4.0)	0/108.4 (0)	0/55.1 (0)	0.0 (-7.0, 3.5)
AE leading to dose delay of study drug	0/95.6 (0)	0/48.2 (0)	0.0 (-8.0, 4.0)	0/108.4 (0)	0/55.1 (0)	0.0 (-7.0, 3.5)
Any AE	228/68.4 (333.1)	102/37.8 (269.9)	63.2 (-7.0, 129.7)	246/81 (303.7)	111/44.6 (248.6)	55.1 (-6.8, 113.6)
Severe and worse	11/95.6 (11.5)	11/48.2 (22.8)	-11.3 (-30.2, 2.1)	13/108.9 (11.9)	12/55.1 (21.8)	-9.8 (-26.9, 2.7)
Moderate	92/89.9 (102.4)	32/44.8 (71.4)	30.9 (-3.8, 62.3)	105/105.3 (99.7)	38/53.3 (71.2)	28.5 (-3.0, 57.2)
Mild	125/79.7 (156.9)	59/43.5 (135.5)	21.4 (-25.1, 64.3)	128/95.6 (133.9)	61/49.7 (122.6)	11.2 (-29.5, 48.5)

Source: Clinical Data Scientist Reviewer, adae.xpt; Software: R
Treatment-emergent adverse events defined as those AEs occurring after the first administration of study treatment until the last study visit.
Duration is 24 weeks for OLYMPIA 1 and 16 weeks for OLYMPIA 2.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; EAIR, exposure-adjusted incidence rate (per 100 person-years); N, number of patients in treatment arm; n, number of patients with at least one event; PY, person-years (total exposure); py, person-years (at risk); Q4W, every four weeks; SAE, serious adverse event

7.7. Key Safety Review Issues

Review of the clinical trial data did not identify any issues that would preclude approval. The Applicant's assessment of potential safety issues was deemed adequate.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Age

The Applicant proposed no dose adjustment for geriatric patients (aged 65 years and older), and the review team agree that this approach is acceptable. In population PK analysis, age was not associated with significant difference in nemolizumab exposure.

Body Weight

Body weight was identified as a significant predictor of nemolizumab exposure in the population PK analysis. The exposure of nemolizumab decreased with increasing body weight with a flat dosing regimen. With a flat dosing regimen of 30 mg Q4W, steady-state systemic C_{trough} exposure was predicted to be 1.7-fold lower between the upper body weight quartile (87 to 181 kg: 1.72 μg/mL) and the lower body weight quartile (31 to 62 kg: 2.92 μg/mL). The PK/PD simulations demonstrated that the variability in systemic exposure due to body weight had no clinically meaningful impact on PP NRS responders at Week 16. However, the IGA simulations showed a lower IGA success for subjects with body weight ≥90 kg when treated with a dose (30 mg Q4W regimen with 60-mg loading dose). Therefore, the phase 3 dosing regimen is based on a body weight cut-off of 90 kg (an initial dose of 60 mg followed by 30 mg given Q4W for patients <90 kg and an initial dose of 60 mg dose followed by 60 mg given Q4W for patients weighing ≥90 kg) to achieve matching systemic exposure and similar efficacy response (IGA) in subjects with body weight <90 kg and ≥90 kg. The proposed dosing regimen was the same dosing regimen studied in the pivotal phase 3 studies.

Hepatic Impairment

The Applicant proposed no dose adjustment for patients with mild to moderate hepatic impairment. The Applicant also states in the label that the effect of severe hepatic impairment on the PK of nemolizumab is unknown. The review team agrees that this approach is acceptable.

The Applicant did not conduct a dedicated hepatic impairment study with the proposed product as nemolizumab is not expected to undergo metabolism by hepatic metabolic enzymes. In the population PK analysis, hepatic impairment was not identified as a clinically relevant predictor of nemolizumab PK. 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.

Renal Impairment

The Applicant proposed no dose adjustment for patients with mild to moderate renal impairment. The Applicant also states in the label that the effect of severe renal impairment on the PK of nemolizumab is unknown. The review team agrees that this approach is acceptable.

The Applicant did not conduct a dedicated renal impairment study with the proposed product as nemolizumab is not expected to undergo renal elimination. In the population PK analysis, renal impairment was not identified as a clinically relevant predictor of nemolizumab PK. 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 of nemolizumab is unknown due to the limited number of subjects in this category.

8.2. Extrinsic Factors

Nemolizumab is a humanized IgG2 monoclonal antibody that inhibits IL-31 signaling by binding selectively to IL-31 RA. Nemolizumab inhibits IL-31-induced responses including the release of proinflammatory cytokines and chemokines. Therefore, treatment with nemolizumab may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes.

No dedicated drug-drug interaction (DDI) study assessing the effect of nemolizumab with CYP450 substrates have been conducted in subjects with PN. The Applicant is conducting a DDI study assessing the effect of nemolizumab administration on the PK of CYP450 substrates in subjects with atopic dermatitis and this study is ongoing.

The following language for the potential DDI has been included under Section 7 in the label:

***Cytochrome P450* Substrates**

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Treatment with NEMLUVIO may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes.

Upon initiation or discontinuation of NEMLUVIO in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.

8.3. Plans for Pediatric Drug Development

Nemolizumab triggers Pediatric Research Equity Act as a new active ingredient. The Applicant requested a Full Waiver for all pediatric age groups for the indication of treatment of PN (because studies are impossible or highly impractical).

The prevalence of PN in the US population is low and the majority of patients with PN are middle-aged or older adults. The prevalence of pediatric PN population is estimated to represent <1% of total PN population in the US.

The Applicant's request for Full Waiver is consistent with the Agreed iPSP Agreement letter conveyed by the FDA to the Applicant on November 2, 2021, and was presented by the review team to the Pediatric Review Committee (PeRC) on July 23, 2024.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

8.4.1. Animal Data

The following nonclinical information was used in support of product labeling (see Section 13.1.4 for detailed information).

In an ePPND study, subcutaneous doses up to 25 mg/kg nemolizumab were administered to pregnant cynomolgus monkeys once every two weeks from the beginning of organogenesis to parturition. The same subcutaneous doses were also administered to the offspring once every 2 weeks for 26 weeks, starting from postnatal day 35. No maternal or embryofetal toxicities were observed at doses up to 25 mg/kg [36 times the MRHD, based on AUC comparison]. Early postnatal death occurred in the offspring of one control monkey and 3 monkeys at 25 mg/kg. The early postnatal death rate in the 25 mg/kg group was higher than the historical control range. A treatment-related effect could not be clearly ruled out. The clinical significance of this nonclinical finding is unknown. No adverse effects were noted in the remaining offspring at doses up to 25 mg/kg (122 times the MRHD, based on AUC comparison).

The multiples of human exposure between the NOAELs identified in this study and the proposed MRHD are shown in Section 7.1.

The animal toxicokinetic data in this ePPND study indicated that nemolizumab crossed the placenta. In addition, nemolizumab was detected in breast milk of monkeys. The concentrations of nemolizumab in milk were approximately 0.3 – 0.5% of the corresponding maternal plasma levels from lactation day 7 to 63.

9. Product Quality

Approval With Post Marketing Commitments

The Office of Pharmaceutical Quality (OPQ) review team has assessed BLA 761390 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this BLA from a quality perspective. The data and information submitted in this application are sufficient to support the conclusion that the manufacture of NEMLUVIO is well controlled and leads to a product that is pure and potent for the duration of the product shelf life. OPQ recommends that this product be approved for human use under the conditions specified in the package insert.

Nemolizumab drug product is supplied as a sterile, white lyophilized powder for solution for injection in single-use, single-dose dual chamber cartridge (DCC) with no preservatives. Each dual chamber cartridge contains 30 mg of nemolizumab in one chamber and water for injection

for reconstitution in the other chamber. The drug product is formulated as 61.5 mg/mL nemolizumab after reconstitution.

The CMC post marketing commitments (and any other post-approval quality agreements) between OPQ and the Applicant are listed below and should be included in the action letter.

4682-1 Conduct three shipping validation runs [(b) (4)] cover dual chamber cartridge (DCC) shipping [(b) (4)] to the USA from a temperature control perspective. Provide the report and summary validation data.

Final Report Submission: 10/25

4682-2 Conduct one shipping validation run in summer 2024 for final packaged autoinjector (AI) to validate the shipping from [(b) (4)] to the US distribution sites from a temperature control perspective. Provide the report and summary validation data.

Final Report Submission: 10/24

4682-3 Implement a test for additional sub-visible particles [(b) (4)] µm in size in the drug product release and annual stability programs for dual chamber cartridge.

Final Report Submission: 10/25

9.1. Device or Combination Product Considerations

The combination product of nemolizumab consists of a pen encasing the dual chamber cartridge for subcutaneous delivery of a single fixed dose.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The review team requested the Office of Scientific Investigations to conduct inspections of the following clinical trial sites for phase 3 trials SPR.202685 (OLYMPIA 1, NCT04501666) and SPR.203065 (OLYMPIA 2, NCT04501679):

- Dr. Sonja Staender (SPR.202685, Site 5307)
- Dr. Franz J. Legat (SPR.202685, Site 5471)
- Dr. Adam Reich (SPR.203065, Site 5495)
- Dr. Carle Paul (SPR.203065, Site 5525)

The Office of Scientific Investigations team provided the following overall assessment of findings and recommendations to the review team in their review memorandum dated June 27, 2024:

“Four clinical investigators (Drs. Staender, Legat, Reich, and Paul) were inspected. The inspections did not find significant concerns regarding the study conduct or oversight of the clinical trials or GCP or regulatory compliance, and based on the results of these inspections, the data generated by the inspected clinical investigators appear acceptable in support of the proposed indication”.

11. Advisory Committee Summary

An Advisory Committee meeting was not held, because no unexpected or significant safety/efficacy issue or controversial/challenging issue was identified that would benefit from discussion at an Advisory Committee meeting. The safety profile did not raise significant safety issues that were unexpected for a drug in this class and there were no significant efficacy issues. The benefit/risk assessment is straightforward, and the application did not raise significant public health questions on the role of the drug in the diagnosis, cure, mitigation, treatment, or prevention of a disease, prurigo nodularis.

III. Additional Analyses and Information

There were no substantive disagreements or dissenting views regarding this application from the members of the review team.

12. Summary of Regulatory History

Biologics license application (BLA) 761390 for CD14152, NEMLUVIO (proposed nonproprietary name nemolizumab) was submitted under section 351(a) of the Public Health Service Act on December 13, 2023. The associated IND (investigational new drug application) (117122) was submitted on September 10, 2013, by Chugai Pharmaceuticals Co. The IND was transferred to Galderma Research and Development, LLC on December 9, 2016.

Nemolizumab is a humanized monoclonal antibody of the IgG2 subclass that inhibits interleukin-31 (IL-31) signaling by binding to the IL-31 receptor alpha (IL-31R). The proposed indication under BLA 761390 is the treatment of prurigo nodularis (PN). (b) (4)

The Agency has had ongoing communication via meetings and specific correspondence with the Applicant regarding the development program for the PN indication as summarized below.

- November 25, 2019: Breakthrough Therapy Designation was granted.
- January 27, 2020, Guidance Meeting: The Agency agreed that the proposal to request a full waiver of pediatric studies was reasonable. The Agency expressed the need for further justification regarding the proposed indication and how the Sponsor might adequately demonstrate that resolution of the PN lesions is independent of control of the pruritus. The Agency expressed concerns with subjects with lower exposure and lower Investigator Global Assessment (IGA) response in subjects with high body weights with the 30 mg flat dose and recommended exploration of a dosing regimen based on weight bands with a cut point of a lower versus higher dose. There was not agreement that the proposed co-primary endpoints, IGA success at Week 16 and Peak Pruritus Numeric Rating Scale (PP-NRS) responder, would support an indication of treatment of PN. There was also not agreement on the key secondary endpoint of the percent change from baseline in the number of lesions in a representative area (Prurigo Activity Score [PAS] item 4) at Week 16.
- February 5, 2020, Chemistry, Manufacturing, and Controls (CMC) Guidance Meeting: (b) (4)

(b) (4)

- May 20, 2020, End of Phase 2 Meeting: The Agency agreed that the proposal to test PP-NRS and, if successful, to test IGA according to the proposed 5-point scale, appeared reasonable, but stated that secondary endpoints intended for labeling should be limited in number, clinically meaningful, and planned with appropriate multiplicity control. The Agency agreed that the overall Clinical Pharmacology program appeared adequate to support a BLA and that a dosing regimen based on weight bands with a cut point of a lower versus higher dose was a reasonable approach, (b) (4) The Agency agreed that the general design of phase 3 trials, RD.06.SPR.202685 and RD.06.SPR.203065 was reasonable, but that the long term extension (LTE) trial would not provide adequate evidence of long-term efficacy because of the open-label design and the adequacy of the safety database should be justified. Agreement was reach on the proposal to analyze the primary and key secondary efficacy endpoints (i.e., all binary endpoints) using a Cochran-Mantel-Haenszel (CMH) test stratified by the factor used to stratify the randomization and the proposal to use non-responder imputation as the primary method for handling missing data. The Agency recommended that the threshold for within-patient meaningful change (i.e., responder definition) for the PP-NRS should be derived from anchor-based methods supplemented with anchor-based empirical cumulative distribution function (eCDF) and probability density function curves. (b) (4)
- December 1, 2020, Guidance Written Responses Only Meeting: Agreement reached that the 570 PN patients exposed to nemolizumab, with ~400 with 6 months exposure, and ~150 with 12 months of exposure was acceptable for the safety database.
- December 8, 2020, Advice letter: The Agency conveyed recommendations regarding the human factors validation study protocol.
- December 1, 2020, Guidance Written Responses Only Meeting: Agreement was reached that the 570 PN patients exposed to nemolizumab, with ~400 with 6 months exposure, and ~150 with 12 months of exposure was acceptable for the safety database.
- July 1, 2021: Human Factors Advice letter: The Agency outlined areas of disagreement.
- September 8, 2021, Guidance Meeting: The Agency agreed that the proposed CMC information appeared sufficient to address the identified gaps between the dual chamber syringe and the auto-injector and offered several recommendations regarding the assessment of analytical comparability. Agreement was reached on the control strategy, stability study program, shelf life, and pharmacokinetics (PK) study comparing the dual-chamber syringe and autoinjector.
- September 26, 2022, Guidance Meeting: The Agency offered comments on the safety analysis strategy for the Integrated Summary of Safety and agreed that the proposed data search and retrieval criteria for Adverse Events of Special Interest (AESIs) and the pooling strategy appeared reasonable. Agreement was reached that Studies SPR.118380 (vaccine study) and SPR.201593 (drug-drug interaction study) could be submitted post-approval.

- December 1, 2021, Advice letter: The Agency conveyed disagreement regarding the Human Factors Validation Study Protocol.
- August 19, 2022, Advice letter: The Agency conveyed disagreement regarding the Human Factors Validation Study Protocol.
- February 15, 2023, Proprietary Name Conditionally Acceptable letter for the proposed proprietary name of NEMLUVIO.
- April 18, 2023, Pre-BLA CMC focused meeting took place to seek the Food and Drug Administration's (FDA) feedback and agreement on: the overall structure and organization of the Quality modules of the Common Technical Document (CTD Module 3) including the Device documentation of the BLA (3.2.R for (b) (4) dual chamber cartridge assembled with an autoinjector [DCC-AI]), the proposal to submit a stability update during the review of the BLA to further support the 24 months shelf-life claim for the auto-injector and to reach an agreement for not considering the update as a substantial amendment, and to discuss the Pre- License Inspection strategy and timeframe of the drug substance manufacturing facilities at Chugai (Japan).
- April 26, 2023, Pre-BLA Meeting: Agreement was reached about the general acceptability of the proposed BLA content and format.
- June 27, 2023, Guidance Meeting: Agreement was not reached regarding the single dosing regimen.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

The nonclinical studies conducted to support nemolizumab were originally submitted to and reviewed under IND 117122. All pertinent studies were also submitted to the present BLA. CIM331 and CH5427227 were the code names for nemolizumab used in nonclinical studies.

13.1.1. Pharmacology (Primary and Secondary)

Nemolizumab is a humanized monoclonal IgG2 antibody recognizing IL-31RA and blocking binding of IL-31. An engineered IgG2 structure was adopted to reduce effector function.

IL-31 is a cytokine produced by activated T cells, and it belongs to the IL-6 cytokine family. IL-31 signals through a heterodimeric receptor, consisting of IL-31RA and the oncostatin M receptor (OSMR) beta chain. Subsequently the down-stream JAK/STAT signaling pathway is activated and the signal is transmitted into the cell. IL-31 has been identified as a cytokine that induces pruritus, barrier disruption, skin inflammation, and fibrosis. Studies have shown that IL-31 plays a role in several skin diseases including atopic dermatitis (AD) and prurigo nodularis (PN). By blocking IL-31 signaling, nemolizumab is expected to ameliorate itching and skin inflammation in AD and PN patients.

In Vitro Studies

Nemolizumab binds to human and cynomolgus monkey IL-31RA with high affinity [dissociation constant (K_D): 0.374 and 0.191 nM, respectively]. Nemolizumab inhibits the binding of IL-31 to human or monkey IL-31RA in a concentration-dependent manner. Nemolizumab inhibited human IL-31-dependent proliferation of the cell line BaF/2C6/16 which was transfected with human IL-31RA and OSMR genes, in a concentration-dependent manner. Similarly, nemolizumab also inhibited monkey IL-31-dependent proliferation of the cell line Ba/F3 which was transfected with monkey IL-31RA and OSMR genes.

Nemolizumab inhibited IL-31-induced STAT3 phosphorylation in an IL-31RA-expressing human cell line (A549) in a concentration-dependent manner. Nemolizumab also inhibited IL-31-induced IL-6 production, MMP-1 production, MMP-3 production, and apoptosis in a human epidermal keratinocyte cell line (HaCaT) in a concentration-dependent manner. In the TF-1 cell line, nemolizumab did not affect the cell proliferation induced by IL-6 or OSM, which are cytokines that utilize gp130, a cytokine receptor that has homology to IL-31RA.

The binding of nemolizumab to human Fcγ receptor and monkey Fcγ receptor was measured by surface plasmon resonance and compared to panitumumab (a control antibody with human IgG2 constant regions) and rituximab (a control antibody with human IgG1 constant regions). The results showed that the binding of nemolizumab, which has modified human IgG2 constant regions, to human Fcγ receptor is similar to that of panitumumab and much weaker than that of rituximab. The results suggested that the risk of antibody-dependent cell-mediated cytotoxicity (ADCC) associated with nemolizumab was likely lower than that for IgG1.

The binding of nemolizumab to human C1q (a complement C1 component protein) was measured by validated enzyme-linked immunosorbent assay (ELISA). Panitumumab and rituximab were also used as comparators. The results showed that the binding of nemolizumab to human C1q was similar to that of panitumumab and weaker than that of rituximab. The results suggested that the risk of complement-dependent cytotoxicity associated with nemolizumab was likely lower than that for IgG1.

The localization of IL-31RA at AD patient skin lesion sites was investigated using an immunohistochemical method. The expression of IL-31RA was noted at skin nerve endings in AD patient skin lesions.

In Vivo Studies

The pharmacological effects of nemolizumab were evaluated in a cynomolgus monkey IL-31-induced itch model, when IV doses of nemolizumab increased incrementally from 3 to 100 μg/kg (administered to the same male monkey). IV doses of monkey IL-31 (1 μg/kg) were administered to induce itching behavior, and the number of itching behavior was counted by reviewing a 2-hour video recording after administration. The results showed that IV doses of IL-31 induced a marked increase in itching behavior, and a clear inhibition of itching behavior was noted at doses of nemolizumab ≥40 μg/kg.

In a second study using the same monkey model, the effects of nemolizumab were evaluated when administered via subcutaneous (SC)route. Two days before nemolizumab administration (Day -2), the background itching behavior was counted. One day before nemolizumab administration (Day -1), 1 μg/kg (IV) monkey IL-31 was administered. On Day 0, a single dose

of 1 mg/kg nemolizumab or vehicle were administered subcutaneously to 6 male monkeys in each group. On Days 28 and 56, the number of itching behaviors induced by an IV dose of 1 µg/kg monkey IL-31 was counted. The results showed that on Day 28 the IL-31-induced itching behavior was almost completely inhibited in the nemolizumab-treated group. When excluding an animal with a positive anti-nemolizumab antibody titer, the inhibition of itching behavior by nemolizumab was still significant on Day 56.

The Applicant created BM095, a mouse IL-31RA neutralizing antibody. The effects of BM095 on a mite antigen-induced mouse AD model were investigated. Dermatitis was induced in the right pinna of female NC/Nga mice by administering 5 µg (1 µg/µl) mite antigen intradermally three times a week for three weeks. In parallel with the initiation of antigen sensitization, 20 mg/kg BM095 was administered intravenously twice a week for a total of seven doses. In addition, as a positive control group, 1 mg/kg dexamethasone was administered orally five times a week, for a total of 17 doses. Body weight, ear thickness, pinna dermatitis score, total number of scratching movements and frequency of scratching movements were measured at regular intervals. The experiment was conducted twice, with nine mice in each group in Experiment 1 and eight mice in each group in Experiment 2. A measurement magnet was subcutaneously implanted in the dorsal aspect of the hind paws of mice in Experiment 2, and the total number and frequency of scratching movements were measured over a 12-hour period using an automated scratch measuring device.

In the BM095 group, there were significant improvements in ear thickness, pinna dermatitis score and total number of scratching movements compared with the disease control group. In the dexamethasone group, there were also significant improvements in ear thickness, pinna dermatitis score and frequency of scratching movements. Suppression of body weight was seen in the dexamethasone group but not in the BM095 group.

Tissue Cross-Reactivity

The cross-reactivity of nemolizumab with IL-31RA of mice, rats and rabbits was analyzed using antigen-antibody interactions as an indicator to identify pharmacologically relevant species. No interactions were detected between nemolizumab and IL-31RA from mice, rats, or rabbits. As a positive control, significant interaction was detected between nemolizumab and human IL-31RA in this assay. Therefore, mouse, rat and rabbit were not considered pharmacologically relevant species for the use in toxicity studies.

A tissue cross-reactivity study of nemolizumab with normal human and cynomolgus monkey tissues was conducted to evaluate potential off-target binding using an immunohistochemical staining method. Nemolizumab was applied to cryosections of normal human and monkey tissues at two concentrations (2 and 10 µg/ml).

The specific reactivity with nemolizumab was generally similar between human and monkey tissues. In both human and monkey tissues, nemolizumab comparably stained epithelium in esophagus, lung, prostate, prostatic urethra, salivary gland, skin, thymus, tonsil, ureter, urinary bladder, and uterus (cervix). In human tissue only, nemolizumab stained epithelium in eye and uterine endometrium. In cynomolgus monkey tissue only, nemolizumab stained epithelium in fallopian tube, stomach, ovary, and neuropil in the dorsal horns of spinal cord.

13.1.2. Safety Pharmacology

No stand-alone safety pharmacology studies were conducted with nemolizumab. The evaluation of safety pharmacology endpoints was included in the repeat-dose toxicity studies in monkeys.

13.1.3. Pharmacokinetics

Table 32. Summary of PK/TK Data for Nemolizumab

Type of Study	Major Findings
Absorption	
Plasma concentration of CH5427227 after single intravenous or subcutaneous administration of CH5427227 in cynomolgus monkeys (Study# B100795)	Monkey (single IV or SC dose) $T_{1/2}$: 0.04 mg/kg: (IV) 3.3 day, (SC) 3.1 day 0.2 mg/kg: (IV) 13.6 day, (SC) 11.5 day 1.0 mg/kg: (IV) 14.9 day, (SC) 12.8 day C_{max}: 0.04 mg/kg (SC): 0.34 µg/ml 0.2 mg/kg (SC): 1.97 µg/ml 1.0 mg/kg (SC): 9.13 µg/ml T_{max}: 0.04 mg/kg (SC): 3.3 day 0.2 mg/kg (SC): 4.0 day 1.0 mg/kg (SC): 4.3 day $AUC_{0\text{-}inf}$: 0.04 mg/kg: (IV) 99 µg·hr/ml, (SC) 72 µg·hr/ml 0.2 mg/kg: (IV) 1370 µg·hr/ml, (SC) 985 µg·hr/ml 1.0 mg/kg: (IV) 6890 µg·hr/ml, (SC) 5140 µg·hr/ml Bioavailability: 0.04 mg/kg (SC): 72.1% 0.2 mg/kg (SC): 71.9% 1.0 mg/kg (SC): 74.6%
Distribution	
Quantitative whole-body autoradiography in male cynomolgus monkeys after single subcutaneous administration of [^{125}I]CH5427227 (Study# B100794)	Monkey A single SC dose of [^{125}I]nemolizumab was administered to male monkeys and the radioactivity concentrations in 22 tissues were quantified by whole-body autoradiography. The highest radioactivity level was observed in thyroid at all time points. This was expected due to iodine uptake of thyroid. Except for the thyroid, the radioactivity levels in all tissues were lower than that in plasma at all time points. The tissue/plasma radioactivity ratios of the lung, liver, kidney, spleen and heart were relatively high among the analyzed tissues. The radioactivity distribution into the brain was extremely low. There were no specific tissues showing accumulation of nemolizumab.
Intermittent subcutaneous dose (once every two weeks) enhanced study for effects on pre- and postnatal development of CIM331 in	Monkey Concentrations of nemolizumab in offspring plasma on postnatal day (PND) 7 were comparable to those in dams, suggesting that nemolizumab crossed the placenta.

cynomolgus monkeys (Study# SBL036-185)	
Excretion	
Intermittent subcutaneous dose (once every two weeks) enhanced study for effects on pre- and postnatal development of CIM331 in cynomolgus monkeys (Study# SBL036-185)	Monkey The secretion of nemolizumab in breast milk in monkeys was minimal. The concentrations of nemolizumab in milk were approximately 0.3 – 0.5% of the corresponding maternal plasma levels from lactation day 7 to 63.
TK data from general toxicology studies A 26-week intermittent subcutaneous dose (once every two weeks, 14 times total) toxicity study of CH5427227 in mature cynomolgus monkeys followed by a 17-week recovery period (Study# SBL036-131)	Monkey (biweekly dosing for 6 months) $AUC_{0\text{-}14\ day}$ (following the 13th dose, data from ADA-positive animals excluded): 1 mg/kg: (M) 6040 µg·hr/ml, (F) 4450 µg·hr/ml 5 mg/kg: (M) 26400 µg·hr/ml, (F) 22100 µg·hr/ml 25 mg/kg: (M) 101000 µg·hr/ml, (F) 86800 µg·hr/ml Accumulation: 1.9-2.2 fold comparing AUC after 13th dose to AUC after 1st dose Dose proportionality: The AUC increase was roughly dose proportional ADAs were detected in 5 animals during the treatment period (4 low dose and 1 high dose) and in 3 animals during the recovery period (1 low dose, 1 mid dose and 1 high dose).
TK data from reproductive toxicology studies Intermittent subcutaneous dose (once every two weeks) enhanced study for effects on pre- and postnatal development of CIM331 in cynomolgus monkeys (Study# SBL036-185)	Maternal monkey (biweekly dosing from gestation day 20 to delivery) $AUC_{0\text{-}14\ day}$ (following the 9th dose, data from ADA-positive animals excluded): 1 mg/kg: 3310 µg·hr/ml 25 mg/kg: 59900 µg·hr/ml ADAs were detected in 4 low dose dams and 3 high dose dams. Offspring monkey (biweekly dosing from PND 35 to 217) $AUC_{0\text{-}14\ day}$ (following the 13th dose, data from ADA-positive animals excluded, sex-combined): 1 mg/kg: 8490 µg·hr/ml 25 mg/kg: 201000 µg·hr/ml ADAs were detected in 3 low dose infants.

Source: Nonclinical study reports
Abbreviations: ADA, anti-drug antibodies; AUC, area under the concentration-time curve; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-}14day}$, area under the concentration-time curve from 0 to 14 days; C_{max}, maximum plasma concentration; F, female; IV, intravenous; M, male; PND, postnatal day; SC, subcutaneous; TK, toxicokinetic; T_{max}, time to maximum concentration; $t_{1/2}$, half-life

13.1.4. Toxicology

13.1.4.1. General Toxicology

Pivotal repeat-dose toxicity studies were conducted in cynomolgus monkeys, with treatment durations of 3 and 6 months. No significant toxicity was noted in either study. The no-observed-adverse-effect level (NOAEL) was identified as the high dose, 25 mg/kg nemolizumab once every two weeks, in both studies. The 6-month study is reviewed below.

Study title / number: A 26-week intermittent subcutaneous dose (once every two weeks, 14 times total) toxicity study of CH5427227 in mature cynomolgus monkeys followed by a 17-week recovery period / Study# SBL036-131, sponsor reference# TOX12-0076

- No significant toxicity was noted in this study. The NOAEL was identified as the high dose, 25 mg/kg once every two weeks.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 1, 5, and 25 mg/kg, once every two weeks for 26 weeks (14 doses in total)
Route of administration:	Subcutaneous injection
Formulation/Vehicle:	20 mM Tris-HCl buffer solution containing 150 mM arginine, 250 mM sucrose and 0.5 mg/ml Poloxamer 188 (pH 7.0)
Species/Strain:	Monkey / Cynomolgus
Number/Sex/Group:	3/sex/group
Age:	3-6 years
Satellite groups/ unique design:	Recovery animals 2/sex/group T-cell dependent antibody response (TDAR) was evaluated. After the dosing of test article on Day 155, animals were anesthetized by an intramuscular injection of ketamine HCl. The sensitizer keyhole limpet hemocyanin (KLH) solution (4 mg/ml) was then injected subcutaneously to the dorsal region at a dose of 0.1 ml/site. Anti-KLH antibody was measured before and after the KLH dosing.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results: changes from control

Parameters	Major findings
Mortality	No mortality occurred.
Clinical Signs	There were no significant treatment-related findings.
General Behavior and Neurobehavioral Function	The following parameters were evaluated: body position, consciousness, behavior, gait, motor power/movement of hand, motor power/movement of leg, palpebral closure, CNS excitation, vomiting, lacrimation, salivation, visual response, sound response, muscle tone, touch response, eyelid reflex, pinna reflex, pupillary reflex, pain response, respiration, and rectal temperature. There were no significant treatment-related findings.
Body Weights	There were no significant treatment-related findings.
Feed Consumption	There were no significant treatment-related findings.
Menstrual Cycle	There were no significant treatment-related findings.
Semen Analysis	The following parameters were examined: color, semen volume, coagulum weight, sperm count, motility, and morphology. There were no significant treatment-related findings.
Testicular Volume	There were no significant treatment-related findings.
Ophthalmology	There were no significant treatment-related findings.
ECG	There were no significant treatment-related findings.
Respiration Rate	There were no significant treatment-related findings.
Blood Pressure	There were no significant treatment-related findings.
Hematology	There were no significant treatment-related findings.
Clinical Chemistry	There were no significant treatment-related findings.
Urinalysis	There were no significant treatment-related findings.
Immunophenotyping in Peripheral Blood	The following lymphocyte subgroups were counted using a flow cytometer: $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^-CD16^+$, and $CD3^-CD20^+$. There were no significant treatment-related findings.
Cytokine Analysis in Serum	The following cytokines were measured: IL-2, IL-4, IL-5, IL-6, TNF-α, and IFN-γ. There were no significant treatment-related findings.
Gross Pathology	There were no significant treatment-related findings.
Organ Weights	There were no significant treatment-related findings.
Histopathology Adequate battery: Yes	There were no significant treatment-related findings.
Anti-Drug Antibody (ADA) Analysis	ADAs were detected in 5 animals during the treatment period (4 low dose and 1 high dose). ADAs were detected in 3 animals during the recovery period (1 low dose, 1 mid dose and 1 high dose).
Anti-KLH antibody Measurement	There were no significant treatment-related findings.

Source: Nonclinical study report
Abbreviations: ADA, anti-drug antibodies; CNS, central nervous system; ECG, electrocardiogram; KLH, keyhole limpet hemocyanin

13.1.4.2. Genetic Toxicology

Genetic toxicology studies are not needed to support the development of nemolizumab, per the International Council for Harmonisation (ICH) S6(R1) guidance(FDA 2012), *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals*.

13.1.4.3. Carcinogenicity

Carcinogenicity studies were not conducted for the evaluation of the carcinogenic potential of nemolizumab. The Applicant submitted a carcinogenicity risk assessment to the corresponding IND, and it was reviewed by the Executive Carcinogenicity Assessment Committee of Center for Drug Evaluation and Research. The Executive Carcinogenicity Assessment Committee provided concurrence on 02/13/2018 that carcinogenicity studies are not needed to support the development of nemolizumab.

In this BLA submission, the Applicant provided an updated carcinogenic risk assessment, which is similar to the previous document. A weight-of-evidence analysis does not raise significant safety concerns for carcinogenicity based on the evaluation of available literature related to IL-31 inhibition. There was no evidence of tissue proliferation (i.e., hyperplasia, preneoplastic lesions) or immunosuppression in the 6-month repeat-dose subcutaneous toxicity study in monkeys.

13.1.4.4. Reproductive Toxicology

Fertility and Early Embryonic Development

Potential effects of nemolizumab on male and female fertility were investigated in the 6-month repeat-dose toxicity study conducted in sexually mature cynomolgus monkeys. Histopathology examinations on endocrine and reproductive organs and additional endpoints (sperm/testicular analysis in males and menstrual cycle in females) did not identify any adverse effects. However, the monkeys were not mated to evaluate fertility.

Embryofetal Development and Pre- and Postnatal Development

Study title / number: Intermittent subcutaneous dose (once every two weeks) enhanced study for effects on pre- and postnatal development of CIM331 in cynomolgus monkeys / Study# SBL036-185, Sponsor reference# TOX14-0140

- The NOAEL for maternal toxicity, embryofetal toxicity, and juvenile toxicity was identified as the high dose, 25 mg/kg.
- The NOAEL for pre- and postnatal development toxicity was conservatively identified as the low dose, 1 mg/kg, considering that an increase in early postnatal death was noted in the high dose group and a treatment-related effect could not be ruled out.

Conducting laboratory and location	(b) (4)
GLP compliance:	Yes

Methods

Dose and frequency of dosing:	0 (vehicle), 1, and 25 mg/kg, once every 2 weeks
Route of administration:	Subcutaneous injection

Formulation/Vehicle:	20 mM Tris-HCl buffer solution containing 150 mM arginine, 250 mM sucrose and 0.5 mg/ml Poloxamer 188 (pH 7.0)
Species/Strain:	Monkey / Cynomolgus
Number/Sex/Group:	F0: 16 females/group
Satellite groups:	None
Study design:	Pregnant females were dosed from the start of organogenesis [gestation day (GD) 20] to delivery. The F1 infants were also dosed at the same dose levels once every 2 weeks for 26 weeks, from postnatal day (PND) 35 to 217. All dams were allowed to nurse the infants until lactation day (LD) 220, and the infants were necropsied on PND 220.
Deviation from study protocol affecting interpretation of results:	No

Observations and Results

<table>
<tr><th>Generation</th><th>Major Findings</th></tr>
<tr><td>F0 Dams</td><td>No mortality occurred. No significant treatment-related findings were observed in clinical signs, gestation length, body weight, food consumption, hematology, or blood chemistry in dams during the gestation or lactation period.</td></tr>
<tr><td>F1 Offspring</td><td>No significant treatment-related findings were observed in clinical signs, body weight, external or skeletal findings, morphological or functional development (including pupillary reflex, Preyer’s reflex, grip strength, and pain response), behavioral development (observation of dam-offspring interaction), hematology, blood chemistry, peripheral blood immunophenotyping, immunocompetence (T-cell dependent antibody reaction), ophthalmology, ECG, necropsy findings, organ weight, or histopathology examination.

The numbers of abortions, stillbirths, early postnatal deaths, euthanized offspring, and offspring that survived to PND 220 are summarized below:

<table>
<tr><th rowspan="2">Dose Level</th><th colspan="6">Number of Animals</th></tr>
<tr><th>Pregnant animals for each group</th><th>Fetal losses before delivery</th><th>Stillbirth</th><th>Early postnatal death</th><th>Euthanized offspring</th><th>Offspring surviving to PND 220</th></tr>
<tr><td>Control</td><td>16</td><td>2</td><td>0</td><td>1</td><td>0</td><td>13</td></tr>
<tr><td>1 mg/kg</td><td>16</td><td>1</td><td>3</td><td>0</td><td>2</td><td>10</td></tr>
<tr><td>25 mg/kg</td><td>16</td><td>2</td><td>0</td><td>3</td><td>0</td><td>11</td></tr>
</table>

The incidence of fetal losses before delivery in the dose groups was comparable to that in the control group. Stillbirth occurred in 3 dams in the low dose group but the incidence rate was within the historical control range (0 - 28.6%). During the early postnatal period, 1 control infant died on PND 0, and 3 high dose infants died on PND 1, 3, and 14, respectively. The early postnatal death rate in the high dose group (3/14, 21.4% by PND 14; and 2/14, 14.3% by PND 7) was higher than the historical control range (0 - 7.7% by PND 7). Malnutrition was observed in two early death high dose infants. A treatment-related effect could not be clearly ruled out. Two low dose infants were euthanized from a humane perspective due to bite wounds caused by its dam or lack of nursing behavior of its dam, which are not considered treatment-related.</td></tr>
</table>

Source: Nonclinical study report
Abbreviations: ECG, electrocardiogram; PND, postnatal day

13.1.4.5. Other Toxicity/Specialized Studies

Local Tolerance

A local tolerance study was conducted in New Zealand White rabbits. The local tolerance of nemolizumab (clinical formulation) was assessed in 6 male rabbits by subcutaneous injection. A single dose of 0.9 ml test article (nemolizumab or saline) was injected subcutaneously to left or right abdomen. The injection sites were observed for the presence/absence of erythema, swelling, ulcer, induration (nodule) and other external findings at 1 hour after dosing and once daily for 14 days. There were no treatment-related findings in the external observations, gross pathology, or histopathology evaluation of the administration sites.

Juvenile Animal Toxicity

Juvenile toxicity was investigated by direct dosing of the offspring in the enhanced pre- and postnatal developmental study in monkeys, at biweekly subcutaneous doses up to 25 mg/kg, for 26 weeks (starting from PND 35). No significant treatment-related juvenile toxicity was noted in the study.

13.1.5. Excipients/Impurities

There are no novel excipients in the clinical formulation. All the inactive ingredients are below approved levels listed in the FDA's inactive ingredient database.

The Applicant provided an impurity characterization and control strategy. The potential impurities that are evaluated and controlled included product-related impurities, process-related impurities, residual solvents, elemental impurities, and contaminants. The proposed control strategy is considered acceptable. There are no safety concerns for potential impurities contained in this biologic product.

13.1.6. Extractables/Leachables

The container closure system for the storage of nemolizumab drug substance (b) (4) . The final container closure system for the NEMLUVIO product is dual-chamber pen (b) (4) Extractable and leachable data were provided for both container closure systems.

The Applicant followed the ICH M7 (R1) guidance *[Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk]* to set the identification threshold and daily acceptable levels for leachables. The proposed maximum clinical dose is 60 mg (two 30 mg pre-filled syringes, 30 mg nemolizumab dissolved in 0.49 ml solution) every 4 weeks. Considering the intermittent dosing of the product, a threshold of toxicological concern (TTC) of 10 µg/day (corresponding to a treatment duration of 1-10 years) was used. The maximum daily dosing volume of this product is 0.98 ml. Therefore, the acceptable limit for unidentified organic leachables was set as 10 µg/ml for the final container closure system.

There are no safety concerns for the extractables and leachables from either the drug substance storage container closure system or the final product container closure system.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable.

13.3. Labeling

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

14. Clinical Pharmacology

14.1. In Vitro Studies

Not applicable.

14.2. In Vivo Studies

Nemolizumab is a recombinant humanized monoclonal antibody (mAb) of the immunoglobulin (Ig)G2 subclass that inhibits interleukin (IL)-31 signaling by binding to the IL-31 receptor alpha (IL-31RA) with high specificity and affinity, that is being developed for the treatment of adult subjects with prurigo nodularis (PN) (BLA 761390) (b) (4) This summary of clinical pharmacology provides an overview of clinical pharmacology data including PK, immunogenicity, biomarkers, and modeling and simulation approaches (population PK, pharmacokinetics/pharmacodynamics [PK/PD], and exposure-safety analyses) to support the application for nemolizumab for the treatment of adults with PN. The proposed dosing regimen is a single SC loading dose of 60 mg followed by SC doses of 30 mg Q4W for subjects weighing <90 kg. The proposed dose for subjects weighing ≥90 kg is 60 mg Q4W.

Clinical Program

The clinical program consists of two phase 1 studies (FIH Study CIM001JP: Part A: SAD in healthy Japanese subjects; Part B: SAD in healthy white subjects; Part C: SAD in Japanese subjects with atopic dermatitis (AD), and Study 201590 PK bridging study evaluating DCC-AI versus DCS), one phase 2 study in PN (Study 115828), two phase 3 trials in PN (Study 203065 and 202685), one ongoing phase 3 long-term extension study (Study 202699), and one ongoing blinded phase 3b durability of response study in PN (Study 203890). The Applicant has also submitted three phase 2 studies and two phase 3 trials in subjects with AD as supporting information. (b) (4)

PK Assessment

PK was assessed in the following trials:

- Study CIM001JP (First-in-human study in healthy subjects and subjects with AD)
- The PK data from 4 clinical studies in subjects with PN (Studies 115828, 202685, 203065, and 202699.
- The PK data from an additional 5 studies in subjects with AD, used in the population PK modeling to provide additional supportive PK information for the proposed indication (Studies CIM003JG, 114322, 116912, 118161, and 118169).
- The PK data from one relative bioavailability bridging study in healthy subjects (Study 201590).

The clinical pharmacology program also includes population PK analyses, PK/PD analyses for efficacy, and exposure-safety analyses. In addition, supportive evidence of the local and systemic effects of nemolizumab in subjects with PN comes from exploratory biomarker evaluations; these were determined in samples collected in phase 2 (Study 115828) and phase 3 (Study 203065). A population PK model was developed to describe the PK profile of nemolizumab and to characterize its interindividual variability (IIV) in subjects with PN or AD. This included an assessment of the impact of intrinsic and extrinsic covariates on the main PK parameters and their variabilities. The population PK model was developed based on data from subjects with PN or AD on active treatment, receiving either single or multiple subcutaneous (SC) doses of nemolizumab across phase 1 to phase 3 clinical trials (0.003- to 3-mg/kg single doses, 0.1- to 2-mg/kg repeated doses, and 10- to 90-mg repeated flat doses). The PK/PD analyses for efficacy and the exposure-safety analyses were based on data only from subjects with PN. The relationships between nemolizumab PK and clinical efficacy assessments over time [Investigator global assessment (IGA) and peak pruritus numerical rating scale (PP NRS)] were characterized using nonlinear mixed effect exposure-response modeling. The relationships between nemolizumab PK and clinical safety endpoints were characterized on the following treatment-emergent AEs: eczematous reactions, headache, newly diagnosed or worsening of asthma, and peripheral or facial edema.

Formulations/Devices

In the clinical development program of nemolizumab, different formulations (lyophilized powder or liquid) and drug product presentations (vial and syringe, DCS, or DCC-AI) were used. (b) (4) . The lyophilized powder was intended for SC injection after reconstitution of the lyophilized nemolizumab powder with water for injection. Upon reconstitution with water for injection, the drug formulation is the same for DCC-AI and DCS. Within the overall development program, a 100-mg liquid formulation in vial or a lyophilized powder for solution for SC injection in different container closure systems (100-mg vial, 30-mg DCS, and 30-mg DCC-AI) were used. The vial presentation, used in the first-in-human study (CIM001JP), contained a liquid formulation. In the phase 2 study in subjects with PN (Study 115828), nemolizumab was supplied as a lyophilized powder in single-dose vial for reconstitution with sterile water for injection (sWFI). Upon reconstitution with 1.3 mL of sWFI, the resulting solution contained 100 mg/mL nemolizumab that was administered by SC injection once every 4 weeks (Q4W). The solution containing 100

mg/mL nemolizumab was diluted with the same solution that was used to reconstitute placebo and the targeted study doses were administered by SC injection Q4W. In the phase 3 studies in subjects with PN (Studies 202685, 203065, and 202699), nemolizumab was supplied as a lyophilized powder in a DCS for solution for injection, which held the lyophilized nemolizumab or placebo and the sWFI separately. Therefore, the drug product dosage form (liquid or lyophilized) and the drug product presentation (vial and DCS) were added as covariates in the final population PK model developed using pooled clinical data obtained in subjects with AD or PN. Neither nemolizumab formulation (liquid versus lyophilized powder) or drug product presentation (vial versus DCS) were found to be significant covariates in the population PK model.

(b) (4)

Study CIM001JP (Phase 1, First-in-Human Study)

CIM001JP was a Phase 1, placebo-controlled, randomized, double-blind, inter-individual, dose-escalation study of single SC doses in healthy Japanese adult males (Part A), healthy White adult males (Part B), and Japanese subjects with AD (Part C). The objective of this first-in-human study was to investigate the tolerability, safety, and PK of SC injected nemolizumab in healthy Japanese and White adult males and in Japanese subjects with AD.

Drug Administration

In Part A (N = 56), either placebo or nemolizumab was administered as a single SC injection to healthy Japanese male subjects at doses of 0.003, 0.01, 0.03, 0.1, 0.3, 1, or 3 mg/kg. Each group comprised 8 subjects (6 for nemolizumab and 2 for placebo). In Part B (N = 24), healthy White male subjects received nemolizumab (0.3, 1, or 3 mg/kg) or placebo. Each group consisted of 8 subjects (6 for nemolizumab and 2 for placebo). In Part C (N = 36), Japanese male and female subjects with AD received nemolizumab (0.3, 1, or 3 mg/kg) or placebo. Each group consisted of 12 subjects (9 for nemolizumab and 3 for placebo).

PK Results

Serum nemolizumab concentrations following a single dose of nemolizumab peaked at 4.46 to 9.18 days, after which the drug was eliminated from the serum with a $t_{1/2}$ of 12.6 to 16.5 days. PK parameters of nemolizumab (C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$) increased in a dose-proportional manner after a single administration in the dose range of 0.03 to 3 mg/kg. Descriptive statistics of nemolizumab PK parameters are displayed in **Table** 33.

Part A: Single Ascending Dose in Healthy Japanese Subjects

After a single SC administration of 0.003 or 0.01 mg/kg, serum nemolizumab concentrations were all below the lower limit of quantification (<0.1 μg/mL). When a single dose of 0.03, 0.1, 0.3, 1, or 3 mg/kg was administered SC, serum nemolizumab concentrations peaked from 4.67 to 8.01 days after administration, after which nemolizumab was gradually eliminated from the serum. The $t_{1/2}$ was similar across dose levels and ranged from 12.7 to 16.4 days.

Part B: Single Ascending Dose in Healthy White Subjects

When a single dose of 0.3, 1, or 3 mg/kg was SC administered, serum nemolizumab concentrations peaked from 5.67 to 9.18 days after administration, after which nemolizumab was gradually eliminated from the serum. The terminal $t_{1/2}$ was similar across dose levels and ranged from 16.0 to 16.5 days.

Part C: Single Ascending Dose in Japanese Subjects With AD

When a single dose of 0.3, 1, or 3 mg/kg was SC administered, serum nemolizumab concentration peaked from 4.46 to 5.66 days after administration, after which nemolizumab was gradually eliminated from the serum. The terminal $t_{1/2}$ was similar across dose levels and ranged from 12.6 to 14.6 days.

Table 33. Mean Pharmacokinetic Parameters by Dose and Population, Study CIM001JP

Population	Dose mg/kg	n	$AUC_{0\text{-}inf}$ (day•µg/mL)	C_{max} (µg/mL)	T_{max} (day)	$t_{1/2}$ (day)	CL/F (mL/day)	V/F (mL)
Healthy Japanese subjects (Part A)	0.03	6	7.01 (1.20)[a]	0.315 (0.0352)	6.50 (4.00, 11.0)	12.7 (3.38)[a]	274 (35.1)[a]	4960 (1150)[a]
	0.1	6	19.7 (5.16)	0.782 (0.143)	7.00 (6.00, 10.0)	14.5 (4.22)	331 (122)	6510 (1620)
	0.3	5	75.7 (12.0)	2.33 (0.486)	10.00 (4.00, 10.0)	15.1 (1.71)	264 (37.3)	5690 (697)
	1.0	6	226 (24.5)	8.82 (1.23)	4.00 (4.00, 7.00)	15.2 (1.81)	269 (47.7)	5840 (842)
	3.0	6	634 (199)	23.9 (3.40)	5.00 (4.00, 6.00)	16.4 (3.92)	319 (75.9)	7250 (1200)
Healthy White subjects (Part B)	0.3	6	79.7 (19.5)	2.28 (0.535)	8.51 (7.00, 14.0)	16.0 (2.87)	300 (117)	6590 (1470)
	1.0	6	272 (103)	8.33 (1.57)	6.50 (3.00, 7.00)	16.3 (7.20)	321 (110)	6760 (1150)
	3.0	6	777 (236)	26.0 (8.01)	6.00 (2.00, 10.0)	16.5 (3.01)	337 (119)	7700 (1850)
Japanese subjects with AD (Part C)	0.3	9	49.2 (14.3)	2.20 (0.689)	5.00 (2.00, 14.0)	12.6 (4.01)	408 (141)	7320 (3150)
	1.0	9	161 (25.1)	6.50 (1.57)	4.24 (2.00, 7.23)	13.2 (3.44)	368 (56.8)	6990 (2160)
	3.0	9	489 (196)	19.4 (5.85)	3.99 (3.01, 7.03)	14.6 (6.18)	459 (207)	8510 (2050)

Source: CIM001JP CSR Table 11.4.1.2-1 and CIM001JP CSR Appendix16.4 Table 1-2 and Table 4-2
Abbreviations: AD, atopic dermatitis; $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to infinity; CL/F, apparent clearance; C_{max}, maximum plasma concentration; n, number of patients meeting criteria; T_{max}, time to maximum concentration; $t_{1/2}$, half-life; V/F, apparent central volume of distribution

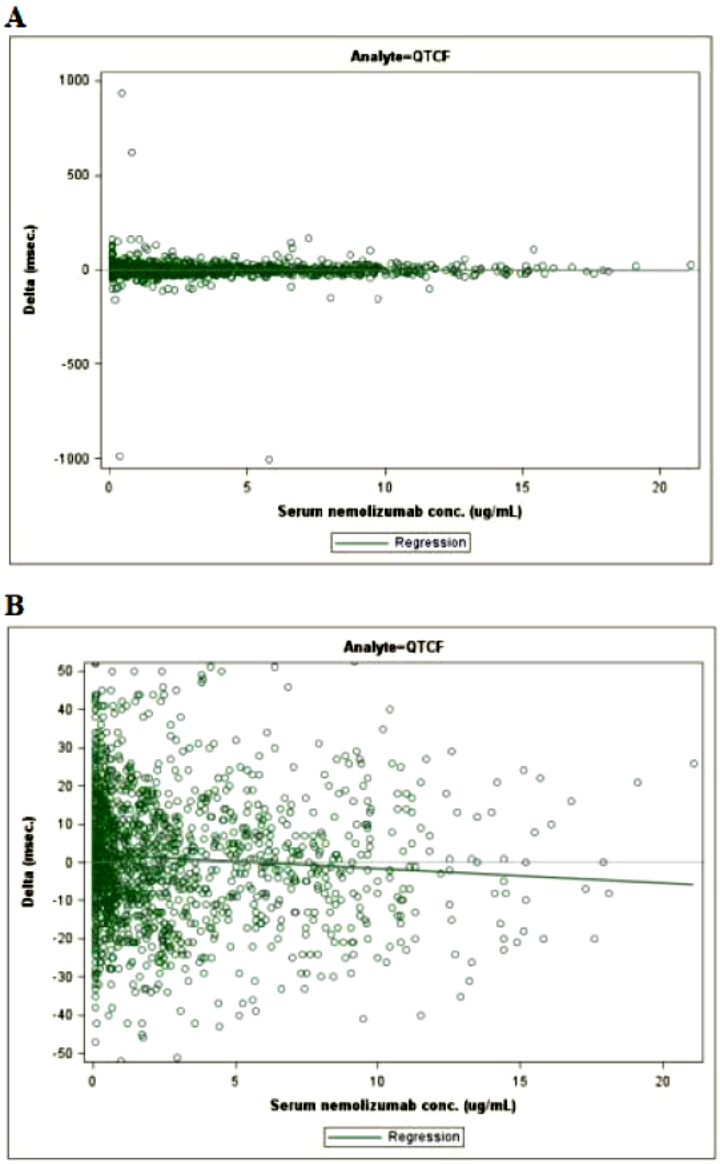
Healthy Japanese Adult Males and Healthy White Adult Males PK Comparison

Serum nemolizumab concentration-time courses in healthy Japanese and White adult males were similar. All of the 90% confidence intervals (CIs) for the geometric mean ratios of area under the concentration-time curve from time 0 extrapolated to infinity ($AUC_{0\text{-}inf}$), area under the concentration-time curve from time 0 to the time of the last quantifiable sample (AUC0-last), and maximum concentration (C_{max}) in healthy White adult males relative to healthy Japanese adult males included the value of 1, and the estimated ratios were close to 1. These results suggested that the PK of nemolizumab is similar among the healthy Japanese and White adult males.

Concentration-QT Analysis

An exposure-safety analysis was conducted assessing the correlation between nemolizumab concentrations and QTc (C-QT) values from 263 evaluable subjects enrolled in Study CIM003JG. Twelve-lead electrocardiograms (ECGs) were recorded at baseline and every 4 weeks for the first 6 months (Weeks 4, 8, 12, 12, 16, 20, and 24), and at Week 64 and at the follow-up visit. Figure 10 shows the results of the correlation analysis for QTcF. The slope of the correlation between systemic exposure and QTc values was not statistically significantly different from zero. In the clinical development program of nemolizumab, there was no evidence to suggest a cardiovascular safety concern associated with nemolizumab treatment in subjects with PN or AD. No clinically relevant changes of electrocardiogram (ECG) parameters have been observed, based on the evaluation of mean values, potentially clinically significant values, and AEs. No cardiac safety concerns have been observed, based on the centralized ECG evaluation by external cardiac ECG experts. Overall, the cardiovascular safety profile of nemolizumab has been adequately characterized and that additional designated studies, including a thorough QT study, are not required.

Figure 10. Correlation Between Nemolizumab Systemic Exposure and QTcF, Study CIM003JG



Source: CIM003JG CSR Section 16.1.12
Abbreviations: QTcF, qualification threshold corrected for heart rate

Study 201590 (Phase 1, Relative Bioavailability Bridging Study)

This study was a randomized, multicenter, open-label, single-dose, parallel-group study in healthy adult subjects (18 to 65 years) to assess the relative bioavailability of a 60-mg SC dose of nemolizumab when administered with a DCC- AI compared to a DCS. The 60-mg dose was administered as 2 successive SC injections of 30 mg (DCC-AI or DCS) in either abdomen, front upper thigh, or outer upper arm. The primary objective was to compare the rate and extent of absorption of a single dose of nemolizumab administered with DCC-AI (test) versus DCS (reference) under controlled conditions in healthy adult volunteers. The secondary objectives were to assess the safety and immunogenicity of nemolizumab following administration with DCC-AI or DCS in healthy adult subjects. The study duration was up to 16 weeks and consisted of an up to 28-day screening period and a 12-week PK evaluation period.

PK Results

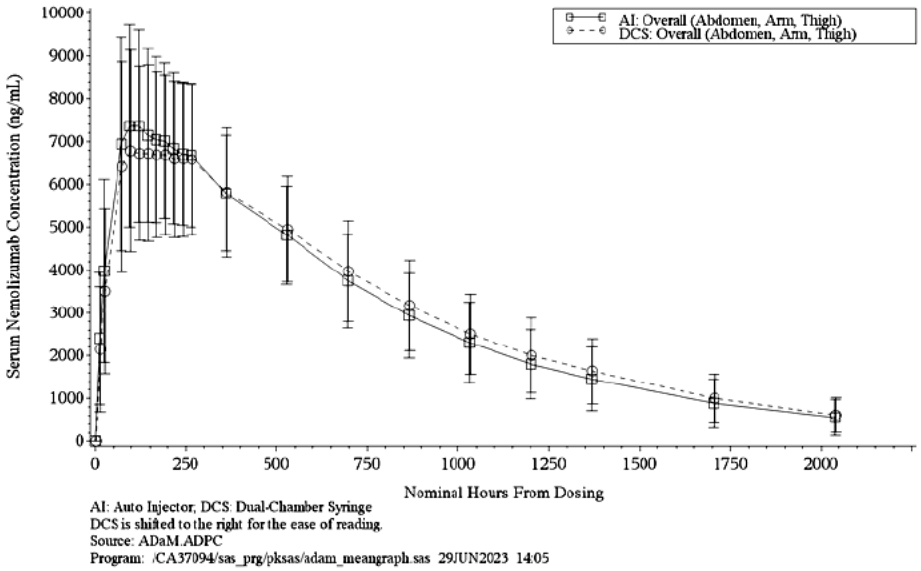
A total of 192 healthy subjects were randomized to receive nemolizumab: 96 by DCC-AI and 96 by DCS. After administration of nemolizumab 60 mg SC, the rate and extent of systemic exposure was similar for DCC-AI and DCS. Descriptive statistics for nemolizumab PK parameters in serum are provided in Table 34. Mean nemolizumab concentration-time profile following a single 60-mg SC dose via the DCC-AI and the DCS are presented in Figure 11.

Table 34. Serum Nemolizumab PK Parameters Following Administration of 60 mg SC Nemolizumab, Study 201590 (PK Population)

PK parameter (unit)	DCC-AI				DCS			
	Abdomen (N=32)	Arm (N=32)	Thigh (N=32)	Overall (N=96)	Abdomen (N=32)	Arm (N=32)	Thigh (N=32)	Overall (N=96)
$AUC_{0\text{-}4\ weeks}$ (µg•day/mL)	167±46.2[a]	144±31.3	160±31.7	157±37.9[b]	158±37.3	146±39.4	160±42.1	155±39.8
$AUC_{0\text{-}last}$ (µg•day/mL)	262±92.9	231±59.9	259±61.5	250±73.6	258±72.0	245±75.8	277±77.3	260±75.4
$AUC_{0\text{-}inf}$ (µg•day/mL)	290±93.9[a]	246±78.7	275±81.1	270±85.8	273±81.7	263±91.4	299±94.6	279±89.7
C_{max} (µg/mL)	8.47±3.00	7.29±1.83	8.23±1.89	8.00±2.34	7.73±1.99	7.05±2.36	7.74±2.54	7.51±2.31
T_{max} (day)	4.00 (1.00, 21.99)	5.97 (2.99, 21.98)	4.99 (2.96, 11.00)	4.99 (1.00, 21.99)	4.49 (2.96, 21.99)	7.48 (1.00, 22.00)	5.00 (2.98, 11.00)	5.99 (1.00, 22.00)
$t_{1/2}$ (day)	18.5±6.22[a]	18.1±5.76	17.3±5.90	18.0±5.91b	17.7±3.62	18.2±5.40	19.6±4.29	18.5±4.52
CL/F (L/day)	0.235±0.096[a]	0.263±0.067	0.235±0.063	0.244±0.077[b]	0.247±0.112	0.262±0.122	0.220±0.070	0.243±0.104
V/F (L)	5.83±2.08[a]	6.59±1.88	5.52±1.04	5.98±1.76b	5.96±1.69	6.34±1.79	5.94±1.22	6.08±1.58

Source: RD.06.SRE.201590 Table 9.
Abbreviations: $AUC_{0\text{-}inf}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-}last}$, area under the concentration-time curve from time 0 to last measured concentration; $AUC_{0\text{-}4\ weeks}$, area under the concentration-time curve from 0 to 4 weeks; CL/F, apparent clearance; C_{max}, maximum plasma concentration; DCC-AI, dual-chamber cartridge assembled with an autoinjector; DCS, dual chamber syringe; N, number of patients in treatment arm; PK, pharmacokinetic; T_{max}, time to maximum concentration; $t_{1/2}$, half-life; V/F, apparent central volume of distribution

Figure 11. Arithmetic Mean (SD) Serum Nemolizumab Concentration Versus Time Profiles Following Administration of 60 mg SC Nemolizumab Via DCC-AI or DCS, Study 201590 (PK Population)



Source: RD.06.SRE.201590 14.2.3.1.
Abbreviations: AI, auto injector; DCC-AI, dual-chamber cartridge assembled with an autoinjector; DCS, dual-chamber syringe

The percentage geometric least square mean ratios (GLSMRs) for C_{max} and for $AUC_{0\text{-inf}}$ were close to 100%; and the 90% CIs were within the no effect boundary of 80.00% to 125.00% (Table 35). The 90% CIs of the percentage GLSMRs for area under the concentration-time curve from time 0 to 4 weeks post-dose ($AUC_{0\text{-4 weeks}}$) and area under the concentration-time curve from time 0 to the time of the last quantifiable sample ($AUC_{0\text{-last}}$) were also within 80.00% to 125.00%. The DCC-AI and DCS also showed comparable elimination half-life ($t_{1/2}$), with a percentage GLSMR of 95.44% (90% CI: 89.50% to 101.78 %). For all the primary and secondary PK parameters, no significant difference was observed between the 3 injection sites (abdomen, arm, and thigh), with p-values >0.05.

Table 35. Statistical Comparison of Serum Nemolizumab Pharmacokinetic Parameters: DCC-AI (Test) Versus DCS (Reference), Study 201590 (PK Population)

Pharmacokinetic parameter (unit)	Geometric LSM DCC-AI (test)	n	Geometric LSM DCS (reference)	n	Geometric LSM mean ratio (%)	90% CI	Inter-subject CV%	Method-by-site interaction P-value	DCC-AI vs DCS P-value
$AUC_{0\text{-inf}}$ (µg•day/mL)	257.62	95	263.71	96	97.69	90.39 – 105.59	33.36	0.5238	0.6201
C_{max} (µg/mL)	7.596	96	7.173	96	105.90	98.01 – 114.41	33.29	0.9354	0.2225
$AUC_{0\text{-last}}$ (µg•day/mL)	229.55	96	248.26	96	92.46	81.95 – 104.32	53.99	0.8407	0.2845
$AUC_{0\text{-4 weeks}}$ (µg•day/mL)	151.81	95	149.29	96	101.69	95.33 – 108.48	27.52	0.9209	0.6683
$t_{1/2}$ (day)	17.18	95	18.00	96	95.44	89.50 – 101.78	27.38	0.1753	0.2321

Source: RD.06.SRE.201590 Table 14.2.1.5.
Abbreviations: $AUC_{0\text{-inf}}$, area under the concentration-time curve from time 0 to infinity; $AUC_{0\text{-last}}$, area under the concentration-time curve from time 0 to last measured concentration; $AUC_{0\text{-4 weeks}}$, area under the concentration-time curve from 0 to 4 weeks; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; DCC-AI, dual-chamber cartridge assembled with an autoinjector; DCS, dual chamber syringe; LSM, least squares mean; $t_{1/2}$, half-life

In the DCC-AI group, 2 of 95 subjects (2.1%) tested positive for ADAs at Day 85, with titers of 40 and 80; however, neither of these subjects had treatment-induced ADAs. In the DCS group, 8 of 96 subjects (8.3%) tested positive for ADAs at Day 85, with titers ranging from 10 to 20. Among these 96 subjects, 3 (3.1%) subjects had treatment-induced ADAs. During the entire study, no subject tested positive for neutralizing antidrug antibody (ADA) (Nab).

An OSIS inspection request was submitted for Study 201590 and OSIS determined not to inspect the sites and all of the sites will be issued a Decline to Inspect memo. For further details, see OSIS Inspection report in DARRTS dated July 12, 2024.

Study 115828 (Phase 2)

This was a randomized, placebo-controlled, double-blind, parallel-group, multicenter study to evaluate the safety and efficacy of nemolizumab in subjects with PN. A total of 70 adult subjects with moderate-to-severe PN for at least 6 months and severe pruritus were randomized in this study. Subjects were randomized in a 1:1 ratio to nemolizumab (N = 34) or placebo (N = 36). Each subject received SC injections of 0.5 mg/kg nemolizumab or matching placebo for 12 weeks. The nemolizumab serum concentration, ADA, and biomarkers (in blood, stratum corneum [D-Squame®], and skin) were assessed as described in Table 36.

Table 36. Schedule of Assessments, Study 115828

Assessment	Treatment period						Observation/ follow-up		ET
Week	Baseline	1	2	4	8	12	16	18	
PK blood	X	X	X	X	X	X	X	X	X
ADA blood	X			X	X	X	X	X	X
Blood biomarkers	X			X		X			
Stratum corneum biomarkers	X			X		X			
Skin biopsy biomarkers	X					X			

Source: RD.03.SPR.115828 Table 2.
Abbreviations: ADA, antidrug antibody; ET, early termination; PK, pharmacokinetic

Formulation

Nemolizumab was supplied as a lyophilized powder in single-dose vial for reconstitution with sterile water for injection (sWFI). Upon reconstitution with 1.3 mL of sWFI, the resulting solution contained 100 mg/mL nemolizumab that was administered by SC injection once every 4 weeks (Q4W). The solution containing 100 mg/mL nemolizumab was diluted with placebo reconstituted solution to reach the targeted study doses administered by SC injection Q4W.

PK Results

A mean ± standard deviation C_{max} of 3.8 ± 1.21 µg/mL was observed 8.8 ± 4 days post-injection. After multiple doses, nemolizumab mean C_{trough} increased from 2.0 ± 0.75 µg/mL at Week 4 to 2.7 ± 1.01 µg/mL at Week 8 and to 3.3 ± 1.46 µg/mL at the end of the treatment period at Week 12. After the last dose, nemolizumab was eliminated from serum with a mean $t_{1/2}$ of 20.7 ± 6.11 days. After 3 injections of nemolizumab at 0.5 mg/kg SC Q4W, limited accumulation of nemolizumab was observed, as assessed by nemolizumab C_{trough}. The ratio of the mean nemolizumab C_{trough} at Week 12 (3.3 µg/mL) versus Week 4 (2.0 µg/mL) was 1.65. Nemolizumab PK parameters are summarized for all subjects receiving active treatment in Table 37.

Table 37. Pharmacokinetic Parameters, Study 115828 (Pharmacokinetic Population)

Period	PK parameter	n	Arithmetic mean (SD)	Minimum, maximum
0 to Week 4	C_{max} (µg/mL)	34	3.8 (1.21)	1, 7
	T_{max} (days)	34	8.8 (4.38)	6, 29
	AUC_{0-4w} (µg•day/mL)	33	73.2 (20.39)	32, 132
Week 4	C_{trough} (µg/mL)	33	2.0 (0.75)	0, 4
Week 8	C_{trough} (µg/mL)	32	2.7 (1.01)	1, 5
Week 12	C_{trough} (µg/mL)	32	3.3 (1.46)	0, 8
Week 12 to Week 18	AUC_{0-t} (µg•day/mL)	31	163.2 (68.73)	61, 372
	AUC_{0-inf} (µg•day/mL)	32	335.7 (142.26)	99, 647
	$t_{1/2}$ (days)	29	20.7 (6.11)	11, 33

Source: RD.03.SRE.115828 Table 14.3.7.1.
Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time 0 to infinity; AUC_{0-t}, area under the concentration-time curve from time 0 to last quantifiable concentration; AUC_{0-4w}, area under the concentration-time curve from 0 to 4 weeks; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; n, number of patients meeting criteria; PK, pharmacokinetic; T_{max}, time to maximum concentration; $t_{1/2}$, half-life

Study 202685 (Pivotal Phase 3)

This was a phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group study designed to evaluate the efficacy and safety of nemolizumab in subjects with PN. A total of 286 subjects with PN were randomized 2:1 to receive either nemolizumab (n = 190) or placebo (n = 96), stratified by study center and body weight (<90 kg versus ≥90 kg). The majority of subjects (64.3%) weighed <90 kg and were randomized to receive either 30 mg nemolizumab (with a 60-mg loading dose at Baseline) or placebo Q4W; 35.7% of subjects weighed ≥90 kg at Baseline and were randomized to receive either 60 mg nemolizumab or placebo Q4W (no loading dose at Baseline). The nemolizumab serum concentration, ADA, and biomarkers (in blood, stratum corneum [D-Squame], and skin) were assessed according to the schedule of assessment as shown in Table 38.

Table 38. Schedule of Assessments, Study 202685

Assessment	Treatment						Follow-up	ET
Week	Baseline	4	8	12	16	24	32	
PK blood	X	X	X	X	X	X	X	X
ADA blood	X		X		X	X		X
Blood biomarkers	X		X		X	X		
Stratum corneum biomarkers	X				X			
Skin biopsy biomarkers	X				X			

Source: RD.06.SPR.202685 Table 5
Abbreviations: ADA, anti-drug antibodies; ET, early termination; PK, pharmacokinetic

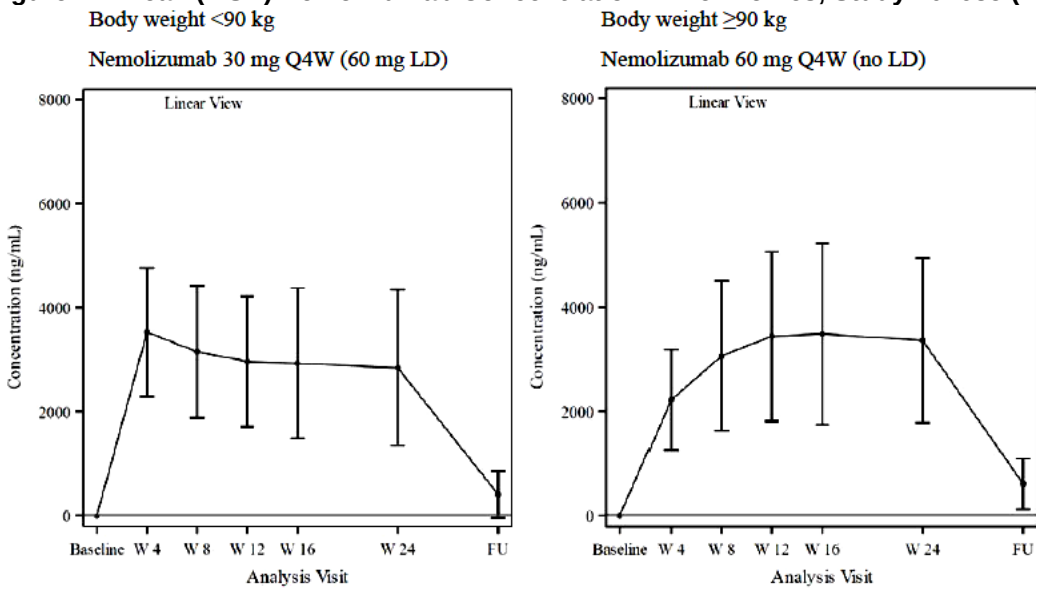
Formulation

Nemolizumab was supplied as a lyophilized powder in a DCS for solution for injection (b) (4) which held the lyophilized nemolizumab or placebo and the sWFI separately.

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are displayed in Figure 12, and nemolizumab C_{trough} values are summarized in Table 39. Subjects with a body weight <90 kg receiving nemolizumab 30 mg Q4W with a 60-mg loading dose reached steady state by Week 4. The arithmetic mean (± SD) C_{trough} values were 3.56 ± 1.19 µg/mL and 2.90 ± 1.46 µg/mL at Week 4 and Week 24, respectively. Subjects with a body weight ≥90 kg receiving nemolizumab 60 mg Q4W reached steady state by Week 12. The arithmetic mean (± SD) C_{trough} values increased from 2.22 ± 0.964 µg/mL at Week 4 to 3.36 ± 1.58 µg/mL at Week 24.

Figure 12. Mean (± SD) Nemolizumab Concentration-Time Profiles, Study 202685 (PK Population)



Source: RD.06.SRE.202685 Figure 14.2.4.2.
Abbreviations: FU, follow-up; LD, loading dose; Q4W, every 4 weeks; W, week

Table 39. Mean (± SD) Nemolizumab Trough Concentrations (µg/mL) by Dosing Regimen, Study 202685

Visit	Subject body weight <90 kg 30 mg Q4W (60 mg LD) N=112	Subject body weight ≥90 kg 60 mg Q4W N=71
Week 4	3.56±1.19	2.22±0.964
Week 8	3.15±1.27	3.07±1.44
Week 12	2.96±1.25	3.44±1.63
Week 16	2.96±1.42	3.48±1.74
Week 24	2.90±1.46	3.36±1.58

Source: RD.06.SRE.202685 Table 14.2.4.1.
Abbreviations: LD, loading dose; N, number of patients in treatment arm; Q4W, every 4 weeks

After 6 injections of nemolizumab 60 mg SC Q4W, limited nemolizumab accumulation was observed, as assessed by nemolizumab C_{trough}. The ratio of the mean nemolizumab C_{trough} at Week 24 (3.36 µg/mL) versus Week 4 (2.22 µg/mL) was 1.5. The nemolizumab C_{trough} values were comparable for the last 3 doses, indicating that steady state was reached by Week 12. Conversely, for subjects with body weight <90 kg, receiving nemolizumab 30 mg SC Q4W with

a 60 mg SC loading dose, the ratio of the mean nemolizumab C_{trough} at Week 24 (2.90 µg/mL) versus Week 4 (3.56 µg/mL) was 0.81. The accumulation ratio below 1 confirmed that steady-state was reached by Week 4.

No loading dose is proposed for subjects with bodyweight ≥90 kg because the 60 mg dose was sufficient to achieve similar steady-state nemolizumab concentrations to the 30 mg dose (with 60-mg loading dose) after the second dose, i.e., Week 8.

Study 203065 (Pivotal Phase 3)

This was a phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group trial designed to evaluate the efficacy and safety of nemolizumab in subjects with PN. A total of 274 subjects with PN were randomized 2:1 to receive either nemolizumab (n=183) or placebo (n=91). The majority of subjects (72.6%) weighed <90 kg and were randomized to receive either 30 mg nemolizumab (with 60-mg loading dose at baseline) or placebo Q4W; 27.4% of subjects weighed ≥90 kg at baseline and were randomized to receive either 60 mg nemolizumab or placebo Q4W. Subjects were treated with a Q4W dose regimen for 16 weeks, with the last dose given at Week 12. The nemolizumab serum concentration, ADA, and biomarkers (in blood, stratum corneum [D-Squame], and skin) were assessed according to the schedule of assessment as shown in Table 40.

Table 40. Schedule of Assessments, Study 203065

Assessment	Treatment period					Follow-up	
Week	Baseline	4	8	12	16	24	ET
PK blood	X	X	X	X	X	X	X
ADA blood	X		X		X		X
Blood biomarkers	X		X		X		
Stratum corneum biomarkers	X				X		
Skin biopsy biomarkers	X				X		

Source: RD.06.SPR.203065 Table 5.
Abbreviations: ADA, antidrug antibody; ET, early termination; PK, pharmacokinetics

Formulation

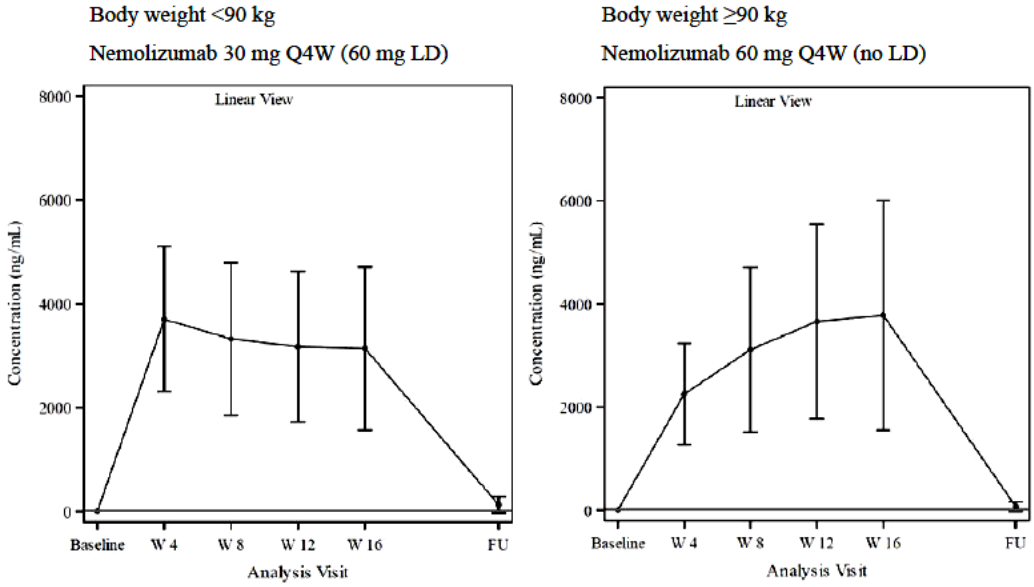
Nemolizumab was supplied as a lyophilized powder in a DCS for solution for injection (b) (4) which held the lyophilized nemolizumab or placebo and the sWFI separately.

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are displayed in Figure 13, and nemolizumab C_{trough} values are summarized in Table 41. Subjects with a body weight <90 kg receiving nemolizumab 30 mg Q4W with a 60-mg loading dose reached steady state by Week 4. The arithmetic mean (± SD) C_{trough} values were 3.73 ± 1.36 µg/mL and 3.19 ± 1.53 µg/mL at Week 4 and Week 16, respectively.

Subjects with a body weight ≥90 kg receiving nemolizumab 60 mg Q4W without a loading dose reached steady state at approximately Week 12 to Week 16. The arithmetic mean (± SD) C_{trough} values increased from 2.25 ± 0.981 µg/mL at Week 4 to 3.78 ± 2.23 µg/mL at Week 16.

Figure 13. Mean (± SD) Nemolizumab Concentration-Time Profiles, Study 203065 (PK Population)



FU=follow-up; LD=loading dose; Q4W=once every 4 weeks; SD=standard deviation; W=week
Source: RD.06.SRE.203065 Figure 14.2.4.2
Abbreviations: FU, follow-up; LD, loading dose; Q4W, every 4 weeks; W, week

Table 41. Mean Nemolizumab Trough Concentrations (µg/mL) by Dosing Regimen, Study 203265

Visit	Subject body weight <90 kg 30 mg Q4W (60 mg LD) N=129	Subject body weight ≥90 kg 60 mg Q4W N=51
Week 4	3.73±1.36	2.25±0.981
Week 8	3.32±1.48	3.11±1.60
Week 12	3.20±1.43	3.67±1.89
Week 16	3.19±1.53	3.78±2.23

Source: RD.06.SRE.203065 Table 14.2.4.1.
Abbreviations: LD, loading dose; N, number of patients in treatment arm; Q4W, every 4 weeks

After 5 injections of nemolizumab 60 mg SC Q4W, limited nemolizumab accumulation was observed, as assessed by nemolizumab C_{trough}. The ratio of the mean nemolizumab C_{trough} at Week 16 (3.78 µg/mL) versus Week 4 (2.25 µg/mL) was 1.7. The nemolizumab C_{trough} values were comparable for the last 2 doses, indicating that steady state was reached by Week 12. Conversely, for subjects with body weight <90 kg, the ratio of the mean nemolizumab C_{trough} at Week 16 (3.19 µg/mL) versus Week 4 (3.73 µg/mL) was 0.86. The accumulation ratio below 1 confirmed that steady state is reached by Week 4.

No loading dose is proposed for subjects with bodyweight ≥90 kg because the 60 mg dose was sufficient to achieve similar steady-state nemolizumab concentrations to the 30 mg dose (with 60-mg loading dose) after the second dose, i.e., Week 8.

Study 202699 (Long-Term Extension)

This is an ongoing prospective, multicenter, LTE study in adult subjects who had been enrolled in the prior nemolizumab PN phase 2a study (Study 115828) or phase 3 pivotal trials (Studies 202685 or 203065) to evaluate the safety and efficacy of nemolizumab in subjects with PN.

Subjects' participation in the study was up to 196 weeks. The study consisted of an up to 4-week screening period, up to a 184-week treatment period, and an 8-week follow-up period (12 weeks after their last study drug injection). Subjects weighing <90 kg at Baseline received open-label 30 mg nemolizumab (with a 60-mg loading dose at Baseline) Q4W. Subjects weighing ≥90 kg at Baseline received 60 mg nemolizumab (two 30-mg injections; no loading dose) Q4W. For all enrolled subjects, beginning at Week 56, nemolizumab dosage was to be adjusted every 6 months in case of body weight change above or below the 90-kg threshold at 2 consecutive designated visits.

The nemolizumab serum concentration and ADA were assessed according to the schedule of assessment as shown in Table 42.

Table 42. Schedule of Assessments, Study 202699

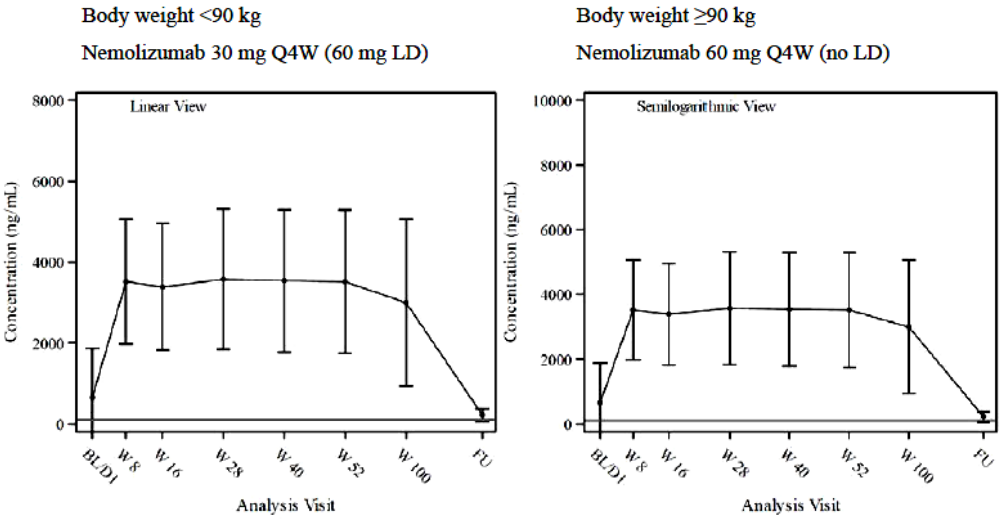
Assessment	Treatment Period									
Week	Baseline	8	16	28	40	52	100	152	184	ET
PK blood	X	X	X	X	X	X	X	X	X	X
ADA blood	X		X	X		X	X	X	X	X

Source: RD.06.SPR.202699 Table 10 to RD.06.SPR.202699Table 13.
Abbreviations: ADA, antidrug antibody; ET, early termination; PK, pharmacokinetic

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are displayed in Figure 14, and nemolizumab C_{trough} values summarized in Table 43. Baseline nemolizumab serum concentrations reported in Table 42 only included subjects who had a separate Baseline Visit in the LTE study. For subjects who rolled over directly from the lead-in study into the LTE (i.e., on the same day), final study assessments from the lead-in studies were used for the LTE study screening. The arithmetic mean (± SD) C_{trough} values were 3.51 ± 1.55 µg/mL and 2.99 ± 2.06 µg/mL at Week 8 and Week 100 (C_{trough} ratio: 0.9), respectively, for subjects with a body weight <90 kg receiving nemolizumab 30 mg Q4W with a 60-mg loading dose. The arithmetic mean (± SD) C_{trough} values were 3.98 ± 1.91 µg/mL and 4.30 ± 1.46 µg/mL at Week 8 and Week 100 (C_{trough} ratio: 1.1), respectively, for subjects with a body weight ≥90 kg receiving nemolizumab 60 mg Q4W.

Figure 14. Mean (± SD) Nemolizumab Concentration-Time Profiles, Study 202699 (PK Population)



Source: RD.06.SRE.202699 Figure 14.2.2.2.
Note: The follow-up visit was conducted 8 weeks after completing the treatment period and/or 12 weeks after the last study drug injection for all subjects. Twelve weeks corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed SC Q4W.
Abbreviations: FU, follow-up; LD, loading dose; Q4W, every 4 weeks; W, week

Table 43. Mean Nemolizumab Trough Concentrations (µg/mL) by Dosing Regimen, Study 202699

Visit	n	Subject body weight <90 kg 30 mg Q4W (60 mg LD) N=340	n	Subject body weight ≥90 kg 60 mg Q4W N=150
Baseline	31	1.54±1.46	12	1.50±1.39
Week 8	318	3.51±1.55	142	3.98±1.91
Week 16	305	3.40±1.56	127	4.29±2.01
Week 28	270	3.58±1.73	110	4.28±2.01
Week 40	236	3.58±1.72	99	4.33±1.99
Week 52	202	3.51±1.77	90	4.31±1.84
Week 100	5	2.99±2.06	3	4.30±1.46

Source: RD.06.SRE.202699 Table 14.2.2.1.
Abbreviations: LD, loading dose; N, number of patients in treatment arm; n, number of patients meeting criteria; Q4W, every 4 weeks

Overall, nemolizumab serum concentrations remained stable based on interim analysis of available data up to 100 weeks, regardless of the subject's body weight range (i.e., <90 kg or ≥90 kg). This suggests that, once steady state had been achieved, no further accumulation occurred over a longer treatment duration, with accumulation ratios ranging from 0.9 to 1.1. When steady state was reached, the C_{trough} for subjects with body weight ≥90 kg (receiving 60 mg Q4W) was approximately 20% higher than the C_{trough} for subjects with body weight <90 kg (receiving 30 mg Q4W).

Summary of Pharmacokinetics

Drug absorption

Following a single SC dose of 60 mg, nemolizumab mean observed C_{max} (SD) was 7.5 ± 2.31 µg/mL using the DCS (Study 201590). The nemolizumab observed T_{max} (time to maximum

concentration) was 6 days (range: 1 to 22 days) after SC administration. Similar PK parameters were obtained with the DCC-AI.

Distribution

Based on the PopPK analysis, the estimated V/F was 7.67 L after SC administration.

Elimination

Based on the PopPK analysis, the estimated apparent clearance (CL/F) was 0.263 L/day after SC administration, while the mean $t_{1/2}$ was approximately 18.9 ± 4.96 days; this value was consistent with the value calculated based on actual data obtained in clinical studies.

Drug Metabolism

The metabolic pathway of nemolizumab has not been characterized. As a humanized mAb, nemolizumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Excretion

The excretion of nemolizumab has not been studied. Nemolizumab is a humanized mAb of the IgG2 subclass and has a molecular weight of approximately 147 kDa; therefore, nemolizumab is unlikely to be filtered by kidney or excreted in urine. Nonspecific (not target-mediated) elimination by the reticuloendothelial system is expected.

Hepatic Impairment

Hepatic impairment was not identified as a clinically relevant predictor of nemolizumab PK. 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.

Renal Impairment

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.

Disease State

No difference was identified in nemolizumab PK profiles between subjects with AD and subjects with PN, thus confirming that the type of disease does not impact the nemolizumab PK profile.

Body Weight

Body weight was identified as a significant covariate on nemolizumab exposure. The exposure of nemolizumab decreases with increasing body weight. Steady-state systemic C_{trough} exposure was predicted to be 1.7-fold lower between the upper body weight quartile (87 to 181 kg: 1.72 μg/mL) and the lower body weight quartile (31 to 62 kg: 2.92 μg/mL). The PK/PD simulations demonstrated that the variability in systemic exposure due to body weight had no clinically

meaningful impact on PP NRS responders at Week 16. However, the IGA simulations showed a lower IGA success for subjects with body weight ≥90 kg when treated with a non-adjusted dose (30 mg Q4W regimen with 60-mg loading dose). Therefore, the proposed dosing regimen is based on a body weight cut-off of 90 kg (an initial dose of 60 mg followed by 30 mg given Q4W for patients <90 kg and an initial dose of 60 mg dose followed by 60 mg given Q4W for patients weighing ≥90 kg) to achieve matching systemic exposure and similar efficacy response (IGA) in subjects with body weight <90 kg and ≥90 kg.

Dose Rationale

The selection of the dosing regimen to be tested in the phase 3 trials was based on the results of the phase 2a study conducted in 70 subjects with PN (Study 115828) along with modeling and simulation analyses. Subjects enrolled in the phase 2a study received a 0.5-mg/kg weight-based dose administered Q4W for 12 weeks. This 0.5-mg/kg dose successfully demonstrated efficacy in the treatment of PN with an acceptable safety profile. Data from the phase 2a study were used to refine population PK and PK/PD models. Population PK simulations showed that the 30-mg dose (60-mg loading dose) was expected to achieve similar steady state systemic exposure and efficacy as the 0.5 mg/kg dose and was therefore selected for the pivotal phase 3 trials. However, a significant impact of body weight was predicted on the nemolizumab PK profile, with increasing body weight resulting in a decrease in the nemolizumab systemic exposure for subjects receiving a flat dose. As the population PK analysis showed an impact of body weight on nemolizumab PK profile, the effect of body weight on efficacy was further assessed using PK/PD simulations. The PK/PD model for PP NRS predicted that the lower systemic exposure in higher body weight subjects would not impact efficacy as measured by the PP NRS responder rate. Conversely, the PK/PD model for IGA score suggested that lower systemic exposure may result in lower efficacy as measured by the IGA success. Based on the above considerations, a body weight tiered dose adjustment was selected in the pivotal phase 3 trials, with a 60-mg loading dose followed by 30 mg Q4W for subjects with body weight <90 kg and a 60-mg dose administered Q4W for subjects with body weight ≥90 kg.

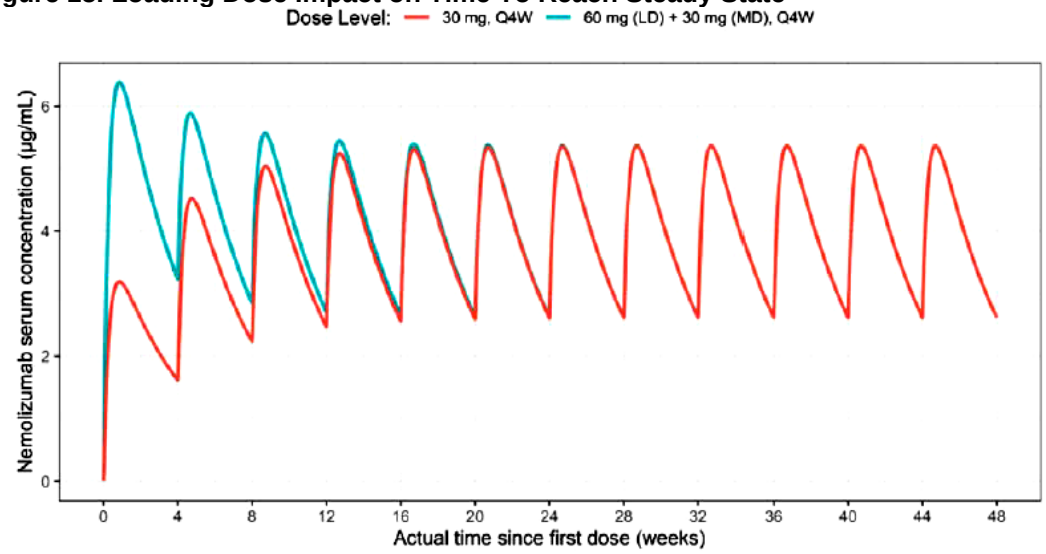
The proposed dose for patients with PN is an initial loading dose of 60 mg, followed by 30 mg given SC Q4W for patients with a body weight <90 kg or nemolizumab 60 mg SC Q4W (no loading dose) for patients with body weight ≥90 kg. The efficacy of nemolizumab for the treatment of PN following this dosing regimen was established in 2 pivotal phase 3 studies.

After the completion of the phase 3 studies, the initial population PK model was refined based on pooled data from the PN and the AD clinical development programs. The PK/PD models for IGA and weekly average PP NRS were developed based only on data from subjects with PN enrolled in phase 2a and pivotal phase 3 studies. The exposure of nemolizumab decreases with increasing body weight. Steady-state systemic C_{trough} exposure was predicted to be 1.7-fold lower between the upper body weight quartile (87 to 181 kg: 1.72 μg/mL) and the lower body weight quartile (31 to 62 kg: 2.92 μg/mL). As the PopPK analysis showed an impact of body weight on nemolizumab PK profile, the effect of body weight on efficacy was further assessed using the PK/PD simulations. PK/PD simulations based on the 2 clinical primary endpoints of the phase 3 studies (IGA success and weekly average PP NRS responders at Week 16) demonstrated that the variability in systemic exposure due to body weight had no clinically meaningful impact on weekly average PP NRS responders at Week 16. However, a lower IGA success was predicted for subjects with body weight ≥90 kg when treated with a non-adjusted dose (30 mg Q4W

regimen with 60 mg loading dose). Therefore, the proposed dosing regimens were selected to achieve matching systemic exposure and similar efficacy response in subjects with body weight <90 kg and ≥90 kg.

The population PK analysis also confirmed the adequacy of the 60-mg loading dose to rapidly reach the desired steady-state concentrations in subjects with PN with body weight <90 kg. Steady state was reached by Week 4 with a loading dose and by Week 12 without a loading dose. Without a loading dose, accumulation of nemolizumab following multiple dosing was predicted to be 1.6-fold to reach the desired steady-state conditions (Figure 15). No loading dose is proposed for subjects with PN and a body weight ≥90 kg, as the 60 mg dose was sufficient to achieve similar steady-state nemolizumab concentrations to the 30 mg dose (with 60-mg loading dose) after the second dose, i.e., Week 8.

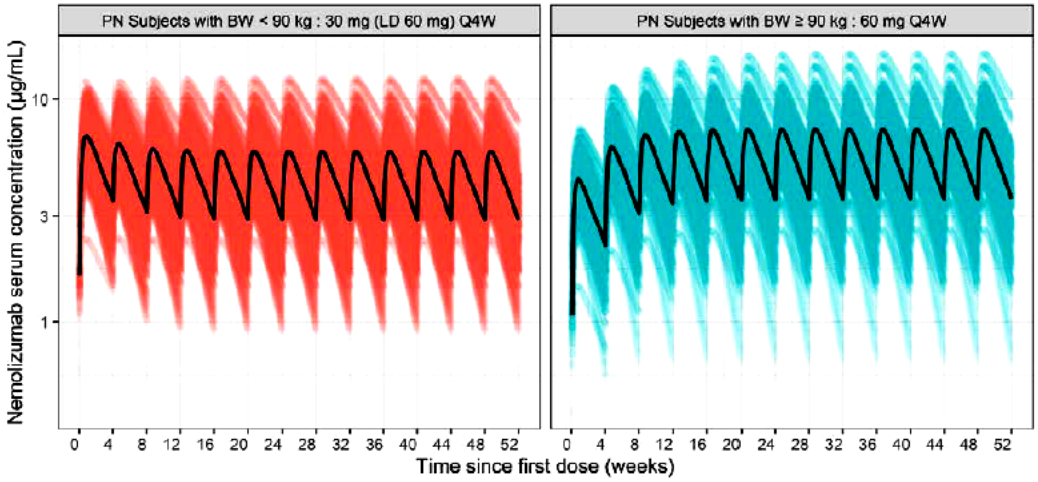
Figure 15. Loading Dose Impact on Time To Reach Steady State



Source: Report GALD-PMX-NEMOLIZUMAB-1787–POPPK Figure 26-A.
Abbreviations: LD, loading dose; MD, maintenance dose; Q4W, every 4 weeks

At steady state, the population PK mean (± SD) nemolizumab C_{trough} was 3.04 ± 1.23 µg/mL for nemolizumab 30 mg Q4W in subjects with body weight <90 kg; and 3.66 ± 1.63 µg/mL for 60 mg Q4W in subjects with body weight ≥90 kg (Figure 16).

Figure 16. Model-Predicted Nemolizumab Concentration-Time Profiles After 30 mg Q4W (LD 60 mg) or 60 mg Q4W



Source: Summary of Clinical Pharmacology Studies, 2.7.2, Figure 23.
Abbreviations: BW, body weight; PN, prurigo nodularis; Q4W, every 4 weeks

In addition, the analyses of exposure-safety relationships did not show evidence for any increased safety events with higher nemolizumab concentrations. Anti-drug antibodies to nemolizumab were not associated with clinically relevant changes in serum nemolizumab concentrations, reduced efficacy, or safety findings. Overall, the clinical PK results, PK/PD, and exposure-safety outcomes provided supportive evidence for the effectiveness and safety of the selected doses and the proposed dosing regimens in subjects with PN. The proposed dose adjustment based on body weight was adequate to achieve therapeutic exposure and clinical benefit in the overall population.

Overall Summary

The clinical pharmacology assessment of nemolizumab was based on clinical data collected in subjects treated with nemolizumab. These data were assessed descriptively as well as using PopPK, PK/PD (efficacy), and exposure-response (safety) approaches. Body weight was identified as the only clinically meaningful covariate on nemolizumab exposure. No clinically relevant impact of other intrinsic factors was identified, including disease state (PN or AD), race, sex, age, renal or hepatic impairment, or immunogenicity. PK/PD models were developed to characterize the relationship between nemolizumab concentrations and efficacy assessments over time (IGA and PP NRS). The analyses of exposure-safety relationships did not show evidence for increased safety events (incidence of eczematous reactions and headache, newly diagnosed asthma or worsening of asthma or between nemolizumab exposure and peripheral or facial edema) with increased nemolizumab exposure. PK/PD simulations of clinical endpoints at Week 16 showed a similar efficacy response in both body weight groups (<90 kg and ≥90kg) when the dose was adjusted according to body weight with a cut-off of 90 kg. Overall, the clinical pharmacology data, including supportive modeling and simulations for PK, efficacy, and safety outcomes, provide support for proposed dosing regimens in subjects with PN, with no dose adjustment necessary based on patients' intrinsic factors other than body weight. Based on Clinical Pharmacology review, the proposed dosing regimen is acceptable for the treatment of PN.

14.3. Bioanalytical Method Validation and Performance

Assay for the *Determination of Nemolizumab Concentrations*

The validation of nemolizumab quantification in serum samples followed a stepwise approach, starting with healthy subjects, then subjects with AD, and finally subjects with PN. Three bioanalytical methods were developed and validated for the measurement of serum nemolizumab concentrations to characterize its PK profile:

- Nemolizumab serum concentrations were measured using a validated cell-based assay method in the first-in-human clinical study (Study CIM001JP).
- In all studies after Study CIM001JP, nemolizumab serum concentrations were only measured using validated ELISA methods. An ELISA method was also used to analyze samples from Study CIM001JP, and a comparison with the cell-based assay was performed.
- The ELISA method was transferred to a second bioanalytical laboratory and validated for the phase 3 PN studies and for the PK bridging study. A cross-validation assessment was also performed to ensure analysis consistency between the bioanalytical laboratories.

Analytical method descriptions, method life cycles, and the performance of methods for the ELISA assay used in the determination of nemolizumab concentrations are presented in Table 44. The ELISA methods were developed and validated for the measurement of nemolizumab concentrations, first by (b) (4). (PBC036-112 and PBC998-274) and then by (b) (4). (197090AVKX). The ELISA method employed a microplate coated with recombinant human IL-31RA to bind to nemolizumab. The captured nemolizumab was detected using a rabbit anti-nemolizumab antibody followed by a horseradish peroxidase (HRP)-conjugated goat anti-rabbit IgG. The bound complex was visualized by addition of 2,2'-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) substrate solution catalyzed by HRP. The luminal-based substrate (ABTS) specific for peroxidase was added to achieve a signal intensity that was proportional to the concentration of nemolizumab. The range of the calibration curve for quantification was from 100 to 6400 ng/mL.

Table 44. Summary Method Performance (Nemolizumab Pharmacokinetics [ELISA], PBC036-112)

Bioanalytical method validation report name, amendments, and hyperlinks	Validation of an Immunoassay Method for the Measurement of CIM331 in Human Serum Method Validation Report PBC036-112 Addendum: PBC036-113, PBC036-198 Partial Validation Report PBC998-274		
Method description	ELISA. Serum sample, rabbit ADA and HRP conjugated goat anti-rabbit IgG were dispensed into a plate with recombinant human IL-31RA previously immobilized, and after adding the substrate, the absorbance was measured.		
Materials used for standard calibration curve and concentration	Nemolizumab, Lot No. SC1101, Chugai Pharmaceutical Co., Ltd. 100, 200, 400, 800, 1600, 3200 and 6400 ng/mL		
Validated assay range	100 to 6400 ng/mL		
Material used for QCs and concentration	200, 800, and 3200 ng/mL		
Minimum required dilutions	500		
Source and lot of reagents	Recombinant human IL-31RA (b) (4) Recombinant human IL-31 (b) (4) Anti-nemolizumab antibody (Chugai Pharmaceutical Co., Ltd.) Lot No. S001F18 HRP conjugate goat anti-rabbit IgG (H+L chain specific) (b) (4) (b) (4) ABTS solution (b) (4)		
Regression model and weighting	4-parameter logistic curve fit type (absorbance: log, concentration: linear) $Y = b + (a - b)/ (1 + (X c)^{d})$ X: Analyte concentration Y: Response a: Absorbance signal at zero concentration b: Absorbance signal at infinite concentration c: The 1/concentration corresponding to 50% specific binding d: Slope factor		
Validation parameters	**Method validation summary**		**Source location**
Standard calibration curve performance during accuracy and precision runs	Number of standard calibrators from LLOQ to ULOQ	7	Report Number, Section and Table 1
	Cumulative accuracy (%bias) from LLOQ to ULOQ	-3.1% to 6.3%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤3.1%	
Performance of QCs during accuracy and precision runs	**Cumulative accuracy (%bias) in 3 QC levels**	-10% to 15.0%	Report Number Table 1, Table 5, and Table 18
	Interbatch %CV	≤8.2%	
	Total error	NR	

Continued

Table 49, continued

Selectivity and matrix effect	Selectivity for nemolizumab with respect to endogenous compounds and matrix effect were considered acceptable in 10 of 10 lots of individual human serum (5 male lots and 5 female lots) tested. Accuracy (%bias): ≤-6.5% IL-31R: Bias: 72.5% to 114.5% in low concentration (IL-31R spiked concentration: 0, 10 and 100 ng/mL), BLQ (spiked concentration at 1000 ng/mL) Bias: 61.9% to 94.4% in high concentration (IL-31R spiked concentration: 0, 10, 100 and 1000 ng/mL) IL-31: Bias: 105.5% to 106.5% in low concentration (IL-31 spiked concentration: 0, 10, 100, and 1000 pg/mL) Bias: 92.2% to 97.8% in high concentration (IL-31 spiked concentration: 0, 10, 100, and 1000 pg/mL)	PBC036-112 Section 15 and Table 3 Section 15 and Table 7 Section 15 and Table 8
Dilution reproducibility	Maximum validated dilution is 10000	PBC036-112 Section 15 and Table 6
Interference and specificity	Nemolizumab concentration was BLQ (<100 ng/mL) in all zero samples	PBC036-112 Section 12.3
Hemolysis effect	NR	NR
Lipemic effect	NR	NR
Dilution linearity and hook effect	NR	NR
Bench-top/process stability	Nemolizumab was stable for 72 hours in human serum at room temperature	PBC036-198 Section 1.2
Freeze-thaw stability	Freeze-thaw stability was demonstrated for 4 freeze-thaw cycles at -20°C and 5 at -70°C or below for both low and high concentration stability samples	PBC036-112 Section 15 and Table 11 Section 15 and Table 12
Long-term storage	Up to 904 days at -70°C or below	PBC036-198 Section 1.2
Parallelism	NR	NR
Carryover	NR	NR

Continued

Table 49, continued

Method performance in clinical Study CIM001JP Bioanalytical report: PBC036-118		
Assay passing rate	100% of runs met acceptance criteria	PBC036-118 Table 8
Standard curve performance	Cumulative accuracy (%bias): -10.3% to 14.0% Cumulative precision (%CV): NR	PBC036-118 Table 4
QC performance	Cumulative accuracy (%bias): -26.5% to 20.6% Cumulative precision (%CV): NR	PBC036-118 Table 7
Method reproducibility	Approximately 10% of all clinical samples were selected as ISR samples. Incurred sample reanalysis samples were selected in clinical samples in all steps (except for steps A-1 and A-2) at concentration of at least 3 times greater than the LLOQ and the C_{max}. Difference was -30.8 to 37.6%. Difference of 203 samples out of 210 was within ±30%.	PBC036-118 Section 11.15, Section 15.3, and Table 3
Study sample analysis stability	All samples were analyzed within the determined stability period (904 days)	PBC036-118 Section 11.1.3
Standard calibration curve performance during accuracy and precision	All accepted.	
Method performance in clinical Study CIM003JG Bioanalytical report: PBC036-149		
Assay passing rate	194 of 195 runs (99.5%) met acceptance criteria	PBC036-149 Table 10
Standard curve performance	Cumulative accuracy (%bias): -11.0% to 14.0% Cumulative precision (%CV): NR	PBC036-149 Table 4
QC performance	Cumulative accuracy (%bias): -25.5% to 34.0% Cumulative precision (%CV): ≤8.8%	PBC036-149 Table 7 and Table 8
Method reproducibility	Approximately 10% of all clinical samples were selected as ISR samples. Incurred sample reanalysis samples were selected in clinical samples at concentration of at least 3 times greater than the LLOQ and the C_{max}. Difference was -33.9 to 37.2%. Difference of 371 out of 382 samples was within ±30%.	PBC036-149 Section 16.3 and Table 3
Study sample analysis stability	All samples were analyzed within the determined stability period (904 days)	PBC036-149 Section 12.1.3, Section 12.5.2, and Section 16.5
Standard calibration curve performance during accuracy and precision	All calibrators in accepted analysis runs were acceptable.	

Continued

Table 49, continued

Method performance in clinical Study 115828 Bioanalytical report: PBC423-002		
Assay passing rate	NR	NA
Standard curve performance	Cumulative accuracy (%bias): -12.4% to 9.1% Cumulative precision (%CV): NR	PBC423-002 Table 3
QC performance	Cumulative accuracy (%bias): -16.3% to 29.4% Cumulative precision (%CV): NR	PBC423-002 Table 5
Method reproducibility	10% of all clinical samples were selected as ISR samples. ISR samples were selected in clinical samples at concentration of at least 3 times greater than the LLOQ. Difference of 50 out of 56 samples was within ±30%.	PBC423-002 Section 12.10 and Table 6
Study sample analysis stability	All samples were analyzed within the determined stability period (904 days)	PBC423-002 Section11.1.3
Standard calibration curve performance during accuracy and precision	All calibrators in accepted analysis runs were acceptable.	
Method performance in clinical Study 114322 Bioanalytical report: PBC423-001		
Assay passing rate	NR	NA
Standard curve performance	Cumulative accuracy (%bias): -7.5% to 11.3 % Cumulative precision (%CV): NR	PBC423-001 Table 2
QC performance	Cumulative accuracy (%bias): −24.1% to 31.5% Cumulative precision (%CV): ≤15% in at least 4 out of 6 samples and in at least 1 sample at each concentration	PBC423-001 Section 12.7 Table 5
Method reproducibility	172 samples were selected for incurred sample reanalysis; of 170 reportable results, 163 (94.8%) were within ±30% of the original result	PBC423-001 Section 12.10 and Table 6
Study sample analysis stability	Maximum duration of sample storage from the start of the clinical study: 480 days All samples were analyzed within the determined stability period (904 days)	PBC423-001 Section 11.1.3
Standard calibration curve performance during accuracy and precision	1 calibrator rejected among all of the accepted analysis runs.	

Continued

Table 49, continued

Method performance in clinical Study 116912 Bioanalytical report: PBC423-003		
Assay passing rate	NR	NA
Standard curve performance	Cumulative accuracy (%bias): -8.5% to 7.5% Cumulative precision (%CV): ≤15%	PBC423-003 Section 11.8.2, Table 2, and Table 3
QC performance	Cumulative accuracy (%bias): -26.3% to 24.4% Cumulative precision (%CV): ≤15% in at least 4 out of 6 samples and in in at least 1 sample at each concentration	PBC423-003 Table 5
Method reproducibility	12 samples were selected for incurred sample reanalysis; of 12 reportable results, 10 (83.3%) were within ±30% of the original result	PBC423-003 Section 11.11 and Table 6
Study sample analysis stability	Maximum duration of sample storage from the start of the clinical study: 512 days All samples were analyzed within the determined stability period (904 days)	PBC423-003 Section 11.1.3
Standard calibration curve performance during accuracy and precision	All calibrators in accepted analysis runs were acceptable.	

Source: Bioanalytical report: PBC423-003.
Abbreviations: ABTS, American Board of Thoracic Surgery; ADA, antidrug antibody; BLQ, below limit of quantification; C_{max}, maximum plasma concentration; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; IgG, immunoglobulin G; ISR, injection site reaction; LLOQ, lower limit of quantification; NR, no response; QC, quality control; ULOQ, upper limit of quantification

Assay for the Measurement of Anti-Drug Antibodies

Refer to OBP review for the immunogenicity sample assay validation.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

In the pivotal trials in subjects with PN (Studies 202685 and 203065) and the LTE study in subjects with PN (Study 202699) up to 116 weeks, the incidence of treatment-emergent ADAs was 12.8% (46 out of 358 subjects); of these, 32 subjects (8.9%) had persistent ADAs and 12 subjects (3.4%) had transient ADAs (Table 45). Treatment-boosted ADAs were rare and were observed in 2 subjects (0.6%) and NAbs were observed in 12 subjects (3.4%). The median time to the development of first post-baseline ADA was 24 weeks (range: 7.86 to 75.7 weeks). The number of ADA evaluable subjects, i.e., subjects with a pre-treatment sample and at least 1 post-treatment sample, and incidence of ADA detected in each study is summarized in Table 45 below for subjects with PN. Median ADA titer over time was low, ranging from 10 to 80.

Table 45. Summary of ADA Classifications in the Phase 3 PN Studies (ADA/NAb Evaluable Population)

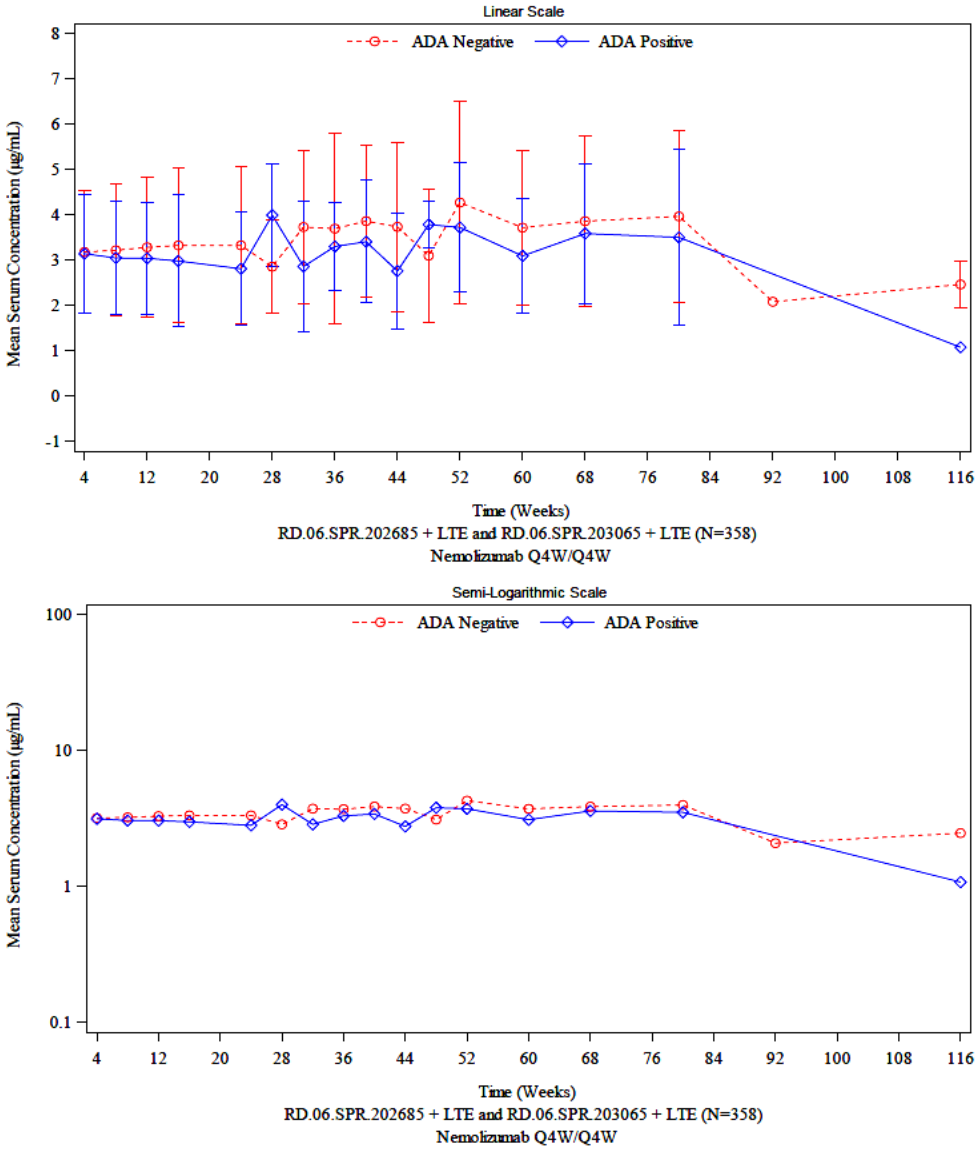
ADA/NAb status	Study 202685 + LTE (Study 202699) (N=182)	Study 203065 + LTE (Study 202699) (N=176)	Study 202685 + LTE and Study 203065 + LTE (N=358)
Pre-existing ADA, n (%)	5 (2.7)	3 (1.7)	8 (2.2)
Treatment-emergent ADA, n (%)	21 (11.5)	25 (14.2)	46 (12.8)
Treatment-induced	21 (11.5)	23 (13.1)	44 (12.3)
Transient	7 (3.8)	5 (2.8)	12 (3.4)
Persistent	14 (7.7)	18 (10.2)	32 (8.9)
Treatment-boosted	0	2 (1.1)	2 (0.6)
NAb positive, n (%)	0	12 (6.8)	12 (3.4)
Time to ADA onset (weeks)			
n	21	23	44
Mean (SD)	28 (14.75)	30 (18.03)	29.1 (16.39)
Median	24.1	32.1	24.1
Min, max	8.14, 75.7	7.86, 68.7	7.86, 75.7
Duration of ADA (weeks)			
n	13	17	30
Mean (SD)	30.6 (16.85)	34.9 (23.16)	33.0 (20.45)
Median	28.1	29.0	28.6
Min, max	8.14, 59.1	8.57, 99.3	8.14, 99.3

Source: Integrated Summary of Immunogenicity Table 64.
Note: Percentages for screening and confirmation tests are based on the number of subjects with available data at the analysis visit within each study and ADA category. Pre-existing ADA refers to baseline from pivotal studies.
Abbreviations: ADA, antidrug antibody; LTE, long-term extension; N, number of subjects in the studies; n, number of subjects with available data; NAb, neutralizing antidrug antibody; PN, prurigo nodularis

Impact of *Immunogenicity on PK*

In most patients, immunogenicity had no significant impact on the PK of nemolizumab in the phase 3 PN studies based on between-subject and within-subject comparisons. Population PK analysis with immunogenicity as a covariate demonstrated that immunogenicity had no impact on the clearance of nemolizumab. Mean serum drug concentrations over time in the phase 3 PN studies were consistent for subjects with treatment-emergent ADAs and those without (Figure 17).

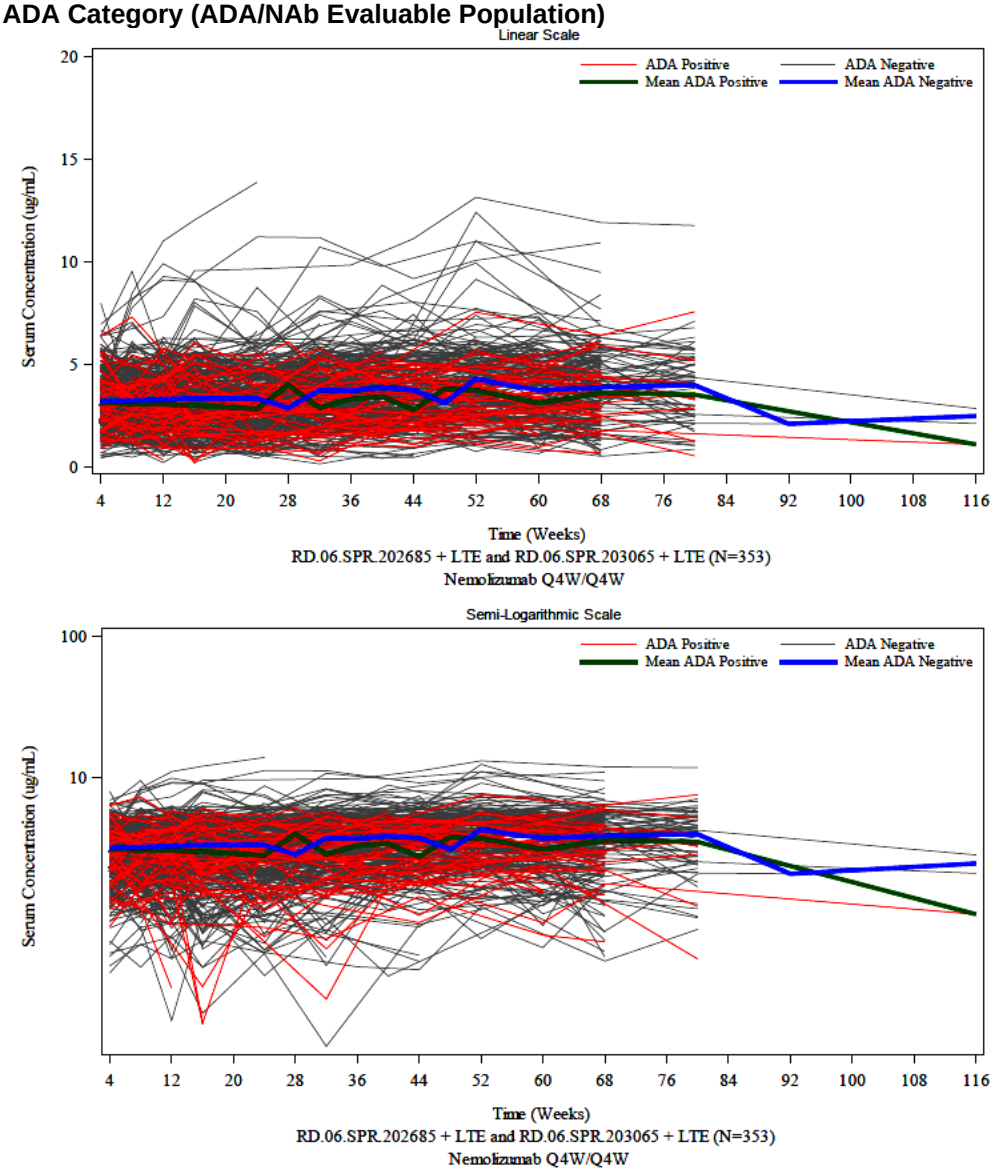
Figure 17. Mean (± SD) Serum Drug Concentration (C_{trough}) Versus Time for the Phase 3 PN Studies by ADA Category (ADA/NAb Evaluable Population)



Source: Integrated Summary of Immunogenicity Figure 32.
Abbreviations: ADA, antidrug antibody; LTE, long-term extension study; NAb, neutralizing antidrug antibody; Q4W, every 4 weeks; RD, risk difference

Due to the limited number of subjects with treatment-emergent ADAs (N=46) and the absence of impact on PK, no formal analysis of the time-dependent analysis of the impact of ADA on PK was conducted. A graphical exploration did not demonstrate any trend associated with the presence of ADA over time (Figure 18).

Figure 18. Individual Serum Drug Concentration (C_{trough}) Versus Time for the Phase 3 PN Studies by ADA Category (ADA/NAb Evaluable Population)



Source: Integrated Summary of Immunogenicity Figure 33.
Abbreviations: ADA, antidrug antibody; LTE, long-term extension study; N, number of patients in treatment arm; NAb, neutralizing antidrug antibody; Q4W, every 4 weeks; RD, risk difference

Impact of Immunogenicity on Efficacy

In most patients, immunogenicity had no significant impact on the efficacy of nemolizumab in the phase 3 PN trials. No trends based on ADA category were observed in the proportion of subjects with IGA success or improvement of PP NRS ≥4 from Baseline at Week 16 or Week 52 (Table 46 and Table 47). This observation was consistent across the Phase 3 studies.

Table 46. Summary of Efficacy Endpoints in the Phase 3 PN Studies at Week 16 by ADA Category (ADA/NAb Evaluable Population)

	Study 202685		Study 203065		Study 202685 and Study 203065	
	TE ADA+ (N=21)	ADA- (N=161)	TE ADA+ (N=25)	ADA- (N=151)	TE ADA+ (N=46)	ADA- (N=312)
Subjects with an IGA success at Week 16, n (%)	8 (38.1)	42 (26.1)	10 (40.0)	55 (36.4)	18 (39.1)	97 (31.1)
Subjects with an improvement of PP NRS ≥4 from baseline to Week 16, n (%)	17 (81.0)	94 (58.4)	15 (60.0)	84 (55.6)	32 (69.6)	178 (57.1)

Source: Integrated Summary of Immunogenicity Table 65.
Abbreviations: ADA, antidrug antibody; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; n, number of patients meeting criteria; NAb, neutralizing antidrug antibody; PP-NRS, Peak Pruritus Numeric Rating Scale; TE, treatment-emergent

Table 47. Summary of Efficacy Endpoints in the Phase 3 PN Studies at Week 52 by ADA Category (ADA/NAb Evaluable Population)

	Study 202685 + LTE (Study 202699)		Study 203065 + LTE (Study 202699)		Study 202685 + LTE and Study 203065 + LTE	
	TE ADA+ (N=21)	ADA- (N=161)	TE ADA+ (N=25)	ADA- (N=151)	TE ADA+ (N=46)	ADA- (N=312)
Subjects with IGA success at Week 16 and Week 52, n (%)	5 (23.8)	15 (9.3)	2 (8.0)	18 (11.9)	7 (15.2)	33 (10.6)
Subjects with an improvement of PP NRS ≥4 at Week 16 and Week 52, n (%)	9 (42.9)	28 (17.4)	2 (8.0)	19 (12.6)	11 (23.9)	47 (15.1)

Source: Integrated Summary of Immunogenicity Table 66.
Abbreviations: ADA, antidrug antibody; IGA, Investigator's Global Assessment; LTE, long-term extension; N, number of patients in treatment arm; n, number of patients meeting criteria; NAb, neutralizing antidrug antibody; PP-NRS, Peak Pruritus Numeric Rating Scale; TE, treatment-emergent

Impact of *Immunogenicity on Safety*

Immunogenicity had no significant impact on the safety of nemolizumab in the phase 3 PN studies. In the phase 3 PN studies, treatment-emergent adverse events (TEAEs), drug-related TEAEs, and AESIs were reported more frequently in subjects with treatment-emergent ADAs (89.1%, 47.8%, and 45.7%, respectively) than in subjects without treatment-emergent ADAs (83.7%, 35.3%, and 34.9%, respectively), while treatment-emergent serious adverse events were reported more frequently in subjects without treatment-emergent ADAs than in subjects with treatment-emergent ADAs (15.7% versus 10.9%; Table 48).

Table 48. Overview of TEAEs in the Phase 3 PN Studies by ADA Category (ADA/NAb Evaluable Population)

	Study 202685 + LTE (Study 202699)		Study 203065 + LTE (Study 202699)		Study 202685 + LTE and Study 203065 + LTE	
	TE ADA+ (N=21)	ADA- (N=161)	TE ADA+ (N=25)	ADA- (N=151)	TE ADA+ (N=46)	ADA- (N=312)
Any TEAE	17 (81.0)	133 (82.6)	24 (96.0)	128 (84.8)	41 (89.1)	261 (83.7)
Any SAE	3 (14.3)	30 (18.6)	2 (8.0)	19 (12.6)	5 (10.9)	49 (15.7)
Any drug-related TEAE	8 (38.1)	56 (34.8)	14 (56.0)	54 (35.8)	22 (47.8)	110 (35.3)
Any AESI	9 (42.9)	57 (35.4)	12 (48.0)	52 (34.4)	21 (45.7)	109 (34.9)

Source: Integrated Summary of Immunogenicity Table 67.
Abbreviations: ADA, antidrug antibody; AESI, adverse event of special interest; LTE, long-term extension; N, number of patients in treatment arm; NAb, neutralizing antidrug antibody; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event

In the phase 3 PN trials, suspected immune-mediated adverse events (AEs) were rare and no discernible pattern was observed based on ADA category for subjects experiencing suspected immune complex-mediated AEs (Table 49).

Table 49. Suspected Immune Complex-Mediated Adverse Events in the Phase 3 PN Studies by Preferred Term and ADA Category (ADA/NAb Evaluable Population)

	Study 202685 + LTE (Study 202699)		Study 203065 + LTE (Study 202699)		Study 202685 + LTE and Study 203065 + LTE	
	TE ADA+ (N=21)	ADA- (N=161)	TE ADA+ (N=25)	ADA- (N=151)	TE ADA+ (N=46)	ADA- (N=312)
Any class, n (%)	1 (4.8)	9 (5.6)	2 (8.0)	13 (8.6)	3 (6.5)	22 (7.1)
Alopecia areata	0	1 (0.6)	0	1 (0.7)	0	2 (0.6)
Anosmia	0	0	0	1 (0.7)	0	1 (0.3)
Arthritis	0	0	0	2 (1.3)	0	2 (0.6)
Autoimmune pancreatitis	0	0	0	1 (0.7)	0	1 (0.3)
Chronic gastritis	0	1 (0.6)	0	0	0	1 (0.3)
Dermatitis	0	2 (1.2)	1 (4.0)	1 (0.7)	1 (2.2)	3 (1.0)
Enteritis	0	0	1 (4.0)	0	1 (2.2)	0
Hypothyroidism	0	1 (0.6)	0	0	0	1 (0.3)
Lichen planus	0	0	0	1 (0.7)	0	1 (0.3)
Lichen sclerosus	0	1 (0.6)	0	0	0	1 (0.3)
Myositis	0	0	0	1 (0.7)	0	1 (0.3)
Palmoplantar keratoderma	0	1 (0.6)	0	1 (0.7)	0	2 (0.6)
Pemphigoid	0	1 (0.6)	0	0	0	1 (0.3)
Polymyalgia rheumatica	0	0	0	1 (0.7)	0	1 (0.3)
Psoriasis	1 (4.8)	1 (0.6)	0	3 (2.0)	1 (2.2)	4 (1.3)

Source: Integrated Summary of Immunogenicity Table 68.
Abbreviations: ADA, antidrug antibody; LTE, long-term extension; N, number of patients in treatment arm; n, number of patients meeting criteria; NAb, neutralizing antidrug antibody; TE, -treatment emergent

Hypersensitivity reactions (defined as injection-related reactions based on the predefined AESI category and standard Medical Dictionary for Regulatory Activities query) in the phase 3 PN studies occurred with similar frequency in subjects with treatment-emergent ADAs (2.2%) and in those for whom ADAs were ND (0.6%). No discernible pattern was observed based on ADA category for subjects experiencing suspected immune-mediated AEs. The incidence of individual preferred terms included in the AESI of injection-related reactions was similar between the ADA category groups. Therefore, there was no impact of immunogenicity on the overall assessment of the clinical benefit and risk of nemolizumab based on data from the phase 3 studies.

In summary, in most patients, ADA had no apparent impact on PK, efficacy or safety.

14.5. Pharmacometrics Assessment

Population Pharmacokinetic Analyses

Executive Summary

- Nemolizumab pharmacokinetics were adequately described by a 1-compartment model with first-order absorption (SC) with lag time and linear elimination in adult and adolescent subjects with atopic dermatitis (AD) or adult subjects with prurigo nodularis (PN).
- Only body weight (WGT) was identified as a statistically significant predictor of nemolizumab exposure. With flat dosage, the exposure of nemolizumab decreases with

increasing WGT. However, the difference in exposure between the upper- and lower weight quartiles in subjects with AD and PN was <2-fold, supporting the appropriateness of flat dosing (30 mg or 60 mg).

- None of the other tested covariates (age, sex, race, ethnicity, region, country, eGFR, creatinine clearance (CrCL), albumin, total protein, bilirubin, mild to moderate hepatic impairment, mild to moderate renal impairment, and disease status) had a clinically relevant impact on nemolizumab exposure.
- The popPK modeling and simulation supports the proposed weight-tiered flat dosing regimen in subjects with PN: A loading dose of nemolizumab 60 mg SC followed by nemolizumab 30 mg Q4W for subjects with body weight <90 kg or nemolizumab 60 mg Q4W (no loading dose) for subjects with body weight ≥90 kg.

PopPK Model

Objectives

The primary objectives of the PopPK analysis were to characterize the population pharmacokinetics of nemolizumab in healthy adults (HV), in adults and adolescents with atopic dermatitis (AD) and adults with PN To assess the impact of internal and external covariates on the nemolizumab PK. And to compare the PK of nemolizumab between AD/PN and HVs.

Model Development

Data

Nemolizumab serum concentration-time data collected from 9 clinical studies, comprising one phase 1 study (CIM001JP), four phase 2 studies (CIM003JG, SPR.114322, SPR.116912 and SPR.115828) and four phase 3 studies (SPR.118161, SPR.118169, SPR.202685 and SPR.203065), were used for the population PK analysis of nemolizumab in subjects with AD, and subjects with PN following SC administration.

The analysis included a total of 1952 subjects (1555 subjects with AD and 397 subjects with PN) evaluable for PK (Table 50), drawn from Studies listed above, who received nemolizumab and had at least one plasma concentration measurement above the lower limit of quantification (LLOQ = 100 ng/mL). Notably, 5.5% out of all observations were considered BLQ and were excluded from the analysis. In summary, 13236 quantifiable serum concentrations from 1952 subjects were used for the PopPK analysis. The distribution of continuous and categorical covariates at baseline are summarized in Table 51 and Table 52.

Table 50. Summary of Nemolizumab PK Data in AD and PN Subjects

Study		Total subjects	PK-evaluable subjects	Bioanalytical Assessed samples	Pre/Post-treatment BLQ	Post-treatment BLQ	Quantifiable observations
AD	CIM001JP	27	27	630	88 (14)	61 (9.7)	542
	CIM003JG	249	248	3767	382 (10)	134 (3.6)	3385
	SPR.114322	169	169	1713	258 (15)	91 (5.3)	1455
	SPR.116912	18	18	118	31 (26)	13 (11)	87
	SPR.118161	614	594	4121	908 (22)	321 (7.8)	3213
	SPR.118169	519	499	3482	739 (21)	248 (7.1)	2743
PN	SPR.115828	34	34	226	1 (0.44)	1 (0.44)	225
	SPR.202685	187	183	1077	190 (18)	8 (0.74)	887
	SPR.203065	183	180	882	183 (21)	7 (0.79)	699
Overall		**2000**	**1952**	**16016**	**2780 (17)**	**884 (5.5)**	**13236**

Source: Table 7. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: AD, atopic dermatitis; BLQ, below limit of quantification; PK, pharmacokinetic; PN, prurigo nodularis

Table 51. Summary of Continuous Covariates in Subjects With AD and PN by Study

Covariate	Mean (SD)	Median	Range (Min, Max)
Age (years)	38.5 (17.7)	35.0	12.0, 85.0
Weight (kg)	76.2 (19.2)	74.0	30.8, 181
Height (cm)	169 (9.7)	169	130, 201
BMI (kg/m^2)	26.4 (5.88)	25.4	14.8, 56.5
BSA (m^2)	1.86 (0.245)	1.85	1.11, 2.94
Serum creatine (mg/dL)	0.811 (0.230)	0.78	0.42, 5.93
CrCL (mL/min)	126 (40.4)	120	22.1, 379
eGFR (mL/min/1.73m^2)	101 (28.2)	97.8	10.8, 279
Bilirubin (mg/dL)	0.477 (0.274)	0.4	0.1, 2.6
AST (U/L)	22.3 (9.32)	20	5, 126
Albumin (g/dL)	4.55 (0.302)	4.5	2.7, 5.5

Source: Reviewer's Summary referencing Table 10. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CRCL, creatinine clearance; eGFR, estimated glomerular filtration rate

Table 52. Summary of Categorical Covariates in Subjects With AD and PN by Study

Covariate	All Subjects (n=1952)	Covariate	All Subjects (n=1952)
Sex		Pre-existing ADA	
Male	951 (48.7%)	Yes	64 (3.3%)
Female	1001 (51.3%)	No	1888 (96.7%)
Race		Treatment-emergent ADA	
White	1483 (76.0%)	Yes	133 (6.81%)
Black	125 (6.4%)	No	1796 (92.0%)
Asian	308 (15.8%)	Missing	23 (1.18%)
Others	36 (1.8%)	Treatment-induced ADA	
Age group		Yes	129 (6.61%)
12 – 17 yrs	191 (9.8%)	No	1800 (92.2%)
18 – 65 yrs	1580 (80.9%)	Missing	23 (1.18%)
>65 yrs	181 (9.3%)	Treatment-boosted ADA	

Covariate	All Subjects (n=1952)	Covariate	All Subjects (n=1952)
Renal impairment		Yes	4 (0.20%)
Normal	1644 (84.2%)	No	1925 (98.6%)
Mild	262 (13.4%)	Missing	23 (1.8%)
Moderate	44 (2.3%)		
Severe	2 (0.1%)		
Hepatic impairment			
Normal	1838 (94.2%)		
Mild	99 (5.1%)		
Moderate	13 (0.7%)		

Source: Reviewer's Summary referencing Table 11. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: ADA, antidrug antibody; n, number of patients meeting criteria

Methodology

The Applicant performed the popPK analysis using NONMEM (Version VII [Level 7.4.3]), and the reviewer assessed its validity.

The overall model development was guided by several criteria, including visual inspection of goodness-of-fit (GOF) plots, prediction-corrected visual predictive checks (pcVPC), significant decreases in the objective function value (OFV), and adequate precision of parameter estimates.

The impact of intrinsic and extrinsic covariates on PK parameters was investigated using an automated stepwise covariate modeling approach with forward selection ($p<0.01$) and backward exclusion ($p<0.001$). Subsequently, all covariates found to be statistically significant during the stepwise covariate modeling approach were evaluated based on the magnitude of their impact and their clinical relevance.

The covariates considered for the analysis were demographic factors, age, albumin, BSA, sex, body weight, lean body weight, antidrug antibody (ADA), estimated glomerular filtration rate (eGFR), hepatic impairment, renal impairment, IgE total bilirubin, total protein, CrCL, serum creatinine, race, region and ethnicity, extrinsic factor (device, formulation), disease status (AD or PN).

Results

The PK characteristics of nemolizumab activity were described using a 1-compartment model with first-order absorption (SC) with lag time and linear elimination adult and adolescent subjects with AD or adult subjects with prurigo nodularis (PN) (Table 53). WGT was identified as a relevant predictor of nemolizumab exposure. The exposure of nemolizumab decreases with increasing WGT. None of the other tested covariates (age, sex, race, ethnicity, region, country, baseline disease severity eGFR, CRCL, ALB, total protein, BILI, mild to moderate hepatic impairment, renal impairment, and disease status) had a clinically relevant impact on nemolizumab PK.

The goodness-of-fit plots (Figure 19) showed a random distribution of observed versus individual or population model-predicted nemolizumab concentrations along the line of unity, the distributions of CWRES showed no trends when plotted against time or population predicted nemolizumab concentrations. Prediction-corrected VPCs for the nemolizumab concentrations in adult and adolescent subjects with AD and PN (Figure 20) demonstrated that the model

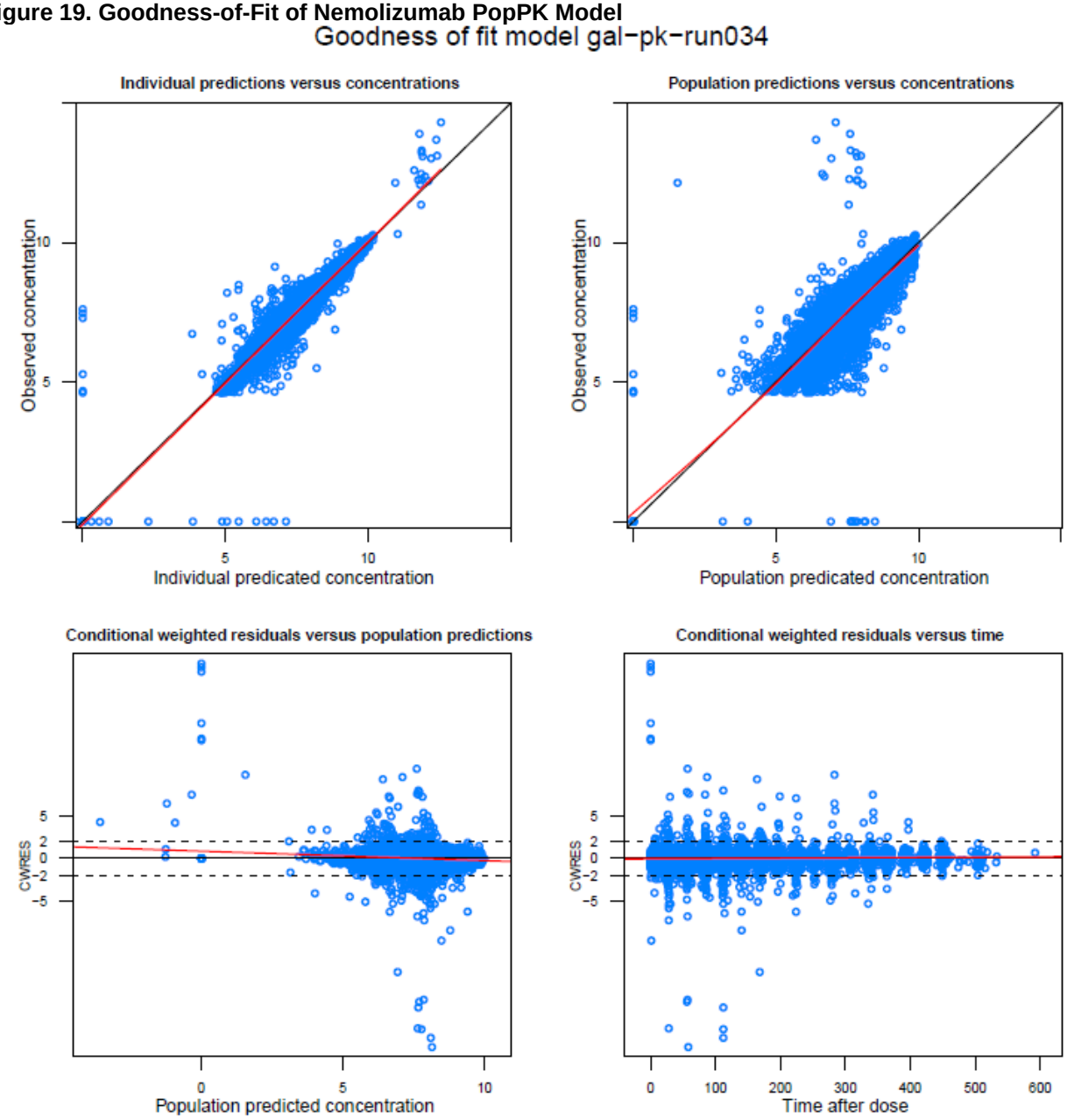
adequately captured the observed nemolizumab concentration time-course and variability of the observed data.

Table 53. Final Parameter Estimates of Nemolizumab

Parameter	Point estimate	IIV (%CV)	RSE%	Asymptotic 95% CI[e]	Bootstrap 95% CI[f]	Shrinkage (%)
Apparent elimination clearance, CL/F (L/day)	0.263	-	1.3	0.257; 0.27	0.257; 0.269	-
Apparent volume of distribution, V/F (L)	7.670	-	1.3	7.48; 7.86	7.47; 7.86	-
Absorption rate constant, K_a (1/day)	0.476	-	7.7	0.405; 0.548	0.419; 0.591	-
Absorption lag-time, ALAG (day)	0.043	-	23.0	0.0236; 0.0626	0.0158; 0.0657	-
Residual unexplained variability, RUV [a]	0.200	-	1.8	0.193; 0.207	0.194; 0.207	11.9
Dose effect on F [b]	-0.144	-	10.0	-0.172; -0.115	-0.172; -0.114	-
Albumin effect on CL/F [b]	-1.350	-	9.2	-1.6; -1.11	-1.6; -1.11	-
CrCL effect on CL/F [b]	0.168	-	15.0	0.119; 0.217	0.12; 0.216	-
Ethnicity (Hispanic or Latino) effect on CL/F	0.226	-	20.0	0.138; 0.313	0.143; 0.314	-
Race (other races) effect on CL/F	0.186	-	9.5	0.151; 0.221	0.152; 0.221	-
Sex (Male) effect on CL/F	0.100	-	16.0	0.0689; 0.132	0.0695; 0.13	-
Weight effect on CL/F [b]	0.662	-	6.0	0.584; 0.739	0.583; 0.739	-
Albumin effect on V/F [b]	-0.535	-	29.0	-0.841; -0.229	-0.832; -0.241	-
Weight effect on V/F [b]	0.802	-	5.3	0.719; 0.886	0.717; 0.888	-
IIV on CL/F [c,d]	0.109	33.9	2.2	0.094; 0.123	0.0989; 0.117	6.2
IIV on V/F [c,d]	0.110	34.1	6.2	0.070; 0.15	0.0832; 0.137	26.3
Covariance (CL/F and V/F [d])	0.068	-	9.97	0.055-0.080	0.054; 0.082	-
IIV on K_a [c]	0.344	64.1	10.0	0.228; 0.46	0.228; 0.483	68.9

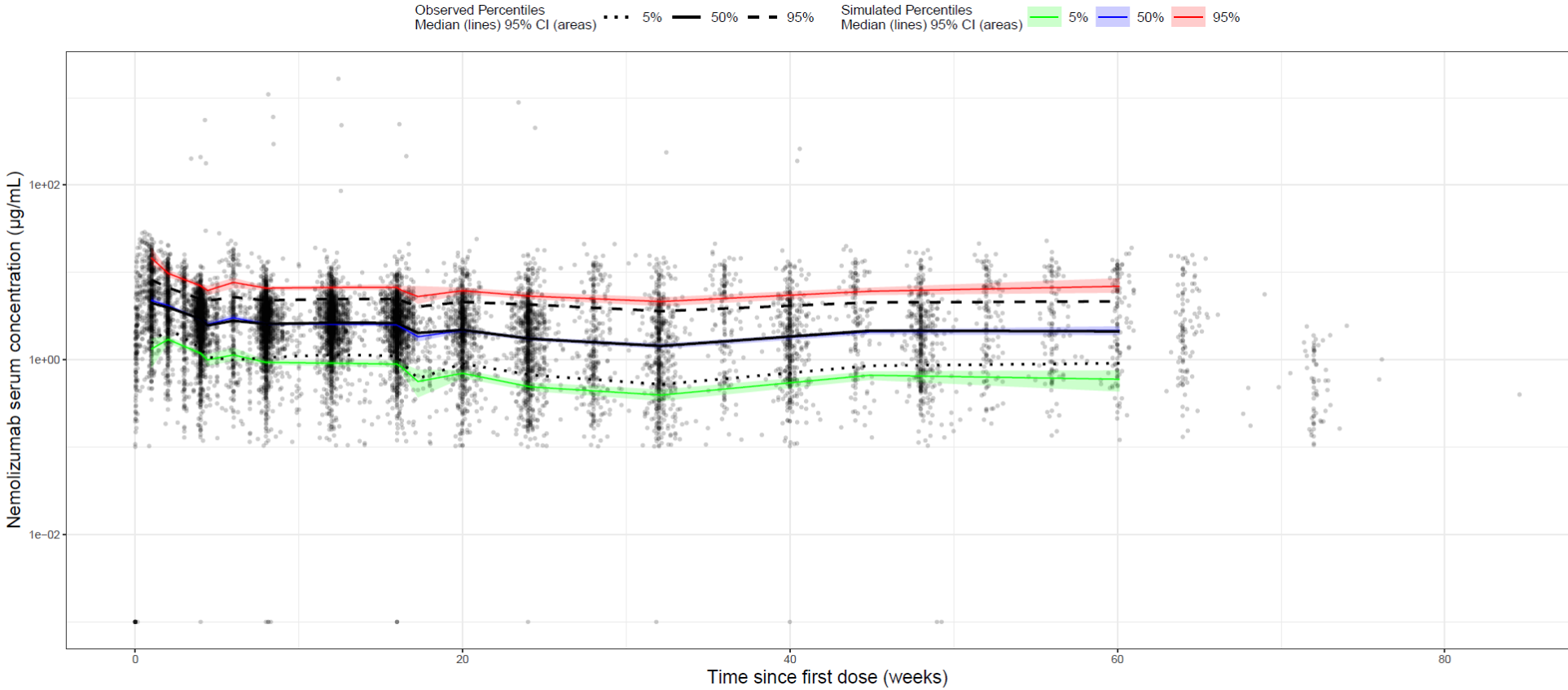
Source: Table 15. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: ALAG, absorption lag time; CI, confidence interval; CL/F, apparent clearance; CrCl, creatinine clearance; F, fraction absorbed (bioavailability); IIV, interindividual variability; K_a, absorption rate constant; RSE, relative standard error; RUV, residual unexplained variability; V/F, apparent central volume of distribution

Figure 19. Goodness-of-Fit of Nemolizumab PopPK Model



Source: Reviewer's analysis
Note: Concentrations in the GOF plots are in logarithm transformed form.
Abbreviations: CWRES, conditional weighted residuals versus time

Figure 20. Prediction-Corrected Visual Predictive Checks of Nemolizumab PopPK Model



Source: Reviewer's analysis
Note: Concentrations in the pcVPC plot are in logarithm transformed form. The x axis was adjusted to up to 90 weeks for demonstration purpose. There are values outside the scale range.
Abbreviations: CI, confidence interval; popPK, population pharmacokinetics

Summary

- The PopPK model parameter estimations were verified by the reviewer, and the results are consistent with the findings reported by the Applicant.
- It's noteworthy that although the final PopPK model converged successfully during the reviewer's independent analysis, the RSE% for corresponding parameters could not be estimated due to an aborted covariance step. Various solutions, including adjusting initial estimates, simplifying the model, increasing iterations, and modifying the estimation method, were attempted without success. The Reviewer believes this issue likely stems from the inclusion of diverse studies and participant groups with different indications and long treatment durations (up to 592 days since first dose), contributing to large data variability and a high percentage of outliers. Though this limits confidence in the precision of the parameter estimates, the totality of model qualification confirms its robustness and supports its use for generating exposure measures and empirical Bayesian estimations (EBEs).
- No difference was identified in nemolizumab PK profile between subjects with AD and PN, thus confirming that the disease does not impact nemolizumab PK.
- Several covariates had a statistically significant impact on PK parameters. Clearance was influenced by WGT, ALB levels, CRCL, ethnicity, race and gender. Volume of distribution was influenced by both WGT, ALB. Among them, WGT is the only covariate with a significant impact leading to ≥ 20% change on both CL/F and V/F. The exposure of nemolizumab decreases with increasing WGT.
- After a 30 mg dose (with 60 mg loading dose) Q4W, the difference in exposure (AUC_{ss}, $C_{trough, ss}$ or $C_{max, ss}$) between the upper and lower weight quartiles in subjects with AD was less than 2-fold, supporting the proposed weight-tiered flat dosing (30 mg or 60 mg).

PopPK Model Based Simulation

Univariate and Multivariate Assessment

Univariate covariate analysis for covariate effects were estimated for each covariate independently via fixing all the other covariates to the median value for the continuous ones or to a predefined reference category for the categorical ones. The simulations were conducted by omitting the IIV but including the parameter uncertainty on all the fixed-effect parameters. Parameter uncertainty was obtained from the results of the nonparametric bootstrap analysis (1000 replicate datasets).

The multivariate assessment aimed to assess the joint effect of the covariates retained in the final popPK model on the derived PK parameters (AUC at steady state [AUC_{ss}], maximum plasma concentration at steady state [$C_{max,ss}$], and trough concentration at Week 16 [$C_{W16,ss}$]). This approach describes the overall impact when two or more covariates act together, enabling thus a more reliable inference on the clinical relevance of the selected covariates. Individual covariates and corresponding individual EBEs information present in the original analysis dataset were used for this assessment. By doing so, the full multivariate distribution of the covariates and EBEs were maintained, ensuring that correlations and intrinsic relationships between them were preserved. The parameter uncertainty and the residual variability were not considered. The IIV was added to enable a more reliable interpretation of covariates' impact in real-life settings.

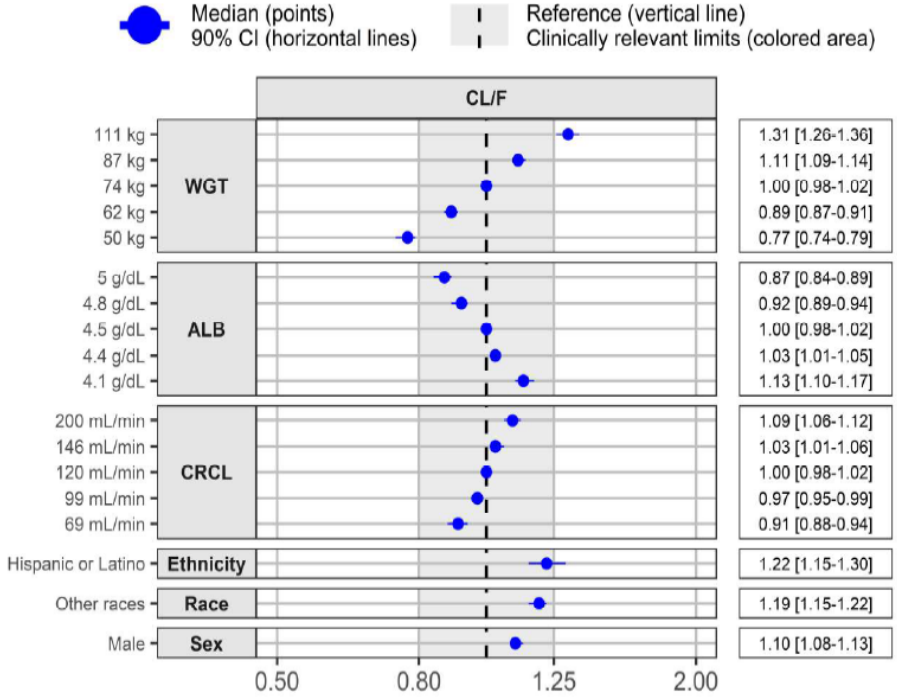
Individual PK parameters as well as the exposure metrics of interest (i.e., AUC_{ss}, and $C_{max,ss}$, and $C_{W16,ss}$) were derived for each individual.

Univariate Assessment of the Covariates

The relative importance of the marginal effect of each covariate included in the final model was evaluated using a forest plot expressing the fold-change of model parameters, CL/F and V/F (Figure 21, Figure 22 16 weeks and Figure 23).

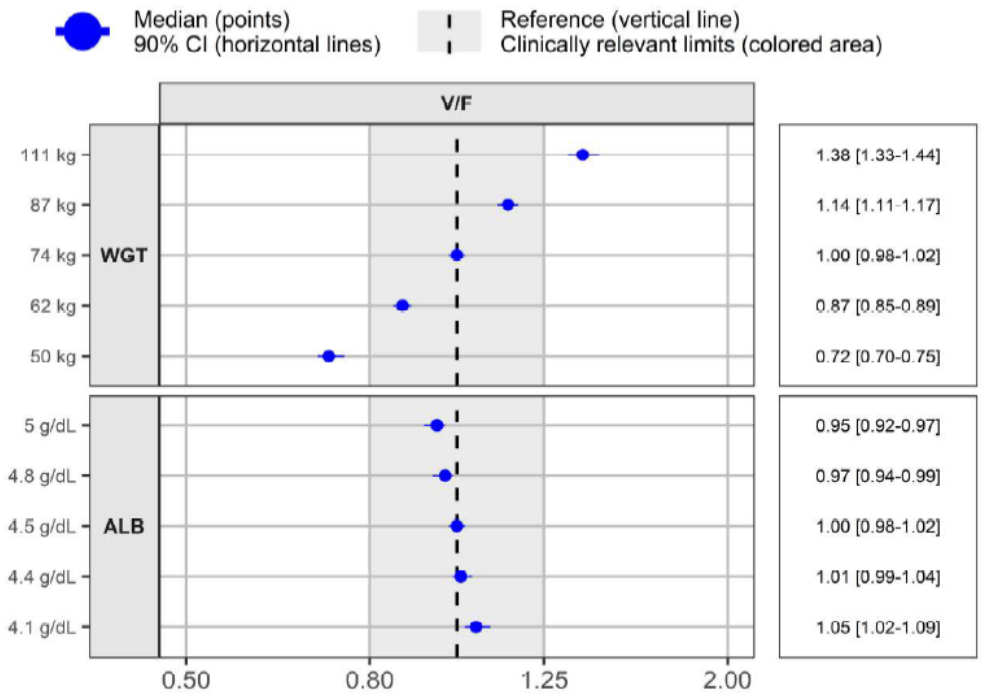
Effects of all covariates, except for weight were at or within the 0.8 to 1.25 exposure ratio interval and were not considered clinically meaningful. Subjects with extreme values of WGT (111 kg; P95) had an approximately 21% lower steady state trough levels, 23% lower $C_{max,ss}$, and a 25% lower AUC_{ss} relative to a typical patient with WGT of 74 kg. Accordingly, subjects with lower values of WGT (50 kg; P5) had approximately 30% higher exposure levels. These WGT effects on steady state exposures were only marginally outside the 0.8 to 1.25 exposure ratio interval.

Figure 21. Univariate Impact of Covariates on CL/F



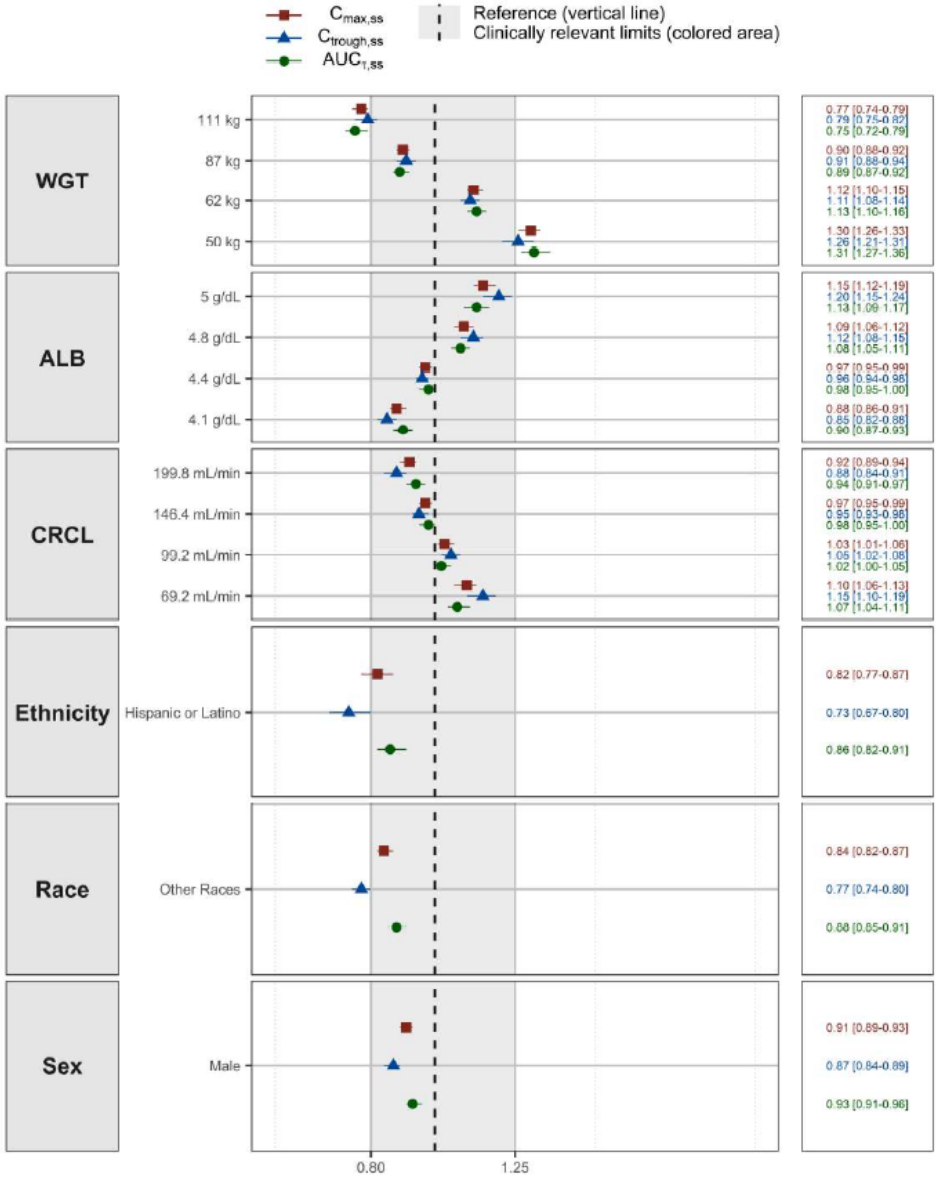
Source: Reviewer's analysis to confirm Figure 15. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: ALB, albumin; CI, confidence interval; CL/F, apparent clearance; CRCL, creatinine clearance; WGT, weight

Figure 22. Univariate Impact of Covariates on V/F



Source: Reviewer's analysis to confirm Figure 16. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: ALB, albumin; CI, confidence interval; V/F, apparent central volume of distribution; WGT, weight

Figure 23. Univariate Impact of Covariates on PK

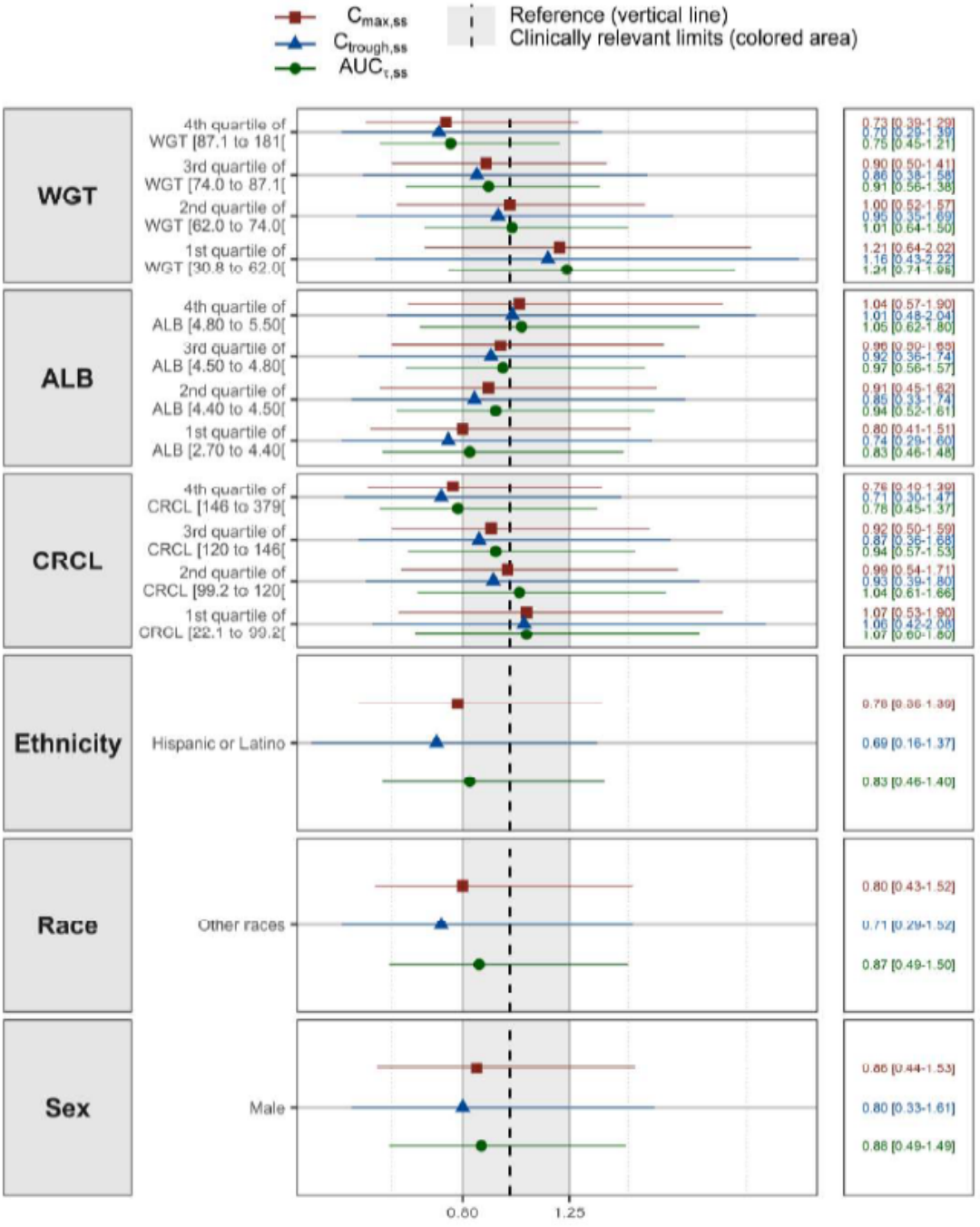


Source: Reviewer's analysis to confirm Figure 17. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: ALB, albumin; $AUC_{t,ss}$, area under the concentration-time curve at time t, at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; CRCL, creatinine clearance; $C_{trough,ss}$, trough plasma concentration at steady state; WGT, weight

Multivariate Assessment of the Covariates

Multivariate assessment results of the covariates influence on PK were shown in Figure 24**.** Similar to results observed in univariate settings, with point estimates indicating relatively lower exposure levels for subjects with higher WGT values. However, the 90% prediction interval crosses the 0.8 to 1.25 exposure ratio interval, indicating potential exposure variations due to flat dosing and clearance variability in patients with different WGT.

Figure 24. Multivariate Assessment of the Impact of Covariates on PK



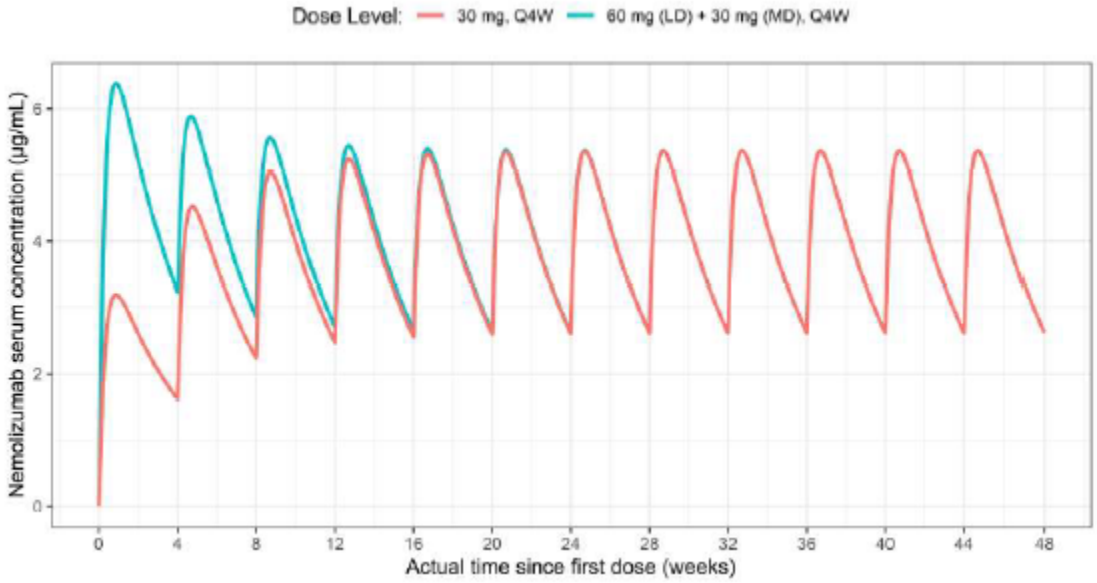
Source: Reviewer's analysis to confirm Figure 18. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: ALB, albumin; $AUC_{t,ss}$, area under the concentration-time curve at time t, at steady state; $C_{max,ss}$, maximum plasma concentration at steady state; CRCL, creatinine clearance; $C_{trough,ss}$, trough plasma concentration at steady state; WGT, weight

Loading Dose Impact on Time to Reach Steady State

Based on the final PopPK model, the effect of loading dose (LD) on the time required to achieve steady-state concentration levels is simulated and illustrated in Figure 25. Based on the simulation conducted for a typical 74 kg subject dosed with nemolizumab 30 mg Q4W with and

without a 60 mg LD, steady state (90% of steady state) is reached at Week 1 with a LD and at Week 12 without a LD.

Figure 25. Impact of Loading Dose on Time To Reach Steady State



Source: Reviewer's analysis to confirm Figure 26. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: LD, loading dose; MD, maintenance dose; Q4W, every 4 weeks

Summary

- Both univariate and multivariate assessments indicate relatively lower exposure levels for subjects with higher WGT, with the 90% prediction interval marginally outside the 0.8 to 1.25 exposure ratio interval. Overall, the impact of WGT was a less than two-fold difference in exposure, expressed as individually predicted C_{trough}, AUC_{ss}, and C_{max} between the upper and lower weight quartiles for subjects, indicating that weight-based dosing is not necessary.
- Steady state serum concentrations were reached earlier with a LD (during the first days) than without a LD (by Week 12). The accumulation after multiple doses with a Q4W dosing regimen was low, with an accumulation ratio of 1.6.

Nemolizumab Exposure Response Assessment

PK/PD for Efficacy

Executive Summary

- Pharmacokinetic/pharmacodynamic models were successfully developed to characterize the relationship between nemolizumab concentrations and efficacy assessments over time (IGA and PP NRS).
- Pharmacokinetic/pharmacodynamic simulations of clinical endpoints at Week 16 showed a similar efficacy response in both body weight groups (<90 kg and ≥90kg) when the dose was adjusted according to body weight with a cutoff of 90 kg, providing supportive evidence for

the effectiveness and safety of the selected doses and the proposed dosing regimens in subjects with PN.

PK/PD for Efficacy

Analysis Objectives:

- To characterize the PK/PD relationships between nemolizumab serum concentrations and the clinical assessments in adults with PN: IGA and weekly average PP NRS.
- To evaluate the impact of relevant covariates, including, but not limited to, body weight (WGT).

Data

The IGA PK/PD analysis dataset included 2893 evaluable IGA observations from 619 subjects enrolled in Studies SPR.115828, SPR.202685 (OLYMPIA 1), and SPR.203065 (OLYMPIA 2).

The PP NRS PK/PD assessment data contained 11710 evaluable observations from 618 subjects enrolled in Studies SPR.115828, SPR.202685 (OLYMPIA 1), and SPR.203065 (OLYMPIA 2).

Table 54. Phase 2 and Phase 3 Studies in Subjects With PN

Study No.	Sponsor	Study Design	Drug Dose and Regimen	PK/PD Endpoint Measurements
Phase 2 studies - subjects with PN				
SPR.115828 N=70 [1]	Galderma	Phase 2a randomized, placebo-controlled, double-blinded, parallel-group, multicenter study to evaluate the safety and efficacy of nemolizumab in subjects suffering from PN	Multiple SC doses of nemolizumab for 12 weeks: 0.5 mg/kg Q4W	PK sampling: Serum nemolizumab concentrations PK/PD endpoints: IGA and PP NRS
Phase 3 studies - adult and adolescent subjects with PN				
SPR.202685 N=270 [2]	Galderma	Phase 3 randomized, double-blind, placebo-controlled study to assess the efficacy and safety of nemolizumab in adult subjects with prurigo nodularis	Multiple SC doses of nemolizumab for 24 weeks: 30 mg (LD 60 mg) Q4W (BW <90 kg) or 60 mg Q4W (BW ≥90 kg)	PK sampling: Serum nemolizumab concentrations PK/PD endpoints: IGA and PP NRS
SPR.203065 N=270 [3]	Galderma	Phase 3 randomized, double-blind, placebo-controlled study to assess the efficacy and safety of nemolizumab in adult subjects with prurigo nodularis	Multiple SC dose of nemolizumab for 16 weeks: 30 mg (LD 60 mg) Q4W (BW <90 kg) or 60 mg Q4W (BW ≥90 kg)	PK sampling: Serum nemolizumab concentrations PK/PD endpoints: IGA and PP NRS

Source: GALD-PMX-NEMOLIZUMAB-1787-POPPK, Table 1.
Abbreviations: BW, body weight; IGA, Investigator's Global Assessment; LD, loading dose; PD, pharmacodynamic; PK, pharmacokinetic; PN, prurigo nodularis; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, every 4 weeks; SC, subcutaneous

Methodology

IGA PK/PD Model

The relationship between nemolizumab concentrations and IGA assessments was described by a continuous-time Markov model. The impact of selected covariates was assessed in two steps: first, with a graphical analysis, followed by a formal stepwise covariate model (SCM) analysis.

PP NRS PK/PD Model

Prior to any modeling, the PP NRS data were summarized as weekly average PP NRS, derived from at least 4 daily peak pruritus numerical rating scores (score ranging from 0 to 10). The relationship between nemolizumab concentrations and weekly averages of PP NRS assessments was described by an indirect turnover model with inhibiting drug effect (EF1) on the rate of production of PD signal. The impact of selected covariates was assessed in 2 steps: first, with a graphical analysis, followed by a formal SCM analysis.

Simulations

The developed PK/PD models were used to conduct simulations to assess the impact of WGT on the different clinical endpoints under the dosing regimens used in phase 3 OLYMPIA studies for PN indication: 60 mg LD + 30 mg for subjects <90 kg and 60 mg for subjects ≥90 kg. The clinical endpoints of interest were the percentage of responders for IGA and PP NRS, defined as follows:

- For IGA: Proportion of subjects with an IGA score of ≤ 1 and a ≥2 points reduction from baseline at Week 16.
- For PP NRS: Proportion of subjects with PN achieving a ≥4-point reduction from the baseline at Week 16.

Results:

IGA PK/PD Model

A 4-compartment continuous-time Markov model was used to describe IGA observations with a common stimulating drug effect E_{desc} (linear relationship with concentrations) on all descending transitions ([λ_{desc}]) and an inhibiting drug effect E_{asc} (linear relationship with concentrations) on all ascending transitions ([λ_{asc}]) (Table 55). No statistically significant covariate, including age, sex, weight (WGT), and race, was identified for key parameters in the IGA PK/PD model.

Both effects had linear relationship with concentrations. The slope parameter of the E_{desc} was found at 0.525 L/µg, while the slope parameter of the E_{asc} was found at -0.0832 L/µg. An effect of baseline IGA score on all λ_{asc} was characterized (higher IGA baseline values being associated with higher λ_{asc}), suggesting a lower response rate for subjects with higher baseline values.

PP NRS PK/PD Model

An indirect response model with a maximum inhibitory effect (Imax) model and a constant placebo effect (P1) on the production of the PP NRS response was found adequate to describe the data. The model accounted for the bounded nature of the PP NRS score (between 0 and 10). The inhibiting concentration effect of nemolizumab resulted in decreasing weekly average PP

NRS with increasing nemolizumab concentrations, with a half maximal inhibitory concentration estimated to be 0.357 µg/mL (Table 56). No statistically significant covariate, including age, gender and weight, was identified for key parameters in the PP NRS PK/PD model.

Covariate Effect of WGT

The effect of WGT was further assessed in the context of nemolizumab efficacy in the PK/PD analysis. To investigate the impact of WGT on the 3 clinical endpoints, a 3-arm study was simulated with nemolizumab administered Q4W until W16. The drug serum concentrations, as well as IGA, and PP NRS were simulated based on the characteristics of the subject with

PN and developed popPK and PK/PD models. The two primary efficacy endpoints were assessed at Baseline and at Week 16 when clinical endpoints of interest (i.e., the percentages of responders) were evaluated.

- **Arm 1**: Low WGT subject population (WGT range: 39 to 89 kg) nemolizumab dosing regimen: 30 mg, Q4W with 60 mg LD for 16 weeks (last subcutaneous [SC] dose given at Week 12)
- **Arm 2**: High WGT subject population (WGT range: 90 to 181 kg) nemolizumab dosing regimen: 30 mg, Q4W with 60 mg LD for 16 weeks (last SC dose given at Week 12)
- **Arm 3**: High WGT subject population (WGT range: 90 to 181 kg) nemolizumab dosing regimen: 60 mg, Q4W for 16 weeks (last SC dose given at Week 12)

Simulations results (Table 57, Figure 26, Figure 27, and Figure 28) showed the following:

- The baseline IGA value impacted the IGA response rate with a response rate decreased by of 27%, 32%, and 27% for subjects with an IGA baseline value of 4 compared to subjects with an IGA baseline of 3 on each simulated arm.
- Dosing regimen and WGT had no impact on the PP NRS responder rate at W16, but impacted the IGA responder rate at W16 in subjects with WGT ≥90 kg with a responder rate decreased by 24% when treated with 30 mg Q4W with 60 mg LD. The response rate at W16 was similar between the 2 WGT groups when subjects with WGT ≥90 kg were treated at the dose of 60 mg Q4W.

Table 55. Parameter Estimates for the IGA PK/PD Final Model in Adults With PN

Parameter	Point Estimate	IIV (%CV)	%RSE[a]	Asymptotic 95% CI[a]	Shrinkage (%)
λ_{12} (day^{-1})	0.00703	-	19	0.00436; 0.0097	-
λ_{21} (day^{-1})	0.00304	-	14	0.00218; 0.0039	-
λ_{23} (day^{-1})	0.0083	-	16	0.00568; 0.0109	-
λ_{32} (day^{-1})	0.00495	-	13	0.0037; 0.00621	-
Parameter	**Point Estimate**	**IIV (%CV)**	**%RSE[a]**	**Asymptotic 95% CI[a]**	**Shrinkage (%)**
λ_{34} (day^{-1})	0.00204	-	17	0.00136; 0.00273	-
λ_{43} (day^{-1})	0.0084	-	13	0.00632; 0.0105	-
Slope/1000 asc. (L/µg)	-0.0832	-	16	-0.109; -0.057	-
Slope/1000 desc. (L/µg)	0.525	-	19	0.332; 0.717	-
θ_{B4} (-)	1.77	-	18	1.14; 2.4	
ETA on desc.	0.832	91.2%	6.7	0.713; 0.951	31.4

Source: Table 10. GALD-PMX-NEMOLIZUMAB-1854-PKPD-PN

Note: λ_{12},λ_{23},λ_{34},λ_{43},λ_{32}, $and\ \lambda_{21}$ correspond to the following transition rate in the NONMEM script: λ_{23}, λ_{34}, λ_{45}, λ_{54}, λ_{43}, λ_{32}, λ_{12}, λ_{23} , $and\ \lambda_{34}$ are λ_{asc}, $and\ \lambda_{21}$, λ_{32} $and\ \lambda_{43}$ are λ_{desc}.

[a] Calculated from the NONMEM R variance-covariance matrix. The RSE for omega is reported on the approximate SD scale (SE/variance estimate)/2.

Abbreviations: asc, ascending; CV, coefficient of variation; desc, descending; ETA, random effect; IGA, Investigator Global Assessment; IIV, interindividual variability; NONMEM, nonlinear mixed-effects modeling software; PD, pharmacodynamic; PK, pharmacokinetic; PN, prurigo nodularis; RSE, relative standard error; θ_{B4}, factor change in λ_{asc} for subjects with baseline IGA of 4; λ_{asc}, rate constant for ascending transitions; λ_{desc}, rate constant for descending transitions; λ_{xy}, transition rate constant from x to y

Table 56. Parameter Estimates for the Weekly Average PP NRS Model

Parameter	Point Estimate	IIV (%CV)	%RSE[a]	Asymptotic 95% CI[a]	Bootstrap 95% CI[b]	Shrinkage (%)
tPP NRS_0 (-)	2.54	--	1.40	2.47; 2.61	2.45; 2.61	--
K_{OUT} (1/day)	0.0531	--	0.29	0.0528; 0.0534	0.0439; 0.0613	--
P_1 (-)	0.786	--	7.30	0.673; 0.898	0.474; 1.12	--
I_{max} (-)	2.08	--	2.50	1.98; 2.18	1.6; 2.62	--
IC_{50} (µg/mL)	0.357	--	8.50	0.298; 0.417	0.173; 0.743	--
Additive RUV (SD)	0.101	--	0.58	0.1; 0.102	0.0785; 0.133	--
Proportional RUV (SD)	0.19	--	0.33	0.189; 0.192	0.163; 0.218	--
IIV on tPP NRS_0	0.095[c]	30.8	2.50	0.0797; 0.11	0.0696; 0.115	7.9
IIV on P_1	3.02[c]	221	3.00	2.92; 3.12	2.47; 3.85	11
IIV on K_{OUT}	1.4[c]	118	4.40	1.3; 1.5	1.17; 1.64	19.9

Source: Table 16. GALD-PMX-NEMOLIZUMAB-1854-PKPD-PN

[a] Calculated from the NONMEM Sandwich estimator of the variance-covariance matrix. The RSE for omega is reported on the approximate SD scale (SE/variance)/2.

[b] A 95% CI based on 791 bootstrap replicates (209 bootstrap replicates were omitted from the calculation because of failed minimization with unreportable number of significant digits).

[c] Estimated variance.

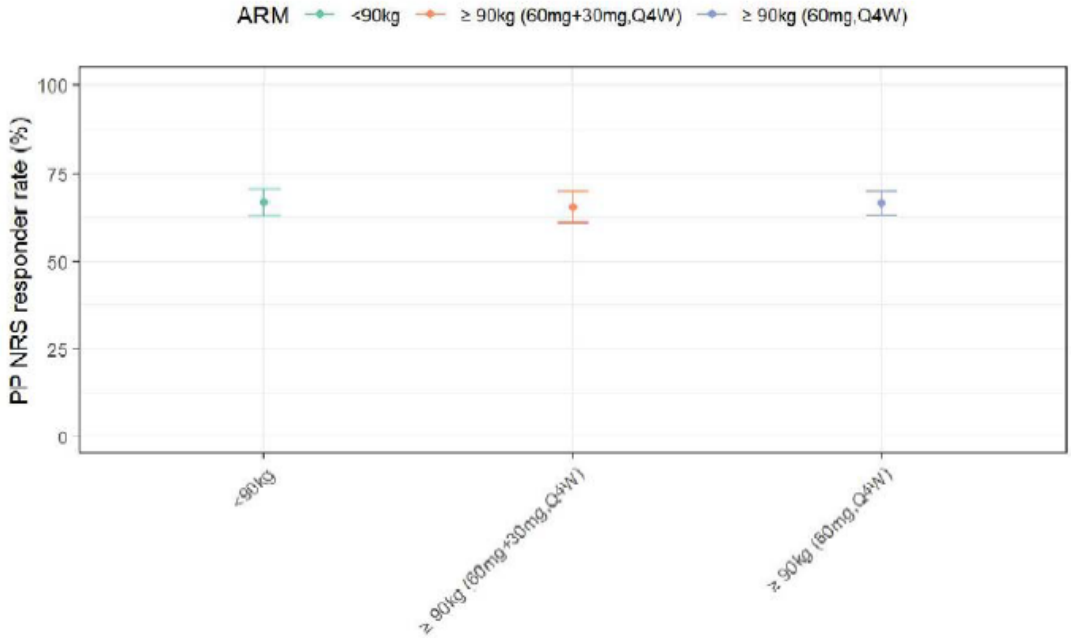
Abbreviations: CI, confidence interval; CV, coefficient of variance; IC_{50}, half-maximal inhibitory concentration; IIV, interindividual variability; I_{max}, maximum inhibition; K_{out}, first order elimination rate constant; NONMEM, Nonlinear Mixed-Effect Modeling; P_1, placebo effect; PP-NRS, Peak Pruritus Numeric Rating Scale; RSE, relative standard error; RUV, random unexplained variability; tPP NRSo, transformed baseline weekly average PP NRS

Table 57. Impact of Body Weight and IGA Baseline Value on the Responder Rate for IGA and PP NRS Across Simulations in Subjects With PN (Median [p5-p95])

Endpoint	Group	<90 kg 30 mg, Q4W (60 mg LD)	≥90 kg 30 mg, Q4W (60 mg LD)	≥90 kg 60 mg, Q4W
C_{trough} at W16 (µg/mL)	All subjects	2.62 [2.54-2.74]	1.85 [1.75-1.93]	3.24 [3.1-3.4]
PP NRS responders	All subjects	66.6 [62.8-70.4]	65.2 [60.9-69.7]	66.3 [63.1-69.7]
IGA responders	All subjects	33.3 [29.2-37]	26.1 [21.8-30.3]	34.4 [30-39.9]
	IGA baseline=3	37.9 [33.2-41.6]	30.6 [25.5-35.4]	38.9 [33.2-44.6]
	IGA baseline=4	27.6 [21.9-32.3]	20.7 [15.1-24.3]	28.4 [22.6-34.6]

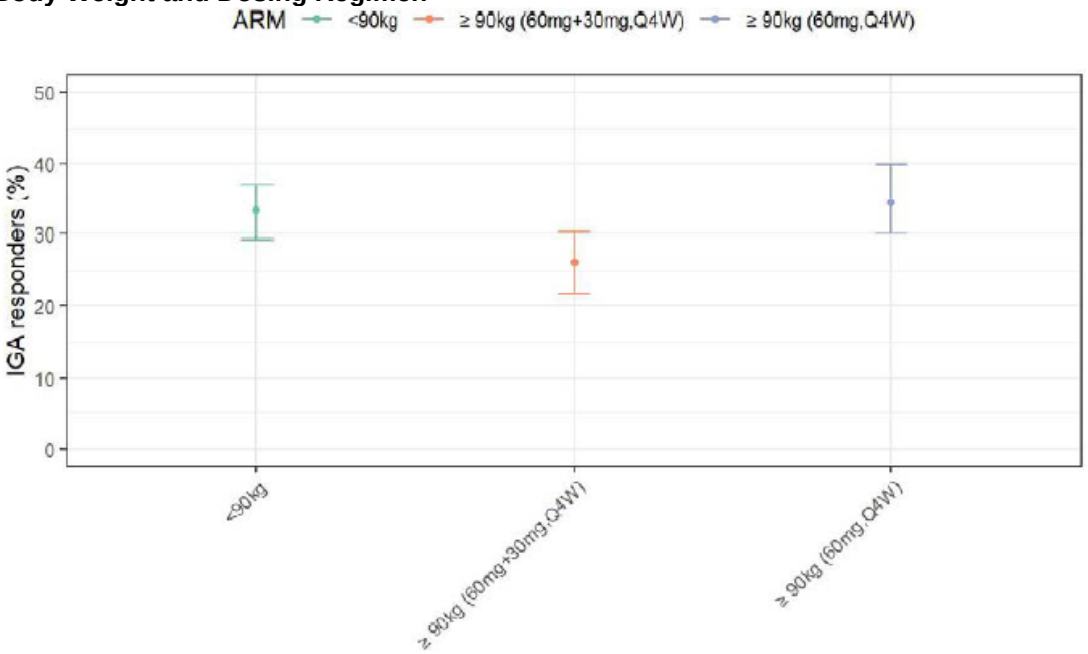
Source: Table 18. GALD-PMX-NEMOLIZUMAB-1854-PKPD-PN
Abbreviations: C_{trough}, trough plasma concentration; IGA, Investigator's Global Assessment; LD, loading dose; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, every 4 weeks

Figure 26. Impact of Body Weight on PP NRS Responder Rate at Week 16 in Subjects With PN Per Body Weight and Dosing Regimen



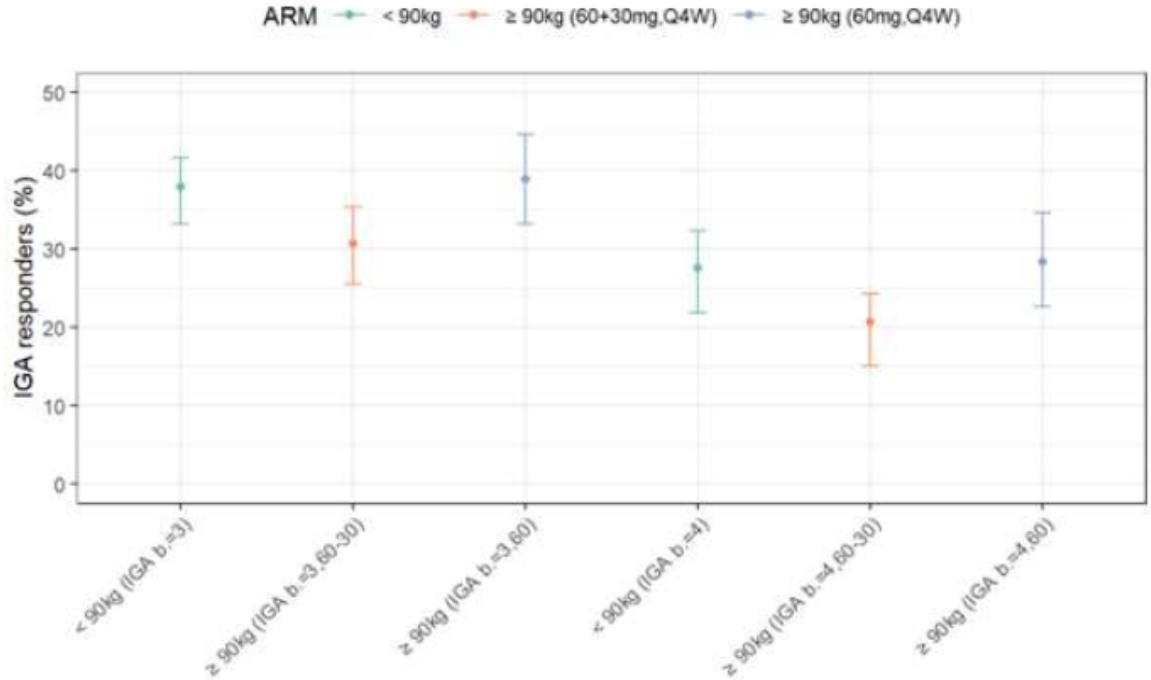
Source: Figure 8. GALD-PMX-NEMOLIZUMAB-1854-PKPD-PN
Abbreviations: PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, every 4 weeks

Figure 27. Impact of Body Weight on IGA Responder Rate at Week 16 in Subjects With PN Per Body Weight and Dosing Regimen



Source: Figure 9. GALD-PMX-NEMOLIZUMAB-1854-PKPD-PN
Abbreviations: IGA, Investigator's Global Assessment; Q4W, every 4 weeks

Figure 28. Impact of Body Weight on IGA Responder Rate at Week 16 in Subjects With PN Per Body Weight and Dosing Regimen Stratified by Baseline IGA Value



Source: Figure 9. GALD-PMX-NEMOLIZUMAB-1854-PKPD-PN
Abbreviations: IGA, Investigator's Global Assessment; Q4W, every 4 weeks

Summary

- Pharmacokinetic/pharmacodynamic simulations of clinical endpoints at Week 16 showed similar efficacy responses in both body weight groups (<90 kg and ≥90kg) when doses were adjusted according to body weight with a 90 kg cutoff. This supports the effectiveness and safety of the selected doses and proposed dosing regimens in subjects with PN.
- With the proposed nemolizumab dosing regimen in adults with PN, which includes a loading dose of 60 mg SC followed by 30 mg Q4W for subjects weighing <90 kg or 60 mg Q4W for subjects weighing ≥90 kg, a similar IGA success was predicted at W16 in both WGT groups (<90 kg and ≥90 kg). The IGA response rate decreased by 24% with no overlap of the CIs in subjects with WGT≥90 kg when receiving the non-adjusted WGT dose (30 mg Q4W + 60 mg LD), confirming that adjusting the dose according to WGT (with a cutoff of 90 kg) is necessary to achieve similar IGA response rates in both weight groups.
- The response rate at Week 16 was influenced by the IGA baseline value: with a lower response rate for subjects with a baseline value of 4 compared to subjects with a baseline value of 3.

Exposure-Safety Assessment

Executive Summary

The analyses of exposure-safety relationships did not show evidence of increased safety events with higher nemolizumab exposure.

Analysis Objective

To assess the exposure-safety relationship between nemolizumab exposure and safety outcomes.

Methodology

The PK metric selected for the exposure-safety analyses was the trough nemolizumab concentration at Week 16 (C_{trough} at Week 16). Subjects were included if they had evaluable PK at Week 16 and had received enough dosing events within the specified dosing window (e.g., for a Q4W regimen during the treatment phase, subjects were required to receive 4 doses from Week 1 to Week 12). This criterion ensured PK assessments were conducted on subjects who adhered to their dosing schedules and achieved reliable steady-state concentrations.

Exposure boxplots were stratified by response values for each adverse drug reaction and TEAE. The probability of events was summarized versus exposure after binning subjects according to exposure quartiles. All categorical variables were converted to binary responses and analyzed using linear logistic regression models. The predicted logistic regression curve and the observed adverse event rate in relevant bins of the observed data (e.g., quartiles of exposure metrics) were plotted for all exposure-safety analyses.

Results

The safety endpoints investigated included eczematous reactions, headache, newly diagnosed asthma or worsening of asthma, facial edema, and peripheral edema. Graphical exploration of exposure metrics between subjects with and without these safety endpoints did not reveal any

significant positive relationships between nemolizumab exposure and the incidences of these safety endpoints. These initial findings were further confirmed by logistic regression analysis, which also did not identify any significant impact of nemolizumab exposure metrics on the incidences of the safety endpoints.

14.6. Pharmacogenetics

Not applicable

15. Study/Trial Design

The protocol synopses were provided by the Applicant. Cross-references in the following subsections are therefore not consistent with the remainder of the review.

15.1. Phase 2a Protocol Synopsis (RD.03.SPR.115828)

Table 58. Phase 2a Protocol Synopsis (Version 2.0; April 9, 2018) for RD.03.SPR.115828 (NCT03181503)

	Synopsis
Clinical trial title	A study to assess the safety and efficacy of nemolizumab (CD14152) in subjects with prurigo nodularis (PN)
Clinical trial phase	II a
Clinical trial population	Adult subjects with clinical diagnosis of PN for at least 6 months with at least 20 nodules on the whole body
Clinical trial objectives	**Primary objective:** • The primary objective is to assess the efficacy of nemolizumab compared to placebo in the treatment of pruritus in patients suffering from PN. **Secondary objective:** The secondary objectives are: • Efficacy and safety: • Evaluation of the safety of nemolizumab compared to its placebo in patients with PN. • Evaluation of the efficacy of nemolizumab compared to its placebo in the treatment of prurigo lesions in patients with PN. • Evaluation of nemolizumab effect compared to its placebo on quality of life in patients with PN **Pharmacokinetics (PK)** • Characterization of nemolizumab PK profile and exposure response relationship in patients with PN **Pharmacodynamics (PD)** • Evaluation of the effect of nemolizumab on biomarkers in patients with PN

Synopsis	
	Biophysical (exploratory) • Evaluation of the efficacy of nemolizumab on scratching events and sleep improvement using actigraphy • Evaluation of the efficacy of nemolizumab on lesions improvement using whole body images device only on equipped sites.
Clinical trial design	This is a randomized, placebo-controlled, double-blinded, parallel group, multicenter study to evaluate the safety and efficacy of nemolizumab in patients suffering from PN. Approximately 70 adult patients suffering from PN for at least 6 months with severe pruritus defined by the mean of the worst daily intensity of the NRS score ≥ 7 over the previous week at baseline will be randomized in the study. Subjects meeting inclusion/exclusion criteria will be randomized in a 1:1 ratio to nemolizumab or placebo. Each subject will receive three subcutaneous injections of 0.5mg/kg of nemolizumab or matching placebo. If a patient weights more than140 kg the study drug should be prepared as for a patient who weighs 140 kg. Thus, the total volume injected should not exceed 2.8mL. Injections will be administered every 4 weeks (baseline, week 4 & week 8). Subjects' participation in the study will be up to 22 weeks, including an up to 4-week screening period, a 12- week treatment period (last study drug injection at week 8) and a 6-week follow-up period (10 weeks after the last study drug injection corresponding to 5 half-lives of nemolizumab). A total of 10 visits per subject is planned. Schedule of assessments is summarized in Table 2. Safety and efficacy assessments will be conducted throughout the study. Pruritus severity will be self-evaluated by the subjects on a daily basis using the ePRO and following instructions provided by the Investigator. The Investigator will evaluate the evolution of prurigo lesions using appropriate scales. PK profile of nemolizumab in PN patients will be assessed according to Table 2. PD assessments will be performed to evaluate cytokines/chemokine profiles, IL31 and IL31 RA quantification by proteomics, genomic and histology analysis using three 4-mm skin biopsies, D-squames and blood samples collected according to Table 2. Skin biopsies will be optional, patients accepting this procedure will have to sign an additional consent. Exploratory biophysical assessments will be performed by measuring scratching events during the night and sleep duration using actigraphy. The subject will have to wear two watches from Day -7 to baseline and during the first four weeks of the study. In addition, photographs of the entire body will be taken in equipped sites using a whole-body imaging device according to Table 2 An interim analysis may be performed once at least 40 subjects will have completed the week 4 visit or discontinued before (decision will be taken by the Sponsor according to the recruitment rate). This analysis will include efficacy data on all subjects up to that time point. In addition to efficacy, all safety data available (not only data up to week 4) will also be analyzed (Section 9.4).
Total number of subjects (planned)	As a screen failure rate of approximately 30 percent is expected, approximately 100 subjects may have to be screened in order to get 70 randomized subjects (35 subjects per treatment group).
Number of clinical trial centers (planned)	Approximately 20 sites

Synopsis	
Regions/countries involved (planned)	Austria, France, Germany, Poland & US
Clinical trial duration	The planned clinical trial duration (from FSFV to LSLV) is approximately 10 months.
Duration of subject participation	Clinical trial participation for each subject is approximately 22 weeks.
Key inclusion criteria	Male or female of at least 18 years at screening Clinical diagnosis of PN for at least 6 months with: • Prurigo lesions on upper limbs with or without lesions on the trunk or lower limbs • At least 20 nodules on the entire body with a bilateral distribution • Severe pruritus defined as follows on a Numerical Rating Scale (NRS) • At the Screening visit 1: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous 3 days • At the Baseline visit: Mean of the worst daily intensity of the NRS score is ≥ 7 over the previous week; *NOTE: NRS score should be measured on at least 5 days during the week preceding the baseline visit*.
Key exclusion criteria	Chronic pruritus resulting from another condition than PN such as scabies, insect bite, lichen simplex chronicus, psoriasis, acne, folliculitis, habitual picking, lymphomatoid papulosis, chronic actinic dermatitis, dermatitis herpetiformis, sporotrichosis, bullous disease Unilateral lesions of prurigo (e.g. only one arm affected) Cutaneous bacterial or viral infection within 1 week before the baseline visit. Infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 1 week before the screening visit, or during the screening period, unless completely resolved at the screening/ baseline visits respectively, Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with the interpretation of the clinical trial results and/or put the subject at significant risk according to Investigator's judgment (e.g., solid cancer, AIDS, serious or uncontrolled cardiac disease…) at screening or baseline. *NOTE: Patients with **controlled diseases such as** diabetes mellitus, thyroid disorders, and psychiatric disorders (such as depression and anxiety) are eligible* Any active dermatoses that would need immediate therapy. Subject with active atopic dermatitis or known with recurrent flares of atopic dermatitis *NOTE: patients with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e. specific IgE), are eligible for the study* Neuropathic and psychogenic pruritus (notalgia paresthetica, brachioradial pruritus, dilutional parasitosis, pathomimia)

Synopsis

Positive serology results hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody or Human Immunodeficiency virus [HIV] antibody) at the screening visit

NOTE: Subject with a positive HBcAb and a negative HBsAg can be included in this trial if HBsAb is positive (considered immune after a natural infection)

Subject having any of the abnormal lab criteria listed below, at the screening visit:

- Elevated ALT / AST ≥3 ULN
- Elevated CPK >1.5 ULN, unless not confirmed on a repeat assessment to be performed at least 72h after the first one
- Neutrophil count <1.5 x 103/□l
- Creatinine clearance <60ml/min/1.73m² calculated with the CKD-EPI formula (Levey et al. 2009)
- Any other abnormal lab result that would be considered as clinically significant by the investigator

- Subjects with a medical history of asthma that fulfill any or more of the conditions below
- Had an asthma exacerbation requiring hospitalization in the last 12 months before screening visit
- Whose asthma has not been well-controlled (i.e. symptoms >2 days per week, nighttime awakenings >1-3 times per week, or some interference with normal activities) during the last 3 months before the screening visit
- PEF <80% of the predicted value at screening or baseline visit
- Latent or active TB, as determined by a positive Quantiferon-based TB test result at screening visit 1.

NOTE: In case of indeterminate result, the test should be repeated in local laboratory at screening visit 2 (only one retest is allowed). If the test is still indeterminate, the subject will not be included.

Investigational product and its comparator

	Investigational Product	**Comparator**
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder	Lyophilized powder
Concentration	100mg/ml when reconstituted	NA
Formula number	NA	NA
Packaging	Vial	Vial
Storage conditions	Stored between 2 to 8°C (36-46°F) and protected from light	Stored between 2 to 8°C (36-46°F) and protected from light
Dosage	0.5 mg/kg*	Not applicable
Route	Subcutaneous injection	Subcutaneous injection
Dose regimen	3 injections (baseline, Week 4, Week 8)	3 injections (baseline, Week 4, Week 8)
Treatment duration	12 weeks	12 weeks

* If a patient weights more than 140 kg the study drug should be prepared as for a patient who weighs 140 kg. Thus, the total volume injected should not exceed 2.8mL.

Synopsis	
Efficacy endpoints	**Primary:** • The primary efficacy outcome will be the percent change from baseline in NRS to week 4 (weekly average of the peak). **Secondary:** • Absolute and Percent change from baseline in weekly average of the peak and average pruritus NRS to each visit • Change from baseline of VRS at each time point • DPS • PAS: Distribution for item 6 (excoriation/crusts and healed lesions stages) and change from baseline for item 5 (in lesions number) • IGA: Distribution score and success rate (defined as IGA=0[clear] or IGA=1[Almost clear] with two point improvement from baseline). **Other endpoints:** • Quality of life (DLQI) • Objective assessments of scratching and sleep by Actigraphy Sleep disturbance NRS
Safety assessments	The safety measures for this study are as follows: • Adverse events • Laboratory tests • Vital signs • Physical exam and body weight • 12-lead ECG • PEF
Pharmacokinetic assessment and anti-drug antibody (ADA) assessment	Blood samples will be collected at specific time points according to Table 2 for measurement of PK profile of nemolizumab and anti-nemolizumab antibodies. The nemolizumab serum exposure will be assessed at the following time-points: baseline, weeks 1, 2, 4, 8, 12, 16 and 18 and at early termination or any unscheduled visit for safety reason. ADA will be assessed at baseline, weeks 4, 8, 12, 16 and 18 and in case of early termination or unscheduled visit for safety reason.

	Synopsis
Pharmacodynamics assessment	Blood and skin samples (D-Squames and skin biopsies) will be collected to investigate the effect of nemolizumab on biomarkers according to Table 2 As much as possible, skin sampling will be performed in similar body areas for all samples in all patients, on a selected area at baseline, such as the upper arms. Skin biopsies on prurigo lesions will be performed on lesional and non lesional skin at baseline, and on lesional skin at week 12 (only for patients consenting to have skin biopsies). Non- lesional sample will be taken in areas with no scratch such as the inner part of the upper arm, approximately 5 cm apart from lesional skin. The detail of the procedure and storage conditions will be described in an operational manual. All collected samples will be sent to GALDERMA R&D for analysis. After performance of the planned investigations, the remaining samples will be integrated into the long term research program being performed in the research department of Galderma R&D (Program (2) – "Physiopathological study on skin disease to identify new dermatological medications; Initial declaration CP ECOH: DC-2008-315, 31/01/2009).
Principal statistical method	The primary efficacy analysis of the percent change from baseline to week 4 of the weekly average of the NRS (weekly average of the worst score) will be an ANOVA including the Treatment group as factor, presence and absence of background of atopy and country as a cofactor. In addition to the per-protocol analysis, several sensitivity analyses on ITT population will be conducted for the primary endpoint. For ITT, NRS will be set to missing after rescue medication is used. The primary imputation method for any missing data will be the LOCF (Last observation carried forward) approach. Multiple Imputation (MI) using the Missing At Random (MAR) assumption will also be used. The MI procedure of the SAS system will be used to generate five sets of data with missing values imputed from observed data. It is expected that the pattern of missing data will be monotonic, with slight deviations being corrected by the Markov Chain Monte Carlo (MCMC) method of the MI procedure. Linear regression will be employed to model the missing NRS score, with the following covariates included in the imputation model: treatment and non-missing data from earlier timepoints. The imputed datasets will be analyzed using the methodology described for percent change from baseline in NRS score. The results from the analysis of the multiple imputed datasets will be combined by the MIANALYZE procedure of the SAS system. The seed number to be used will be the protocol number (115828). The PD parameters will be visualized by boxplots (with a logarithm base 10 Y axis where needed). The compound effect will be estimated by Student's t test comparing the change at D85 from D1 for CD14152 versus the change at D85 from D1 for placebo (or other if more appropriate). The multiple testing problem will be taken into account by the Benjamini- Hochberg approach (1995) (or other if more appropriate). Summary statistics will be provided by treatment group for treatment emergent adverse events.

	Synopsis
Sample size	With an effect size of (30/35=) 0.857, a power of 90% and a type I error of 5% two-sided; at least 30 subjects are needed per group. In order to maintain the power of the tests, for per-protocol population, in case of dropouts/major deviations at Week 4, the sample size will be increased to 35 subjects per group, i.e. 70 to be randomized.

Abbreviations: ADA, anti-drug antibodies; ALT, alanine aminotransferase; ANOVA, analysis of variance; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CPK, creatine phosphokinase; DLQI, Dermatology Life Quality Index; DPS, Dynamic Pruritus Score; ECG, electrocardiogram; ePRO, Electronic Patient Reported Outcome; FSFV, first subject first visit; HIV, human immunodeficiency virus; IGA, Investigator's Global Assessment; ITT, intent-to-treat; LOCF, last observation carried forward; LSLV, last subject last visit; MAR, missing at random; MCMC, Markov Chain Monte Carlo; MI, myocardial infarction; NRS, numeric rating scale; PAS, Prurigo Activity Score; PD, pharmacodynamic; PEF, peak expiratory flow; PK, pharmacokinetic; PN, prurigo nodularis; TB, tuberculosis

Table 59. Clinical Trial Schematic

.	Screening (Approximately 100) Randomization (Approximately 70)	
	Group 1 N=approximately 35	**Group 2 N=approximately 35**
Treatment	CD14152 0.5mg/kg*	CD14152 placebo
Treatment frequency	Every 4 weeks (Q4W)	Every 4 weeks (Q4W)
Treatment duration	12 weeks (last study drug injection at week 8)	12 weeks (last study drug injection at week 8)
Follow up	6 weeks (10 weeks after the last study drug injection)	6 weeks (10 weeks after the last study drug injection)

* If a patient weights more than 140 kg the study drug should be prepared as for a patient who weighs 140 kg. Thus, the total volume injected should not exceed 2.8mL
Abbreviations: N, number of patients in treatment arm; Q4W, every 4 weeks

15.2. Phase 3 Protocol Synopsis, OLYMPIA 1 (RD.06.SPR.202685)

Table 60. Phase 3 Protocol Synopsis (Version 5.0; November 19, 2021) for OLYMPIA 1 (RD.06.SPR.202685; NCT04501666)

Title of study	A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of nemolizumab (CD14152) in subjects with prurigo nodularis
Protocol number	RD.06.SPR.202685
Investigators/study sites/centers	Approximately 70 sites in Europe, North America, and Asia Pacific
Phase of development	Phase 3
Objectives	The primary objective is to assess the efficacy of nemolizumab (CD14152) compared to placebo in subjects ≥ 18 years of age with prurigo nodularis (PN) after a 16-week treatment period. The secondary objectives are to assess the safety, pharmacokinetics, and immunogenicity of nemolizumab (CD14152) compared to placebo.
Study endpoints	**Primary endpoints:** • Proportion of subjects with an improvement of ≥ 4 from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16 • Proportion of subjects with an Investigator Global Assessment (IGA) success (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point improvement from baseline) at Week 16

Key secondary endpoints:

- Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 4
- Proportion of subjects with PP NRS < 2 at Week 16
- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 16
- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 4
- Proportion of subjects with PP NRS < 2 at Week 4

Secondary efficacy endpoints:

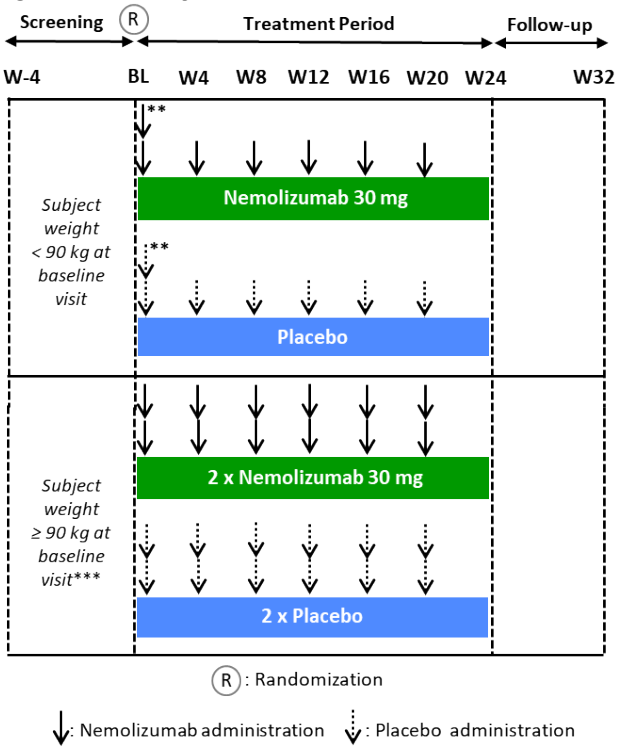
- IGA success rate at each visit through Week 24
- Percentage of pruriginous lesions with excoriations/crusts (Prurigo Activity Score [PAS] item 5a) at each visit through Week 24
- Percentage of healed prurigo lesions (PAS item 5b) at each visit through Week 24
- Change from baseline in number of lesions in representative area (PAS item 4) at each visit through Week 24
- Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS through Week 24
- Proportion of subjects with PP NRS < 2 from baseline through Week 24
- Proportion of subjects with PP NRS < 3 from baseline through Week 24
- Absolute change from baseline in PP NRS through Week 24
- Percent change from baseline in PP NRS through Week 24
- Proportion of subjects with an improvement of ≥4 from baseline in Average Pruritus (AP) NRS through Week 24
- Proportion of subjects with PP NRS improvement ≥4 from baseline and IGA success at Week 16, Week 20, and Week 24
- Proportion of subjects with AP NRS <2 from baseline through Week 24
- Absolute change from baseline in AP NRS through Week 24
- Percent change from baseline in AP NRS through Week 24
- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS through Week 24
- Absolute change from baseline in SD NRS through Week 24
- Percent change from baseline in SD NRS through Week 24
- Change from baseline in sleep diary endpoints (sleep onset latency, wakefulness after sleep onset [WASO], total awake time, total sleep time, sleep efficiency, WASO related to PN, number of WASO related to PN) based on recordings from subject sleep diary through Week 24
- Change from baseline in PN-associated pain frequency through Week 24
- Change from baseline in PN-associated pain intensity through Week 24
- Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on Patient Global Assessment of Disease (PGAD) at Week 24
- Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on Patient Global Assessment of Treatment (PGAT) at Week 24

	• Proportion of subjects with an improvement of ≥ 4 in Dermatology Life Quality Index (DLQI) through Week 24 • Change from baseline in DLQI through Week 24 • Change from baseline in Hospital Anxiety and Depression Scale (HADS) for each subscale (i.e., depression and anxiety) at Week 24 • Change from baseline in EuroQoL 5-Dimension (EQ-5D) at Week 24 **Safety endpoints:** • Incidence and severity of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), and serious AEs (SAEs). **Pharmacokinetic endpoints:** • Nemolizumab (CD14152) serum concentrations **Immunogenicity endpoints:** • ADA assay (screening, confirmatory, titer, NAb)
Study design	This phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group study is designed to evaluate the efficacy and safety of nemolizumab in subjects with PN. Approximately 270 subjects with PN will be randomized 2:1 to receive either nemolizumab (CD14152) or placebo, stratified by study center and body weight (< 90 kg versus ≥ 90 kg). Subjects weighing < 90 kg at baseline will receive either 30 mg nemolizumab (with 60 mg loading dose at baseline) or placebo every 4 weeks (Q4W). Subjects weighing ≥ 90 kg at baseline will receive either 60 mg nemolizumab or placebo Q4W (no loading dose at baseline). Subjects' participation in the study will be up to 36 weeks. The study consists of a screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow up period (12 weeks after their last study drug injection). Refer to Figure 1 for an overview of study design. Following provision of written informed consent, subjects with PN will be screened for enrolment in the study. Eligible subjects will return for a baseline visit where, following randomization, they will be administered either a dose of 60 mg nemolizumab or placebo via 2 subcutaneous (SC) injections. Thereafter, study drug will be administered Q4W at Week 4, 8, 12, 16 and 20 by either a single SC injection of either nemolizumab 30 mg or placebo for subjects weighing < 90 kg at baseline or by two SC injections of either nemolizumab 30 mg or placebo for subjects weighing ≥ 90 kg at baseline. Refer to Table 1 for an overview of the study therapy. Efficacy and safety assessments will be performed at visits throughout the screening and treatment period, as outlined in the Schedule of Assessments (Table 5). At the end of the 24-week treatment period, consenting subjects may be eligible to enter an active treatment/long-term extension (LTE) study (RD.06.SPR.202699). Subjects who participate in the LTE are not required to complete the follow-up visit. Subjects who do not participate in the LTE will return for a follow-up visit at Week 32 (12 weeks after the last study drug injection).

Subjects who prematurely discontinue the study drug will be asked to continue participation in the study and return for all remaining visits and assessments (including daily assessments of pruritus and sleep disturbance). Subjects who discontinue study drug due to required rescue therapy may be eligible to participate in the LTE study following completion of study visits through Week 24. Subjects who discontinue the study prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection.

An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related events throughout the study. The IDMC and IAC charters provide details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and the procedures, roles, responsibilities, and communications.

Figure 29. Study Schema



* Applicable for subjects who do not participate in the LTE study only
** Loading dose (two injections) administered at baseline visit for subjects weighing < 90 kg
*** Two injections administered at all applicable visits for subjects weighing ≥ 90 kg at the baseline visit

:Abbreviations: BL, baseline; LTE, long-term extension; R, randomization; W, week

Selection of subjects	**Inclusion Criteria:** • Individuals must meet all of the following criteria to be included in the study: • Male or female and aged ≥18 years at the time of screening

- Clinical diagnosis of PN for at least 6 months with:
- Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs
- At least 20 nodules on the entire body with a bilateral distribution
- IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits
- Severe pruritus defined as follows on the PP NRS:
- At the screening visit (Visit 1): PP NRS score is ≥ 7.0 for the 24-hour period immediately preceding the screening visit
- At the baseline visit (Visit 2): Mean of the daily intensity of the PP NRS score is ≥ 7.0 over the previous week;

Note: PP NRS score should be measured on at least 4 days during the week preceding the baseline visit. Rounding of the mean NRS score is not permitted.

Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use at least 1 adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection.

Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:

- True abstinence, when in line with the preferred and usual lifestyle of the subject. See Appendix 1 for details. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Progestogen-only oral hormonal contraception
- Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception)

Note: “Double barrier methods” refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) together with a spermicide is not acceptable.

- Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
- Injectable or implanted hormonal contraception
- Intrauterine devices or intrauterine hormone releasing system
- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Bilateral vasectomy of male partner at least 3 months before the study

Female subjects of non-childbearing potential must meet 1 of the following criteria:

- Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range
- Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study
- Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily

diary recordings by the subject using an electronic handheld device provided for this study

- Read, understood and signed an informed consent form (ICF) before any investigational procedure(s) are performed

Exclusion Criteria:

- Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:
- Body weight <30 kg
- 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 disorder, sporotrichosis, 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
- Unilateral lesions of prurigo (e.g., only one arm affected)
- History of or current confounding skin condition (e.g., Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis)
- Subjects meeting 1 or more of the following criteria at screening or baseline:
- Had an exacerbation of asthma requiring hospitalization in the preceding 12 months
- Reporting asthma that has not been well-controlled (i.e., symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months
- Asthma Control Test (ACT) ≤19 (only for subjects with a history of asthma)
- Peak expiratory flow (PEF) <80% of the predicted value

Note: In the event that PEF is < 80% of the predicted value at the screening visit in subjects without any history of asthma or in subjects with history of asthma but with the ACT score >19, PEF testing can be repeated once within 48 hours.

- Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis
- Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.4.2.
- Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive confirmatory test for HCV [e.g., polymerase chain reaction (PCR)], or human immunodeficiency virus antibody) at the screening visit

Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study.

- In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.
- Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit
- Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months

Note: Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e., specific immunoglobulin E), are eligible for the study.

- Neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis
- Having received any of the following treatments below within the specified timeframe before the baseline visit:

Treatments	**Timeframe**
Topical calcineurin inhibitors (tacrolimus, pimecrolimus), and topical corticosteroids	2 weeks
Topical vitamin D analogs	2 weeks
Topical or systemic PDE-4 inhibitors	2 weeks
Any other topical treatment other than moisturizer (e.g., capsaicin, cryotherapy for treatment of PN)	2 weeks
Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim	1 week
Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy)	1 week
Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (e.g., amitriptyline), SSRIs (e.g., paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening	1 week
Phototherapy or tanning beds	4 weeks
Immunosuppressive or immunomodulatory drugs (e.g., cyclosporine, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (e.g., etanercept, adalimumab, infliximab, omalizumab)	8 weeks or 5 half-lives (whichever is longer)

Dupilumab	10 weeks
Systemic retinoids	8 weeks or 5 half-lives (whichever is longer)
Systemic roxithromycin, erythromycin	1 week
Opioid antagonists (e.g., naltrexone, naloxone), opioid partial/mixed agonists (e.g., nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (e.g., aprepitant, serlopitant)	4 weeks or 5 half-lives (whichever is longer)
Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions	4 weeks
Cannabinoids (e.g., dronabinol)	2 weeks
Alternative medicine for PN (e.g., traditional Chinese medicine)	2 weeks
Live vaccines	12 weeks
Non-live vaccines	4 weeks

Abbreviations: JAK, Janus kinase; NK1, neurokinin; PDE-4, phosphodiesterase-4; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

Previous participation in a clinical study with nemolizumab

- Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study
- History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for:
  - Basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit, or;
  - Actinic keratoses that have been treated
- History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g., monoclonal antibody) or to any of the study drug excipients
- Current active or latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines

Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit.

	• Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment • Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), 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 (e.g., poor venous access or needle-phobia) • History of alcohol or substance abuse within 6 months of the screening visit • Planned or expected major surgical procedure during the clinical study • Subject is unwilling to refrain from using prohibited medications during the clinical study (see Section 9.10.3) • Currently participating or participated in any other study of an investigational drug or device, within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study For subjects accepting optional biopsy sampling (by signing an additional consent), the following exclusion criteria also apply. If any of the below criteria are met, biopsy samples must not be collected: • History of coagulation disorders • Known sensitivity to local anesthetics • Using platelet aggregation inhibitors, or anticoagulants (sporadic intake or continuous low-dose intake of aspirin or other non-steroidal anti-inflammatory drugs is allowed) • History or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of scars.
Planned sample size	Approximately 270 subjects are planned to be randomized in this study
Therapy	Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for subcutaneous injection only after reconstitution in a single-use, pre-filled, dual-chamber syringe (DCS). During the treatment period, eligible subjects will be randomized to receive either nemolizumab (CD14152) or placebo, administered Q4W for 24 weeks (last injection at Week 20). Subjects weighing < 90 kg at baseline will receive either nemolizumab 30 mg or placebo via a single SC injection (with a loading dose of 60 mg on Day 1/baseline); subjects weighing ≥ 90 kg at baseline will receive either nemolizumab 60 mg or placebo via two SC injections at all visits (no loading dose). Subjects will have the option to self-inject study drug while at the study center under staff supervision. Subjects will be trained on injecting the study drug and will be allowed to inject study drug at all subsequent visits, while at the study center, under staff supervision. If the subject does not wish to perform the injections, study staff can administer study drug at each visit.

Table 61. Investigational Therapy

	Investigational Product	Placebo
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Packaging	DCS	DCS
Storage conditions	Stored between 2°C to 8°C (36°F to 46°F), protected from light, protected from freezing	Stored between 2°C to 8°C (36°F to 46°F), protected from light, protected from freezing
Dosage	Subjects weighing <90 kg at baseline: 30 mg, with a loading dose of 60 mg at baseline; Subjects weighing ≥90 kg at baseline: 60 mg	Not applicable
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution
Dose regimen	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥90 kg at baseline: 2 injections at baseline, then 2 injections Q4W	Subjects weighing <90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥90 kg at baseline: 2 injections at baseline, then 2 injections Q4W
Treatment duration	24 weeks with last injection at Week 20	24 weeks with last injection at Week 20

Abbreviations: DCS, dual chamber syringe; Q4W, every 4 weeks; SC, subcutaneous

Rescue therapies

If deemed to be medically necessary by the investigator (e.g., to control intolerable signs/symptoms of PN), rescue therapies can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving rescue therapies during the screening period are not eligible to participate in the study.

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure.

Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy.

	Whenever possible, investigators should first use topical medication or oral antihistamines as rescue therapy before escalating to other systemic therapies. If subjects receive topical treatments, oral antihistamines, or ultraviolet B (UVB) phototherapy as rescue therapy, study drug administration should be continued unless there is a concern according to the investigator's judgment. If subjects receive systemic rescue therapy (other than oral antihistamines), intralesional corticosteroids, or oral psoralen + ultraviolet A (PUVA) treatment, the study drug administration must be permanently discontinued. See Section 9.10.2 for a complete list of allowed rescue therapies. Subjects requiring rescue medication (with or without study drug discontinuation) may be eligible for LTE participation. These subjects must continue with study visits through Week 24 to be considered for LTE participation.
Treatment duration	The expected duration of each subject's participation in the study is up to 36 weeks, including a screening period (up to 4 weeks), a 24-week treatment period, and an 8-week follow-up period (12-weeks after the last study drug injection). Subjects who rollover into the LTE are not required to complete the follow-up visit.
Efficacy	The following efficacy assessments are planned according to the Schedule of Assessments (Table 5): • IGA • Peak and Average Pruritus NRS • PAS • SD NRS • Subject Sleep Diary • PN-associated pain intensity and frequency • PGAD and PGAT • Clinical photographs (optional and subject to a specific, separate ICF at selected sites) The following quality of life assessments are planned according to the Schedule of Assessments (Table 5): • DLQI • HADS • EQ-5D • Additional Patient-Reported Outcomes assessments are planned according to the Schedule of Assessments (Table 5), as follows: • Patient Global Impression of Severity-Pruritus • Patient Global Impression of Change-Pruritus • Patient Global Impression of Severity-Sleep Disturbance • Patient Global Impression of Change-Sleep Disturbance

Safety	The following safety assessments are planned according to the Schedule of Assessments (Table 5): • AEs, including TEAEs, AESIs, and SAEs • Physical examination and vital signs • Clinical laboratory tests • Electrocardiogram (ECG) • Respiratory examination and assessments
Pharmacokinetics, immunogenicity, pharmacodynamics, and pharmacogenomics	The following assessments are planned according to the Schedule of Assessments (Table 5): • Serum nemolizumab concentrations • Anti-drug antibody (ADA) assessments (screening, confirmatory, titer, and neutralizing antibody (NAb) • Biomarkers (e.g., interleukin-31 and/or other biomarkers) from blood, stratum corneum (D-Squames), and optional skin biopsies (subject to specific, separate ICF) (select centers only) • Pharmacogenomic testing (optional and subject to a specific, separate ICF)
Statistical methods and planned analyses	The intent-to-treat (ITT) population will consist of all randomized subjects. The safety population will include all randomized subjects who receive at least 1 dose of study drug. The Per-Protocol (PP) population will consist of all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. The ITT population will be the primary population for all efficacy analyses, and all safety data will be summarized based on the safety population. The PP population will be used as the population for sensitivity analyses of the primary and key secondary efficacy endpoints. **Primary efficacy endpoints** There are 2 primary efficacy endpoints • The proportion of subjects with at least 4 points of improvement in PP NRS at Week 16. • The proportion of subjects reporting success on the IGA at Week 16, defined as an IGA response of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point reduction from baseline. Both primary endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for randomized stratification variable analysis center and baseline body weight (<90 kg and ≥90 kg). The estimate of the treatment difference (nemolizumab minus placebo), p-value and 2-sided 95% confidence interval will be presented. Missing data at Week 16, and any data for subjects in receipt of rescue medication up to Week 16, will be regarded as a non-responder for the primary analysis of the endpoint. A number of sensitivity analyses are included for the primary endpoints, as per Section 15.4.3. **Key secondary endpoints** All binary key secondary efficacy endpoints will be analyzed as per the primary endpoint.

Additionally, sensitivity analyses using multiple-imputation assuming missing at random (MAR) and observed case (OC) analysis will be performed for key secondary endpoints as outlined in Section 15.4.4.

Secondary efficacy endpoints
Binary secondary endpoints will be analyzed in the same manner as the primary endpoint; missing values will be imputed as non-responder.

Continuous secondary endpoints (except EQ-5D, HADS) will be analyzed using multiple-imputation assuming MAR and using mixed effect model for repeated measure (MMRM) approach, including analysis center as factor and baseline as covariate where applicable. The estimated treatment difference for each endpoint at each visit will be displayed in the summary of statistical analysis together with the 95% CI and associated p-value. EQ-5D and HADS endpoints will be analyzed using analysis of covariance (ANCOVA) including analysis center as factor and baseline as covariate. All secondary endpoints will be presented descriptively using OC.

Further details will be provided in the Statistical Analysis Plan.

Multiplicity
To control the type I error at 5%, a fixed sequential testing approach will be implemented. For testing purposes both primary endpoints will be tested first in a predefined order (as listed in Section 15.4.1) at 5% significance level and testing of key secondary endpoints will start only if both primary endpoints are successful at 5% level of significance. Key secondary endpoints will be tested in an order listed in section 15.4.4, stopping when a non-significant result (p> 0.05) is found.

Safety analyses
The incidence of TEAEs, vital signs, laboratory values and ECG will be summarized by treatment groups.

Pharmacokinetics (PK)
Summary statistics will be used to describe the PK profile of nemolizumab. Individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics of the serum concentrations versus time will be presented as well as for the PK parameters.

Sample size
In order to achieve at least 90% power for both primary endpoint at 5% significance level, 270 (180 nemolizumab, 90 placebo) subjects will be required to detect the following difference in both primary endpoints between treatment groups with 2:1 randomization, assuming 15% dropout rate during treatment period.

NRS responders (≥4 point reduction from baseline): Based on phase 2a data, it is expected that the NRS response at Week 16 would be 50% in Nemolizumab group and 20% in placebo.

IGA response (0/1): It is expected that the IGA response at Week 16 would be 30% in Nemolizumab group and 10% in placebo.

Abbreviations: ACT, Asthma Control Test; ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AP, Average Pruritus; AST, aspartate aminotransferase; CMH, Cochran-Mantel-Haenszel; DCS, dual chamber syringe; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EQ-5D,

EuroQol 5-Dimension; ET, early termination; FSH, follicle stimulating hormone; HADS, Hospital Anxiety and Depression Scale; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; IAC, independent adjudication committee; ICF, informed consent form; IDMC, Independent Data Monitoring Committee; IGA, Investigator's Global Assessment; ITT, intent-to-treat; LTE, long-term extension study; MAR, missing at random; MMRM, mixed model repeated measures; Nab, neutralizing antidrug antibody; NRS, numeric rating scale;OC, observed case; PAS, Prurigo Activity Score; PCR, polymerase chain reaction; PEF, peak expiratory flow; PGAD, Patient Global Assessment of Disease; PGAT, Patient Global Assessment of Treatment; PK, pharmacokinetic; PN, prurigo nodularis; PP, per protocol; PP-NRS, Peak Pruritus Numeric Rating Scale; PUVA, psoralen + ultraviolet A; Q4W, every 4 weeks; SAE, serious adverse event; SC, subcutaneous; SD-NRS, Sleep Disturbance Numeric Rating Scale; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TB, tuberculosis; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UVB, ultraviolet B; WASO, wakefulness after sleep onset

15.3. Phase 3 Protocol Synopsis, OLYMPIA 2 (RD.06.SPR.203065)

Table 62. Phase 3 Protocol Synopsis (Version 5.0; November 19, 2021) for OLYMPIA 2 (RD.06.SPR.203065; NCT04501679)

Title of study	A randomized, double-blind, placebo-controlled study to assess the efficacy and safety of nemolizumab (CD14152) in subjects with prurigo nodularis
Protocol number	RD.06.SPR.203065
Investigators/study sites/centers	Approximately 70 sites in Europe, North America, and Asia Pacific
Phase of development	Phase 3
Objectives	The primary objective is to assess the efficacy of nemolizumab (CD14152) compared to placebo in subjects ≥ 18 years of age with prurigo nodularis (PN) after a 16-week treatment period. The secondary objectives are to assess the safety, pharmacokinetics, and immunogenicity of nemolizumab (CD14152) compared to placebo.
Study endpoints	**Primary endpoints:** • Proportion of subjects with an improvement of ≥ 4 from baseline in Peak Pruritus Numeric Rating Scale (PP NRS) at Week 16 • Proportion of subjects with an Investigator Global Assessment (IGA) success (defined as an IGA of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point improvement from baseline) at Week 16 **Key secondary endpoints:** • Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS at Week 4 • Proportion of subjects with PP NRS < 2 at Week 16 • Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 16 • Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS at Week 4 • Proportion of subjects with PP NRS < 2 at Week 4 **Secondary efficacy endpoints:** • IGA success rate at each visit through Week 16 • Percentage of pruriginous lesions with excoriations/crusts (Prurigo Activity Score [PAS] item 5a) at each visit through Week 16 • Percentage of healed prurigo lesions (PAS item 5b) at each visit through Week 16 • Change from baseline in number of lesions in representative area (PAS item 4) at each visit through Week 16

- Proportion of subjects with an improvement of ≥ 4 from baseline in PP NRS through Week 16
- Proportion of subjects with PP NRS < 2 from baseline through Week 16
- Proportion of subjects with PP NRS < 3 from baseline through Week 16
- Absolute change from baseline in PP NRS through Week 16
- Percent change from baseline in PP NRS through Week 16
- Proportion of subjects with an improvement of ≥ 4 from baseline in Average Pruritus (AP) NRS through Week 16
- Proportion of subjects with PP NRS improvement ≥ 4 from baseline and IGA success at Week 16
- Proportion of subjects with AP NRS < 2 from baseline through Week 16
- Absolute change from baseline in AP NRS through Week 16
- Percent change from baseline in AP NRS through Week 16
- Proportion of subjects with an improvement of ≥ 4 from baseline in SD NRS through Week 16
- Absolute change from baseline in SD NRS through Week 16
- Percent change from baseline in SD NRS through Week 16
- Change from baseline in sleep diary endpoints (sleep onset latency, wakefulness after sleep onset [WASO], total awake time, total sleep time, sleep efficiency, WASO related to PN, number of WASO related to PN) based on recordings from subject sleep diary through Week 16
- Change from baseline in PN-associated pain frequency through Week 16
- Change from baseline in PN-associated pain intensity through Week 16
- Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on Patient Global Assessment of Disease (PGAD) at Week 16
- Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on Patient Global Assessment of Treatment (PGAT) at Week 16
- Proportion of subjects with an improvement of ≥ 4 in Dermatology Life Quality Index (DLQI) through Week 16
- Change from baseline in DLQI through Week 16Change from baseline in Hospital Anxiety and Depression Scale (HADS) for each subscale (i.e., depression and anxiety) at Week 16
- Change from baseline in EuroQoL 5-Dimension (EQ-5D) at Week 16

Safety endpoints:

- Incidence and severity of adverse events (AEs), including treatment-emergent AEs (TEAEs), AEs of special interest (AESIs), and serious AEs (SAEs).

Pharmacokinetic endpoints:

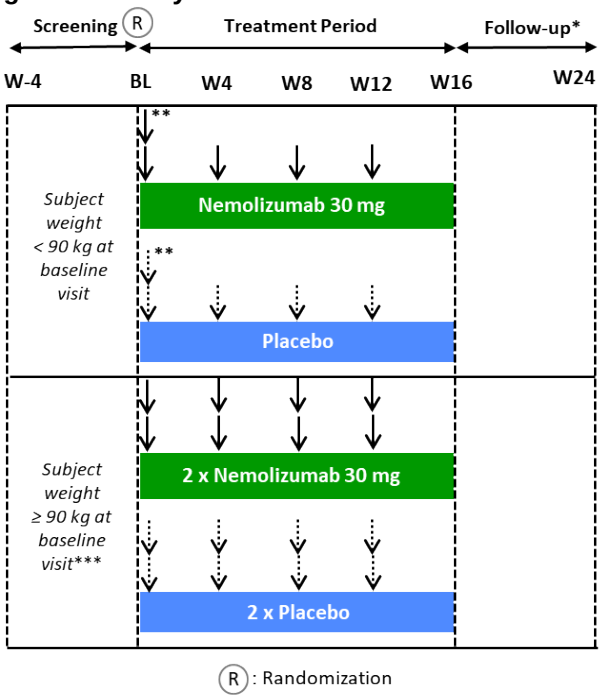
- Nemolizumab (CD14152) serum concentrations

Immunogenicity endpoints:

- ADA assay (screening, confirmatory, titer, NAb)

Study design	This phase 3, multicenter, double-blind, placebo-controlled, randomized, parallel-group study is designed to evaluate the efficacy and safety of nemolizumab in subjects with PN. Approximately 270 subjects with PN will be randomized 2:1 to receive either nemolizumab (CD14152) or placebo, stratified by study center and body weight (< 90 kg versus ≥ 90 kg). Subjects weighing < 90 kg at baseline will receive either 30 mg nemolizumab (with 60 mg loading dose at baseline) or placebo every 4 weeks (Q4W). Subjects weighing ≥ 90 kg at baseline will receive either 60 mg nemolizumab or placebo Q4W (no loading dose at baseline). Subjects' participation in the study will be up to 28 weeks. The study consists of a screening period (up to 4 weeks), a 16-week treatment period, and an 8-week follow up period (12 weeks after their last study drug injection). Refer to Figure 30 for an overview of study design. Following provision of written informed consent, subjects with PN will be screened for enrolment in the study. Eligible subjects will return for a baseline visit where, following randomization, they will be administered either a dose of 60 mg nemolizumab or placebo via 2 subcutaneous (SC) injections. Thereafter, study drug will be administered Q4W at Week 4, 8, and 12 by either a single SC injection of either nemolizumab 30 mg or placebo for subjects weighing < 90 kg at baseline or by two SC injections of either nemolizumab 30 mg or placebo for subjects weighing ≥ 90 kg at baseline. Refer to Table 1 for an overview of the study therapy. Efficacy and safety assessments will be performed at visits throughout the screening and treatment period, as outlined in the Schedule of Assessments (Table 5). At the end of the 16-week treatment period, consenting subjects may be eligible to enter an active treatment/long-term extension (LTE) study (RD.06.SPR.202699). Subjects who participate in the LTE are not required to complete the follow-up visit. Subjects who do not participate in the LTE will return for a follow-up visit at Week 24 (12 weeks after the last study drug injection). Subjects who prematurely discontinue the study drug will be asked to continue participation in the study and return for all remaining visits and assessments (including daily assessments of pruritus and sleep disturbance). Subjects who discontinue study drug due to required rescue therapy may be eligible to participate in the LTE study following completion of study visits through Week 16. Subjects who discontinue the study prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection. An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related events throughout the study. The IDMC and IAC charters provide details on the IDMC and IAC, including the plan of analysis for outputs; the composition of the committees; and the procedures, roles, responsibilities and communications.

Figure 30. Study Schema



* Applicable for subjects who do not participate in the LTE study only
** Loading dose (two injections) administered at baseline visit for subjects weighing < 90 kg
*** Two injections administered at all applicable visits for subjects weighing ≥ 90 kg at the baseline visit

Abbreviations: BL, baseline; LTE, long-term extension; R, randomization; W, week

Selection of subjects

Inclusion criteria:

Individuals must meet all of the following criteria to be included in the study:

- Male or female and aged ≥18 years at the time of screening
- Clinical diagnosis of PN for at least 6 months with:
  - Pruriginous nodular lesions on upper limbs, trunk, and/or lower limbs
  - At least 20 nodules on the entire body with a bilateral distribution
  - IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both the screening and baseline visits
- Severe pruritus defined as follows on the PP NRS:
  - At the screening visit (Visit 1): PP NRS score is ≥ 7.0 for the 24-hour period immediately preceding the screening visit
  - At the baseline visit (Visit 2): Mean of the daily intensity of the PP NRS score is ≥ 7.0 over the previous week;

Note: PP NRS score should be measured on at least 4 days during the week preceding the baseline visit. Rounding of the mean NRS score is not permitted.

Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to

use at least 1 adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection.

Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:

- True abstinence, when in line with the preferred and usual lifestyle of the subject. See Appendix 1 for details. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
- Progestogen-only oral hormonal contraception
- Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods)

Note: *"Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condom) together with a spermicide is not acceptable.*

- Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
- Injectable or implanted hormonal contraception
- Intrauterine devices or intrauterine hormone releasing system
- Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
- Bilateral vasectomy of male partner at least 3 months before the study

Female subjects of non-childbearing potential must meet 1 of the following criteria:

- Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range
- Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study
- Subject is willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including daily diary recordings by the subject using an electronic handheld device provided for this study
- Read, understood and signed an informed consent form (ICF) before any investigational procedure(s) are performed

Exclusion criteria:
Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

- Body weight < 30 kg
- 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 disorder, sporotrichosis, 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
- Unilateral lesions of prurigo (e.g., only one arm affected)

- History of or current confounding skin condition (e.g., Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis)
- Subjects meeting 1 or more of the following criteria at screening or baseline:
  - Had an exacerbation of asthma requiring hospitalization in the preceding 12 months
  - Reporting asthma that has not been well-controlled (i.e., symptoms occurring on > 2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months
  - Asthma Control Test (ACT) ≤ 19 (only for subjects with a history of asthma)
  - Peak expiratory flow (PEF) < 80% of the predicted value

Note: In the event that PEF is < 80% of the predicted value at the screening visit in subjects without any history of asthma or in subjects with history of asthma but with the ACT score > 19, PEF testing can be repeated once within 48 hours.

- Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis
- Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics, or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.4.2.
- Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C [HCV] antibody with positive confirmatory test for HCV [e.g., polymerase chain reaction (PCR)], or human immunodeficiency virus antibody) at the screening visit

Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study.

In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.

- Requiring rescue therapy for PN during the screening period or expected to require rescue therapy within 4 weeks following the baseline visit
- Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months

Note: *Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e., specific immunoglobulin E), are eligible for the study.*

- Neuropathic and psychogenic pruritus such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis
- Having received any of the following treatments in below within the specified timeframe before the baseline visit:

Treatments	**Timeframe**
Topical calcineurin inhibitors (tacrolimus, pimecrolimus), and topical corticosteroids	2 weeks
Topical vitamin D analogs	2 weeks
Topical or systemic PDE-4 inhibitors	2 weeks
Any other topical treatment other than moisturizer (e.g., capsaicin, cryotherapy for treatment of PN)	2 weeks
Emollients or moisturizers with menthol, polidocanol or other having “anti-itch” claim	1 week
Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Oral antihistamines (unless these treatments were taken at a stable dose for 3 months prior to screening or for a seasonal allergy)	1 week
Drugs with sedative effect such as benzodiazepines, imidazopyridines, barbiturates, sedative anti-depressants (e.g., amitriptyline), SSRIs (e.g., paroxetine), or SNRIs, except if these treatments were taken at a stable dose for at least 3 months before screening	1 week
Phototherapy or tanning beds	4 weeks
Immunosuppressive or immunomodulatory drugs (e.g., cyclosporine, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (e.g., etanercept, adalimumab, infliximab, omalizumab)	8 weeks or 5 half-lives (whichever is longer)
Dupilumab	10 weeks
Systemic retinoids	8 weeks or 5 half-lives (whichever is longer)
Systemic roxithromycin, erythromycin	1 week
Opioid antagonists (e.g., naltrexone, naloxone), opioid partial/mixed agonists (e.g., nalbuphine, butorphanol), or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (e.g., aprepitant, serlopitant)	4 weeks or 5 half-lives (whichever is longer)
Gabapentinoids, unless used at a stable dose for at least 6 months or used for non-prurigo conditions	4 weeks
Cannabinoids (e.g., dronabinol)	2 weeks
Alternative medicine for PN (e.g., traditional Chinese medicine)	2 weeks
Live vaccines	12 weeks
Non-live vaccines	4 weeks

Abbreviations: JAK, Janus kinase; NK1, neurokinin; PDE-4, phosphodiesterase-4; PN, prurigo nodularis; SNRI, serotonin-norepinephrine reuptake inhibitor SSRI, selective serotonin reuptake inhibitor.

Note: Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.

Previous participation in a clinical study with nemolizumab

- Pregnant women (positive serum pregnancy test result at the screening visit or positive urine pregnancy test at the baseline visit), breastfeeding women, or women planning a pregnancy during the clinical study
- History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for:
  - Basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit, or;
  - Actinic keratoses that have been treated
- History of hypersensitivity (including anaphylaxis) to an immunoglobulin product (plasma-derived or recombinant, e.g., monoclonal antibody) or to any of the study drug excipients
- Current active or latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines

Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.

In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit.

- Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment
- Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (> 3 × upper limit of normal [ULN]) in combination with elevated bilirubin (> 2 × ULN), 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 (e.g., poor venous access or needle-phobia)
- History of alcohol or substance abuse within 6 months of the screening visit
- Planned or expected major surgical procedure during the clinical study
- Subject is unwilling to refrain from using prohibited medications during the clinical study (see Section 9.10.3)
- Currently participating or participated in any other study of an investigational drug or device, within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study

For subjects accepting optional biopsy sampling (by signing an additional consent), the following exclusion criteria also apply. If any of the below criteria are met, biopsy samples must not be collected:

	• History of coagulation disorders • Known sensitivity to local anesthetics • Using platelet aggregation inhibitors, or anticoagulants (sporadic intake or continuous low-dose intake of aspirin or other non-steroidal anti-inflammatory drugs is allowed) • History or physical evidence of keloids or hypertrophic scarring resulting from skin trauma. The clinical examination will include the observation of scars.
Planned sample size	Approximately 270 subjects are planned to be randomized in this study
Therapy	Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for subcutaneous injection only after reconstitution in a single-use, pre-filled, dual-chamber syringe (DCS). During the treatment period, eligible subjects will be randomized to receive either nemolizumab (CD14152) or placebo, administered Q4W for 16 weeks (last injection at Week 12). Subjects weighing < 90 kg at baseline will receive either nemolizumab 30 mg or placebo via a single SC injection (with a loading dose of 60 mg on Day 1/baseline); subjects weighing ≥ 90 kg at baseline will receive either nemolizumab 60 mg or placebo via two SC injections at all visits (no loading dose). Subjects will have the option to self-inject study drug while at the study center under staff supervision. Subjects will be trained on injecting the study drug and will be allowed to inject study drug at all subsequent visits, while at the study center, under staff supervision. If the subject does not wish to perform the injections, study staff can administer study drug at each visit.

Table 63. Investigational Therapy

	Investigational Product	**Placebo**
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Packaging	DCS	DCS
Storage conditions	Stored between 2°C to 8°C (36°F to 46°F), protected from light, protected from freezing	Stored between 2°C to 8°C (36°F to 46°F), protected from light, protected from freezing
Dosage	Subjects weighing < 90 kg at baseline: 30 mg, with a loading dose of 60 mg at baseline; Subjects weighing ≥ 90 kg at baseline: 60 mg	Not applicable
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution
Dose regimen	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥ 90 kg at baseline: 2 injections at	Subjects weighing < 90 kg at baseline: 2 injections at baseline, then 1 injection Q4W; Subjects weighing ≥ 90 kg at baseline: 2 injections at

	baseline, then 2 injections Q4W	baseline, then 2 injections Q4W
Treatment duration	16 weeks with last injection at Week 12	16 weeks with last injection at Week 12

Abbreviations: DCS, dual chamber syringe; Q4W, every 4 weeks; SC, subcutaneous

Rescue therapies

If deemed to be medically necessary by the investigator (e.g., to control intolerable signs/symptoms of PN), rescue therapies can be prescribed to the subjects at any time during the study except during the screening period. Subjects receiving rescue therapies during the screening period are not eligible to participate in the study.

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure.

Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy.

Whenever possible, investigators should first use topical medication or oral antihistamines as rescue therapy before escalating to other systemic therapies. If subjects receive topical treatments, oral antihistamines, or ultraviolet B (UVB) phototherapy as rescue therapy, study drug administration should be continued unless there is a concern according to the investigator's judgment. If subjects receive systemic rescue therapy (other than oral antihistamines), intralesional corticosteroids, or oral psoralen + ultraviolet A (PUVA) treatment, the study drug administration must be permanently discontinued. See Section 9.10.2 for a complete list of allowed rescue therapies.

Subjects requiring rescue medication (with or without study drug discontinuation) may be eligible for LTE participation. These subjects must continue with study visits through Week 16 to be considered for LTE participation.

Treatment duration	The expected duration of each subject's participation in the study is up to 28 weeks, including a screening period (up to 4 weeks), a 16-week treatment period, and an 8-week follow-up period (12-weeks after the last study drug injection). Subjects who rollover into the LTE are not required to complete the follow-up visit.

Efficacy	The following efficacy assessments are planned according to the Schedule of Assessments (Table 5): • IGA • Peak and Average Pruritus NRS • PAS • SD NRS • Subject Sleep Diary • PN-associated pain intensity and frequency • PGAD and PGAT • Clinical photographs (optional and subject to a specific, separate ICF at selected sites) The following quality of life assessments are planned according to the Schedule of Assessments (Table 5): • DLQI • HADS • EQ-5D Additional Patient-Reported Outcomes assessments are planned according to the Schedule of Assessments (Table 5), as follows: • Patient Global Impression of Severity-Pruritus • Patient Global Impression of Change-Pruritus • Patient Global Impression of Severity-Sleep Disturbance • Patient Global Impression of Change-Sleep Disturbance
Safety	The following safety assessments are planned according to the Schedule of Assessments (Table 5): • AEs, including TEAEs, AESIs, and SAEs • Physical examination and vital signs • Clinical laboratory tests • Electrocardiogram (ECG) • Respiratory examination and assessments
Pharmacokinetics, immunogenicity, pharmacodynamics, and pharmacogenomics	The following assessments are planned according to the Schedule of Assessments (Table 5): • Serum nemolizumab concentrations • Anti-drug antibody (ADA) assessments (screening, confirmatory, titer, and neutralizing antibody (NAb) • Biomarkers (e.g., interleukin-31 and/or other biomarkers) from blood, stratum corneum (D-Squames), and optional skin biopsies (subject to specific, separate ICF) (select centers only) • Pharmacogenomic testing (optional and subject to a specific, separate ICF)
Statistical methods and planned analyses	The intent-to-treat (ITT) population will consist of all randomized subjects. The safety population will include all randomized subjects who receive at least 1 dose of study drug. The Per-Protocol (PP) population will consist of all subjects in the ITT population who have no major protocol deviations that would have a significant effect on the efficacy of the study treatment. The ITT population will be the primary population for all efficacy analyses, and all safety data will be summarized based on the safety population. The PP population will be used as the population for sensitivity analyses of the primary and key secondary efficacy endpoints.

Primary efficacy endpoints
There are 2 primary efficacy endpoints

- The proportion of subjects with at least 4 points of improvement in PP NRS at Week 16.
- The proportion of subjects reporting success on the IGA at Week 16, defined as an IGA response of 0 [Clear] or 1 [Almost clear] and a ≥ 2-point reduction from baseline.

Both primary endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) test adjusted for randomized stratification variable analysis center and baseline body weight (< 90 kg and ≥ 90 kg). The estimate of the treatment difference (nemolizumab minus placebo), p-value and 2-sided 95% confidence interval will be presented. Missing data at Week 16, and any data for subjects in receipt of rescue medication up to Week 16, will be regarded as a non-responder for the primary analysis of the endpoint.

A number of sensitivity analyses are included for the primary endpoints, as per Section 15.4.3.

Key secondary endpoints
All binary key secondary efficacy endpoints will be analyzed as per the primary endpoint.

Additionally, sensitivity analyses using multiple imputation assuming missing at random (MAR) and observed case (OC) analysis will be performed for key secondary endpoints as outlined in Section 15.4.4.

Secondary efficacy endpoints
Binary secondary endpoints will be analyzed in the same manner as the primary endpoint; missing values will be imputed as non-responder.

Continuous secondary endpoints (except EQ-5D, HADS) will be analyzed using multiple-imputation assuming MAR and using mixed effect model for repeated measure (MMRM) approach, including analysis center as factor and baseline as covariate where applicable. The estimated treatment difference for each endpoint at each visit will be displayed in the summary of statistical analysis together with the 95% CI and associated p-value. EQ-5D and HADS endpoints will be analyzed using analysis of covariance (ANCOVA) including analysis center as factor and baseline as covariate. All secondary endpoints will be presented descriptively using OC.

Further details will be provided in the Statistical Analysis Plan.

Multiplicity
To control the type I error at 5%, a fixed sequential testing approach will be implemented. For testing purposes both primary endpoints will be tested first in a predefined order (as listed in Section 15.4.1) at 5% significance level and testing of key secondary endpoints will start only if both primary endpoints are successful at 5% level of significance. Key secondary endpoints will be tested in an order listed in section 15.4.4, stopping when a non-significant result (p> 0.05) is found.

Safety analyses

	The incidence of TEAEs, vital signs, laboratory values and ECG will be summarized by treatment groups. **Pharmacokinetics (PK)** Summary statistics will be used to describe the PK profile of nemolizumab. Individual and mean serum concentration versus time curves will be presented for both linear and semi-log scales. Descriptive statistics of the serum concentrations versus time will be presented as well as for the PK parameters. **Sample size** In order to achieve at least 90% power for both primary endpoint at 5% significance level, 270 (180 nemolizumab, 90 placebo) subjects will be required to detect the following difference in both primary endpoints between treatment groups with 2:1 randomization, assuming 15% dropout rate during treatment period. NRS responders (≥4-point reduction from baseline): Based on phase 2a data, it is expected that the NRS response at Week 16 would be 50% in Nemolizumab group and 20% in placebo. IGA response (0/1): It is expected that the IGA response at Week 16 would be 30% in Nemolizumab group and 10% in placebo.

Abbreviations: ACT, Asthma Control Test; ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; ANCOVA, analysis of covariance; AP, Average Pruritus; AST, aspartate aminotransferase; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; DCS, dual chamber syringe; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EQ-5D, EuroQol 5-Dimension; ET, early termination; FSH, follicle stimulating hormone; HADS, Hospital Anxiety and Depression Scale; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; IAC, independent adjudication committee; ICF, informed consent form; IDMC, Independent Data Monitoring Committee; IGA, Investigator's Global Assessment; ITT, intent-to-treat; LTE, long-term extension study; MAR, missing at random; MMRM, mixed model repeated measures; Nab, neutralizing antidrug antibody; NRS, numeric rating scale; OC, observed case; PAS, Prurigo Activity Score; PCR, polymerase chain reaction; PEF, peak expiratory flow; PGAD, Patient Global Assessment of Disease; PGAT, Patient Global Assessment of Treatment; PK, pharmacokinetic; PN, prurigo nodularis; PP, per protocol; PP-NRS, Peak Pruritus Numeric Rating Scale; PUVA, psoralen + ultraviolet A; Q4W, every 4 weeks; SAE, serious adverse event; SC, subcutaneous; SD-NRS, Sleep Disturbance Numeric Rating Scale; TB, tuberculosis; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UVB, ultraviolet B; WASO, wakefulness after sleep onset

15.4. Open-Label Extension Protocol Synopsis (RD.06.SPR.202699)

Table 64. Open-Label Extension Protocol Synopsis (Version 8.0; February 8, 2024) [RD.06.SPR.202699; NCT04204616]

Title of study	A prospective multicenter, long-term study to assess the safety and efficacy of nemolizumab (CD14152) in subjects with prurigo nodularis
Protocol number	RD.06.SPR.202699
Investigators/ study sites	Approximately 160 study sites in Europe, North America, and Asia Pacific
Phase of development	Phase 3
Objectives	The primary objective is to assess the long-term safety of nemolizumab (CD14152) in subjects with prurigo nodularis (PN). The secondary objective is to assess the long-term efficacy of nemolizumab (CD14152) in subjects with PN.
Study endpoints	**Primary** endpoint:

- Incidence and severity of adverse events (AEs), including AEs of special interest, treatment-emergent AEs, and serious AEs.

Secondary efficacy endpoints:

- Proportion of subjects with an Investigator Global Assessment (IGA) success (defined as IGA of 0 [Clear] or 1 [Almost clear]) at each visit up to Week 184
- Proportion of subjects with an improvement of ≥4 from baseline in Peak Pruritus numeric rating scale (PP NRS) up to Week 184
- Proportion of subjects with low disease activity state (i.e., IGA ≤2) at each visit up to Week 184
- Percentage of pruriginous lesions with excoriations/crusts (Prurigo Activity Score [PAS] item 5a) at each visit up to Week 184
- Percentage of healed prurigo lesions (PAS item 5b) at each visit up to Week 184
- Change from baseline in number of lesions in representative area (PAS item 4) at each visit up to Week 184
- Proportion of subjects with PP NRS <2 up to Week 184
- Absolute and percent change from baseline in PP NRS up to Week 184
- Proportion of subjects with Average Pruritus (AP) NRS <2 up to Week 52
- Proportion of subjects with an improvement of ≥4 from baseline in AP NRS up to Week 52
- Absolute and percent change from baseline in AP NRS up to Week 52
- Proportion of subjects with an improvement of ≥4 from baseline in Sleep Disturbance (SD) NRS up to Week 184
- Absolute and percent change from baseline in Sleep Disturbance NRS up to Week 184
- Change from baseline in PN-associated pain frequency up to Week 184
- Change from baseline in PN-associated pain intensity up to Week 184
- Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on Patient Global Assessment of Disease (PGAD) at each visit up to Week 52
- Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on Patient Global Assessment of Treatment (PGAT) at each visit up to Week 52
- Proportion of subjects with an improvement of ≥4 from baseline in Dermatology Life Quality Index (DLQI) up to Week 184
- Change from baseline in EuroQoL 5-Dimension (EQ-5D) up to Week 184
- Time to permanent study drug discontinuation
- Time to rescue therapy use
- Proportion of subjects receiving any rescue therapy by rescue treatment
- For subjects who re-entered from durability study (RD.06.SPR.203890):
- Proportion of subjects with an Investigator Global Assessment (IGA) success (defined as IGA of 0 [Clear] or 1 [Almost clear]) at each visit up to Week R132 by treatment and overall [relapsed, non-relapsed subjects]
- Proportion of subjects with an improvement of ≥4 from re-entry baseline in Peak Pruritus numeric rating scale (PP NRS) up to Week R132 by treatment and overall [relapsed subjects]

	• Proportion of subjects with an improvement of ≥4 from baseline in Peak Pruritus numeric rating scale (PP NRS) up to Week R132 by treatment and overall [non-relapsed subjects] • Proportion of subjects with recapture of clinical response, defined as: Investigator Global Assessment (IGA) success and an improvement of • ≥4 from re-entry baseline in Peak Pruritus numeric rating scale (PP NRS) up to Week R132 by treatment and overall [relapsed subjects] • Proportion of subjects with maintenance of clinical response, defined as: Investigator Global Assessment (IGA) success and an improvement of • ≥4 from baseline in Peak Pruritus numeric rating scale (PP NRS) up to Week R132 by treatment and overall [non-relapsed subjects] • Proportion of subjects with an improvement ≥4 from baseline in Sleep Disturbance numeric rating scale (SD NRS) up to Week R132 by treatment and overall [relapsed and non-relapsed subjects] • Proportion of subjects with an improvement ≥4 from baseline in • Dermatology Life Quality Index (DLQI) up to Week R132 by treatment and overall [relapsed and non-relapsed subjects] • Time to recapture of clinical response for relapsed subjects who received placebo in the durability study (RD.06.SPR.203890)
Study design	This is a prospective, multicenter, long-term extension (LTE) study in adult subjects who had been enrolled in prior nemolizumab PN phase 2a (RD.03.SPR.115828) or phase 3 (RD.06.SPR.202685 or RD.06.SPR.203065) studies to evaluate the safety and efficacy of nemolizumab in subjects with PN. Entry into the LTE study is as follows: • Subjects who were previously randomized in the phase 2a study (RD.03.SPR.115828) can be considered for eligibility in this LTE study. • Subjects completing the treatment period in a phase 3 study (RD.06.SPR.202685 or RD.06.SPR.203065) may be eligible to enroll immediately into the LTE study. • Subjects' participation in the study will be up to 196 weeks. The study consists of an up to 4-week screening period, up to a 184-week treatment period, and an 8- week follow up period (12 weeks after their last study drug injection). Approximately 500 subjects are planned to be enrolled in this study, depending on rollover rate from the lead-in studies. Refer to Figure 31 (below) for an overview of the study design. **Screening** Subjects from the previous designated nemolizumab studies are eligible to undergo screening for participation in the LTE study. Final study assessments from a phase 3 lead-in study (RD.06.SPR.202685 or RD.06.SPR.203065) will be used for LTE study screening purposes for subjects who enroll within 28 days of lead-in study completion, unless the subject discontinued study drug before completing the treatment period. Subjects who rollover into the LTE after 28 days but no later than 56 days following the last visit of the phase 3 lead-in study or who prematurely discontinued study drug but otherwise completed the lead-in study, must undergo a separate, complete screening visit, within 28 days before the baseline visit/first dose of study drug.

Subjects who do not rollover within 56 days from a phase 3 lead-in study are ineligible for participation in the LTE.

Subjects who enroll from the phase 2a study (RD.03.SPR.115828) are required to complete all study screening assessments within 28 days before the baseline visit/first dose of study medication.

Treatment period
For subjects who enroll from the phase 2a study (RD.03.SPR.115828), subjects weighing <90 kg at baseline will receive open-label 30 mg nemolizumab (with 60 mg loading dose at baseline) every 4 weeks (Q4W). Subjects weighing ≥90 kg at baseline will receive 60 mg nemolizumab (two 30-mg injections; no loading dose) Q4W. Beginning at Week 56, nemolizumab dosage will be adjusted every 6 months for subjects with a documented weight change above or below the 90 kg threshold at 2 consecutive designated visits as indicated in the Schedule of Assessments in the protocol.

For subjects who enroll from a phase 3 study (RD.06.SPR.202685 or RD.06.SPR.203065), the Day 1/baseline dose will use blinded study medication as assigned by interactive response technology (IRT), based on the assigned pivotal study treatment, to maintain the blind of the lead-in study. Thus, subjects may receive either 2 blinded 30-mg injections of nemolizumab, or 1 blinded 30- mg injection of nemolizumab and 1 blinded placebo injection. After Day 1/baseline, subjects will receive open-label nemolizumab using the same dosing regimen received in the phase 3 study (1 or 2 SC injections of 30 mg nemolizumab, based on subject weight at baseline of the lead-in study). Beginning at Week 56, nemolizumab dosage will be adjusted every 6 months for subjects with a documented weight change above or below the 90 kg threshold at 2 consecutive designated visits as indicated in the Schedule of Assessments in the protocol.

Refer to Table 65 for a summary of study treatment for subjects enrolling from the phase 2 and phase 3 studies. All subjects will receive nemolizumab Q4W for a total treatment period of 184 weeks, with final dose administered at Week 180.

Table 65. Treatment Summary for Subjects Enrolling From a Lead-In

Prior Study	Prior Study Assigned Treatment	Dose on Day 1/Baseline (2 Injections)[a]	Weight at Baseline	Open-Label Dose Q4W for 180 Weeks[c]
RD.06.SPR.202685 or RD.06.SPR.203065	Nemolizumab (CD14152) 30 mg	Blinded Nemolizumab (CD14152) 30 mg (one 30-mg injection and one placebo injection)	NA[b]	Nemolizumab (CD14152) 30 mg
	Placebo	Blinded Nemolizumab (CD14152) 60 mg		
	Nemolizumab (CD14152) 2 x 30 mg			Nemolizumab (CD14152) 2 x 30 mg
	2 x placebo			

		(two 30-mg injections)		
RD.03.SPR.115828	Placebo or Nemolizumab (CD14152) 0.5 mg/kg	Open-label Nemolizumab (CD14152) 60 mg (two 30-mg injections)	< 90 kg	Nemolizumab (CD14152) 30 mg
			≥ 90 kg	Nemolizumab (CD14152) 2 x 30 mg

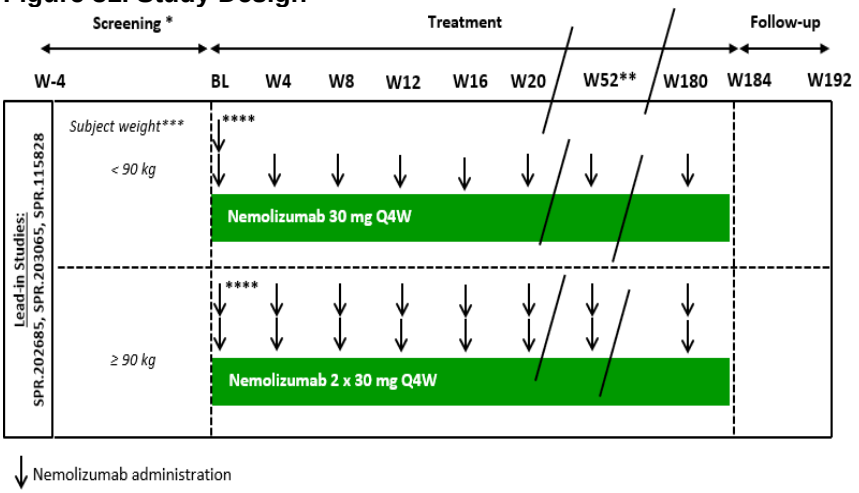
a Any subject with a >12-week interval since the last dose of study drug will receive a 60- mg dose of nemolizumab via two 30-mg injections at the Day 1/baseline visit.
b For subjects rolling over from RD.06.SPR.202685 or RD.06.SPR.203065, dose will initially be assigned based on weight at baseline of lead-in study
c Beginning at Week 56, nemolizumab dosage will be adjusted every 6 months for subjects with a documented weight change above or below the 90 kg threshold at 2 consecutive designated visits.
Abbreviations: Nab, neutralizing antidrug antibody; Q4W, every 4 weeks.

Follow-up period
The follow-up visit will be conducted 8 weeks after completing the treatment period and/or 12 weeks after the last study drug injection for all subjects. Twelve weeks corresponds to approximately 5 half-lives when nemolizumab (CD14152) 30 mg is dosed subcutaneously every 4 weeks.

Independent data monitoring committee and independent adjudication committee
An independent data monitoring committee (IDMC) will review and monitor subject safety throughout the study, and an independent adjudication committee (IAC) will review all asthma-related events throughout the study up until approval (at the site level) of protocol V8.0. Details on the IDMC and IAC, including the plan of analysis for outputs, the composition of the committee, the procedures, roles, responsibilities and their communications are provided in the IDMC and IAC charters, respectively.

Study design schematic
An overview of the study design is presented in Figure 31.

Figure 31. Study Design



* Subjects who immediately rollover (within 28 days from last visit of lead-in study) into the LTE study are not required to complete a separate screening visit.
** At Week 52 (selected countries/selected sites), Clinical Responders will be eligible to enter the durability study RD.06.SPR.203890. Clinical responder (CR) is defined as a subject with an Investigator Global Assessment (IGA) score = 0 or 1 and improvement in Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥4 from baseline of the lead-in study at Week 52 visit of the long-term extension (LTE) study. Note: Lead-in study baseline is defined as baseline PP NRS score in the Phase 3 studies RD.06.SPR.202685 or RD.06.SPR.203065 for subjects who rolled over into the LTE from these studies. For subjects who entered the LTE study from the Phase 2 study RD.03.SPR.115828, the baseline PP NRS score at entry into the LTE study RD.06.SPR.202699 will be used.
Subjects who exit at Week 52 to enter the durability study will not receive study drug at Week 52, however, all other study assessments will be completed.
***Lead-in studies RD.06.SPR.202685, RD.06.SPR.203065: Subject weight at baseline visit of lead-in study
Lead-in study RD.03.SPR.115828: Subject weight at baseline visit of this study Beginning at Week 56, dosage will be adjusted every 6 months for subjects with a
documented weight change above or below the 90 kg threshold at 2 consecutive designated visits.
****Lead-in studies RD.06.SPR.202685, RD.06.SPR.203065: Blinded baseline dose (nemolizumab 60 mg or nemolizumab 30 mg + placebo injection to maintain the blind, as assigned by IRT); Lead-in study RD.03.SPR.115828: Open-label dose of nemolizumab 60 mg for all subjects at Baseline.
Abbreviations: BL, baseline; Q4W, every 4 weeks; W, week

Subject exit to durability study (RD.06.SPR.203890) and re-entry from durability study (RD.06.SPR.203890) (selected countries/selected sites)
At Week 52, clinical responders are eligible to enter the phase 3b durability study (RD.06.SPR.203890); in this case, study drug administration will not occur at Week 52, but all other assessments scheduled for Week 52 will still take place.

Clinical responder (CR) is defined as a subject with an Investigator Global Assessment (IGA) score= 0 or 1 and improvement in Peak Pruritus Numeric Rating Scale (PP NRS) score of ≥4 from baseline of the lead-in study at Week 52 visit of the long-term extension (LTE) study (See Figure 4).

Subjects who complete through Week 24 of the durability study (RD.06.SPR.203890) or who meet the criteria for relapse at any point during the treatment period are eligible to re-enter the LTE study. Subjects must re-enter within 28 days of exiting the durability study. For subjects who rollover on the same day as the last study visit in the durability study, the final study assessments from the durability study can be used for LTE study re-entry baseline (R0) to avoid duplication of assessments. Any assessment required

at the R0 visit but not completed as part of the last visit of the durability study must then be completed at the R0 visit.

The re-entry baseline (R0) dose will be assigned by IRT, based on the assigned study drug in the durability study, followed by open-label nemolizumab, with final dose administered at Week R128 (See Table 2).

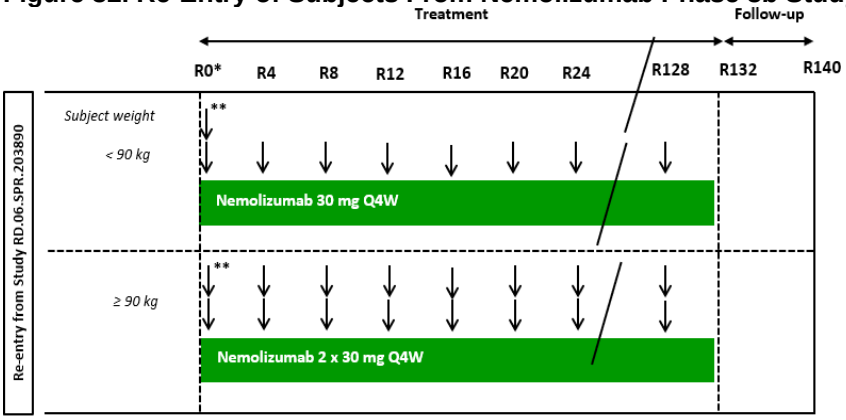
Table 66. Treatment Summary for Subjects Re-Entering From the Durability Study, RD.06.SPR.203890

Lead-In Study	Weight	Prior Assigned Treatment	Dose at Re-Entry Baseline (R0) Visit[a]	Open-Label Dose Q4W for 128 Weeks From Re-Entry Week R4[b]
RD.06.SPR.203890	<90 kg	Nemolizumab (CD14152)	Blinded Nemolizumab (CD14152) 30 mg (one 30-mg injection and one placebo injection)	Nemolizumab (CD14152)
		Placebo	Blinded Nemolizumab (CD14152) 60 mg (two 30-mg injections)	30 mg
	≥90 kg	Nemolizumab (CD14152) or placebo	Open-Label Nemolizumab (CD14152) 60 mg (two 30-mg injections)	Nemolizumab (CD14152) 2 x 30 mg

[a] All subjects will receive 2 SC injections, as assigned by IRT at the re-entry visit (Week R0), based on the assigned study drug in the durability study
[b] Dosage will be adjusted every 6 months for subjects with a documented weight change above or below the 90 kg threshold at 2 consecutive designated visits.
Abbreviations: Q4W, every 4 weeks; R0, re-entry baseline

Clinical assessments will occur according to the Schedule of Assessments in the protocol through the re-entry Week R132 visit (See Figure 2). Subjects who are discontinued before the re-entry Week R132 should complete the re-entry early termination (R-ET) visit and a re-entry follow-up (R-FU) visit, 12 weeks after the last study drug injection.

Figure 32. Re-Entry of Subjects From Nemolizumab Phase 3b Study



↓ Nemolizumab administration

* Subjects must re-enter within 28 days of exiting the durability study. For subjects who rollover on the same day as the last study visit in the phase 3b durability study (RD.06.SPR.203890), the final study assessments from the durability study can be used for LTE study re-entry baseline (R0) to avoid duplication of assessments. Any assessment required at the R0 visit but not completed as part of the last visit of the durability study must then be completed at the R0 visit.
** Subjects will receive 2 SC injections, as assigned by IRT at the re-entry baseline visit (Week R0), based on the assigned study drug in the durability study (RD.06.SPR.203890).
Abbreviations: Q4W, every 4 weeks; R, re-entry

Selection of subjects	**Inclusion criteria:** Individuals must meet all of the following criteria at screening and baseline, as applicable, to be included in the study (individuals re-entering from the phase 3b durability study RD.06.SPR.203890 must meet all inclusion criteria at re-entry Week R0): • Subjects who may benefit from study participation in the opinion of the investigator and participated in a prior nemolizumab study for PN including: – Subjects who completed the treatment period in a phase 3 pivotal study (RD.06.SPR.202685 or RD.06.SPR.203065) and enroll within 56 days OR – Subjects who were previously randomized in the nemolizumab phase 2a PN study (RD.03.SPR.115828). OR – Subjects who completed through Week 24 of the phase 3b durability study (RD.06.SPR.203890) or who exit the study due to relapse may be eligible to re-enter in the LTE study within 28 days of exiting the durability study (selected countries/ selected sites) *Note*: Transfer into the LTE study from a phase 3 study can occur immediately but must occur within 56 days of lead-in study completion, provided other eligibility criteria are met. Subjects from the phase 2 study, subjects who rollover between 29 to 56 days after completion of a phase 3 study, or subjects who discontinued study drug but otherwise completed a phase 3 study must undergo a separate screening visit prior to the baseline visit. Subjects from a phase 3 study who do not rollover within 56 days are ineligible for participation in the LTE.

- Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree to use an adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection
- Adequate and approved methods of contraception applicable for the subject and/or her partner are defined below:
  - True abstinence, when in line with the preferred and usual lifestyle of the subject. See Appendix 1 for details. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
  - Progestogen-only oral hormonal contraception
  - Combination of male condom with cap, diaphragm, or sponge with spermicide (double barrier methods) (*In Germany only, double barrier methods are not considered an adequate and approved method of contraception)

Note: *"Double barrier methods" refers to simultaneous use of a physical barrier by each partner. Use of a single barrier method (e.g., condo*m) together with a spermicide is not acceptable.

  - Combined (estrogen- and progestogen-containing) oral, intravaginal, or transdermal hormonal contraception
  - Injectable or implanted hormonal contraception
  - Intrauterine devices or intrauterine hormone releasing system
  - Bilateral tubal ligation or tube insert (such as the Essure system) at least 3 months before the study
  - Bilateral vasectomy of partner at least 3 months before the study
- Female subjects of non-childbearing potential must meet one of the following criteria:
  - Absence of menstrual bleeding for 1 year prior to screening without any other medical reason, confirmed with follicle stimulating hormone (FSH) level in the postmenopausal range

OR

  - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before the study.

- Subject willing and able to comply with all of the time commitments and procedural requirements of the clinical study protocol, including periodic weekly recordings by the subject using an electronic handheld device provided for this study.
- Understand and sign an informed consent form before any investigational procedure(s) are performed.

Exclusion criteria

- Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study (individuals re-entering from the phase 3b durability study RD.06.SPR.203890 meeting any of the following criteria at the re-entry Week R0 visit are ineligible):
  - Subjects who, during their participation in a prior nemolizumab study, experienced an AE which in the opinion of the investigator could

indicate that continued treatment with nemolizumab may present an unreasonable risk for the subject.

- Body weight < 30 kg.
- Having received any of the following treatments in Table 3 within the specified timeframe before the baseline visit or re-entry Week R0 visit:

Table 67. Prior Treatments

Treatment(s)[a]	Timeframe
Systemic or intralesional corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Immunosuppressive or immunomodulatory drugs (e.g., cyclosporine A, methotrexate, thalidomide, oral tacrolimus, cyclophosphamide, azathioprine, mycophenolate mofetil, JAK inhibitors)	8 weeks or 5 half-lives (whichever is longer)
Biologics and their biosimilars (e.g. etanercept, adalimumab, infliximab, omalizumab, etc.)	8 weeks or 5 half-lives (whichever is longer)
Dupilumab	10 weeks
Systemic retinoids	8 weeks or 5 half-lives (whichever is longer)
Systemic roxithromycin, erythromycin	1 week
Opioid antagonists (e.g., naltrexone, naloxone), opioid partial/mixed agonists (e.g., nalbuphine, butorphanol) or opioid agonists (except when used for short term/acute pain); NK1 receptor antagonists (e.g., aprepitant)	4 weeks or 5 half-lives (whichever is longer)
Anti-epileptics (e.g., gabapentin, pregabalin) unless used at a stable dose for 6 months or for a non-pruritic condition	4 weeks
Psoralen + ultraviolet A phototherapy	4 weeks
Alternative medicine for PN (e.g., traditional Chinese medicine)	2 weeks
Cannabinoids (e.g., dronabinol)	2 weeks
Live vaccines	12 weeks
Non-live vaccines	4 weeks

[a] Subjects should not interrupt ongoing treatment with medications important for the subject's health for the sole purpose of participating in this study.
Abbreviations: JAK, Janus kinase; NK1, neurokinin 1 antagonist; PN, prurigo nodularis

- Pregnant women (positive pregnancy test result at screening or baseline or re- entry Week R0 visit), breastfeeding women, or women planning a pregnancy during the clinical study.
- Any medical or psychological condition 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 (e.g., poor venous access or needle-phobia).
- Planning or expected to have a major surgical procedure during the clinical study.
- Subjects unwilling to refrain from using prohibited medications during the clinical study.
- History of alcohol or substance abuse within 6 months of the screening visit or re-entry Week R0 visit.

- For subjects who do not rollover within 28 days from a prior nemolizumab study or who completed study visits but prematurely discontinued study drug, the following exclusion criteria also apply:
- Subjects with a history of asthma meeting 1 or more of the following criteria:
- Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.
- Reporting asthma that has not been well-controlled (i.e., symptoms occurring on >2 days per week, nighttime awakenings 2 or more times per week, or some interference with normal activities) during the preceding 3 months.
- Asthma Control Test (ACT) ≤19 (only for subjects with a history of asthma) at screening and baseline.
- Peak expiratory flow (PEF) <80% of the predicted value.

Note: In the event that PEF is <80% of the predicted value at screening in patients without any history of asthma or in patients with history of asthma but with the ACT score >19, PEF testing can be repeated once within 48 hours.

- Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.
- Cutaneous infection within 1 week before the baseline visit, any infection requiring treatment with oral or parenteral antibiotics, antivirals, antiparasitics or antifungals within 2 weeks before the baseline visit, or any confirmed or suspected coronavirus disease (COVID)-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved. Resolution of COVID-19 infection can be confirmed by recovery assessment methods, as described in Section 8.4.2.
- Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C (HCV) antibody with positive confirmatory test for HCV (e.g., polymerase chain reaction [PCR]), or human immunodeficiency virus antibody) at screening.

Note: Subjects with a positive HBcAb and a negative HBsAg can be included in this clinical study if hepatitis B surface antibody is positive (considered immune after a natural infection). Subjects with negative confirmatory test for HCV can be included in this clinical study.

In the event of rescreening, the serology tests results (e.g., HBV, HCV, HIV) from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if those tests were performed within 6 weeks prior to the baseline visit.

- Chronic pruritus resulting from another active condition than PN, such as but not limited to scabies, lichen simplex chronicus, psoriasis, atopic dermatitis, contact dermatitis, acne, folliculitis, lichen planus, habitual picking/excoriation disorder, sporotrichosis, bullous autoimmune disease, end-stage renal disease, or cholestatic liver disease (e.g., primary biliary cirrhosis), or diabetes mellitus or thyroid disease that is not adequately treated, as per standard of care.
- History of or current confounding skin condition (e.g., Netherton syndrome, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], chronic actinic dermatitis, dermatitis herpetiformis).

	• Subjects with active atopic dermatitis (signs and symptoms other than dry skin) in the last 3 months. *Note*: *Subjects with atopic diathesis, as diagnosed by the medical history and/or laboratory analysis (i.e.,* specific immunoglobulin e [IgE]), are eligible for the study. • Neuropathic and psychogenic pruritus, such as but not limited to notalgia paresthetica, brachioradial pruritus, small fiber neuropathy, skin picking syndrome, or delusional parasitosis. • History of lymphoproliferative disease or history of malignancy of any organ system within the last 5 years, except for: (1) basal cell carcinoma, squamous cell carcinoma in situ (Bowen's disease), or carcinomas in situ of the cervix that have been treated and have no evidence of recurrence in the last 12 weeks before the screening visit, or (2) actinic keratoses that have been treated. • History of hypersensitivity (including anaphylaxis) to an immunoglobulin (plasma-derived or recombinant) product (e.g., monoclonal antibody) or to any of the study drug excipients. • Current active or latent tuberculosis (TB) infection or history of either untreated or inadequately treated active or latent TB according to the local applicable guidelines. *Note*: Subjects who have a documented history of completion of an appropriate TB treatment regimen for latent or active TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study. In the event of rescreening, the TB tests result from the first screening can be used by the investigator to assess the eligibility of rescreened subjects if the test was performed within 6 weeks prior to the baseline visit. • Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment. • Any clinically relevant laboratory abnormalities, such as but not limited to elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST) (>3 × upper limit of normal [ULN]) in combination with elevated bilirubin (>2 × ULN), 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. • Currently participating or participated in any other study of an investigational drug or device, within the past 8 weeks (or 5 half-lives of the investigational drug, whichever is longer) before the screening visit, or is in an exclusion period (if verifiable) from a previous study, other than the nemolizumab studies for PN (studies RD.03.SPR.115828, RD.06.SPR.202685, or RD.06.SPR.203065).
Planned sample size	Approximately (b) (4) subjects are planned to be enrolled in this study, depending on rollover rate from the lead-in studies.

Investigational therapy

Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for injection for SC use only after reconstitution in a pre-filled, single-use, dual-chamber syringe [DCS].

Subjects who rollover from a phase 3 study (RD.06.SPR.202685 or RD.06.SPR.203065) will receive 2 SC injections of blinded study medication administered on Day 1/baseline, as assigned by IRT and based on the assigned lead-in study treatment, to maintain the blind of the lead-in study. (Thus, subjects may receive either 2 blinded 30-mg injections of nemolizumab, or 1 blinded 30- mg injection of nemolizumab and 1 blinded placebo injection.) Table 1 summarizes the study treatment for subjects enrolling from the phase 3 study.

Subjects who enroll from the prior phase 2a study (RD.03.SPR.115828) will receive 2 open-label nemolizumab 30-mg SC injections administered on Day 1/baseline. Table 1 summarizes the study treatment for subjects enrolling from the phase 2 study.

Subjects who re-enter from the phase 3b durability study (RD.06.SPR.203890) will receive study drug as assigned by IRT at the re-entry visit (Week R0), based on the assigned study drug in the durability study (See Table 2).

Subjects will have the option to self-inject study drug while at the study center under staff supervision. Subjects will be trained on injecting the study drug and will be allowed to inject study drug at all subsequent visits, while at the study center, under staff supervision. If the subject does not wish to perform the injections, study staff can administer study drug at each visit. Table 4 presents details on the investigational therapy.

Table 68. Investigational Therapy

.	**Investigational Product**	**Placebo[a]**
Name	Nemolizumab	Nemolizumab placebo
Internal code	CD14152	NA
Pharmaceutical form	Lyophilized powder in a DCS for solution for injection	Lyophilized powder in a DCS for solution for injection
Packaging	DCS	DCS
Storage conditions	Blinded kits: Stored between 2°C to 8°C (36°F to 46°F); protected from freezing; protected from light Open-label kits: Stored at room temperature; do not store above 30°C; protected from freezing; protected from light; until current stock is depleted. Then newer stock should be stored between 2 to 8°C (36 to 46°F); protected from freezing; protected from light, as per product label.	Blinded kits: Stored between 2°C to 8°C (36°F to 46°F); protected from freezing; protected from light
Dosage[b]	Refer to Table 1 and Table 2	
Route	SC use by subjects or clinic staff after reconstitution	SC use by subjects or clinic staff after reconstitution
Dose regimen	Refer to Table 1 and Table 2	

	Treatment duration	Up to 184 weeks with last injection at Week 180 (or re-entry Week R128)	4 weeks with injection at Day 1/baseline, depending on lead-in study

[a] Placebo used for blinded dosing at Day 1/baseline/re-entry Week R0 visit only.
[b] Subjects who rollover from a phase 3 lead-in study (RD.06.SPR.202685 or RD.06.SPR.203065) will receive blinded study medication as assigned by IRT at the baseline visit, based on the assigned lead-in study treatment, to maintain the blind of the lead-in study. All other subjects will receive an open-label 60 mg dose of nemolizumab at the baseline visit. Subjects who re-enter from the phase 3b durability study (RD.06.SPR.203890) will receive study drug as assigned by IRT at the re-entry baseline (Week R0), based on the assigned study drug in the durability study. See Table 1 and Table 2 for details.
Abbreviations: DCS, dual chamber syringe; SC, subcutaneous

Rescue therapies
If deemed to be medically necessary by the investigator (e.g., to control intolerable pruritus, and/or signs/symptoms), rescue therapies can be prescribed to the subjects at any time during the study.

As a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 4 weeks after baseline to allow a minimum time for study drug exposure.

Investigator assessments of efficacy should be performed before initiating rescue therapy. Subjects requiring rescue therapy between scheduled visits should return to the clinic (unscheduled visit) for investigator assessment of efficacy before starting rescue therapy.

Whenever possible, investigators should first use topical medication or oral antihistamines as rescue therapy before escalating to other systemic therapies. If subjects receive topical treatments, oral antihistamines, or ultraviolet B (UVB) phototherapy as rescue therapy, study drug administration should be continued unless there is a concern according to the investigator's judgment. If subjects receive systemic rescue therapy (other than oral antihistamines), intralesional corticosteroids, or psoralen + ultraviolet A (PUVA) treatment, the study drug administration must be discontinued. The protocol provides a complete list of prohibited therapies, unless otherwise specified as rescue therapies.

Treatment duration	The expected duration of each subject's participation in the study is up to 196 weeks, including a screening period (up to 4 weeks), up to a 184-week treatment period, and an 8-week follow-up period (12-weeks after the last study drug injection).

Efficacy	The following efficacy assessments are planned according to the Schedule of Assessments in the protocol: • IGA • Peak and Average Pruritus NRS • PAS • SD NRS • PN-associated pain intensity and frequency • PGAD and PGAT • Worst Itch NRS (approximately 50 English-speaking subjects in United States only) The following quality of life assessments are planned according to the Schedule of Assessments in the protocol: • Dermatology Life Quality Index (DLQI) • EuroQoL 5-Dimension (EQ-5D)
Safety	The following safety assessments are planned according to the Schedule of Assessments in the protocol: • AEs, including treatment emergent AEs (TEAEs), AEs of special interest (AESIs), and serious AEs (SAEs) • Physical examination and vital signs • Clinical laboratory tests • Electrocardiogram (ECG) • Respiratory examination and assessments
Pharmacokinetics /immunogenicity	The following pharmacokinetic and immunogenicity assessments are planned according to the Schedule of Assessments in the protocol: • Serum nemolizumab concentrations • Anti-drug antibody (ADA) assessments (screening, confirmatory, titer, and neutralizing antibody)
Statistical methods and planned analyses	The safety population (SAF) will include all subjects who receive at least 1 dose of LTE study drug and will be used for all analyses of efficacy and safety. The PK Analysis Population (PKAP) will include all subjects included in the SAF, with at least 1 measurable post-baseline PK assessment; the PKAP will be used for analyses of PK. **Safety analyses** The incidence of TEAEs, Drug-Related TEAEs, SAEs, TEAEs leading to study drug discontinuation and TEAEs of Special Interest will be included in incidence tables, summarized by System Organ Class (SOC) and Preferred Term (PT). Additionally, the incidence of TEAEs by maximum severity will be presented by SOC and PT. Clinical laboratory data and vital signs will be summarized, including observed values and change from baseline values, as well as numbers of subjects with values outside limits of the normal range, including shifts from baseline at each time point. Summary tables will be provided for 12-Lead ECG, full Physical Examination, ACT, PEF, and Respiratory Exam by treatment group. Listings for Symptom-directed physical examination and Skin/ integumentary system plus Symptom-directed physical examination will also be provided.

Pharmacokinetics (PK) and pharmacodynamics (PD) analyses
Summary statistics will be used to describe the PK profile of nemolizumab. Individual and mean serum concentration versus time curves will be presented. Descriptive statistics (arithmetic and geometric mean, SD, coefficient of variation [CV%], minimum [min], maximum [max], and median) of the serum concentrations versus time will be presented.

Incidence of positive ADA results will be summarized (absolute occurrence, percent of subjects, and treatment-related ADA). The ADA results presentation will be detailed in the SAP.

Efficacy analyses
All efficacy analyses will be performed on the SAF and will be descriptive in nature. Subgroup analyses based on demographic and baseline factors may be presented.

Sample size
No formal sample size calculations were performed for this LTE study.

Abbreviations: ACT, Asthma Control Test; ADA, anti-drug antibodies; AE, adverse event; AESI, adverse event of special interest; ALT, alanine aminotransferase; AP, Average Pruritus; AST, aspartate aminotransferase; CR, clinical responder; CV, coefficient of variation; DCS, dual chamber syringe; DLQI, Dermatology Life Quality Index; ECG, electrocardiogram; EQ-5D, EuroQol 5-Dimension; FSH, follicle stimulating hormone; HBsAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; IAC, independent adjudication committee; IDMC, Independent Data Monitoring Committee; IGA, Investigator's Global Assessment; IgE, immunoglobulin e; IRT, interactive response technology; LTE, long-term extension; NRS, numeric rating scale; PAS, Prurigo Activity Score; PCR, polymerase chain reaction; PD, pharmacodynamic; PGAD, Patient Global Assessment of Disease; PGAT, Patient Global Assessment of Treatment; PK, pharmacokinetic; PKAP, PK Analysis Population; PN, prurigo nodularis; PP-NRS, Peak Pruritus Numeric Rating Scale; PT, preferred term; PUVA, psoralen + ultraviolet A; Q4W, every 4 weeks; R-ET, re-entry early termination; R-FU, re-entry follow-up; R0, re-entry baseline; SAF, safety population; SAE, serious adverse event; SAP, statistical analysis plan; SD-NRS, Sleep Disturbance Numeric Rating Scale; SOC, system organ class; TB, tuberculosis; TEAE, treatment-emergent adverse event; ULN, upper limit of normal; UVB, ultraviolet B

16. Efficacy

16.1. Different Approaches for Handling Missing Data

Table 69 and Table 70 present the results for the primary efficacy endpoints by the various imputation methods in OLYMPIA 1 and OLYMPIA 2, respectively. The results for both endpoints were generally similar across the primary analysis and the sensitivity analyses in both trials.

Table 69. Comparison of Approaches for Handling Missing Data, OLYMPIA 1 (ITT[1])

Endpoint/Approach	Nemolizumab (N=190)	Placebo (N=96)	Adjusted Difference (95% CI)[2]	p-Value[2]
≥4-point improvement on the PP-NRS from baseline to Week 16				
With extended bounds[3]				
NRI (primary)[5]	58%	17%	40% (29%, 51%)	<0.001
MI-MAR[6]	64%	20%	43% (31%, 54%)	<0.001
MI-MNAR[7]	63%	21%	41% (29%, 52%)	<0.001
LOCF[8]	64%	21%	41% (30%, 53%)	<0.001
OC[9]	67%	21%	47% (36%, 59%)	<0.001

Endpoint/Approach	Nemolizumab (N=190)	Placebo (N=96)	Adjusted Difference (95% CI)[2]	p-Value[2]
Without extended bounds[4]				
NRI (primary)[5]	56%	16%	38% (27%, 48%)	<0.001
MI-MAR[6]	64%	21%	42% (31%, 54%)	<0.001
MI-MNAR[7]	63%	21%	41% (29%, 52%)	<0.001
LOCF[8]	64%	21%	42% (30%, 53%)	<0.001
OC[9]	69%	20%	49% (37%, 60%)	<0.001
IGA score of 0 or 1 at Week 16				
NRI (primary)[5]	26%	7%	15% (7%, 23%)	0.0025
MI-MAR[6]	29%	8%	17% (8%, 25%)	0.0013
MI-MNAR[7]	27%	8%	14% (6%, 23%)	0.0036
LOCF[8]	28%	7%	16% (8%, 24%)	0.0014
OC[9]	30%	8%	17% (8%, 26%)	0.0013

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFFMI.xpt, ADEFF2.xpt, ADEFFMI2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Except for the Observed Case (OC) analysis, subjects who received rescue therapy were imputed as non-responders.
[2] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
[3] The Applicant's original analysis allowed for extensions to the bounds of the 7-day period for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[4] This analysis does not include the extensions to the bounds for calculating the weekly average for the PP-NRS.
[5] Missing data imputed using non-responder imputation (NRI).
[6] Missing data imputed using multiple imputation (MI) assuming missing at random (MAR).
[7] Missing data imputed using multiple imputation (MI) assuming missing not at random (MNAR).
[8] Missing data imputed using last observation carried forward (LOCF).
[9] For this observed case (OC) analysis, all observed data even after use of rescue therapy is used without imputation of missing data.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; LOCF, last observation carried forward; MAR, missing at random; MI, multiple imputation; MNAR, missing not at random; N, number of patients in treatment arm; NRI, non-responder imputation; OC, observed case; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 70. Comparison of Approaches for Handling Missing Data, OLYMPIA 2 (ITT[1])

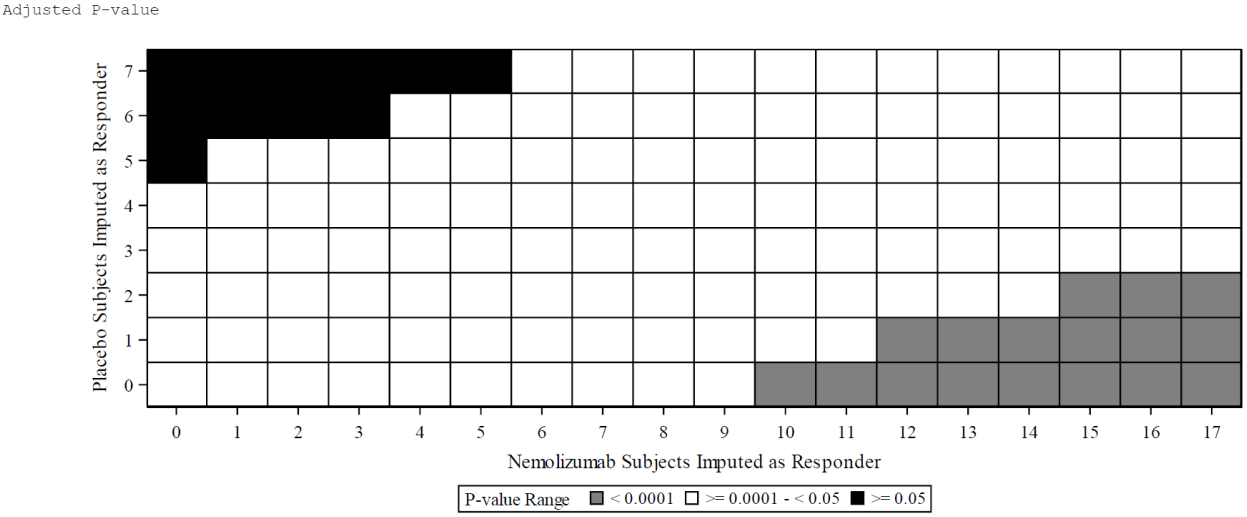
Endpoint/Approach	Nemolizumab (N=183)	Placebo (N=91)	Adjusted Difference (95% CI)[2]	p-Value[2]
≥4-point improvement on the PP-NRS from baseline to Week 16				
With extended bounds[3]				
NRI (primary)[5]	56%	21%	37% (26%, 48%)	<0.001
MI-MAR[6]	63%	24%	41% (29%, 52%)	<0.001
MI-MNAR[7]	60%	24%	38% (27%, 50%)	<0.001
LOCF[8]	60%	22%	40% (29%, 51%)	<0.001
OC[9]	65%	24%	43% (31%, 55%)	<0.001
Without extended bounds[4]				
NRI (primary)[5]	49%	16%	34% (23%, 45%)	<0.001
MI-MAR[6]	60%	20%	42% (31%, 53%)	<0.001
MI-MNAR[7]	59%	19%	42% (30%, 53%)	<0.001
LOCF[8]	60%	19%	42% (31%, 53%)	<0.001
OC[9]	65%	24%	41% (27%, 54%)	<0.001

Endpoint/Approach	Nemolizumab (N=183)	Placebo (N=91)	Adjusted Difference (95% CI)[2]	p-Value[2]
IGA score of 0 or 1 at Week 16				
NRI (primary)[5]	38%	11%	29% (19%, 38%)	<0.001
MI-MAR[6]	41%	14%	29% (18%, 40%)	<0.001
MI-MNAR[7]	41%	16%	27% (15%, 38%)	<0.001
LOCF[8]	40%	12%	30% (20%, 40%)	<0.001
OC[9]	41%	11%	32% (22%, 42%)	<0.001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt, ADEFFMI.xpt, ADEFF2.xpt, ADEFFMI2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Except for the Observed Case (OC) analysis, subjects who received rescue therapy were imputed as non-responders.
[2] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
[3] The Applicant's original analysis allowed for extensions to the bounds of the 7-day period for calculating the weekly average score for the PP-NRS, see Section 6.2.6.
[4] This analysis does not include the extensions to the bounds for calculating the weekly average for the PP-NRS.
[5] Missing data imputed using non-responder imputation (NRI).
[6] Missing data imputed using multiple imputation (MI) assuming missing at random (MAR).
[7] Missing data imputed using multiple imputation (MI) assuming missing not at random (MNAR).
[8] Missing data imputed using last observation carried forward (LOCF).
[9] For this observed case (OC) analysis, all observed data even after use of rescue therapy is used without imputation of missing data.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; LOCF, last observation carried forward; MAR, missing at random; MI, multiple imputation; MNAR, missing not at random; N, number of patients in treatment arm; NRI, non-responder imputation; OC, observed case; PP-NRS, Peak Pruritus Numeric Rating Scale

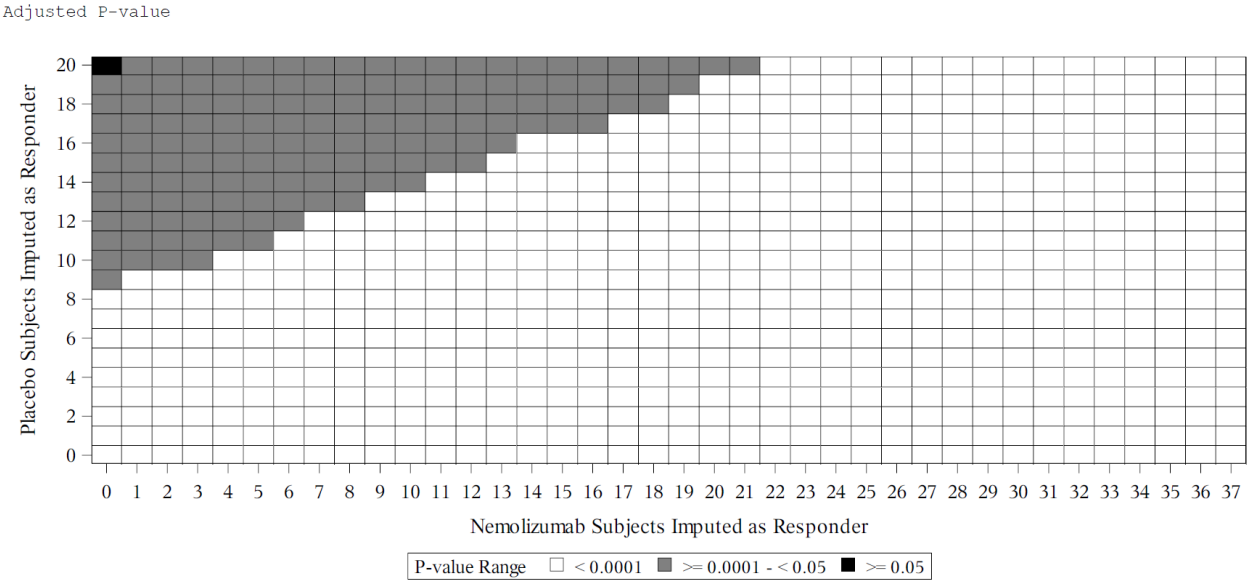
The Applicant conducted tipping point analyses for the primary efficacy endpoints. For OLYMPIA 1, the results for the primary endpoint of ≥4-point improvement on the PP-NRS from baseline to Week 16 with and without the extended bounds remained statistically significant (i.e., p-value <0.05) even under the worst-scenario (i.e., subjects with missing data in the nemolizumab group are imputed as non-responders and subjects with missing data in the placebo group are imputed as responders), and the results for the primary endpoint of IGA score of 0 or 1 at Week 16 tip (i.e., no longer significant at the 0.05 level) when a high proportion of the missing data in the nemolizumab group is imputed as non-responders and a high proportion of subjects in the placebo group is imputed as responders, see Figure 33. For OLYMPIA 2, only the results for the primary endpoint of ≥4-point improvement on the PP-NRS from baseline to Week 16 without the extended bounds tip under the worst-case scenario, see Figure 34.

Figure 33. Applicant's Tipping Point Analysis for the Primary Efficacy Endpoint of IGA Score of 0 or 1 at Week 16, OLYMPIA 1 (ITT[1])



Source: Figure 14.2.1.2.6 in clinical study report for OLYMPIA 1
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders.

Figure 34. Applicant's Tipping Point Analysis for the Primary Efficacy Endpoint of ≥4-Point Improvement on the PP-NRS From Baseline to Week 16 (Without Extended Bounds), OLYMPIA 2 (ITT[1])



Source: Figure 14.2.1.1.6 in "Report Body Ad Hoc 13Mar2024" for OLYMPIA 2 submitted on March 27, 2024
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders.

Table 71 presents the results for the sensitivity analyses based on the number of diary assessments (i.e., ≥2 diary assessments out of 7 days and ≥3 diary assessments out of 7 days to calculate the weekly score) for the primary efficacy endpoint of ≥4-point improvement on the PP-NRS from Baseline to Week 16. The results for these sensitivity analyses are generally similar to the results for the primary analysis (i.e., ≥4 diary assessments).

Table 71. Sensitivity Analyses for the Primary Efficacy Endpoint of ≥4-Point Improvement on the PP-NRS From Baseline to Week 16 Based on the Number of Diary Assessments in the 7-Day Period, OLYMPIA 1 and OLYMPIA 2 (ITT[1])

	OLYMPIA 1		OLYMPIA 2	
	Nemolizumab (N=190)	Placebo (N=96)	Nemolizumab (N=183)	Placebo (N=91)
Sensitivity analysis #1: ≥2 diary assessments in 7-day period				
≥4-point improvement on the PP-NRS from baseline to Week 16	108 (57%)	15 (16%)	102 (56%)	19 (21%)
Adjusted difference (95% CI)[2]	39% (29%, 50%)		37% (26%, 48%)	
p-value[4]	<0.0001		<0.0001	
Sensitivity analysis #2: ≥3 diary assessments in 7-day period				
≥4-point improvement on the PP-NRS from baseline to Week 16	108 (57%)	15 (16%)	96 (52%)	15 (16%)
Adjusted difference (95% CI)[2]	39% (29%, 50%)		38% (27%, 48%)	
p-value[2]	<0.0001		<0.0001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADEFF.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
[2] Adjusted difference in proportions is the weighted average of the treatment differences across the strata (i.e., analysis center and body weight at randomization [<90 kg, ≥90 kg]) using Cochran-Mantel-Haenszel (CMH) weights. Two-sided 95% CI is based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by analysis center and body weight at randomization (<90 kg, ≥90 kg).
Abbreviations: CI, confidence interval; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

16.2. Findings in Special/Subgroup Populations

Results for subgroup analyses by age (<65 and ≥65 years), sex, race, ethnicity, weight (<90 and ≥90 kg), country (United States and outside United States), history of atopy, previous systemic treatment for PN, and baseline IGA score are presented in Table 72 to Table 77. The treatment effect was generally consistent across these subgroups. For race, the sample sizes for some of the subgroups were relatively small; therefore, it would be difficult to detect any differences in efficacy between these subgroups and their complements.

Table 72. Results for ≥4-Point Improvement on the PP-NRS From Baseline to Week 16 (Without Extended Bounds) by Age, Sex, Race, Ethnicity, Weight, Country, History of Atopy, Previous Systemic Treatment for PN, and Baseline IGA Score, OLYMPIA 1 (ITT[1])

Subgroup	Nemolizumab (N=190)	Placebo (N=96)	Unadjusted Difference (95% CI)
Age (years)			
<65	75/136 (55%)	13/68 (19%)	36% (23%, 49%)
≥65	31/54 (57%)	2/28 (7%)	50% (34%, 67%)
Sex			
Male	44/80 (55%)	7/40 (18%)	38% (21%, 54%)
Female	62/110 (56%)	8/56 (14%)	42% (29%, 55%)
Race			
White	90/160 (56%)	15/81 (19%)	38% (26%, 49%)
Black or African American	10/18 (56%)	0/10 (0%)	56% (33%, 79%)
Asian	5/10 (50%)	0/2 (0%)	50% (19%, 81%)
Other	1/2 (50%)	0/3 (0%)	50% (-19%, 100%)
Ethnicity			
Hispanic or Latino	2/4 (50%)	0/5 (0%)	50% (1%, 99%)
Not Hispanic or Latino/unknown or not reported	104/186 (56%)	15/91 (16%)	39% (29%, 50%)

Subgroup	Nemolizumab (N=190)	Placebo (N=96)	Unadjusted Difference (95% CI)
Weight (kg)			
< 90	61/117 (52%)	9/67 (13%)	39% (27%, 51%)
≥ 90	45/73 (62%)	6/29 (21%)	41% (22%, 59%)
Country			
United States	23/44 (52%)	4/23 (17%)	35% (13%, 56%)
Outside United States	83/146 (57%)	11/73 (15%)	42% (30%, 53%)
History of atopy			
Yes	36/60 (60%)	6/33 (18%)	42% (24%, 60%)
No	70/130 (54%)	9/63 (14%)	40% (27%, 52%)
Previous systemic treatment for PN			
Yes	47/79 (59%)	2/33 (6%)	53% (40%, 70%)
No	59/111 (53%)	13/63 (21%)	33% (19%, 46%)
Baseline IGA score			
3 – moderate	60/107 (56%)	13/62 (21%)	35% (21%, 49%)
4 – severe	46/83 (55%)	2/34 (6%)	50% (36%, 63%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PN, prurigo nodularis

Table 73. Results for ≥4-Point Improvement on the PP-NRS From Baseline to Week 16 (Without Extended Bounds) by Age, Sex, Race, Ethnicity, Weight, Country, History of Atopy, Previous Systemic Treatment for PN, and Baseline IGA Score, OLYMPIA 2 (ITT[1])

Subgroup	Nemolizumab (N=183)	Placebo (N=91)	Unadjusted Difference (95% CI)
Age (years)			
<65	71/137 (52%)	13/77 (17%)	35% (23%, 47%)
≥65	18/46 (39%)	2/14 (14%)	25% (2%, 48%)
Sex			
Male	29/70 (41%)	5/36 (14%)	28% (11%, 44%)
Female	60/113 (53%)	10/55 (18%)	35% (21%, 49%)
Race			
White	76/147 (52%)	11/68 (16%)	36% (24%, 47%)
Black or African American	3/5 (60%)	2/7 (29%)	31% (-23%, 86%)
Asian	7/23 (30%)	2/14 (14%)	16% (-10%, 42%)
Other	3/8 (38%)	0/2 (0%)	38% (4%, 71%)
Ethnicity			
Hispanic or Latino	2/5 (40%)	1/7 (14%)	26% (-24%, 76%)
Not Hispanic or Latino/unknown or not reported	87/178 (49%)	14/84 (17%)	32% (21%, 43%)
Weight (kg)			
<90	67/132 (51%)	13/67 (19%)	31% (19%, 44%)
≥90	22/51 (43%)	2/24 (8%)	35% (17%, 52%)
Country			
United States	11/23 (48%)	1/9 (11%)	37% (8%, 66%)
Outside United States	78/160 (49%)	14/82 (17%)	32% (20%, 43%)
History of atopy			
Yes	25/57 (44%)	4/31 (13%)	31% (13%, 48%)
No	64/126 (51%)	11/60 (18%)	32% (19%, 46%)

Subgroup	Nemolizumab (N=183)	Placebo (N=91)	Unadjusted Difference (95% CI)
Previous systemic treatment for PN			
Yes	52/104 (50%)	11/57 (19%)	31% (17%, 45%)
No	37/79 (47%)	4/34 (12%)	35% (20%, 51%)
Baseline IGA Score			
3 – moderate	49/108 (45%)	10/48 (21%)	25% (10%, 39%)
4 – severe	40/75 (53%)	5/43 (12%)	42% (27%, 57%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PN, prurigo nodularis

Table 74. Results for IGA Score of 0 or 1 at Week 16 by Age, Sex, Race, Ethnicity, Weight, Country, History of Atopy, Previous Systemic Treatment for PN, and Baseline IGA Score, OLYMPIA 1 (ITT[1])

Subgroup	Nemolizumab (N=190)	Placebo (N=96)	Unadjusted Difference (95% CI)
Age (years)			
<65	37/136 (27%)	6/62 (9%)	18% (8%, 28%)
≥65	13/54 (24%)	1/28 (4%)	21% (7%, 34%)
Sex			
Male	21/80 (26%)	3/40 (8%)	19% (6%, 31%)
Female	29/110 (26%)	4/56 (7%)	19% (9%, 30%)
Race			
White	42/160 (26%)	7/81 (9%)	18% (8%, 27%)
Black or African American	5/18 (28%)	0/10 (0%)	28% (7%, 48%)
Asian	3/10 (30%)	0/2 (0%)	30% (2%, 58%)
Other	0/2 (0%)	0/3 (0%)	Not calculable
Ethnicity			
Hispanic or Latino	2/4 (50%)	1/5 (20%)	30% (-30%, 90%)
Not Hispanic or Latino/unknown or not reported	48/186 (26%)	6/91 (7%)	19% (11%, 27%)
Weight (kg)			
<90	30/117 (26%)	5/67 (7%)	18% (8%, 28%)
≥90	20/73 (27%)	2/29 (7%)	21% (7%, 34%)
Country			
United States	12/44 (27%)	4/23 (17%)	10% (-10%, 30%)
Outside United States	38/146 (26%)	3/73 (4%)	22% (13%, 30%)
History of atopy			
Yes	15/60 (25%)	0/33 (0%)	25% (14%, 36%)
No	35/130 (27%)	7/63 (11%)	16% (5%, 27%)
Previous systemic treatment for PN			
Yes	21/79 (27%)	2/33 (6%)	21% (8%, 33%)
No	29/111 (26%)	5/63 (8%)	18% (8%, 29%)
Baseline IGA score			
3 – moderate	34/107 (32%)	6/62 (10%)	22% (11%, 34%)
4 – severe	16/83 (19%)	1/34 (3%)	16% (6%, 27%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADEFF.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PN, prurigo nodularis

Table 75. Results for IGA Score of 0 or 1 at Week 16 by Age, Sex, Race, Ethnicity, Weight, Country, History of Atopy, Previous Systemic Treatment for PN, and Baseline IGA Score, OLYMPIA 2 (ITT[1])

Subgroup	Nemolizumab (N=183)	Placebo (N=91)	Unadjusted Difference (95% CI)
Age (years)			
<65	58/137 (42%)	10/77 (13%)	29% (18%, 41%)
≥65	11/46 (24%)	0/14 (0%)	24% (12%, 36%)
Sex			
Male	21/70 (30%)	5/36 (14%)	16% (1%, 32%)
Female	48/113 (42%)	5/55 (9%)	33% (22%, 45%)
Race			
White	57/147 (39%)	5/68 (7%)	31% (21%, 41%)
Black or African American	1/5 (20%)	2/7 (29%)	-9% (-57%, 40%)
Asian	8/23 (35%)	3/14 (21%)	13% (-16%, 42%)
Other	3/8 (38%)	0/2 (0%)	38% (4%, 71%)
Ethnicity			
Hispanic or Latino	4/5 (80%)	1/7 (14%)	66% (22%, 100%)
Not Hispanic or Latino/unknown or not reported	65/178 (37%)	9/84 (11%)	26% (16%, 35%)
Weight (kg)			
<90	55/132 (42%)	7/67 (10%)	31% (20%, 42%)
≥90	14/51 (27%)	3/24 (13%)	15% (-3%, 33%)
Country			
United States	7/23 (30%)	1/9 (11%)	19% (-9%, 47%)
Outside United States	62/160 (39%)	9/82 (11%)	28% (18%, 38%)
History of atopy			
Yes	20/57 (35%)	3/31 (10%)	25% (9%, 42%)
No	49/126 (39%)	7/60 (12%)	27% (15%, 39%)
Previous systemic treatment for PN			
Yes	47/104 (45%)	6/57 (11%)	35% (22%, 47%)
No	22/79 (28%)	4/34 (12%)	16% (1%, 31%)
Baseline IGA score			
3 – moderate	39/108 (36%)	8/48 (17%)	19% (6%, 33%)
4 – severe	30/75 (40%)	2/43 (5%)	35% (23%, 48%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADEFF.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PN, prurigo nodularis

Table 76. Results for Achieving Both ≥4-Point Improvement on the PP-NRS From Baseline (Without Extended Bounds) and an IGA Score of 0 or 1 at Week 16 by Age, Sex, Race, Ethnicity, Weight, Country, History of Atopy, Previous Systemic Treatment for PN, and Baseline IGA Score, OLYMPIA 1 (ITT[1])

Subgroup	Nemolizumab (N=190)	Placebo (N=96)	Unadjusted Difference (95% CI)
Age (years)			
<65	31/136 (23%)	2/68 (3%)	20% (12%, 28%)
≥65	10/54 (19%)	0/28 (0%)	19% (8%, 29%)
Sex			
Male	15/80 (19%)	1/40 (3%)	16% (6%, 26%)
Female	26/110 (24%)	1/56 (2%)	22% (13%, 31%)

Subgroup	Nemolizumab (N=190)	Placebo (N=96)	Unadjusted Difference (95% CI)
Race			
White	33/160 (21%)	2/81 (2%)	18% (11%, 25%)
Black or African American	5/18 (28%)	0/10 (0%)	28% (7%, 48%)
Asian	3/10 (30%)	0/2 (0%)	30% (2%, 58%)
Other	0/2 (0%)	0/3 (0%)	Not calculable
Ethnicity			
Hispanic or Latino	1/4 (25%)	0/5 (0%)	25% (-17%, 67%)
Not Hispanic or Latino/unknown or not reported	40/186 (22%)	2/91 (2%)	19% (13%, 26%)
Weight (kg)			
<90	25/117 (21%)	1/67 (1%)	20% (12%, 28%)
≥90	16/73 (22%)	1/29 (3%)	18% (7%, 30%)
Country			
United States	9/44 (20%)	1/23 (4%)	16% (2%, 31%)
Outside United States	32/146 (22%)	1/73 (1%)	21% (13%, 28%))
History of atopy			
Yes	14/60 (23%)	0/33 (0%)	23% (13%, 34%)
No	27/130 (21%)	2/63 (3%)	18% (9%, 26%)
Previous systemic treatment for PN			
Yes	18/79 (23%)	1/33 (3%)	20% (9%, 31%)
No	26/107 (24%)	2/63 (3%)	21% (12%, 30%)
Baseline IGA score			
3 – moderate	26/107 (24%)	2/62 (3%)	21% (12%, 30%)
4 – severe	15/83 (18%)	0/34 (0%)	18% (10%, 26%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PN, prurigo nodularis

Table 77. Results for Achieving Both ≥4-Point Improvement on the PP-NRS From Baseline (Without Extended Bounds) and an IGA Score of 0 or 1 at Week 16 by Age, Sex, Race, Ethnicity, Weight, Country, History of Atopy, Previous Systemic Treatment for PN, and Baseline IGA Score, OLYMPIA 2 (ITT[1])

Subgroup	Nemolizumab (N=183)	Placebo (N=91)	Unadjusted Difference (95% CI)
Age (years)			
<65	39/137 (28%)	4/77 (5%)	23% (14%, 32%)
≥65	7/46 (15%)	0/14 (0%)	15% (5%, 26%)
Sex			
Male	12/70 (17%)	1/36 (3%)	14% (4%, 25%)
Female	34/113 (30%)	3/55 (5%)	25% (14%, 35%)
Race			
White	40/147 (27%)	2/68 (3%)	24% (16%, 33%)
Black or African American	1/5 (20%)	1/7 (14%)	6% (-38%, 49%)
Asian	4/23 (17%)	1/14 (7%)	10% (-10%, 31%)
Other	1/8 (13%)	0/2 (0%)	13% (-10%, 35%)
Ethnicity			
Hispanic or Latino	1/5 (20%)	0/7 (0%)	20% (-15%, 55%)
Not Hispanic or Latino/unknown or not reported	45/178 (25%)	4/84 (5%)	21% (13%, 28%)

Subgroup	Nemolizumab (N=183)	Placebo (N=91)	Unadjusted Difference (95% CI)
Weight (kg)			
<90	38/132 (29%)	4/67 (6%)	23% (13%, 32%)
≥90	8/51 (16%)	0/24 (0%)	16% (6%, 26%)
Country			
United States	5/23 (22%)	0/9 (0%)	22% (5%, 39%)
Outside United States	41/160 (26%)	4/82 (5%)	21% (13%, 29%)
History of atopy			
Yes	13/57 (23%)	2/31 (6%)	16% (2%, 30%)
No	33/126 (26%)	2/60 (3%)	23% (14%, 32%)
Previous systemic treatment for PN			
Yes	33/104 (32%)	3/57 (5%)	26% (16%, 37%)
No	13/79 (16%)	1/34 (3%)	14% (4%, 23%)
Baseline IGA score			
3 – moderate	26/108 (24%)	3/48 (6%)	18% (7%, 28%)
4 – severe	20/55 (27%)	1/43 (2%)	24% (13%, 35%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADCM.xpt, ADEFF2.xpt
[1] Intent-to-treat (ITT) population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.
Abbreviations: CI, confidence interval; IGA, Investigator's Global Assessment; N, number of patients in treatment arm; PN, prurigo nodularis

16.3. Human Factors Study Reports Review

The review evaluates the human factors (HF) study results reports submitted under BLA 761390 (b) (4) dual chamber autoinjector (AI). Please refer to the document in DARRTS, Reference ID 5421421.

17. (b) (4) dual chamber autoinjector (AI) Clinical Safety

Not applicable

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable

21. Other Drug Development Considerations

Not applicable

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The Applicant, Galderma Laboratories, L.P., submitted clinical data for nemolizumab injection for the treatment of prurigo nodularis (PN) from Studies SPR.202685 (NCT04501666) and SPR.203065 (NCT04501679).

Four clinical investigators (Drs. Staender, Legat, Reich, and Paul) were inspected. The inspections did not find significant concerns regarding the study conduct or oversight of the clinical trials or Good Clinical Practice or regulatory compliance, and based on the results of these inspections, the data generated by the inspected clinical investigators appear acceptable in support of the proposed indication.

23. Labeling: Key Changes

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the (Applicant's draft PI submitted on March 20, 2024) (Table 78). The PI was reviewed to ensure that PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 78. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
1 INDICATIONS AND USAGE	The age group (adults) was added to the indication statement.
2 DOSAGE AND ADMINISTRATION	For readability, subheadings were added for "Adult Patients Weighing Less Than 90 kg" and "Adult Patients Weighing 90 kg or More". Removed the claim, "(b) (4)" Removed the information concerning (b) (4) (b) (4)
4 CONTRAINDICATIONS	No major changes

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
5 WARNINGS AND PRECAUTIONS	5.1 Hypersensitivity: Added the statement NEMLUVIO is contraindicated in patients with a known hypersensitivity to nemolizumab-ilto or to any of the excipients in NEMLUVIO in accordance with the guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format* (October 2011). 5.2 Vaccinations: No major changes
6 ADVERSE REACTIONS	6.1 Clinical Trials Experience: The baseline demographics of the safety and efficacy populations are generally the same and the description of the baseline demographics are included the CLINICAL STUDIES section, instead of repeating the same baseline demographics in the ADVERSE REACTIONS section, a cross-reference to the CLINICAL STUDIES section was added per the recommendation on page 41 of the Labeling Review Tool. Included the dose and duration for the NEMLUVIO and placebo groups in Trials OLYMPIA 1 and OLYMPIA 2. Removed the statement (b) (4) n.
7 DRUG INTERACTIONS	Added language for potential of drug interaction of nemolizumab with CYP450 substrates since nemolizumab may modulate the release of proinflammatory cytokines and chemokines. Cytochrome P450 Substrates "The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Treatment with NEMLUVIO may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes. Upon initiation or discontinuation of NEMLUVIO in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate."

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	8.1 Pregnancy and 8.2 Lactation: Revised according to the recommendations of the Division of Pediatrics and Maternal Health (DPMH) and Nonclinical review team. Refer to the June 6, 2024, DPMH review in DARRTS (Reference ID: 5393123) and the Nonclinical sections of the IAMA review for additional information. 8.4 Pediatric Use: No major changes. 8.5 Geriatric Use: Added the percentage of subjects 65 years of age and older that were assessed for long-term safety. (b) (4) clinical trials of NEMLUVIO in prurigo nodularis did not include sufficient number of subjects 65 years of age or older to determine whether they respond differently than younger adult subjects, the statement (b) (4) was removed.
10 OVERDOSAGE	No major changes
12 CLINICAL PHARMACOLOGY	Revised according to the recommendations of the Clinical Pharmacology review team. Refer to the Clinical Pharmacology sections of the IAMA review for additional information. 12.2 Pharmacodynamics: Deleted the proposed (b) (4)
13 NONCLINICAL TOXICOLOGY	Revised according to the recommendations of the Nonclinical review team. Refer to the Nonclinical sections of the IAMA review for additional information.
14 CLINICAL STUDIES	Additional baseline demographic information concerning the race, ethnicity, and disease history of subjects and enrolled in Trials OLYMPIA 1 and OLYMPIA 2 was included. The presentation of the efficacy results was revised according to the recommendation of the review team regarding the Applicant's extensions to the bounds for calculating the weekly scores for the Peak Pruritus Numerical Rating Scale (PP-NRS). The results that were included in the label for endpoints based on the PP-NRS are those without the extended bounds. Refer to the Sections 6.2.6 and 6.2.7 for additional information. Included the results for a multi-component efficacy endpoint defined as the proportion of subjects that achieve BOTH a ≥4-point improvement on the PP-NRS from baseline and an IGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-point improvement from baseline at Week 16, as this multi-component endpoint is the Division's recommended primary efficacy endpoint for the treatment of PN. Removed (b) (4)

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	of the Clinical Outcome Assessment (COA) review team. Refer to Section 6.3.2 and the July 9, 2024, COA review in DARRTS (Reference ID: 5410009) for additional information.
17 PATIENT COUNSELING INFORMATION	Revisions were made to align the Administration Instructions with the additional information added to the Dosage and Administration section.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	(b) (4)

[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviations: COA, Clinical Outcome Assessment; CYP450, cytochrome P450; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Division of Pediatrics and Maternal Health; IGA, Investigator's Global Assessment; PD, pharmacodynamic; PI, prescribing information; PN, prurigo nodularis; PP-NRS, Peak Pruritus Numeric Rating Scale; SD-NRS, Sleep Disturbance Numerical Rating Scale

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing information
- Patient Package Insert
- Instructions for use (IFU)
- Carton labeling
- Container labeling

24. Postmarketing Requirements and Commitments

Product quality postmarketing commitments are detailed in Section 9.

25. Financial Disclosure

Table 79. Covered Clinical Studies: [SPR.202685 (OLYMPIA 1)]]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 100		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): Not specified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 6 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

Table 80. Covered Clinical Studies: [SPR.203065 (OLYMPIA 2)]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 68		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): Not specified		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 3 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in the Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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27. Review Team

Table 81. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Kimberle Searcy, MPH Susan Rhee, PharmD CPMS
Nonclinical reviewer	Jianyong Wang, MD, PhD
Nonclinical team leader	Barbara Hill, PhD
OCP reviewer(s)	Nisha Kwatra, PhD
OCP team leader(s)	Chinmay Shukla, PhD
Clinical reviewer	Hamid Tabatabai, MD
Clinical team leader	David Kettl, MD
Biometrics reviewer	Matthew Guerra, PhD
Biometrics team leader	Kathleen Fritsch, PhD
Cross-discipline team leader	David Kettl, MD
Division director (pharm/tox)	Andrew Goodwin, PhD
Division director (OCP)	Jianmeng Cheng, PhD
Division director (OB)	NA
Division director (clinical)	Jill Lindstrom, MD
Office director (or designated signatory authority)	Kathleen Donohue, MD

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 82. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ/OPQA III/DPQA XVI	Jacek Cieslak, PhD, Application Technical Lead Xiaoxiao Pan, PhD, Mamta Kapoor-Bhushan, PhD
OPQ/OPMA/DPMA	Liqun Zhao, PhD, Bo Chi, PhD, Maxwell Van Tassell, PhD, Zhong Li, PhD
OPQ/OPQA III	Vicky Borders-Hemphill, Pharm D
OPQ/OPRO/DRBPMII	Anita Brown
OPDP	SaintJuste Montherson
DMPP	Maria Nguyen
ADL	Matthew White
OSI	Stephanie Coquia Michelle Fedowitz
OSE/DEPI	Xi Wang, Benjamin Booth
OSE/DMEPA	Madhuri Patel, PharmD Oluwamurewa Oguntimein, PhD Lisa Huang, Wana Manitpisitkul
OSE/DRISK	Donna Fitzgerald, Pharm D
COA	Selena Daniels, Pharm D Yasmin Choudry, MD
Other-DPMH	Kristie Baisden, MD Tamara Johnson, MD Heather Buck

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPQA, Office of Product Quality Assessment; OMPA, Office of Pharmaceutical Manufacturing Assessment; DPQA, Division of Product Quality Assessment; DMPA, Division of Pharmaceutical Manufacturing Assessment; OPRO, Office of Program and Regulatory Operations; DRBPM, Division of Regulatory Business Process Management; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

27.1. Reviewer Signatures

Table 27-83 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Nisha Kwatra OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Nisha Kwatra

Digitally signed by Nisha Kwatra

Date: 8/12/2024 3:04 PM EDT
GUID: 202481219418

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Chinmay Shukla OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Chinmay Shukla

Digitally signed by Chinmay Shukla

Date: 8/12/2024 3:07 PM EDT
GUID: 20248121978

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Jianmeng Chen OCP DIIP	Sections: 5.2, 6.1, 8.1, 8.2, 14, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jianmeng Chen

Digitally signed by Jianmeng Chen

Date: 8/12/2024 3:07 PM EDT
GUID: 202481219715

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Kimberle Searcy ORO DROII	Sections: Regulatory History Section 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kimberle Searcy

Digitally signed by Kimberle Searcy

Date: 8/12/2024 3:07 PM EDT
GUID: 202481219746

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Andrew Goodwin OII DPTII	Sections: 5.1, 7.1, 8.4, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Andrew Goodwin			**Digitally signed by Andrew Goodwin** **Date: 8/12/2024 3:08 PM EDT** **GUID: 202481219857**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Matthew White OII DDD	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew White			**Digitally signed by Matthew White** **Date: 8/12/2024 3:09 PM EDT** **GUID: 202481219951**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Matthew Guerra OB DBIII	Sections: 6, 15, and 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Matthew Guerra

Digitally signed by Matthew Guerra

Date: 8/12/2024 3:11 PM EDT
GUID: 2024812191123

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Kathleen Fritsch OB DBIII	Sections: 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kathleen Fritsch

Digitally signed by Kathleen Fritsch

Date: 8/12/2024 3:13 PM EDT
GUID: 2024812191328

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Hamid Tabatabai OII DDD	Sections: 1.2, 2.1, 2.2, 3, 4, 7.2 to 7.7, 8.3, 10, 11, 22, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Approval
Signature: **Hamid Tabatabai**			**Digitally signed by Hamid Tabatabai** **Date: 8/12/2024 3:15 PM EDT** **GUID: 2024812191516**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline CPMS	Margaret Kober ORO DRORDPURM	Sections: Regulatory History	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Margaret Kober**			**Digitally signed by Margaret Kober** **Date: 8/12/2024 3:17 PM EDT** **GUID: 202481219174**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Barbara Hill OII DPTII	Sections: 5.1, 8.4.1, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Barbara Hill			**Digitally signed by Barbara Hill** **Date: 8/12/2024 3:17 PM EDT** **GUID: 202481219179**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Jianyong Wang OII DPTII	Sections: 5.1, 7.1, 8.4, and 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jianyong Wang			**Digitally signed by Jianyong Wang** **Date: 8/12/2024 3:18 PM EDT** **GUID: 2024812191852**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Susan Rhee ORO DROII	Sections: Section 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	Split action: Approval for pre-filled pen presentation (b) (4)

Signature: Susan Rhee

Digitally signed by Susan Rhee

Date: 8/12/2024 3:20 PM EDT
GUID: 2024812192012

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Secondary Reviewer	Jacek Cieslak OPQAIII DPQAXVI	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jacek Cieslak

Digitally signed by Jacek Cieslak

Date: 8/12/2024 3:24 PM EDT
GUID: 2024812192423

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Jill Lindstrom OII DDD	Sections: 13.3	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jill Lindstrom

Digitally signed by Jill Lindstrom

Date: 8/12/2024 3:25 PM EDT
GUID: 202481219251

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/OBP) Discipline Secondary Reviewer	Jacek Cieslak OPQAIII DPQAXVI	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Jacek Cieslak

Digitally signed by Jacek Cieslak

Date: 8/12/2024 3:25 PM EDT
GUID: 202481219253

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Hamid Tabatabai OII DDD	Sections: 1.2, 2.1, 2.2, 3, 4, 7.2 to 7.7, 8.3, 10, 11, 22, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Approval
Signature: Hamid Tabatabai			**Digitally signed by Hamid Tabatabai** **Sign on behalf of Signing on behalf of Dr. David Kettl** **Date: 8/12/2024 3:26 PM EDT** **GUID: 2024812192644**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Outcomes Assessment Reviewer Discipline Primary Reviewer	Yasmin Choudhry ODES DCOA	Sections: Sections 4.0, 6.3 Key issues COA related	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Yasmin Choudhry			**Digitally signed by Yasmin Choudhry** **Date: 8/12/2024 3:54 PM EDT** **GUID: 2024812195419**	

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HAMID N TABATABAI
08/12/2024 04:07:50 PM
Signing on behalf of Dr. David Kettl

JILL A LINDSTROM
08/12/2024 04:10:59 PM

KATHLEEN M DONOHUE
08/12/2024 04:18:15 PM