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RESEARCH**

APPLICATION NUMBER:

761391Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761391
Priority or standard	Standard
Submit date(s)	12/13/2024
Received date(s)	12/13/2023
PDUFA goal date	12/13/2024
Division/office	Division of Dermatology and Dentistry (DDD)
Review completion date	12/10/2024
Established/proper name	Nemolizumab-ilto
(Proposed) proprietary name	NEMLUVIO
Pharmacologic class	Interleukin-31 receptor antagonist
Other product name(s)	CIM331/CD14152
Applicant	Galderma R&D LLC
Dosage form(s)/formulation(s)	Injection, Powder, Lyophilized, for Solution
Dosing regimen	An initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W). After 16 weeks of treatment, for patients who achieve clear or almost clear skin, a dosage of 30 mg every 8 weeks (Q8W) is recommended
Applicant-proposed indication(s)/ population(s)	Treatment of moderate-to-severe Atopic Dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies
SNOMED CT code for proposed indication disease term(s)¹	24079001 [Atopic dermatitis (disorder)]
Regulatory action	Approval
Approved dosage (if applicable)	(b) (4) an initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (b) (4) (b) (4)
Approved indication(s)/ population(s) (if applicable)	Treatment of adult and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies.
SNOMED CT code for approved indication disease term(s)¹	63501000 [Prurigo nodularis (disorder)]

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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Glossary

AE	adverse event
AD	atopic dermatitis
ADA	antidrug antibody
AELD	adverse event leading to discontinuation of treatment
AESI	adverse event of special interest
ALT	alanine aminotransferase
AP-NRS	Average Pruritus Numerical Rating Scale
AR	adverse reaction
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BLA	biologics license application
BRF	Benefit-Risk Framework
BSF	body surface area
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CPK	creatine phosphokinase
DCC	dual-chamber cartridge
DCC-AI	dual-chamber cartridge assembled with an autoinjector
DCS	dual-chamber syringe
ECG	electrocardiogram
FDA	Food and Drug Administration
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
HF	human factor
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IL	interleukin
IND	investigational new drug
IR	information request
ISS	integrated summary of safety
ITP	initial treatment period
ITT	intent-to-treat
LD	loading dose
LTE	long-term extension
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
MTP	maintenance treatment period
NDA	new drug application
NOAEL	no observed adverse effect level
OPQ	Office of Pharmaceutical Quality
PD	pharmacodynamic
PI	Prescribing Information

BLA 761391
NEMLUVIO (nemolizumab-ilto)

PK	pharmacokinetic
PN	prurigo nodularis
PP-NRS	Peak Pruritus Numeric Rating Scale
PRO	patient-reported outcome
SCORAD	SCORing Atopic Dermatitis
SAE	serious adverse event
SAP	statistical analysis plan
SEE	substantial evidence of effectiveness
SC	subcutaneous
TCS	topical corticosteroids
TEAE	treatment-emergent adverse event
T _{max}	time to maximum concentration
ULN	upper limit of normal

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Galderma Laboratories, L.P., submitted this biologics license application (BLA) for nemolizumab-ilto (tradename NEMLUVIO), seeking approval of this interleukin (IL)-31 receptor antagonist for the treatment of moderate to severe atopic dermatitis (AD) in patients aged 12 years and older whose disease is not adequately controlled with topical prescription therapies (b) (4). 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)

(b) (4). A separate BLA (761390) for nemolizumab was approved Aug 12, 2024, for the treatment of prurigo nodularis.

AD is a chronic inflammatory skin disease characterized by pruritus, xerosis and eczematous lesions marked by erythema, infiltration/papulation, and oozing/crusting. The pathophysiology is understood to be multifactorial, involving susceptibility genes, immunological factors, infections, and environmental factors resulting in skin barrier disturbance, immune dysregulation, and inflammation.

Substantial evidence of effectiveness for nemolizumab was established using data from two adequate and well-controlled trials. The two pivotal trials, ARCADIA1 and ARCADIA 2, enrolled 941 and 787 subjects, respectively (1728 total), aged 12 years and older, with moderate-to-severe AD and randomized them (2:1) to nemolizumab or placebo. Subjects applied low or medium potency topical corticosteroids (TCS) or topical calcineurin inhibitors (TCI) for ≥ 14 days prior to baseline and concomitantly during the study. Nemolizumab was administered via subcutaneous injection, beginning with a 60 mg loading dose followed by 30mg every four weeks. Subjects were followed for 16 weeks; investigators were asked to assess the subjects' AD using the Investigator Global Assessment, a five-point scale ranging from clear to severe, and the Eczema Area and Severity Index, an assessment of extent and severity for which scores range from 0 to 72. Compared to placebo, a higher proportion of patients randomized to nemolizumab achieved IGA success, defined as an IGA of 0/clear or 1/almost clear, and a >2 -point reduction from baseline, (36% vs 25% in ARCADIA 1 and 38% vs 26% in ARCADIA 2), and EASI-75, $>75\%$ improvement in EASI from baseline (44% vs. 29% in ARCADIA 1 and 42% vs 30% in ARCADIA 2). These results were statistically significant, with a treatment difference of 12% (IGA; 95% CI 6% to 17%) and 15% (EASI75; 95% CI 9% to 21%) for ARCADIA 1 and 12% (IGA; 95%CI 6 to 19%) and 12% (EASI75; 95%CI 6 to 19%) for ARCADIA 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 reported slightly more commonly in the nemolizumab group (1.7%) than the placebo group (1.2%). Hypersensitivity reactions were reported with the use of nemolizumab and will be included in labeling 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, arthralgia, urticaria and myalgia.

The BLA included appropriate preapproval nonclinical and clinical pharmacology studies. In a drug interaction study of 14 subjects with moderate-to-severe AD treated with nemolizumab, no clinically significant changes in the exposure of CYP450 substrates before or after multiple nemolizumab injections were observed, hence labeling will reflect that concomitant use of nemolizumab is unlikely to influence the PK profiles of CYP substrates. Because a minority of patients with AD have moderate-to-severe disease and nemolizumab provides modest efficacy with concomitant use of TCS/TCI while monotherapy options exist, it is not anticipated that there will be sufficient pregnancy exposures to meaningfully inform pregnancy exposure registry or lactation studies. Pediatric studies in children 2-<12 years of age and 6 months to <2 years of age will be required as postmarketing requirements.

The review team concludes that the improvement in AD 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 moderate to severe AD in combination with topical corticosteroids and/or calcineurin inhibitors when the disease is not adequately controlled with topical prescription therapies.

The action for the pen dosage form will be Approval.

(b) (4)

(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 ARCADIA 1 and ARCADIA 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 patients ≥ 12 years of age with moderate to severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- AD is a chronic, relapsing, inflammatory cutaneous disorder, which is characterized by intensely pruritic, xerotic skin. Other clinical features may include erythema, edema, erosions, oozing, and lichenification. It is clinically diagnosed and relies principally on disease pattern (morphology and distribution), disease history, and medical history (e.g., personal and/or family history of atopy) (Eichenfield et al. 2014). - Although it may affect all age groups, AD is most common in children. Onset is typically between the ages of 3 and 6 months, with approximately 60% of patients developing the disease during the first year of life and 90% by the age of 5 years. For most patients, the disease resolves by adulthood. However, for 10 to 30% of individuals, AD persists into the adult years, and, for a smaller proportion of subjects, the disease initially presents in adulthood. The prevalence of AD in adults in the United States has been reported (Silverberg and Hanifin 2013) to be 3%, but may be as high as 7.3% (Chiesa Fuxench et al. 2019). - Comorbidities may include asthma, allergic rhinoconjunctivitis, and food allergies.	Although AD is not a life-threatening condition, it can be serious. It may significantly impact the quality of life of the patient and family members. Pruritus is a hallmark of the condition and is responsible for much of the disease burden for patients and their families (Weston 2021). The intense pruritus may disrupt sleep, which can have a carryover effect of tiredness during the day. The dysfunctional skin barrier, further compromised by scratching, may predispose patients to secondary infections. The primary and secondary disease-related skin changes may distort the appearance of the skin. The disease may also impact mood, and affected individuals may experience depression and feelings of social isolation (Drucker et al. 2017).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	For the Applicant's target population of moderate-to-severe AD, available FDA-approved systemic treatments include corticosteroids, dupilumab (Dupixent), tralokinumab (Adbry), and lebrikizumab (Ebglyss). For refractory cases not adequately controlled with other systemic drug products, including biologics, available treatments include the JAK inhibitors upadacitinib (Rinvoq) and abrocitinib (Cibinqo). Phototherapy (narrow-band ultraviolet B as the first-line) is an option for this population, but its drawbacks include a potentially time-intensive, in-office treatment schedule. Risks from phototherapy may vary according to the type of phototherapy and can include actinic damage, sunburn-like reactions, skin cancer (nonmelanoma and melanoma), and cataracts. Dupilumab (Dupixent) is an interleukin-4 receptor alpha antagonist indicated for the treatment of patients aged 6 months and older with moderate-to-severe AD whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent can be used with or without topical corticosteroids. Tralokinumab (Adbry) is an interleukin-13 antagonist indicated for the treatment of moderate-to-severe atopic dermatitis in patients 12 years of age and older whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable. Adbry can be used with or without topical corticosteroids. Lebrikizumab (Ebglyss) is an interleukin-13 antagonist indicated for the treatment of adults and pediatric patients 12 years of age and older who weigh at least 40 kg with moderate-to-severe atopic dermatitis whose disease is not adequately controlled with topical prescription therapies or when those	Approval for licensure of Nemolizumab would represent an important addition to the treatment options for patients with moderate-to-severe AD that is not manageable by topical therapies; a population for whom approved treatment options are limited. Nemolizumab would be the fourth systemic product (other than corticosteroids) approved for treatment of moderate-to-severe AD, following the approvals of dupilumab, tralokinumab, and lebrikizumab. Nemolizumab offers a novel therapeutic target, inhibiting the IL-31 cascade. Nemolizumab would represent an alternative to other biologics for the systemic treatment of moderate-to-severe AD. Corticosteroids, although approved, are not generally recommended for this indication and the JAK inhibitors upadacitinib and abrocitinib are generally reserved for refractory patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	therapies are not advisable. Ebglyss can be used with or without topical corticosteroids. Systemic corticosteroids: The American Academy of Dermatology recommends that systemic corticosteroids generally be avoided because of the potential for short- and long-term adverse reactions. Tacrolimus ointment, 0.1%, is approved for moderate-to severe AD as a second-line, short-term, noncontinuous chronic treatment for patients unresponsive to other topical treatments. Systemic products that are used off-label to treat moderate-to-severe AD include cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil.	
Benefit	The efficacy of nemolizumab was demonstrated in two Randomized, Double-Blind, Placebo-Controlled trials, ARCADIA 1 and ARCADIA 2. Nemolizumab was statistically superior to placebo for the co-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 EASI-75 ($\geq 75\%$ improvement in EASI from baseline) at Week 16. Key secondary efficacy endpoints included an improvement (reduction) of ≥ 4 points from baseline in PP-NRS at Week 16 and PP-NRS<2 at Week 16.	Nemolizumab demonstrated efficacy in subjects with moderate to severe AD, who also received concomitant topical therapy, in adequate and well-controlled trials. The clinical trial design and endpoints were appropriate for the AD 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 moderate to severe AD patients is based primarily on the two phase 3 AD trials ARCADIA 1 and ARCADIA 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 1135 subjects in the nemolizumab group and 584 subjects in the placebo group. The AD exposure pool included a total of 2007 subjects (who received treatment with a dose of nemolizumab 30 mg) enrolled in the two phase 3 trials, a phase 2 trial, a DDI study, and a long-term phase 3 trial. Of the 2007 subjects in the AD exposure pool treated with nemolizumab 30 mg, 1497 [including 258 adolescents] subjects were treated for ≥6 months, 1148 [including 180 adolescent] subjects were treated for ≥1 year, 645 [including 61 adolescent] subjects were treated for ≥18 months, and 171 [including 20 adolescent] subjects were treated for ≥2 years. The most common adverse reactions reported at a frequency of ≥1% in the nemolizumab group (and more frequently than in the placebo group) through Week 16, for the nemolizumab group compared to the placebo group, respectively, included: • Dermatitis atopic (9.9% versus 8.4%) • Headache (4.1% versus 3.6%) • Asthma (3.9% versus 3.4%) • Back pain (1.3% versus 1.2%) • Dyspnea (1.1% versus 0.9%)	Based on the available data, nemolizumab has a reasonable safety profile for use in this indication and would be acceptable for approval for licensure based on the data in 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. PMRs for pregnancy and lactation studies will not be required for NEMLUVIO in patients with AD. These studies were not requested by FDA for the prurigo nodularis indication, a less common condition than AD, as it was not anticipated that there would be sufficient pregnancy exposures to obtain meaningful information from a PMR. It is not clear that the new indication, moderate to severe AD, will generate sufficient pregnancy exposures to meaningfully inform a pregnancy exposure study, either. While AD is more common than PN, moderate to severe AD represents only ~20% of all AD, and there are multiple approved therapies (e.g., dupilumab, lebrikizumab, upadacitinib, tralokinumab); additionally, because of the modest efficacy results for nemolizumab in moderate to severe AD, market share may be less than proportional. Furthermore recent work conducted within the DDD in conjunction with OSE identified the absence of impact of required post-marketing safety studies, including pregnancy registries, in psoriasis and other inflammatory diseases. PREA PMRs will be required for studies to be conducted for the pediatric population with moderate to severe AD (ages between
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BLA 761391
NEMLUVIO (nemolizumab-ilto)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Urticaria (1.1% versus 0.3%) • Nausea (1.1% versus 0.5%) • Fatigue (1.1% versus 0.5%) • Arthralgia, (1.1% versus 0.2%) • Urinary tract infection (1.1% versus 0.9%) • Myalgia (1.0% versus 0.2%). During the phase 3 AD trials, immunogenicity had no significant impact on the efficacy or safety of nemolizumab. Refer to the Clinical Pharmacology section of this review for a discussion of the impact of Immunogenicity on the PK of nemolizumab.	6 months to <12 years) for nemolizumab, and will be recommended by the review team as postmarketing requirements.

Abbreviations: AD, atopic dermatitis; DDD, Division of Dermatology and Dentistry; DDI, drug-drug interaction; EASI, EASI, Eczema Area and Severity Index; FDA, U.S. Food and Drug Administration; IGA, Investigator's Global Assessment; OSE, Office of Surveillance and Epidemiology; PK, pharmacokinetic; PMR, postmarketing requirement; PP-NRS, Peak Pruritus Numeric Rating Scale; PREA, Pediatric Research Equity Act; REMS, risk evaluation and mitigation strategy

2.2. Conclusions Regarding Benefit-Risk

Review of the application supports an approval recommendation for biologics license application (BLA) 761391 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 moderate to severe atopic dermatitis for patients 12 years of age and older.

The Applicant conducted two phase 3, randomized, double-blind, placebo-controlled trials (ARCADIA 1 and ARCADIA 2) which enrolled 1719 subjects ≥ 12 years of age with moderate to severe AD; with a baseline Investigator's Global Assessment (IGA) scores ≥ 3 , Eczema Area and Severity Index (EASI) score ≥ 16 , AD-affected body surface area $\geq 10\%$, and a weekly average Peak Pruritus Numeric Rating Scale (PP-NRS) score of ≥ 4 .

The results of trials ARCADIA 1 and ARCADIA 2 showed statistically significant improvements for the nemolizumab groups compared to the placebo groups, respectively, for the co-primary efficacy endpoints ("the proportion of subjects with an IGA score of 0 [clear] or 1 [almost clear]" at Week 16 [ARCADIA 1 (36% vs. 25%), ARCADIA 2 (38% vs. 26%)] and "the proportion of subjects with EASI-75 at week 16 [ARCADIA 1 (44% vs. 29%), ARCADIA 2 (42% vs. 30%)]. The results for the Key secondary efficacy endpoints of " ≥ 4 -point improvement (reduction) from baseline in PP-NRS" at Week 16 [ARCADIA 1 (33% vs. 15%), ARCADIA 2 (36% vs. 15%)] and "PP-NRS < 2 " at Week 16 [ARCADIA 1 (23% vs. 10%), ARCADIA 2 (24% vs. 9%)] were consistent with the results for the co-primary efficacy endpoints.

The safety results of trials ARCADIA 1 and ARCADIA 2 demonstrated an acceptable safety profile. During the initial treatment period through Week 16, adverse events reported for $\geq 1\%$ of subjects treated with nemolizumab (and at a greater frequency than vehicle) compared to the vehicle group, respectively, included Dermatitis atopic (9.9% vs. 8.4%), Headache (4.1% vs. 3.6%), Asthma (3.9% vs. 3.4%), Back pain (1.3% vs. 1.2%), Dyspnea (1.1% vs. 0.9%), Urticaria (1.1% vs. 0.3%), Nausea (1.1% vs. 0.5%), Fatigue (1.1% vs. 0.5%), Arthralgia, (1.1% vs. 0.2%), Urinary tract infection (1.1% vs. 0.9%), and Myalgia (1.0% vs. 0.2%).

The clinical review team recommends an initial dose of nemolizumab 30 mg administered every 4 Weeks (Q 4W) followed by a maintenance dose of nemolizumab 30 mg administered every 8 weeks (Q8W) [after achievement of clinical response following the initial treatment period] based on similar efficacy results for the nemolizumab Q 4W compared to the nemolizumab Q 8W groups, respectively, for IGA success at W 48 [combined ARCADIA 1 and ARCADIA 2 (61.5% vs. 60.4%)] and EASI-75 response at Week 48 [combined ARCADIA 1 and ARCADIA 2 (76.3% vs. 75.7%)] and similar safety profiles reported during the maintenance treatment periods (weeks 16-48 of ARCADIA 1 and ARCADIA 2 trials) for the Q4W compared to the Q8W groups, respectively, including serious adverse events (SAEs) [combined ARCADIA 1 and ARCADIA 2 (5.9% vs. 1.8%)], AELDs [combined ARCADIA 1 and ARCADIA 2 (2.4% vs. 3.0%)], and TEAEs [combined ARCADIA 1 and ARCADIA 2 (53.5% vs. 53.9%)].

The WARNINGS AND PRECAUTIONS section of the label will retain subsections for hypersensitivity (5.1) and vaccinations (5.2) consistent with Section 5 of NEMLUVIO label

already approved with the PN indication. The Clinical Trials Experience Subsection (6.1) of the label will include the addition of herpes zoster infections under the heading of Specific Adverse Reactions.

Pediatric Research Equity Act postmarketing requirements will be issued for studies to be conducted in pediatric patients with moderate to severe AD between 6 months to < 12 years of age.

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 [a component of the Food and Drug Administration'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 the Division of Epidemiology because the review of safety data reported during the clinical trials did not identify any serious safety concerns that would warrant assessment by Active Risk Identification and Analysis System; and routine pharmacovigilance appears adequate for postmarketing surveillance.

The review team recommends an Approval action for this biologics license application 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 moderate to severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4).

The Applicant has submitted supportive safety data from several clinical studies conducted by the Applicant or their affiliated sponsors (Maruho and Chugai) [in healthy subjects or subjects with AD, Prurigo nodularis, or chronic kidney disease associated pruritus] under this biologics license application (BLA). However, the Applicant's primary safety population to support the Approval of this BLA is comprised of safety data from the following one phase 2b and two phase 3 trials in subjects with AD:

- A phase 2b clinical trial (SPR.114322)
- Two (pivotal) phase 3 clinical trials (SPR.118161 [ARCADIA 1] and SPR.118169 [ARCADIA 2])

Additionally, interim safety data (up to the data lock point) for the following study was submitted to support the long-term safety of nemolizumab for chronic treatment of AD:

- A phase 3, (4-year) long-term extension (LTE) study (SPR.118163 [ARCADIA LTE]) (ongoing)

The two phase 3 trials (ARCADIA 1 and ARCADIA 2) were used to demonstrate the safety and superior efficacy of nemolizumab compared to placebo, and to establish substantial evidence of effectiveness (SEE) for the treatment of patients with moderate to severe AD.

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 30 mg every 4 weeks.

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

No Critical Efficacy Issues Identified.

3.1.2. Key Safety Review Issues

No Critical Safety Concerns Identified.

3.2. Approach to the Clinical Review

The following table (Table 3) provides an overview of the phase 3 clinical trials (ARCADIA 1 and ARCADIA 2) conducted by the Applicant and submitted to biologics license application (BLA) 761391 to support the benefit-risk assessment of nemolizumab for the treatment of AD. Each trial had a 16-week initial treatment period (ITP) and a 32-week maintenance treatment period (MTP).

Table 3. Clinical Trials Submitted¹ 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
ITP of ARCADIA 1 (spr118161)	Male or female subjects ≥12 years of age with chronic AD documented for at least two years before the screening visit and confirmed according to the AADCC	Control type: Placebo Controlled Randomization: Randomized 2:1 Stratification: By baseline disease severity Intervention: Parallel-group study Blinding: Double blind Biomarkers: None Innovative design features: None	Nemolizumab 30 mg Q4W Number treated: 620 Placebo Number treated: 321 Duration: 16 weeks	Primary: 1. The proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear]) and a ≥2-point reduction from baseline 2. The proportion of subjects with EASI-75 at Week 16 Secondary: See footnotes ²	Planned: 1333 Actual: 941	Centers:161 Countries: 14: Australia, Austria, Canada, Czech Republic, Germany, Great Britain, Korea, Latvia, Lithuania, Netherlands, New Zealand, Poland, Spain, and the US

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
MTP of ARCADIA 1 (spr118161)	Male or female subjects ≥12 years of age with chronic AD documented for at least two years before the screening visit and confirmed according to the AADCC	Control type: Placebo controlled Randomization: Re-randomized 1:1:1 Stratification: By baseline disease severity Intervention: Parallel-group study Blinding: Double blind Biomarkers: None Innovative design features: None	Nemolizumab Q4W to Nemolizumab Q4W Dose: 30 mg Number treated: 90 Nemolizumab Q4W to Nemolizumab Q8W Dose: 30 mg Number treated: 91 Nemolizumab Q4W to Placebo Number treated: 91 Placebo to Placebo Number treated: 100 Duration: 32 weeks	Primary: 1. The proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear]) and a ≥2-point reduction from baseline 2. The proportion of subjects with EASI-75 at Week 16 Secondary: See footnotes ²	Actual: 372	Centers:161 Countries: 14

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
ITP of ARCADIA 2 (spr118169)	Male or female subjects ≥12 years of age with chronic AD documented for at least two years before the screening visit and confirmed according to the AADCC	Control type: Placebo controlled Randomization: Randomized 2:1 Stratification: by baseline disease severity Intervention: Parallel- group study Blinding: Double blind Biomarkers: None Innovative design features: None	Nemolizumab 30 mg Q4W Number treated: 519 Placebo Number treated: 263 Duration: 16 weeks	Primary: 1. The proportion of subjects with an IGA success (defined as an IGA of 0 [clear] or 1 [almost clear]) and a ≥2- point reduction from baseline 2. The proportion of subjects with EASI-75 at Week 16 Secondary: See footnotes ²	Planned: 1071 Actual: 787	Centers:120 Countries: 11: Belgium, Bulgaria, Estonia, France, Georgia, Germany, Hungary, Italy, Poland, Singapore, and the US

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
MTP of ARCADIA 2 (spr118169)	Male or female subjects ≥12 years of age with chronic AD documented for at least two years before the screening visit and confirmed according to the AADCC	Control type: Placebo controlled Randomization: Randomized 1:1:1 Stratification: By baseline disease severity Intervention: Parallel-group study Blinding: Double blind Biomarkers: None Innovative design features: None	Nemolizumab Q4W to Nemolizumab Q4W Dose: 30 mg Number treated: 79 Nemolizumab Q4W to Nemolizumab Q8W Dose: 30 mg Number treated: 78 Nemolizumab Q4W to Placebo Number treated: 78 Placebo to Placebo Number treated: 85 Duration: 32 weeks	Primary: 1. An IGA success (defined as an IGA of 0 [clear] or 1 [almost clear]) and a ≥2-point reduction from baseline 2. EASI-75 at Week 16 Secondary: See footnotes ²	Planned: 320 Actual: 317	Centers:120 Countries: 11

Source: Clinical Data Scientist Review, Clinical Study Report and adsl.xpt

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

² Secondary key endpoints: (1) Improvement of PP-NRS ≥4 at Week 16; (2) PP-NRS <2 at Week 16; (3) Improvement of SD-NRS ≥4 at Week 16; (4) Improvement of PP-NRS ≥4; (5) PP-NRS <2 at Week 4; (6) Improvement of PP-NRS ≥4 at Week 2; (7) Improvement of PP-NRS ≥4 at Week 1; (8) EASI-75 and improvement of PP-NRS ≥4 at Week 16; (9) IGA success and improvement of PP-NRS ≥4 at Week 16.

Abbreviations: AADCC, American Academy of Dermatology Consensus Criteria; AD, atopic dermatitis; EASI-75, 75% improvement in the Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITP, initial treatment period; MTP, maintenance treatment period; PP-NRS, Peak Pruritus Numerical Rating Scale; Q4W, every four weeks; SD-NRS, Sleep Disturbance Numerical Rating Scale

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):

The treatment of moderate-to-severe atopic dermatitis in patients aged 12 years and older, whose disease is not adequately controlled with topical prescription therapies (b) (4)

2. SEE was established 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^{1,2,3}
 - 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*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (2019)

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* (1998)

³ 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 outcome • Peak Pruritus Numeric Rating Scale (PP-NRS) • Sleep Disturbance Numeric Rating Scale (SD-NRS) • SCORing Atopic Dermatitis (SCORAD) and its components • AD-associated pain • Patient Global Assessment of Disease (PGAD) • Patient Global Assessment of Treatment (PGAT) • Dermatology Life Quality Index (DLQI) or Children's DLQI total score • Patient-Oriented Eczema Measure (POEM) • Hospital Anxiety and Depression Scale (HADS) • Work Productivity and Activity Impairment: Atopic Dermatitis (WPAI:AD) • European Quality of Life (EuroQoL) 5-Dimension (EQ-5D) • Patient-Reported Outcomes Measurement Information System (PROMIS®) Itch Questionnaire (PIQ) T-Score	The PP-NRS is discussed in Section 6.2.5.1 The SD-NRS is discussed in Sections 6.2.5.2 .
☐	Observer-reported outcome	
☒	Clinician-reported outcome • Investigator's Global Assessment (IGA) • Eczema Area and Severity Index (EASI)	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☒	Patient-focused drug development meeting summary • Externally Led PFDD Meeting on Atopic Dermatitis held at College Park Marriott, Hyattsville, MD on 9/23/2019	See DCOA review for a summary of the evidence dossier.
☒	Qualitative studies (e.g., individual patient interviews, focus group interviews, expert interviews, Delphi Panel) • Evidence dossier for SD-NRS and SSD EVM-25004	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
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 13 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 atopic dermatitis (AD). 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.

Characteristic	Drug Information
	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 AD.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Parameter Mean $\pm$ SD AUC 117 $\pm$ 46.0 $\mu\text{g}\cdot\text{day/mL}$ for subjects receiving 60 mg loading dose followed by 30 mg every 4 weeks (Q4W) and 34.2 $\pm$ 17.4 $\mu\text{g}\cdot\text{day/mL}$ for subjects receiving 60 mg loading dose followed by 30 mg every 8 weeks (Q8W). C_{max} 5.59 $\pm$ 1.95 $\mu\text{g/mL}$ for subjects receiving 60 mg loading dose followed by 30 mg Q4W and 1.92 $\pm$ 0.84 $\mu\text{g/mL}$ for subjects receiving 60 mg loading dose followed by 30 mg Q8W. C_{24} 2.63 $\pm$ 1.27 $\mu\text{g/mL}$ for subjects receiving 60 mg loading dose followed by 30 mg Q4W and 0.74 $\pm$ 0.44 $\mu\text{g/mL}$ for subjects receiving 60 mg loading dose followed by 30 mg Q8W.
Range of effective dose(s) or exposure	In the phase 2a study (Study CIM003JG), 0.5 mg/kg and 2.0 mg/kg dose administered Q4W achieving marked reduction of pruritus visual analogue scale (VAS) compared to 0.1 mg/kg in subjects with AD. Although the study was not designed to compare the different dose groups formally, there was no evidence that 2.0 mg/kg nemolizumab administered Q4W or Q8W was more effective than the 0.5-mg/kg Q4W dose. In the phase 2b study (114322) in subjects with AD, nemolizumab 30 mg Q4W (with 60 mg loading dose) was statistically significantly more effective than placebo in reducing Eczema Area and Severity Index (EASI) scores at Week 24. The most marked effects on secondary endpoints of PP-NRS and Investigator's Global Assessment (IGA) scores were also seen in nemolizumab 30 mg Q4W compared with placebo. The phase 2 study results suggested that a plateau of efficacy was achieved with the 30 mg Q4W dose (with 60 mg loading dose), and no additional benefit was expected with a higher dose.
Maximally tolerated dose or exposure	In the pivotal phase 3 trials (Studies 118161 and 118169), an initial dose of 60 mg followed by 30 mg given Q4W was superior to placebo with respect to the co-primary endpoints of IGA success and EASI-75.
Dose proportionality	The highest studied single dose was 3 mg/kg in the first-in-human (FIH) Study CIM001JP. The highest-studied multiple dose was 60 mg Q4W using the to-be-marketed formulation.
Accumulation	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.
Time to achieve steady-state	The accumulation index (R_{ac}) of nemolizumab following multiple-dose administration was 1.6, calculated using Population PK analysis.
Bridge between to-be-marketed and clinical trial/study formulations	For subjects receiving nemolizumab 30 mg SC Q4W with a 60 mg SC loading dose, steady-state was reached by Week 4.
	In the phase 3 trials in subjects with AD (Studies 118161, 118169, and 118163), 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

Characteristic	Drug Information
	the DCC-AI and the DCS has been conducted. Results from Study 201590 provide support for the DCC-AI as (b) (4) An OSIS inspection request was submitted for Study 201590 and OSIS determined not to inspect the sites. For further details, see OSIS Inspection report in DARRTS dated July 12, 2024.
Bioavailability T _{max}	Absorption Absolute BA was not assessed. 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.
Volume of distribution Plasma protein binding Drug as substrate of transporters	Distribution 7.67 L. NA as this is a monoclonal antibody. NA as this is a monoclonal antibody.
Mass balance results Clearance Half-life Metabolic pathway(s)	Elimination NA as this is a monoclonal antibody. 0.263 L/day 18.9 days 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.
Body weight	Intrinsic Factors and Specific Populations 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. However, the difference in exposure between the upper- and lower-body weight quartiles was less than 2-fold, and no impact of body weight on efficacy was observed, supporting the appropriateness of the proposed flat dosing regimen for patients with AD.
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.
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

Characteristic	Drug Information
	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.
Inhibition/induction of metabolism	Drug Interaction Liability (Drug as Perpetrator) 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, the Applicant conducted a phase 2, open-label, single-sequence, drug-drug interaction (DDI) study in adult subjects with moderate-to-severe AD to evaluate the effect of nemolizumab on the PK of a drug “cocktail” representative of cytochrome P450 (CYP450) sensitive index substrates (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5). Results of this study showed that for all CYP substrates, the observed geometric means for both C_{max} and AUC were similar before and after nemolizumab treatment, with geometric mean test/reference ratios ranging from 88.24% to 107.81%. There was no clinically meaningful effect of nemolizumab treatment on the metabolism of the assessed CYP substrates, defined as a greater than 2-fold decrease of observed geometric means after nemolizumab injections, indicating that nemolizumab is unlikely to affect the expression of CYP enzymes.
Inhibition/induction of transporter systems	NA
Bioanalysis	Immunogenicity (if Applicable) 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 AD (Studies 118161 and 118169) and the long-term extension (LTE) study in subjects with AD (Study 118163), the incidence of treatment-emergent ADAs was 11.2% (46 out of 358 subjects).
Clinical impact	Antidrug antibodies (ADAs) to nemolizumab were associated with reduced serum nemolizumab concentrations beyond Week 16. In the phase 3 trials, nemolizumab treated subjects who developed ADAs had nemolizumab concentrations that were 20% to 70% lower compared to subjects who did not develop ADAs. There was no clinically significant effect of ADAs on safety or efficacy of nemolizumab over the treatment duration of 48 weeks.

Abbreviations: ADA, anti-drug antibodies; AE, adverse event; AUC_{t-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; RA, receptor alpha; 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 identically designed phase 3 trials (ARCADIA 1 [SPR 118161] and ARCADIA 2 [SPR 118169]). 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 2b dose-ranging trial conducted in 226 randomized subjects with AD (Study 114322) with background topical corticosteroids (TCS) therapy. Subjects enrolled in the phase 2b trial were randomized 1:1:1:1 to nemolizumab 10 mg Q4W with a 20 mg LD, nemolizumab 30 mg Q4W with a 60 mg LD, nemolizumab 90 mg Q4W with no LD, or placebo Q4W. A phase 2a study (Study CIM003JG) demonstrated comparable efficacy across 0.5 mg/kg or 2.0 mg/kg Q4W, or 2.0 mg/kg Q8W. For safety, pharmacokinetic (PK) simulations were conducted to demonstrate that the average systemic exposure was similar for the same dose administered once or twice a month. Ultimately, the Q4W dosing regimen was chosen to promote compliance.

The proposed dose for patients with AD is an initial LD of 60 mg, followed by 30 mg given subcutaneous (SC) Q4W. The efficacy of nemolizumab for the treatment of AD following this dosing regimen was established in 2 pivotal phase 3 trials (ARCADIA 1 and ARCADIA 2).

After the completion of phase 3 trials, population PK analysis was performed on pooled data from the AD and the prurigo nodularis (PN) clinical development programs. Population PK analyses identified only body weight as a relevant predictor of nemolizumab exposure. The exposure of nemolizumab decreased with increasing body weight. However, the difference in exposure between the upper- and lower weight quartiles was less than 2-fold, supporting the appropriateness of a 30 mg flat dose. The population PK analyses also confirmed the adequacy of the 60 mg loading dose to rapidly reach the desired steady-state concentrations. Steady state was expected to be reached by Week 1 with a loading dose and by Week 12 without a loading dose. Pharmacokinetics/pharmacodynamics (PK/PD) models were developed based on pooled data from the AD to characterize the relationship between nemolizumab concentrations and efficacy assessments Eczema Area and Severity Index (EASI), Investigator's Global Assessment (IGA), and Peak Pruritus Numeric Rating Scale [PP-NRS]). As the population PK analysis showed that body weight has an impact on nemolizumab exposure, PK/PD simulations of clinical endpoints at Week 16, were conducted for all subjects, subjects with body weight <90 kg, and subjects with body weight ≥90 kg. Overall, PK/PD simulations of clinical endpoints showed a similar response across body weight groups, thus, confirming that exposure variability due to subject body weight did not result in a clinically meaningful difference in efficacy. Therefore, the proposed dosing regimen is considered as adequate, and no dose adjustment based on body weight is necessary.

The analyses of exposure-safety relationships did not show evidence for any increased safety events with higher nemolizumab concentrations. Overall, the clinical efficacy and safety results from the 2 pivotal phase 3 trials, PK results, PK/PD, and exposure-safety outcomes provided evidence for the effectiveness and safety of the 30 mg Q4W (60 mg loading dose) dosing

regimen in adult and adolescent subjects with moderate-to-severe AD. For further details on the exposure-response analyses for efficacy and safety, refer to Section [14.5](#)

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Trial Design

ARCADIA 1 and ARCADIA 2 were identically designed, randomized, double-blind, multicenter, parallel-group, placebo-controlled phase 3 trials to assess the safety and efficacy of nemolizumab in subjects with moderate-to-severe AD and a documented history of inadequate response to topical AD medications.

[Figure 1](#) presents the study design schematics for both trials. The treatment duration was 16 weeks for both trials. Each trial was designed to enroll and randomize approximately 750 subjects from about 150 centers in a 2:1 ratio to receive either nemolizumab or placebo. The protocol specified stratifying the randomization by disease severity (moderate: IGA = 3; severe: IGA = 4) and PP-NRS severity (PP-NRS ≥ 7 ; PP-NRS < 7) and randomizing a minimum of 250 subjects in each PP-NRS stratum.

For both ARCADIA 1 and ARCADIA 2, subjects were scheduled to have the following site visits: Screening (2 to 4 weeks before Day 1), Baseline (Day 1), Weeks 4, 8, 12, and 16. The protocol specified that at the end of the treatment period, consenting subjects (including clinical non-responders at the end of the 16-week initial treatment period) may be eligible to enter an LTE study (SPR.118163). Subjects who declined or were not eligible to enter the LTE study were asked to complete a follow-up visit 12 weeks after the last study drug injection.

The protocol specified that subjects applied moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions beginning at Screening and throughout the duration of the studies. The protocol specified that to allow for accurate assessment of skin dryness, moisturizer should not be used within 8 hours before each clinic/office visit, and whenever possible, subjects should use the same moisturizer throughout the study.

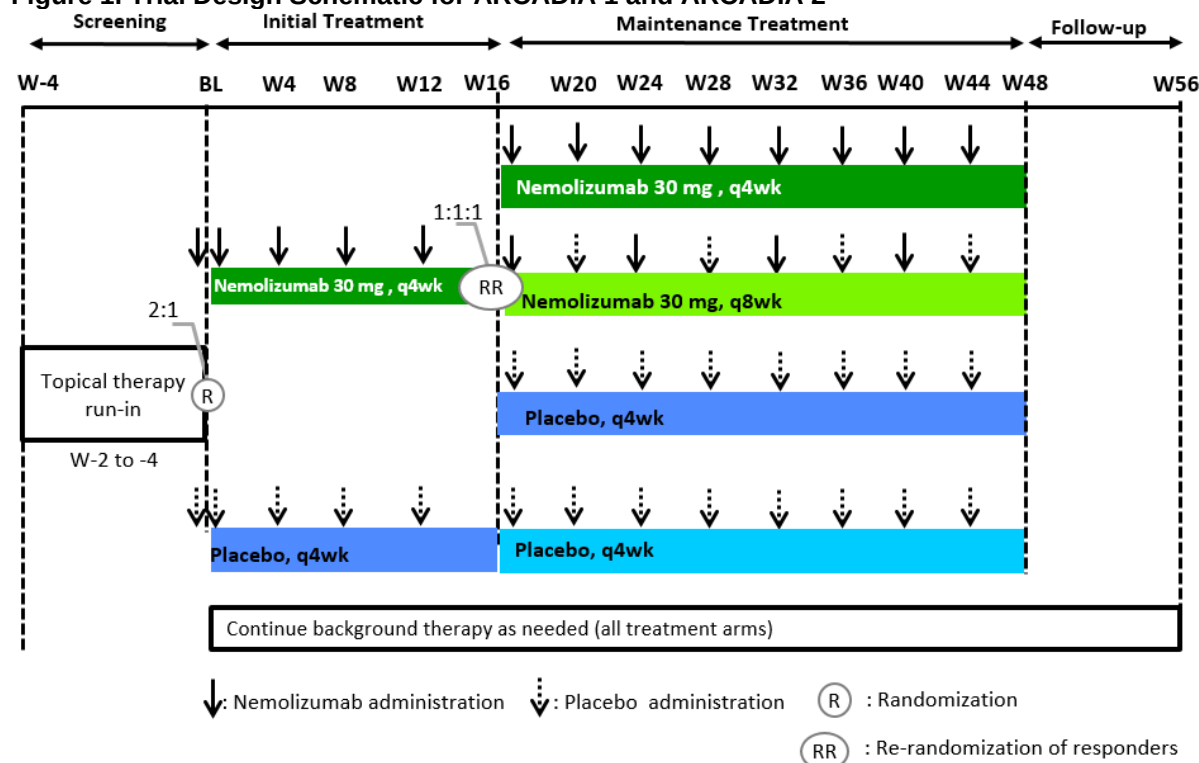
In addition to the moisturizer, the protocol specified that subjects would be provided or prescribed authorized background topical therapy for use during the study, beginning at Screening: (a) Medium-potency TCS background therapy would be applied in non-sensitive areas of the body where use of medium-potency TCS is considered safe (e.g., trunk and extremities), and (b) low-potency TCS or TCI therapy would be applied in sensitive areas of the body that are considered either TCS-sensitive (e.g., face, neck, or intertriginous areas) or intolerant of medium-potency TCS. The protocol specified that the investigator may use discretion to select either low-potency TCS or TCI for each subject.

The protocol specified that rescue therapies can be prescribed to the subjects at any time during the study, except during the run-in period (i.e., at least 2 weeks [14 days] before Day 1/Baseline), if deemed to be medically necessary by the investigator (e.g., to control intolerable AD signs, symptoms, or both). The protocol specified that as a general guideline and per individual investigator judgment, rescue therapy should not be prescribed within the first 2 weeks after Baseline (i.e., Week 2) to allow a minimum time for study drug exposure in the presence of

background therapy. The protocol specified the following as rescue therapies: higher-potency TCS (equivalent to class I-II according to the United States classification); oral corticosteroids; biologics (including their biosimilars); systemic nonsteroidal immunosuppressants or immunomodulators; and phototherapy. The protocol stated:

“For the purpose of efficacy analysis, subjects receiving any rescue therapies will be considered as treatment failures (i.e., non-responders). 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 case report form.”

Figure 1. Trial Design Schematic for ARCADIA 1 and ARCADIA 2



Source: Page 20 of the protocol (Version 8) for ARCADIA 1

Abbreviations: BL, baseline; q4w, every 4 weeks; q8w, every 8 weeks; R, randomization; RR, re-randomization of responders; W, week

6.2.2. Eligibility Criteria

Key eligibility criteria for both trials are summarized in this section and the full criteria are available in Sections [15.1](#) and [15.2](#).

Inclusion Criteria

- Male or female ≥ 12 years of age at the screening visit.
- Chronic AD for at least 2 years before the screening visit and confirmed according to the American Academy of Dermatology Consensus Criteria at the time of the screening visit.
- EASI score ≥ 16 at both screening and baseline visits.
- IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) at both screening and baseline visits.
- AD involvement $\geq 10\%$ of body surface area at both screening and baseline visits.
- Peak (maximum) pruritus NRS score of at least 4.0 at screening and baseline visits.
 - Screening visit: PP-NRS score is ≥ 4.0 for the 24-hour period immediately preceding the Screening visit.
 - Baseline visit: Mean of the daily intensity of the PP-NRS score is ≥ 4.0 over the previous week. The protocol specified that the PP-NRS score be measured on at least 4 days during the week preceding the baseline visit. In addition, the protocol specified that rounding of the mean PP-NRS score is not permitted.
 - Documented recent history (within 6 months before the screening visit) of inadequate response to topical medication (TCS with or without TCI). Inadequate response to TCS is defined as any one or more of the following three:
 - Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a regimen of a medium-, high-, or very high-potency TCS (Class I-III according to the US classification) (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information; OR
 - Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I-II according to the US classification) (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2); OR
 - If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments

Exclusion Criteria

- Body weight < 30 kg.
- 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 time per week, or some interference with normal activities) during the preceding 3 months
 - Asthma control test ≤ 19 (only for subjects with a history of asthma)
 - PEF $< 80\%$ for the predicted value

- Subjects with a current medical history of chronic obstructive pulmonary disease, chronic bronchitis, or both.
- 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 suspected COVID-19 infection within 2 weeks before the screening or baseline visit. Subjects may be rescreened once the infection has resolved.
- Requiring rescue therapy for AD during the run-in period or expected to require rescue therapy within 2 weeks following the baseline visit.
- 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. (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).)
- Previous treatment with nemolizumab.
- Subjects who, after a full treatment course of 16 weeks with dupilumab, experienced worsening of their AD or failed to achieve minimal improvement (e.g., $\leq 10\%$ reduction in EASI or no reduction in IGA).

6.2.3. Clinical Endpoints, Trials ARCADIA 1 and ARCADIA 2

The protocol specified the following co-primary efficacy endpoints:

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

The protocol and statistical analysis plan (SAP) specified the following key secondary efficacy endpoints:

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

Reviewer's Note

The Agency noted in the Advice Letter dated June 7, 2022 that the responder for endpoints of PP-NRS < 2 at Week 16 and Week 4 could represent less than a 4-point change from baseline (i.e., smaller than the clinically meaningful change threshold) if based on the intent-to-treat (ITT) population and recommended that these endpoints be limited to only subjects with a baseline PP-NRS score that would result in a ≥ 4 -point change from baseline for responders (e.g., baseline PP-NRS score ≥ 7). The Applicant analyzed all endpoints—primary and key secondary—based on both the full ITT population (i.e., baseline PP-NRS ≥ 4) and the baseline PP-NRS ≥ 7 population.

The protocol and SAP specified many secondary efficacy endpoints and secondary maintenance endpoints that were not controlled for multiplicity. They are not discussed in this review.

6.2.4. Clinical Outcome Assessment Instruments Used to Assess the Co-Primary Endpoints, Studies ARCADIA 1 and ARCADIA 2

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

6.2.4.1. Investigator's Global Assessment

The Investigator's Global Assessment (IGA) (Table 6) is a single-item clinician-reported outcome (ClinRO) instrument designed to assess AD severity using a 5-point scale verbal rating scale ranging from 0 ("Clear") to 4 ("Severe"). The recall period is current state. In ARCADIA 1 and ARCADIA 2, the IGA was administered at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

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

Status	Score	Definition
Clear	0	Minor, residual hypopigmentation/hyperpigmentation, no erythema or induration/papulation, no oozing/crusting.
Almost clear	1	Trace faint pink erythema, with barely perceptible induration/papulation and no oozing/crusting.
Mild	2	Faint pink erythema with mild induration/papulation and no oozing/crusting.
Moderate	3	Pink-red erythema with moderate induration/papulation with or without oozing/crusting.
Severe	4	Deep or bright red erythema with severe induration/papulation with oozing/crusting.

Source: Page 158 of the protocol (Version 8) for ARCADIA 1
Abbreviations: IGA, Investigator's Global Assessment

6.2.4.2. Eczema Area and Severity Index

The EASI (Table 7) is a ClinRO designed to assess the extent (area) and severity of atopic eczema in four body regions (head and neck, lower limbs, upper limbs and trunk). The degree of severity of each sign (E = erythema, I = induration/papulation, Ex = excoriation, L=lichenification) in each of the 4 body regions is evaluated based on a scale ranging from 0 to 3 (0: none; 1: mild; 2: moderate; 3: severe), with half points allowed. Area (the affected body area) is defined as follows: 0 = 0%; 1 = 1 to 9%; 2 = 10 to 29%; 3 = 30 to 49%; 4 = 50 to 69%; 5 = 70 to 89%; 6 = 90 to 100%. Among the four zones, trunk includes the genital area, and lower limbs include the buttocks.

The recall period is current state. In ARCADIA 1 and ARCADIA 2, the EASI was administered at Screening, Baseline (Day 1), and Weeks 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, and 48.

Table 7. Eczema Area and Severity Index (EASI)

Body region	EASI score
Head/Neck (H)	$(E + I + Ex + L) \times \text{Area} \times 0.1$
Upper limbs (UL)	$(E + I + Ex + L) \times \text{Area} \times 0.2$
Trunk (T)	$(E + I + Ex + L) \times \text{Area} \times 0.3$
Lower limbs (LL)	$(E + I + Ex + L) \times \text{Area} \times 0.4$
EASI =	Sum of the above 4 body region scores

Source: Page 159 of the protocol (Version 8) for ARCADIA 1
Abbreviations: EASI, Eczema Area and Severity Index

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

The PP-NRS was used to assess the ranked secondary efficacy endpoints #1, #2, #4, #5, #6, #7, #8, and #9 in ARCADIA 1 and ARCADIA 2. The SD-NRS was used to assess the ranked secondary efficacy endpoint #3 in ARCADIA 1 and ARCADIA 2. The serial gatekeeping approach to control the overall Type I error rate is specified in Section 6.2.6. The instruments are described briefly below.

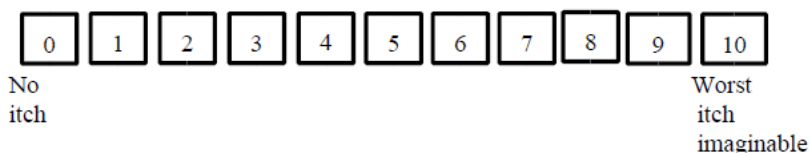
6.2.5.1. Peak Pruritus Numeric Rating Scale

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 in the evening (Visit 1/Screening through Visit 6/Week 16), beginning after the screening visit for ARCADIA 1 and ARCADIA 2.

The PP-NRS generated a weekly score that ranged from 0 to 10, with higher scores indicating greater itch intensity. See Section 6.2.6 for details on the calculation of the weekly scores based on the daily diary data.

Figure 2. Peak Pruritus Numeric Rating Scale

For maximum itch intensity: “On a scale of 0 to 10, with 0 being ‘no itch’ and 10 being the ‘worst itch imaginable’, how would you rate your itch at the worst moment during the previous 24 hours?”



Source: Page 160 of the protocol (Version 8) for ARCADIA 1
Abbreviations: PP-NRS, Peak Pruritus Numeric Rating Scale

6.2.5.2. 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 AD 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; 2-4 weeks before Day 1) to Week 16 for Study ARCADIA 1 and from Screening (Visit 1; 2-4 weeks before Day 1) to Week 16 for Study ARCADIA 2.

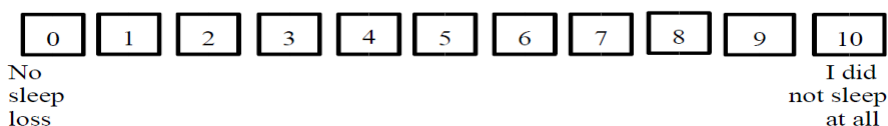
The SD-NRS generated a weekly score that ranged from 0 to 10, with higher scores indicating greater sleep loss. The baseline weekly SD-NRS score was determined based on the average of the SD-NRS (score ranging from 0 to 10) during the seven days immediately preceding baseline

(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.

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.

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

“On a scale of 0 to 10, with 0 being ‘no sleep loss related to the symptoms of atopic dermatitis’ and 10 being ‘I did not sleep at all due to the symptoms of atopic dermatitis’, how would you rate your sleep last night?”



Source: Page 161 of the protocol (Version 8) for ARCADIA 1
Abbreviations: SD-NRS, Sleep Disturbance Numeric Rating Scale

6.2.6. Statistical Analysis Plan

Analysis Populations

The primary analysis population specified in the SAP was ITT population, defined as all randomized subjects. The protocol and SAP specified conducting supportive analyses using the per-protocol (PP) population, defined as all subjects in the ITT population who have no major protocol deviations that would have a significant effect on efficacy. The protocol listed the following as major protocol deviations:

- Eligibility deviations (inclusion/exclusion criteria)
- Improper reconstitution and administration of study medication
- Noncompliance with study medication 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, and/or is not in line with Good Clinical Practice/International Council for Harmonisation (ICH) guidelines
- Use of prohibited concomitant therapies

Estimands

The protocol and 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 variable at a specified timepoint.
- Intercurrent Events and Handling Strategy:

- *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 protocol and SAP specified analyzing the co-primary endpoints and binary secondary endpoints (all binary endpoints) using the Cochran-Mantel-Haenszel test stratified by the stratification factors at randomization (i.e., IGA severity [baseline IGA of 3 or 4] and PP-NRS severity [baseline PP-NRS of ≥ 7 or < 7]). The SAP specified calculating the adjusted treatment difference in proportions using the weighted average of the treatment differences across the strata with the Cochran-Mantel-Haenszel weights, along with the associated two-sided 97.5% confidence intervals (Cis) using a normal approximation to the weighted average. The co-primary and key secondary endpoints were analyzed once based on the ITT population and once more based on the baseline PP-NRS ≥ 7 population. Missing data was specified to be imputed using the non-responder imputation (NRI) approach.

Multiplicity Adjustment Strategy

The SAP specified using a serial gatekeeping approach to control the overall Type I error rate at the two-sided 0.05 level. The 0.05 significance level was split in half for the ITT population and the baseline PP-NRS ≥ 7 population. If all endpoints—both co-primary and key secondary—were statistically significant in either population, then the allotted 0.025 level was recycled to test the other population at 0.05 level. The key secondary endpoints were tested in a fixed sequence only if the co-primary endpoints were both statistically significant; testing would stop if one secondary endpoint was not significant. The key secondary efficacy endpoints were specified to be tested in the following order:

1. Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 16
2. Proportion of subjects with PP-NRS < 2 at Week 16
3. Proportion of subjects with an improvement of SD-NRS ≥ 4 at Week 16
4. Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 4
5. Proportion of subjects with PP-NRS < 2 at Week 4
6. Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 2
7. Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 1
8. Proportion of subjects with EASI-75 and improvement of PP-NRS ≥ 4 at Week 16
9. Proportion of subjects with IGA success and improvement of PP-NRS ≥ 4 at Week 16

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

The non-monotone missing data will be first imputed 50 times using the Markov chain Monte Carlo method. The monotone missing data will be then imputed using the regression method (ordinal logistic regression for IGA and linear regression for EASI scores). The model will include treatment, randomization strata, and assessments from earlier timepoints as covariates.

Last Observation Carried Forward

Subjects who use rescue medication will have the value prior to start of the medication carried forward. The SAP specifies that missing post-baseline values will be carried forward from the last non-missing post-baseline value.

Observed Case

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 observed case 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 23, 2021, the Applicant submitted the SAP (“Stable Version 0.2”) for ARCADIA 1 to the investigational new drug (IND). 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 March 27, 2024), an extension of the analysis window was considered at Week 16 by 1 day at a time up to a maximum of 10 days (up to 5 for the upper bound and up to 5 for the lower bound) to minimize the impact of the unavailable data. According to the Applicant, when the analysis window is restricted to 7 days prior to the Week 16 visit, there are approximately 34% of missing weekly score for PP-NRS at Week 16 in ARCADIA 1 and 32% in ARCADIA 2, in contrast to the 18% and 19% missing with the extensions to the analysis window. The Applicant decided to extend the analysis window at both Baseline and Week 16 for the PP-NRS and SD-NRS. The SAP (“Final Version 1.0”) for ARCADIA 1 was finalized with the following extensions on November 9, 2022:

- Baseline: “If there are less than 4 days non-missing data available within window, the lower bound of interval will be extended up to 7 additional days to obtain 4 days non-missing data for Baseline weekly score calculation. The timeframe window will not be considered.”

- **Week 16:** “If <4 days non-missing data within Week 16 window, the upper bound will be extended first up to +5 days to obtain 4 non-missing data. If still <4 non-missing data after extending the upper bound, the lower bound will be extended again up to +5 days to obtain 4 days non-missing data. For evening assessment, only the data before Week 16 dosing (or re-randomization if missing Week 16 dosing) will be considered for Initial Treatment Period analysis.”

In addition, the Applicant added sensitivity analyses using at least 2 assessments out of 7 and at least 3 assessments out of 7 for calculating the weekly scores, not in the relevant section of the final SAP, but in Section 19. Index of Tables.

The database lock for ARCADIA 2 occurred on December 6, 2022. The SAP (“Final Version 1.0”) for ARCADIA 1 was finalized with the extensions on November 9, 2022, and the database lock for ARCADIA 1 occurred on November 15, 2022. The finalized SAPs for ARCADIA 1 and ARCADIA 2 were not submitted to the IND.

On March 13, 2024, the Agency sent an information request (IR) to the Applicant and requested the Applicant submit results for the 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

Subject Disposition, Demographics, and Baseline Disease Characteristics

ARCADIA 1 enrolled 941 subjects from 177 centers with 620 randomized to nemolizumab and 321 randomized to placebo. ARCADIA 2 enrolled 787 subjects from 136 centers with 522 randomized to nemolizumab and 265 randomized to placebo. Table 8 presents the subject disposition for the placebo-controlled phase of the trials. The trial discontinuation rate was overall similar and uniformly below 10% across arms and studies, with the placebo arm in ARCADIA 1 having the lowest discontinuation rate of 6.9%. The most common reason for study discontinuation was withdrawal by subject request in both arms of both studies.

Table 8. Subject Disposition – ARCADIA 1 and ARCADIA 2 (ITT¹)

Subject Disposition	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Discontinued Initial Treatment Period, n (%)	59 (9.5)	22 (6.9)	49 (9.4)	22 (8.3)
Adverse event	9 (1.5)	9 (2.8)	17 (3.3)	4 (1.5)
Lack of efficacy	5 (<1)	2 (<1)	3 (<1)	0
Lost to follow-up	10 (1.6)	0	1 (<1)	1 (<1)
Physician decision	1 (<1)	0	1 (<1)	0
Pregnancy	2 (<1)	0	1 (<1)	0
Protocol deviation	5 (<1)	3 (<1)	4 (<1)	4 (1.5)
Withdrawal by subject	25 (4.0)	11 (3.4)	25 (4.8)	15 (5.7)
No IMP available at baseline, sponsor decides that patient is a study failure	0	0	1 (<1)	0

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Subject Disposition				
Previous Use of Any Biologic Therapy for AD, n (%)				
No	582 (93.9)	297 (92.5)	494 (94.6)	246 (92.8)
Yes	38 (6.1)	24 (7.5)	28 (5.4)	19 (7.2)
Previous Use of Dupilumab for AD, n (%)				
No	584 (94.2)	302 (94.1)	495 (94.8)	248 (93.6)
Yes	36 (5.8)	19 (5.9)	27 (5.2)	17 (6.4)
Discontinued From Study, n (%)				
Adverse event	14 (2.3)	6 (1.9)	26 (5.0)	6 (2.3)
Lack of efficiency	22 (3.5)	6 (1.9)	10 (1.9)	3 (1.1)
Lost to follow-up	12 (1.9)	1 (<1)	8 (1.5)	1 (<1)
Other	5 (<1)	3 (<1)	12 (2.3)	3 (1.1)
Pregnancy	3 (<1)	0	0	0
Protocol deviation	10 (1.6)	3 (<1)	4 (<1)	3 (1.1)
Withdrawal by subject	39 (6.3)	21 (6.5)	32 (6.1)	19 (7.2)

Source: Statistical Reviewer Analysis; adsl.xpt; Software: SAS

¹ ITT population: all randomized subjects.

The percentages were calculated based on the number of randomized subjects.

Abbreviations: AD, atopic dermatitis; IQR, interquartile range; ITT, Intent to treat; n, number of patients meeting criteria; N, number of patients in treatment arm; SD, standard deviation

The demographics of the trials are presented in Table 9. The demographic characteristics were generally balanced between the two treatment arms of either study, although in ARCADIA 1, more male subjects were randomized to placebo (55.1%) than to nemolizumab (44.9%). However, a notable imbalance exists in the distribution of Black or African American subjects in ARCADIA 2, with 25 randomized to nemolizumab and 20 to placebo, deviating from the 2:1 randomization ratio. Note that the Applicant, both in the study reports and in the analysis datasets, grouped the subjects into “18-65 years” and “≥ 66 years.” There were 10 subjects of age 65 in ARCADIA 1 and 11 subjects in ARCADIA 2. This review uses the age groups compliant with the ICH E7 Guidance, *Studies in Support of Special Populations: Geriatrics* (i.e., “18-64 years” and “≥ 65 years”).

The racial makeup of the two studies was not comparable. In ARCADIA 2, White subjects accounted for 87.7% of subjects randomized to nemolizumab and 85.7% of those randomized to placebo—approximately 10% higher than the proportions of White subjects in the two arms of ARCADIA 1. Furthermore, ARCADIA 1 enrolled and randomized a total of 168 Asian subjects, three times as many as the 53 Asian subjects enrolled and randomized in ARCADIA 2.

Table 9. Demographics – ARCADIA 1 and ARCADIA 2 (ITT¹)

Demographic Characteristics	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sex, n (%)				
Female	297 (47.9)	144 (44.9)	270 (51.7)	136 (51.3)
Male	323 (52.1)	177 (55.1)	252 (48.3)	129 (48.7)
Age (years)				
Mean (SD)	33.5 (15.92)	33.3 (15.61)	34.9 (17.66)	35.2 (16.98)
Median	29.0	29.0	30.0	32.0
IQR	21.0, 43.0	21.0, 45.0	20.0, 48.0	21.0, 46.0
Min, max	12.0, 82.0	12.0, 81.0	12.0, 84.0	12.0, 85.0

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Demographic Characteristics				
Age group (years), n (%)				
12 to <18	85 (13.7)	49 (15.3)	91 (17.4)	41 (15.5)
18 to <65	503 (81.1)	259 (80.7)	388 (74.3)	206 (77.7)
≥65	32 (5.2)	13 (4.0)	43 (8.2)	18 (6.8)
Race, n (%)				
American Indian or Alaska Native	2 (<1)	3 (<1)	1 (<1)	-
Asian	117 (18.9)	51 (15.9)	35 (6.7)	18 (6.8)
Black or African American	36 (5.8)	18 (5.6)	25 (4.8)	20 (7.5)
Multiple	10 (1.6)	4 (1.2)	-	-
Native Hawaiian or other Pacific Islander	1 (<1)	-	1 (<1)	-
Other	3 (<1)	1 (<1)	2 (<1)	-
White	451 (72.7)	244 (76.0)	458 (87.7)	227 (85.7)
Ethnicity, n (%)				
Hispanic or Latino	64 (10.3)	32 (10.0)	44 (8.4)	19 (7.2)
Not Hispanic or Latino	552 (89.0)	288 (89.7)	464 (88.9)	244 (92.1)
Not reported	2 (<1)	1 (<1)	12 (2.3)	2 (<1)
Unknown	2 (<1)	-	2 (<1)	-

Source: Statistical Reviewer Analysis; adsl.xpt; Software: SAS

¹ ITT population: all randomized subjects.

Abbreviations: IQR, interquartile range; ITT, Intent to treat; n, number of patients meeting criteria; N, number of patients in treatment arm; SD, standard deviation

Table 10 presents a summary of the baseline disease characteristics in ARCADIA 1 and ARCADIA 2. The baseline disease characteristics were generally balanced across treatment arms. Approximately equal proportions of subjects with an IGA score of 3 (moderate) and 4 (severe) were enrolled in the studies. More than half of the randomized subjects (60% in ARCADIA 1 and 55% in ARCADIA 2) had a peak pruritus NRS greater than 7 at Baseline.

Table 10. Baseline Disease Characteristics – ARCADIA 1 and ARCADIA 2 (ITT¹)

Disease Characteristics	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
EASI Score				
Mean (SD)	27.8 (10.6)	27.1 (9.4)	27.4 (10.8)	27.6 (10.9)
Median	24.4	24.8	24.3	24.4
IQR	19.7, 32.4	19.7, 32.2	19.0, 32.6	18.6, 33.3
Min, max	16.0, 70.8	16.0, 61.7	13.4, 72.0	16.0, 66.0
IGA Score, n (%)				
3 - moderate	438 (70.6)	236 (73.5)	351 (67.4)	185 (69.8)
4 - severe	182 (29.4)	85 (26.5)	170 (32.6)	80 (30.2)
Peak Pruritus				
n	618	320	521	264
Mean (SD)	7.2 (1.4)	7.2 (1.4)	7.0 (1.5)	7.2 (1.5)
Median	7.3	7.3	7.0	7.2
IQR	6.3, 8.0	6.2, 8.1	6.0, 8.2	6.0, 8.3
Min, max	1.7, 10.0	4.0, 10.0	3.4, 10.0	3.7, 10.0
Categories, n (%)				
≥7	372 (60.0)	193 (60.1)	280 (53.6)	151 (57.0)
<7	246 (39.7)	127 (39.6)	241 (46.2)	113 (42.6)
Missing	2 (<1)	1 (<1)	1 (<1)	1 (<1)

Disease Characteristics	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Body Surface Area				
Mean (SD)	44.9 (19.9)	43.8 (18.7)	44.6 (19.4)	45.0 (19.3)
Median	41.8	41.0	41.3	43.0
IQR	30.0, 57.0	29.0, 56.0	30.0, 57.0	30.0, 57.5
Min, max	11.0, 99.0	11.5, 99.0	10.0, 98.0	11.0, 97.0

Source: Statistical Reviewer Analysis; adsl.xpt; Software: SAS

¹ ITT population: all randomized subjects.

Abbreviations: EASI, Eczema Area and Severity Index; IGA; Investigator's Global Assessment; IQR, interquartile range; ITT, Intent to treat; n, number of patients meeting criteria; N, number of patients in treatment arm; SD, standard deviation

Rescue Therapy Use

The use of rescue therapy is summarized in Table 11. A marginally greater proportion of subjects in the placebo group (8% in ARCADIA 1 and 4% in ARCADIA 2) used rescue medication than in the nemolizumab group (5% in ARCADIA 1 and 3% ARCADIA 2). In both trials, subjects used both topical and systemic rescue medications at a similar rate, overall.

Table 11. Rescue Therapy Use – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Any rescue therapy	33 (5%)	24 (8%)	16 (3%)	11 (4%)
Topical medication	21 (3%)	13 (4%)	11 (2%)	11 (4%)
Systemic medication	15 (2%)	15 (5%)	8 (2%)	2 (1%)

Source: Table 14.2.3.22.1.1 of Clinical Study Reports for ARCADIA 1 (RD.06.SRE.118161) and ARCADIA 2 (RD.06.SRE.118169).

¹ ITT population: all randomized subjects.

Abbreviations: ITT, intent to treat; N, number of subjects in treatment arm

Results for the Primary Efficacy Endpoints

Table 12 presents the results for the co-primary efficacy endpoint of IGA success at Week 16 (defined as an IGA score of 0 (“clear”) or 1 (“almost clear”) and a ≥ 2 -point reduction from Baseline at Week 16 for the ITT population in both trials) and the co-primary efficacy endpoint of EASI-75 (defined as $\geq 75\%$ reduction in EASI) score from Baseline at Week 16).

Nemolizumab was statistically superior to placebo in both trials. The treatment effect was comparable between the trials. The results based on the PP population—not presented here—were generally similar to those based on the ITT population.

Table 12. Results for the Co-Primary Efficacy Endpoints at Week 16 – ARCADIA 1 and ARCADIA 2 (ITT¹)

Co-Primary	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
IGA success ²	221 (36%)	79 (25%)	38%	26%
Adjusted difference (97.5% CI) ³	12% (5%, 18%)		12% (5%, 20%)	
Adjusted difference (95% CI) ³	12% (6%, 17%)		12% (6%, 19%)	
p-value ³	0.0004		0.0008	
EASI-75 ⁴	270 (44%)	93 (29%)	42%	30%
Adjusted difference (97.5% CI) ³	15% (8%, 22%)		12% (5%, 20%)	
Adjusted difference (95% CI) ³	15% (9%, 21%)		12% (6%, 19%)	
p-value ³	< 0.0001		0.0008	

Source: Statistical Reviewer Analysis; adeff.xpt; Software: SAS, R

¹ ITT population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.

² IGA success is defined as IGA score of 0 ("clear") or 1 ("almost clear") with a ≥ 2 -point reduction from baseline at Week 16.

³ Adjusted difference in proportions is the weighted average of the treatment differences across the randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS < 7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS < 7]).

⁴ EASI-75 is defined as at least 75% reduction in EASI score.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intent-to-treat; N, number of subjects in treatment arm

Table 13 presents the number and percentage of subjects who had missing data at Baseline and Week 16. Subjects with an intercurrent event (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 comparable between ARCADIA 1 and ARCADIA 2.

The Applicant also conducted tipping point analyses for the co-primary efficacy endpoints. For ARCADIA 1, the results for the primary endpoint of IGA success at Week 16 remained statistically significant even under the worst-case scenario (strata-adjusted p-value = 0.0203), where all subjects on the nemolizumab arm with missing data at Week 16 are imputed as non-responders and all such subjects on the placebo arm are imputed as responders. For ARCADIA 2, the results for the primary efficacy endpoint of IGA success tip 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 31](#) in Section [16.1](#)).

The tipping point analysis results for the primary efficacy endpoint of EASI-75 closely mirrored those for the primary efficacy endpoint of IGA success. For ARCADIA 1, the results remained statistically significant even under the worst-case scenario (strata-adjusted p-value of 0.0012), i.e., most unfavorable to nemolizumab. However, for ARCADIA 2, the results for the primary efficacy endpoint of EASI-75 tip when a high proportion of 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 32](#) in Section [16.1](#)).

Table 13. Missing Data at Baseline and Week 16 – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Missing Data at Baseline				
IGA	0	0	0	0
PP-NRS (with extended bounds)	2 (0%)	1 (0%)	1 (0%)	1 (0%)
PP-NRS (without extended bounds)	2 (0%)	1 (0%)	1 (0%)	1 (0%)
SD-NRS (with extended bounds)	10 (2%)	1 (0%)	5 (1%)	2 (1%)
SD-NRS (without extended bounds)	10 (2%)	1 (0%)	5 (1%)	2 (1%)
Missing Data at Week 16 (Excluding Subjects With ICE)				
IGA	54 (9%)	15 (5%)	44 (8%)	22 (8%)
PP-NRS (with extended bounds)	104 (17%)	51 (16%)	93 (18%)	44 (17%)
PP-NRS (without extended bounds)	204 (33%)	89 (28%)	158 (30%)	78 (29%)
SD-NRS (with extended bounds)	115 (19%)	54 (17%)	88 (17%)	42 (16%)
SD-NRS (without extended bounds)	187 (30%)	92 (29%)	155 (30%)	76 (29%)

Source: Statistical Reviewer's Analysis; adsl.xpt, adefx.xpt

¹ ITT population: all randomized subjects.

Abbreviation: ICE, intercurrent event; IGA, Investigator's Global Assessment; ITT, intent to treat; 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 without the extended bounds in the ITT population and the Severe Baseline PP-NRS population, respectively. Note that for the Severe Baseline PP-NRS population, the endpoint of PP-NRS <2 translates to ≥5-point reduction in PP-NRS from Baseline at Week 16, a higher bar than the ≥4-point reduction in PP-NRS endpoint. For both trials, nemolizumab was statistically superior to placebo in either population. Due to all the endpoints being statistically significant based on the ITT population, the endpoints were tested at the full 0.05 significance level for the Severe Baseline PP-NRS population, according to the prespecified multiplicity control. The treatment effects based on the Severe Baseline PP-NRS population were generally larger than the treatment effects based on the ITT population. The results for the key secondary efficacy endpoints with the extended bounds are presented in Table 85 and Table 86 in Section [16.1](#).

Table 14. Results for the Key Secondary Efficacy Endpoints Without Extended Bounds¹ – ARCADIA 1 and ARCADIA 2 (ITT²)

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
≥4-point reduction in PP-NRS (Week 16)	207 (33%)	49 (15%)	186 (36%)	40 (15%)
Adjusted difference (97.5% CI) ³		18% (12%, 24%)		21% (14%, 28%)
Adjusted difference (95% CI) ³		18% (13%, 23%)		21% (15%, 27%)
p-value ³		< 0.0001		< 0.0001
PP-NRS < 2 (Week 16)	144 (23%)	31 (10%)	125 (24%)	24 (9%)
Adjusted difference (97.5% CI) ³		14% (8%, 19%)		15% (9%, 21%)
Adjusted difference (95% CI) ³		14% (9%, 18%)		15% (10%, 20%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in SD-NRS (Week 16)	193 (31%)	58 (18%)	149 (29%)	36 (14%)
Adjusted difference (97.5% CI) ³		13% (7%, 19%)		15% (9%, 22%)
Adjusted difference (95% CI) ³		13% (7%, 18%)		15% (10%, 21%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 4)	170 (27%)	21 (7%)	136 (26%)	14 (5%)
Adjusted difference (97.5% CI) ³		21% (16%, 26%)		21% (16%, 26%)
Adjusted difference (95% CI) ³		21% (16%, 25%)		21% (16%, 25%)
p-value ³		< 0.0001		< 0.0001
PP-NRS < 2 (Week 4)	99 (16%)	12 (4%)	83 (16%)	7 (3%)
Adjusted Difference (97.5% CI) ³		12% (8%, 16%)		13% (9%, 17%)
Adjusted Difference (95% CI) ³		12% (9%, 16%)		13% (10%, 17%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 2)	110 (18%)	10 (3%)	88 (17%)	5 (2%)
Adjusted difference (97.5% CI) ³		15% (11%, 19%)		15% (11%, 19%)
Adjusted difference (95% CI) ³		15% (11%, 18%)		15% (11%, 19%)
p-value ³		< 0.0001		< 0.0001

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
≥4-point reduction in PP-NRS (Week 1)	29 (5%)	4 (1%)	35 (7%)	1 (0%)
Adjusted difference (97.5% CI) ³		3% (1%, 6%)		6% (4%, 9%)
Adjusted difference (95% CI) ³		3% (1%, 6%)		6% (4%, 9%)
p-value ³		0.0064		< 0.0001
EASI-75 & ≥4-point reduction in PP-NRS (Week 16)	114 (18%)	31 (10%)	106 (20%)	21 (8%)
Adjusted difference (97.5% CI) ³		9% (4%, 14%)		13% (7%, 18%)
Adjusted difference (95% CI) ³		9% (4%, 13%)		13% (8%, 17%)
p-value ³		0.0004		< 0.0001
IGA Success & ≥4-point reduction in PP-NRS (Week 16)	96 (15%)	27 (8%)	95 (18%)	18 (7%)
Adjusted difference (97.5% CI) ³		7% (2%, 12%)		12% (7%, 17%)
Adjusted difference (95% CI) ³		7% (3%, 11%)		12% (7%, 16%)
p-value ³		0.0019		< 0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt; Software: SAS, R

¹ The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS and SD-NRS; see the footnote of Table 8.2 in Section 8.4 of the Statistical Analysis Plan.

² 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, at least 75% reduction in Eczema Area and Severity Index score from baseline; IGA, Investigator's Global Assessment, ITT, intent-to-treat; 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 Bounds¹ – ARCADIA 1 and ARCADIA 2 (Severe Baseline PP-NRS Population²)

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=372)	Placebo (N=193)	Nemolizumab (N=280)	Placebo (N=151)
≥4-point reduction in PP-NRS (Week 16)	143 (38%)	32 (17%)	122 (44%)	27 (18%)
Adjusted difference (97.5% CI) ³		22% (14%, 30%)		25% (16%, 35%)
Adjusted difference (95% CI) ³		22% (15%, 29%)		25% (17%, 34%)
p-value ³		< 0.0001		< 0.0001
PP-NRS < 2 (Week 16)	79 (21%)	11 (6%)	62 (22%)	9 (6%)
Adjusted difference (97.5% CI) ³		16% (9%, 22%)		16% (9%, 23%)
Adjusted difference (95% CI) ³		16% (10%, 21%)		16% (10%, 22%)
p-value ³		< 0.0001		< 0.0001

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=372)	Placebo (N=193)	Nemolizumab (N=280)	Placebo (N=151)
≥4-point reduction in PP-NRS (Week 4)	115 (31%)	14 (7%)	89 (30%)	12 (8%)
Adjusted difference (97.5% CI) ³		24% (17%, 31%)		24% (16%, 32%)
Adjusted difference (95% CI) ³		24% (18%, 30%)		24% (17%, 31%)
p-value ³		< 0.0001		< 0.0001
PP-NRS < 2 (Week 4)	47 (13%)	5 (3%)	29 (10%)	2 (1%)
Adjusted difference (97.5% CI) ³		10% (6%, 15%)		9% (4%, 14%)
Adjusted difference (95% CI) ³		10% (6%, 14%)		9% (5%, 13%)
p-value ³		< 0.0001		0.0001
≥4-point reduction in PP-NRS (Week 2)	82 (22%)	7 (4%)	56 (20%)	2 (1%)
Adjusted difference (97.5% CI) ³		19% (13%, 24%)		17% (11%, 23%)
Adjusted difference (95% CI) ³		19% (14%, 24%)		17% (12%, 23%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 1)	25 (7%)	4 (2%)	25 (9%)	1 (1%)
Adjusted difference (97.5% CI) ³	5% (1%, 8%)			8% (4%, 12%)
Adjusted difference (95% CI) ³	5% (1%, 8%)			8% (5%, 12%)
p-value ³	0.019			0.0006
EASI-75 & ≥4-point reduction in PP-NRS (Week 16)	80 (22%)	20 (10%)	70 (25%)	13 (9%)
Adjusted difference (97.5% CI) ³		11% (4%, 18%)		16% (9%, 24%)
Adjusted difference (95% CI) ³		11% (5%, 17%)		16% (10%, 23%)
p-value ³		0.001		< 0.0001
IGA Success & ≥4-point reduction in PP-NRS (Week 16)	63 (17%)	17 (9%)	62 (22%)	12 (8%)
Adjusted difference (97.5% CI) ³		8% (2%, 14%)		14% (7%, 22%)
Adjusted difference (95% CI) ³		8% (2%, 13%)		14% (8%, 21%)
p-value ³		0.01		0.0002

Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt; Software: SAS, R

¹ The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS; see the footnote of Table 8.2 in Section 8.4 of the Statistical Analysis Plan.

² 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, at least 75% reduction in Eczema Area and Severity Index score from baseline; IGA, Investigator's Global Assessment, ITT, intent-to-treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Efficacy in Adolescent Subjects

Table 16 presents the results for the co-primary efficacy endpoints at Week 16 in adolescent subjects. The table also presents the results for the key secondary efficacy endpoint of pruritus response (i.e., 4-point reduction in PP-NRS from baseline) at Week 16 without the extended bounds.

Table 16. Results for the Co-primary Efficacy Endpoints at Week 16 and for the Key Secondary Efficacy Endpoint of Pruritus Response (≥ 4 -point reduction in PP-NRS [Without Extended Bounds¹]) at Week 16 in Adolescent Subjects – ARCADIA 1 and ARCADIA 2 (ITT²)

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=85)	Placebo (N=49)	Nemolizumab (N=91)	Placebo (N=41)
IGA success ³	47 (55%)	16 (33%)	39 (43%)	15 (37%)
Adjusted difference e (95% CI) ⁴		18% (0%, 35%)		8% (-11%, 26%)
EASI-75	49 (58%)	21 (43%)	45 (49%)	18 (44%)
Adjusted difference (95% CI) ⁴		12% (-6%, 30%)		7% (-12%, 25%)
≥ 4 -point reduction in PP-NRS	26 (31%)	8 (16%)	27 (30%)	8 (20%)
Adjusted difference (95% CI) ⁴		10% (-4%, 25%)		12% (-3%, 27%)

Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt

¹ The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS and SD-NRS; see the footnote of Table 8.2 in Section 8.4 of the Statistical Analysis Plan.

² ITT population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders. Missing data was imputed as non-responders.

³ IGA success is defined as IGA score of 0 ("clear") or 1 ("almost clear") with a ≥ 2 -point reduction from baseline.

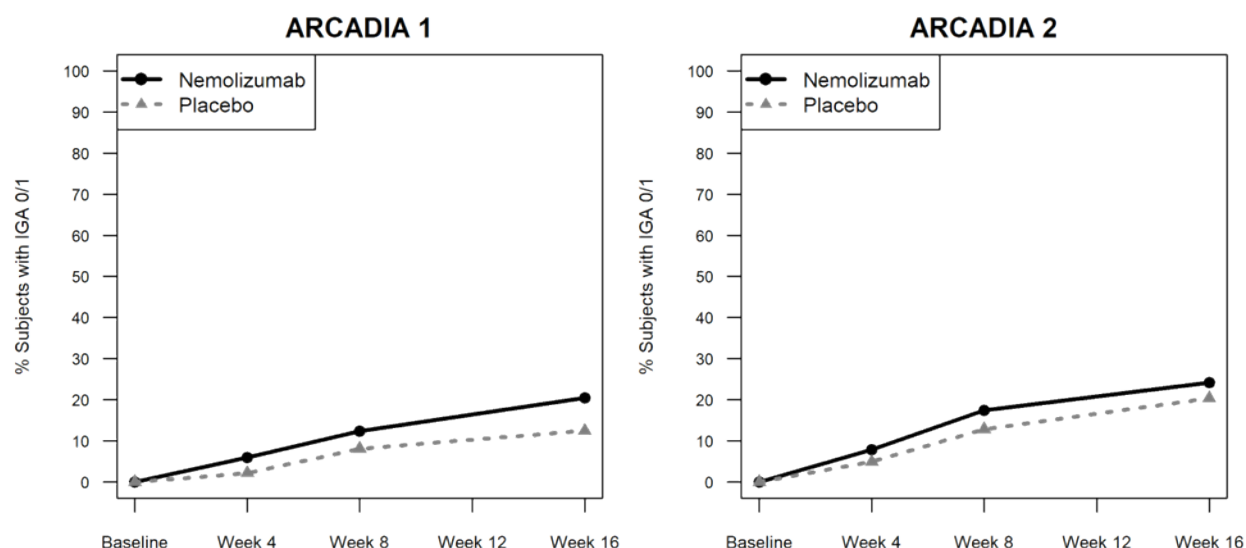
⁴ Adjusted difference in proportions is the weighted average of the treatment differences across the randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, at least 75% reduction in Eczema Area and Severity Index score from baseline; IGA, Investigator's Global Assessment; ITT, intent-to-treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Efficacy Over Time

[Figure 4](#) and [Figure 5](#) present the results over time during the initial treatment period for the two primary efficacy endpoints in both trials.

Figure 4. Proportion of Subjects with IGA Success¹ Over Time – ARCADIA 1 and ARCADIA 2 (ITT²)



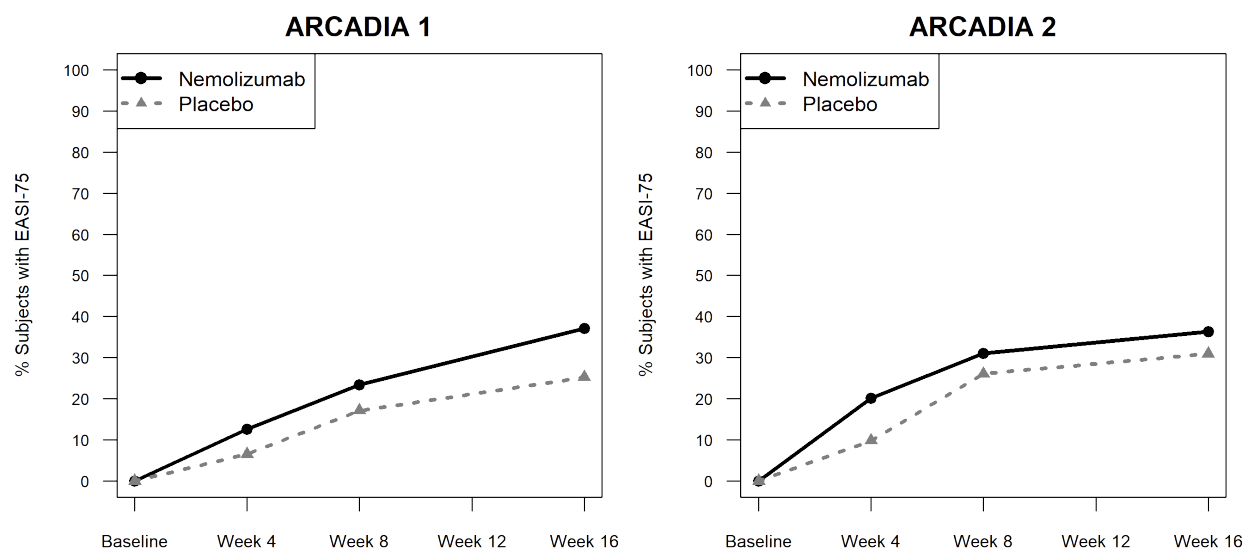
Source: Statistical Reviewer's Analysis; adefx.xpt

¹ IGA success is defined as IGA score of 0 ("clear") or 1 ("almost clear") with a ≥ 2 -point reduction from baseline.

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: IGA, Investigator's Global Assessment; ITT, intent-to-treat

Figure 5. Proportion of Subjects with EASI-75 Over Time – ARCADIA 1 and ARCADIA 2 (ITT¹)



Source: Statistical Reviewer's Analysis; adefx.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: EASI, Eczema Area and Severity Index; ITT, intent-to-treat

Maintenance of Response

[Table 17](#) presents the results for the maintenance period. IGA responders AND/OR EASI-75 responders at Week 16 were re-randomized 1:1:1 to receive nemolizumab Q4W + TCS/TCI, nemolizumab Q8W + TCS/TCI, or placebo + TCS/TCI. Overall, the nemolizumab Q8W regimen showed slightly higher maintenance rates of response at Week 48 than the nemolizumab Q4W regimen.

Table 17. Results for the Maintenance Period

	Nemolizumab Q4W + TCS/TCI	Nemolizumab Q8W + TCS/TCI	Placebo + TCS/TCI
ARCADIA 1			
Number of subjects who were IGA Responders ¹ at Week 16	77	73	68
Proportion of subjects with IGA 0 or 1 ² at Week 48	61%	59%	50%
Number of subjects who were EASI-75 Responders at Week 16	89	88	88
Proportion of subjects with EASI-75 ² at Week 48	74%	75%	61%
ARCADIA 2			
Number of subjects who were IGA Responders ¹ at Week 16	65	69	63
Proportion of subjects with IGA 0 or 1 ² at Week 48	66%	70%	60%
Number of subjects who were EASI-75 Responders at Week 16	74	75	69
Proportion of subjects with EASI-75 ² at Week 48	77%	79%	70%
Pooled Analysis			
Number of subjects who were IGA Responders ¹ at Week 16	142	142	131
Proportion of subjects with IGA 0 or 1 ² at Week 48	63%	64%	55%
Number of subjects who were EASI-75 Responders at Week 16	163	163	157
Proportion of subjects with EASI-75 ² at Week 48	75%	77%	65%

Source: Statistical Reviewer's Analysis; adsl.xpt, adeff.xpt

¹ Responder was defined as a subject with an IGA of 0 (clear) or 1 (almost clear) and a ≥ 2 -point reduction from baseline.

² Subjects who receive rescue treatment or with missing data were considered non-responders.

Abbreviations: EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; TCI, topical calcineurin inhibitor; TCS, topical corticosteroid; Q4W, every 4 weeks; Q8W, every 8 weeks

Subgroup Analyses

Results for subgroup analyses by age (<65 and ≥ 65 years), sex, race, ethnicity, baseline IGA, and baseline PP-NRS are presented in [Table 95](#) and Table 96 in Section [16.2](#). The treatment effect was generally consistent across these subgroups. For race, the sample sizes for some subgroups were relatively small (e.g., American Indian or Alaskan Native, and Native Hawaiian or Pacific Islander); therefore, it would be difficult to detect 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 of atopic dermatitis.

6.3.1. Fitness-for-Purpose of the SD-NRS

(b) (4)

(b) (4)

Issue

There are pruritic skin conditions that may cause sleep disturbances (Podder et al. 2021). (b) (4)

In the clinical program conducted to support this BLA, the Applicant used the SD-NRS to assess the third ranked key secondary efficacy endpoints. This section discusses whether the SD-NRS is fit-for-purpose.

Background

The Applicant proposed using the SD-NRS to assess the impact of AD on sleep disturbance. There have been previous communications regarding the assessment of sleep disturbance in patients with atopic dermatitis in which the Agency expressed concern regarding the use of a single item to assess sleep disturbance. Advice was given to supplement the single item with a sleep diary and possibly other objective measures. For the atopic dermatitis development program, the Applicant was informed that the adequacy of the SD- NRS would be a review issue [Type C Preliminary Meeting Comments dated April 16, 2020, Type B (End of Phase 2) Meeting Minutes IND 117122 dated May 8, 2019, and Type C Meeting Minutes dated September 17, 2018)].

Assessment

The Applicant submitted an evidence dossier for the SD- NRS, in which the SD-NRS was reviewed for content validity. Because of issues related to content validity (See Content Validity section below), the other measurement properties and score interpretability of the SD- NRS were not reviewed.

Content Validity

The Applicant completed the following instrument development activities to evaluate the content validity of the SD- NRS:

- Literature review
- Expert input (clinician interviews)
- Patient input (hybrid concept elicitation and cognitive interviews in adults)

The review team evaluated the data generated from these instrument development activities. Based on the literature review, there were no existing PRO measures specifically designed and/or validated to assess sleep disturbance in patients with AD. The Applicant provided limited details regarding the extent of expert input obtained for the SD- NRS; the evidence dossier only indicates that the original SD- NRS was developed by the Applicant's clinical team. While patient input confirmed that the sleep disturbance is relevant to the patient experience of AD, it is unclear what the extent of importance of sleep disturbance is to the target population.

During the Agency's review of the hybrid concept elicitation and cognitive interviews in US adults and adolescents with moderate-to-severe AD and moderate-to-severe pruritus. The review team noted the following:

- Insufficient qualitative evidence to support that sleep disturbance is an important concept to the target AD population. Participants were not queried regarding what AD associated impact was most important or bothersome to them.
- Sleep disturbance may not always be directly due to AD. Based on the qualitative findings, approximately one-third of adults (n=7/19, 35%) and adolescents (n=3/7, 30%) attributed sleep disturbance solely to the itching from their AD. Further, half (50%) of the adult participants provided a reason other than symptoms of AD for their sleep disturbance.
- The SD-NRS, which is a single item, does not reflect the entirety of the sleep disturbance concept. Based on the qualitative data, there are different aspects of sleep disturbance which vary across participants (e.g., difficulty falling/staying asleep, nighttime awakenings, early morning awakening, lack of sleep, unspecified sleep disturbance). However, the SD-NRS only assesses "sleep loss" as a whole. Further, it is unclear what attribute of sleep loss is being measured with the SD-NRS (e.g., severity, frequency, amount of sleep) as participants in the qualitative study interpreted the item differently. For example, one participant perceived the item to measure how much AD affected their sleep while another participant interpreted it as how much sleep they lost.
- It is unknown whether participants understood the SD-NRS response scale after migrating from paper to an electronic format. There is concern regarding the formatting and layout changes of the response scale which may have been the result of migration from paper to electronic mode. Specifically, the placement of the anchors ("No sleep loss" and "I did not sleep at all") spans over 2 to 3 points at each end of the NRS in the electronic format, while it should have been located at the 0 and 10 points similar to the original paper format. It is unclear whether a usability study was conducted in the target population.

Data Interpretability

- Because the SD-NRS is a single item, it is unclear which aspect of sleep loss is improving and/or worsening.
- For the measurement concept of sleep loss, the NRS is not directly interpretable without descriptors at the intermediate level.
- While the Applicant administered the Subject Sleep Diary to supplement the SD-NRS, it provides limited information about the participant's sleep experience due to the variability of the participants' experience. Further, qualitative findings indicated that sleep disturbance or sleep loss may not be directly due to AD. For example, over half of the participants (adults: n = 12/20, 60.0%; adolescents: n = 14/10, 70.0%) woke up during the night for other things outside of their condition (e.g., going to bathroom, drinking water). These factors make data interpretation difficult.

Conclusion

While the data from ARCADIA 1 and ARCADIA 2 demonstrated that nemolizumab had a statistically significant greater proportion of participants with an improvement of >4 from

Baseline in weekly average SD-NRS compared to placebo at Weeks 4 and 16, the data are difficult to interpret due to the following:

- Because the SD-NRS is a single item, it is unclear which aspect of sleep loss is improving and/or worsening.
- Sleep disturbance may not always be directly due to AD. Based on the qualitative findings, only a subset of adults (n = 7/19, 35%) and adolescents (n = 3/7, 30%) attributed sleep disturbance solely to the itching from their AD.
- For the measurement concept of sleep loss, the NRS is not directly interpretable without descriptors at the intermediate level. The qualitative study further corroborated that subjects had inconsistent descriptions of each level of the SD-NRS.
- While the Applicant administered the Subject Sleep Diary to supplement the SD-NRS, it provides limited information about the participant's sleep experience due to the variability of the participants' experience.

Overall, there is insufficient evidence to support that the SD-NRS and its corresponding endpoint is fit-for-purpose for the context of this development program. (b) (4)

(b) (4)

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 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 loading dose, followed by 30 mg every 4 weeks) are shown in Table 18 below.

Table 18. 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*	72
Enhanced pre- and postnatal development study in monkeys	Subcutaneous	Maternal: 25	59900	50
		Embryofetal: 25	59900	50
		Pre- and postnatal: 1	3310	2.8
		Juvenile: 25	201000	168

Source: Nonclinical reviewer’s analysis

*The lower mean AUC value between males and females was used for the calculation.

**The mean human AUC_{0-28 day} value in the phase 2b clinical trial in subjects with atopic dermatitis (SPR.114322) exposed to 60 mg loading dose was 100 µg·day/ml (2400 µg·hr/ml). A factor of 2 was used to convert it to the AUC_{0-14 day} value (1200 µg·hr/ml), which was used for the multiple calculation.

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-14 day}, area under the concentration-time curve from 0 to 14 days; AUC_{0-28 day}, area under the concentration-time curve from 0 to 28 days; 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.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

NEMLUVIO was approved by the Food and Drug Administration (FDA) on August 12, 2024, for the indication of treatment of PN. However, there is no postmarketing data available from the US.

Nemolizumab (Mitchga®) was approved for marketing on 3/28/2022 and launched on 8/8/2022 in Japan for the indication of treatment of “pruritus associated with AD (only when existing treatments are inadequate)” for patients ≥13 years of age.

7.3.1. Adverse Events Identified in Postmarket Experiences

At the time of this BLA submission, available postmarketing safety data for an estimated 4,000 patients treated with nemolizumab in Japan (as of the DSUR data cut-off date of 21 Jul 2023)

included 676 AEs in 474 patients (including 34 serious adverse events [SAEs] in 27 patients [30 SAEs in 25 patients were 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

Not applicable.

7.3.3. Additional Safety Issues From Other Disciplines

None.

7.4. FDA Approach to the Safety Review

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

- Two phase 3 (pivotal) trials (ARCADIA 1 (SPR.118161) [N = 941], and ARCADIA 2 (SPR.118169) [N = 787]) of identical design.

Each trial had a total duration of 56 weeks, including a 4-week screening period, a 16-week initial treatment period (ITP), a 32-week MTP, and an 8-week follow-up period.

- A phase 3, long-term extension study (ARCADIA LTE (SPR.118163) [N = 1740]) of up to 200 weeks duration.
- A phase 2 dose-ranging (P2-DR) trial (SPR.114322) (N = 200), including a 24-week treatment and an 8-week follow-up period. This trial included 4 dose cohorts (n = 50 per cohort) of nemolizumab 10 mg, 30 mg, 90 mg, or placebo Q4 weeks.

The Applicant's main safety data pool for the integrated summary of safety includes the phase 2 and phase 3 AD trials (ARCADIA 1, ARCADIA 2, and P2-DR). Safety data for the primary safety population for the ITP are pooled from all 3 trials, but the safety data for the MTP does not include the P2-DR trial.

The focus of the safety analyses by the review team for this BLA will be on the pooled safety data for the phase 3 trials (P3 pool) ARCADIA 1 and ARCADIA 2 (for both the ITP and MTP), and will not include the P2-DR trial, because of the following:

- Compared to ARCADIA 1 and ARCADIA 2 trials, the P2-DR trial had a different treatment duration of 24 weeks (vs. 16 weeks) and a different randomization ratio of 1:1:1:1 (versus 2:1).
- The contribution of the P2-DR trial to the overall safety pool was small and included approximately 50 subjects in each dose group of the P2-DR trial (out of 1192 subjects treated with the [to-be-marketed] dose of nemolizumab 30 mg Q 4W and 640 subjects treated with placebo Q 4W in the Applicant's main safety data pool) were included in the safety analyses

for the ITP; no subjects from the P2-DR trial were included in the Applicant's safety analyses for the MTP.

- The safety results for the ITP are similar for the P3 pool and the Applicant's main safety data pool in the integrated summary of safety.

Additional interim safety data from the ARCADIA LTE study (up to the data lock point) will be summarized and discussed separately from the ARCADIA 1 and ARCADIA 2 safety data pool.

The AD exposure pool (used by the Applicant only for the summary of subject exposure and disposition data) includes subjects from trials ARCADIA 1, ARCADIA 2, the study ARCADIA LTE, the trial P2-DR, and the study SPR.116912 (a phase 2, open-label, PK study in adolescents with moderate to severe AD-associated pruritus [N = 20]), and SPR.201593 (a phase 2, open-label, single-sequence, drug-drug interaction study in adult subjects with moderate to severe AD [N=12]).

The Applicant also submitted additional safety data from 5 AD studies and 9 studies in healthy subjects, subjects with PN, and subjects with pruritus of chronic kidney disease conducted by the Applicant or its affiliates.

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
7. Asthma control test

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) ($>3 \times$ the upper limit of normal [ULN]) in combination with elevated bilirubin ($>2 \times$ ULN).

In addition, the Applicant conducted analyses of safety data for subgroups based on age groups (12 to 17 years, 18 to 65 years, or >65 years of age), sex (male, female), race (White, Black, or African American, Asian, Other Race), region (North America, Europe, Asia), and Country.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (v. 25.0). The Clinical Data Scientist team for BLA 761391 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 761391.

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 ARCADIA 1 and ARCADIA 2 trials were reviewed and found to be acceptable.

Treatment-emergent adverse events (TEAEs) were defined in the protocols 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 TEAEs reported for the primary safety population were categorized by the treatment period (the Initial Treatment Period (ITP), the Maintenance Treatment Period (MTP), and the Follow-up Period), and 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/resolved, not recovered/not resolved, recovered with sequelae, or 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 ($>3 \times \text{ULN}$) in combination with elevated bilirubin ($>2 \times \text{ULN}$).

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. Subjects with abnormal laboratory values deemed as potentially clinically significant by the investigators were assessed for the occurrence of AEs (e.g., a potentially clinically significant elevation in creatine kinase and occurrence of AEs in the system organ class of Musculoskeletal and Connective Tissue Disorders).

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.

The AD exposure pool included exposure data from ARCADIA 1, ARCADIA 2, ARCADIA LTE, the P2-DR study, SPR.116912 [a phase 2, open-label, PK study in adolescents with AD], and SPR.201593 (drug-drug interaction study). Of the 2007 subjects in the AD exposure pool treated with nemolizumab 30 mg, 1497 subjects (including 258 adolescents) treated for ≥ 6 months, 1148 (including 180 adolescent) subjects treated for ≥ 1 year, 645 (including 61 adolescent) subjects treated for ≥ 18 months, and 171 (including 20 adolescent) subjects treated for ≥ 2 years.

During the ITP for the P3 exposure pool, 1135 subjects received treatment with nemolizumab 30 mg Q 4W for a mean (SD) of 11.4 (2.7) weeks (a median of 12.1 weeks, a minimum 0.1 weeks to a maximum of 16.9 weeks), for a total exposure of 249 person-years. Duration of exposure for the P3 safety pool was similar for the nemolizumab and placebo groups during the ITP, as summarized in Table 19.

Table 19. Duration of Exposure, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Parameters	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16	
	Nemolizumab 30 mg N=616	Placebo N=321	Nemolizumab 30 mg N=519	Placebo N=263	Nemolizumab 30 mg N=1135	Placebo N=584
Duration of treatment, weeks						
Mean (SD)	11.4 (2.7)	11.5 (2.5)	11.5 (2.6)	11.6 (2.5)	11.4 (2.7)	11.5 (2.5)
Median	12.1	12.1	12.1	12.1	12.1	12.1
(Q1, Q3)	(12, 12.3)	(12, 12.3)	(12, 12.3)	(12, 12.3)	(12, 12.3)	(12, 12.3)
Min, max	0.1, 16.9	0.1, 14.6	0.1, 16.3	0.1, 14.9	0.1, 16.9	0.1, 14.9
Total exposure (person years)	135	71	114	58	249	129
Patients treated, by duration, n (%)						
<4 weeks	25 (4.1)	10 (3.1)	19 (3.7)	9 (3.4)	44 (3.9)	19 (3.3)
≥4 to <8 weeks	24 (3.9)	13 (4.0)	15 (2.9)	6 (2.3)	39 (3.4)	19 (3.3)
≥8 to <12 weeks	96 (15.6)	52 (16.2)	88 (17.0)	39 (14.8)	184 (16.2)	91 (15.6)
≥12 to <16 weeks	470 (76.3)	246 (76.6)	395 (76.1)	209 (79.5)	865 (76.2)	455 (77.9)
≥16 weeks	1 (0.2)	0	2 (0.4)	0	3 (0.3)	0

Source: CDS Reviewer, adex.xpt and adsl.xpt; Software: R

Initial treatment period duration is 16 weeks.

Abbreviations: ITP, initial treatment period; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

During the ITP, the P3 safety pool included 1135 subjects in the nemolizumab group and 584 (out of 586 randomized) subjects in the placebo group. Of these subjects, 105/1135 (9.2%) in the nemolizumab group and 47/584 (8%) in the placebo group discontinued study drug.

During the MTP, the P3 safety pool included 170, 167, 168, and 184 subjects in the nemolizumab Q4W/Q4W, Q4W/Q8W, Q4W/PBO, and PBO/PBO groups, respectively. Of these subjects, 27 (15.9%), 22 (13.2%), 34 (20.2%), and 28 (15.2%) in each group, respectively, discontinued study drug.

7.6. Safety Results

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

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

An overview of the TEAEs for the P3 pool during the ITP and MTP are summarized in the following tables (Table 20 and Table 21).

Table 20. Overview of Adverse Events, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Event Category	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab		Nemolizumab		Nemolizumab		Nemolizumab
	30 mg N=616 n (%)	Placebo N=321 n (%)	30 mg N=519 n (%)	Placebo N=263 n (%)	30 mg N=1135 n (%)	Placebo N=584 n (%)	30 mg Versus Placebo Risk Difference % (95% CI)
SAE	6 (1.0)	4 (1.2)	13 (2.5)	3 (1.1)	19 (1.7)	7 (1.2)	0.5 (-0.9, 1.6)
SAEs with fatal outcome	0	0	0	0	0	0	0.0 (-0.7, 0.3)
Life-threatening SAEs	0	0	0	0	0	0	0.0 (-0.7, 0.3)
SAEs requiring hospitalization	4 (0.6)	4 (1.2)	13 (2.5)	3 (1.1)	17 (1.5)	7 (1.2)	0.3 (-1.1, 1.4)
AE leading to permanent discontinuation of study drug	11 (1.8)	13 (4.0)	18 (3.5)	3 (1.1)	29 (2.6)	16 (2.7)	-0.2 (-2.0, 1.3)
AE leading to dose modification of study drug	20 (3.2)	2 (0.6)	12 (2.3)	7 (2.7)	32 (2.8)	9 (1.5)	1.3 (-0.3, 2.7)
AE leading to interruption of study drug	20 (3.2)	2 (0.6)	12 (2.3)	7 (2.7)	32 (2.8)	9 (1.5)	1.3 (-0.3, 2.7)
AE leading to reduction of study drug	0	0	0	0	0	0	0.0 (-0.7, 0.3)
AE leading to dose delay of study drug	0	0	0	0	0	0	0.0 (-0.7, 0.3)
Any AE	306 (49.7)	146 (45.5)	215 (41.4)	117 (44.5)	521 (45.9)	263 (45.0)	0.9 (-4.1, 5.8)
Severe and worse	18 (2.9)	8 (2.5)	21 (4.0)	7 (2.7)	39 (3.4)	15 (2.6)	0.9 (-1.0, 2.5)
Moderate	120 (19.5)	49 (15.3)	81 (15.6)	44 (16.7)	201 (17.7)	93 (15.9)	1.8 (-2.0, 5.4)
Mild	168 (27.3)	89 (27.7)	113 (21.8)	66 (25.1)	281 (24.8)	155 (26.5)	-1.8 (-6.2, 2.5)

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs occurring after the first administration of study treatment until the last study visit.

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients with at least one event; SAE serious adverse event

Table 21. Overview of Adverse Events, Safety Population, MTPs and Full Periods, ARCADIA 1 & ARCADIA 2

Event Category	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
SAE	10 (5.9)	3 (1.8)	4 (2.4)	2 (1.1)	10 (5.9)	5 (3.0)	6 (3.6)	3 (1.6)
SAEs with fatal outcome	0	0	0	0	0	0	0	0
Life-threatening SAEs	0	0	0	0	0	0	0	0
SAEs requiring hospitalization	10 (5.9)	3 (1.8)	3 (1.8)	2 (1.1)	10 (5.9)	4 (2.4)	5 (3.0)	3 (1.6)
AE leading to permanent discontinuation of study drug	4 (2.4)	5 (3.0)	5 (3.0)	4 (2.2)	4 (2.4)	5 (3.0)	5 (3.0)	4 (2.2)
AE leading to dose modification of study drug	8 (4.7)	13 (7.8)	10 (6.0)	7 (3.8)	11 (6.5)	16 (9.6)	13 (7.7)	9 (4.9)
AE leading to interruption of study drug	8 (4.7)	13 (7.8)	10 (6.0)	7 (3.8)	11 (6.5)	16 (9.6)	13 (7.7)	9 (4.9)
AE leading to reduction of study drug	0	0	0	0	0	0	0	0
AE leading to dose delay of study drug	0	0	0	0	0	0	0	0
Any AE	91 (53.5)	90 (53.9)	98 (58.3)	92 (50.0)	113 (66.5)	112 (67.1)	121 (72.0)	114 (62.0)
Severe and worse	5 (2.9)	6 (3.6)	5 (3.0)	2 (1.1)	6 (3.5)	7 (4.2)	5 (3.0)	4 (2.2)
Moderate	39 (22.9)	36 (21.6)	41 (24.4)	35 (19.0)	53 (31.2)	48 (28.7)	57 (33.9)	50 (27.2)
Mild	47 (27.6)	48 (28.7)	52 (31.0)	55 (29.9)	54 (31.8)	57 (34.1)	59 (35.1)	60 (32.6)

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events occurring after the first administration of study treatment until the last study visit.

Duration is 36 weeks for MTP and 48 weeks for full period.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; MTP, maintenance treatment period; N, number of patients in treatment arm; n, number of patients with at least one event; Nemo, nemolizumab; Q4W, every four weeks; Q8W, every eight weeks; SAE, serious adverse event

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

No deaths were reported in the P3 safety pool during the ITP or MTP. During the follow-up period of the P2-DR trial, one death was reported for an 82-year-old male subject ((b) (6)) (treated with nemolizumab 10 mg Q 4W) who was hospitalized on Day 66 for asthenia/methicillin resistant staphylococcus aureus sepsis/hypoxic respiratory failure from aspiration and acute respiratory distress syndrome. On Day 70, subject was reported with a SAE of aspiration pneumonia, was transferred to the inpatient hospice. On Day 83, subject died from aspiration pneumonia and cardiopulmonary arrest. His death was deemed as unrelated to the study drug (last dose of study drug was on Day 57).

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

During the ITP, SAEs were reported with a slightly higher frequency for the nemolizumab Q4W group 19/1135 (1.7%) compared to the placebo group 7/584 (1.2%). SAEs (reported for >1 subject in the nemolizumab group) included Intervertebral disc protrusion (2 [0.2%] versus 0 [0%]) and Dermatitis atopic (5 [0.4%] versus 3 [0.5%]) for subjects in the nemolizumab group compared to the placebo group. The only SAE (reported by the narrow Food and Drug Administration Medical Dictionary for Regulatory Activities query (FMQ) for >1 subject in the nemolizumab group) was “viral infection” reported at a similar frequency of 2 (0.2%) subjects in the nemolizumab group compared to 1 (0.2%) subject in the placebo group.

During the MTP, SAEs were reported at a higher frequency in the nemolizumab Q4W/Q4W group at 10/170 (5.6%), compared to Q4W/Q8W group at 3/167 (1.8%), Q4W/PBO group at 4/168 (2.4%), and PBO/PBO group at 2/184 (1.1%), respectively. No SAE was reported for >1 subject in the nemolizumab group or by narrow FMQ.

SAEs reported for the ITP, MTP, and full periods were consistent with those reported by the narrow FMQs. SAEs and SAE narratives are summarized in the following tables (Table 22, Table 23 and Table 24).

Table 22. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

System Organ Class Preferred Term	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
Any SAE	6 (1.0)	4 (1.2)	13 (2.5)	3 (1.1)	19 (1.7)	7 (1.2)	0.5 (-0.9, 1.6)
Blood and lymphatic system disorders (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Lymphadenopathy	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Cardiac disorders (SOC)	0	0	0	1 (0.4)	0	1 (0.2)	-0.2 (-1.0, 0.2)
Coronary artery disease	0	0	0	1 (0.4)	0	1 (0.2)	-0.2 (-1.0, 0.2)
Congenital, familial and genetic disorders (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Congenital cyst	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Gastrointestinal disorders (SOC)	0	0	2 (0.4)	1 (0.4)	2 (0.2)	1 (0.2)	0.0 (-0.8, 0.5)
Abdominal adhesions	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Eosinophilic colitis	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Small intestinal obstruction	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Inguinal hernia	0	0	0	1 (0.4)	0	1 (0.2)	-0.2 (-1.0, 0.2)
General disorders and administration site conditions (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Oedema peripheral	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Hepatobiliary disorders (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Cholelithiasis	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)

System Organ Class Preferred Term	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
Infections and infestations (SOC)	0	1 (0.3)	3 (0.6)	2 (0.8)	3 (0.3)	3 (0.5)	-0.2 (-1.3, 0.4)
Herpes simplex	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Herpes zoster	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Infected cyst	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Ophthalmic herpes zoster	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Superinfection bacterial	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Appendicitis	0	0	0	1 (0.4)	0	1 (0.2)	-0.2 (-1.0, 0.2)
Chronic sinusitis	0	0	0	1 (0.4)	0	1 (0.2)	-0.2 (-1.0, 0.2)
COVID-19 pneumonia	0	1 (0.3)	0	0	0	1 (0.2)	-0.2 (-1.0, 0.2)
Musculoskeletal and connective tissue disorders (SOC)	0	0	3 (0.6)	0	3 (0.3)	0	0.3 (-0.4, 0.8)
Intervertebral disc protrusion	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Groin pain	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	2 (0.3)	0	0	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Salivary gland cancer	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Uterine leiomyoma	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Nervous system disorders (SOC)	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Lumbar radiculopathy	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)

System Organ Class Preferred Term	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
Psychiatric disorders (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Psychogenic tremor	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Renal and urinary disorders (SOC)	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Renal colic	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Skin and subcutaneous tissue disorders (SOC)	2 (0.3)	3 (0.9)	3 (0.6)	0	5 (0.4)	3 (0.5)	-0.1 (-1.1, 0.6)
Dermatitis atopic	2 (0.3)	3 (0.9)	3 (0.6)	0	5 (0.4)	3 (0.5)	-0.1 (-1.1, 0.6)

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as 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.

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; incl, including; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; SAE, serious adverse event; SOC, system organ class

Table 23. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, MTPs and Full Periods for ARCADIA 1 & ARCADIA 2

System Organ Class Preferred Term	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Any SAE	10 (5.9)	3 (1.8)	4 (2.4)	2 (1.1)	10 (5.9)	5 (3.0)	6 (3.6)	3 (1.6)
Endocrine disorders (SOC)	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Goitre	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Gastrointestinal disorders (SOC)	1 (0.6)	0	0	0	2 (1.2)	0	0	1 (0.5)
Duodenal ulcer haemorrhage	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Eosinophilic colitis	0	0	0	0	1 (0.6)	0	0	0
Inguinal hernia	0	0	0	0	0	0	0	1 (0.5)
Infections and infestations (SOC)	3 (1.8)	1 (0.6)	1 (0.6)	0	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.5)
Appendicitis	1 (0.6)	0	0	0	1 (0.6)	0	0	1 (0.5)
COVID-19	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Gastroenteritis	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Cellulitis	0	1 (0.6)	0	0	0	1 (0.6)	0	0
Erysipelas	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Injury, poisoning and procedural complications (SOC)	1 (0.6)	1 (0.6)	0	2 (1.1)	1 (0.6)	1 (0.6)	0	2 (1.1)
Comminuted fracture	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Meniscus injury	0	0	0	1 (0.5)	0	0	0	1 (0.5)
Post procedural haematoma	0	0	0	1 (0.5)	0	0	0	1 (0.5)
Splenic injury	0	1 (0.6)	0	0	0	1 (0.6)	0	0
Musculoskeletal and connective tissue disorders (SOC)	3 (1.8)	0	0	0	3 (1.8)	1 (0.6)	1 (0.6)	0
Dupuytren's contracture	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Intervertebral disc protrusion	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)	0	0
Periarthritis	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Groin pain	0	0	0	0	0	0	1 (0.6)	0

System Organ Class Preferred Term	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0
Plasmablastic lymphoma	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Uterine leiomyoma	0	0	0	0	0	1 (0.6)	0	0
Psychiatric disorders (SOC)	0	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)	0
Anxiety	0	1 (0.6)	0	0	0	1 (0.6)	0	0
Psychogenic tremor	0	0	0	0	0	0	1 (0.6)	0
Reproductive system and breast disorders (SOC)	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0
Adenomyosis	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Endometriosis	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0
Asthma	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Pulmonary embolism	0	0	1 (0.6)	0	0	0	1 (0.6)	0

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events 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 36 weeks for MTP and 48 weeks for full period.

Abbreviations: incl, including; MTP, maintenance treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; Nemo, nemolizumab; Q4W, every four weeks; Q8W, every eight weeks; SAE, serious adverse event; SOC, system organ class

Table 24. SAE Narratives for ARCADIA 1 and ARCADIA 2 for the ITP and MTP Treatment Periods (Safety Population)

ITP: Nemolizumab 30 mg Q4W

USUBJID	Age (Years)/ Sex	PT	Start/End Day Severity	Action Taken	AESI	Related to Study Drug	Recovered/ Resolved	Comments
(b) (6)	24/M	Eosinophilic colitis	106/194 Moderate	none	no	yes	yes	History of allergic rhino-conjunctivitis, (+) Lyme disease test
	15/F	Congenital cyst	71/ongoing mild	Study drug interrupted		no	no	Lateral neck congenital cyst.
		Infected cyst	73/91 moderate		yes	no	yes	Treated with antibiotics and surgical excision
			112/ongoing mild			no	no	
	31/F	Intervertebral disc protrusion	20/133 severe	none	no	no	Yes, with sequelae	L4/5 Disc prolapse on MRI, treated with NSAIDs
			168/174 severe				yes	Hospitalized for spinal surgery
	41/M	Abdominal adhesions Small intestinal obstruction	86/99 severe	Study drug interrupted	no	yes	yes	hospitalized for emergency laparotomy, adhesiolysis.
	36/M	Dermatitis exfoliative generalised	86/93 severe	Study drug discontinued	no	yes	yes	hospitalized for erythro- derma of BSA=90%, resolved without treatment. (+) Reactive lymphadenopathy on biopsy of inguinal LN.
	41/M	Dermatitis atopic	84/95 moderate	none	no	no	yes	Hospitalized, treated with sulfur baths daily for AD exacerbation
	24/F	Psychogenic tremor	100/101 moderate	none	no	no	yes	Hospitalized, treated with duloxetine. Neurologic exam unremarkable
	31/M	Dermatitis atopic	32/65 severe	Study drug discontinued	no	no	Yes, with sequelae	Hospitalized, treated for AD exacerbation with TCS, Cyclosporin, cefuroxime
	27/F	Renal colic	61/65 mild	none	no	no	yes	Hospitalized, treated with Lithotripsy
	45/M	Salivary gland cancer (left parotid gland)	21/ongoing severe	Study drug discontinued	no	no	no	incidental finding on CT scan on D 3 for dental implant. Hospitalized for surgical excision of malignant acinar cell carcinoma

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(b) (6)	52/M	Dermatomyositis (suspect)	172/ongoing moderate	none	no	yes	no	CK elevated, moderate, related on D 60, (+) anti-polymyositis /systemic sclerosis-75. Study drug discontinued.
	37/F	Lymphadenopathy, edema peripheral, dermatitis atopic	21/37, moderate	Study drug discontinued	<u>no</u> <u>yes</u> <u>no</u>	yes	yes	Hospitalized, (-) LN biopsy, treated with prednisone for AD exacerbation, diuretics for congestive heart failure, cefuroxime, levothyroxine for hypothyroidism
	31/M	Herpes simplex	25/30 moderate	none	yes	yes	yes	Hospitalized for extensive herpes simplex infection (on previous AD-affected areas without AD exacerbation) and bacterial superinfection. Treated with acyclovir, IV antibiotics.
		Superinfection bacterial		none	yes	yes	yes	
	16/M	Dermatitis atopic	51/ongoing severe	Study drug discontinued	no	no	no	Hospitalized for erythroderma and AD exacerbation (possibly related to COVID-19 vaccine), treated with oral steroids
	65/F	Cholelithiasis	50/51 severe	none	no	no	yes	Hospitalized for chole- cystectomy
	48/F	Intervertebral disc protrusion	32/216 severe	none	no	no	Yes, with sequelae	Hospitalized, underwent surgery on D 77
	18/M	Dermatitis atopic	40/55, moderate	none	no	no	yes	hospitalized for rescue therapy due to AD exacerbation
	15/M	Herpes zoster Ophthalmic herpes zoster	96/112, moderate	<u>none</u> <u>none</u>	<u>no</u> <u>yes</u>	yes	yes	Hospitalized for tingling, eyelid rash, conjunctivitis treated with antibiotics, acyclovir, ganciclovir

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(b) (6)	25/M	Groin pain	101/116 moderate	Study drug interrupted	no	no	yes	History of right femoral head and neck fracture with internal fixation. Hospitalized for Right groin pain, lymphadenopathy, underwent extraction of femoral fixation.
	67/F	Lumbar radiculopathy	104/109 moderate	none	no	no	yes, with sequelae	Hospitalized for back pain MRI, and treated with medications
	52/F	Uterine leiomyoma	73/190 moderate	none	no	no	yes	Hospitalized for total hysterectomy for pelvic pain, abnormal vaginal bleeding

MTP: Nemolizumab 30 mg Q4W to Q4W

USUBJID	Age (Years)/ Sex	PT	Start/End Day Severity	Action Taken	AESI	Related to Study Drug	Recovered/ Resolved	Comments
(b) (6)	14/F	Asthma	226/228 moderate	none	yes	no	yes	History of bronchial hyperactivity, multiple allergies. hospitalized for new onset asthma (per independent adjudication committee)
	16/M	Duodenal ulcer haemorrhage	300/306 moderate	none	no	no	yes	Hospitalized, endoscopy (+) for chronic gastritis and duodenitis and treated for H. pylori.
	12/M	Comminuted fracture	239/240 moderate	none	no	no	Yes, with sequelae	Due to bicycle accident, hospitalized for surgery.
	24/M	Gastroenteritis	292/ ongoing, moderate	Study drug discontinued	no	yes	no	Hospitalized for endoscopy. Not related to SAE of eosinophilic colitis during ITP
	49/F	Adenomyosis	185/189 moderate	none	no	no	yes	Hospitalized, hysterectomy for hypermenorrhoea and dysmenorrhea
	53/F	Periarthritis	267/269 moderate	none	no	no	yes	History of chronic right shoulder pain and synovial cyst. Hospitalized for arthroscopic surgery.
	22/F	COVID-19	201/212 severe	none	yes	no	yes	(not vaccinated against COVID19) Hospitalized for symptomatic COVID19 infection.
	27/M	Appendicitis	289/306 severe	Study drug interrupted	yes	no	yes	Hospitalized for appendectomy
	34/M	Dupuytren's contracture	207/209 severe	none	no	no	yes	Hospitalized for surgical repair of Left fifth digit contracture

MTP: Nemolizumab 30 mg Q4W to Q8W

USUBJID	Age (Years)/ Sex	PT	Start/End Day Severity	Action Taken	AESI	Related to Study Drug	Recovered/ Resolved	Comments
(b) (6)	18/F	Anxiety	319/320 Mild	none	no	no	yes	History of depersonalization/ derealization disorder. hospitalized with an anxiety attack
	15/M	Splenic injury	274/290 severe	Study drug interrupted	no	no	yes	fell from bicycle, hospitalized.
	75/M	Cellulitis	133/141 severe	Study drug discontinued	yes	no	yes	No history of cellulitis. Hospitalized for left lower abdomen cellulitis.

MTP: Nemolizumab 30 mg Q4W to Placebo

USUBJID	Age (Years)/ Sex	PT	Start/End Day Severity	Action taken	AESI	Related to Study Drug	Recovered /Resolved	Comments
(b) (6)	48/M	Pulmonary embolism	236/244 Severe	none	no	yes	yes, with sequelae	History of obesity. Hospitalized treated for pulmonary embolism and deep venous thrombosis
		Pulmonary embolism	274/283 Severe	Study drug discontinued	no	yes		Hospitalized for pulmonary embolism
	32/F	Endometriosis	254/256 Moderate	none	no	no	yes	Hospitalized for hysteroscopy, laparoscopy
	63/F	Erysipelas (Left leg)	196/224 Moderate	none	yes	no	yes	Hospitalized treated with cefuroxime
		Struma multinodosa	207/218 Severe	none	no	no	yes	Goiter treated with metamizole. Atrial fibrillation treated with edoxaban
	72/M	Plasmablastic lymphoma	286/ongoing severe	Study drug discontinued	no	no	no	History of PUVA treatment. Rhinoscopy and nasal polypectomy, (+) EBV in neoplasm. Treated with doxorubicin, cyclophosphamide, vincristine.
		COVID-19	354/363 severe	none	yes	no	yes	Hospitalized (follow up period) with febrile neutropenia and COVID19 infection. Treated with levofloxacin and filgrastim.

Source: M 2.7.4, Table 16 and ARCADIA 1 and ARCADIA 2 Narratives (Sec. 14.3.3) of CSRs.

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; COVID-19, coronavirus disease of 2019; CT, computed tomography; D, day; EBV, Epstein-Barr virus; EEG, electroencephalogram; F, female; M, male; MRI, magnetic resonance imaging; NSTEMI, non-ST-elevation myocardial infarction; PT, preferred term; PUVA, S psoralen plus ultraviolet; AE, serious adverse event; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SCC, squamous cell carcinoma; SVT, supraventricular tachycardia; TCS, Treacher Collins Syndrome; US, ultra-sound; UTI, urinary tract infection; XR, extended release

During the P2-DR trial, the following SAEs were reported for subjects treated with nemolizumab:

- Nemolizumab 10 mg Q4W: dermatitis atopic (1), post-concussion syndrome/post-traumatic amnesic disorders (1), death (1) [asthenia/staphylococcal sepsis/aspiration pneumonia/cardiopulmonary arrest].
- Nemolizumab 30 mg Q4W: Cellulitis (1), dermatitis atopic (1).
- Nemolizumab 90 mg Q4W: Septic shock (1) [subject with history of endocarditis and (+) blood culture for methicillin sensitive staphylococcus aureus], urinary tract infection (1).

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

During the ITP, adverse events leading to discontinuation from treatment (AELDs) were reported at a similar overall frequency for the nemolizumab group (2.6%) compared to the placebo group (2.7%). AELDs reported in >1 subject in the nemolizumab group included lymphadenopathy (2 [0.2%] versus 0), peripheral edema (2 [0.2%] versus 0), and dermatitis atopic (19 [1.7%] versus 15 [2.6%]) for subject in the nemolizumab group compared to the placebo group, respectively. The results are consistent with the AELDs reported by the narrow FMQ.

During the MTP, AELDs were reported at a similar overall frequency in the nemolizumab Q4W/Q4W group at 4/170 (2.4%), compared to Q4W/Q8W at 5/167 (3.0%), Q4W/PBO at 5/168 (3.0%), and PBO/PBO at 4/184 (2.2%) groups, respectively. Dermatitis atopic was the only adverse event leading to discontinuation of treatment (AELD) reported for >1 subject in any group. The results are consistent with the AELDs reported by the narrow FMQs.

A summary of AELDs for the ITP and MTP are presented in the following tables (Table 25 and Table 26).

Table 25. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

System Organ Class Preferred Term	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab		Nemolizumab		Nemolizumab		Nemolizumab 30 mg vs. Placebo Risk Difference % (95% CI)
	30 mg N=616 n (%)	Placebo N=321 n (%)	30 mg N=519 n (%)	Placebo N=263 n (%)	30 mg N=1135 n (%)	Placebo N=584 n (%)	
Any AE leading to discontinuation	11 (1.8)	13 (4.0)	18 (3.5)	3 (1.1)	29 (2.6)	16 (2.7)	-0.2 (-2.0, 1.3)
Blood and lymphatic system disorders (SOC)	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Lymphadenopathy	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Eye disorders (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Eyelid oedema	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
General disorders and administration site conditions (SOC)	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Oedema peripheral	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Infections and infestations (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
COVID-19	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Investigations (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Blood creatine phosphokinase increased	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Prostate cancer	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Salivary gland cancer	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Nervous system disorders (SOC)	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Bell's palsy	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Psychiatric disorders (SOC)	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Depression	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Panic attack	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Restlessness	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	2 (0.4)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Asthma	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Nasal oedema	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)

System Organ Class Preferred Term	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab		Nemolizumab		Nemolizumab		Nemolizumab
	30 mg N=616 n (%)	Placebo N=321 n (%)	30 mg N=519 n (%)	Placebo N=263 n (%)	30 mg N=1135 n (%)	Placebo N=584 n (%)	30 mg vs. Placebo Risk Difference % (95% CI)
Skin and subcutaneous tissue disorders (SOC)	10 (1.6)	13 (4.0)	10 (1.9)	3 (1.1)	20 (1.8)	16 (2.7)	-1.0 (-2.8, 0.4)
Dermatitis	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Diffuse alopecia	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Alopecia areata	0	0	0	1 (0.4)	0	1 (0.2)	-0.2 (-1.0, 0.2)
Dermatitis atopic	10 (1.6)	13 (4.0)	9 (1.7)	2 (0.8)	19 (1.7)	15 (2.6)	-0.9 (-2.6, 0.5)

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs occurring after the first administration of study treatment until the last study visit.

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; incl, including; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; SOC, system organ class

Table 26. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, MTPs for ARCADIA 1 & ARCADIA 2

System Organ Class Preferred Term	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Any AE leading to discontinuation	4 (2.4)	5 (3.0)	5 (3.0)	4 (2.2)	4 (2.4)	5 (3.0)	5 (3.0)	4 (2.2)
Infections and infestations (SOC)	1 (0.6)	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0	0
Gastroenteritis	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Cellulitis	0	1 (0.6)	0	0	0	1 (0.6)	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Plasmablastic lymphoma	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0	1 (0.6)	0
Asthma	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Pulmonary embolism	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Skin and subcutaneous tissue disorders (SOC)	2 (1.2)	4 (2.4)	3 (1.8)	4 (2.2)	2 (1.2)	4 (2.4)	3 (1.8)	4 (2.2)
Dermatitis atopic	2 (1.2)	4 (2.4)	3 (1.8)	4 (2.2)	2 (1.2)	4 (2.4)	3 (1.8)	4 (2.2)

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events occurring after the first administration of study treatment until the last study visit.

Duration is 36 weeks for MTP and 48 weeks for full period.

Abbreviations: AE, adverse event; incl, including; MTP, maintenance treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; Nemo, nemolizumab; Q4W, every four weeks; Q8W, every eight weeks; SOC, system organ class

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

During the ITP, TEAEs were reported at a similar overall frequency in the nemolizumab group for 521/1135 (45.9%) subjects, compared to the placebo group for 263/584 (45.0%) subjects. TEAEs reported by $\geq 1\%$ of subjects in the nemolizumab group (and at a greater frequency than the placebo group) include the following PTs:

- Dermatitis atopic (9.9% versus 8.4%)
- Headache (4.1% versus 3.6%)
- Asthma (3.9% versus 3.4%)
- Back pain (1.3% versus 1.2%)
- Dyspnea (1.1% versus 0.9%)
- Urticaria (1.1% versus 0.3%)
- Nausea (1.1% versus 0.5%)
- Fatigue (1.1% versus 0.5%)
- Arthralgia, (1.1% versus 0.2%)
- Urinary tract infection (1.1% versus 0.9%)
- Myalgia (1.0% versus 0.2%)

During the ITP, TEAEs identified by narrow FMQ were consistent with those listed above. A summary of TEAEs reported in $\geq 1\%$ of subjects in the nemolizumab group, and TEAEs by narrow FMQ are presented in the following tables ([Table 27](#) and [Table 28](#)).

Table 27. Patients With Common Adverse Events Occurring at ≥1% Frequency, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Preferred Term	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	
Any AE	306 (49.7)	146 (45.5)	215 (41.4)	117 (44.5)	521 (45.9)	263 (45.0)	0.9 (4.1, 5.8)
Dermatitis atopic	75 (12.2)	34 (10.6)	37 (7.1)	15 (5.7)	112 (9.9)	49 (8.4)	1.5 (1.5, 4.2)
Arthralgia	2 (0.3)	1 (0.3)	10 (1.9)	0	12 (1.1)	1 (0.2)	0.9 (0.0, 1.7) *
Myalgia	7 (1.1)	0	4 (0.8)	1 (0.4)	11 (1.0)	1 (0.2)	0.8 (0.1, 1.6)
Urticaria	4 (0.6)	1 (0.3)	8 (1.5)	1 (0.4)	12 (1.1)	2 (0.3)	0.7 (0.3, 1.6)
Nausea	8 (1.3)	1 (0.3)	5 (1.0)	2 (0.8)	13 (1.1)	3 (0.5)	0.6 (0.4, 1.5)
Fatigue	6 (1.0)	2 (0.6)	6 (1.2)	1 (0.4)	12 (1.1)	3 (0.5)	0.5 (0.5, 1.4)
Headache	28 (4.5)	11 (3.4)	18 (3.5)	10 (3.8)	46 (4.1)	21 (3.6)	0.5 (1.6, 2.3)
Asthma	33 (5.4)	13 (4.0)	11 (2.1)	7 (2.7)	44 (3.9)	20 (3.4)	0.5 (1.6, 2.2)
Oedema peripheral	2 (0.3)	1 (0.3)	7 (1.3)	1 (0.4)	9 (0.8)	2 (0.3)	0.5 (0.5, 1.2)
Dyspnoea	7 (1.1)	5 (1.6)	6 (1.2)	0	13 (1.1)	5 (0.9)	0.3 (0.9, 1.2)
Urinary tract infection	9 (1.5)	3 (0.9)	4 (0.8)	2 (0.8)	13 (1.1)	5 (0.9)	0.3 (0.9, 1.2)
Hypertension	7 (1.1)	2 (0.6)	2 (0.4)	1 (0.4)	9 (0.8)	3 (0.5)	0.3 (0.8, 1.1)
Back pain	11 (1.8)	4 (1.2)	4 (0.8)	3 (1.1)	15 (1.3)	7 (1.2)	0.1 (1.2, 1.2)
Peak expiratory flow rate decreased	5 (0.8)	1 (0.3)	4 (0.8)	3 (1.1)	9 (0.8)	4 (0.7)	0.1 (1.0, 0.9)
Skin infection	7 (1.1)	2 (0.6)	1 (0.2)	2 (0.8)	8 (0.7)	4 (0.7)	0.0 (1.1, 0.8)
Conjunctivitis	2 (0.3)	0	3 (0.6)	3 (1.1)	5 (0.4)	3 (0.5)	0.1 (1.1, 0.6)
Cough	8 (1.3)	5 (1.6)	4 (0.8)	2 (0.8)	12 (1.1)	7 (1.2)	0.1 (1.5, 0.9)
Oral herpes	4 (0.6)	2 (0.6)	4 (0.8)	3 (1.1)	8 (0.7)	5 (0.9)	0.2 (1.3, 0.7)
Pruritus	1 (0.2)	0	2 (0.4)	3 (1.1)	3 (0.3)	3 (0.5)	0.2 (1.3, 0.4)
COVID-19	10 (1.6)	6 (1.9)	14 (2.7)	8 (3.0)	24 (2.1)	14 (2.4)	0.3 (2.0, 1.1)
Diarrhoea	8 (1.3)	3 (0.9)	8 (1.5)	7 (2.7)	16 (1.4)	10 (1.7)	0.3 (1.8, 0.9)
Rhinitis	3 (0.5)	2 (0.6)	3 (0.6)	3 (1.1)	6 (0.5)	5 (0.9)	0.3 (1.5, 0.5)
Gastroenteritis	4 (0.6)	1 (0.3)	0	3 (1.1)	4 (0.4)	4 (0.7)	0.3 (1.4, 0.3)
Blood creatine phosphokinase increased	3 (0.5)	4 (1.2)	4 (0.8)	2 (0.8)	7 (0.6)	6 (1.0)	0.4 (1.7, 0.4)

	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		Nemolizumab 30 mg
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Versus Placebo Risk Difference % (95% CI)
Preferred Term							
Conjunctivitis allergic	6 (1.0)	4 (1.2)	1 (0.2)	2 (0.8)	7 (0.6)	6 (1.0)	0.4 (1.7, 0.4)
Alopecia areata	0	0	1 (0.2)	3 (1.1)	1 (0.1)	3 (0.5)	0.4 (1.4, 0.1)
Rhinitis allergic	3 (0.5)	4 (1.2)	1 (0.2)	1 (0.4)	4 (0.4)	5 (0.9)	0.5 (1.7, 0.2)
Herpes simplex	2 (0.3)	4 (1.2)	2 (0.4)	2 (0.8)	4 (0.4)	6 (1.0)	0.7 (1.9, 0.1)
Viral upper respiratory tract infection	1 (0.2)	4 (1.2)	1 (0.2)	1 (0.4)	2 (0.2)	5 (0.9)	0.7 (1.8, 0.0) *
Nasopharyngitis	9 (1.5)	8 (2.5)	19 (3.7)	12 (4.6)	28 (2.5)	20 (3.4)	1.0 (2.9, 0.7)
Upper respiratory tract infection	9 (1.5)	14 (4.4)	6 (1.2)	5 (1.9)	15 (1.3)	19 (3.3)	1.9 (3.8, 0.5) *

Source: CDS Reviewer, adae.xpt; Software: R

*95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AEs occurring after the first administration of study treatment until the last study visit.

Initial treatment period duration is 16 weeks.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; ITP, initial treatment period; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event

Table 28. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

System Organ Class FMQ (Narrow)	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
Blood and lymphatic system disorders (SOC)							
Leukopenia	3 (0.5)	0	0	0	3 (0.3)	0	0.3 (-0.4, 0.8)
Thrombocytopenia	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Anemia	2 (0.3)	0	0	1 (0.4)	2 (0.2)	1 (0.2)	0.0 (-0.8, 0.5)
Cardiac disorders (SOC)							
Systemic hypertension	9 (1.5)	3 (0.9)	2 (0.4)	1 (0.4)	11 (1.0)	4 (0.7)	0.3 (-0.8, 1.2)
Arrhythmia	1 (0.2)	0	2 (0.4)	0	3 (0.3)	0	0.3 (-0.4, 0.8)
Palpitations	1 (0.2)	0	2 (0.4)	0	3 (0.3)	0	0.3 (-0.4, 0.8)
Tachycardia	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Cardiac conduction disturbance	1 (0.2)	0	2 (0.4)	1 (0.4)	3 (0.3)	1 (0.2)	0.1 (-0.7, 0.6)
Heart failure	0	0	1 (0.2)	1 (0.4)	1 (0.1)	1 (0.2)	-0.1 (-0.9, 0.3)
Ear and labyrinth disorders (SOC)							
Vertigo	0	2 (0.6)	0	1 (0.4)	0	3 (0.5)	-0.5 (-1.5, -0.2) *
Endocrine disorders (SOC)							
Hyperglycemia	1 (0.2)	0	0	1 (0.4)	1 (0.1)	1 (0.2)	-0.1 (-0.9, 0.3)
Eye disorders (SOC)							
Glaucoma	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Gastrointestinal disorders (SOC)							
Abdominal pain	10 (1.6)	1 (0.3)	2 (0.4)	1 (0.4)	12 (1.1)	2 (0.3)	0.7 (-0.3, 1.6)
Nausea	8 (1.3)	1 (0.3)	5 (1.0)	2 (0.8)	13 (1.1)	3 (0.5)	0.6 (-0.4, 1.5)
Vomiting	5 (0.8)	1 (0.3)	0	0	5 (0.4)	1 (0.2)	0.3 (-0.5, 0.9)
Constipation	2 (0.3)	0	1 (0.2)	0	3 (0.3)	0	0.3 (-0.4, 0.8)
Dry mouth	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Dyspepsia	5 (0.8)	2 (0.6)	1 (0.2)	1 (0.4)	6 (0.5)	3 (0.5)	0.0 (-1.0, 0.7)
Diarrhea	8 (1.3)	3 (0.9)	8 (1.5)	7 (2.7)	16 (1.4)	10 (1.7)	-0.3 (-1.8, 0.9)

System Organ Class FMQ (Narrow)	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)							
Fatigue	10 (1.6)	2 (0.6)	10 (1.9)	1 (0.4)	20 (1.8)	3 (0.5)	1.2 (0.1, 2.3) *
Peripheral edema	3 (0.5)	1 (0.3)	9 (1.7)	1 (0.4)	12 (1.1)	2 (0.3)	0.7 (-0.3, 1.6)
Local administration reaction	13 (2.1)	4 (1.2)	7 (1.3)	4 (1.5)	20 (1.8)	8 (1.4)	0.4 (-1.0, 1.6)
Decreased appetite	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Dizziness	5 (0.8)	2 (0.6)	2 (0.4)	2 (0.8)	7 (0.6)	4 (0.7)	-0.1 (-1.2, 0.7)
Pyrexia	6 (1.0)	3 (0.9)	4 (0.8)	3 (1.1)	10 (0.9)	6 (1.0)	-0.1 (-1.4, 0.8)
Hepatobiliary disorders (SOC)							
Hepatic injury	1 (0.2)	1 (0.3)	3 (0.6)	1 (0.4)	4 (0.4)	2 (0.3)	0.0 (-0.9, 0.6)
Immune system disorders (SOC)							
Hypersensitivity	1 (0.2)	0	1 (0.2)	0	2 (0.2)	0	0.2 (-0.5, 0.6)
Anaphylactic reaction ⁴	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Angioedema ⁵	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Infections and infestations (SOC)							
Bacterial infection	52 (8.4)	14 (4.4)	20 (3.9)	11 (4.2)	72 (6.3)	25 (4.3)	2.1 (-0.3, 4.2)
Fungal infection	3 (0.5)	1 (0.3)	3 (0.6)	0	6 (0.5)	1 (0.2)	0.4 (-0.5, 1.0)
Pneumonia	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Purulent material	2 (0.3)	2 (0.6)	1 (0.2)	1 (0.4)	3 (0.3)	3 (0.5)	-0.2 (-1.3, 0.4)
Viral infection	31 (5.0)	25 (7.8)	30 (5.8)	19 (7.2)	61 (5.4)	44 (7.5)	-2.2 (-4.9, 0.2)
Nasopharyngitis	25 (4.1)	29 (9.0)	30 (5.8)	21 (8.0)	55 (4.8)	50 (8.6)	-3.7 (-6.5, -1.3) *
Metabolism and nutrition disorders (SOC)							
Lipid disorder	5 (0.8)	3 (0.9)	4 (0.8)	1 (0.4)	9 (0.8)	4 (0.7)	0.1 (-1.0, 0.9)

⁴ Subject (b) (6) in trial ARCADIA 2 was reported with AESI/AELDs of peripheral edema and nasal edema [initially considered as an acute allergic reaction] with no signs or symptoms of anaphylaxis or angioedema; deemed as related to the study drug, was treated with corticosteroids and recovered/resolved.

⁵ Subject (b) (6) in trial ARCADIA 2 with history of multiple food allergies/urticaria/angioedema was reported with an AESI of angioedema of hands [after eating a coconut cake]; deemed unrelated to study drug and resolved after receiving treatment with antihistamines, corticosteroids, and epinephrine. Subject withdrew from the trial.

System Organ Class FMQ (Narrow)	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
Musculoskeletal and connective tissue disorders (SOC)							
Arthralgia	2 (0.3)	1 (0.3)	10 (1.9)	0	12 (1.1)	1 (0.2)	0.9 (0.0, 1.7) *
Myalgia	7 (1.1)	0	4 (0.8)	1 (0.4)	11 (1.0)	1 (0.2)	0.8 (-0.1, 1.6)
Fracture	2 (0.3)	1 (0.3)	3 (0.6)	1 (0.4)	5 (0.4)	2 (0.3)	0.1 (-0.8, 0.7)
Arthritis	5 (0.8)	1 (0.3)	1 (0.2)	2 (0.8)	6 (0.5)	3 (0.5)	0.0 (-1.0, 0.7)
Gout	1 (0.2)	0	1 (0.2)	1 (0.4)	2 (0.2)	1 (0.2)	0.0 (-0.8, 0.5)
Tendinopathy	2 (0.3)	1 (0.3)	0	0	2 (0.2)	1 (0.2)	0.0 (-0.8, 0.5)
Back pain	11 (1.8)	5 (1.6)	4 (0.8)	3 (1.1)	15 (1.3)	8 (1.4)	-0.0 (-1.5, 1.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)							
Malignancy	1 (0.2)	1 (0.3)	1 (0.2)	0	2 (0.2)	1 (0.2)	0.0 (-0.8, 0.5)
Nervous system disorders (SOC)							
Headache	31 (5.0)	12 (3.7)	21 (4.0)	10 (3.8)	52 (4.6)	22 (3.8)	0.8 (-1.3, 2.7)
Somnolence	3 (0.5)	0	1 (0.2)	1 (0.4)	4 (0.4)	1 (0.2)	0.2 (-0.6, 0.8)
Dysgeusia	1 (0.2)	0	0	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Tremor	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Syncope	1 (0.2)	0	1 (0.2)	1 (0.4)	2 (0.2)	1 (0.2)	0.0 (-0.8, 0.5)
Paresthesia	1 (0.2)	2 (0.6)	0	1 (0.4)	1 (0.1)	3 (0.5)	-0.4 (-1.4, 0.1)
Psychiatric disorders (SOC)							
Anxiety	4 (0.6)	1 (0.3)	2 (0.4)	1 (0.4)	6 (0.5)	2 (0.3)	0.2 (-0.7, 0.9)
Depression	4 (0.6)	1 (0.3)	3 (0.6)	2 (0.8)	7 (0.6)	3 (0.5)	0.1 (-0.9, 0.8)
Irritability	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Study agent abuse potential	0	0	1 (0.2)	1 (0.4)	1 (0.1)	1 (0.2)	-0.1 (-0.9, 0.3)
Insomnia	1 (0.2)	2 (0.6)	2 (0.4)	1 (0.4)	3 (0.3)	3 (0.5)	-0.2 (-1.3, 0.4)
Renal and urinary disorders (SOC)							
Renal & urinary tract infection	12 (1.9)	4 (1.2)	5 (1.0)	3 (1.1)	17 (1.5)	7 (1.2)	0.3 (-1.1, 1.4)
Reproductive system and breast disorders (SOC)							
Abnormal uterine bleeding	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)

System Organ Class FMQ (Narrow)	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n (%)	Placebo N=321 n (%)	Nemolizumab 30 mg N=519 n (%)	Placebo N=263 n (%)	Nemolizumab 30 mg N=1135 n (%)	Placebo N=584 n (%)	Nemolizumab 30 mg Versus Placebo Risk Difference % (95% CI)
Respiratory, thoracic and mediastinal disorders (SOC)							
Bronchospasm	34 (5.5)	13 (4.0)	11 (2.1)	7 (2.7)	45 (4.0)	20 (3.4)	0.5 (-1.5, 2.3)
Dyspnea	9 (1.5)	5 (1.6)	6 (1.2)	0	15 (1.3)	5 (0.9)	0.5 (-0.8, 1.5)
Cough	8 (1.3)	6 (1.9)	4 (0.8)	2 (0.8)	12 (1.1)	8 (1.4)	-0.3 (-1.7, 0.7)
Skin and subcutaneous tissue disorders (SOC)							
Rash	20 (3.2)	8 (2.5)	17 (3.3)	2 (0.8)	37 (3.3)	10 (1.7)	1.5 (-0.1, 3.0)
Urticaria	7 (1.1)	1 (0.3)	10 (1.9)	1 (0.4)	17 (1.5)	2 (0.3)	1.2 (0.1, 2.1) *
Erythema	3 (0.5)	2 (0.6)	6 (1.2)	2 (0.8)	9 (0.8)	4 (0.7)	0.1 (-1.0, 0.9)
Alopecia	4 (0.6)	2 (0.6)	5 (1.0)	4 (1.5)	9 (0.8)	6 (1.0)	-0.2 (-1.5, 0.7)
Pruritus	2 (0.3)	1 (0.3)	3 (0.6)	5 (1.9)	5 (0.4)	6 (1.0)	-0.6 (-1.8, 0.2)
Vascular disorders (SOC)							
Hemorrhage	6 (1.0)	3 (0.9)	8 (1.5)	2 (0.8)	14 (1.2)	5 (0.9)	0.4 (-0.8, 1.4)
Thrombosis	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)
Thrombosis venous	0	0	1 (0.2)	0	1 (0.1)	0	0.1 (-0.6, 0.5)

Source: CDS Reviewer, adae.xpt; Software: R

* 95% confidence interval excludes zero.

Treatment-emergent adverse events defined as AEs occurring after the first administration of study treatment until the last study visit.

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)"

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; incl, including; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

During the MTP, TEAEs were reported at a similar overall frequency in the following treatment groups: Q4W/Q4W group at 91/170 (53.5%), Q4W/Q8W group at 90/167 (53.9%), Q4W/PBO group at 98/168 (58.3%), and PBO/PBO group at 92/184 (50.0%), respectively. In general, TEAEs reported by $\geq 1\%$ of subjects in any treatment group did not identify clinically significant differences between treatment groups and were consistent with the TEAEs reported by the narrow FMQ, as summarized in the following tables (Table 29 and Table 30).

Table 29. Patients With Common Adverse Events Occurring at $\geq 1\%$ Frequency in Any Group, Safety Population, MTPs and Full Periods for ARCADIA 1 & ARCADIA 2

Preferred Term	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Any AE	91 (53.5)	90 (53.9)	98 (58.3)	92 (50.0)	113 (66.5)	112 (67.1)	121 (72.0)	114 (62.0)
Nasopharyngitis	14 (8.2)	8 (4.8)	12 (7.1)	12 (6.5)	17 (10.0)	10 (6.0)	15 (8.9)	14 (7.6)
COVID-19	13 (7.6)	13 (7.8)	19 (11.3)	16 (8.7)	16 (9.4)	15 (9.0)	23 (13.7)	21 (11.4)
Dermatitis atopic	13 (7.6)	11 (6.6)	18 (10.7)	15 (8.2)	15 (8.8)	15 (9.0)	20 (11.9)	16 (8.7)
Asthma	6 (3.5)	6 (3.6)	6 (3.6)	5 (2.7)	12 (7.1)	8 (4.8)	10 (6.0)	8 (4.3)
Headache	6 (3.5)	7 (4.2)	3 (1.8)	4 (2.2)	12 (7.1)	10 (6.0)	11 (6.5)	11 (6.0)
Abdominal pain upper	4 (2.4)	1 (0.6)	0	2 (1.1)	4 (2.4)	2 (1.2)	1 (0.6)	3 (1.6)
Diarrhoea	4 (2.4)	3 (1.8)	6 (3.6)	2 (1.1)	7 (4.1)	4 (2.4)	8 (4.8)	4 (2.2)
Dyspnoea	4 (2.4)	1 (0.6)	3 (1.8)	0	7 (4.1)	1 (0.6)	4 (2.4)	0
Upper respiratory tract infection	4 (2.4)	5 (3.0)	10 (6.0)	11 (6.0)	5 (2.9)	9 (5.4)	11 (6.5)	15 (8.2)
Gastroenteritis	3 (1.8)	2 (1.2)	1 (0.6)	0	3 (1.8)	2 (1.2)	1 (0.6)	0
Herpes dermatitis	3 (1.8)	2 (1.2)	1 (0.6)	0	3 (1.8)	2 (1.2)	2 (1.2)	0
Nausea	3 (1.8)	0	1 (0.6)	2 (1.1)	5 (2.9)	1 (0.6)	4 (2.4)	3 (1.6)
Oral herpes	3 (1.8)	3 (1.8)	1 (0.6)	0	3 (1.8)	5 (3.0)	1 (0.6)	2 (1.1)
Pharyngitis	3 (1.8)	2 (1.2)	1 (0.6)	2 (1.1)	4 (2.4)	3 (1.8)	1 (0.6)	2 (1.1)
Pyrexia	3 (1.8)	3 (1.8)	0	3 (1.6)	4 (2.4)	4 (2.4)	0	5 (2.7)
Urinary tract infection	3 (1.8)	3 (1.8)	1 (0.6)	2 (1.1)	3 (1.8)	5 (3.0)	2 (1.2)	4 (2.2)
Angular cheilitis	2 (1.2)	0	0	0	2 (1.2)	0	0	0
Asymptomatic COVID-19	2 (1.2)	3 (1.8)	4 (2.4)	2 (1.1)	3 (1.8)	3 (1.8)	5 (3.0)	3 (1.6)
Blood creatine phosphokinase increased	2 (1.2)	3 (1.8)	3 (1.8)	2 (1.1)	5 (2.9)	4 (2.4)	3 (1.8)	4 (2.2)
Conjunctivitis allergic	2 (1.2)	1 (0.6)	1 (0.6)	0	2 (1.2)	1 (0.6)	3 (1.8)	1 (0.5)
Cough	2 (1.2)	1 (0.6)	4 (2.4)	1 (0.5)	4 (2.4)	3 (1.8)	6 (3.6)	1 (0.5)

Preferred Term	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Depression	2 (1.2)	0	0	2 (1.1)	2 (1.2)	1 (0.6)	1 (0.6)	2 (1.1)
Duodenal ulcer	2 (1.2)	0	0	0	2 (1.2)	0	0	0
Gastroesophageal reflux disease	2 (1.2)	0	0	0	2 (1.2)	0	1 (0.6)	1 (0.5)
Hypertension	2 (1.2)	0	2 (1.2)	0	3 (1.8)	2 (1.2)	2 (1.2)	1 (0.5)
Influenza	2 (1.2)	0	0	0	2 (1.2)	0	1 (0.6)	0
Neck pain	2 (1.2)	1 (0.6)	0	0	2 (1.2)	1 (0.6)	0	0
Oropharyngeal pain	2 (1.2)	3 (1.8)	0	0	2 (1.2)	3 (1.8)	0	1 (0.5)
Peak expiratory flow rate decreased	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.5)	4 (2.4)	3 (1.8)	2 (1.2)	1 (0.5)
Tonsillitis	2 (1.2)	1 (0.6)	1 (0.6)	0	2 (1.2)	2 (1.2)	1 (0.6)	0
Tooth abscess	2 (1.2)	0	0	0	2 (1.2)	0	0	0
Urticaria	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.5)	3 (1.8)	2 (1.2)	2 (1.2)	2 (1.1)
Vomiting	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.5)	2 (1.2)	1 (0.6)	2 (1.2)	2 (1.1)
Wheezing	2 (1.2)	0	1 (0.6)	1 (0.5)	3 (1.8)	0	1 (0.6)	1 (0.5)
Abdominal pain	1 (0.6)	1 (0.6)	0	0	1 (0.6)	2 (1.2)	2 (1.2)	0
Acne	1 (0.6)	6 (3.6)	1 (0.6)	1 (0.5)	2 (1.2)	8 (4.8)	1 (0.6)	3 (1.6)
Anxiety	1 (0.6)	1 (0.6)	0	1 (0.5)	2 (1.2)	1 (0.6)	0	1 (0.5)
Asthenia	1 (0.6)	1 (0.6)	0	0	1 (0.6)	2 (1.2)	1 (0.6)	0
Back pain	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.1)	3 (1.8)	3 (1.8)	2 (1.2)	5 (2.7)
Bronchitis	1 (0.6)	1 (0.6)	0	0	1 (0.6)	3 (1.8)	0	1 (0.5)
Constipation	1 (0.6)	0	0	0	3 (1.8)	0	0	0
Dyspepsia	1 (0.6)	1 (0.6)	2 (1.2)	0	1 (0.6)	1 (0.6)	2 (1.2)	0
Folliculitis	1 (0.6)	3 (1.8)	2 (1.2)	2 (1.1)	2 (1.2)	3 (1.8)	4 (2.4)	3 (1.6)
Gastrointestinal infection	1 (0.6)	2 (1.2)	0	1 (0.5)	1 (0.6)	2 (1.2)	0	1 (0.5)
Herpes simplex	1 (0.6)	0	1 (0.6)	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.6)	4 (2.2)
Hyperlipidaemia	1 (0.6)	0	1 (0.6)	0	1 (0.6)	2 (1.2)	1 (0.6)	0
Injection site irritation	1 (0.6)	0	0	0	2 (1.2)	0	0	0
Intervertebral disc protrusion	1 (0.6)	1 (0.6)	0	0	1 (0.6)	2 (1.2)	0	0
Joint dislocation	1 (0.6)	0	0	0	2 (1.2)	0	0	0
Migraine	1 (0.6)	1 (0.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	4 (2.4)	1 (0.5)
Oedema peripheral	1 (0.6)	0	0	0	1 (0.6)	1 (0.6)	2 (1.2)	0
Pharyngitis streptococcal	1 (0.6)	0	1 (0.6)	0	1 (0.6)	1 (0.6)	2 (1.2)	0
Pruritus	1 (0.6)	0	2 (1.2)	1 (0.5)	1 (0.6)	0	2 (1.2)	3 (1.6)

Preferred Term	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Rhinitis allergic	1 (0.6)	0	2 (1.2)	2 (1.1)	1 (0.6)	1 (0.6)	2 (1.2)	4 (2.2)
Skin laceration	1 (0.6)	0	0	0	1 (0.6)	0	0	2 (1.1)
Vaccination site pain	1 (0.6)	1 (0.6)	3 (1.8)	0	1 (0.6)	3 (1.8)	3 (1.8)	2 (1.1)
Viral upper respiratory tract infection	1 (0.6)	1 (0.6)	2 (1.2)	4 (2.2)	1 (0.6)	1 (0.6)	2 (1.2)	6 (3.3)
Alopecia	0	0	0	0	3 (1.8)	1 (0.6)	0	0
Arthralgia	0	2 (1.2)	1 (0.6)	1 (0.5)	3 (1.8)	4 (2.4)	2 (1.2)	1 (0.5)
Arthritis	0	0	2 (1.2)	0	0	1 (0.6)	2 (1.2)	1 (0.5)
Aspartate aminotransferase increased	0	1 (0.6)	1 (0.6)	0	0	2 (1.2)	2 (1.2)	0
Blood pressure increased	0	0	0	2 (1.1)	0	0	0	2 (1.1)
Blood triglycerides increased	0	1 (0.6)	0	0	0	1 (0.6)	0	2 (1.1)
Cellulitis	0	3 (1.8)	1 (0.6)	0	0	3 (1.8)	2 (1.2)	0
Chest discomfort	0	1 (0.6)	0	0	0	3 (1.8)	0	1 (0.5)
Conjunctivitis	0	1 (0.6)	0	2 (1.1)	0	2 (1.2)	0	3 (1.6)
Cystitis	0	0	0	0	2 (1.2)	1 (0.6)	1 (0.6)	0
Dizziness	0	1 (0.6)	0	2 (1.1)	1 (0.6)	1 (0.6)	0	2 (1.1)
Dry eye	0	0	3 (1.8)	0	0	0	3 (1.8)	0
Dysmenorrhoea	0	0	0	0	0	0	2 (1.2)	0
Face oedema	0	1 (0.6)	1 (0.6)	0	0	2 (1.2)	1 (0.6)	0
Fatigue	0	1 (0.6)	1 (0.6)	1 (0.5)	2 (1.2)	2 (1.2)	3 (1.8)	3 (1.6)
Foot fracture	0	0	0	0	0	0	2 (1.2)	0
Foreign body in eye	0	0	1 (0.6)	0	0	0	2 (1.2)	0
Hand fracture	0	0	0	0	0	2 (1.2)	0	0
Herpes zoster	0	0	0	0	1 (0.6)	0	2 (1.2)	0
Hordeolum	0	0	0	2 (1.1)	0	0	0	2 (1.1)
Inguinal hernia	0	0	0	1 (0.5)	0	0	0	2 (1.1)
Injection site haematoma	0	0	0	0	0	0	2 (1.2)	0
Injection site pain	0	0	0	0	1 (0.6)	2 (1.2)	0	0
Insomnia	0	1 (0.6)	1 (0.6)	0	0	1 (0.6)	2 (1.2)	0
Leukopenia	0	0	0	0	0	2 (1.2)	0	0
Ligament sprain	0	3 (1.8)	0	0	0	3 (1.8)	0	1 (0.5)
Lymphadenopathy	0	0	1 (0.6)	0	0	0	3 (1.8)	0

	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Preferred Term								
Muscle rupture	0	0	0	1 (0.5)	0	0	0	2 (1.1)
Myalgia	0	1 (0.6)	0	1 (0.5)	1 (0.6)	2 (1.2)	0	2 (1.1)
Nasal congestion	0	1 (0.6)	1 (0.6)	0	0	2 (1.2)	1 (0.6)	0
Neutropenia	0	2 (1.2)	0	0	0	2 (1.2)	0	0
Pain in extremity	0	0	0	0	2 (1.2)	1 (0.6)	0	1 (0.5)
Palpitations	0	0	0	0	2 (1.2)	0	0	0
Pelvic pain	0	2 (1.2)	0	0	1 (0.6)	2 (1.2)	0	0
Rhinitis	0	2 (1.2)	1 (0.6)	1 (0.5)	2 (1.2)	4 (2.4)	1 (0.6)	1 (0.5)
Rhinorrhoea	0	2 (1.2)	1 (0.6)	1 (0.5)	0	2 (1.2)	2 (1.2)	1 (0.5)
Sinusitis	0	3 (1.8)	4 (2.4)	1 (0.5)	1 (0.6)	5 (3.0)	6 (3.6)	3 (1.6)
Sinusitis bacterial	0	2 (1.2)	1 (0.6)	0	0	2 (1.2)	1 (0.6)	0
Somnolence	0	0	0	1 (0.5)	0	0	1 (0.6)	2 (1.1)
Toothache	0	1 (0.6)	1 (0.6)	1 (0.5)	0	2 (1.2)	2 (1.2)	1 (0.5)

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events occurring after the first administration of study treatment until the last study visit.

Duration is 36 weeks for MTP and 48 weeks for full period.

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; MTP, maintenance treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; Nemo, nemolizumab; Q4W, every four weeks; Q8W, every eight weeks

Table 30. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, MTPs and Full Periods for ARCADIA 1 & ARCADIA 2

System Organ Class FMQ (Narrow)	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Blood and lymphatic system disorders (SOC)								
Anemia	1 (0.6)	0	1 (0.6)	1 (0.5)	1 (0.6)	0	1 (0.6)	1 (0.5)
Leukopenia	0	0	0	0	1 (0.6)	2 (1.2)	0	0
Thrombocytopenia	0	0	0	1 (0.5)	0	0	1 (0.6)	1 (0.5)
Cardiac disorders (SOC)								
Systemic hypertension	2 (1.2)	1 (0.6)	2 (1.2)	2 (1.1)	4 (2.4)	3 (1.8)	2 (1.2)	3 (1.6)
Cardiac conduction disturbance	1 (0.6)	0	0	0	1 (0.6)	0	1 (0.6)	1 (0.5)
Arrhythmia	0	0	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0
Palpitations	0	0	0	0	2 (1.2)	0	0	0
Tachycardia	0	0	0	0	0	1 (0.6)	0	0
Ear and labyrinth disorders (SOC)								
Vertigo	0	0	0	0	0	0	0	1 (0.5)
Endocrine disorders (SOC)								
Hyperglycemia	0	0	0	0	0	1 (0.6)	0	1 (0.5)
Gastrointestinal disorders (SOC)								
Abdominal pain	5 (2.9)	2 (1.2)	0	2 (1.1)	5 (2.9)	3 (1.8)	3 (1.8)	3 (1.6)
Dyspepsia	5 (2.9)	2 (1.2)	2 (1.2)	2 (1.1)	5 (2.9)	3 (1.8)	3 (1.8)	3 (1.6)
Diarrhea	4 (2.4)	3 (1.8)	7 (4.2)	2 (1.1)	7 (4.1)	4 (2.4)	9 (5.4)	4 (2.2)
Nausea	3 (1.8)	0	1 (0.6)	2 (1.1)	5 (2.9)	1 (0.6)	4 (2.4)	3 (1.6)
Vomiting	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.5)	2 (1.2)	1 (0.6)	2 (1.2)	2 (1.1)
Constipation	1 (0.6)	0	0	0	3 (1.8)	0	0	0

System Organ Class FMQ (Narrow)	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
General disorders and administration site conditions (SOC)								
Pyrexia	3 (1.8)	3 (1.8)	0	3 (1.6)	4 (2.4)	4 (2.4)	1 (0.6)	6 (3.3)
Local administration reaction	2 (1.2)	1 (0.6)	4 (2.4)	1 (0.5)	4 (2.4)	5 (3.0)	7 (4.2)	3 (1.6)
Fatigue	1 (0.6)	2 (1.2)	1 (0.6)	2 (1.1)	3 (1.8)	4 (2.4)	4 (2.4)	4 (2.2)
Peripheral edema	1 (0.6)	0	0	0	2 (1.2)	1 (0.6)	2 (1.2)	0
Decreased appetite	0	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0	0
Dizziness	0	1 (0.6)	0	2 (1.1)	1 (0.6)	1 (0.6)	1 (0.6)	3 (1.6)
Hepatobiliary disorders (SOC)								
Hepatic injury	0	2 (1.2)	1 (0.6)	0	1 (0.6)	2 (1.2)	2 (1.2)	0
Immune system disorders (SOC)								
Hypersensitivity	1 (0.6)	1 (0.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	2 (1.2)	0
Anaphylactic reaction	0	0	0	0	0	0	1 (0.6)	0
Angioedema ⁶	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Infections and infestations (SOC)								
Viral infection	2 (14.7)	21 (12.6)	30 (17.9)	27 (14.7)	30 (17.6)	26 (15.6)	37 (22.0)	37 (20.1)
Nasopharyngitis	22 (12.9)	15 (9.0)	26 (15.5)	25 (13.6)	29 (17.1)	25 (15.0)	31 (18.5)	31 (16.8)
Bacterial infection	12 (7.1)	13 (7.8)	10 (6.0)	11 (6.0)	18 (10.6)	21 (12.6)	17 (10.1)	15 (8.2)
Purulent material	3 (1.8)	1 (0.6)	1 (0.6)	1 (0.5)	3 (1.8)	2 (1.2)	1 (0.6)	1 (0.5)
Fungal infection	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.1)	4 (2.4)	1 (0.6)	2 (1.2)	2 (1.1)
Pneumonia	0	0	0	1 (0.5)	0	0	0	1 (0.5)
Metabolism and nutrition disorders (SOC)								
Lipid disorder	1 (0.6)	1 (0.6)	1 (0.6)	0	1 (0.6)	3 (1.8)	1 (0.6)	2 (1.1)

⁶ Subject (b) (6) in trial ARCADIA 2 reported with mild AESI of angioedema/bilateral eye edema deemed as not related to study drug and resolved without treatment. A TEAE of hives was reported 15 days prior to the onset of angioedema/eye edema which also was reported as resolved without treatment. A TEAE of angioedema of labia majora was also reported for this subject near the end of study, deemed as not related to study drug and reported as resolved without treatment.

System Organ Class FMQ (Narrow)	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Musculoskeletal and connective tissue disorders (SOC)								
Arthritis	2 (1.2)	1 (0.6)	3 (1.8)	0	2 (1.2)	3 (1.8)	4 (2.4)	1 (0.5)
Back pain	1 (0.6)	1 (0.6)	2 (1.2)	2 (1.1)	3 (1.8)	3 (1.8)	3 (1.8)	5 (2.7)
Fracture	1 (0.6)	0	0	0	1 (0.6)	2 (1.2)	2 (1.2)	1 (0.5)
Tendinopathy	1 (0.6)	2 (1.2)	0	0	1 (0.6)	2 (1.2)	0	1 (0.5)
Arthralgia	0	2 (1.2)	1 (0.6)	1 (0.5)	3 (1.8)	4 (2.4)	2 (1.2)	1 (0.5)
Gout	0	0	0	0	0	1 (0.6)	1 (0.6)	0
Myalgia	0	1 (0.6)	0	1 (0.5)	1 (0.6)	2 (1.2)	0	2 (1.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)								
Malignancy	0	0	1 (0.6)	1 (0.5)	0	0	1 (0.6)	1 (0.5)
Nervous system disorders (SOC)								
Headache	7 (4.1)	8 (4.8)	4 (2.4)	4 (2.2)	13 (7.6)	11 (6.6)	15 (8.9)	11 (6.0)
Seizure	1 (0.6)	1 (0.6)	0	0	1 (0.6)	1 (0.6)	0	0
Syncope	1 (0.6)	1 (0.6)	1 (0.6)	0	1 (0.6)	1 (0.6)	1 (0.6)	0
Dysgeusia	0	0	0	0	1 (0.6)	0	0	0
Paresthesia	0	1 (0.6)	0	0	0	1 (0.6)	0	1 (0.5)
Somnolence	0	0	0	1 (0.5)	0	0	1 (0.6)	2 (1.1)
Tremor	0	0	0	0	0	0	1 (0.6)	0
Psychiatric disorders (SOC)								
Depression	3 (1.8)	0	0	2 (1.1)	3 (1.8)	1 (0.6)	1 (0.6)	3 (1.6)
Anxiety	1 (0.6)	1 (0.6)	0	1 (0.5)	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.5)
Insomnia	0	1 (0.6)	1 (0.6)	0	0	1 (0.6)	2 (1.2)	0
Study agent abuse potential	0	0	0	1 (0.5)	0	0	1 (0.6)	2 (1.1)
Renal and urinary disorders (SOC)								
Renal & urinary tract infection	3 (1.8)	3 (1.8)	2 (1.2)	2 (1.1)	5 (2.9)	6 (3.6)	4 (2.4)	4 (2.2)

System Organ Class FMQ (Narrow)	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)	Nemo Q4W to Nemo Q4W N=170 n (%)	Nemo Q4W to Nemo Q8W N=167 n (%)	Nemo Q4W to Placebo N=168 n (%)	Placebo to Placebo N=184 n (%)
Reproductive system and breast disorders (SOC)								
Abnormal uterine bleeding	0	1 (0.6)	2 (1.2)	0	0	1 (0.6)	2 (1.2)	0
Amenorrhea	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Decreased menstrual bleeding	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Erectile dysfunction	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Excessive menstrual bleeding	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Sexual dysfunction	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Respiratory, thoracic and mediastinal disorders (SOC)								
Bronchospasm	8 (4.7)	6 (3.6)	6 (3.6)	5 (2.7)	14 (8.2)	8 (4.8)	10 (6.0)	8 (4.3)
Dyspnea	5 (2.9)	1 (0.6)	3 (1.8)	0	7 (4.1)	1 (0.6)	5 (3.0)	0
Cough	2 (1.2)	1 (0.6)	4 (2.4)	1 (0.5)	4 (2.4)	3 (1.8)	6 (3.6)	1 (0.5)
Skin and subcutaneous tissue disorders (SOC)								
Rash	4 (2.4)	8 (4.8)	2 (1.2)	2 (1.1)	7 (4.1)	13 (7.8)	5 (3.0)	6 (3.3)
Urticaria	2 (1.2)	1 (0.6)	1 (0.6)	1 (0.5)	4 (2.4)	3 (1.8)	3 (1.8)	2 (1.1)
Alopecia	1 (0.6)	0	0	0	4 (2.4)	1 (0.6)	0	0
Pruritus	1 (0.6)	0	2 (1.2)	1 (0.5)	1 (0.6)	0	2 (1.2)	3 (1.6)
Erythema	0	0	0	1 (0.5)	1 (0.6)	0	2 (1.2)	1 (0.5)
Vascular disorders (SOC)								
Hemorrhage	2 (1.2)	3 (1.8)	2 (1.2)	2 (1.1)	3 (1.8)	4 (2.4)	5 (3.0)	3 (1.6)
Hypotension	1 (0.6)	0	0	0	1 (0.6)	0	0	0
Thrombosis	0	0	1 (0.6)	0	0	0	1 (0.6)	0
Thrombosis venous	0	0	1 (0.6)	0	0	0	1 (0.6)	0

Source: CDS Reviewer, adae.xpt; Software: R

Treatment-emergent adverse events defined as adverse events occurring after the first administration of study treatment until the last study visit.

Duration is 36 weeks for MTP and 48 weeks for full period.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term"

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)"

Abbreviations: FMQ, FDA medical query; incl, including; MTP, maintenance treatment period; N, number of patients in treatment arm; n, number of patients with adverse event;

Nemo, nemolizumab; PT, preferred term; Q4W, every four weeks; Q8W, every eight weeks; SOC, system organ class

AESIs

Injection-Related Reactions (Included Anaphylactic Reactions, Acute Allergic Reactions Requiring Treatment, and Severe Injection Site Reactions With a Duration >24 Hours)

During the ITP, one subject ((b) (6)) was reported with an IRR of severe injection site pain which lasted ≥24 hours on Day 61 and resolved on Day 71. Causality was assessed as not related to study drug. No IRR was reported during the MTP.

Newly Diagnosed Asthma or Worsening of Asthma (Adjudicated by the Independent Adjudication Committee)

During the ITP, 51 (4.3%) [including 19 study drug-related] subjects in the nemolizumab group compared to 20 (3.1%) [including 12 study drug-related] subjects in the placebo group were reported with AESI of newly diagnosed or worsening of asthma. None were SAEs. Of these subjects, 43 (3.8%) in the nemolizumab group and 19 (3.3%) in the placebo group were confirmed by the IAC.

During the MTP, this AESI was reported for 7 (4.1%) [including one SAE] subjects in the Q4W/Q4W group, 6 (3.6%) subjects in the Q4W/Q8W group, 4 (2.4%) subjects in Q4W/PBO group, and 5 (2.7%) subjects in the PBO/PBO groups. Of these subjects, 9 (5.3%), 6 (3.6%), 6 (3.6%), and 5 (2.7%) subjects, respectively were confirmed by the IAC.

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 ITP, 232 (19.5%) nemolizumab-treated subjects and 144 (22.5%) placebo- treated subjects, respectively, were reported with a TEAE in the system organ class of “Infections and Infestations”, including the AESI of infections for 40 (3.4%) [29/40 related to COVID-19] and 22 (3.4%) subjects [18/22 related to COVID-19].

The following AESIs of infections (not related to COVID-19) were reported for nemolizumab group compared to placebo group, respectively: skin infection (3 versus 1), superinfection bacterial (2 versus 0); Herpes simplex (1 versus 0), Infected cyst (1 versus 0), Ophthalmic herpes zoster (1 versus 0), Staphylococcal impetigo (1 versus 0), Staphylococcal infection (1 versus 0), Tooth abscess (1 versus 0), and Urinary tract infection (1 versus 0). These AESIs included SAEs reported for (3 versus 1) and adverse reactions (drug-related AEs) for (9 versus 3) subjects.

During the MTP, TEAEs in the system organ class of “Infections and Infestations” were reported for 53 (31.2%) subjects in the Q4W/Q4W group, 48 (28.7%) subjects in the Q4W/Q8W group, 55 (32.7%) subjects in Q4W/PBO group, and 58 (31.5%) subjects in the PBO/PBO groups, respectively. These included AESIs of infections for 16 (9.4%) [15 related to COVID-19], 17 (10.2%) [15 related to COVID-19], 25 (14.9%) [23 related to COVID-19], and 21 (11.4%) [18 related to COVID-19] subjects, respectively. One infection reported as AESI was considered related to study drug. Cellulitis (2) was the only AESI reported in > 1 subject in any group.

Peripheral Edema- Limbs, Bilateral

During the ITP, AESIs of peripheral edema were reported for 9 (0.8%) nemolizumab-treated subjects compared to 2 (0.3%) placebo-treated subjects. Peripheral edema in 6/9 nemolizumab-treated subjects were considered as related to the study drug; included one SAE, one severe adverse event (AE), and one AELD and recovered/resolved in all subjects. Concurrent or a history of potential contributing factors to peripheral edema were present in 5 subjects, including peripheral edema, varicose vein, autoimmune thyroiditis, or aquagenic urticaria.

During the MTP, AESIs of peripheral edema were reported for 1 (0.6) subject each in the Q4W/Q4W group, the Q4W/Q8W group, and the Q4W/PBO group, and no subject in the PBO/PBO group. None were SAEs.

Facial Edema

During the ITP, AESIs of facial edema were reported for 6 (0.5%) nemolizumab-treated subjects compared to 1 (0.2%) placebo-treated subject; including 5/6 nemolizumab-treated subjects considered as related to the study drug and all recovered/resolved. None were SAE or severe AEs. Concurrent or a history of potential contributing factors to facial edema were present in 4 subjects, including atopy, hypothyroidism, or aquagenic urticaria.

During the MTP, AESIs of facial edema were reported for 1 (0.6) subject in the Q4W/Q8W group and resolved following treatment with antihistamines.

Elevated ALT or AST ($>3 \times \text{ULN}$) in Combination With Elevated Bilirubin ($>2 \times \text{ULN}$)

No subject was reported with an elevated ALT or AST $>3 \times \text{ULN}$ in combination with elevated bilirubin $>2 \times \text{ULN}$.

Other Safety Topics

Malignancy

During the treatment period of the P2-DR trial, squamous cell carcinoma of moderate severity (upper elbow) was reported for a 66-year-old white male (subject ID: (b) (6)) with history of facial basal cell carcinoma excision (and possible long term sun exposure).

During the P3 AD trials, the following 3 subjects were reported with AELDs of malignancy:

- Prostate cancer (subject ID: (b) (6)): a 65-year-old White male subject was treated with nemolizumab 30 mg Q4W during the ITP and diagnosed on Day 182. Risk factors included sex, advanced age, and obesity.
- Salivary gland cancer (subject ID: (b) (6)): a 45-year-old White male subject diagnosed with severe salivary gland cancer (left parotid gland) on Day 23 of treatment with nemolizumab 30 mg Q4W during the ITP, which was discovered incidentally before a dental procedure. No risk factors were identified from the reported medical history and smoking status. No information is available about a possible exposure to radiation.
- Plasmablastic lymphoma (subject ID: (b) (6)): a 73-year-old White male subject was diagnosed with plasmablastic lymphoma on Day 286 (during MTP treatment with placebo). Risk factors included evidence of a prior Epstein-Barr virus infection (intense positivity in biopsied neoplastic cells of nasal polyp).

Malignancies reported for nemolizumab-treated subjects during the AD long-term extension study ARCADIA LTE (up to the data cut-off point of 3/10/2023) included cutaneous T-cell lymphoma (1) (present at baseline, but misdiagnosed), renal cell carcinoma (1), non-small cell lung cancer (1), invasive papillary breast carcinoma (1), rectal adenocarcinoma (1), and colorectal cancer (1). The potential relationship of the reported malignancies to the study drug is unknown.

Pregnancy

Pregnant subjects in the AD trials were discontinued from treatment. Subjects reported with pregnancy who had received treatment with nemolizumab included one (1) subject in the P2-DR trial (delivered a healthy infant) and 8 subjects in the ARCADIA 1 and 2 trials or the ARCADIA LTE study with the following outcomes: unknown (4), delivered healthy infant (1), spontaneous abortion with no congenital malformations (2), elective abortion (1).

Injection Site Reactions

Injection site reactions (ISRs) included erythema, pain, irritation, edema, hematoma, and pruritus at the subcutaneous injection site; and were reported with similar frequency for the nemolizumab group in 15 (1.3%) subjects and for the placebo group in 7 (1.1%) subjects during the ITP. All but one ISRs were mild, and none was an AELD.

Herpes Virus (Herpes Simplex Virus, Herpes Zoster Virus) Related TEAEs

Grouped Query for the TEAEs related to herpes simplex and herpes zoster infections were conducted by the clinical data scientist reviewer at the request of the clinical review team. During the ITP, for the nemolizumab group compared to the placebo group, respectively:

- Herpes simplex was reported for 17 (1.5%) versus 17 (2.9%) subjects, including Eczema herpeticum for 4 (0.4%) versus 2 (0.3%), Nasal herpes for 1 (0.1%) versus 1 (0.2%), Oral herpes for 8 (0.7%) versus 5 (0.9%), Herpes simplex for 4 (0.4%) versus 6 (1.0%), and Ophthalmic herpes simplex for 0 (0%) versus 4 (0.7%).
- Herpes zoster was reported for 5 (0.4%) versus 0 (0%), including an SAE of ophthalmic herpes zoster for 1 (0.1%) subject. None were AELDs.

During the MTP, for subjects in the Q4W/Q4W group, the Q4W/Q8W group, the Q4W/PBO group, and the PBO/PBO group, respectively:

- Herpes simplex was reported for 5 (2.9%) [including oral herpes (3), herpes simplex (1), and ophthalmic herpes simplex (1)], 3 (1.8%) [including oral herpes (3)], 4 (2.4%) [including oral herpes (1), herpes simplex (1), and ophthalmic herpes simplex (1)], and 2 (1.1%) [including herpes simplex (2)].
- Herpes zoster was reported for 0, 0, 0, and 1 [including ophthalmic herpes zoster (1)] subject.

Autoimmune Related TEAEs

Grouped Queries for the TEAEs related to autoimmune disorders were conducted by the clinical data scientist reviewer at the request of the clinical review team.

During the ITP, the GQ identified the following AEs for the nemolizumab group compared to the placebo group, respectively: Dermatitis 4 (0.4%) versus 1 (0.2%), Enteritis 2 (0.2%) versus 0 (0%), Arthritis 3 (0.3%) versus 1 (0.2%), Hypothyroidism 1 (0.1%) versus 0 (0%), Raynaud's phenomenon 1 (0.1%) versus 0 (0%), Uveitis 0 (0%) versus 1 (0.2%), and alopecia areata for 1 (0.1%) versus 3 (0.5%).

During the MTP, for subjects in the Q4W/Q4W group, the Q4W/Q8W group, the Q4W/PBO group, and the PBO/PBO group, respectively:

Immune-mediated/autoimmune disorders were reported for 2 (1.2%) [including alopecia areata (1), colitis (1), enteritis (1)], 3 (1.8%) [including Arthritis (1), Autoimmune thyroiditis (1), and Pemphigoid (1)], 4 (2.4%) [including Arthritis (2), Neuropathy peripheral (1), Raynaud's phenomenon (1)], and 1 (0.5%) [Arthritis (1)].

During the follow-up period, one subject was diagnosed with dermatomyositis (1).

Neurologic TEAEs

An information request (IR) was conveyed to the Applicant to provide a clinical update for all subjects in the nemolizumab AD clinical development program who received treatment with nemolizumab and were reported with potential TEAEs of seizure or syncope. The clinical review team requested a consultation from the Division of Neurology 2 to evaluate a potential causal relationship between nemolizumab and the reported neurologic TEAEs and whether these TEAEs should be included in the label; and to evaluate the Applicant's response to the IR (dated 9/5/2024). The Division of Neurology 2 made the following recommendations in a consultation memorandum dated 10/11/2024:

Question 1. Does Neurology think there is a causal relationship between nemolizumab and these TEAEs?

No, based on the limited data available, DN2 does not consider the events described as epilepsy, tremors, hyperactivity, syncope or near syncope to be related to nemolizumab exposure. Most of the syncope events appeared to have etiologies that were clearly not attributable to nemolizumab exposure. However, none of these subjects had an appropriate work up to definitively exclude seizures and without a clearly established etiology, a definitive conclusion regarding an association between these events and nemolizumab exposure, and whether these events represent potential seizures, cannot be rendered, but what evidence exists does not constitute strong

evidence a causal relationship exists. There was no obvious pattern or predictability to the occurrence of these events and initiation or administration of nemolizumab. The events did not recur, and none of these subjects had recurrence of the events while in the studies, and so there does not appear to be a consistent safety signal present.

Question 2. If so, does Neurology recommend inclusion in labeling of these events?

No. DN2 does not recommend updating the labeling to include these events in response to these adverse event reports because there is not a clearly defined safety signal present. The evidence for a definitive identification of these events as being seizures in this clinical trial population is lacking. Routine pharmacovigilance for NEMLUVIO in the postmarketing setting should remain adequate to continue surveillance for a potential signal of seizures, syncopal events, tremors, or hyperactivity.

LTE Phase 3 AD Study SPR.118163- Interim Safety Data

The Applicant submitted safety data for interim analysis for all TEAEs up to 9/30/2022, and updated safety data for deaths, SAEs, AELDs, study drug related AESIs, and pregnancies up to 3/10/2023.

As of the data cut-off date of 9/30/2022, 1110/1740 (63.8%) subjects enrolled in this study were reported with a TEAE; most were mild or moderate in severity. TEAEs reported with a frequency ($\geq 5.0\%$) included COVID-19 (16.1%), dermatitis atopic (13.0%), nasopharyngitis (9.5%), and upper respiratory tract infection (5.6%).

Nemolizumab-related TEAEs (Adverse Reactions) were reported by 291 (16.7%) subjects; adverse reactions (ARs) reported at a frequency of ($\geq 1.0\%$) included dermatitis atopic (3.6%), asthma (1.9%), nasopharyngitis (1.3%), and upper respiratory tract infection (1.1%).

No deaths were reported. SAEs were reported for 72 (4.1%) subjects [including 8 SAEs considered by the investigators as related to nemolizumab], and included the following SAEs reported for >1 subject: dermatitis atopic (8 [0.5%]) subjects; myocardial infarction, cholecystitis acute, COVID-19, COVID-19 pneumonia, cellulitis, syncope, and urinary retention each reported for (2 [0.1%]) subjects.

Adverse events that led to study drug discontinuation (AELD) were reported for 57 (3.3%); most were mild to moderate in severity. AELDs were considered as related to nemolizumab for 31 [1.8%] subjects including the following AELDs reported for >1 subject: dermatitis atopic (14 [0.8%] subjects; asthma and toxic skin eruption for 2 (0.1%) subjects each.

AESIs (per investigators) were reported for 413 (23.7%) subjects, including the following:

- IRR of injection site pruritus/injection site swelling (1) of moderate severity, related to nemolizumab, considered as an AELD, and led to discontinuation from the study.
- Infections were reported for 353 (20.3%) subjects. AESIs of infection considered as related to nemolizumab were reported for 20 (1.1%) subjects and included the following AESIs reported for >1 subject: COVID-19 for 10 (0.6%), and asymptomatic COVID-19 for 2 (0.1%) subjects.

- Peripheral edema (limbs, bilateral) and facial edema were reported for 17 (1.0%) subjects. None were SAEs or severe AEs. Eight (0.5%) subjects were reported with nemolizumab-related AESIs including face edema 3 (0.2%), peripheral edema 2 (0.1%); and 1 (0.1%) subject each reported with eyelid edema, periorbital edema, lip edema, and non-pitting edema. AELDs were reported for 4/8 subjects with nemolizumab-related AESIs of facial/peripheral edema.
- AESI of ALT or AST $>3 \times$ ULN and bilirubin $>2 \times$ ULN was reported for 1 subject who was diagnosed with a SAE of moderate-severity hepatitis A, considered as not related to nemolizumab and the outcome reported as resolved.
- Newly diagnosed asthma or worsening of asthma was reported for 75 (4.3%) subjects, including 33 (1.9%) subjects considered as related to nemolizumab. The Applicant's SMQ for "asthma/bronchospasm" identified 41 (2.4%) subjects adjudicated by the IAC as newly diagnosed asthma/worsening of asthma and considered as related to nemolizumab; included no SAEs or severe AEs and 2 AELDs; most were reported as resolved.

As of the data cut-off date of 3/10/2023, SAEs were reported for 99 (5.2%) subjects and included dermatitis atopic for 9 (0.5%) subjects, and acute cholecystitis for 3 (0.2%) subjects; 2 (0.1%) subjects each were reported with SAEs of myocardial infarction, food allergy, appendicitis, COVID-19, COVID-19 pneumonia, cellulitis, pneumonia, syncope, urinary retention, and asthma. The remaining SAEs were each reported for 1 subject.

SAEs related to nemolizumab were reported for 14 (0.7%) subjects and included 2 (0.1%) subjects each reported with asthma or dermatitis atopic, and 1 (0.1%) subject each reported with dyspepsia, appendicitis, dermatitis infected, diverticulitis intestinal perforated, erysipelas, eye infection, wound abscess, rectal adenocarcinoma, third nerve paralysis, syncope, and pneumothorax spontaneous.

AELDs were reported for 69 (3.6%) subjects and included dermatitis atopic for 35 (1.8%) subjects, toxic skin eruption for 2 (0.1%) subjects, and asthma for 2 (0.1%) subjects.

AESIs related to nemolizumab were reported for 68 (3.6%) subjects and included asthma for 31 (1.6%) subjects, COVID-19 for 12 (0.1%) subjects, peak expiratory flow rate decreased for 7 (0.4%) subjects, asymptomatic COVID-19 for 3 (0.2%) subjects, face edema for 3 (0.2%) subjects, and peripheral edema for 2 (0.1%) subjects. The remaining AESIs were each reported for 1 subject.

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

No trends over time were reported during the ITP or the MTP for clinically significant shifts from baseline in laboratory parameters for clinical chemistry, lipids, liver function, kidney function, urinalysis, or hematology. 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 (outliers).

Refer to the summary of subjects with eosinophils increased and subjects with creatinine phosphokinase (CPK) increased at the end of this section of the clinical review. The proportion of subjects with laboratory values reported as outliers during the ITP are summarized in the following tables (Table 31 through Table 35).

Table 31. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
Sodium, low (mEq/L)							
Level 1 (<132)	1/591 (0.2)	1/317 (0.3)	3/497 (0.6)	1/251 (0.4)	4/1088 (0.4)	2/568 (0.4)	0.0 (-0.9, 0.7)
Level 2 (<130)	0/591 (0)	0/317 (0)	0/497 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Level 3 (<125)	0/591 (0)	0/317 (0)	0/497 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Sodium, high (mEq/L)							
Level 1 (>150)	0/591 (0)	0/317 (0)	0/497 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Level 2 (>155)	0/591 (0)	0/317 (0)	0/497 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Level 3 (>160)	0/591 (0)	0/317 (0)	0/497 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Potassium, low (mEq/L)							
Level 1 (<3.6)	5/576 (0.9)	5/310 (1.6)	5/487 (1.0)	5/249 (2.0)	10/1063 (0.9)	10/559 (1.8)	-0.8 (-2.4, 0.3)
Level 2 (<3.4)	2/576 (0.3)	1/310 (0.3)	1/487 (0.2)	1/249 (0.4)	3/1063 (0.3)	2/559 (0.4)	-0.1 (-1.0, 0.5)
Level 3 (<3)	0/576 (0)	0/310 (0)	1/487 (0.2)	0/249 (0)	1/1063 (0.1)	0/559 (0)	0.1 (-0.6, 0.5)
Potassium, high (mEq/L)							
Level 1 (>5.5)	3/576 (0.5)	4/310 (1.3)	2/487 (0.4)	1/249 (0.4)	5/1063 (0.5)	5/559 (0.9)	-0.4 (-1.6, 0.4)
Level 2 (>6)	1/576 (0.2)	2/310 (0.6)	0/487 (0)	0/249 (0)	1/1063 (0.1)	2/559 (0.4)	-0.3 (-1.2, 0.2)
Level 3 (>6.5)	0/576 (0)	2/310 (0.6)	0/487 (0)	0/249 (0)	0/1063 (0)	2/559 (0.4)	-0.4 (-1.3, 0.0)
Chloride, low (mEq/L)							
Level 1 (<95)	2/590 (0.3)	1/317 (0.3)	6/498 (1.2)	1/252 (0.4)	8/1088 (0.7)	2/569 (0.4)	0.4 (-0.6, 1.2)
Level 2 (<88)	0/590 (0)	0/317 (0)	0/498 (0)	0/252 (0)	0/1088 (0)	0/569 (0)	0.0 (-0.7, 0.4)
Level 3 (<80)	0/590 (0)	0/317 (0)	0/498 (0)	0/252 (0)	0/1088 (0)	0/569 (0)	0.0 (-0.7, 0.4)
Chloride, high (mEq/L)							
Level 1 (>108)	2/590 (0.3)	0/317 (0)	1/498 (0.2)	0/252 (0)	3/1088 (0.3)	0/569 (0)	0.3 (-0.4, 0.8)
Level 2 (>112)	0/590 (0)	0/317 (0)	0/498 (0)	0/252 (0)	0/1088 (0)	0/569 (0)	0.0 (-0.7, 0.4)
Level 3 (>115)	0/590 (0)	0/317 (0)	0/498 (0)	0/252 (0)	0/1088 (0)	0/569 (0)	0.0 (-0.7, 0.4)
Bicarbonate, low (mEq/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Bicarbonate, high (mEq/L)							
Missing	NA	NA	NA	NA	NA	NA	NA

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
Glucose, low (mg/dL)							
Level 1 (<70)	16/589 (2.7)	15/314 (4.8)	21/498 (4.2)	10/250 (4.0)	37/1087 (3.4)	25/564 (4.4)	-1.0 (-3.3, 0.9)
Level 2 (<54)	2/589 (0.3)	0/314 (0)	0/498 (0)	1/250 (0.4)	2/1087 (0.2)	1/564 (0.2)	0.0 (-0.8, 0.5)
Level 3 (<40)	0/589 (0)	0/314 (0)	0/498 (0)	0/250 (0)	0/1087 (0)	0/564 (0)	0.0 (-0.7, 0.4)
Glucose, fasting, high (mg/dL)							
Level 1 (≥100 to 125)	49/265 (18.5)	23/148 (15.5)	57/327 (17.4)	28/154 (18.2)	106/592 (17.9)	51/302 (16.9)	1.0 (-4.4, 6.1)
Level 2 (≥126)	19/265 (7.2)	4/148 (2.7)	13/327 (4.0)	5/154 (3.2)	32/592 (5.4)	9/302 (3.0)	2.4 (-0.5, 5.0)
Glucose, random, high (mg/dL)							
Level 2 (≥200)	2/422 (0.5)	3/232 (1.3)	0/241 (0)	1/143 (0.7)	2/663 (0.3)	4/375 (1.1)	-0.8 (-2.4, 0.2)
Level 3 (>250)	2/422 (0.5)	3/232 (1.3)	0/241 (0)	1/143 (0.7)	2/663 (0.3)	4/375 (1.1)	-0.8 (-2.4, 0.2)
Calcium, low (mg/dL)							
Level 1 (<8.4)	2/590 (0.3)	1/317 (0.3)	4/496 (0.8)	1/251 (0.4)	6/1086 (0.6)	2/568 (0.4)	0.2 (-0.8, 0.9)
Level 2 (<8)	1/590 (0.2)	1/317 (0.3)	2/496 (0.4)	1/251 (0.4)	3/1086 (0.3)	2/568 (0.4)	-0.1 (-1.0, 0.5)
Level 3 (<7.5)	0/590 (0)	1/317 (0.3)	0/496 (0)	1/251 (0.4)	0/1086 (0)	2/568 (0.4)	-0.4 (-1.3, 0.0)
Calcium, high (mg/dL)							
Level 1 (>10.5)	12/590 (2.0)	4/317 (1.3)	11/496 (2.2)	3/251 (1.2)	23/1086 (2.1)	7/568 (1.2)	0.9 (-0.6, 2.1)
Level 2 (>11)	1/590 (0.2)	1/317 (0.3)	0/496 (0)	0/251 (0)	1/1086 (0.1)	1/568 (0.2)	-0.1 (-0.9, 0.4)
Level 3 (>12)	0/590 (0)	0/317 (0)	0/496 (0)	0/251 (0)	0/1086 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Magnesium, low (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Magnesium, high (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Phosphate, low (mg/dL)							
Missing	NA	NA	NA	NA	NA	NA	NA
Protein, total, low (g/dL)							
Level 1 (<6)	7/588 (1.2)	1/317 (0.3)	2/499 (0.4)	0/252 (0)	9/1087 (0.8)	1/569 (0.2)	0.7 (-0.2, 1.4)
Level 2 (<5.4)	1/588 (0.2)	0/317 (0)	1/499 (0.2)	0/252 (0)	2/1087 (0.2)	0/569 (0)	0.2 (-0.5, 0.7)
Level 3 (<5)	1/588 (0.2)	0/317 (0)	0/499 (0)	0/252 (0)	1/1087 (0.1)	0/569 (0)	0.1 (-0.6, 0.5)
Albumin, low (g/dL)							
Level 1 (<3.1)	2/589 (0.3)	1/316 (0.3)	0/496 (0)	0/251 (0)	2/1085 (0.2)	1/567 (0.2)	0.0 (-0.8, 0.5)
Level 2 (<2.5)	0/589 (0)	0/316 (0)	0/496 (0)	0/251 (0)	0/1085 (0)	0/567 (0)	0.0 (-0.7, 0.4)
Level 3 (<2)	0/589 (0)	0/316 (0)	0/496 (0)	0/251 (0)	0/1085 (0)	0/567 (0)	0.0 (-0.7, 0.4)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
CPK, high (U/L)							
Level 1 (>3X ULN)	10/577 (1.7)	3/309 (1.0)	4/489 (0.8)	5/247 (2.0)	14/1066 (1.3)	8/556 (1.4)	-0.1 (-1.6, 1.0)
Level 2 (>5X ULN)	6/577 (1.0)	1/309 (0.3)	0/489 (0)	1/247 (0.4)	6/1066 (0.6)	2/556 (0.4)	0.2 (-0.8, 0.9)
Level 3 (>10X ULN)	1/577 (0.2)	0/309 (0)	0/489 (0)	0/247 (0)	1/1066 (0.1)	0/556 (0)	0.1 (-0.6, 0.5)
Amylase, high (U/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Lipase, high (U/L)							
Missing	NA	NA	NA	NA	NA	NA	NA
Blood urea nitrogen, high (mg/dL)							
Level 1 (>23)	17/590 (2.9)	8/317 (2.5)	13/499 (2.6)	8/251 (3.2)	30/1089 (2.8)	16/568 (2.8)	-0.1 (-2.0, 1.5)
Level 2 (>27)	4/590 (0.7)	5/317 (1.6)	8/499 (1.6)	2/251 (0.8)	12/1089 (1.1)	7/568 (1.2)	-0.1 (-1.5, 0.9)
Level 3 (>31)	1/590 (0.2)	2/317 (0.6)	2/499 (0.4)	1/251 (0.4)	3/1089 (0.3)	3/568 (0.5)	-0.3 (-1.3, 0.4)

Source: CDS 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](#).

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients meeting criteria; NA, not applicable; Nw, number of patients with data; ULN, upper limit of normal

Table 32. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg vs. Placebo Risk Difference % (95% CI)
Creatinine, high (mg/dL)							
Level 1 ($\geq 1.5X$ baseline)	4/589 (0.7)	2/317 (0.6)	4/499 (0.8)	1/251 (0.4)	8/1088 (0.7)	3/568 (0.5)	0.2 (-0.9, 1.0)
Level 2 ($\geq 2X$ baseline)	0/589 (0)	0/317 (0)	0/499 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
Level 3 ($\geq 3X$ baseline)	0/589 (0)	0/317 (0)	0/499 (0)	0/251 (0)	0/1088 (0)	0/568 (0)	0.0 (-0.7, 0.4)
eGFR, low (mL/min/1.73 m ²)							
Level 1 ($\geq 25\%$ decrease)	7/578 (1.2)	7/312 (2.2)	10/497 (2.0)	6/251 (2.4)	17/1075 (1.6)	13/563 (2.3)	-0.7 (-2.4, 0.6)
Level 2 ($\geq 50\%$ decrease)	0/578 (0)	0/312 (0)	0/497 (0)	0/251 (0)	0/1075 (0)	0/563 (0)	0.0 (-0.7, 0.4)
Level 3 ($\geq 75\%$ decrease)	0/578 (0)	0/312 (0)	0/497 (0)	0/251 (0)	0/1075 (0)	0/563 (0)	0.0 (-0.7, 0.4)

Source: CDS Reviewer, adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

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; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 33. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab		Nemolizumab		Nemolizumab		Nemolizumab
	30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	30 mg vs. Placebo Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)							
Level 1 (>1.5X ULN)	7/589 (1.2)	3/317 (0.9)	6/497 (1.2)	2/250 (0.8)	13/1086 (1.2)	5/567 (0.9)	0.3 (-0.9, 1.3)
Level 2 (>2X ULN)	1/589 (0.2)	1/317 (0.3)	2/497 (0.4)	0/250 (0)	3/1086 (0.3)	1/567 (0.2)	0.1 (-0.7, 0.7)
Level 3 (>3X ULN)	0/589 (0)	0/317 (0)	0/497 (0)	0/250 (0)	0/1086 (0)	0/567 (0)	0.0 (-0.7, 0.4)
Alanine aminotransferase, high (U/L)							
Level 1 (>3X ULN)	1/586 (0.2)	1/315 (0.3)	0/495 (0)	0/252 (0)	1/1081 (0.1)	1/567 (0.2)	-0.1 (-0.9, 0.4)
Level 2 (>5X ULN)	0/586 (0)	0/315 (0)	0/495 (0)	0/252 (0)	0/1081 (0)	0/567 (0)	0.0 (-0.7, 0.4)
Level 3 (>10X ULN)	0/586 (0)	0/315 (0)	0/495 (0)	0/252 (0)	0/1081 (0)	0/567 (0)	0.0 (-0.7, 0.4)
Aspartate aminotransferase, high (U/L)							
Level 1 (>3X ULN)	2/585 (0.3)	0/316 (0)	0/495 (0)	0/251 (0)	2/1080 (0.2)	0/567 (0)	0.2 (-0.5, 0.7)
Level 2 (>5X ULN)	1/585 (0.2)	0/316 (0)	0/495 (0)	0/251 (0)	1/1080 (0.1)	0/567 (0)	0.1 (-0.6, 0.5)
Level 3 (>10X ULN)	0/585 (0)	0/316 (0)	0/495 (0)	0/251 (0)	0/1080 (0)	0/567 (0)	0.0 (-0.7, 0.4)
Bilirubin, total, high (mg/dL)							
Level 1 (>1.5X ULN)	4/589 (0.7)	3/314 (1.0)	3/496 (0.6)	0/251 (0)	7/1085 (0.6)	3/565 (0.5)	0.1 (-1.0, 0.9)
Level 2 (>2X ULN)	0/589 (0)	0/314 (0)	1/496 (0.2)	0/251 (0)	1/1085 (0.1)	0/565 (0)	0.1 (-0.6, 0.5)
Level 3 (>3X ULN)	0/589 (0)	0/314 (0)	0/496 (0)	0/251 (0)	0/1085 (0)	0/565 (0)	0.0 (-0.7, 0.4)

Source: CDS Reviewer, adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

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; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

Table 34. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)							
Level 1 (>200)	147/588 (25.0)	102/316 (32.3)	138/495 (27.9)	75/250 (30.0)	285/1083 (26.3)	177/566 (31.3)	-5.0 (-9.6, -0.4) *
Level 2 (>210)	106/588 (18.0)	79/316 (25.0)	103/495 (20.8)	52/250 (20.8)	209/1083 (19.3)	131/566 (23.1)	-3.8 (-8.1, 0.3)
Level 3 (>225)	63/588 (10.7)	49/316 (15.5)	61/495 (12.3)	33/250 (13.2)	124/1083 (11.4)	82/566 (14.5)	-3.0 (-6.6, 0.3)
HDL, males, low (mg/dL)							
Level 1 (<40)	78/308 (25.3)	38/175 (21.7)	71/239 (29.7)	36/123 (29.3)	149/547 (27.2)	74/298 (24.8)	2.4 (-3.9, 8.4)
Level 2 (<30)	6/308 (1.9)	8/175 (4.6)	7/239 (2.9)	3/123 (2.4)	13/547 (2.4)	11/298 (3.7)	-1.3 (-4.3, 1.0)
Level 3 (<20)	0/308 (0)	0/175 (0)	0/239 (0)	0/123 (0)	0/547 (0)	0/298 (0)	0.0 (-1.3, 0.7)
HDL, females, low (mg/dL)							
Level 1 (<50)	92/280 (32.9)	32/141 (22.7)	82/258 (31.8)	36/128 (28.1)	174/538 (32.3)	68/269 (25.3)	7.1 (0.4, 13.4) *
Level 2 (<40)	19/280 (6.8)	11/141 (7.8)	21/258 (8.1)	11/128 (8.6)	40/538 (7.4)	22/269 (8.2)	-0.7 (-5.1, 3.0)
Level 3 (<20)	0/280 (0)	0/141 (0)	0/258 (0)	0/128 (0)	0/538 (0)	0/269 (0)	0.0 (-1.4, 0.7)
LDL, high (mg/dL)							
Level 1 (>130)	126/588 (21.4)	87/315 (27.6)	112/495 (22.6)	58/250 (23.2)	238/1083 (22.0)	145/565 (25.7)	-3.7 (-8.1, 0.6)
Level 2 (>160)	36/588 (6.1)	24/315 (7.6)	37/495 (7.5)	19/250 (7.6)	73/1083 (6.7)	43/565 (7.6)	-0.9 (-3.7, 1.7)
Level 3 (>190)	8/588 (1.4)	5/315 (1.6)	8/495 (1.6)	2/250 (0.8)	16/1083 (1.5)	7/565 (1.2)	0.2 (-1.2, 1.4)
Triglycerides, high (mg/dL)							
Level 1 (>150)	133/591 (22.5)	88/315 (27.9)	125/499 (25.1)	62/252 (24.6)	258/1090 (23.7)	150/567 (26.5)	-2.8 (-7.3, 1.6)
Level 2 (>300)	15/591 (2.5)	12/315 (3.8)	17/499 (3.4)	9/252 (3.6)	32/1090 (2.9)	21/567 (3.7)	-0.8 (-2.8, 1.0)
Level 3 (>500)	4/591 (0.7)	4/315 (1.3)	2/499 (0.4)	1/252 (0.4)	6/1090 (0.6)	5/567 (0.9)	-0.3 (-1.5, 0.5)

Source: CDS Reviewer, adlb.xpt; Software: R

* 95% confidence interval excludes zero.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

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; ITP, initial treatment period; LDL, low-density lipoprotein; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data

Table 35. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
Complete blood count							
WBC, low (10 ³ cells/uL)							
Level 1 (<3.5)	10/586 (1.7)	6/313 (1.9)	11/494 (2.2)	4/249 (1.6)	21/1080 (1.9)	10/562 (1.8)	0.2 (-1.4, 1.5)
Level 2 (<3)	5/586 (0.9)	0/313 (0)	5/494 (1.0)	2/249 (0.8)	10/1080 (0.9)	2/562 (0.4)	0.6 (-0.4, 1.4)
Level 3 (<1)	0/586 (0)	0/313 (0)	0/494 (0)	0/249 (0)	0/1080 (0)	0/562 (0)	0.0 (-0.7, 0.4)
WBC, high (10 ³ cells/uL)							
Level 1 (>10.8)	32/586 (5.5)	13/313 (4.2)	42/494 (8.5)	11/249 (4.4)	74/1080 (6.9)	24/562 (4.3)	2.6 (0.2, 4.8) *
Level 2 (>13)	6/586 (1.0)	6/313 (1.9)	10/494 (2.0)	3/249 (1.2)	16/1080 (1.5)	9/562 (1.6)	-0.1 (-1.6, 1.1)
Level 3 (>15)	3/586 (0.5)	4/313 (1.3)	3/494 (0.6)	1/249 (0.4)	6/1080 (0.6)	5/562 (0.9)	-0.3 (-1.6, 0.5)
Hemoglobin, low (g/dL)							
Level 2 (>1.5 g/dL dec. from baseline)	19/589 (3.2)	13/315 (4.1)	16/500 (3.2)	7/250 (2.8)	35/1089 (3.2)	20/565 (3.5)	-0.3 (-2.4, 1.4)
Level 3 (>2 g/dL dec. from baseline)	6/589 (1.0)	3/315 (1.0)	5/500 (1.0)	2/250 (0.8)	11/1089 (1.0)	5/565 (0.9)	0.1 (-1.1, 1.1)
Hemoglobin, high (g/dL)							
Level 2 (>2 g/dL inc. from baseline)	5/589 (0.8)	1/315 (0.3)	7/500 (1.4)	3/250 (1.2)	12/1089 (1.1)	4/565 (0.7)	0.4 (-0.8, 1.3)
Level 3 (>3 g/dL inc. from baseline)	1/589 (0.2)	0/315 (0)	2/500 (0.4)	0/250 (0)	3/1089 (0.3)	0/565 (0)	0.3 (-0.4, 0.8)
Platelets, low (10 ³ cells/uL)							
Level 1 (<140)	8/585 (1.4)	3/313 (1.0)	6/494 (1.2)	6/250 (2.4)	14/1079 (1.3)	9/563 (1.6)	-0.3 (-1.8, 0.9)
Level 2 (<125)	4/585 (0.7)	1/313 (0.3)	1/494 (0.2)	4/250 (1.6)	5/1079 (0.5)	5/563 (0.9)	-0.4 (-1.6, 0.4)
Level 3 (<100)	3/585 (0.5)	0/313 (0)	0/494 (0)	0/250 (0)	3/1079 (0.3)	0/563 (0)	0.3 (-0.4, 0.8)

Laboratory Parameter	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616 n/N _w (%)	Placebo N=321 n/N _w (%)	Nemolizumab 30 mg N=519 n/N _w (%)	Placebo N=263 n/N _w (%)	Nemolizumab 30 mg N=1135 n/N _w (%)	Placebo N=584 n/N _w (%)	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
WBC differential							
Lymphocytes, low (10 ³ cells/uL)							
Level 1 (<1)	15/584 (2.6)	18/313 (5.8)	15/492 (3.0)	11/249 (4.4)	30/1076 (2.8)	29/562 (5.2)	-2.4 (-4.7, -0.4) *
Level 2 (<0.75)	3/584 (0.5)	4/313 (1.3)	5/492 (1.0)	3/249 (1.2)	8/1076 (0.7)	7/562 (1.2)	-0.5 (-1.9, 0.5)
Level 3 (<0.5)	0/584 (0)	0/313 (0)	0/492 (0)	0/249 (0)	0/1076 (0)	0/562 (0)	0.0 (-0.7, 0.4)
Lymphocytes, high (10 ³ cells/uL)							
Level 1 (>4)	1/584 (0.2)	0/313 (0)	2/492 (0.4)	1/249 (0.4)	3/1076 (0.3)	1/562 (0.2)	0.1 (-0.7, 0.7)
Level 2 (>10)	0/584 (0)	0/313 (0)	0/492 (0)	0/249 (0)	0/1076 (0)	0/562 (0)	0.0 (-0.7, 0.4)
Level 3 (>20)	0/584 (0)	0/313 (0)	0/492 (0)	0/249 (0)	0/1076 (0)	0/562 (0)	0.0 (-0.7, 0.4)
Neutrophils, low (10 ³ cells/uL)							
Level 1 (<2)	28/585 (4.8)	15/313 (4.8)	16/492 (3.3)	14/248 (5.6)	44/1077 (4.1)	29/561 (5.2)	-1.1 (-3.5, 1.0)
Level 2 (<1)	2/585 (0.3)	0/313 (0)	0/492 (0)	0/248 (0)	2/1077 (0.2)	0/561 (0)	0.2 (-0.5, 0.7)
Level 3 (<0.5)	0/585 (0)	0/313 (0)	0/492 (0)	0/248 (0)	0/1077 (0)	0/561 (0)	0.0 (-0.7, 0.4)
Eosinophils, high (10 ³ cells/uL)							
Level 1 (>0.65)	124/583 (21.3)	44/311 (14.1)	113/491 (23.0)	40/248 (16.1)	237/1074 (22.1)	84/559 (15.0)	7.0 (3.1, 10.8) *
Level 2 (>1.5)	17/583 (2.9)	2/311 (0.6)	20/491 (4.1)	2/248 (0.8)	37/1074 (3.4)	4/559 (0.7)	2.7 (1.3, 4.1) *
Level 3 (>5)	0/583 (0)	0/311 (0)	0/491 (0)	0/248 (0)	0/1074 (0)	0/559 (0)	0.0 (-0.7, 0.4)
Coagulation studies							
PT, high (sec)							
Missing	NA	NA	NA	NA	NA	NA	NA
PTT, high (sec)							
Missing	NA	NA	NA	NA	NA	NA	NA

Source: CDS Reviewer, adlb.xpt; Software: R

* 95% confidence interval excludes zero.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Initial treatment period duration is 16 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients meeting criteria; NA, not applicable; N_w, number of patients with data; PT, prothrombin time; PTT, partial thromboplastin time; WBC, white blood cells

Eosinophil Count Increased

During the ITP, for subjects in the nemolizumab group compared to the placebo group, increased eosinophil counts ($>650/\text{mcL}$) were reported for 22.1% versus 15.0% of subjects; eosinophil counts ($>1,500/\text{mcL}$) were reported for 3.4% versus 0.7%; and eosinophil counts ($>5,000/\text{mcL}$) were reported for no subject. Two subjects were reported with a TEAE of eosinophilia.

During the MTP, no subject was reported with a TEAE of eosinophilia. One subject was reported with a potentially clinically significant increase in eosinophil counts ($>5,000/\text{mcL}$). This subject (ID: (b) (6)) was a 13-year-old White male with no pertinent history (other than AD) who received treatment with nemolizumab Q 4W during the ITP and nemolizumab Q8W during the MTP and completed the trial at Week 48; was reported with an eosinophil counts of 600/mcL at baseline, 1000/mcL on Day 55, 800/mcL on Day 115, 5500/mcL on Day 225, and 800 on Day 335. A non-serious TEAE of acne was reported on Day 237 considered as not related to nemolizumab. The increase in eosinophil count was considered transient and reversible, without clinical manifestations.

Creatinine Phosphokinase Increased

During the ITP, for subjects in the nemolizumab group compared to the placebo group, respectively; increased CPK measurements ($>3 \times \text{ULN}$) were reported for 1.3% versus 1.4% of subjects; ($>5 \times \text{ULN}$) were reported for 0.6% versus 0.4%; and ($>10 \times \text{ULN}$) were reported for 0.1% versus 0% of subjects. TEAEs of “Blood creatine phosphokinase increased” were reported for 7 (0.6%) subjects [including 1 AELD] for subjects in the nemolizumab group compared to 6 (1.0%) subjects in the placebo group. Four (4) subjects in the nemolizumab group were reported with increased CPK measurements and TEAEs of “myalgia” at or near the same timepoints; myalgia in 3 subjects was reported as mild, nonserious, did not require treatment [resolved in 2 subjects]; a fourth subject was reported with myalgia and arthralgia of moderate severity and later diagnosed with dermatomyositis (on Day 172).

During the MTP, for subjects in the Q4W/Q4W group, the Q4W/Q8W group, the Q4W/PBO group, and the PBO/PBO group, respectively; TEAEs of CPK increased were reported for 2 (1.2%), 3 (1.8%), 3 (1.8%), and 2 (1.1%) subjects. A TEAE of “Blood creatine phosphokinase increased” was reported for 1 subject in the PBO/PBO group.

No TEAE of “Rhabdomyolysis” was reported during ARCADIA 1 and ARCADIA 2 trials.

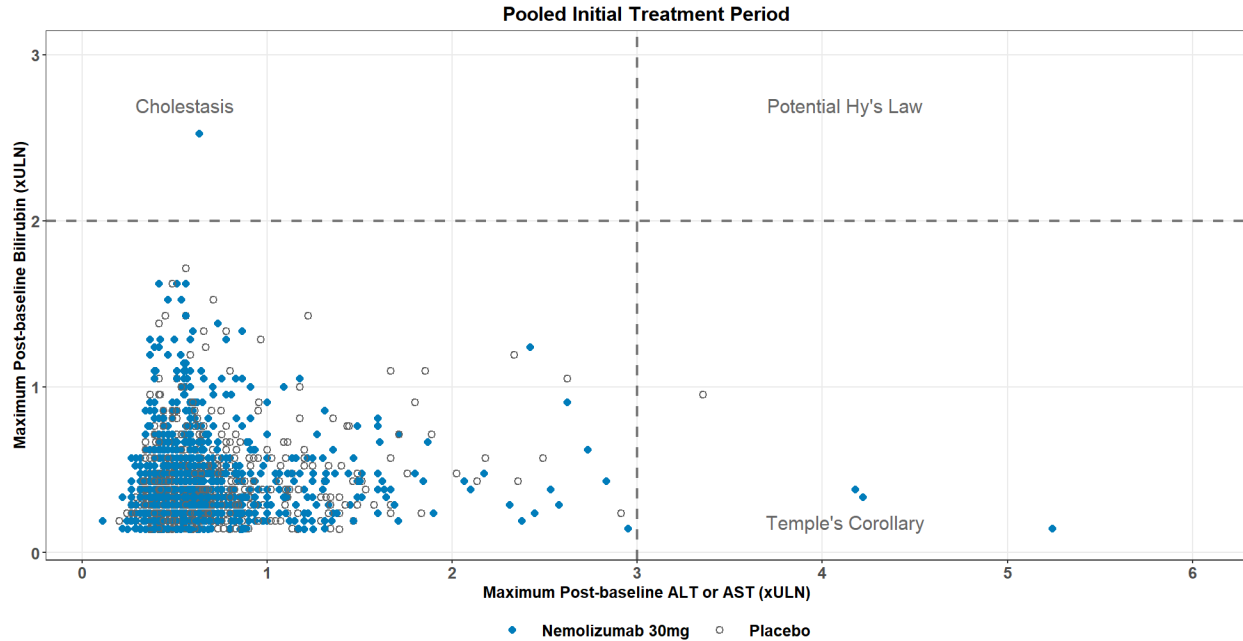
7.6.1.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials ARCADIA 1 and ARCADIA 2

No subject was reported with concomitantly elevated transaminases (ALT or AST $>3 \times \text{ULN}$) and bilirubin ($>2 \times \text{ULN}$) 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 during ARCADIA 1 and ARCADIA 2 trials.

During the ITP of ARCADIA 2 trial, a 26-year-old female subject (ID: (b) (6)) was reported with an elevated bilirubin level ($>2 \times \text{ULN}$). This subject’s ALT, AST, and ALP measurements were within normal range (depicted in the left upper [cholestasis] quadrant of [Figure 6](#) below). This subject’s pattern of liver enzymes elevation does not appear to be consistent with a drug-

induced liver injury. Drug-induced liver injury screening plots are depicted in Figure 6 and Table 36.

Figure 6. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)



Source: CDS Reviewer, adlb.xpt; Software: R

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: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ITP, initial treatment period; ULN, upper limit of normal

Table 36. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Quadrant	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16	
	Nemolizumab		Nemolizumab Placebo		Nemolizumab	
	30 mg N=616	Placebo N=321	30 mg N=519	N=263 n/N _w	30 mg N=1135	Placebo N=584
	n/N _w (%)	n/N _w (%)	n/N _w (%)	(%)	n/N _w (%)	n/N _w (%)
Potential Hy's law (right upper)	0/589 (0)	0/314 (0)	0/496 (0)	0/251 (0)	0/1085 (0)	0/565 (0)
Cholestasis (left upper)	0/589 (0)	0/314 (0)	1/496 (0.2)	0/251 (0)	1/1085 (0.1)	0/565 (0)
Temple's corollary (right lower)	3/589 (0.5)	1/314 (0.3)	0/496 (0)	0/251 (0)	3/1085 (0.3)	1/565 (0.2)
Total	3/589 (0.5)	1/314 (0.3)	1/496 (0.2)	0/251 (0)	4/1085 (0.4)	1/565 (0.2)

Source: 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: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ITP, initial treatment period; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of patients with data; ULN, upper limit of normal

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

No trends for changes over time or clinically significant changes in weight, systolic or diastolic blood pressures, heart rate, temperature, or ECGs (evaluated by external cardiac ECG experts) were reported for subjects in the nemolizumab or placebo groups during the ITP or MTP. No TEAEs of weight increased or weight decreased was reported in any subject treated with nemolizumab.

7.6.1.9. Subgroups, Pooled Analyses, Trials ARCADIA 1 and ARCADIA 2

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 (a relatively small number of subjects of Hispanic or Latino ethnicity were enrolled in the ARCADIA 1 and ARCADIA 2 trials [including 107/1135 in the nemolizumab group and 51/584 subjects in the placebo groups]).

The results for the subgroup analysis by the Applicant and by the Clinical Data Scientist Reviewer for BLA 761391 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. A trend for the reported frequency of TEAEs during the ITP is summarized below. During the MTP, no meaningful comparisons could be made among different subgroups by age, sex, race, or ethnicity for the frequency of TEAEs reported for nemolizumab-treated subjects because of the small number of subjects in each subgroup.

An overview of TEAEs by demographic subgroups reported during the ITP are presented below and summarized in the following tables (Table 37 and Table 38).

TEAEs by Age Groups

For the nemolizumab-treated subjects, the frequency of TEAEs reported was greater for ages between 18 to 65 years of age (48.7%), compared to subjects between 12 to 17 years of age (36.4%) or subjects > 65 years of age (33.3%). ARs were reported for subjects between 18 to 65 years of age (19.1%), compared to subjects between 12 to 17 years of age (10.8%) or subjects > 65 years of age (11.1%). SAEs, severe AEs, AELDs, and AESIs were reported with similar frequency. The only TEAEs reported at ($\geq 5\%$) frequency for any subgroup included dermatitis atopic for (11.3% versus 5.7% versus 9.7%) respectively.

TEAEs by Sex

For the nemolizumab-treated subjects, the frequency of TEAEs reported was similar between female (46.4%) and male (45.5%) subjects. SAEs, ARs, AELDs, and AESIs were reported with similar frequency. Severe TEAEs were reported at a lower frequency for female (2.7%) compared to male (4.5%) subjects. TEAEs reported at ($\geq 5\%$) frequency for female compared to male subjects, respectively, included dermatitis atopic (8.1% versus 12.7%) and headache (6.4% versus 2.0%).

TEAEs by Race and Ethnicity

For the nemolizumab-treated subjects, the frequency of TEAEs reported by race subgroups was similar between Asian, Black/African American, or White subjects. No meaningful comparison could be made among small number of subjects in other Race subgroups.

For the nemolizumab-treated subjects, the frequency of TEAEs reported by ethnicity subgroups was higher for Non-Hispanic/Non-Latino (48.0%) subjects compared to Hispanic/Latino (27.1%) subjects.

Table 37. Overview of Adverse Events by Demographic Subgroup, Safety Population, ITPs for ARCADIA 1 (spr118161) & ARCADIA 2 (spr118169)

Characteristic	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab 30 mg N=616	Placebo N=321	Nemolizumab 30 mg N=519	Placebo N=263	Nemolizumab 30 mg N=1135	Placebo N=584	Nemolizumab 30 mg Vs. Placebo Risk Difference % (95% CI)
	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	
Sex							
Female	150/295 (50.8)	69/144 (47.9)	112/270 (41.5)	67/136 (49.3)	262/565 (46.4)	136/280 (48.6)	-2.2 (-9.3, 4.9)
Male	156/321 (48.6)	77/177 (43.5)	103/249 (41.4)	50/127 (39.4)	259/570 (45.4)	127/304 (41.8)	3.7 (-3.3, 10.5)
Age group, years							
12 to 17	32/85 (37.6)	19/49 (38.8)	32/91 (35.2)	16/40 (40.0)	64/176 (36.4)	35/89 (39.3)	-3.0 (-15.5, 9.1)
18 to 65	260/501 (51.9)	123/263 (46.8)	175/392 (44.6)	97/208 (46.6)	435/893 (48.7)	220/471 (46.7)	2.0 (-3.6, 7.6)
>65	14/30 (46.7)	4/9 (44.4)	8/36 (22.2)	4/15 (26.7)	22/66 (33.3)	8/24 (33.3)	-0.0 (-22.9, 20.1)
Age group ≥65, years							
≥65	14/32 (43.8)	5/13 (38.5)	10/42 (23.8)	5/18 (27.8)	24/74 (32.4)	10/31 (32.3)	0.2 (-20.2, 18.4)
Age group ≥75, years							
≥75	2/3 (66.7)	0/2 (0)	4/12 (33.3)	0/4 (0)	6/15 (40.0)	0/6 (0)	40.0 (-5.0, 64.8)
Race							
American Indian or Alaska Native	2/2 (100)	1/3 (33.3)	0/1 (0)	0/0 (NA)	2/3 (66.7)	1/3 (33.3)	33.3 (-45.0, 82.7)
Asian	51/115 (44.3)	19/51 (37.3)	14/35 (40.0)	8/17 (47.1)	65/150 (43.3)	27/68 (39.7)	3.6 (-10.6, 17.2)
Black or African American	7/36 (19.4)	7/18 (38.9)	9/25 (36.0)	6/20 (30.0)	16/61 (26.2)	13/38 (34.2)	-8.0 (-26.9, 10.2)
Multiple	7/10 (70.0)	4/4 (100)	0/0 (NA)	0/0 (NA)	7/10 (70.0)	4/4 (100)	-30.0 (-61.3, 26.5)
Native Hawaiian or other Pacific Islander	0/1 (0)	0/0 (NA)	1/1 (100)	0/0 (NA)	1/2 (50.0)	0/0 (NA)	NA
Other	3/3 (100)	1/1 (100)	1/2 (50.0)	0/0 (NA)	4/5 (80.0)	1/1 (100)	-20.0 (-65.6, 70.0)
White	236/449 (52.6)	114/244 (46.7)	190/455 (41.8)	103/226 (45.6)	426/904 (47.1)	217/470 (46.2)	1.0 (-4.6, 6.5)

Characteristic	ARCADIA 1 ITP Baseline to Week 16		ARCADIA 2 ITP Baseline to Week 16		Pooled ITP Period Baseline to Week 16		
	Nemolizumab		Nemolizumab		Nemolizumab		Nemolizumab
	30 mg N=616 n/N _s (%)	Placebo N=321 n/N _s (%)	30 mg N=519 n/N _s (%)	Placebo N=263 n/N _s (%)	30 mg N=1135 n/N _s (%)	Placebo N=584 n/N _s (%)	30 mg Vs. Placebo Risk Difference % (95% CI)
Ethnicity							
Hispanic or Latino	19/64 (29.7)	9/32 (28.1)	10/43 (23.3)	4/19 (21.1)	29/107 (27.1)	13/51 (25.5)	1.6 (-13.9, 15.4)
Not Hispanic or Latino	285/548 (52.0)	136/288 (47.2)	200/463 (43.2)	113/242 (46.7)	485/1011 (48.0)	249/530 (47.0)	1.0 (-4.3, 6.2)
Not reported	1/2 (50.0)	1/1 (100)	4/11 (36.4)	0/2 (0)	5/13 (38.5)	1/3 (33.3)	5.1 (-50.0, 48.0)
Unknown	1/2 (50.0)	0/0 (NA)	1/2 (50.0)	0/0 (NA)	2/4 (50.0)	0/0 (NA)	NA
Is in United States							
United States	45/137 (32.8)	31/72 (43.1)	29/129 (22.5)	19/64 (29.7)	74/266 (27.8)	50/136 (36.8)	-8.9 (-18.8, 0.6)
Non-United States	261/479 (54.5)	115/249 (46.2)	186/390 (47.7)	98/199 (49.2)	447/869 (51.4)	213/448 (47.5)	3.9 (-1.8, 9.6)

Source: CDS Reviewer, adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; ITP, initial treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

Table 38. Overview of Adverse Events by Demographic Subgroup, Safety Population, MTP and Full Periods for ARCADIA 1 & ARCADIA 2

Characteristic	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170	Nemo Q4W to Nemo Q8W N=167	Nemo Q4W to Placebo N=168	Placebo to Placebo N=184	Nemo Q4W to Nemo Q4W N=170	Nemo Q4W to Nemo Q8W N=167	Nemo Q4W to Placebo N=168	Placebo to Placebo N=184
	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)
Sex								
Female	67/100 (67.0)	66/96 (68.8)	79/107 (73.8)	55/93 (59.1)	67/100 (67.0)	66/96 (68.8)	79/107 (73.8)	55/93 (59.1)
Male	46/70 (65.7)	46/71 (64.8)	42/61 (68.9)	59/91 (64.8)	46/70 (65.7)	46/71 (64.8)	42/61 (68.9)	59/91 (64.8)
Age group, years								
12 to 17	17/35 (48.6)	24/32 (75.0)	24/31 (77.4)	30/42 (71.4)	17/35 (48.6)	24/32 (75.0)	24/31 (77.4)	30/42 (71.4)
18 to 65	93/128 (72.7)	84/128 (65.6)	86/119 (72.3)	82/129 (63.6)	93/128 (72.7)	84/128 (65.6)	86/119 (72.3)	82/129 (63.6)
>65	3/7 (42.9)	4/7 (57.1)	11/18 (61.1)	2/13 (15.4)	3/7 (42.9)	4/7 (57.1)	11/18 (61.1)	2/13 (15.4)
Age group ≥65, years								
≥65	3/7 (42.9)	5/9 (55.6)	12/19 (63.2)	2/14 (14.3)	3/7 (42.9)	5/9 (55.6)	12/19 (63.2)	2/14 (14.3)
Age group ≥75, years								
≥75	1/2 (50.0)	1/1 (100)	2/4 (50.0)	0/4 (0)	1/2 (50.0)	1/1 (100)	2/4 (50.0)	0/4 (0)
Race								
American Indian or Alaska Native	0/0 (NA)	0/0 (NA)	0/1 (0)	0/0 (NA)	0/0 (NA)	0/0 (NA)	0/1 (0)	0/0 (NA)
Asian	11/15 (73.3)	11/19 (57.9)	5/11 (45.5)	6/10 (60.0)	11/15 (73.3)	11/19 (57.9)	5/11 (45.5)	6/10 (60.0)
Black or African American	5/8 (62.5)	1/6 (16.7)	6/8 (75.0)	4/8 (50.0)	5/8 (62.5)	1/6 (16.7)	6/8 (75.0)	4/8 (50.0)
Multiple	0/1 (0)	0/0 (NA)	2/2 (100)	2/2 (100)	0/1 (0)	0/0 (NA)	2/2 (100)	2/2 (100)
Other	0/0 (NA)	1/1 (100)	0/0 (NA)	0/0 (NA)	0/0 (NA)	1/1 (100)	0/0 (NA)	0/0 (NA)
White	97/146 (66.4)	99/141 (70.2)	108/146 (74.0)	102/164 (62.2)	97/146 (66.4)	99/141 (70.2)	108/146 (74.0)	102/164 (62.2)

Characteristic	MTPs (Week 16 to Week 48) ARCADIA 1 & 2				Full Period (Week 0 to Week 48) ARCADIA 1 & 2			
	Nemo Q4W to Nemo Q4W N=170	Nemo Q4W to Nemo Q8W N=167	Nemo Q4W to Placebo N=168	Placebo to Placebo N=184	Nemo Q4W to Nemo Q4W N=170	Nemo Q4W to Nemo Q8W N=167	Nemo Q4W to Placebo N=168	Placebo to Placebo N=184
	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)	n/N _s (%)
Ethnicity								
Hispanic or Latino	5/12 (41.7)	16/26 (61.5)	12/23 (52.2)	6/22 (27.3)	5/12 (41.7)	16/26 (61.5)	12/23 (52.2)	6/22 (27.3)
Not Hispanic or Latino	108/158 (68.4)	96/138 (69.6)	109/144 (75.7)	108/161 (67.1)	108/158 (68.4)	96/138 (69.6)	109/144 (75.7)	108/161 (67.1)
Not reported	0/0 (NA)	0/3 (0)	0/1 (0)	0/1 (0)	0/0 (NA)	0/3 (0)	0/1 (0)	0/1 (0)
Is in United States								
United States	15/31 (48.4)	25/44 (56.8)	28/46 (60.9)	17/46 (37.0)	15/31 (48.4)	25/44 (56.8)	28/46 (60.9)	17/46 (37.0)
Non-United States	98/139 (70.5)	87/123 (70.7)	93/122 (76.2)	97/138 (70.3)	98/139 (70.5)	87/123 (70.7)	93/122 (76.2)	97/138 (70.3)

Source: CDS Reviewer, adae.xpt; Software: R

Abbreviations: MTP, maintenance treatment period; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; Nemo, nemolizumab; Ns, total number of patients for each specific subgroup and were assigned to that specific arm; Q4W, every four weeks; Q8W, every eight weeks

7.7. Key Safety Review Issues

No Key Safety Review Issues were identified.

8. Therapeutic Individualization

8.1. Intrinsic Factors

Age

The Applicant proposed no dose adjustment for adolescent (12 to 17 years) or 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. No clinically meaningful differences could be observed in the PK of nemolizumab across different age categories (12 to 17 years, 18 to 65 years, and >65 years).

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. However, the difference in exposure between the upper- and lower-weight quartiles was less than 2-fold, and no impact on efficacy was observed, supporting the appropriateness of the proposed flat dosing of 30 mg Q4W (with an initial dose of 60 mg) for patients with AD. PK/PD simulations of clinical endpoints at Week 16 showed a similar response across body weight groups (EASI-75 responder rates and PP-NRS responder rates), suggesting that exposure variability due to subject body weight did not result in a clinically meaningful difference in efficacy. Therefore, the proposed dosing regimen of 30 mg Q4W (with an initial dose of 60 mg) is considered adequate, and no dose adjustment based on body weight is necessary.

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. Therefore, the Applicant conducted a phase 2, open-label, single-sequence, drug-drug interaction study in adult subjects with moderate-to-severe AD to evaluate the effect of nemolizumab on the PK of a drug “cocktail” representative of cytochrome P450 (CYP450) sensitive index substrates (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) (Study 201593). Results of this study showed that for all CYP substrates, the observed geometric means for both maximum plasma concentration (C_{max}) and AUC were similar before and after nemolizumab treatment, with geometric mean test/reference ratios ranging from 88.24% to 107.81%. There was no clinically meaningful effect of nemolizumab treatment on the metabolism of the assessed CYP substrates, defined as a greater than 2-fold decrease of observed geometric means after nemolizumab injections.

8.3. Plans for Pediatric Drug Development

Refer to Section [24](#) (Postmarketing Requirements and Postmarketing Commitments) of this IAMA review regarding the planned postmarketing studies for pediatric subjects between 6 months to <12 years of age.

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](#) 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 (PND) 35. No maternal or embryofetal toxicities were observed at doses up to 25 mg/kg (50 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 (168 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 to 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 761391 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 postmarketing commitments (and any other post-approval quality agreements) between OPQ and the Applicant are listed below and should be included in the action letter.

4721-3	Conduct three shipping validation runs	(b) (4)
		(b) (4)
	to cover DCC shipping	(b) (4) to the USA

from a temperature control perspective. Provide the report and summary validation data.

Final Report Submission: 10/2025

- 4721-4 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: 10/2025

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

Refer to Sections [22](#) and [25](#) of this IAMA review.

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, atopic dermatitis.

III. Additional Analyses and Information

12. Summary of Regulatory History

Biologics License Application (BLA) 761391 for NEMLUVIO (nemolizumab-ilto) for the treatment of atopic dermatitis (AD) was submitted under section 351(a) of the Public Health Service (PHS) Act on December 13, 2023. The associated investigational new drug (IND) (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 IL-31 signaling by binding to the IL-31 receptor alpha (IL-31R). The Applicant submitted BLA 761390 simultaneously for the treatment of prurigo nodularis (PN). This approach was discussed during the two pre-BLA meetings which took place on April 24, 2023, for the AD indication and April 26, 2023, for the PN indication. The PN indication was approved August 12, 2024, for the pre-filled pen, 30 mg/0.49 mL presentation at which time the proprietary name of NEMLUVIO was approved.

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

- February 20, 2013, Pre-IND meeting.
- November 22, 2013: IND 117122 Study May Proceed.
- August 5, 2014, Pediatric Study Plan - Written Response.
- July 2, 2014, chemistry, manufacturing, and control (CMC) Meeting: to discuss Chemistry, Manufacturing and Controls nemolizumab (CIM331) development program.
- March 13, 2017, Guidance Meeting: The Agency agreed that the proposed doses are supported by the available clinical safety data. The Agency expressed concern that the pruritus visual analog scale endpoint and the exposure-response relationship from pharmacokinetic/pharmacodynamic (PKPD) modeling were the basis for the dose selection and stated that phase 2 dose-ranging trials should include the efficacy endpoints that will be used in the phase 3 studies. The initial Pediatric Study Plan (iPSP) should be submitted for review. The Agency agreed that the Sponsor's plan to request a waiver for the Thorough QT/QTc study but continue to perform electrocardiograms (ECGs) for safety appeared reasonable. The Agency agreed that the existing nonclinical and clinical data appear to support the proposed phase 2b dose-ranging study. The Agency requested that the Sponsor should revise their proposed Eczema Area and Severity Index (EASI) score in order that patients with moderate-to-severe disease will be enrolled. The proposed use of topical corticosteroids (TCS) as adjunctive therapy to nemolizumab and the choice of TCS and proposed TCS regimen during run-in period and during treatment period of the study appeared to be acceptable. The Agency asked for additional qualitative and quantitative evidence to support the relevance of the Sleep Disturbance NRS. The Agency expressed concerns regarding the SCORing Atopic Dermatitis (SCORAD) design.
- July 6, 2017, PSP – Initial No Agreement.

- March 7, 2018, Stalled Development Pediatric Study Plan Meeting. The Agency stated that the proposed stepwise approach to pediatric development of nemolizumab is acceptable. The Agency did not agree with the partial extrapolation approach for efficacy (i.e., use of controlled data from the adult and adolescent studies). The Agency expressed concerns that the use of M&S would be adequate to support partial extrapolation for efficacy for nemolizumab in pediatrics with AD. The Agency agreed that it would be difficult to establish the failure of topical therapy to adequately control disease in children <6 months and that the Sponsor's request for waiver was acceptable. The proposal to defer submission of data from completed studies in the 2 to 11 year age group until post-BLA approval was acceptable. The Sponsor's proposal regarding deferral of evaluation of subjects 6 to 23 months was acceptable. The proposed age categorizations were acceptable. However, the Agency did not agree with the definitions of disease severity for the study populations, nor the proposed corresponding indications. The Sponsor's approach to assessment of long-term use of nemolizumab in pediatric populations appeared to be acceptable. The Sponsor's waiver request for conduct of carcinogenicity studies was granted, at that time.
- September 12, 2018, Guidance Meeting: The Agency did not commit to review the pediatric study protocols within a 60-day window. The Agency agreed to review assess the pharmacokinetic (PK) sampling scheme of the phase 3 studies when the protocols are submitted in the IND. The proposal appeared to be reasonable for evaluation of whether the phase 3 dosing regimen is appropriate for adolescents. The Sponsor proposed not pre-specify the MCID and will instead use "multiple approaches to determine the MCID and to evaluate its robustness." The Agency did not agree with this approach and stated that the endpoints should be pre-specified. The proposed safety assessments appeared to be acceptable. Post-treatment follow-up through five half-lives seemed reasonable. The Agency expressed concerns with respect to the proposed PRO instruments to measure sleep disturbance had some concerns based on the current version of the instruments. The Agency recommended a safety database that includes 750 subjects with moderate to severe atopic dermatitis who have received the to-be marketed dose for at least 1 year; and of the 750 subjects, a minimum of 30% should be between the ages of 12 and 17 years old. The Agency provided comments on visual analog scale, Average Pruritus Numerical Rating Scale (AP-NRS), Peak Pruritus Numeric Rating Scale (PP-NRS), patient global impression of severity [PGIS] scale, and the Patient global impression of change [PGIC] scale.
- October 24, 2018, Guidance Meeting: The Agency expressed concerns that (b) (4)
(b) (4). The Agency expressed concerns regarding how the Sponsor would ensure consistent and routine training to be provided in real world use. The Agency requested that the HF validation study protocol be submitted to the IND for review.

- October 30, 2018, chemistry, CMC Meeting: The Agency provided advice regarding the CMC development program for nemolizumab. The Agency expressed concerns that (b) (4)
(b) (4)
(b) (4)
(b) (4) The Agency did not agree with the comparability assessment plan to support comparability of Phase 2b clinical products and Phase 3 clinical products and provided advice regarding data needed to support the comparability.
- March 20, 2019, End of Phase 2 Meeting: The Agency agreed that the Sponsor should provide complete information for the device constituent of your combination product in your future BLA submission. Additionally, a device description and design control information should be provided under the IND. The Agency stated that the to-be-marketed product be evaluated in the clinical studies. The Agency agreed that the nonclinical program appears reasonable to support the BLA submission of nemolizumab. The Agency stated that although the pharmacokinetics/pharmacodynamics (PK/PD) approach could be a viable approach, it was premature to provide any agreement based on the new evidence that was submitted. The Agency stated that it was premature to provide any agreement at this stage as PK assessment to support dosing in adolescent subjects is pending. The popPK approach is reasonable. The PK/PD approach is reasonable. The Agency did not agree that the Sponsor use lyophilized powder for solution supplied in single-use vials (Vial) for administration of nemolizumab in previous clinical studies including the phase 2b dose ranging study RD.03.SPR.114322 and in the phase 3 clinical studies, the Sponsor use lyophilized powder for reconstitution in a DCS. The Agency recommended that the Sponsor submit additional modeling and simulation PK and efficacy data to support their dose selection. The Agency provided comments regarding the pivotal phase 3 proposed study design.
- May 31, 2019, Pediatric Study Plan – Written Response.
- November 27, 2019, Advice: The Agency provided advice regarding two phase 3 protocols (RD.06.SPR.118161 and RD.06.SPR.118169) both entitled, “A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis.”
- April 22, 2020, Guidance Meeting: The Agency agreed that no further validation of the PP-NRS was needed in adult and adolescent patients who can validly and reliably self-report. The Agency expressed concerns about the psychometric properties of the sleep disturbance (SD) NRS. The Agency expressed concerns for the revised Subject Sleep Diary.
- October 13, 2020, Advice/information request: The Agency provided comments and recommendations regarding a drug-drug interaction phase 3 protocol entitled, “An Open-label Drug-Drug Interaction Study to Assess the Effects of Nemolizumab on Cytochrome P450 Substrates in Subjects with Moderate-to-Severe Atopic Dermatitis”
- December 1, 2020, Guidance Meeting: The Agency agreed that the direct enrollment of adolescents into an LTE study in addition to the 2 pivotal studies. A total of 120 adolescent subjects exposed for 1 year may be reasonable for assessing safety in this population.

- December 8, 2020, Advice letter: The Agency conveyed recommendations regarding the HF validation study protocol.
- July 1, 2021: Human Factors Advice letter: The Agency outlined areas of disagreement.
- August 2, 2021, Pediatric Study Plan – Amended Agreement.
- September 8, 2021, CMC 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 AP-NRS comparability. Agreement was reached on the control strategy, stability study program, shelf life, and study comparing the dual-chamber syringe and autoinjector.
- 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.
- 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 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.
- 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 24, 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.
- August 22, 2023, Advice: The Agency agreed with the request of not conducting a dedicated QT/QTc study/substudy for nemolizumab.

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 AD and 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 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 (CDC) 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 behaviors 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 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 39. 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)	<u>Monkey (single IV or SC dose)</u> $T_{1/2}$: 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-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)	<u>Monkey</u> 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 cynomolgus monkeys (Study# SBL036-185)	<u>Monkey</u> Concentrations of nemolizumab in offspring plasma on postnatal day (PND) 7 were comparable to those in dams, suggesting that nemolizumab crossed the placenta.

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)	<u>Monkey</u> 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)	<u>Monkey (biweekly dosing for 6 months)</u> AUC _{0-14 day} (following the 13 th 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 13 th dose to AUC after 1 st 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)	<u>Maternal monkey (biweekly dosing from gestation day 20 to delivery)</u> AUC _{0-14 day} (following the 9 th 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. <u>Offspring monkey (biweekly dosing from PND 35 to 217)</u> AUC _{0-14 day} (following the 13 th 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--inf}, area under the concentration-time curve from time 0 to infinity; AUC_{0--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:

(b) (4) mM Tris-HCl (b) (4) solution containing (b) (4) mM arginine, (b) (4) mM sucrose and (b) (4) 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.

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, *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 (ECAC) of Center for Drug Evaluation and Research. The ECAC 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

Key Study Findings

- 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:	(b) (4) mM Tris-HCl (b) (4) solution containing (b) (4) mM arginine, (b) (4) mM sucrose and (b) (4) 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

Generation	Major Findings																																		
F0 Dams	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.																																		
F1 Offspring	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.	Dose Level	Number of Animals						Pregnant animals for each group	Fetal losses before delivery	Stillbirth	Early postnatal death	Euthanized offspring	Offspring surviving to PND 220	Control	16	2	0	1	0	13	1 mg/kg	16	1	3	0	2	10	25 mg/kg	16	2	0	3	0	11
Dose Level	Number of Animals																																		
	Pregnant animals for each group	Fetal losses before delivery	Stillbirth	Early postnatal death	Euthanized offspring	Offspring surviving to PND 220																													
Control	16	2	0	1	0	13																													
1 mg/kg	16	1	3	0	2	10																													
25 mg/kg	16	2	0	3	0	11																													

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, (b) (4), 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 is (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 (FDA 2023) to set the identification threshold and daily acceptable levels for leachables. The proposed maximum clinical dose is 30 mg 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 to 10 years) was used. The maximum daily dosing volume of this product is (b) (4) ml. Therefore, the acceptable limit for unidentified organic leachables was set as (b) (4) 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

Recommended revisions to the Applicant's proposed wording for the nonclinical portions of labeling are provided below. It is recommended that the underlined wording be inserted into and the ~~striketrough~~ wording be deleted from the text of the NEMLUVIO label proposed by the Applicant.

(b) (4)

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

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 moderate-to-severe atopic dermatitis (AD) in patients aged 12 years and older. Nemolizumab was previously approved for the treatment of adult patients with PN on August 12, 2024 (BLA 761390). This summary of clinical pharmacology provides an overview of clinical pharmacology data including PK, immunogenicity, and modeling and simulation approaches (population PK, PK/PD), and exposure-safety analyses) to support the application for nemolizumab for the treatment of adolescent and adult patients with AD. The proposed dosing regimen by the Applicant is an initial dose of 60 mg followed by SC doses of 30 mg given every 4 weeks (Q4W). After 16 weeks of treatment, for those who achieve clear or almost clear skin, a dosage of 30 mg (b) (4)

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), 3 phase 2 studies in AD (Studies CIM003JG, 114322, and 116912), two phase 3 trials in AD (Study 118161 and 118169), and one ongoing phase 3 long-term extension study (Study 118163). The Applicant has also submitted one phase 2 study and two phase 3 trials in

subjects with PN as supporting information. The PK results of the PN trials are not individually summarized in this review and were included as part of the review for BLA 761390.

PK Assessment

PK was assessed in the following studies:

- Study CIM001JP (First-in-human study in healthy subjects and subjects with AD)
- The PK data from 7 clinical studies in subjects with moderate-to-severe AD (CIM001JP Part C, CIM003JG, 114322, 116912, 118161, 118169, and 118163).
- The PK data from an additional 3 studies in subjects with PN, used in the population PK modeling to provide additional supportive PK information for the proposed indication (Studies 115828, 202685, and 203065).
- The PK data from one relative bioavailability bridging study in healthy subjects (Study 201590).
- PK data from one open-label drug-drug interaction study to assess the effects of nemolizumab on Cytochrome P450 substrates in subjects with moderate-to-severe atopic dermatitis.

The clinical pharmacology program also includes population PK analyses, PK/PD analyses for efficacy, and exposure-safety analyses. 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 SC doses of nemolizumab across phase 1, phase 2 and 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 AD. The relationships between nemolizumab PK and clinical efficacy assessments over time (EASI, IGA and 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 adverse events (TEAEs): dermatitis atopic flares, newly diagnosed asthma or worsening of asthma, facial edema, and peripheral edema defined based on the Medical Dictionary for Regulatory Activities preferred terms.

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)

[REDACTED]. 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 AD (Studies CIM003JG, 114322, and 116912), 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. In the phase 3 studies in subjects with AD (Studies 118161, 118169, AND 118163), 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). 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 (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-last} , and AUC_{0-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 40.

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 ($<0.1 \mu\text{g/mL}$). 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 40. Mean Pharmacokinetic Parameters by Dose and Population, Study CIM001JP

Population	Dose mg/kg	n	AUC _{0-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-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

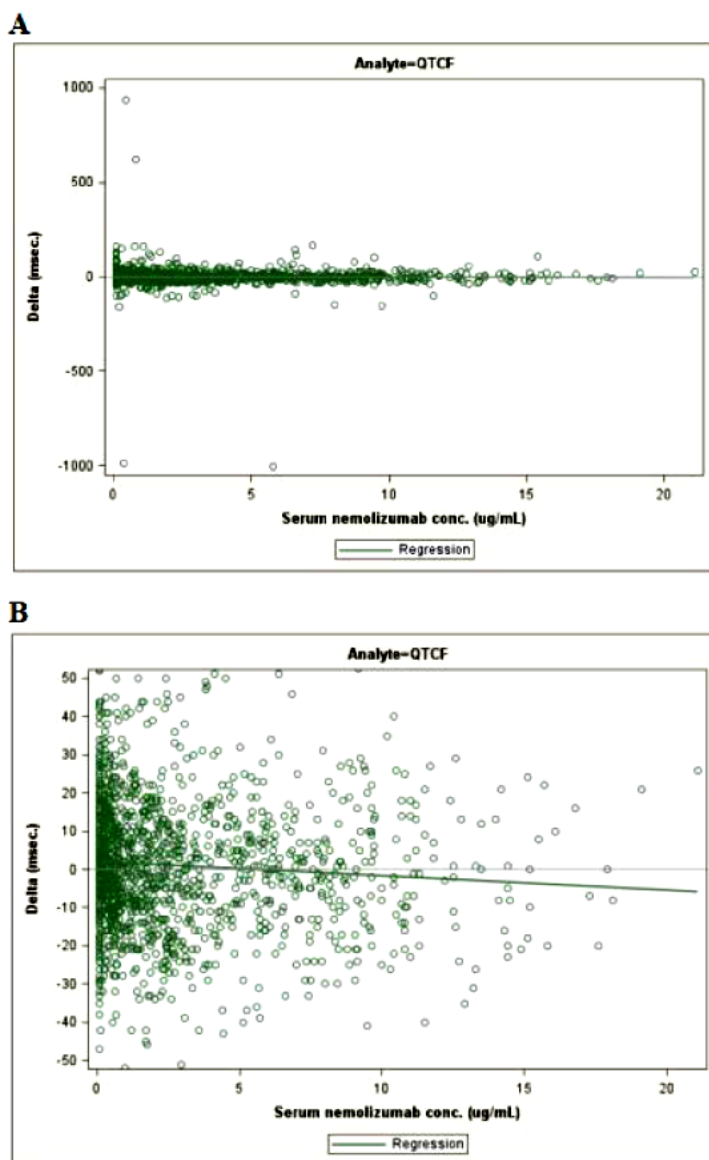
Healthy Japanese Adult Males and Healthy White Adult Males PK Comparison

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-inf}), area under the concentration-time curve from time 0 to the time of the last quantifiable sample (AUC_{0-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 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 7](#) 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 ECG parameters have been observed, based on the evaluation of mean values, potentially clinically significant values, and adverse events (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 7. 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 41. Mean nemolizumab concentration-time profile following a single 60-mg SC dose via the DCC-AI and the DCS are presented in [Figure 8](#)

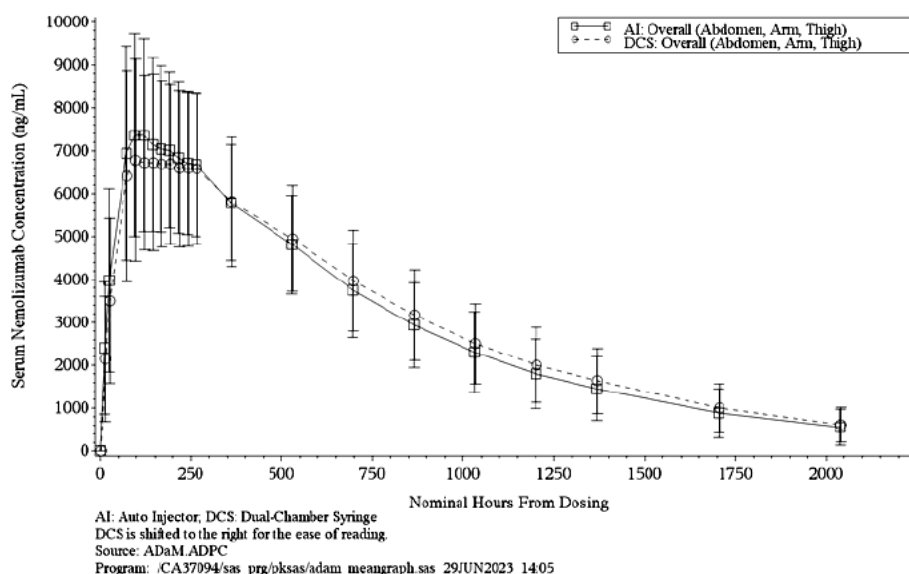
Table 41. Serum Nemolizumab PK Parameters Following Administration of 60 mg SC Nemolizumab, Study 201590 (PK Population)

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 _{0-4 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-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-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±5.91 ^b	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±1.76 ^b	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-inf}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last measured concentration; AUC_{0-4 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 8. 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; PK, pharmacokinetic; SC, subcutaneous; SD, standard deviation

The percentage geometric least square mean ratios (GLSMRs) for C_{max} and for AUC_{0-inf} were close to 100%; and the 90% CIs were within the no effect boundary of 80.00% to 125.00% (Table 42). The 90% CIs of the percentage GLSMRs for area under the concentration-time curve from time 0 to 4 weeks post-dose ($AUC_{0-4 \text{ weeks}}$) and area under the concentration-time curve from time 0 to the time of the last quantifiable sample (AUC_{0-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 42. 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-inf} ($\mu\text{g}\cdot\text{day}/\text{mL}$)	257.62	95	263.71	96	97.69	90.39 – 105.59	33.36	0.5238	0.6201
C_{max} ($\mu\text{g}/\text{mL}$)	7.596	96	7.173	96	105.90	98.01 – 114.41	33.29	0.9354	0.2225
AUC_{0-last} ($\mu\text{g}\cdot\text{day}/\text{mL}$)	229.55	96	248.26	96	92.46	81.95 – 104.32	53.99	0.8407	0.2845
$AUC_{0-4 \text{ weeks}}$ ($\mu\text{g}\cdot\text{day}/\text{mL}$)	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-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-last} , area under the concentration-time curve from time 0 to last measured concentration; $AUC_{0-4 \text{ weeks}}$, 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 (antidrug antibodies) 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 ADAs (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 CIM003JG (Phase 2 in Adults)

This was a phase 2, randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety, tolerability, and efficacy of nemolizumab in subjects with AD. Part A was a 12-week, randomized, double-blind, placebo-controlled, parallel-group evaluation of 4 different dosage regimens of nemolizumab (0.1 mg/kg SC Q4W, 0.5 mg/kg SC Q4W, 2 mg/kg SC Q4W, and 2 mg/kg SC Q8W). Part B was a double-blind extension phase in which subjects continued to receive treatment with nemolizumab for a further 52 weeks (Weeks 12 to 64). Subjects who were randomized to placebo in Part A were re-randomized to nemolizumab (0.1, 0.5, or 2.0 mg/kg) SC Q4W in Part B. Placebo-treated subjects were not re-randomized to nemolizumab 2.0 mg/kg Q8W in Part B. Subjects randomized to 1 of the 4 regimens of nemolizumab in Part A continued to receive the same dosage they were receiving in Part A. A total of 264 subjects were randomized in the study, and 216 (81.8%) completed Part A. Of the 216 subjects who completed Part A, 191 (88.4%) participated in Part B. Of the 191 subjects, 131 (68.6%) completed Part B. The nemolizumab serum concentration, ADAs were assessed in Parts A and B as described in Table 43 and Table 44.

Table 43. Schedule of Assessments, Study CIM003JG - Part A

Assessment	Treatment period visit										Withdrawal	Safety FU
Week	0	1	2	3	4	6	8	10	12			
PK blood ^a	X	X	X	X	X	X	X		X	X	X	
ADA blood	X				X		X		X	X	X	
Biomarkers ^b	X				X				X	X		
TARC	X	X	X	X	X	X	X	X	X	X	X	

Source: CIM003JG CSR Table 9.3.

Abbreviations: ADA, antidrug antibody; FU, follow-up; PK, pharmacokinetic; TARC, thymus and activation-regulated chemokine

Table 44. Nemolizumab Pharmacokinetic Parameters (Study CIM003JG)

Assessment	Treatment period visit														Withdrawal	Safety FU
Week	12	16	20	24	28	32	36	40	44	48	52	56	60	64		
PK blood ^a	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ADA blood	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TARC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Source: CIM003JG CSR Table 9.4.

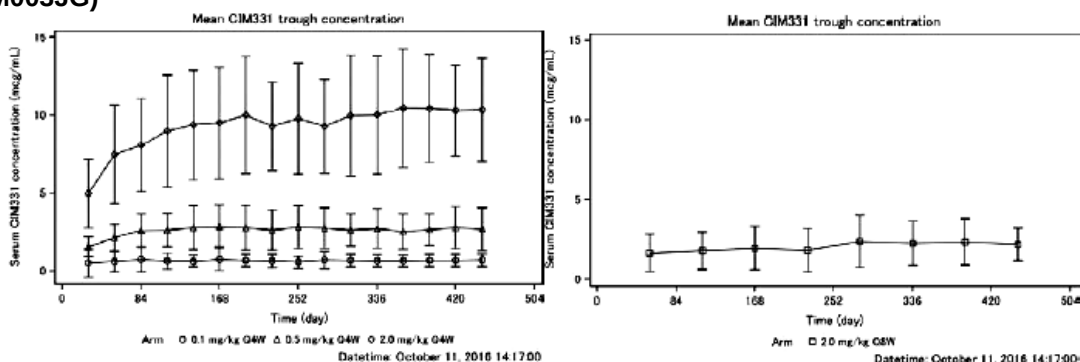
Abbreviations: ADA, antidrug antibody; FU, follow-up; PK, pharmacokinetic; TARC, thymus and activation-regulated chemokine

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are displayed in [Figure 9](#). Descriptive statistics of nemolizumab PK parameters are displayed in Table 45. PK analysis showed an initial peak in mean serum nemolizumab at approximately

7 days post-dose, which decreased slowly until Day 28. Exposure assessed by C_{max} and area under the concentration-time curve (AUC) appeared to increase with increasing dose. The mean time to maximum concentration (T_{max}) ranged from 7 to 9 days. The mean $t_{1/2}$ was 16 days. The median accumulation ratio of serum nemolizumab concentrations ranged from 1.54 to 1.84 when administered using the Q4W regimen. Mean serum nemolizumab C_{trough} values increased with increasing dose.

Figure 9. Serum Trough Concentration of Nemolizumab Administered Q4W or Q8W (Study CIM003JG)



Source: CIM003JG CSR Figure 11.11.

Abbreviations: CIM331, nemolizumab; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Table 45. Nemolizumab Pharmacokinetic Parameters (Study CIM003JG)

Arm	n	AUC _{0-28d} (day·µg/mL)	AUC _{0-last} (day·µg/mL)	AUC _{0-inf} (day·µg/mL)	C _{max} (µg/mL)	T _{max} (day)	t _{1/2} (day)
Q4W 0.1 mg/kg	51	21.3 (14.6)	21.4 (24.6)	—	1.26 (1.19)	6.96 (5.94, 20.9)	—
Q4W 0.5 mg/kg	54	64.9 (19.1)	62.8 (20.1)	—	3.45 (1.02)	6.95 (5.79, 21.0)	—
Q4W 2 mg/kg	52	228 (65.1)	228 (65.1)	—	12.7 (3.64)	6.98 (4.96, 29.0)	—
Q8W 2 mg/kg	51	231 (76.0)	291 (129)	363 (143)	12.7 (4.03)	6.94 (5.37, 13.9)	15.7 (5.10)

Source: CIM003JG CSR Table 11.63.

Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last measured concentration; AUC_{0-28d}, area under the concentration-time curve from 0 to 28 days; C_{max}, maximum plasma concentration; T_{max}, time to maximum concentration; t_{1/2}, half-life; Q4W, once every 4 weeks; Q8W, once every 8 weeks

For details on the efficacy results, refer to Section 6.

Study 114322 (Phase 2b in Adults)

This was a phase 2 randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study to evaluate the efficacy and safety of various doses of nemolizumab in subjects with moderate-to-severe AD. Nemolizumab was administered as an initial dose of 20, 60, or 90 mg on Day 1, followed by 10, 30, or 90 mg, respectively, Q4W until Week 20 (injections at Weeks 4, 8, 12, 16, and 20) and a 12-week follow-up period until Week 32. The total treatment duration was 24 weeks. A total of 226 subjects, with a mean age of 39.3 years (range: 18 to 82 years), were randomized across the 4 treatment groups and 182 subjects (80.5%) completed the study. The nemolizumab serum concentration, ADAs were assessed as described in Table 46.

Table 46. Schedule of Assessments (Study 114322)

Assessment	Treatment period visit										FU		ET	Unscheduled
Week	0	1	2	4	8	12	16	20	24	28	32			
PK blood	X	X	X	X	X	X	X	X	X	X	X	(X)	X	
ADA blood	X			X	X		X		X		X	(X)	X	
Biomarkers (including IgE)	X			X	X		X		X		X			
TARC	X	X	X	X	X	X	X	X	X	X	X	(X)		

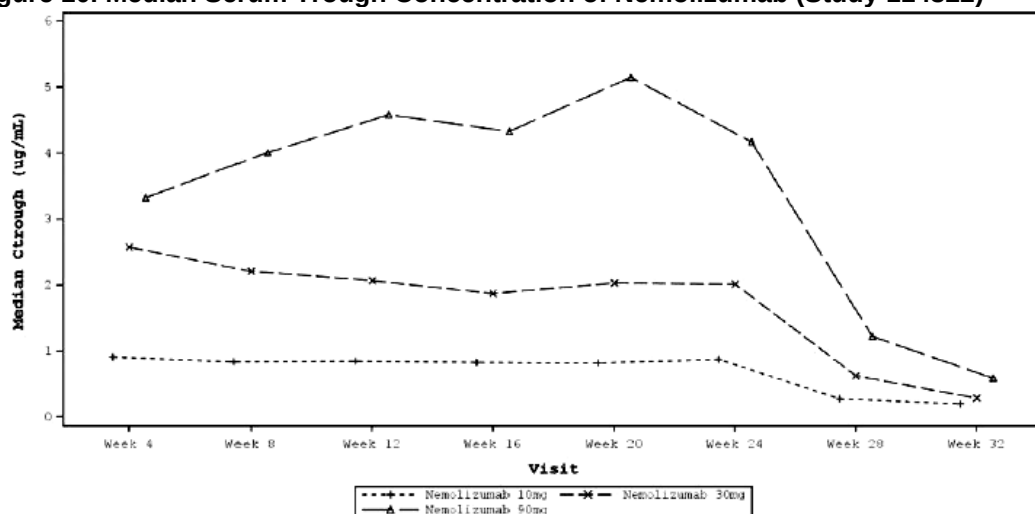
Source: 114322 CSR Table 2.

Abbreviations: ADA, antidrug antibody; ET, end of treatment; FU, follow-up; IgE, immunoglobulin E; PK, pharmacokinetics; TARC, thymus and activation-regulated chemokine

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are displayed in [Figure 10](#). Descriptive statistics of nemolizumab PK parameters are displayed in Table 47. For all dose groups, the peak concentrations after administration were reached approximately at the same time, with average mean T_{max} values of approximately 8 days. After the last administration, nemolizumab serum concentrations declined with a mono-exponential disposition. The $t_{1/2}$ was similar across each dose group around 18 to 20 days. Within the lower 2 dose groups, median C_{trough} values were comparable over the 24-week treatment period, with the median values ranging from 0.82 to 0.91 $\mu\text{g/mL}$ in the nemolizumab 10 mg group and from 1.87 to 2.58 $\mu\text{g/mL}$ for the 30 mg group. The median accumulation ratios for the nemolizumab 10 and 30 mg groups were 0.86 and 0.83, respectively. This time-consistency and the accumulation ratios below 1.0 suggested that the initial loading doses allowed nemolizumab concentrations to reach steady-state condition after the first administration., i.e., from Week 4. For the nemolizumab 90 mg group, the median C_{trough} increased from 3.33 $\mu\text{g/mL}$ at Week 4 to 5.15 $\mu\text{g/mL}$ at Week 20. Slight accumulation of nemolizumab was observed in the highest dose group, with a median accumulation ratio of 1.42. For the 90-mg dose group, steady state was reached at approximately Week 16 of treatment. PK assessments after SC injections of 3 flat doses (10 mg with 20 mg loading dose, 30 mg with 60 mg loading dose, and 90 mg without a loading dose) showed an increase of nemolizumab serum concentrations with the administered dose that was less than proportional to dose.

Figure 10. Median Serum Trough Concentration of Nemolizumab (Study 114322)



Source: 114322 CSR Figure 14.3.7.3.3.

Table 47. Nemolizumab Pharmacokinetic Parameters (Study 114322)

Treatment	N	AUC _{0-last} (day·µg/mL)	AUC _{0-28d} (day·µg/mL)	AUC _{0-12w} (day·µg/mL)	AUC _{0-24w} (day·µg/mL)	AUC _{0-inf} (day·µg/mL)	C _{max} (µg/mL)	T _{max} (day)	t _{1/2} (day)
10 mg (20 mg LD)	55	176 (99.7)	42.6 (24.4)	99.2 (49.0)	171 (81.6)	98.6 (48.0)	2.38 (1.569)	7.03 (5.6, 27.0)	19.6 (3.87)
30 mg (60 mg LD)	57	442 (183)	100 (29.4)	233 (75.5)	408 (145)	149 (55.8)	5.46 (1.713)	6.99 (4.9, 22.0)	18.4 (3.64)
90 mg	57	761 (393)	130 (37.6)	355 (119)	706 (297)	306 (151)	7.17 (2.020)	6.98 (5.8, 27.8)	18.1 (3.93)

Source: 114322 CSR Table 14.3.7.1.1.

Abbreviations: AUC_{0-inf}, area under the concentration-time curve from time 0 to infinity; AUC_{0-last}, area under the concentration-time curve from time 0 to last measured concentration; AUC_{0-28d}, area under the concentration-time curve from 0 to 28 days; AUC_{0-12w}, area under the concentration-time curve from 0 to 12 weeks; AUC_{0-24w}, area under the concentration-time curve from 0 to 24 weeks; C_{max}, maximum plasma concentration; LD, loading dose; N, number of patients in treatment arm; t_{1/2}, half-life; T_{max}, time to maximum concentration

Efficacy Results

In Study 114322, nemolizumab 30 mg Q4W was statistically significantly more effective than placebo in reducing EASI scores at Week 24. The percentage change in EASI score at Week 24 was statistically significant versus placebo for nemolizumab 30 mg Q4W ($p = 0.016$) and borderline statistically significant for nemolizumab 10 mg Q4W ($p = 0.051$). No statistically significant difference was seen between nemolizumab 90 mg Q4W and placebo ($p = 0.322$). The most marked effects on secondary endpoints of PP-NRS and IGA scores were also seen in nemolizumab 30 mg Q4W compared with placebo. For further details, refer to Section 6.

Study 116912 (Phase 2 in 12- to 17-Year-Old Adolescent Subjects)

This was an open-label, single-group study to evaluate the PK and safety of 30 mg of nemolizumab in adolescent subjects (12 to 17 years of age), with moderate-to-severe AD and associated pruritus not adequately controlled with topical therapy. Subjects were enrolled and received SC injections of nemolizumab 30 mg Q4W over a 16-week treatment period, with a loading dose of 60 mg on Day 1. Study participation included a maximum of 28 weeks for subjects who complete the screening, treatment, and follow-up periods. This study included a 2- to 4-week run-in period followed by a 16-week treatment period. There were 20 subjects

enrolled in the intent-to-treat (ITT) population. The nemolizumab serum concentration, ADAs were assessed according to the schedule of assessment described in Table 48.

Table 48. Schedule of Assessments (Study 116912)

Assessment	Treatment period visit						FU	ET
Week	(1)	1 to 2	4	8	12	16	24	
PK blood ^a	X	X	X	X	X	X	X	X
ADA blood	X		X	X		X	X	X
Blood biomarkers	X		X	X		X		X
Stratum corneum biomarkers	X					X		X

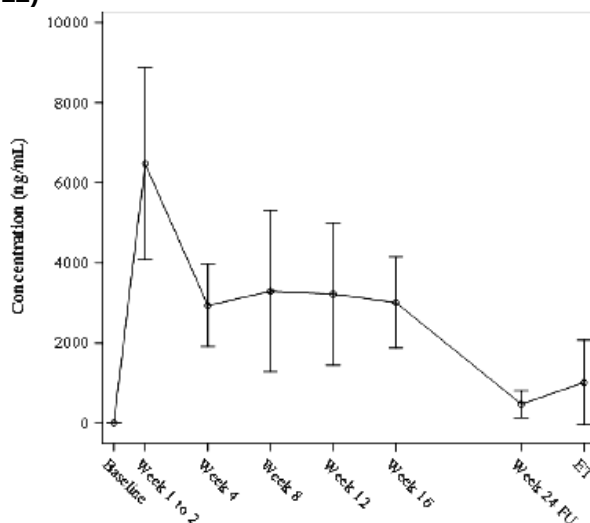
Source: 116912 CSR Table 7

Abbreviations: ADA, antidrug antibody; ET, end of treatment; FU, follow-up; PK; pharmacokinetics

PK Results

Nemolizumab T_{max} was 1 or 2 weeks after the first SC injection of the 60-mg loading dose (Figure 11). The maximal concentrations ranged from 2.55 to 11.10 $\mu\text{g/mL}$, with a mean value of 6.53 $\mu\text{g/mL}$. Steady-state condition was achieved by Week 4, with mean observed C_{trough} ranging from 2.94 to 3.29 $\mu\text{g/mL}$ at steady state. The mean observed C_{trough} from Weeks 4 to 16 are shown in Table 49, together with the correspondent model-predicted values. Individual Bayes estimates of model-derived PK parameters predicted AUC values from Baseline up to 4, 8, 12, and 16 weeks of 144 ± 50.8 , 284 ± 97.1 , 412 ± 143 , and 550 ± 184 $\mu\text{g}\cdot\text{day/mL}$, respectively. Model-derived values of 5.98 ± 2.175 $\mu\text{g/mL}$ for C_{max} and of 16.7 ± 4.12 days for $t_{1/2}$ were also predicted. See Section 14.5 for further details on the results of population PK analyses.

Figure 11. Mean ($\pm$ SD) Nemolizumab Concentration-Time Profiles (Pharmacokinetic Population; Study 116912)



Source: 116912 CSR Figure 14.2.3.5.

Abbreviations: FU, follow-up; SD, standard deviation; ET, end of treatment

Table 49. Mean ($\pm$ SD) Nemolizumab Serum Trough Concentrations Observed and Predicted in Adolescents (Pharmacokinetic Population; Study 116912)

Week	Observed concentrations (C_{trough}) in adolescents ^a (μ g/mL)	Predicted concentrations (C_{trough}) in adolescents ^b (μ g/mL)
4	2.94 (1.03)	3.27 (1.27)
8	3.29 (2.02)	3.06 (1.37)
12	3.22 (1.78)	2.89 (1.44)
16	3.01 (1.13)	2.98 (1.17)

Source: 116912 CSR Table 14.2.3.1 and 14.2.3.2.

Abbreviations: C_{trough} , lowest plasma concentration at steady-state; SD, standard deviation

Trial 118161 (Pivotal Phase 3, ARCADIA 1)

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group trial in adult and adolescent subjects with moderate-to-severe AD not adequately controlled with topical treatments. A total of 941 subjects, including 135 adolescents, were randomized (2:1) to receive either nemolizumab 30 mg Q4W (with 60 mg initial dose) or placebo (620 nemolizumab and 321 placebo). The PK analysis population included all subjects in the safety population who provided at least 1 post-baseline evaluable drug concentration value (N = 593 for initial treatment, N = 175 for maintenance treatment period). At the end of the initial treatment (Week 16), clinical responders were defined as: IGA of 0 (clear) or 1 (almost clear), or EASI-75. Among the 941 randomized subjects during the initial treatment period, 272 nemolizumab-treated subjects were clinical responders at Week 16 and were re-randomized to receive nemolizumab or placebo either Q4W or Q8W during the maintenance period.

The nemolizumab serum concentration and ADAs were assessed according to the schedule of assessment described in Table 50.

Table 50. Schedule of Assessments (Trial 118161)

Assessment	Initial treatment visit					Maintenance visit					
Week	BL	4	8	12	16/ ET	20	24	32	40	48/ ET	FU
PK blood ^a	X	X	X	X	X	X	X	X	X	X	X
ADA blood ^a	X	X	X		X		X	X		X	X
Blood biomarkers	X		X		X						
Stratum corneum biomarkers	X				X						

Source: 118161 CSR Section 8.1.2.

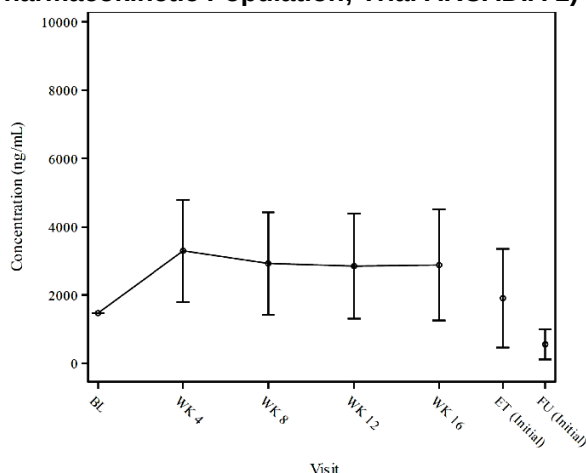
Abbreviations: ADA, antidrug antibody; BL, baseline; ET, end of treatment; FU, follow-up; PK, pharmacokinetics

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are shown in [Figure 12](#) and [Figure 13](#). The PK population subjects (N = 593) receiving nemolizumab in the initial treatment period (30 mg Q4W with 60 mg loading dose) reached steady state by Week 4. The arithmetic mean ($\pm$ SD) C_{trough} ranged from 2.85 ± 1.54 to 3.30 ± 1.50 μ g/mL between Weeks 4 and 16 (Table 51). The accumulation ratio was 0.87. A total of 89 PK population subjects originally randomized to nemolizumab Q4W in the initial treatment period were re-randomized to the same Q4W dosing regimen in the maintenance period. For those subjects, steady state was maintained with arithmetic mean ($\pm$ SD) C_{trough} ranging from 3.15 ± 1.61 to 3.28 ± 1.75 μ g/mL between Weeks 16 and 48. A total of 86 PK population subjects originally randomized to nemolizumab Q4W in the initial treatment period were re-randomized to the Q8W dosing regimen in the maintenance period. For those subjects, the arithmetic mean

($\pm$ SD) C_{trough} decreased from 2.84 ± 1.34 $\mu\text{g/mL}$ at Week 16 to 0.760 ± 0.53 $\mu\text{g/mL}$ at Week 48. After the switch at Week 16 from Q4W to Q8W, the mean C_{trough} at Week 48 in this group (0.76 $\mu\text{g/mL}$) was approximately 4 times lower than that observed in the Q4W group (3.20 $\mu\text{g/mL}$).

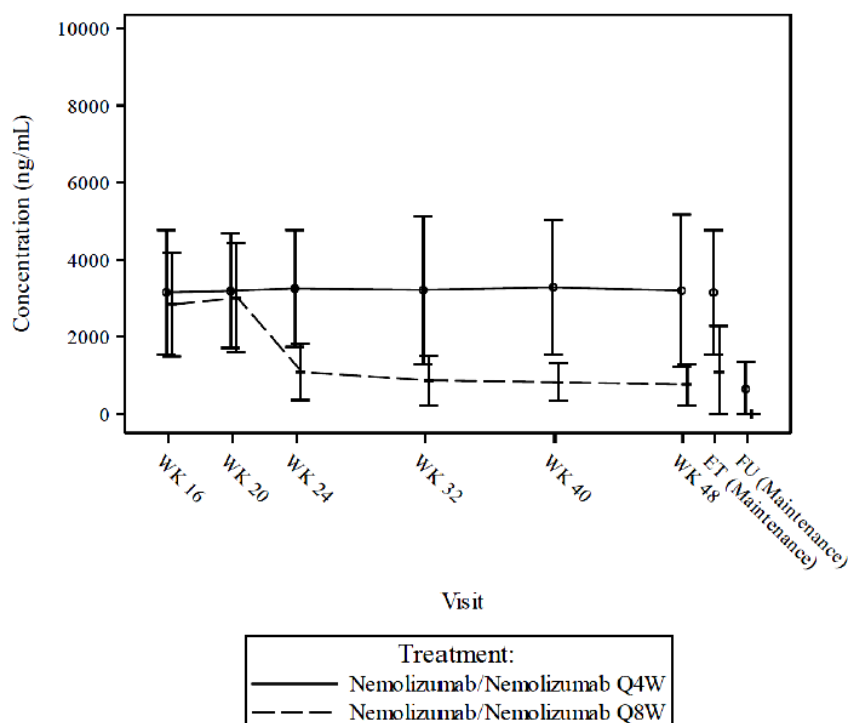
Figure 12. Mean ($\pm$ SD) Nemolizumab Concentration-Time Profile - Initial Q4W Treatment period (Pharmacokinetic Population; Trial ARCADIA 1)



Source: 118161 CSR Figure 14.2.4.3.

Abbreviations: ET, end of treatment; FU, follow-up; WK, week

Figure 13. Mean ($\pm$ SD) Nemolizumab Concentration-Time Profile – Maintenance Period (Enrolled Pharmacokinetic Subjects in Maintenance Period Population; Trial ARCADIA 1)



Source: 118161 CSR Figure 14.2.4.4.

Abbreviations: ET, end of treatment; FU, follow-up; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SD, standard deviation; WK, week

Table 51. Mean ($\pm$ SD) Nemolizumab Serum Trough Concentrations (Pharmacokinetic Population; Trial ARCADIA 1)

Visit	Initial treatment period (Weeks 0 to 16)	Maintenance treatment period (Weeks 16 to 48)	
	Q4W N=593	Q4W re-randomized to Q4W N=89	Q4W re-randomized to Q8W N=86
	Nemolizumab C _{trough} (μ g/mL)		
Week 4	3.30 $\pm$ 1.50	—	—
Week 8	2.93 $\pm$ 1.50	—	—
Week 12	2.85 $\pm$ 1.54	—	—
Week 16	2.88 $\pm$ 1.63	3.15 $\pm$ 1.61	2.84 $\pm$ 1.34
Week 20	—	3.19 $\pm$ 1.48	3.01 $\pm$ 1.41
Week 24	—	3.25 $\pm$ 1.52	1.08 $\pm$ 1.08
Week 32	—	3.21 $\pm$ 1.92	0.865 $\pm$ 0.642
Week 40	—	3.28 $\pm$ 1.75	0.818 $\pm$ 0.484
Week 48	—	3.20 $\pm$ 1.99	0.760 $\pm$ 0.531

Source: 118161 CSR Table 14.2.4.1.

Abbreviations: C_{trough}, lowest plasma concentration at steady-state; N, number of patients in treatment arm; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Efficacy Results

Trial ARCADIA 1 met its co-primary endpoints:

- The proportion of subjects with IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a $\geq$ 2-grade improvement from baseline) was clinically and statistically significantly greater with nemolizumab (35.6%) compared with placebo (24.6%) at Week 16. The proportion of subjects in the full population with EASI-75 (defined as $\geq$ 75% improvement in EASI from baseline) was clinically and statistically significantly (strata-adjusted $p < 0.0001$) greater with nemolizumab (43.5%) compared with placebo (29.0%) at Week 16.
- The proportion of subjects in the full population with EASI-75 (defined as $\geq$ 75% improvement in EASI from baseline) was clinically and statistically significantly greater with nemolizumab (43.5%) compared with placebo (29.0%) at Week 16.

For further details, refer to Section 6.

Trial 118169 (Pivotal Phase 3, ARCADIA 2)

This was a randomized, double-blind, placebo-controlled, multicenter, parallel-group trial in adult and adolescent subjects with moderate-to-severe AD not adequately controlled with topical treatments. A total of 787 subjects, including 130 adolescents, were randomized (2:1) to receive either nemolizumab 30 mg Q4W (with 60 mg initial dose) or placebo. Among the 787 randomized subjects during the initial treatment period, 235 nemolizumab-treated subjects were clinical responders at Week 16 and were re-randomized to receive nemolizumab or placebo either Q4W or Q8W during the maintenance period. The PK population included 499 subjects for the initial treatment period and 152 subjects for the maintenance treatment period. At the end of the initial treatment (Week 16), clinical responders were defined as: IGA of 0 (clear) or 1 (almost clear), or EASI-75.

The nemolizumab serum concentration and ADA were assessed according to the schedule of assessment described in Table 52.

Table 52. Schedule of Assessments (Trial ARCADIA 2)

Assessment	Initial treatment visit					Maintenance visit					
Week	BL	4	8	12	16/ ET	20	24	32	40	48/ ET	FU
PK blood ^a	X	X	X	X	X	X	X	X	X	X	X
ADA blood ^a	X	X	X		X		X	X		X	X
Blood biomarkers	X		X		X						
Stratum corneum biomarkers	X				X						

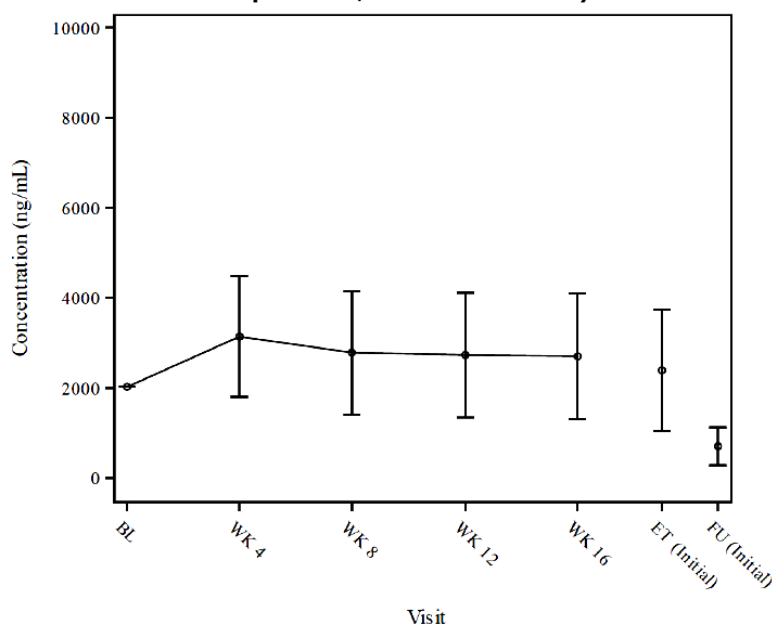
Source: 118169 CSR Section 8.1.2.

Abbreviations: ADA, antidrug antibody; BL, baseline; ET, end of treatment; FU, follow-up; PK, pharmacokinetics

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are shown in [Figure 14](#) and [Figure 15](#). Subjects receiving nemolizumab in the initial treatment period (30 mg Q4W with 60-mg loading dose, N = 593) reached steady state by Week 4. The arithmetic mean ($\pm$ SD) C_{trough} values ranged from 2.70 ± 1.40 to 3.14 ± 1.34 $\mu\text{g/mL}$ between Weeks 4 and 16 (Table 53). The accumulation ratio was 0.86. A total of 89 subjects originally randomized to nemolizumab Q4W in the initial treatment period were re-randomized to the same Q4W dosing regimen in the maintenance period. For those subjects, steady state was maintained with arithmetic mean ($\pm$ SD) C_{trough} ranging from 2.62 ± 1.21 to 2.92 ± 1.39 $\mu\text{g/mL}$ between Weeks 16 and 48. A total of 86 subjects originally randomized to nemolizumab Q4W in the initial treatment period were re-randomized to the Q8W dosing regimen in the maintenance period. For those subjects, the arithmetic mean ($\pm$ SD) C_{trough} decreased from 3.06 ± 1.42 $\mu\text{g/mL}$ at Week 16 to 0.862 ± 0.535 $\mu\text{g/mL}$ at Week 48. After the switch at Week 16 from Q4W to Q8W, the mean C_{trough} at Week 48 in this group (0.86 $\mu\text{g/mL}$) was approximately 3.5 times lower than that observed in the Q4W group (2.91 $\mu\text{g/mL}$).

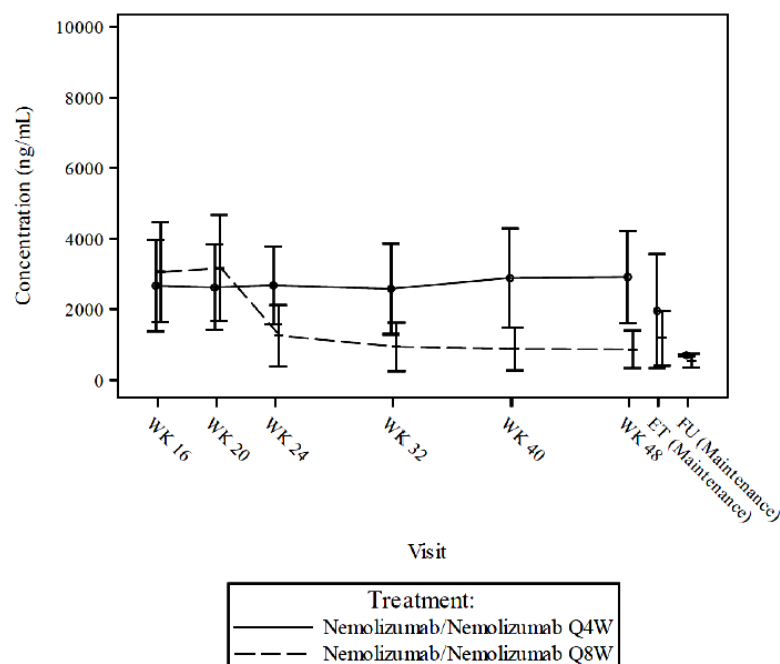
Figure 14. Mean ($\pm$ SD) Nemolizumab Concentration-Time Profile - Initial Q4W Treatment Period (Pharmacokinetic Population; Trial ARCADIA 2)



Source: 118169 CSR Figure 14.2.4.3.

Abbreviations: ET, end of treatment; FU, follow-up; Q4W, once every 4 weeks; SD, standard deviation; WK, week

Figure 15. Mean ($\pm$ SD) Nemolizumab Concentration-Time Profile – Maintenance Period (Enrolled Pharmacokinetic Subjects in Maintenance Period Population; Trial ARCADIA 2)



Source: 118169 CSR Figure 14.2.4.4.

Abbreviations: ET, end of treatment; FU, follow-up; Q4W, once every 4 weeks; Q8W, once every 8 weeks; SD, standard deviation; WK, week

Table 53. Mean ($\pm$ SD) Nemolizumab Serum Trough Concentrations (Pharmacokinetic Population; Trial ARCADIA 2)

Visit	Initial treatment period (Weeks 0 to 16)	Maintenance treatment period (Weeks 16 to 48)	
	Q4W N=593	Q4W re-randomized to Q4W N=89	Q4W re-randomized to Q8W N=86
	Nemolizumab C _{trough} (µg/mL)		
Week 4	3.14±1.34	—	—
Week 8	2.78±1.37	—	—
Week 12	2.73±1.38	—	—
Week 16	2.70±1.40	2.67±1.30	3.06±1.42
Week 20	—	2.62±1.21	3.17±1.50
Week 24	—	2.68±1.10	1.26±0.878
Week 32	—	2.65±1.25	0.937±0.694
Week 40	—	2.92±1.39	0.872±0.617
Week 48	—	2.91±1.31	0.862±0.535

Source: 118169 CSR Table 14.2.4.1 and Table 14.2.4.2.

Abbreviations: C_{trough}, lowest plasma concentration at steady-state; N, number of patients in treatment arm; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Efficacy Results

Trial ARCADIA 2 met its co-primary endpoints:

- The proportion of subjects in the full population with IGA success (defined as an IGA of 0 [clear] or 1 [almost clear] and a ≥ 2 -grade improvement from baseline) was clinically and statistically significantly greater with nemolizumab (37.7%) compared with placebo (26.0%) at Week 16.
- The proportion of subjects in the full population with EASI-75 (defined as $\geq 75\%$ improvement in EASI from baseline) was clinically and statistically significantly greater with nemolizumab (42.1%) compared with placebo (30.2%) at Week 16.

For further details, refer to Section [6](#).

Study 118163 (ARCADIA Long-Term Extension)

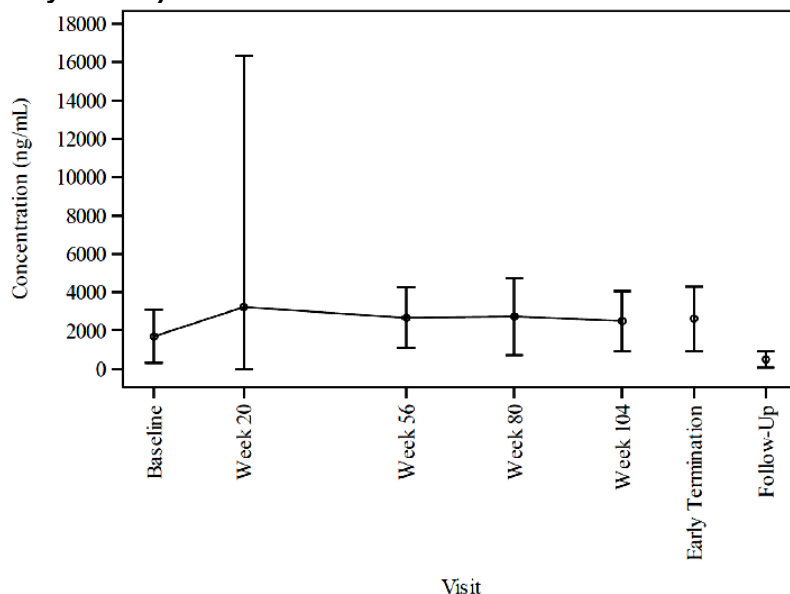
This is an ongoing, phase 3, multicenter, open-label, LTE study in adult and adolescent subjects with moderate-to-severe AD who had been previously enrolled in nemolizumab AD phase 2b dose-ranging (114322), phase 2 adolescent PK/safety (116912), phase 2 vaccination safety (118380), phase 2 drug-drug interaction (201593), phase 3 pivotal (118169 [Trial ARCADIA 2], 118161 [Trial ARCADIA 1]), or phase 3b (201591) studies, or in new adolescents who had not previously participated in a nemolizumab study. The study includes up to a 4-week screening period, up to a 200-week treatment period, and an 8-week follow-up period (12 weeks after the last dose of investigational product). After Day 1 (Baseline), all subjects received (open-label) SC injections of nemolizumab Q4W for up to 196 weeks, with the final dose administered at Week 196. The nemolizumab serum concentrations and ADA were assessed at Baseline and at Weeks 20, 56, 80, 104, 152, and 200.

PK Results

Mean serum concentration-time profiles of nemolizumab after repeated SC administrations are shown in [Figure 16](#) and nemolizumab C_{trough} summarized in [Table 54](#). Baseline nemolizumab serum concentrations reported in [Table 54](#) only included subjects who had a separate Baseline visit in the LTE study. For subjects who rolled over directly from the lead-in studies into the LTE (i.e., on the same day), final study assessments from the lead-in study were used for the LTE study screening. Common assessments with the Baseline in the LTE were not repeated. Overall, nemolizumab serum concentrations remained stable over the Weeks 20 to 104 period,

suggesting that no further systemic accumulation is expected over chronic treatment with nemolizumab up to 104 weeks.

Figure 16. Mean ($\pm$ SD) Nemolizumab Concentration-Time Profiles (Pharmacokinetic Population; Study 118163)



Source: 118163 CSR Figure 14.2.3.2.
Abbreviations: SD, standard deviation

Table 54. Mean Nemolizumab Trough Concentrations by Previous Treatment (Study 118163)

Visit	Nemolizumab C_{trough} after administration nemolizumab of 30 mg SC Q4W (μ g/mL)	
	n	All subjects (pretreated and naïve) N=1346
Baseline	52	1.69 $\pm$ 1.37
Week 20	1210	3.22 $\pm$ 13.1
Week 56	628	2.66 $\pm$ 1.58
Week 80	210	2.73 $\pm$ 2.02
Week 104	32	2.50 $\pm$ 1.57

Source: 118163 CSR Table 14.2.3.1.
Abbreviations: C_{trough} , lowest plasma concentration at steady-state; N, number of patients in treatment arm; SC, subcutaneous; Q4W, once every 4 weeks

Study 201593 (Drug-Drug Interaction Study in Subjects With AD)

This study was a phase 2 open-label, single-sequence, drug-drug interaction study to assess the effects of nemolizumab on Cytochrome P450 substrates in subjects with moderate-to-severe AD. The primary objective was to evaluate the effect of nemolizumab on the PK of a drug “cocktail” representative of cytochrome P450 (CYP450) sensitive index substrates (CYP1A2 [caffeine 100 mg], CYP2C9 [warfarin 10 mg], CYP2C19 [omeprazole 20 mg], CYP2D6 [metoprolol 100 mg], and CYP3A4/5 [midazolam 2 mg]) in adult subjects with AD. The study consisted of a 2- to 4-week screening period, a 1-week pre-dose period, a 12-week nemolizumab treatment period, and an 8-week follow-up period. After a ≥ 10 -hour fast, subjects meeting enrolment criteria received a single oral dose of the selected CYP450 substrates (caffeine, warfarin sodium, midazolam, omeprazole, and metoprolol tartrate) administered 1 at a time in sequence at

Baseline. After a 1-week washout period, subjects were to receive nemolizumab by SC injection every 4 weeks for a treatment period of 12 weeks. A 60 mg loading dose of nemolizumab (given via 2 consecutive SC 30-mg injections) was to be administered at Week 1, followed by a single 30 mg SC dose at Weeks 5 and 9. After fasting for at least 10 hours, subjects were to receive a second oral dosing of CYP450 substrates, administered 1 at a time in sequence at Week 10, 9 weeks after the first injection of nemolizumab, at the anticipated peak serum concentration of nemolizumab. The study planned to enroll approximately 25 subjects; 17 subjects were enrolled in the study. Blood samples were collected at Baseline/Day1 and Week 10 for assessment of the full concentration-time profiles of the CYP450 substrates up to 24 hours after each dose of midazolam, omeprazole, caffeine, and metoprolol, and up to 120 hours after dose of warfarin:

- A total of 12 blood samples up to 24 hours after dosing (i.e., pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours) were collected for caffeine, metoprolol, midazolam, and omeprazole PK assessment.
- A total of 14 blood samples up to 120 hours after dosing (i.e., pre-dose and 0.25, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, 24, 72, and 120 hours) were collected for warfarin PK assessment.

Five additional blood samples were to be collected for nemolizumab proof-of-exposure assessment (i.e., at baseline/Week 0 and Weeks 1, 5, 9, 10, and 13). Immunogenicity was assessed with a total of 3 blood samples collected before and after nemolizumab SC injection (i.e., at Weeks 1, 9, and 13).

PK Results

The statistical analysis of the geometric mean ratios of C_{max} , AUC_{0-inf} , and AUC_{0-last} for the 5 CYP450 substrates when given with (test) or without (reference) nemolizumab are summarized in Table 55, Table 56, Table 57, Table 58, and Table 59. For all CYP probes, the observed geometric means for both C_{max} and AUC were similar before and after nemolizumab treatment, with geometric mean test/reference ratios ranging from 88.24% to 107.81%. The 90% CIs were mainly within the 80% to 125% range that defined nemolizumab as a non-inducer for the CYP substrate of interest, with some CIs lower limit slightly below 80% (74.33% to 79.57%). There was no clinically meaningful effect of nemolizumab treatment on the metabolism of the assessed CYP substrates, defined as a greater than 2-fold decrease of observed geometric means after nemolizumab injections. No subject developed a treatment-emergent ADA.

Table 55. Statistical Comparisons of Plasma Caffeine Pharmacokinetic Parameters Before or After Multiple SC Nemolizumab Injections

Pharmacokinetic parameter (unit)	Condition	n	Geometric LSM	T/R ratio (%)	90% CI	P-value
C_{max} (µg/mL)	Before Nemolizumab (R)	14	3715	91.22	77.30, 107.63	0.3431
	After Nemolizumab (T)	14	3389			
AUC_{0-last} (h·µg/L)	Before Nemolizumab (R)	14	21417	95.82	80.72, 113.75	0.6665
	After Nemolizumab (T)	14	20522			
AUC_{0-inf} (h·µg/L)	Before Nemolizumab (R)	14	22665	94.59	79.57, 112.45	0.5789
	After Nemolizumab (T)	14	21439			

Source: 201593 CSR Table 14.2.1.3.

Abbreviations: AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-last} , area under the concentration-time curve from time 0 to last measured concentration; CI, confidence interval; C_{max} , maximum plasma concentration; LSM, least square mean; R, reference; SC, subcutaneous; T, test

Table 56. Statistical Comparisons of Plasma Metoprolol Pharmacokinetic Parameters Before or After Multiple SC Nemolizumab Injections

Pharmacokinetic parameter (unit)	Condition	n	Geometric LSM	T/R ratio (%)	90% CI	P-value
C_{max} (µg/mL)	Before Nemolizumab (R)	14	161.6	91.05	74.33, 111.53	0.4277
	After Nemolizumab (T)	14	147.1			
AUC_{0-last} (h·µg/L)	Before Nemolizumab (R)	14	601.7	99.15	83.43, 117.83	0.9316
	After Nemolizumab (T)	14	596.6			
AUC_{0-inf} (h·µg/L)	Before Nemolizumab (R)	14	611.2	99.34	83.66, 117.96	0.9468
	After Nemolizumab (T)	14	607.1			

Source: 201593 CSR Table 14.2.1.3.

Abbreviations: AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-last} , area under the concentration-time curve from time 0 to last measured concentration; CI, confidence interval; C_{max} , maximum plasma concentration; LSM, least square mean; R, reference; SC, subcutaneous; T, test

Table 57. Statistical Comparisons of Plasma Midazolam Pharmacokinetic Parameters Before or After Multiple SC Nemolizumab Injections

Pharmacokinetic parameter (unit)	Condition	n	Geometric LSM	T/R ratio (%)	90% CI	P-value
C_{max} (µg/mL)	Before Nemolizumab (R)	14	11.62	94.79	82.80, 108.52	0.4963
	After Nemolizumab (T)	14	11.01			
AUC_{0-last} (h·µg/L)	Before Nemolizumab (R)	14	24.23	107.75	99.12, 117.13	0.1371
	After Nemolizumab (T)	14	26.11			
AUC_{0-inf} (h·µg/L)	Before Nemolizumab (R)	14	25.04	107.81	99.14, 117.24	0.1364
	After Nemolizumab (T)	14	26.99			

Source: 201593 CSR Table 14.2.1.3.

Abbreviations: AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-last} , area under the concentration-time curve from time 0 to last measured concentration; CI, confidence interval; C_{max} , maximum plasma concentration; LSM, least square mean; R, reference; SC, subcutaneous; T, test

Table 58. Statistical Comparisons of Plasma Omeprazole Pharmacokinetic Parameters Before or After Multiple SC Nemolizumab Injections

Pharmacokinetic parameter (unit)	Condition	n	Geometric LSM	T/R ratio (%)	90% CI	P-value
C_{max} (µg/mL)	Before Nemolizumab (R)	14	308.0	88.24	75.08, 103.70	0.1931
	After Nemolizumab (T)	14	271.8			
AUC_{0-last} (h·µg/L)	Before Nemolizumab (R)	14	597.9	88.66	78.72, 99.85	0.0962
	After Nemolizumab (T)	14	530.1			
AUC_{0-inf} (h·µg/L)	Before Nemolizumab (R)	13	617.1	92.13	82.85, 102.44	0.1915
	After Nemolizumab (T)	11	568.5			

Source: 201593 CSR Table 14.2.1.3.

Abbreviations: AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-last} , area under the concentration-time curve from time 0 to last measured concentration; CI, confidence interval; C_{max} , maximum plasma concentration; LSM, least square mean; R, reference; SC, subcutaneous; T, test

Table 59. Statistical Comparisons of Plasma S-Warfarin Pharmacokinetic Parameters Before or After Multiple SC Nemolizumab Injections

Pharmacokinetic parameter (unit)	Condition	n	Geometric LSM	T/R ratio (%)	90% CI	P-value
C_{max} (µg/mL)	Before Nemolizumab (R)	14	677.9	92.94	82.51, 104.69	0.2960
	After Nemolizumab (T)	14	630.1			
AUC_{0-last} (h·µg/L)	Before Nemolizumab (R)	14	17603	100.81	97.45, 104.29	0.6807
	After Nemolizumab (T)	14	17746			
AUC_{0-inf} (h·µg/L)	Before Nemolizumab (R)	14	19679	101.67	97.41, 106.12	0.5059
	After Nemolizumab (T)	14	20007			

Source: 201593 CSR Table 14.2.1.3.

Abbreviations: AUC_{0-inf} , area under the concentration-time curve from time 0 to infinity; AUC_{0-last} , area under the concentration-time curve from time 0 to last measured concentration; CI, confidence interval; C_{max} , maximum plasma concentration; LSM, least square mean; R, reference; SC, subcutaneous; T, test

Summary of Pharmacokinetics

Drug Absorption

Following a single SC dose of 60 mg, nemolizumab mean observed $C_{\max}$ (SD) was 7.5 ± 2.31 $\mu\text{g/mL}$ using the DCS (Study 201590). The nemolizumab observed $T_{\max}$ 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 $\mu\text{g/mL}$) and the lower body weight quartile (31 to 62 kg: 2.92 $\mu\text{g/mL}$). The difference in exposure between the upper- and lower-weight quartiles was less than 2-fold, and no impact of body weight on efficacy was observed in subjects with AD. These results support the appropriateness of flat dosing for subjects with AD.

Drug-Drug Interactions

The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNF α , IFN) during chronic inflammation. Treatment with nemolizumab may modulate serum levels of some cytokines and influence the formation of CYP450 enzymes. Therefore, the Applicant conducted a phase 2, open-label, single-sequence, drug-drug interaction study in adult subjects with moderate-to-severe AD to evaluate the effect of nemolizumab on the PK of a drug “cocktail” representative of cytochrome P450 (CYP450) sensitive index substrates (CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5) (Study 201593). Results of this study showed that for all CYP probes, the observed geometric means for both C_{max} and AUC were similar before and after nemolizumab treatment, with geometric mean test/reference ratios ranging from 88.24% to 107.81%. There was no clinically meaningful effect of nemolizumab treatment on the metabolism of the assessed CYP substrates, defined as a greater than 2-fold decrease of observed geometric means after nemolizumab injections.

Dose Rationale

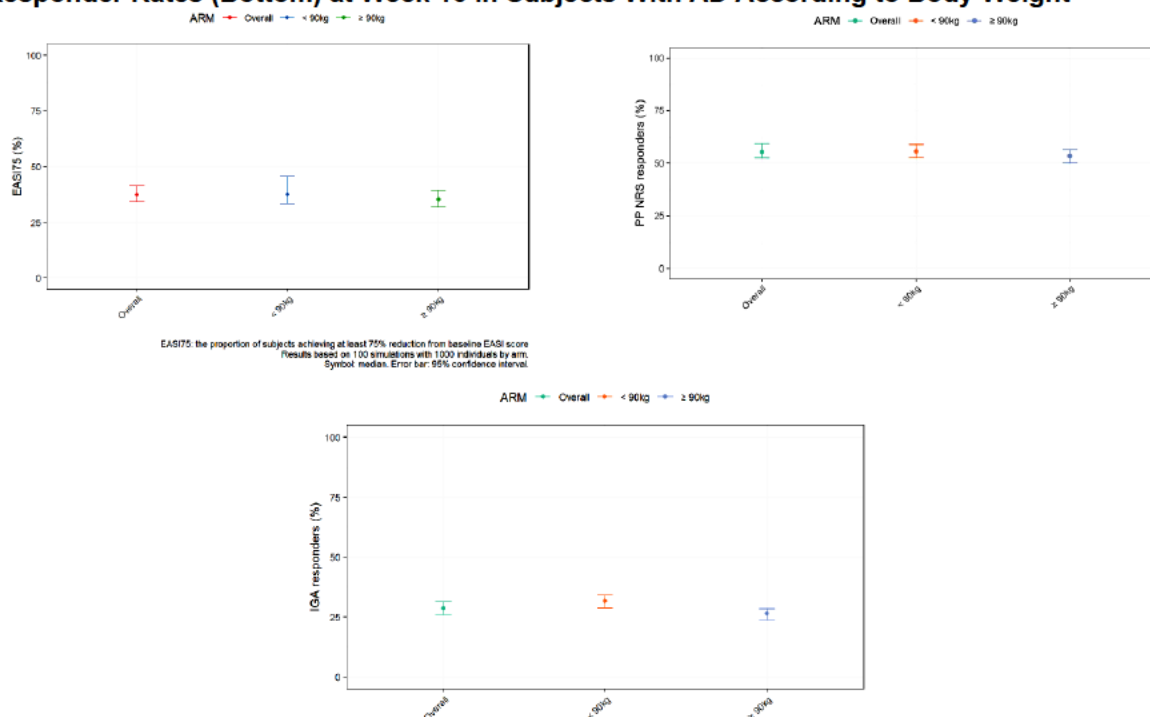
The selection of the dosing regimen used in the phase 3 trials was based on the results of the phase 2b study conducted in subjects with AD (Study 114322) along with modeling and simulation analyses. In the phase 2b study, nemolizumab was administered as 10 mg (with a 20 mg loading dose), 30 mg (with a 60 mg loading dose), and 90 mg SC doses Q4W for 24 weeks. The primary efficacy endpoint was percentage change from baseline in EASI score at Week 24. There were several secondary endpoints including EASI-75 responders, IGA success, and PP-NRS responders at Week 24. The percentage change in EASI score at Week 24 was statistically significantly higher than placebo for the 30 mg Q4W nemolizumab dose with no additional benefit observed at the higher 90 mg Q4W dose. The most marked effects on secondary endpoints, PP-NRS and IGA scores, were also observed in the 30 mg Q4W nemolizumab arm compared to the placebo arm. Overall, the phase 2b study results demonstrated that nemolizumab 30 mg (with 60 mg loading dose) was optimal for efficacy based on IGA success, EASI (both in improvement over time and in proportion of EASI-75 responders), and pruritus over the 3 tested doses.

Pharmacokinetic/pharmacodynamic simulations were conducted to assess the potential benefit of a lower dose. The PK/PD simulations were conducted to guide phase 3 dose selection by comparing the efficacy outcomes (EASI-75 responders, IGA success, and PP-NRS responders) at Week 16 in an adult population with the following treatment regimens: 10 mg Q4W (20 mg loading dose), 30 mg Q4W (60 mg loading dose), 0.5 mg/kg Q4W (no loading dose), and 1 clinically untested regimen of 20 mg Q4W (40 mg loading dose). These simulations showed that the 30 mg dose (60 mg loading dose) was the optimal dose to achieve therapeutic benefit and was selected for the phase 3 pivotal studies. The PK/PD models were also used to evaluate the impact of

switching from a Q4W dosing regimen to a Q8W dosing regimen during the maintenance phase up to Week 48. The Q8W dose regimen was predicted to maintain clinical benefit for the 3 clinical endpoints compared to placebo. In addition, the results of the phase 2 study (Study 116912) showed that the PK profile of nemolizumab observed in 12- to 17-year-old adolescents was similar to the that observed in adults. Overall, the phase 2b study clinical efficacy and safety results, together with the PK/PD simulations, supported the selection of 30 mg Q4W (60 mg loading dose) as the optimal dosing regimen for the initial period of the phase 3 studies in adults and adolescents with AD. For the maintenance period, both Q4W and Q8W dosing regimens were tested.

The efficacy of nemolizumab for the treatment of moderate-to-severe AD was established in 2 pivotal phase 3 trials (Trials 118161 and 118169) using this dosing regimen. After the completion of phase 3 trials, population PK analysis was performed on pooled data from the AD and the PN clinical development programs. Population PK analyses identified only body weight as a relevant predictor of nemolizumab exposure. The exposure of nemolizumab decreased with increasing body weight. However, the difference in exposure between the upper- and lower weight quartiles was less than 2-fold, supporting the appropriateness of a 30 mg flat dose. The population PK analyses also confirmed the adequacy of the 60 mg loading dose to rapidly reach the desired steady-state concentrations. Steady state was expected to be reached by Week 1 with a loading dose and by Week 12 without a loading dose. PK/PD models were developed based on pooled data from the AD to characterize the relationship between nemolizumab concentrations and efficacy assessments (EASI, IGA, and PP-NRS). As the population PK analysis showed that body weight has an impact on nemolizumab exposure, PK/PD simulations of clinical endpoints at Week 16, were conducted for all subjects, subjects with body weight <90 kg, and subjects with body weight ≥ 90 kg. Overall, PK/PD simulations of clinical endpoints showed a similar response across body weight groups, thus, confirming that exposure variability due to subject body weight did not result in a clinically meaningful difference in efficacy ([Figure 17](#)). Therefore, the proposed dosing regimen is considered as adequate, and no dose adjustment based on body weight is necessary. For further details on the exposure-response analyses for efficacy, refer to Section [14.5](#).

Figure 17. Simulated EASI-75 Responder Rates (Top), PP-NRS Responder Rates (Middle), and IGA Responder Rates (Bottom) at Week 16 in Subjects With AD According to Body Weight



Source: Report GALD-PMX-NEMOLIZUMAB-1787-PKPD AD Figures 13, 14, and 15.

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment PP-NRS, Peak Pruritus Numeric Rating Scale

The analyses of exposure-safety relationships did not show evidence for any increased safety events with higher nemolizumab concentrations. Overall, the clinical efficacy and safety results from the 2 pivotal phase 3 trials, PK results, PK/PD assessment, and exposure-safety outcomes provided evidence for the effectiveness and safety of the 30 mg Q4W (60 mg loading dose) dosing regimen in adult and adolescent subjects with moderate-to-severe AD. For further details on the exposure-response analyses for safety, refer to Section 14.5.

After 16 weeks of treatment, for subjects who achieve clear or almost clear skin, the Applicant has proposed (b) (4)

This was based on the clinical efficacy results from the 2 pivotal phase 3 trials (b) (4)

See Section 6.2 for further details.

Based on Clinical Pharmacology review, the proposed dosing regimen is acceptable for the treatment of AD.

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 60 and Table 61. The bioanalytical method for determination of nemolizumab concentrations were considered acceptable.

Table 60. 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) 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	<u>Cumulative accuracy (%bias) in 3 QC levels</u>	-10% to 15.0%	Report Number Table 1, Table 5, and Table 18
	<u>Interbatch %CV</u>	≤8.2%	
	<u>Total error</u>	NR	

Source: Summary of Biopharmaceutical Studies, Table 8.

Abbreviations: ADA, antidrug antibody; CIM331, nemolizumab; CV, coefficient of variation; ELISA, enzyme-linked immunosorbent assay; HRP, horseradish peroxidase; IgG; immunoglobulin G; IL, interleukin; LLOQ, lower limit of quantitation; NR, no response; QC, quality control; ULOQ, upper limit of quantitation

Table 61. Summary Method Performance (Nemolizumab Pharmacokinetics [ELISA], PBC036-112) (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): $\leq 6.5\%$ 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

Source: Summary of Biopharmaceutical Studies, Table 8.

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

Executive Summary

Recommended Dosing Regimen

- Initial treatment period (16 weeks): Initial dose of 60 mg, followed by 30 mg Q4W.
- Maintenance treatment: 30 mg (b) (4) in patients who achieve clear or almost clear skin at 16 weeks. Q8W may be considered at the prescriber's discretion.

Incidence of ADA and NAb

- ADA incidence
 - Initial treatment period: 5.6% (33/593) to 6.8% (34/499).
 - Maintenance treatment: 11.2% to 16.9% for Q4W and 8% to 12.8% for Q8W
- NAb incidence: 2.9% to 6% among the ADA+ subjects throughout 48 weeks.

ADA Assay Can Reliably Detect the ADA in the Presence of Drug in the Study Samples

All ADA samples (100%) had drug concentration < drug tolerance.

Observed Impact of ADA on PK

ADA Impact

In the maintenance treatment period, the ADA+ group had significantly lower C_{trough} than ADA-group (by approximately 40-65%) at up to 3 out of the 4 timepoints with time-matched ADA and PK data.

NAb Impact

Not feasible to evaluate because of the small number of NAb+ subjects.

Conclusion

No outstanding issues in the clinical pharmacology assessment of immunogenicity impact on PK. The current assessment should be interpreted with consideration of the performance quality of ADA assay and NAb assay; refer to the OPQAI review for detailed assessment on the assays' quality.

Summary of Clinical Studies

Two pivotal phase 3 studies (118161 and 118169) provide immunogenicity information relevant for nemolizumab labeling. Both studies had a similar design and evaluated the recommended dose regimen in the intended population. They had an initial treatment period (16 weeks) in which participants received dosing once every 4 weeks (Q4W) and a maintenance treatment period (up to 48 weeks) in which participants were randomized to receive either Q4W dosing or once every 8 weeks (Q8W) dosing. Table 62 summarizes the study information for these two

studies and results for the ADA incidence, the neutralizing antibody (NAb) incidence, and the pharmacokinetics (PK) represented by the trough concentrations. For immunogenicity data from the long-term extension (LTE) study, refer to the Integrated Summary of Immunogenicity.

Table 62. Summary of Clinical Trials 118161 and 118169, Including Immunogenicity Results and C_{trough}

Clinical Study Information	
Study	118161 118169
Recommended dose regimen	Initial dose of 60 mg (two 30 mg injections), followed by 30 mg given every 4 weeks (Q4W) After 16 weeks of treatment for patients who achieve clear or almost clear skin, a dose of 30 mg every (b) (4)
Treatment duration (planned)	48 weeks48 weeks
Treatment duration (actual) [Median (min, max)] ^a	Initial 16 weeks Q4W followed by 196 (1, 212) days for Q4W 197 (1, 214) days for Q8WInitial 16 weeks Q4W followed by 196 (1, 222) days for Q4W 197 (28, 209) days for Q8W
PK sampling	At Baseline, Week 4, 8, 12, 16, 20, 24, 32, 40, 48, and Follow-up Visit. (All samples are collected at pre-dose before each dose administration.)
ADA sampling	At Baseline, Week 4, 8, 16, 24, 32, 48, and Follow-up Visit.
Initial Treatment Period (Baseline – Week 16)	
No. of subjects received treatment	616522
Applicant reported ADA incidence @Week 16 ^b	4.08% (22/539)5.8% (26/447)
Applicant reported NAb incidence (entire trial) ^b	N=2N=1
FDA reported ADA incidence @Week 16 ^c	5.6% (33/593)6.8% (34/499)
FDA reported NAb incidence (entire trial) ^c among ADA+	6% (2/33)2.9% (1/34)
Maintenance Treatment Period (Week 16 – Week 48)	
Arm	Q4WQ8WQ4WQ8W
No. of subjects received maintenance treatment	90917978
Applicant reported ADA incidence (by timepoint) ^b	Up to 9.4% (8/85)Up to 11% (6/81)Up to 13.8% (9/65)Up to 5.8% (4/69)
FDA calculated ADA incidence (overall) ^c	11.2% (10/89)12.8% (11/86)16.9% (13/77)8% (6/75)
Nemolizumab concentration (µg/mL); Mean ± SD of C _{trough}	
Applicant analysis	W16: 3.15 ± 1.61W16: 2.84 ± 1.34W16: 2.67 ± 1.30W16: 3.06 ± 1.42
Mean (standard deviation) of C _{trough} ^d	W48: 3.20 ± 1.99W48: 0.76 ± 0.53W48: 2.91 ± 1.31W48: 0.86 ± 0.53

Source: [SharePoint folder](#)

^a Treatment duration: Table 117 in CSR of study 118161 and study 118169

^b Table 112 and the associated text (CSR for study 118161 and study 118169). The Applicant reported ADA incidence by timepoint, and this table includes the highest incidence among all timepoints.

^c ADA incidence from an independent analysis by the reviewer using an internal analysis tool. NAb incidence represents the fraction of ADA+ subjects who are NAb positive.

^d C_{trough}: Table 14.2.4.2 of CSR for study 118161 (p305) and study 118169 (p335)

Abbreviations: ADA, antidrug antibody; CSR, clinical study report; C_{trough}, lowest plasma concentration at steady-state; FDA, U.S. Food and Drug Administration; Nab, neutralizing antibody; Q4W, once every 4 weeks; PK, pharmacokinetics; Q8W, once every 8 weeks; SD, standard deviation; W, week

Highlight of Key Characteristics of Immunogenicity Assays Relevant to This Review

The Applicant used one ligand binding assay to assess the ADA and one cell-based assay to assess the NAb. Table 63 and Table 64 contain the key assay characteristics for ADA and NAb, respectively, that are relevant to the clinical pharmacology review of the immunogenicity data. Consistent with the recommendation in the FDA guidance (<https://www.fda.gov/media/119788/download>), the Applicant tested the drug tolerance of ADA assay using 100 ng/mL positive control. Whereas the guidance has no recommendation for the positive control in the NAb assay.

The ADA assay has adequate drug tolerance and can reliably detect the antidrug antibodies to nemolizumab. All study samples contain drug concentrations lower than the drug tolerance of 15 µg/mL. Therefore, the presence of nemolizumab in the ADA samples does not interfere with the detection of ADA.

Table 63. Summary of Key ADA Assay Characteristics Related to Current Immunogenicity Assessment

Study Number	118161 and 118169
Validation Report number	197091AVKZ
Method	Electrochemiluminescence (ECL) Immunoassay (Ligand binding assay)
Positive Control (PC)	50 ng/mL
Drug Tolerance	15 µg/mL at 50 ng/mL of PC
% of Samples With Observed Drug Concentration >Drug Tolerance	0% *

Source: Integrated Summary of Immunogenicity, Table 17.

* C_{trough} are below 5 ug/mL in studies 111861 and 118169

Abbreviations: ECL, electrochemiluminescence; PC, positive control

Table 64. Summary of Key NAb Assay Characteristics Related to Current Immunogenicity Assessment

Study Number	118161 and 118169
Validation Report Number	14224.060319
Method	Cell-based assay
Positive Control (PC)	16010 ng/mL (LPC)
Drug Tolerance	10 µg/mL at 16010 ng/mL
% of Samples With Observed Drug Concentration >Drug Tolerance	0% *

Source: Integrated Summary of Immunogenicity, Table 41.

* C_{trough} are below 5 ug/mL in studies 111861 and 118169

Abbreviations: LPC, low positive control; PC, positive control

Methods for Evaluating the Effect of Immunogenicity (ADA) on PK of Drug

To evaluate the impact of immunogenicity on PK, we compared the observed concentrations in two groups (ADA+ and ADA-) among subjects with time-matched PK and ADA data. The analysis was conducted using the Immunogenicity Specimen tool (IS Tool) developed in-house. At each timepoint, the geometric mean values of drug concentrations were tabulated by the ADA status, i.e., ADA+ group and ADA- group. The statistical comparisons between two groups used the geometric mean ratio (GMR), ADA+/ADA-, and the corresponding 90% CI. To conclude a difference between groups, the upper bound of the 90% CI should be less than 1.0, indicating a significantly lower exposure in the ADA+ group compared to the ADA- group.

Effect of Immunogenicity on PK of Drug – Results

Table 65 and Table 66 summarized the statistical comparisons of nemolizumab concentrations in ADA+ and ADA- groups for Trial ARCADIA 1 and Trial ARCADIA 2, respectively.

During the initial treatment period (i.e., the first 16 weeks), there were no differences observed between ADA+ and ADA- groups because the 90% CI of GMR contains 1.0 at all three timepoints with ADA and PK samples in Trial ARCADIA 1. Whereas the 90% CI of GMR at Week 16 does not contain 1.0 in Trial ARCADIA 2.

ADA had a negative impact on PK was observed in the maintenance treatment period at up to 3 out of 4 timepoints with time-matched ADA and PK samples in each study. In Trial Arcadia 1, the 90% CI of GMR is entirely below 1.0 at Weeks 24 and 32 in Q4W group and at Week 24, 32, and 48 in Q8W group. The GMR at these time points indicate 40-50% lower exposure in ADA+ group compared to the ADA- group (Table and Figure 18). In Trial ARCADIA 2, the 90% CI of GMR is entirely below 1.0 at Week 48 in Q4W group and at Week 24, 32, and 48 in Q8W group. The GMR at these time points indicate 46-65% lower exposure in ADA+ group compared to the ADA- group (Table 66 and Figure 19).

Table 65. Comparison of Nemolizumab Trough Concentration by ADA Status at Each Visit for Trial ARCADIA 1

Arm	Timepoint	Geometric Mean Concentration (ng/mL)				ADA+ to ADA- Ratio	
		ADA+ Group	N	ADA- Group	N	GMR	90%CI
Initial	Week 4	2677.724	13	2858.641	557	0.937	(0.70, 1.25)
Q4W dosing	Week 8	2459.942	13	2479.786	534	0.992	(0.74, 1.32)
	Week 16	2186.856	22	2297.442	517	0.952	(0.71, 1.27)
Maintenance Q4W dosing	Week 16	2190.023	3	2778.894	86	0.7881	(0.45, 1.37)
	Week 24	1876.438	8	3031.356	77	0.619	(0.46, 0.84)
	Week 32	1393.103	7	2622.283	75	0.531	(0.31, 0.92)
	Week 48	1408.244	4	2598.494	72	0.542	(0.28, 1.07)
Maintenance Q8W dosing	Week 16	1900.754	3	2525.347	82	0.753	(0.44, 1.28)
	Week 24	415.361	9	852.565	73	0.487	(0.30, 0.79)
	Week 32	287.333	8	569.086	70	0.505	(0.27, 0.95)
	Week 48	289.306	8	529.497	65	0.546	(0.30, 0.98)

Source: file location [SharePoint folder](#)

Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of patients in treatment arm; Q4W, every 4 weeks; Q8W, every 8 weeks

Table 66. Comparison of Nemolizumab Trough Concentration by ADA Status at Each Visit for Trial ARCADIA 2

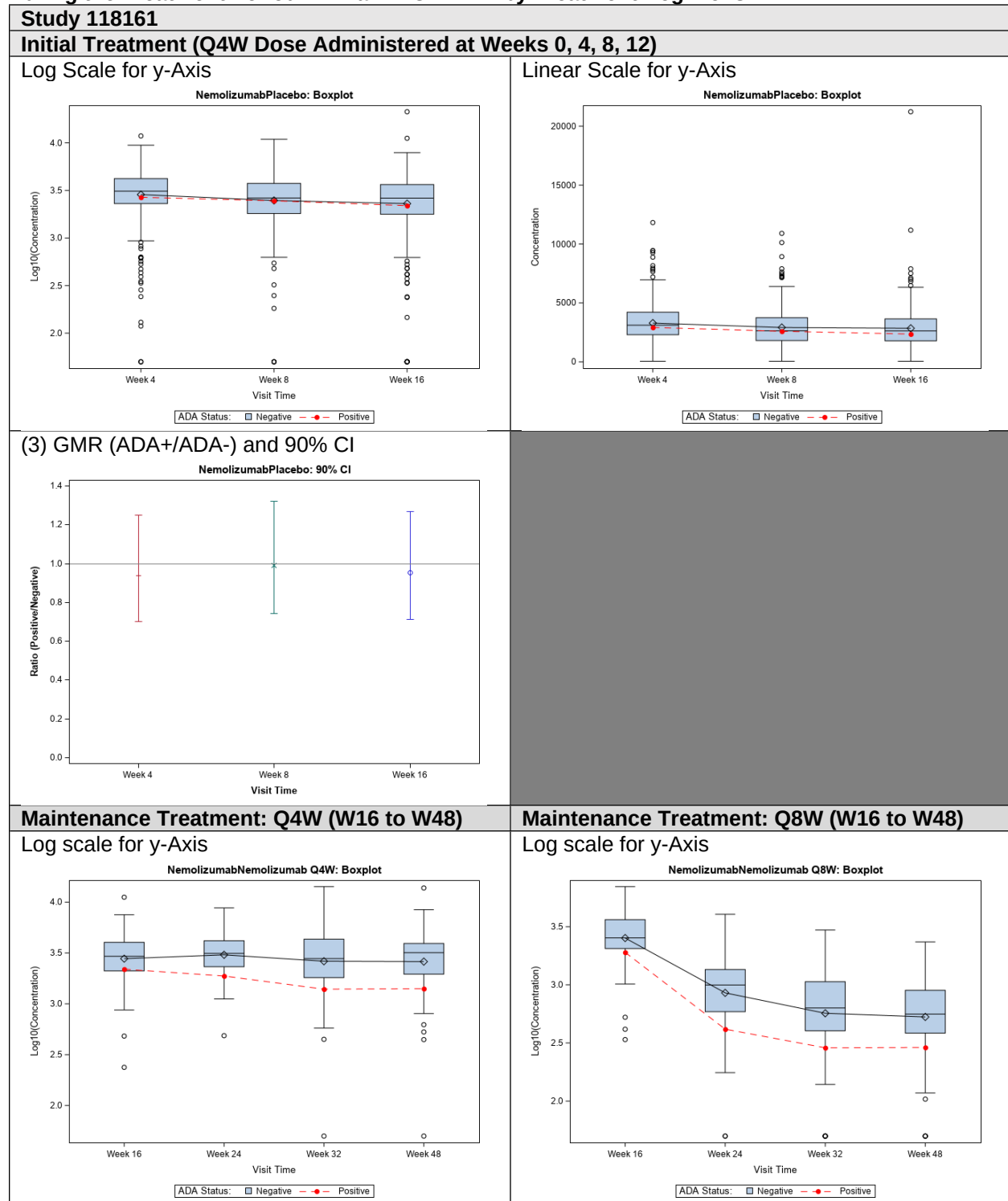
Arm	Timepoint	Geometric Mean Concentration (ng/mL)				ADA+ to ADA- ratio	
		ADA+ Group	N	ADA- Group	N	GMR	90%CI
Initial	Week 4	2795.657	12	2703.139	466	1.034	(0.76, 1.41)
Q4W dosing	Week 8	2536.89	9	2398.265	461	1.058	(0.76, 1.47)
	Week 16	1736.911	26	2349.361	421	0.739	(0.60, 0.91)
Maintenance Q4W dosing	Week 16	1777.019	8	2369.53	65	0.750	(0.52, 1.06)
	Week 24	1751.412	9	2368.85	66	0.739	(0.50, 1.10)
	Week 32	1390.811	8	2054.115	61	0.677	(0.39, 1.19)
	Week 48	1424.272	9	2661.034	56	0.5352	(0.36, 0.81)
Maintenance	Week 16	2151.9	3	2757.786	72	0.7803	(0.48, 1.27)

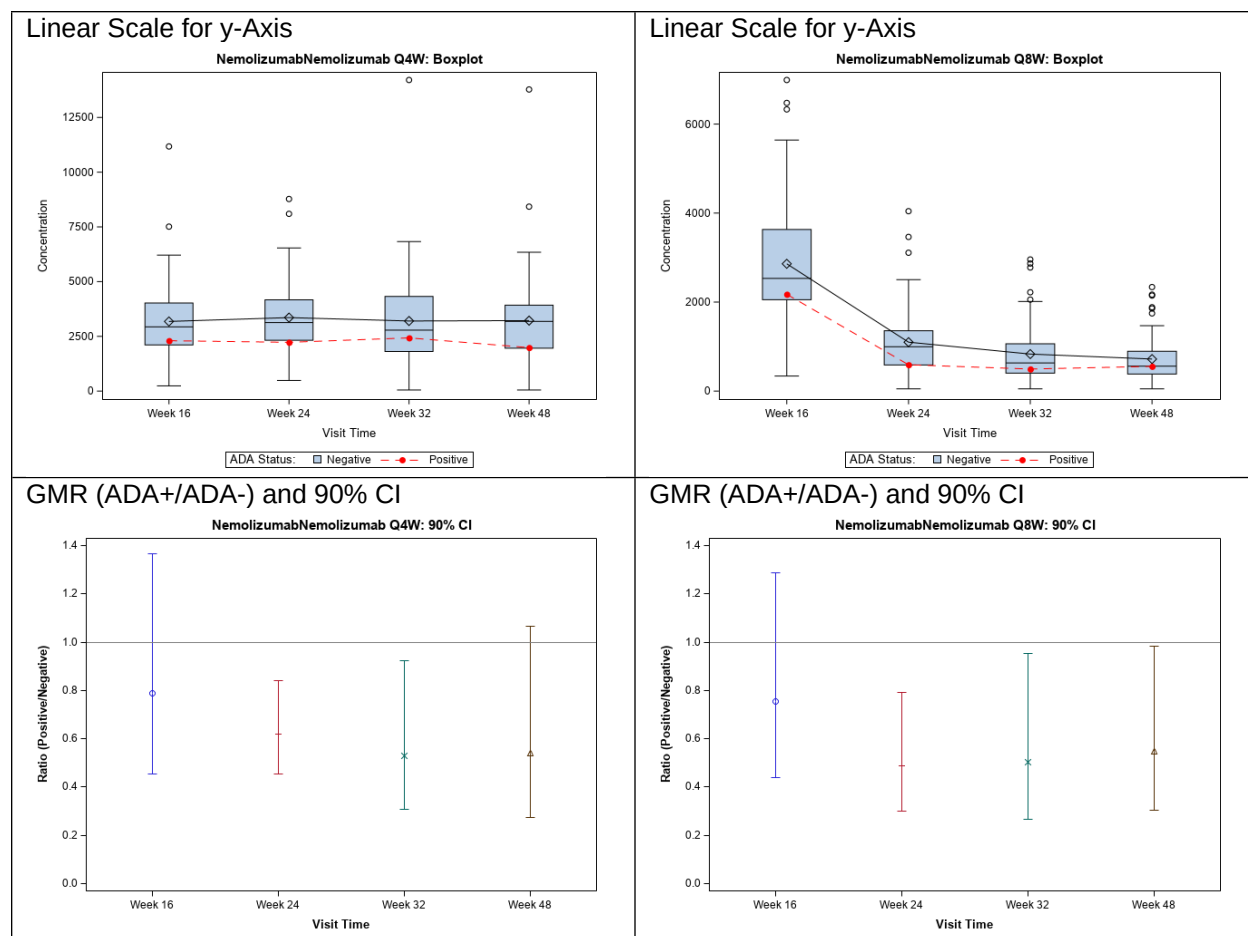
Arm	Timepoint	Geometric Mean Concentration (ng/mL)				ADA+ to ADA- ratio	
		ADA+ Group	N	ADA- Group	N	GMR	90%CI
Q8W dosing	Week 24	452.5182	4	1034.831	70	0.4373	(0.24, 0.79)
	Week 32	240.7516	4	687.5836	66	0.3501	(0.17, 0.74)
	Week 48	311.0616	3	694.4176	61	0.4479	(0.21, 0.94)

Source: file location [SharePoint folder](#)

Abbreviations: ADA, antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; N, number of patients in treatment arm; Q4W, every 4 weeks; Q8W, every 8 weeks

Figure 18. Comparison of Nemolizumab Concentration Over Time in ADA+ and ADA- Samples During the Treatment Period in Trial ARCADIA 1 by Treatment Regimens





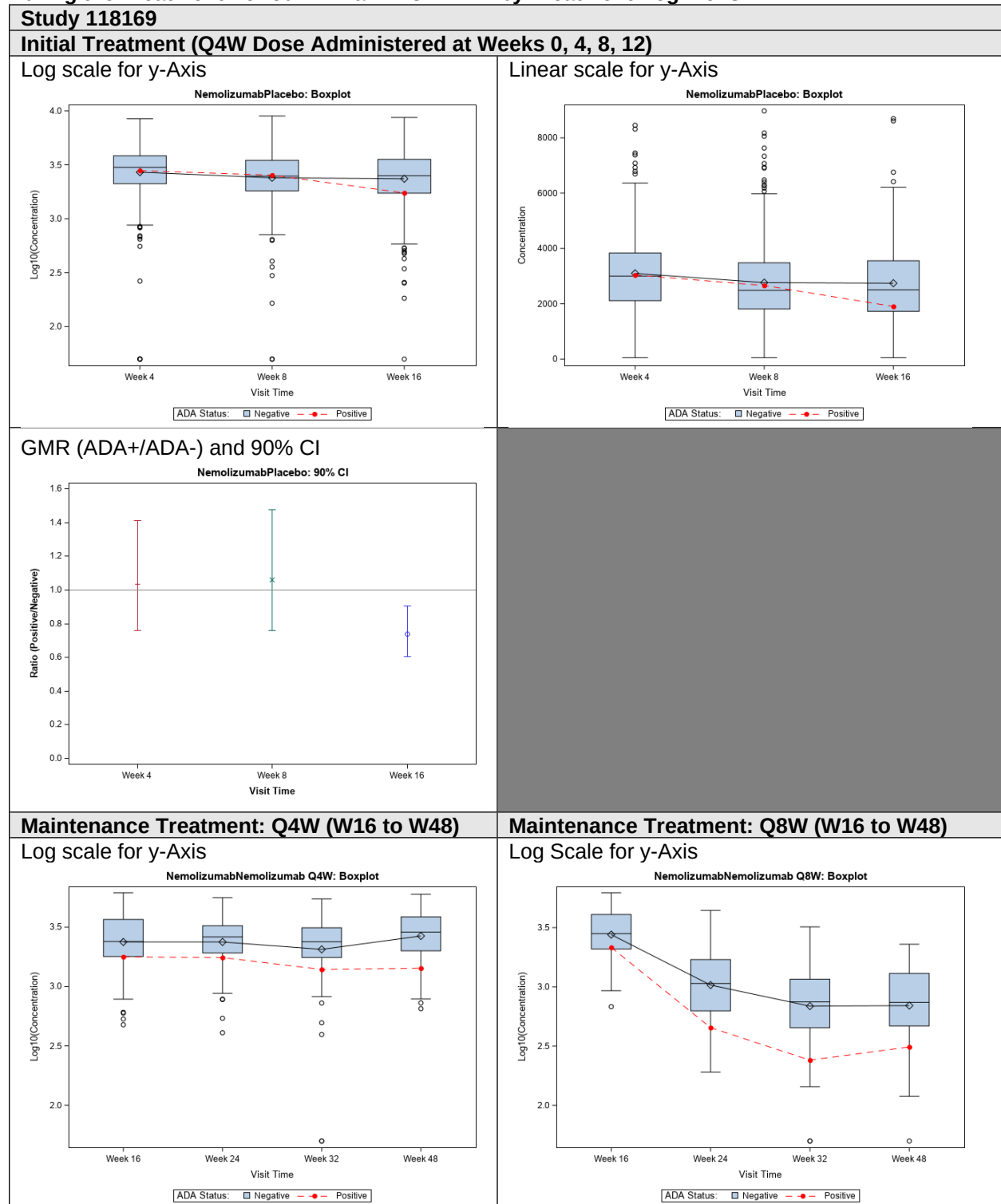
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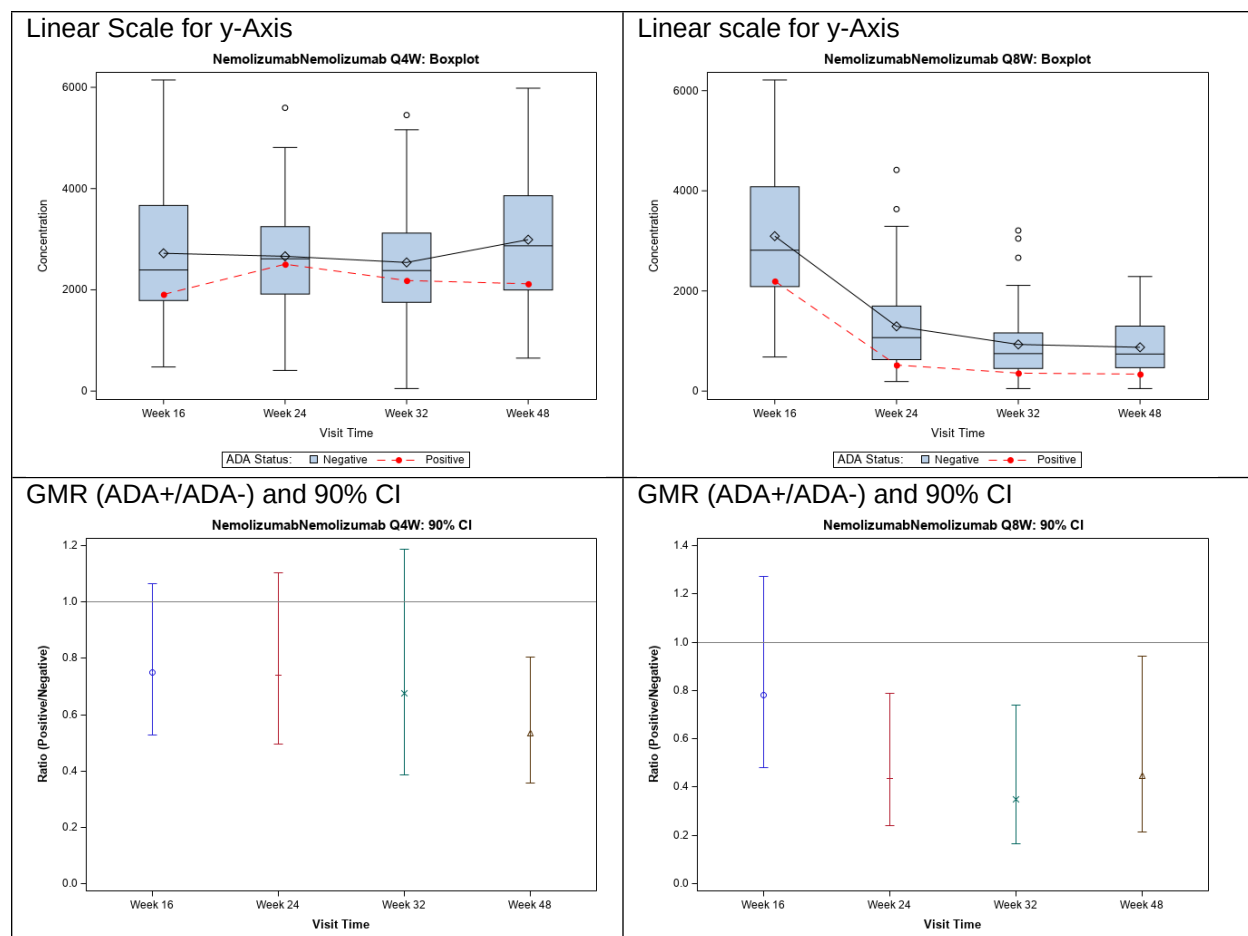
Concentration unit: ng/mL

Three panels for each treatment period and each regimen in the maintenance treatment period: (1) boxplot of nemolizumab concentration in logarithmic scale, (2) boxplot of nemolizumab concentration in linear scale, (3) GMR of nemolizumab concentration (ADA+ to ADA- ratio) and 90% CI

Abbreviations: ADA, Antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Figure 19. Comparison of Nemolizumab Concentration Over Time in ADA+ and ADA- Samples During the Treatment Period in Trial ARCADIA 2 by Treatment Regimens





Source: Location of source files: [Sharepoint folder](#)

Concentration unit: ng/mL

Three panels for each treatment period and each regimen in the maintenance treatment period: (1) boxplot of nemolizumab concentration in logarithmic scale, (2) boxplot of nemolizumab concentration in linear scale, (3) the geometric mean ratio (GMR) of nemolizumab concentration (ADA+ to ADA- ratio) and 90% confidence interval (CI)

Abbreviations: ADA, Antidrug antibody; CI, confidence interval; GMR, geometric mean ratio; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Impact of Immunogenicity on Efficacy

In the phase 3 AD studies, immunogenicity had no significant impact on the efficacy of nemolizumab. No trends based on ADA category or ADA titer were observed in the proportion of subjects with Eczema Area and Severity Index (EASI)-75, Investigator's Global Assessment (IGA) success, or improvement of PP-NRS ≥ 4 from baseline at Week 16 or Week 48 (Table 67 and Table 68). These observations were consistent across the Phase 3 studies and across dose subgroups.

Table 67. Summary of Efficacy Endpoints in the Phase 3 AD Studies at Week 16 by ADA Category

	Study 118161		Study 118169		Study 118161 and Study 118169	
	TE ADA+ (N=67)	ADA- (N=529)	TE ADA+ (N=56)	ADA- (N=448)	TE ADA+ (N=123)	ADA- (N=977)
Subjects with EASI-75 ($\geq 75\%$ improvement in EASI from baseline) at Week 16, n (%)	38 (56.7)	230 (43.5)	27 (48.2)	188 (42.0)	65 (52.8)	418 (42.8)
Subjects with an IGA success at Week 16, n (%)	30 (44.8)	190 (35.9)	23 (41.1)	169 (37.7)	53 (43.1)	359 (36.7)
Subjects with an improvement of PP NRS ≥ 4 from baseline to Week 16, n (%)	30 (44.8)	233 (44.0)	21 (37.5)	192 (42.9)	51 (41.5)	425 (43.5)

Source: Integrated Summary of Immunogenicity Table 58.

Abbreviations: ADA, antidrug antibody; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, number of patients meeting the criteria; N, number of patients in study arm; TE, treatment-emergent; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 68. Summary of Efficacy Endpoints in the Phase 3 AD Studies at Week 16 and at Week 48 by ADA Category and Dose Regimen

	Study 118161						Study 118169						Study 118161 and Study 118169					
	Nemolizumab Q4W/Q4W (N=90)		Nemolizumab Q4W/Q8W (N=89)		Nemolizumab Q4W/PBO (N=91)		Nemolizumab Q4W/Q4W (N=79)		Nemolizumab Q4W/Q8W (N=74)		Nemolizumab Q4W/PBO (N=76)		Nemolizumab Q4W/Q4W (N=169)		Nemolizumab Q4W/Q8W (N=163)		Nemolizumab Q4W/PBO (N=167)	
	TE ADA+ (N=11)	ADA- (N=79)	TE ADA+ (N=13)	ADA- (N=76)	TE ADA+ (N=12)	ADA- (N=79)	TE ADA+ (N=10)	ADA- (N=69)	TE ADA+ (N=8)	ADA- (N=66)	TE ADA+ (N=10)	ADA- (N=66)	TE ADA+ (N=21)	ADA- (N=148)	TE ADA+ (N=21)	ADA- (N=142)	TE ADA+ (N=22)	ADA- (N=145)
Subjects maintaining EASI-75 response at Week 16 and Week 48, n (%)	7 (63.6)	59 (74.7)	11 (84.6)	53 (69.7)	7 (58.3)	47 (59.5)	8 (80.0)	50 (72.5)	6 (75.0)	49 (74.2)	8 (80.0)	39 (59.1)	15 (71.4)	109 (73.6)	17 (81.0)	102 (71.8)	15 (68.2)	86 (59.3)
Subjects maintaining IGA success at Week 16 and Week 48, n (%)	6 (54.5)	42 (53.2)	8 (61.5)	33 (43.4)	5 (41.7)	29 (36.7)	6 (60.0)	37 (53.6)	5 (62.5)	41 (62.1)	5 (50.0)	32 (48.5)	12 (57.1)	79 (53.4)	13 (61.9)	74 (52.1)	10 (45.5)	61 (42.1)
Subjects maintaining an improvement of PP NRS ≥ 4 at Week 16 and Week 48, n (%)	1 (9.1)	20 (25.3)	4 (30.8)	17 (22.4)	2 (16.7)	12 (15.2)	1 (10.0)	25 (36.2)	1 (12.5)	15 (22.7)	1 (10.0)	11 (16.7)	2 (9.5)	45 (30.4)	5 (23.8)	32 (22.5)	3 (13.6)	23 (15.9)

Source: Integrated Summary of Immunogenicity Table 59.

Abbreviations: ADA, antidrug antibody; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; n, number of patients meeting the criteria; N, number of patients in study arm; TE, treatment-emergent; PBO, placebo; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Impact of Immunogenicity on Safety

Immunogenicity had no significant impact on the safety of nemolizumab in the phase 3 AD studies. In the phase 3 AD studies, the incidence of TEAEs, treatment emergent serious adverse events (SAEs), drug-related TEAEs, and TEAEs of special interest (AESIs) was similar in subjects with treatment-emergent ADA (76.4%, 4.9%, 30.1%, and 53.7%, respectively) and in those for whom ADAs were not detected (ND; 78.4%, 7.6%, 27.1%, and 54.5%, respectively; Table 69).

Table 69. Overview of TEAEs in the Phase 3 AD Studies by ADA Category (ADA/Nab Evaluable Population)

	Study 118161 + LTE (Study 118163)		Study 118169 + LTE (Study 118163)		Study 118161 + LTE and Study 118169 + LTE	
	TE ADA+ (N=67) n (%)	ADA- (N=529) n (%)	TE ADA+ (N=56) n (%)	ADA- (N=448) n (%)	TE ADA+ (N=123) n (%)	ADA- (N=977) n (%)
Any TEAE	56 (83.6)	423 (80.0)	38 (67.9)	343 (76.6)	94 (76.4)	766 (78.4)
Any SAE	4 (6.0)	34 (6.4)	2 (3.6)	40 (8.9)	6 (4.9)	74 (7.6)
Any drug-related TEAE	24 (35.8)	165 (31.2)	13 (23.2)	100 (22.3)	37 (30.1)	265 (27.1)
Any AESI	43 (64.2)	289 (54.6)	23 (41.1)	243 (54.2)	66 (53.7)	532 (54.5)

Source: Integrated Summary of Immunogenicity Table 60.

Abbreviations: ADA, antidrug antibody; AESI, adverse event of special interest; LTE, long-term extension; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event

In the phase 3 AD trials, suspected immune-mediated AEs were rare and no discernible pattern was observed based on ADA category for subjects experiencing suspected immune complex-mediated AEs (Table 70).

Table 70. Suspected Immune Complex-Mediated Adverse Events in the Phase 3 PN Studies by Preferred Suspected Immune Complex-Mediated Adverse Events in the Phase 3 AD Studies by Preferred Term and ADA Category (ADA/Nab Evaluable Population)

	Study 118161 + LTE (Study 118163)		Study 118169 + LTE (Study 118163)		Study 118161 + LTE and Study 118169 + LTE	
	TE ADA+ (N=67) n (%)	ADA- (N=529) n (%)	TE ADA+ (N=56) n (%)	ADA- (N=448) n (%)	TE ADA+ (N=123) n (%)	ADA- (N=977) n (%)
Any class	4 (6.0)	15 (2.8)	1 (1.8)	18 (4.0)	5 (4.1)	33 (3.4)
Alopecia areata	0	3 (0.6)	0	3 (0.7)	0	6 (0.6)
Arthritis	0	6 (1.1)	0	2 (0.4)	0	8 (0.8)
Autoimmune thyroiditis	0	0	0	1 (0.2)	0	1 (0.1)
Colitis	0	0	1 (1.8)	0	1 (0.8)	0
Dermatitis	2 (3.0)	2 (0.4)	0	3 (0.7)	2 (1.6)	5 (0.5)
Dermatomyositis	0	0	0	1 (0.2)	0	1 (0.1)
Diabetes mellitus	0	1 (0.2)	0	0	0	1 (0.1)
Enteritis	1 (1.5)	0	1 (1.8)	0	2 (1.6)	0
Hyperthyroidism	1 (1.5)	1 (0.2)	0	0	1 (0.8)	1 (0.1)
Hypothyroidism	0	1 (0.2)	0	3 (0.7)	0	4 (0.4)
Multiple sclerosis	0	0	0	1 (0.2)	0	1 (0.1)
Myocarditis	0	0	0	1 (0.2)	0	1 (0.1)
Neuropathy peripheral	0	0	0	1 (0.2)	0	1 (0.1)
Palmoplantar keratoderma	0	0	0	1 (0.2)	0	1 (0.1)
Pemphigoid	0	0	0	1 (0.2)	0	1 (0.1)
Raynaud's phenomenon	0	1 (0.2)	0	0	0	1 (0.1)
Sjogren's syndrome	0	0	0	1 (0.2)	0	1 (0.1)

Source: Integrated Summary of Immunogenicity Table 61.

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 adverse events of special interest (AESI) category and standard Medical Dictionary for Regulatory Activities [MedDRA] query) in the phase 3 AD studies occurred with similar frequency in subjects with treatment-emergent ADAs and in those for whom ADAs were ND (22.0% for each). No discernible pattern was observed based on ADA category for subjects experiencing suspected immune-mediated adverse events (including drug-related drug hypersensitivity reactions). The incidence of individual preferred terms included in the AESI of injection-related reactions was similar between the ADA category groups.

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

14.5. Pharmacometrics Assessment

14.5.1. 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).
- None of the tested covariates (weight, 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.
- Only Body weight (WT) was identified as a statistically significant predictor of nemolizumab exposure. With flat dosage, the exposure of nemolizumab decreases with increasing WT. 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).
- The PopPK modeling and simulation supports the proposed flat dosing regimen in subjects with AD: an initial loading dose of 60 mg, followed by 30 mg given Q4W. After 16 weeks of treatment, for patients who achieve clear or almost clear skin, a dosage of 30 mg (b) (4)

(b) (4)

14.5.1.1. 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 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 trials, 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 [Trial ARCADIA 1], SPR.118169 [Trial ARCADIA 2], 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 71), drawn from studies and trials 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 72 and Table 73.

Table 71. 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 the limit of quantification; PK, pharmacokinetics; PN, prurigo nodularis

Table 72. Summary of Continuous Covariates in Subjects With AD and PN by Study

Variables	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: AD, atopic dermatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; BSA, body surface area; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; P, prurigo nodularis; SD, standard deviation

Table 73. Summary of Categorical Covariates in Subjects With AD and PN by Study

Variables	All Subjects (n =1952)
Sex	
Male	951 (48.7%)
Female	1001 (51.3%)
Race	
White	1483 (76.0%)
Black	125 (6.4%)
Asian	308 (15.8%)
Others	36 (1.8%)
Age Group	
12 – 17 yrs	191 (9.8%)
18 – 65 yrs	1580 (80.9%)
>65 yrs	181 (9.3%)
Renal Impairment	
Normal	1644 (84.2%)
Mild	262 (13.4%)
Moderate	44 (2.3%)
Severe	2 (0.1%)
Hepatic Impairment	
Normal	1838 (94.2%)
Mild	99 (5.1%)
Moderate	13 (0.7%)
Treatment-emergent ADA	
Yes	133 (6.81%)
No	1796 (92.0%)
Missing	23 (1.18%)
Treatment-induced ADA	
Yes	129 (6.61%)
No	1800 (92.2%)
Missing	23 (1.18%)
Treatment-boosted ADA	
Yes	4 (0.20%)
No	1925 (98.6%)
Missing	23 (1.8%)

Source: Reviewer's Summary referencing Table 11. GALD-PMX-NEMOLIZUMAB-1787-POPPK
Abbreviations: AD, atopic dermatitis; ADA, antidrug antibody; PN, prurigo, nodularis

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, body surface area (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 74). WT was identified as a relevant predictor of nemolizumab exposure. The exposure of nemolizumab decreases with increasing WT. 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 20](#)) showed a random distribution of observed versus individual or population model-predicted nemolizumab concentrations along the line of unity, the distributions of conditional weighted residuals 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 21](#)) demonstrated that the model adequately captured the observed nemolizumab concentration time-course and variability of the observed data.

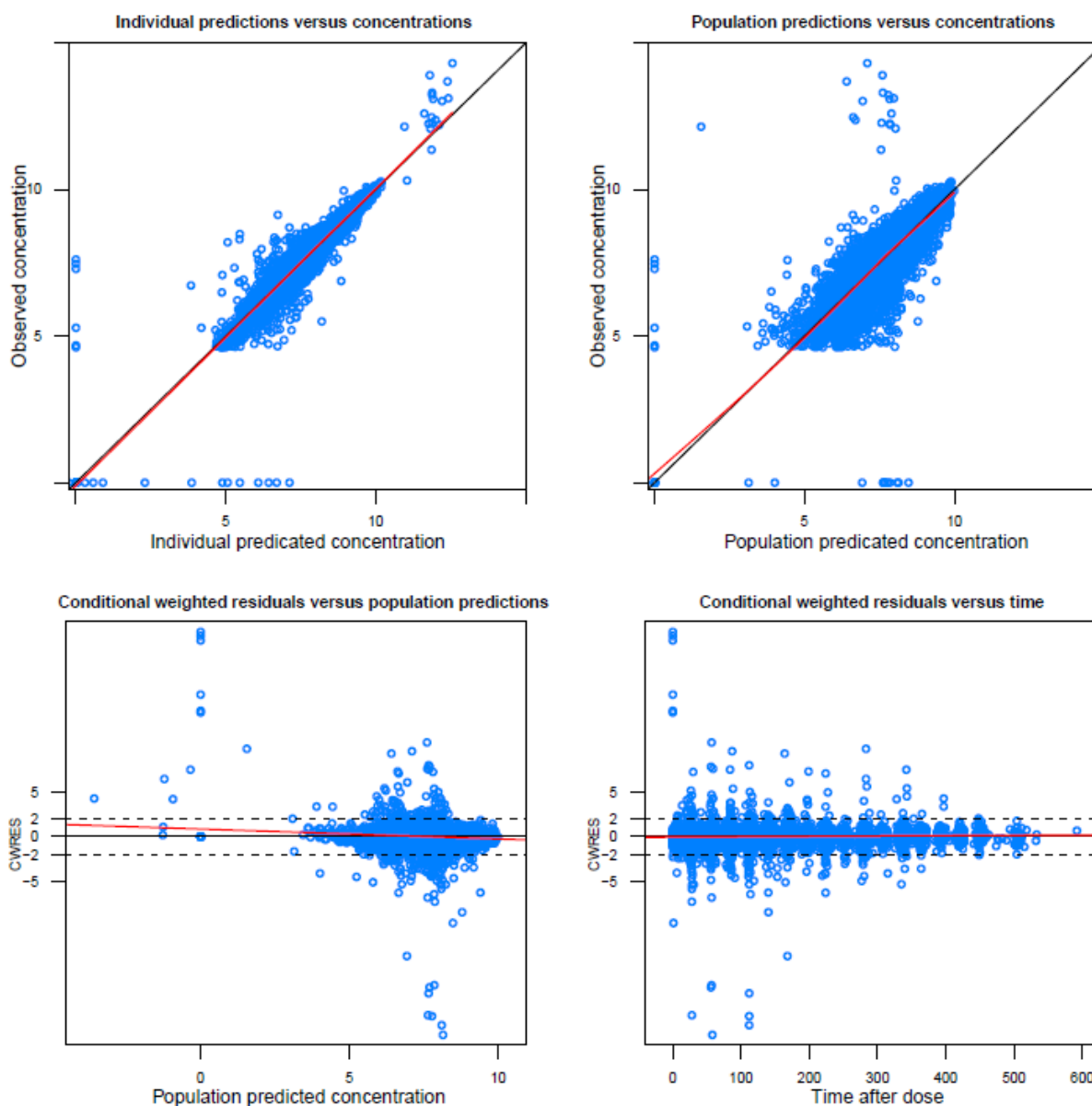
Table 74. Final Parameter Estimates of Nemolizumab

Parameter	Point estimate	IIV (%CV)	RSE%	Asymptotic 95% CI ^a	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 ^e	0.344	64.1	10.0	0.228; 0.46	0.228; 0.483	68.9

Source: Table 15. GALD-PMX-NEMOLIZUMAB-1787-POPPK

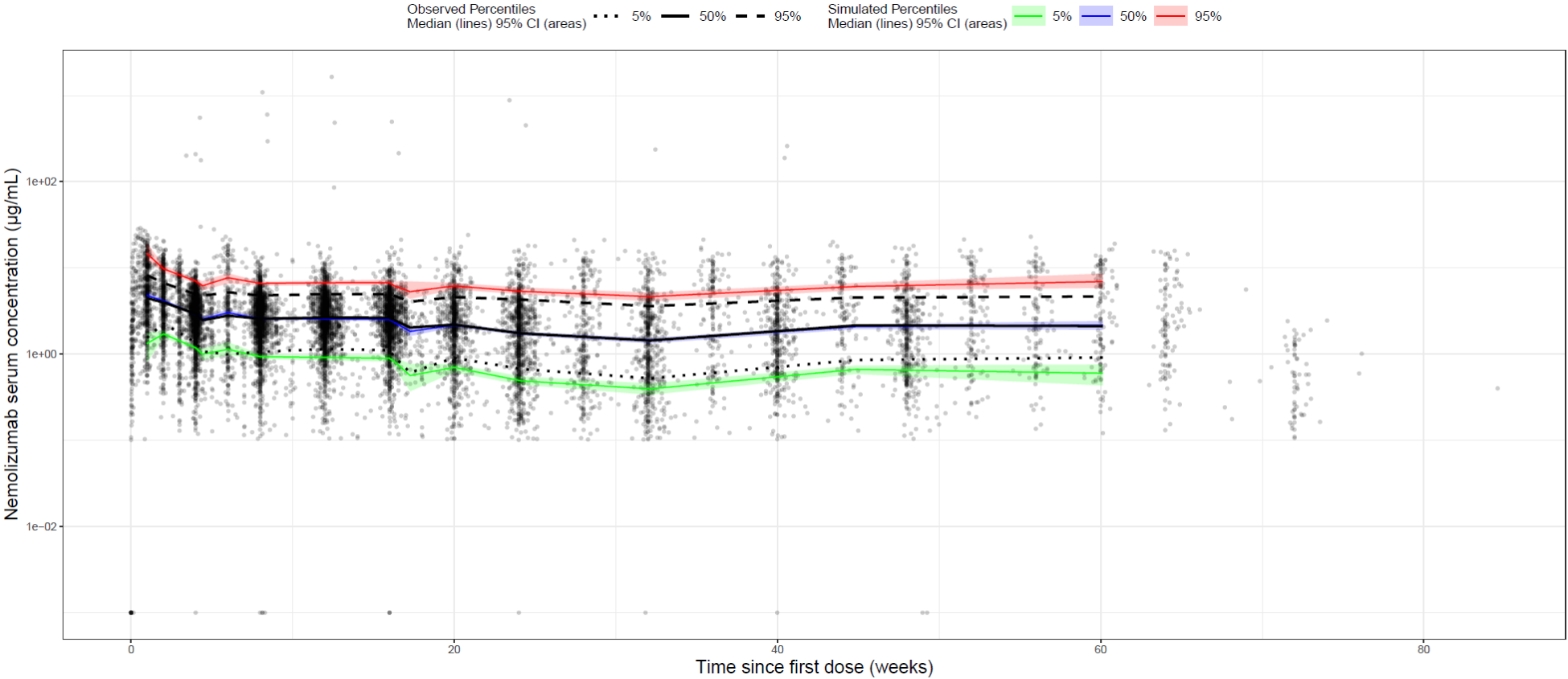
Abbreviations: ALAG, absorption lag time; CI, confidence interval; CL/F, apparent clearance at steady-state; CrCL, creatinine clearance; CV, coefficient of variation; F, bioavailability; IIV, interindividual variability; K_a, absorption rate constant; RSE, relative standard error; RUV, residual unexplained variability; V/F, apparent central volume of distribution

Figure 20. Goodness of Fit of Nemolizumab PopPK Model
Goodness of fit model gal-pk-run034



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

Figure 21. Prediction-Corrected Visual Predictive Checks of Nemolizumab PopPK Model



Source: Reviewer's analysis.
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 pharmacokinetic

Reviewer's Note:

- *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 trials 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) for subsequent exposure response analysis.*
- *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 WT, ALB levels, CRCL, ethnicity, race and [REDACTED]. Volume of distribution was influenced by both WT, ALB. Among them, WT is the only covariate with a significant impact leading to $\geq 20\%$ change on both CL/F and V/F. The exposure of nemolizumab decreases with increasing WT.*
- *Although weight is a statistically significant covariate on clearance, the difference in exposure (AUC_{ss} , $C_{trough, ss}$ or $C_{max, ss}$) between the upper and lower weight quartiles in subjects with AD who received a 30 mg dose Q4W was less than 2-fold, supporting the proposed flat dosing in patients with AD.*

14.5.1.2. PopPK Model Based Simulation

14.5.1.2.1. 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_{ss} , $C_{max, ss}$ and $C_{W16, ss}$). 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

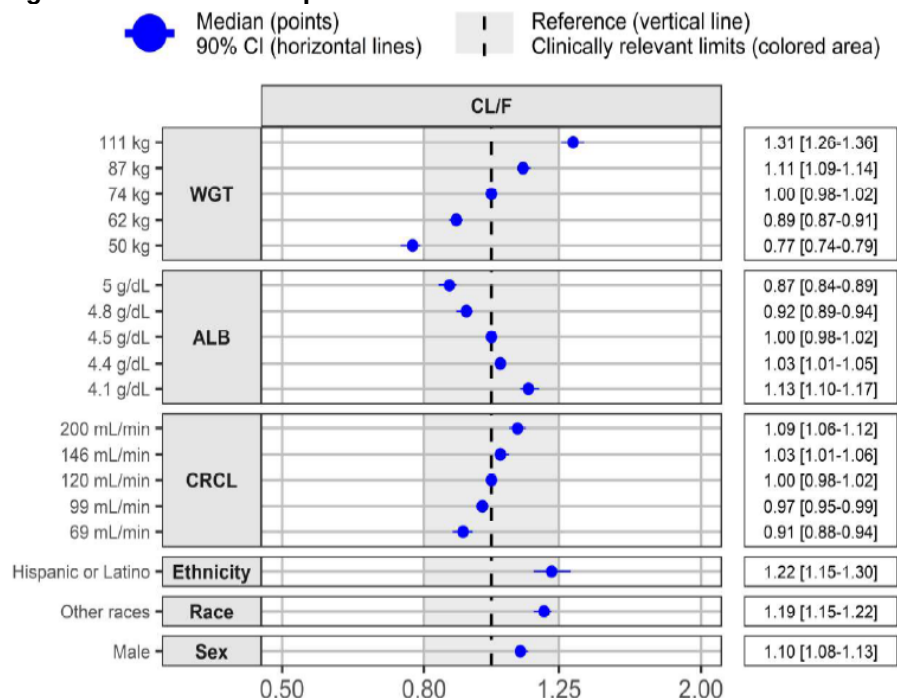
enable a more reliable interpretation of covariates' impact in real-life settings. Individual PK parameters as well as the exposure metrics of interest (i.e., AUC_{ss} , and $C_{max,ss}$, and $C_{W16,ss}$) were derived for each individual.

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 22, Figure 23 and Figure 24).

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 WT (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 WT of 74 kg. Accordingly, subjects with lower values of WT (50 kg; P5) had approximately 30% higher exposure levels. These WT effects on steady state exposures were only marginally outside the 0.8 to 1.25 exposure ratio interval.

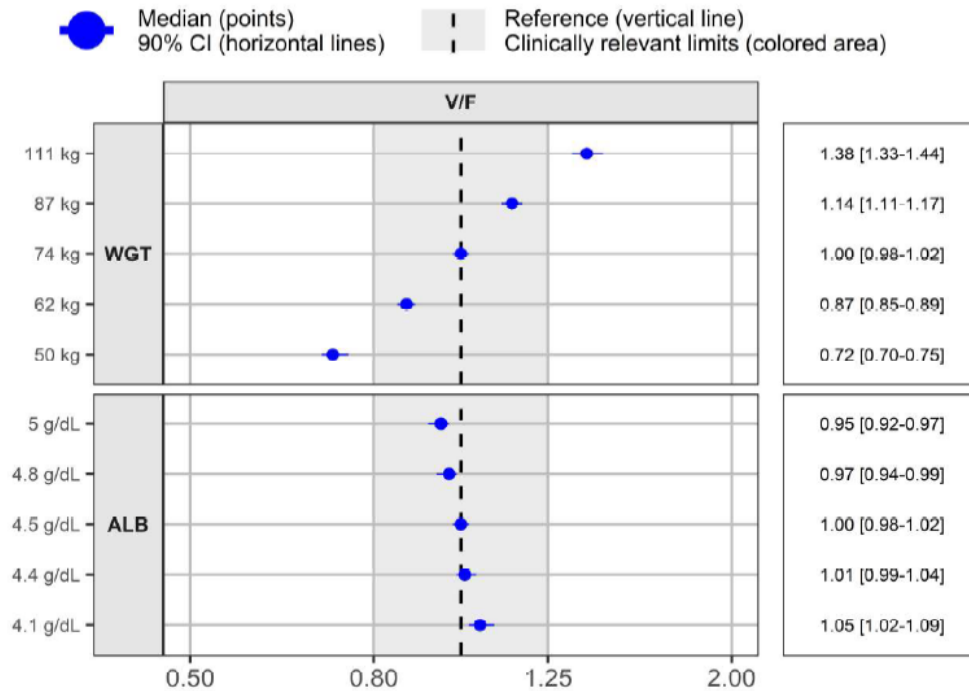
Figure 22. Univariate Impact of Covariates on CL/F



Source: Reviewer's analysis to confirm Figure 15. GALD-PMX-NEMOLIZUMAB-1787-POPPK

The dashed vertical line represents the typical patient (defined as a female, white, not Hispanic nor Latino, with a WT of 74 kg, CrCl of 120 mL/min, ALB of 4.5 g/dL), while the gray shaded area covers the 0.8- to 1.25-fold change in exposure metric relative to typical patient's value. For all covariate scenarios, all other covariates were maintained at values for the typical patient. Table in the right panel summarizes the results, numerically.

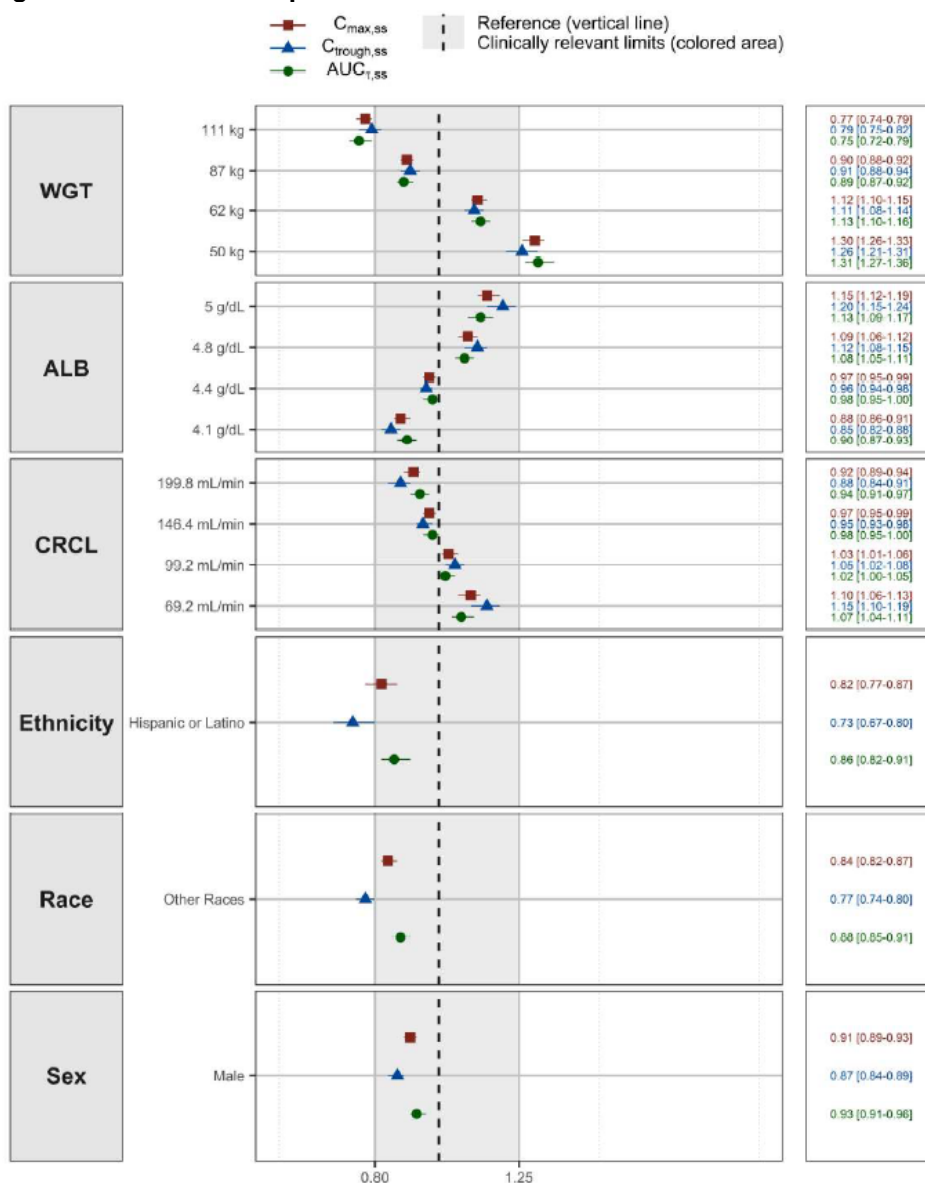
Abbreviations: ALB, albumin; CI, confidence interval; CL/F, apparent clearance at steady-state; CrCl, creatinine clearance; WGT, weight

Figure 23. Univariate Impact of Covariates on V/F

Source: Reviewer's analysis to confirm Figure 16. GALD-PMX-NEMOLIZUMAB-1787-POPPK.

Note: The dashed vertical line represents the typical patient (defined as a female, white, not Hispanic nor Latino, with a WT of 74 kg, CrCl of 120 mL/min, ALB of 4.5 g/dL), while the gray shaded area covers the 0.8- to 1.25-fold change in exposure metric relative to typical patient's value. For all covariate scenarios, all other covariates were maintained at values for the typical patient. Table in the right panel summarizes the results, numerically.

Abbreviations: ALB, albumin; CI, confidence interval; CL/F, apparent clearance at steady-state; CrCl, creatinine clearance; WGT, weight

Figure 24. Univariate Impact of Covariates on PK

Source: Reviewer's analysis to confirm Figure 17. GALD-PMX-NEMOLIZUMAB-1787-POPPK

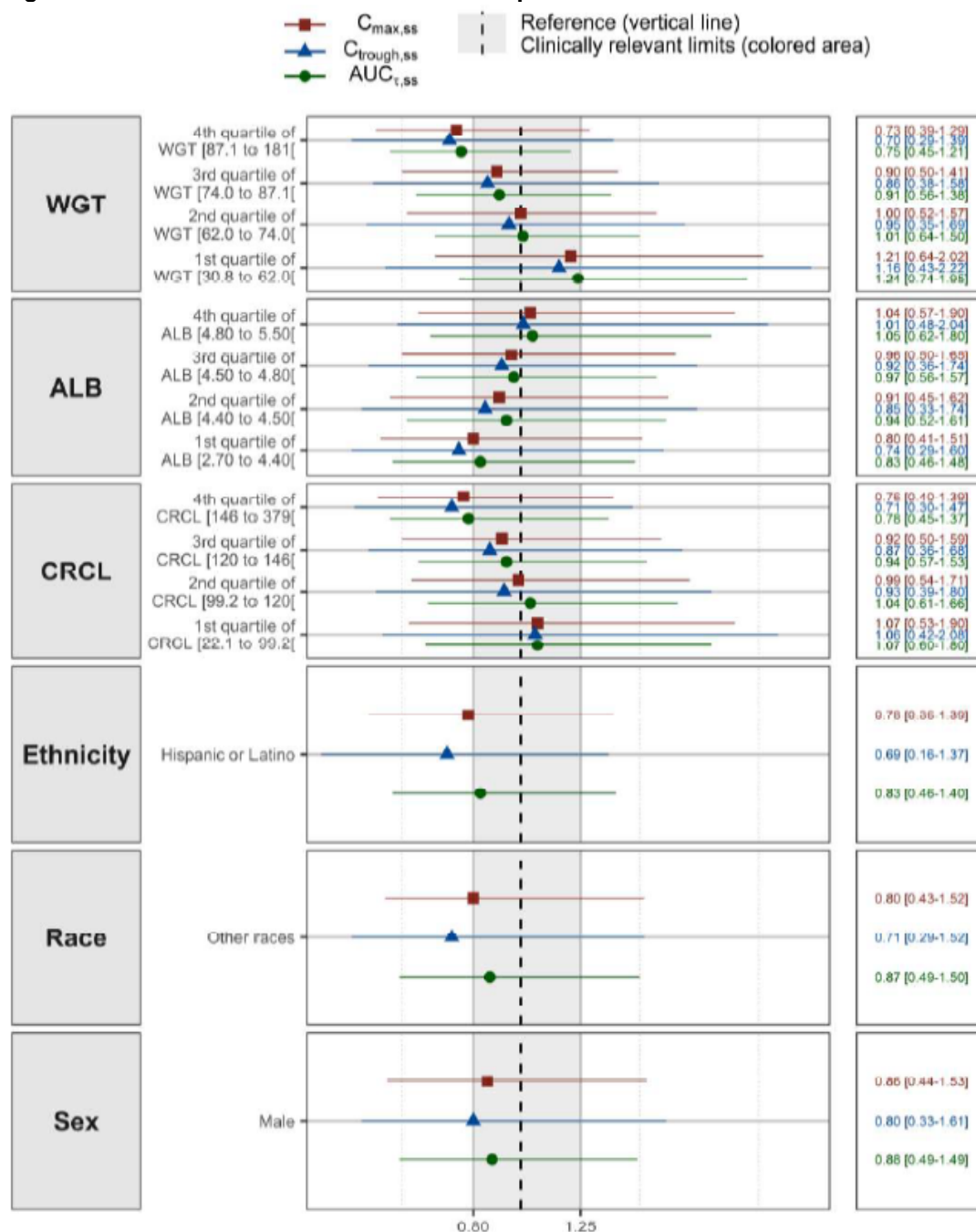
The dashed vertical line represents the typical patient (defined as a female, white, not Hispanic nor Latino, with a WT of 74 kg, CrCl of 120 mL/min, ALB of 4.5 g/dL), while the gray shaded area covers the 0.8- to 1.25-fold change in exposure metric relative to typical patient's value. For all covariate scenarios, all other covariates were maintained at values for the typical patient. Table in the right panel summarizes the results, numerically.

Abbreviations: ALB, albumin; $AUC_{1,ss}$, area under the plasma concentration versus the time curve within a dosing interval at steady state; CI, confidence interval; CL/F, apparent clearance at steady-state; $C_{max,ss}$, maximum plasma concentration at steady state; CrCl, creatinine clearance; $C_{trough,ss}$, lowest plasma concentration at steady-state; PK, pharmacokinetics; WGT, weight

Multivariate Assessment of the Covariates

Multivariate assessment results of the covariates influence on PK were shown in [Figure 25](#).

Similar to results observed in univariate settings, with point estimates indicating relatively lower exposure levels for subjects with higher WT 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 WT.

Figure 25. Multivariate Assessment of the Impact of Covariates on PK

Source: Reviewer's analysis to confirm Figure 18. GALD-PMX-NEMOLIZUMAB-1787-POPPK

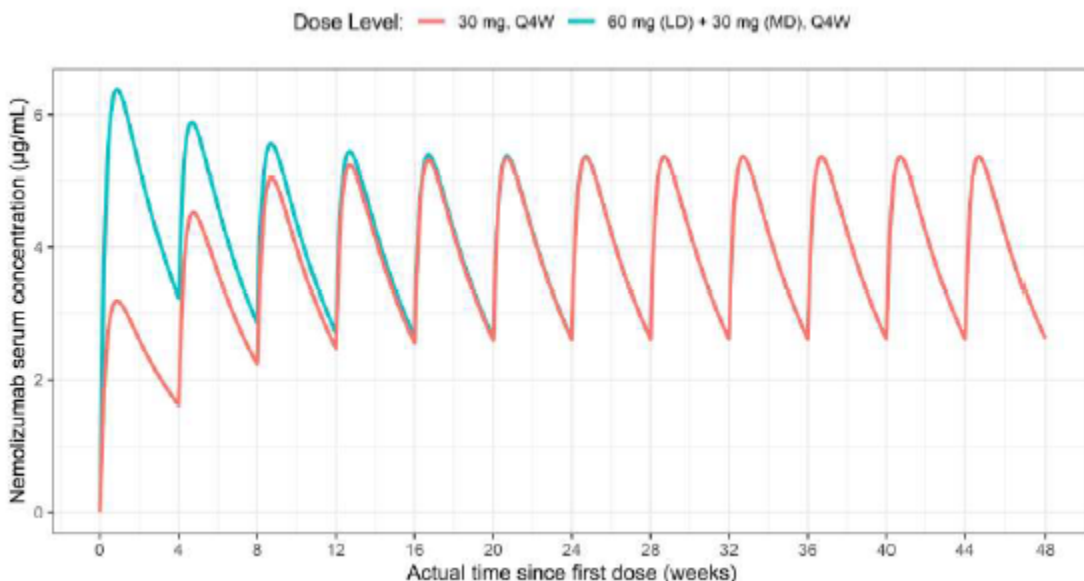
The dashed vertical line represents the typical patient (defined as a female, white, not Hispanic nor Latino, with a WT of 74 kg, CrCl of 120 mL/min, ALB of 4.5 g/dL), while the gray shaded area covers the 0.8- to 1.25-fold change in exposure metric relative to typical patient's value. For all covariate scenarios, all other covariates were maintained at values for the typical patient. Table in the right panel summarizes the results, numerically.

Abbreviations: ALB, albumin; $AUC_{t,ss}$, area under the plasma concentration versus the time curve within a dosing interval at steady state; CI, confidence interval; CL/F, apparent clearance at steady-state; $C_{\max,ss}$ maximum plasma concentration at steady state; CrCl, creatinine clearance; $C_{\text{trough},ss}$, lowest plasma concentration at steady-state; PK, pharmacokinetics; WGT, weight

14.5.1.2.2. Simulated Impact of Loading Dose and Steady State PK

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 26](#). 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.

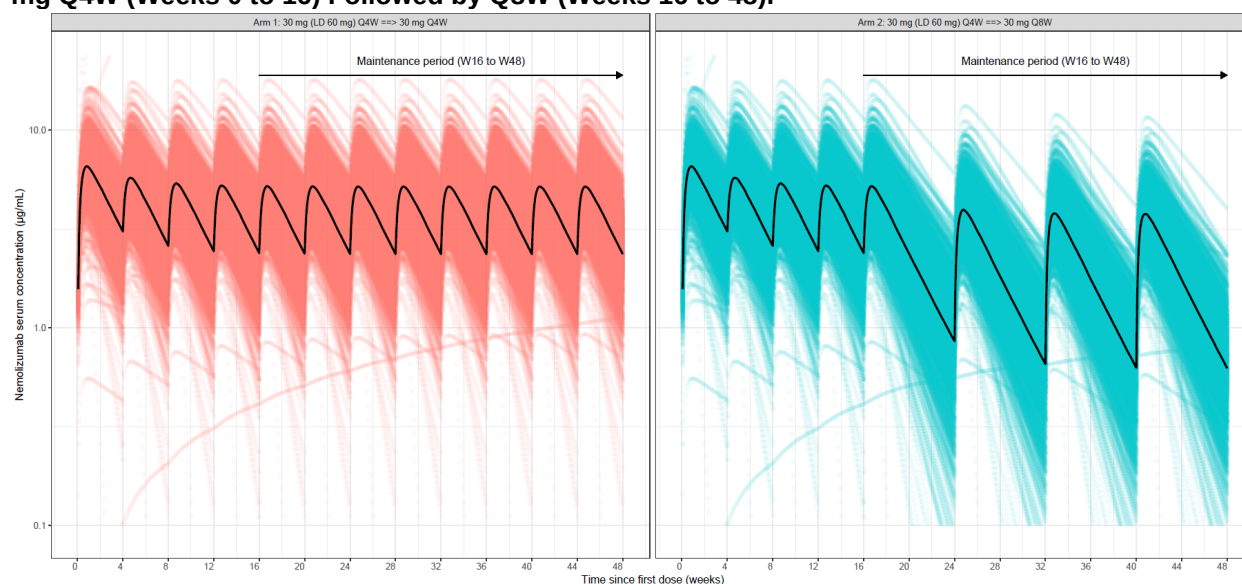
Figure 26. Impact of Loading Dose on Time to Reach Steady State



Source: Reviewer's analysis to confirm Figure 26. GALD-PMX-NEMOLIZUMAB-1787-POPPK

Abbreviations: LD, loading dose; MD, mid-dose; Q4W, once every 4 weeks; Q8W, once every 8 weeks

At steady state, the PopPK mean ($\pm$ SD) nemolizumab C_{trough} were 2.63 ± 1.27 µg/mL for nemolizumab 30 mg administered Q4W and 0.74 ± 0.44 µg/mL for 30 mg administered Q8W ([Figure 27](#)).

Figure 27. Simulations of Nemolizumab PK Profiles Following 30 mg Q4W (Weeks 0 to 48) and 30 mg Q4W (Weeks 0 to 16) Followed by Q8W (Weeks 16 to 48).

Source: Reviewer's analysis to confirm Figure 26. GALD-PMX-NEMOLIZUMAB-1787-POPPK

Abbreviations: PK, pharmacokinetic; Q4W, once every 4 weeks; Q8W, once every 8 weeks; W, week

Reviewer's Note

- Both univariate and multivariate assessments indicate relatively lower exposure levels for subjects with higher WT, with the 90% prediction interval marginally outside the 0.8 to 1.25 exposure ratio interval. Overall, the impact of WT 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.
- The PopPK-based simulation confirmed that the steady state was reached at Week 4 after the 60 mg loading dose and at Week 12 without a 60-mg loading dose. The accumulation after multiple doses with a Q4W dosing regimen was low, with an accumulation ratio of 1.6.
- During the maintenance period, steady-state systemic exposure of nemolizumab was approximately 3.6 times lower with a Q8W dosing compared to Q4W. Despite the reduced exposure with the Q8W regimen (switching from an initial treatment of Q4W to a Q8W maintenance phase), it consistently showed better maintenance of IGA success and EASI-75 response compared to either continuing the Q4W regimen from the initial to maintenance stages or switching from Q4W to placebo, across all clinical and patient-reported outcomes (refer to the clinical review in Section 6). This supports the proposed nemolizumab dosing regimen for patients with AD.

14.5.1.3. Nemolizumab Exposure Response Assessment

14.5.1.3.1. PK/PD for Efficacy

Executive Summary

- Pharmacokinetic/pharmacodynamic models were developed to characterize the relationship between nemolizumab concentrations and efficacy assessments over time (EASI, 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 ≥ 90 kg), providing supportive evidence for the effectiveness and safety of the selected doses and the proposed dosing regimens in subjects with AD.

PK/PD for Efficacy

Analysis Objectives

- To characterize the PK/PD relationships between nemolizumab serum concentrations and the following assessments of clinical efficacy in adults and adolescents with moderate to severe AD not adequately controlled by topical therapy: EASI, IGA, and weekly average PP-NRS.
- To evaluate the impact of relevant covariates, including, but not limited to, body weight (BW) on clinical outcomes in AD subjects using model-based PK/PD simulations).

Data

The PK/PD analysis dataset included 13042 EASI observations from 2338 subjects enrolled in Studies CIM001JP, CIM003JG, SPR.114322, SPR.116912, SPR.118161 (Trial ARCADIA 1), and SPR.118169 (Trial ARCADIA 2) (Table 75).

For IGA, the PK/PD analysis dataset included 10537 observations from 2222 subjects enrolled in Studies CIM003JG, SPR.114322, SPR.114322, SPR.118161 (Trial ARCADIA 1), and SPR.118169 (Trial ARCADIA 2) (Table 76).

The PK/PD analysis dataset also included 33755 weekly average PP-NRS observations from 1958 subjects enrolled in Studies SPR.114322, SPR.116912, SPR.118161 (Trial ARCADIA 1), and SPR.118169 (Trial ARCADIA 2) (Table 77).

Table 75. EASI Observations Collected in Clinical Studies

Study	Subjects Included in the Dataset N (% of total)	Subjects without evaluable PK Data N (% of total)	Subjects without evaluable EASI Data N (% of total)	Number of Observations in Analysis n (% of total)	Number of Missing Observations n (% of total)
CIM001JP	116 (5.0%)	69 (63.3%)	20 (100.0%)	222 (1.7%)	0 (0%)
CIM003JG	264 (11.3%)	1 (0.9%)	0 (0%)	2188 (16.9%)	0 (0%)
SPR.114322	225 (9.6%)	0 (0%)	0 (0%)	2272 (17.6%)	0 (0%)
SPR.116912	20 (0.9%)	2 (1.8%)	0 (0%)	116 (0.9%)	0 (0%)
SPR.118161	937 (40.1%)	22 (20.2%)	0 (0%)	4470 (34.5%)	0 (0%)
SPR.118169	776 (33.2%)	15 (13.8%)	0 (0%)	3673 (28.4%)	0 (0%)
Total	2338	109	20	12941^a	0

Source: Table 11. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: EASI, Eczema Area and Severity Index; n, number of patients meeting criteria; N, number of patients in treatment arm; PK, pharmacokinetics; PK/PD, pharmacokinetics/pharmacodynamics

Table 76. IGA Observations Collected in Clinical Studies

Study	Subjects Included in the Dataset N (% of total)	Subjects without Evaluable PK N (% of total)	Subjects without Evaluable IGA N (% of total)	Number of Observations in Analysis n (% of total)	Number of Missing Observations n (% of total)
CIM003JG	264 (11.9%)	0 (0%)	0 (0%)	1932 (18.3%)	0 (0%)
SPR.114322	225 (10.1%)	0 (0%)	0 (0%)	2045 (19.4%)	0 (0%)
SPR.116912	20 (0.9%)	0 (0%)	2 (66.7%)	98 (0.9%)	0 (0%)
SPR.118161	937 (42.2%)	21 (58.3%)	1 (33.3%)	3552 (33.7%)	0 (0%)
SPR.118169	776 (35%)	15 (41.7%)	0 (0%)	2910 (27.6%)	0 (0%)
Total	2222	36	3	10537	0

Source: Table 17. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: IGA, Investigator's Global Assessment; n, number of patients meeting criteria; N, number of patients in treatment arm; PK, pharmacokinetics; PK/PD, pharmacokinetics/pharmacodynamics

Table 77. Weekly Average PP-NRS Observations Collected in Clinical Studies

Study	Subjects Included in the Dataset N (% of total)	Subjects without Evaluable PK Data N (% of total)	Subjects without Evaluable PP NRS Data N (% of total)	Number of Observations in Analysis n (% of total)	Number of Missing Observations n (% of total)
SPR.114322	225 (11.5%)	0 (0%)	0 (0%)	5842 (19.3%)	543 (15.5%)
SPR.116912	20 (1.0%)	2 (5.1%)	0 (0%)	302 (1.0%)	80 (2.3%)
SPR.118161	937 (47.9%)	22 (56.4%)	1 (33.3%)	13103 (43.3%)	1580 (45.1%)
SPR.118169	776 (39.6%)	15 (38.5%)	2 (66.7%)	11008 (36.4%)	1297 (37.1%)
Total	1958	39	3	30 255	3500

Source: Table 24. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: n, number of patients meeting criteria; N, number of patients in treatment arm; PK, pharmacokinetics; PK/PD, pharmacokinetics/pharmacodynamics; PP-NRS, Peak Pruritus Numeric Rating Scale

Methodology

EASI PK/PD Model

The impact of nemolizumab PK on the EASI scores during treatment with placebo or nemolizumab was characterized by a turnover model with inhibiting effect (sum of the placebo effect [P1] and drug effect [EF1], described as a maximum inhibitory effect ($I_{\max}$) model on the rate of production of the EASI response. A combined additive and proportional residual error were applied to EASI, which was then back transformed with an inverse logistic transformation to get an EASI prediction on the 0 to 72 scale.

IGA PK/PD Model

The relationship between nemolizumab concentrations and IGA assessments was described by a continuous-time Markov model (CTMM). Using the base IGA model, a covariate analysis was performed and aimed to determine the putative effects of age, sex, BW and race. Covariates were tested on λ_{desc} .

PP-NRS PK/PD

The impact of nemolizumab PK on the weekly average PP-NRS scores during treatment with placebo or nemolizumab was characterized by an indirect response model with an inhibitory $I_{\max}$ model for nemolizumab effect on the production of the PP-NRS response.

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.

Results

EASI PK/PD Model

The parameter estimates for the final EASI model are presented in Table 78. None of the evaluated covariates (age, BW, sex, race, ethnicity, region and baseline weekly average PP-NRS) had a relevant impact on the EASI time course.

IGA PK/PD Model

The final IGA model consisted of a 4-compartment CTMM that included a stimulating drug λ_{desc} (E_{desc}) common to all descending transitions (Table 79). This effect resulted in faster transitions toward lower (e.g., better) IGA score with increasing nemolizumab concentrations. A simplified IIV structure was implemented using 1 term common to all λ_{desc} . Baseline IGA scores of 4 or 5 (i.e., severe disease status) were associated with higher λ_{desc} , compared to baseline scores of 3, suggesting that subjects with higher IGA baseline scores were less likely to decrease toward lower IGA scores. Overall, subjects with severe IGA score at baseline were less responsive to nemolizumab treatment.

Female subjects were found to have approximately 41% higher descending transition rate constants (i.e., are more likely to improve) compared to male subjects.

An indirect response model with a maximum inhibitory effect ($I_{\max}$) 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 $\mu\text{g/mL}$ (Table 80). None of the evaluated covariates (age, BW, sex, race, ethnicity, region and baseline weekly average PP-NRS) had a relevant impact on the weekly average PP-NRS time course.

Table 78. Parameter Estimates for the EASI PK/PD Final Model

Parameter	Point Estimate	IIV (%CV)	%RSE ^b	Asymptotic 95% CI ^c	Bootstrap 95% CI ^d	Shrinkage (%)
K_{OUT} (1/day)	0.0328	--	4.1	0.0302, 0.0355	0.0296, 0.0362	--
P_1 (-)	1.43	--	4.5	1.31, 1.56	1.29, 1.56	--
$I_{\max}$ (-)	1.40	--	20.8	0.831, 1.97	0.85, 2.54	--
IC_{50} ($\mu\text{g/mL}$)	4.27	--	43.1	0.654, 7.89	1.02, 12.6	--
Additive RUV (SD)	0.0451	--	8.3	0.0377, 0.0525	0.0372, 0.054	--
Proportional RUV (SD)	0.278	--	3.0	0.261, 0.294	0.259, 0.295	--
IIV on K_{OUT}	0.946 ^a	97.3	3.7	0.875, 1.02	0.811, 1.12	35.4
IIV on P_1	2.18 ^a	103	2.7	2.1, 2.25	1.94, 2.44	14.4

Source: Table 16. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: CI, confidence interval; CV, coefficient of variation; IC_{50} , half maximal inhibitory concentration; EASI, Eczema Area and Severity Index; IIV, interindividual variability; $I_{\max}$, maximum total inhibitor concentration in plasma; K_{OUT} , first-order elimination rate constant; PK/PD, pharmacokinetics/pharmacodynamics; RSE, relative standard error; RUV, residual unexplained variability; SD, standard deviation

Table 79. Parameter Estimates for IGA PK/PD Final Model in Adults with AD

Parameter	Point Estimate	IIV (%CV)	%RSE ^a	Asymptotic 95% CI ^a	Shrinkage (%)
λ_{12} (day^{-1})	0.00794	-	7.8	0.00673, 0.00916	-
λ_{21} (day^{-1})	0.00708	-	6.4	0.00619, 0.00797	-
λ_{23} (day^{-1})	0.00909	-	5.8	0.00806, 0.0101	-
λ_{32} (day^{-1})	0.01200	-	5.1	0.0108, 0.0132	-
λ_{34} (day^{-1})	0.00334	-	6.9	0.00289, 0.00379	-
λ_{43} (day^{-1})	0.02660	-	6.2	0.0234, 0.0299	-
Slope/1000, λ_{desc} (L/ μg)	0.09640	-	14.0	0.0699, 0.123	-
$\theta_{\text{st_CIM003JG}}(-)$	3.36000	-	7.8	2.84, 3.88	-
$\theta_{B4/5}$ (-)	2.25000	-	6.9	1.95, 2.55	-
Sex effect female (-), λ_{desc}	0.41200	-	16.0	0.28, 0.543	-
ETA on λ_{desc}	0.44400	66.6	5.3	0.375, 0.513	39.2

Source: Table 23. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: AD, atopic dermatitis; CI, confidence interval; CV, coefficient of variation; ETA, estimate of interindividual variability; IGA, Investigator's Global Assessment; IV, interindividual variability; PK/PD, pharmacokinetics/pharmacodynamics; RSE, relative standard error

Table 80. Final 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 (-)	1.82	--	0.76	1.79, 1.84	1.78, 1.85	--
K _{OUT} (1/day)	0.0396	--	2.50	0.0378, 0.0414	0.035, 0.045	--
P ₁ (-)	0.545	--	8.10	0.464, 0.626	0.164, 0.86	--
I _{max} (-)	2.23	--	0.60	2.2, 2.26	1.79, 3.04	--
IC ₅₀ (µg/mL)	0.654	--	2.60	0.621, 0.688	0.425, 1.550	--
Additive RUV (SD)	0.124	--	0.36	0.123, 0.125	0.11, 0.134	--
Proportional RUV (SD)	0.174	--	0.27	0.173, 0.175	0.162, 0.189	--
IIV on tPP NRS ₀	0.132 ^c	36.3	1.50	0.121, 0.142	0.118, 0.143	7.2
IIV on P ₁	2.34 ^c	281	1.80	2.29, 2.4	2.08, 2.91	11.6
IIV on K _{OUT}	1.28 ^c	113	2.50	1.22, 1.34	1.14, 1.45	23.8

Source: Table 29. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: CI, confidence interval; CV, coefficient of variation; IC₅₀, half maximal inhibitory concentration; IIV, interindividual variability; I_{max}, maximum total inhibitor concentration in plasma; K_{out}, first-order elimination rate constant; PK/PD, pharmacokinetics/pharmacodynamics; PP-NRS, Peak Pruritus Numeric Rating Scale; RSE, relative standard error; RUV, residual unexplained variability; SD, standard deviation

Simulations

The developed PK/PD models were used to conduct simulations to assess the impact of BW on the different clinical endpoints under the dosing regimen used in phase 3 ARCADIA Trials for AD indication: 60 mg LD+30 mg. The clinical endpoints of interest were the proportion of responders for EASI-75, IGA, and PP-NRS:

A 3-arm study was simulated, and each arm is defined as follows:

- Arm 1: Overall subject population (BW range observed in the clinical studies: 31 to 171 kg) nemolizumab dosing regimen: 60 mg LD + 30 mg, Q4W for 12 weeks.
- Arm 2: Low BW subject population (BW range: 31 to <90 kg) nemolizumab dosing regimen: 60 mg LD + 30 mg, Q4W for 12 weeks.
- Arm 3: High BW subject population (BW range: 90 to 171 kg) nemolizumab dosing regimen: 60 mg LD + 30 mg, Q4W for 12 weeks.

Each arm consisted of 1000 virtual subjects whose relevant covariates, as well as the baseline for the different endpoints, were sampled with resampling from the characteristics of the subjects included in the two phase 3 Trials.

In each arm, subjects received nemolizumab every 4 weeks until Week 12, and nemolizumab, EASI, PP-NRS, and IGA were assessed on Weeks 4, 8, 12, and 16.

The responders were defined based on the 3 clinical endpoints and were defined as follows:

- For EASI: Proportion of subjects with EASI-75 at Week 16
- For IGA: Proportion of subjects with an IGA success at Week 16
- For PP-NRS: Proportion of PP-NRS responders Week 16

Results

When administered as a flat dose of 60 mg LD+30 mg Q4W, the percentage of responders were similar in the 2 different BW-arms, independently of sex or baseline IGA value, as shown in Table 81. The slight differences in responder rates across the BW-arms and between females and males were considered not clinically relevant ([Figure 28](#), [Figure 29](#), and [Figure 30](#)).

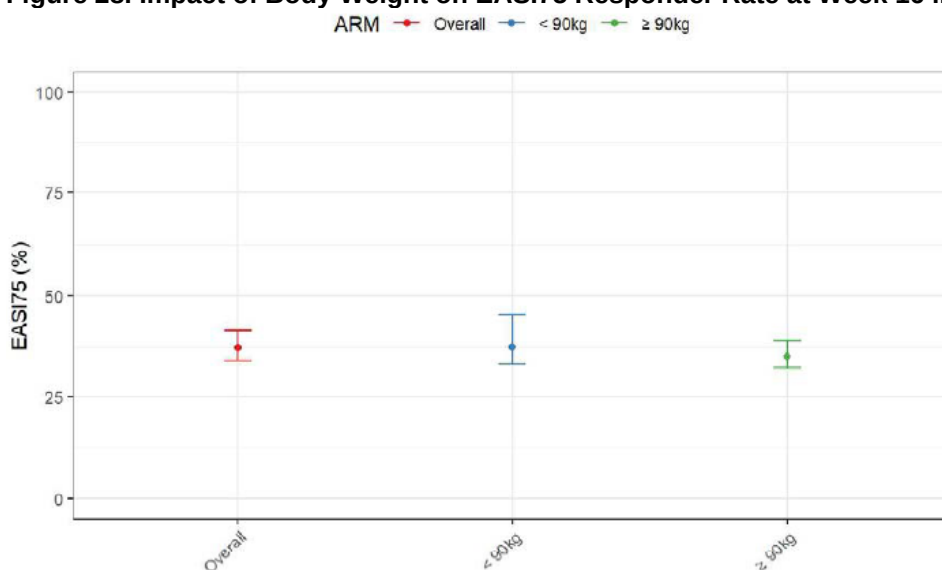
Table 81. Impact of Body Weight on the Responder Rate for EASI-75, IGA, and PP-NRS Across Simulations in Subjects With AD (Median [p5-p95])

Endpoint	Sex	Overall	<90 kg	≥90 kg
C _{trough, W16} (µg/mL)	All subjects	2.34 [2.23-2.44]	2.51 [2.41-2.62]	1.71 [1.64-1.79]
EASI75	All subjects	37.3 [34.2-41.6]	37.5 [33.2-45.4]	35.1 [31.8-39.1]
NRS responders	All subjects	55.3 [52.5-59.2]	55.6 [52.6-58.9]	53.4 [50-56.4]
IGA responders	All subjects	28.6 [25.9-31.4]	31.6 [28.7-34]	26.3 [23.6-28.5]
	Male	23.4 [19.2-27.2]	25.6 [21.7-29.4]	23.3 [19.6-26.3]
	Female	34 [30.7-39]	36.5 [32.2-41.1]	32.5 [26.8-37.4]
	IGA baseline=3	32.3 [29.5-37.1]	35.9 [32.4-39.3]	30.5 [27-33.1]
	IGA baseline=4	19.3 [15.2-23.2]	21.6 [16.4-26.1]	17 [13.1-20.9]

Source: Table 31. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

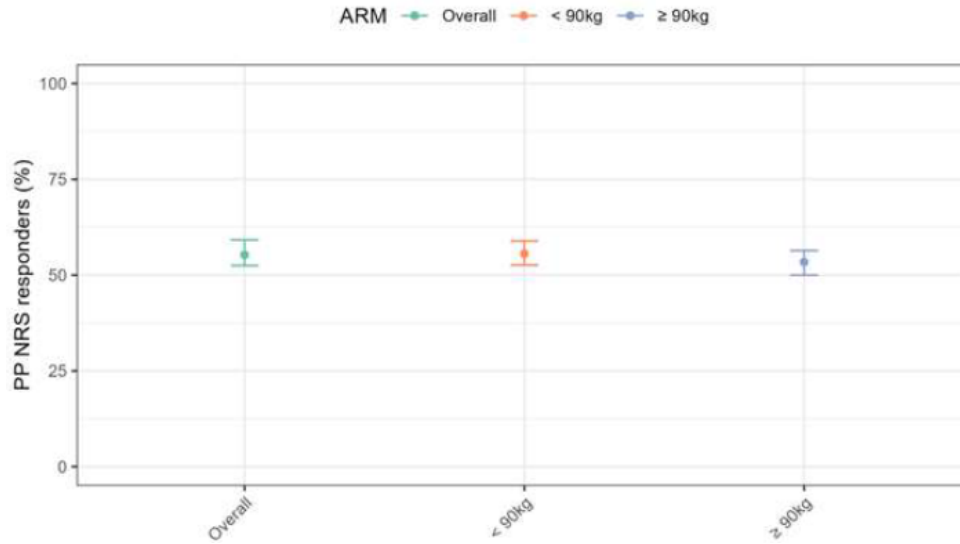
Abbreviations: C_{trough, W16}, through nemolizumab concentration at Week 16; EASI-75, proportion of subjects achieving at least 75% reduction from the baseline; Eczema Area and Severity Index score; IGA, Investigator's Global Assessment; LD, loading dose; p5, 5th percentile; p95, 95th percentile; PP-NRS, Peak Pruritus Numeric Rating Scale; Q4W, once every 4 weeks

Figure 28. Impact of Body Weight on EASI75 Responder Rate at Week 16 in Subjects With AD



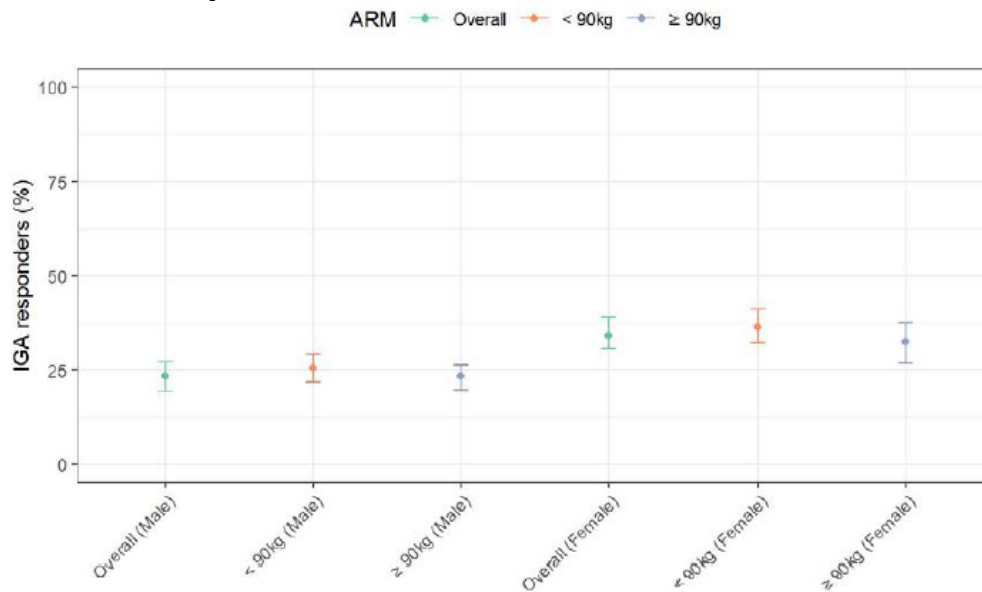
Source: Figure 13. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: AD, atopic dermatitis; EASI, Eczema Area and Severity Index

Figure 29. Impact of Body Weight on PP-NRS Responder Rate at Week 16 in Subjects With AD

Source: Figure 14. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: AD, atopic dermatitis; PP-NRS, Peak Pruritus Numeric Rating Scale

Figure 30. Impact of Body Weight on IGA Responder Rate at Week 16 in Subjects With AD (In Male and Female Subjects)

Source: Figure 13. PK/PD Modeling and Simulation Report in Subjects With AD, October 14, 2023

Abbreviations: AD, atopic dermatitis; IGA, Investigator's Global Assessment

Reviewer's Note

- *The PK-PD model predictions for the co-primary efficacy endpoints, specifically the proportion of subjects achieving IGA success and EASI-75 at Week 16, were 15 to 20% lower than the clinical observations, while the model's predictions for the secondary efficacy endpoint, PP-NRS, were 30% higher (refer to [Table 81](#) and the clinical review in section 6). This discrepancy might be explained by methodological differences: the PK-PD modeling aims to capture the PK-PD relationship over the entire initial treatment duration, whereas the clinical endpoints focus more on point estimates at the end of the initial treatment.*
- *Despite the variability in efficacy endpoint predictions, the overall trend in exposure efficacy remains consistent. Based on the PK-PD model and simulations, the selected pivotal trial dosing regimen demonstrated significant efficacy.*
- *PK/PD simulations of clinical endpoints at Week 16 also demonstrated similar efficacy responses across both body weight groups (<90 kg and ≥90 kg), supporting the effectiveness and safety of the selected flat nemolizumab dose and proposed dosing regimens in subjects with AD.*

14.5.1.3.2. Exposure-Safety Assessment

Executive Summary

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

PK/PD for Safety

Analysis Objective

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

Methodology

The safety analysis was conducted based on the Phase 3 studies (Studies 118161 and 118169), including the information of both the initial phase (i.e., until Week 16) for all subjects and the maintenance phase from Weeks 16 to 48 for responder subjects. The responder subjects were reallocated to either placebo or nemolizumab 30 mg Q4W or nemolizumab Q8W treatment groups. A total of 1719 subjects were initially included in the initial phase, then a total of 689 responders were maintained and reallocated to the treatment groups (Table 82).

Table 82. Number of Subjects Per Treatment Group and Study During Initiation Phase and Maintenance Phase (Report GALD-PMX-NEMOLIZUMAB-1787-PKPD-AD)

Treatment group	Study 118161 N (% of total)	Study 118169 N (% of total)	Total number of subjects in each treatment group N (% of total)
Initial phase (up to Week 16)			
Nemolizumab Q4W	616 (65.7)	519 (66.4)	1135 (66.0)
Placebo Q4W	321 (34.3)	263 (33.6)	584 (34.0)
Total	937	782	1719
Maintenance phase (Weeks 16 to 48)			
Nemolizumab Q4W/Q4W	91 ^a (24.5)	79 ^b (24.9)	170 (24.7)
Nemolizumab Q4W/Q8W	90 ^a (24.2)	77 ^b (24.3)	167 (24.2)
Nemolizumab Q4W/Placebo Q4W	91 (24.5)	77 (24.3)	168 (24.4)
Placebo Q4W/Q4W	100 (26.9)	84 (26.5)	184 (26.7)
Total	372	317	689

Source: Table 25. 2.7.2 Summary of Clinical Pharmacology Studies

Abbreviations: N, number of patients in treatment arm; Q4W, once every 4 weeks; Q8W, once every 8 weeks

Nemolizumab trough concentration at steady state ($C_{\text{trough,ss}}$) at Week 16 (initial phase) and Week 40 (maintenance phase) were used as PK metrics to assess the exposure-response relationship in this analysis. Both C_{trough} values were steady-state concentrations.

Results

Based on the logistic regression, no relationship could be established between nemolizumab exposure and the incidence of dermatitis atopic flares. Similarly, no relationship was established between nemolizumab exposure and newly diagnosed asthma or worsening of asthma or between nemolizumab exposure and peripheral or facial edema.

Reviewer's Note

- The analyses of exposure-safety relationships did not show evidence of positive relationship between nemolizumab concentrations and tested safety events.*
- Overall, the clinical pharmacology data, including supportive modeling and simulations for PK, efficacy, and safety outcomes, confirmed the adequacy of the proposed dosing regimens in subjects aged 12 years and older with moderate-to-severe AD, with no dose adjustment necessary based on patients' intrinsic factors.*

14.6. Pharmacogenetics

NA

15. Study/Trial Design

15.1. Phase 2 Protocol Synopsis – RD.03.SPR.114322

Phase 2 Protocol Synopsis (Version 2.0; June 1, 2018) for RD.03.SPR.114322 (NCT03100344)

APPEARS THIS WAY ON ORIGINAL

SYNOPSIS																	
Clinical Trial Title: A randomized, double-blind, multi-center, parallel-group, placebo-controlled dose-ranging study to assess the efficacy and safety of nemolizumab (CD14152) in moderate-to-severe atopic dermatitis subjects with severe pruritus receiving topical corticosteroids																	
Short Title: Dose-ranging study of nemolizumab in atopic dermatitis																	
Clinical Trial phase: 2	Clinical Trial Population: Moderate-to-severe atopic dermatitis (AD) subjects with severe pruritus receiving topical corticosteroids (TCS)																
Clinical Trial objectives:	The primary objective is to assess the efficacy of several subcutaneous doses of nemolizumab in moderate-to-severe AD subjects with severe pruritus receiving TCS, who were not adequately controlled with topical treatments. The secondary objectives are to evaluate the safety of nemolizumab and to characterize its pharmacokinetic (PK) profile.																
Clinical Trial design:	This is a randomized, placebo-controlled, double-blind, parallel-group, dose-ranging study. Eligible subjects will be randomized (1:1:1:1) to receive subcutaneous injection of various doses of nemolizumab or its placebo every 4 weeks, in addition to background TCS therapy. Randomization will be stratified by AD severity (Investigator's Global Assessment [IGA] 3 or 4). <table border="1" data-bbox="532 835 1425 982"> <thead> <tr> <th>Group</th><th>Dose on day 1</th><th>Dose at weeks 4, 8, 12, 16 & 20</th></tr> </thead> <tbody> <tr> <td>1</td><td>20 mg</td><td>10 mg</td></tr> <tr> <td>2</td><td>60 mg</td><td>30 mg</td></tr> <tr> <td>3</td><td>90 mg</td><td>90 mg</td></tr> <tr> <td>4</td><td>placebo</td><td>placebo</td></tr> </tbody> </table>		Group	Dose on day 1	Dose at weeks 4, 8, 12, 16 & 20	1	20 mg	10 mg	2	60 mg	30 mg	3	90 mg	90 mg	4	placebo	placebo
Group	Dose on day 1	Dose at weeks 4, 8, 12, 16 & 20															
1	20 mg	10 mg															
2	60 mg	30 mg															
3	90 mg	90 mg															
4	placebo	placebo															
Total number of subjects (Planned):	Approximately 250 subjects will be screened to result in 200 randomized subjects (50 subjects per group).																
Number of clinical trial centers (Planned):	Approximately 70 sites																
Region(s) involved (Planned):	Europe/North America/Asia-Pacific																
Clinical trial duration:	The planned duration of this clinical trial (from First Subject In [FSI] to Last Subject Out [LSO]) is approximately 15 months, with approximately 6 months of recruitment (from FSI to Last Subject In [LSI]).																
Duration of subject participation:	Each subject will participate in the clinical trial for up to 36 weeks, with a 2 to 4-week run-in period, a 24-week treatment period (with the last drug injection at week 20), and an 8-week follow-up period (12 weeks after the last study drug injection).																

Inclusion criteria (at the screening visit)	Male or female subjects ≥ 18 years (or legal age when higher) Chronic AD (according to American Academy of Dermatology Consensus Criteria [Eichenfield 2014]), that has been present for at least 2 years before the visit Eczema Area and Severity Index (EASI) score ≥ 12 IGA score ≥ 3 (based on the IGA scale ranging from 0 to 4, in which 3 is moderate and 4 is severe) AD involvement $\geq 10\%$ of Body Surface Area (BSA) Severe pruritus (according to the definition of the Pruritus Categorical Scale [PCS]) on at least 3 of the last 7 days before the visit Documented recent history (within 6 months before the visit) of inadequate response to topical medications Note: - Inadequate response to topical treatments is defined as: 1) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a daily regimen of a medium or high potency TCS, applied for at least 4 weeks or for the maximum duration per prescribing information - Or 2) Requirement of a long term treatment (>4 weeks) with a high potency TCS to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) - AND 3) Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) with a topical calcineurin inhibitor (TCI), when applicable - 4) Subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) are also considered as inadequate responders to topical treatments. - Subjects will be considered as having inadequate response to topical treatments if they fulfill any of the three scenarios below or any combination of these three scenarios: 1) and 3) 2) and 3) 4) Have an ongoing TCS treatment (regardless of the potency of the TCS, the dose or the dose regimen), and agree to stop it and to apply the authorized TCS throughout the study starting from the screening visit Agree to apply a moisturizer at least once daily throughout the study starting from the screening visit Female subjects must fulfill one of the criteria below: Female subjects of non-childbearing potential (postmenopausal [absence of menstrual bleeding for 1 year prior to screening, without any other medical reason], hysterectomy or bilateral oophorectomy); Female subjects of childbearing potential who agree to a true abstinence (when in line with the preferred and usual lifestyle of the subject), or to use an effective or highly effective method of contraception throughout the clinical trial and for 120 days after the last study drug administration Willing and able to comply with all of the time commitments and procedural requirements of the clinical trial protocol Apprised of the Health Insurance Portability and Accountability Act (HIPAA), if in the U.S., Personal Information Protection and Electronic Documents Act (PIPEDA), if in Canada, or local privacy act if in other countries, and willing to share personal information and data, as verified by signing a written authorization. Understand and sign an Informed Consent Form (ICF) prior to any investigational procedures being performed.
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Screening (Approximately 250 subjects)				
↓				
Randomization (Approximately 200 subjects)				
	Group 1	Group 2	Group 3	Group 4
	n= 50	n= 50	n= 50	n= 50
Treatment	Nemolizumab 10mg (loading dose: 20mg)	Nemolizumab 30mg (loading dose: 60mg)	Nemolizumab 90mg	Nemolizumab placebo
Treatment Frequency	Every 4 weeks (Q4W)	Q4W	Q4W	Q4W
Treatment Duration	24 weeks (last study drug injection at week 20)	24 weeks (last study drug injection at week 20)	24 weeks (last study drug injection at week 20)	24 weeks (last study drug injection at week 20)
Duration of follow-up period	8 weeks (12 weeks after last study drug administration)	8 weeks (12 weeks after last study drug administration)	8 weeks (12 weeks after last study drug administration)	8 weeks (12 weeks after last study drug administration)

15.2. Phase 3 Protocol Synopsis – ARCADIA 1 (RD.06.SPR.118161)

Protocol Number:

RD.06.SPR.118161

Title:

A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Efficacy and Safety of Nemolizumab (CD14152) in Subjects with Moderate-to-Severe Atopic Dermatitis

Investigational Product:

Nemolizumab (CD14152)

IND Number:

117122

Study Centers:

Approximately 150 study centers are planned in Europe, Americas, and Asia-Pacific.

Phase:

3

Objectives:

Primary objective: The primary objective is to assess the efficacy and safety of nemolizumab (CD14152) after a 16-week treatment period in adult and adolescent subjects with moderate-to-severe atopic dermatitis (AD) not adequately controlled with topical treatments.

Secondary objective: The secondary objective is to evaluate the efficacy and safety of maintenance treatment with nemolizumab (CD14152) for up to an additional 32 weeks.

Study Design:

This is a randomized, double-blind, placebo-controlled, multicenter, parallel-group study in adult and adolescent subjects with moderate-to-severe AD. Eligible subjects must have a documented history of inadequate response to topical AD medication(s).

Approximately 750 total subjects will be randomized (2:1) to receive either nemolizumab (CD14152) or placebo, stratified by baseline disease severity (Investigator's Global Assessment [IGA]; moderate: IGA = 3; severe:

NEMLUVIO (nemolizumab-ilto)

IGA = 4) and peak pruritus numeric rating scale (PP-NRS) severity (PP-NRS ≥ 7 ; PP-NRS < 7). A minimum of 250 subjects will be randomized in each PP-NRS strata. Clinical responders at Week 16 (i.e., the end of initial treatment/beginning of maintenance) will be re-randomized (1:1:1) to different treatment regimens (injections every 4 weeks [Q4W] or every 8 weeks [Q8W] of nemolizumab [CD14152] or placebo Q4W).

Subjects will apply a moisturizer at least once daily, beginning at screening. Subjects will also be provided or prescribed background topical therapy for AD (including a medium-potency topical corticosteroid [TCS] for the body and a low-potency TCS or topical calcineurin inhibitor (TCI) for sensitive areas such as the face, neck, intertriginous areas, etc for use throughout the study. If deemed to be medically necessary by the investigator (e.g., to control intolerable AD signs/symptoms), rescue therapies can be prescribed to the subjects during the study, except during the run-in period (i.e., at least 2 weeks [14 days] before Day 1/baseline).

The study consists of 4 periods over approximately 60 weeks: screening (including run-in), initial treatment, maintenance, and follow-up (unless the subject is a non-responder at Week 16, at which their participation could last up to 28 weeks). Refer to figure 1 for an overview of the treatment/study design.

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. 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 are provided in the respective IDMC and IAC charters.

Screening Period (Screening to Initial Randomization/Baseline)

The screening period (approximately 2-4 weeks before planned Day 1/baseline) will evaluate subject eligibility and introduce standardized background topical therapy over a run-in period of at least 2 weeks (i.e., 14 days) before Day 1/baseline.

Initial Treatment Period (Baseline/Day 1 to Week 16 Pre-dose)

The initial treatment period is defined as Day 1/baseline through Week 16 (before the Week 16 dose, with last dose at Week 12). Eligible subjects will be randomized in a ratio of 2:1 at baseline to receive subcutaneous injections of nemolizumab (CD14152) or placebo Q4W.

Subjects will continue to use background topical therapy, which should be adjusted according to the disease activity and tolerability, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur, based on investigator clinical judgment.

Table 2. Initial Treatment Period Randomized Group Assignments

Group	Treatment	Loading dose (Day 1/Baseline)	Dose at Week 4, 8, 12	Route	Schedule
1	Nemolizumab(CD14152)	60 mg (two 30-mg injections)	30 mg	sc	Q4W
2	Placebo	Placebo (two injections)	Placebo	sc	Q4W

Abbreviation(s): Q4W = every 4 weeks; sc = subcutaneous.

Clinical assessments will occur according to the schedule of assessments through the Week 16 visit (see Section 8.1.2). Subjects who are clinical responders at Week 16 will continue to the maintenance period. Subjects who are non-responders at Week 16 may be eligible to enrol into a long-term extension (LTE) study (Protocol 118163). Subjects who require rescue therapy for clinical worsening of AD before Week 16 may also be considered for the LTE study but will be required to continue with study visits until the Week 16 visit. The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible to enter into the LTE study will complete a follow-up visit 12 weeks after their last study drug injection.

Subjects who discontinue the initial treatment period prematurely should complete an early termination (ET) visit and a follow-up visit 12 weeks after the last study drug injection.

Initial treatment period results may be analyzed after all subjects have either completed the Week 16 visit or have withdrawn or been discontinued from the study before Week 16. To maintain the blind during the maintenance period, personnel directly involved with the ongoing conduct of the study from the Sponsor, contract research organization, or investigational study centers will not have access to any information that may lead to unblinding.

Maintenance Period (Re-Randomization: Week 16 to Week 48)

The maintenance period is defined as Week 16 (maintenance baseline) to Week 48. All nemolizumab (CD14152)-treated subjects (i.e., group 1) who are clinical responders at Week 16 will be re-randomized (1:1:1) to study medication, as follows: group 1A, nemolizumab (CD14152) 30 mg Q4W; group 1B, nemolizumab 30 mg Q8W; or group 1C, placebo Q4W.

Clinical responders are defined as:

- IGA of 0 (clear) or 1 (almost clear) at Week 16
- OR**
- Eczema Area and Severity Index (EASI)-75 at Week 16

All placebo-treated subjects (i.e., subjects in group 2 from the initial treatment period) who responded to placebo during the initial treatment period will continue to receive placebo Q4W in the maintenance period.

Subjects who receive rescue therapy will be considered non-responders.

Based on the phase 2b results (Protocol 114322), it is estimated that 15% of subjects will drop out from the initial treatment period. Assuming a 45% responder rate in active treatment and 12% with placebo, approximately 216 subjects will participate in the maintenance period (190 nemolizumab and 26 placebo subjects).

Table 3. Maintenance Period Re-Randomized Group Assignments

Group	Treatment	Dose	Week(s)	Route	Schedule
1A	Nemolizumab (CD14152)	30 mg	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W
1B	Nemolizumab (CD14152)	30 mg	16, 20*, 24, 28*, 32, 36*, 40, 44*	sc	Q8W*
1C	Placebo	Placebo	16, 20, 24, 28, 32, 36, 40, 44	sc	Q4W

**with placebo Q4W at Week 20, 28, 36, and 44 to maintain blind*

Abbreviation(s): Q4W=every 4 weeks; Q8W=every 8 weeks; sc=subcutaneous.

Beginning at Week 16, subjects in group 1A will receive active (i.e., nemolizumab [CD14152]) study drug injections Q4W up to Week 44. Subjects in group 1B will receive active study drug injections Q8W, with placebo at alternating visits to maintain the blind. Group 1B subjects will receive the last active study drug injection at Week 40 (final injection at Week 44 will be placebo). Group 1C subjects will receive placebo Q4W (i.e., through Week 44).

Subjects should continue the same background topical therapy used in the initial treatment period leading up to the Week 16 visit, including tapering or complete cessation (no use), if applicable. Throughout the maintenance period, adjustments to background topical therapy, as determined by the investigator, are permitted based on the subject's clinical response.

Primary maintenance effect will be evaluated based on Week 48 assessments. All maintenance endpoints will be analyzed independently from each pivotal study and by using pooled data after the completion of both trials.

Subjects requiring rescue therapy before the Week 32 visit must undergo a required wait period (with continued study visits) until the Week 32 visit, at which time they may be considered for LTE eligibility/participation. Thereafter, no wait period is required.

Subjects who complete the Week 48 visit may be eligible to enrol into the LTE study (Protocol 118163). Subjects requiring rescue medication before the Week 48 visit may be considered for LTE eligibility. The follow-up visit is not required for subjects who participate in the LTE study.

Subjects who decline or are not eligible for the LTE study will be asked to complete the follow-up visit.

Subjects who discontinue the maintenance period prematurely should complete an ET visit and a follow-up visit 12 weeks after the last study drug injection.

Follow-up

The follow-up visit will be conducted 12 weeks after the last study drug injection for subjects who decline or are not eligible to enter the LTE study. (Twelve weeks corresponds to approximately 5 half-lives when nemolizumab 30 mg is dosed subcutaneously Q4W.) The follow-up visit is not required for subjects who participate in the LTE study.

Number of Subjects:

Approximately 750 total subjects are planned to be randomized, including a minimum of 130 adolescent subjects aged 12 to 17 years.

Treatment:

Nemolizumab (CD14152) or placebo will be provided as lyophilized powder for solution for injection for subcutaneous use only after reconstitution in a single-use, pre-filled, dual-chamber syringe (DCS).

During the initial treatment period, eligible subjects will be randomized to receive either 30 mg of nemolizumab (CD14152) in group 1 or placebo in group 2, administered as a subcutaneous injection only after reconstitution Q4W for 16 weeks (last injection at Week 12), with a loading dose of 60 mg on Day 1/baseline.

Subjects (and/or their caregivers) will have the option to self-inject study drug while at the study center under staff supervision. Subjects (and/or their caregivers) will be trained on injecting the study drug at Day 1 and will be allowed to inject study drug at all subsequent visits, while at the study center, under staff supervision. If the subject (and/or caregivers) is unwilling to perform the injections, study staff can administer study drug at each visit.

In the maintenance period, group 1 subjects who are clinical responders will be re-randomized to receive either 30 mg of nemolizumab (CD14152) or placebo for 32 weeks. Subjects in group 1A will receive a subcutaneous injection of nemolizumab Q4W (last injection at Week 44); group 1B will receive an injection of nemolizumab Q8W, with alternating placebo Q8W (last active injection at Week 40 and last placebo injection at Week 44); and group 1C will receive placebo Q4W. Subjects in group 2 who are clinical responders will continue to receive placebo Q4W.

Moisturizer

Subjects will apply a moisturizer at least once daily, and liberally as needed, to dry skin and AD lesions beginning at screening, and throughout the study. The subjects' current moisturizer or a moisturizer recommended by the investigator may be used. To allow for accurate assessment of skin dryness, use should not occur within 8 hours before each clinic/office visit. Whenever possible, subjects should use the same moisturizer throughout the study.

Background topical therapies

Subjects will be provided or prescribed authorized background topical therapy for use during the study, beginning at screening:

- Medium-potency TCS therapy for non-sensitive areas: Subjects will apply the authorized medium-potency TCS background therapy in areas of the body where use of medium-potency TCS is considered safe (e.g., trunk and extremities), beginning within the screening period and ≥ 14 days before Day 1 (i.e., run-in). Refer to the current version of the pharmacy manual for a listing of permitted medium-potency TCS medications that are commercially available in planned countries.
- Low-potency TCS or TCI therapy for sensitive areas: Subjects will apply an authorized background therapy (i.e., low-potency TCS or TCI) to areas of the body considered TCS-sensitive (e.g., face, neck, intertriginous areas) or in cases where medium-potency TCS is not tolerated, beginning within the screening period and ≥ 14 days before Day 1 (i.e., run-in). The investigator may select either low-potency TCS or TCI for each subject, per investigator discretion. The subject may only apply **one** medication to each affected area; concomitant use of low-potency TCS and TCI on the same lesion is not permitted. Refer to the current version of the pharmacy manual for a listing of permitted low-potency TCS and TCI medications that are commercially available in planned countries.

Subjects will apply a thin layer of authorized background topical therapy on all AD lesions at a frequency that is necessary to ensure disease stability and prevent AD flare but which does not exceed the daily frequency

recommended in the product labeling. Refer to the current version of the pharmacy manual for the authorized topical medications and permitted daily frequency of use. “As needed” (PRN) use of TCS or TCI is not permitted. Only topical therapies specifically provided or prescribed for use in this study are permitted.

Background therapy use should be adjusted to the disease activity and tolerability of the subject, including tapering when signs and symptoms improve, discontinuation when lesions clear, and restarting if signs and symptoms recur, at the discretion of the investigator.

Rescue Therapies

If deemed to be medically necessary by the investigator (e.g., to control intolerable AD signs/symptoms), rescue therapies can be prescribed to the subjects at any time during the study except during the run-in period. Subjects receiving rescue therapies during the run-in 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 2 weeks after baseline (i.e., Week 2) to allow a minimum time for study drug exposure in the presence of background therapy.

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.

Rescue treatments are only treatments that directly treat AD (mainly those that are approved or are standard of care) and include topical and systemic treatments as outlined. Rescue therapies include:

- Higher potency of TCS (equivalent to class I-II according to the United States classification)²
- Oral corticosteroids
- Biologics (including their biosimilars)
- Systemic nonsteroidal immunosuppressants/immunomodulators
- Phototherapy

Antihistamines, sleep aids, topical and systemic antibiotics, and anti-itch creams are **not** considered to be rescue therapy because they do not directly treat AD.

Whenever possible, investigators should first use topical medications as rescue therapy before escalating to systemic therapies. If subjects receive topical treatments or phototherapy as rescue therapy, study drug administration should be continued unless there is a safety concern according to the investigator’s judgment. If subjects receive systemic rescue therapy, the study drug administration must be permanently discontinued.

Study Duration:

The expected duration for each subject’s participation in the study depends on the clinical response and may be:

- Up to 28 weeks (including a 4-week screening period, a 16-week initial treatment period and an 8-week follow-up period [12-weeks after the last study medication injection]) for subjects who are non-responders at the completion of the initial treatment period (Week 16)
- Up to 60 weeks (including a 4-week screening period, a 16-week initial treatment period, a 32-week maintenance period, and an 8-week follow-up period [12-weeks after the last study medication injection]) in subjects who are clinical responders at the completion of the initial treatment period (Week 16)

The 12-week follow-up visit is not required for subjects who will continue in the LTE study (Protocol 118163).

Study Population:

Inclusion Criteria: To be eligible for study entry, subjects must satisfy all of the following inclusion criteria.

1. Male or female subjects aged ≥ 12 years at the screening visit.

Note: Enrollment of subjects aged 12 to 17 years has been opened after the IDMC has assessed interim safety data from the phase 2 study (Protocol 116912) and provided recommendations to the Sponsor, who then determined the eligibility of this age group for enrollment in the study. The sponsor sent a written communication to the site confirming that the study is open for enrollment of adolescents. Adolescents could not be enrolled in the study until such communication was received.

2. Chronic AD for at least 2 years before the screening visit, and confirmed according to American Academy of Dermatology Consensus Criteria (Appendix)² at the time of the screening visit.
3. EASI score ≥ 16 at both the screening and baseline visits.
4. 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.
5. AD involvement $\geq 10\%$ of body surface area (BSA) at both the screening and baseline visits.
6. Peak (maximum) pruritus NRS score of at least 4.0 at the screening and baseline visit.

Screening PP-NRS score will be determined by a single PP-NRS assessment (score ranging from 0 to 10) for the 24-hour period immediately preceding the screening visit.

Baseline PP-NRS score will be determined based on the average of daily PP-NRS scores (score ranging from 0 to 10) during the 7 days immediately preceding baseline (rounding is not permitted). A minimum of 4 daily scores out of the 7 days immediately preceding baseline is required for this calculation.

7. Documented recent history (within 6 months before the screening visit) of inadequate response to topical medications (TCS with or without TCI). All subjects must demonstrate inadequate response to TCS. All subjects who have used TCI within 6 months of the screening visit, or for whom TCI is selected as background therapy for sensitive areas, must also demonstrate inadequate response to TCI. Acceptable documentation includes patient records with information on TCS (with or without TCI) prescription and treatment outcome, or written documentation of the conversation with the subject's treating physician, if different than the investigator.

Inadequate response to TCS treatments (with or without TCI) is defined as:

- 7a. Failure to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2) despite treatment with a regimen of a medium-, high-, or very high-potency TCS (Class I-III according to the US classification)² (with or without TCI), applied for at least 4 weeks or for the maximum duration per prescribing information;
or
- 7b. Requirement of a long-term treatment (> 4 weeks) with a high- or very high-potency TCS (Class I-II according to the US classification)² (with or without TCI) to achieve or maintain remission or low disease activity (equivalent to IGA ≤ 2);
or
- 7c. If documentation of inadequate response to topical treatments is not available, subjects with a documented recent course of systemic treatment or phototherapy for AD (within 6 months before the visit) will also be considered as inadequate responders to topical treatments.

If documentation is inadequate, subjects may be re-screened after such documentation is obtained.

8. Agree to apply a moisturizer throughout the study from the screening visit; agree to apply authorized topical therapy from the screening visit and throughout the study as determined appropriate by the investigator.
9. Female subjects of childbearing potential (i.e., fertile, following menarche and until becoming post-menopausal unless permanently sterile) must agree either to commit to true abstinence throughout the study and for 12 weeks after the last study drug injection, when this is in line with the preferred and usual lifestyle of the subject, or to use an adequate and approved method of contraception throughout the study and for 12 weeks after the last study drug injection. This criterion also applies to a prepubertal female subject who begins menses during the study. *In Germany only, if a subject has reached Tanner stage 3 breast development, even if not having menarche, the subject will be considered a female of childbearing potential.

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

- 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 a highly effective method of contraception)
- (1) 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 partner at least 3 months before the study

10. 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
 - Documented hysterectomy, bilateral salpingectomy, or bilateral oophorectomy at least 3 months before screening
- Note: Bilateral tubal ligation is not accepted as a reason for non-childbearing potential.

11. Subject (and guardian, when applicable) 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.

12. Understand and sign an informed consent form (and assent form, when applicable) before any investigational procedure(s) are performed.

Exclusion Criteria: Subjects will be excluded from the study if 1 or more of the following exclusion criteria are applicable.

1. Body weight < 30 kg.
2. Subjects meeting 1 or more of the following criteria at screening or baseline:
 - 2a. Had an exacerbation of asthma requiring hospitalization in the preceding 12 months.
 - 2b. 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.
 - 2c. Asthma Control Test ≤ 19 (only for subjects with a history of asthma).
 - 2d. Peak expiratory flow < 80% of the predicted value.
3. Subjects with a current medical history of chronic obstructive pulmonary disease and/or chronic bronchitis.
4. 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 8.3.4.2
Note: Subjects with chronic, stable use of prophylactic treatment for recurrent herpes viral infection can be included in this study.
5. Requiring rescue therapy for AD during the run-in period or expected to require rescue therapy within 2 weeks following the baseline visit.
6. Positive serology results (hepatitis B surface antigen [HBsAg] or hepatitis B core antibody [HBcAb], hepatitis C antibody, 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).
7. Having received any of the following treatments in Table 3 within the specified timeframe before the baseline visit:

Table 4. Prior Treatments

<i>Treatment(s)</i>	<i>Timeframe</i>
Coal tar products	2 weeks
Topical PDE-4 inhibitor	2 weeks
Non-authorized TCS	2 weeks
Topical medications, including authorized TCS/TCI, with occlusive dressings (e.g., wet wraps)	2 weeks
Systemic corticosteroids (corticosteroid inhalers are permitted)	4 weeks
Phototherapy or tanning beds	4 weeks
Immunosuppressive or immunomodulatory drugs (e.g., cyclosporine A, oral tacrolimus, cyclophosphamide, azathioprine, methotrexate, mycophenolate mofetil, Janus kinase inhibitors)	4 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
Live attenuated vaccine	12 weeks
Drugs with a 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 (Stable treatment with antihistamines with sedative effect is allowed at a dose that, based on previous experience, is well tolerated by the subject.)	1 week
Gabapentinoids (e.g., gabapentin, pregabalin)	4 weeks
Cannabinoids	2 weeks
Alternative medicine for AD (e.g., traditional Chinese medicine)	2 weeks

Abbreviation(s): AD=atopic dermatitis; PDE-4=phosphodiesterase-4; SNRI= serotonin-norepinephrine reuptake inhibitor; SSRI= selective serotonin reuptake inhibitor; TCI=topical calcineurin inhibitor; TCS=topical corticosteroid.

Note:

Subjects should not interrupt ongoing treatment with medications important for the subject's health

8. Previous treatment with nemolizumab.
9. Subjects who, after a full treatment course of 16 weeks with dupilumab, experienced worsening of their AD or failed to achieve minimal improvement (e.g., $\leq 10\%$ reduction in EASI or no reduction in IGA).
10. 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.
11. 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 baseline visit, or (2) actinic keratoses that have been treated.
12. 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.
13. History of intolerance to TCS or for whom TCS is not advisable (e.g., hypersensitivity, significant skin atrophy).
14. Known active or untreated latent tuberculosis infection.
- (2) Note: Subjects who have a documented history of completion of an appropriate TB treatment regimen for active or latent TB with no history of re-exposure to TB since their treatment was completed are eligible to participate in the study.
15. Known or suspected immunosuppression or unusually frequent, recurrent, severe, or prolonged infections as per investigator judgment.
16. Presence of confounding skin condition that may interfere with study assessments (e.g., Netherton syndrome, psoriasis, cutaneous T-cell lymphoma [mycosis fungoides or Sezary syndrome], contact dermatitis, chronic actinic dermatitis, dermatitis herpetiformis)
17. Any medical or psychological condition or any clinically relevant laboratory abnormalities, such as but not limited to elevated ALT or AST ($> 3 \times$ upper limit of normal [ULN]) in combination with elevated bilirubin ($> 2 \times$ 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).
18. Planned or expected major surgical procedure during the clinical study.
19. Subjects unwilling to refrain from using prohibited medications during the clinical study (see Section 8.4.9.2)
20. Currently participating or participated in any other study of a drug or device, within the past 8 weeks before the screening visit, (or 5 half-lives of the investigational drug, whichever is longer), or is in an exclusion period (if verifiable) from a previous study.
21. History of alcohol or substance abuse within 6 months of the screening visit.

Endpoints:Co-Primary Endpoints:

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

Key Secondary Endpoints:

- Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 16
- Proportion of subjects with PP-NRS < 2 at Week 16
- Proportion of subjects with an improvement of sleep disturbance NRS (SD-NRS) ≥ 4 at Week 16

- Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 4
- Proportion of subjects with PP-NRS < 2 at Week 4
- Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 2
- Proportion of subjects with an improvement of PP-NRS ≥ 4 at Week 1
- Proportion of subjects with EASI-75 **and** improvement of PP-NRS ≥ 4 at Week 16
- Proportion of subjects with IGA success **and** improvement of PP-NRS ≥ 4 at Week 16

Both primary and key secondary endpoints will be evaluated for the following populations:

- **Baseline PP-NRS ≥ 4** (full population)
- **Baseline PP-NRS ≥ 7**

Secondary Endpoints:

Initial Treatment Period

- Proportion of subjects achieving IGA success (defined as IGA 0 [clear] or 1 [almost clear] and a ≥ 2 -point reduction from baseline) at each visit up to Week 16
- Change from baseline in EASI at each visit up to Week 16
- Proportion of subjects achieving 50%, 75%, or 90% response from baseline in EASI (EASI-50, EASI-75, and EASI-90) at each visit up to Week 16
- Change from baseline in PP-NRS at each visit up to Week 16
- Proportion of subjects with an improvement of PP-NRS ≥ 4 from baseline at Week 8 and at Week 12
- Proportion of subjects with PP-NRS < 2 at Week 1, Week 2, Week 8, and Week 12

(3)

- Proportion of subjects with an improvement of average pruritus (AP) NRS ≥ 4 from baseline at each visit up to Week 16

(4)

- Proportion of subjects with AP-NRS < 2 at each visit up to Week 16
- Proportion of subjects achieving EASI-75 **and** an improvement of PP-NRS ≥ 4 from baseline at each visit up to Week 12
- Proportion of subjects achieving IGA success **and** an improvement of PP-NRS ≥ 4 from baseline at each visit up to Week 12
- Change from baseline in percent BSA affected at each visit up to Week 16
- Change from baseline in SCORing Atopic Dermatitis (SCORAD) and its components at each visit up to Week 16
- Proportion of subjects with an improvement of SD-NRS ≥ 4 from baseline at each visit up to Week 12
- Change from baseline in sleep metrics (sleep onset latency, wakefulness after sleep onset [WASO], total awake time, total sleep time, sleep efficiency, WASO related to AD, number of WASO related to AD) based on recordings from subject sleep diary from Week 2 to Week 16
- Change from baseline in AD-associated pain frequency up to Week 16
- Change from baseline in AD-associated pain intensity up to Week 16
- 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 16
- 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 16

- Change from baseline in individual components of the EASI (averaged across body regions) at each visit up to Week 16
- Number of days free of topical AD therapy throughout the initial treatment period (Day 1 to Week 16)
- Incidence of topical rescue therapy use at each visit up to Week 16
- Incidence of phototherapy or systemic rescue therapy use at each visit up to Week 16
- Change from baseline in percentage of itch-free days (based on PP-NRS = 0/1) up to Week 16
- Change from baseline in percentage of itch-free days (based on AP-NRS = 0/1) up to Week 16
- Change from baseline up to Week 16 in Dermatology Life Quality Index (DLQI) or Children's DLQI (cDLQI) total score
- Change from baseline up to Week 16 in Patient-Oriented Eczema Measure (POEM) total score
- Change from baseline up to Week 16 in Hospital Anxiety and Depression Scale (HADS) for each subscale (i.e., depression and anxiety)
- Change from baseline up to Week 16 in Work Productivity and Activity Impairment: Atopic Dermatitis (WPAI:AD) for each subscale (i.e., work productivity and activity impairment)
- Change from baseline up to Week 16 in EuroQoL 5-Dimension (EQ-5D)
- Change from baseline up to Week 16 in Patient-Reported Outcomes Measurement Information System (PROMIS®) Itch Questionnaire (PIQ) T-Score: Scratching
- Change from baseline up to Week 16 in PIQ T-Score: Interference

Maintenance Treatment Period

All maintenance endpoints will be analyzed by study and by using pooled data from 2 phase 3 pivotal trials after the completion of both trials. For maintenance endpoints, Week 16 will be considered as baseline, where applicable.

- Proportion of subjects maintaining EASI-75 response at each visit from Week 16 to Week 48 for the subset of subjects with EASI-75 response at Week 16
- Proportion of subjects maintaining IGA success at each visit from Week 16 to Week 48 for the subset of subjects with IGA success at Week 16
- Proportion of subjects with relapse
Note: Relapse is defined as worsening of AD requiring rescue therapy, if judged to be medically necessary by the investigator (i.e., clinically significant worsening of signs and/or symptoms of AD).
- Time to the first relapse from Week 16
- Change in EASI at each visit from Week 16 to Week 48
- Proportion of subjects with EASI-50, EASI-75, and EASI-90 at each visit from Week 16 to Week 48
- Proportion of subjects with IGA success at each visit from Week 16 to Week 48
- Change in PP-NRS from Week 16 up to Week 48
- Change in AP-NRS from Week 16 up to Week 48
- Proportion of subjects with an improvement of PP-NRS ≥ 4 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16
- Proportion of subjects with an improvement of AP-NRS ≥ 4 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16

- Proportion of subjects with PP-NRS < 2 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16
- Proportion of subjects with AP-NRS < 2 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16
- Proportion of subjects with EASI-75 AND improvement in PP-NRS ≥ 4 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16
- Proportion of subjects with IGA success AND improvement in PP-NRS ≥ 4 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16
- Change in SCORAD and its components at each visit from Week 16 to Week 48
- Proportion of subjects with an improvement of SD-NRS ≥ 4 from Week 16 up to Week 48 and for the subset of subjects with such a response at Week 16
- Change in AD-associated pain frequency from Week 16 up to Week 48
- Change in AD-associated pain intensity from Week 16 up to Week 48
- Proportion of subjects reporting low disease activity (clear, almost clear, or mild) based on PGAD from Week 16 up to Week 48
- Proportion of subjects satisfied with study treatment (good, very good, or excellent) based on PGAT from Week 16 up to Week 48
- Change in individual components of the EASI (averaged across body regions) at each visit from Week 16 to Week 48
- Change in sleep metrics based on recordings from subject sleep diary from Week 16 up to Week 48
- Number of days free of topical therapy from Week 16 to Week 48
- Incidence of topical rescue therapy use at each visit from Week 16 to Week 48
- Incidence of phototherapy or systemic rescue therapy use at each visit from Week 16 to Week 48
- Change in DLQI or cDLQI total score from Week 16 up to Week 48
- Change in POEM total score from Week 16 up to Week 48
- Change in HADS for each subscale from Week 16 up to Week 48
- Change in WPAI:AD for each subscale from Week 16 up to Week 48
- Change in EQ-5D from Week 16 up to Week 48

Safety Endpoints:

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

Procedures and Assessments:

The following assessments are planned according to Section 9 and the schedule of assessments in Section 8.1.2

Safety Assessments:

- Physical examination, vital signs, clinical laboratory tests, electrocardiogram, peak expiratory flow, Asthma Control Test (ACT)

Pharmacokinetics, Immunogenicity, Pharmacodynamics, and Pharmacogenomics Assessments:

- Nemolizumab (CD14152) serum concentrations
- Anti-drug antibody concentrations

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NEMLUVIO (nemolizumab-ilto)

- Biomarkers (e.g., thymus and activation-regulated chemokine, IgE, interleukin-31, and/or other biomarkers) from blood and stratum corneum (D-squames) only at selected sites
- Pharmacogenomic testing (optional and only for subjects who consent).

Patient Reported Outcomes Assessments:

- Pruritus Categorical Scale, 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
- Subject interviews (optional and only for subjects who consent in English-speaking countries)

Clinical photographs:

- Standardized clinical photographs of AD lesions (optional and only for subjects who consent at selected sites)

Statistical Analysis:

Principal Statistical Method

Populations: 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 ITT population will be the primary population for all efficacy analyses, and all safety data will be summarized based on the safety population.

Primary Endpoint:

The 2 co-primary endpoints will be analyzed using a Cochran-Mantel-Haenszel test adjusted for randomized stratification variables (IGA severity and PP-NRS).

Key Secondary Endpoints:

All key secondary endpoints will be analyzed similar to the analysis of primary endpoint using a stratified Cochran-Mantel-Haenszel test.

Secondary Endpoints during Initial Period

Binary endpoints will be analysed with the same method as primary endpoint using non-responder imputation.

Continuous and QoL endpoints will be analyzed using an analysis of covariance (ANCOVA) including treatment group and randomization stratification factors as factors and appropriate baseline values as a covariate, if applicable. Missing values will be imputed using MI under MAR assumption. In addition, EASI, PP-NRS, BSA and SCORAD will be analyzed using a mixed-effect model for repeated measures (MMRM) approach, including terms of treatment group, stratification factors, and appropriate baseline values. An unstructured covariance will be used to model the within-patient errors in the analysis. A linear contrast will be used, within the MMRM framework, to estimate difference between nemolizumab and placebo. Treatment difference between nemolizumab and placebo will be estimated along with associated 95% confidence intervals.

Secondary Endpoints during Maintenance Period

All secondary endpoints during the maintenance period will be descriptively summarized.

Multiplicity Adjustment:

The primary comparison of interest is nemolizumab 30 mg compared to placebo for the co-primary endpoints in both populations (baseline PP-NRS ≥ 4 ; baseline PP-NRS ≥ 7).

To control the type I error at 5% significance level, a serial gatekeeping approach will be implemented. The co-primary endpoints will be tested at 2.5% significance level for each population. If both co-primary endpoints are statistically significant at 2.5% significance level, the key secondary endpoints will be tested sequentially following hierarchical testing procedure using the pre-specified order of endpoints for each population. The comparisons for key secondary endpoints will be made sequentially, and the subsequent tests will be stopped when no statistical difference is found.

Other secondary endpoint comparisons will not be adjusted for multiplicity.

Sample Size

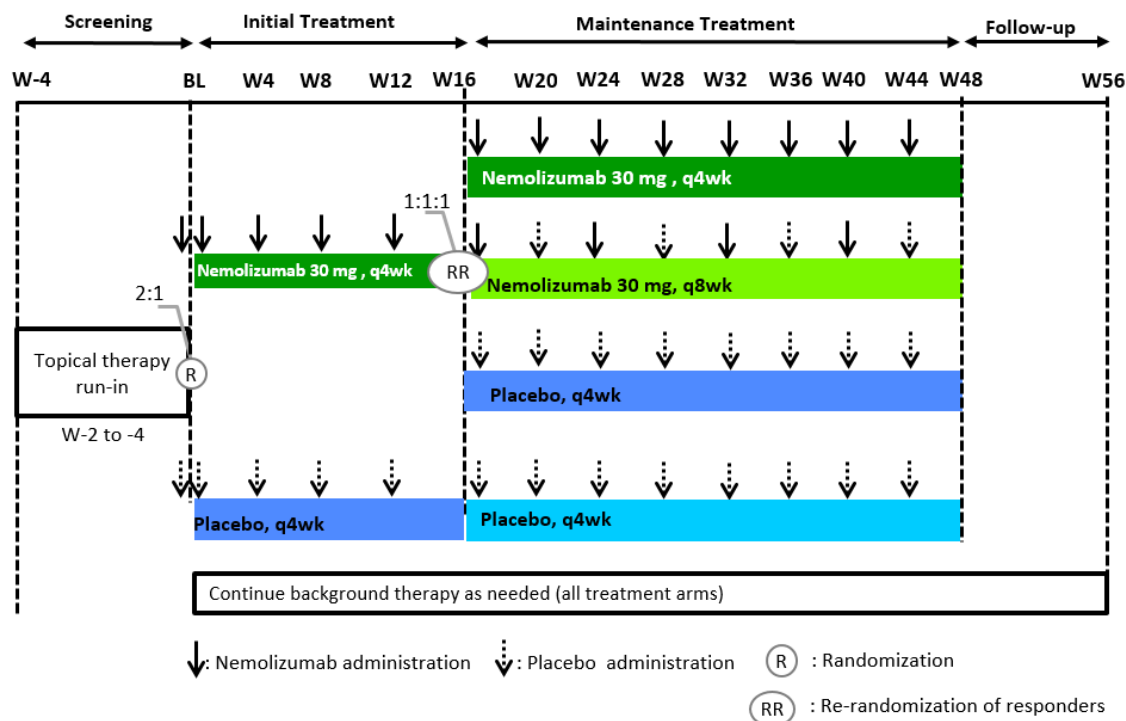
To achieve at least 90% power for both co-primary endpoints at 2.5% significance level, 150 subjects per group will be required to detect the following differences between treatment groups for 2 co-primary endpoints with 1:1 randomization ratio, assuming 15% dropout rate during the initial treatment period.

With a 2:1 randomization, 180 subjects in nemolizumab and 90 subjects in placebo will be required to detect the differences in both co-primary endpoints to achieve 90% power.

IGA Success: To detect a difference of 18%, assuming IGA response for nemolizumab 30% and placebo 12% at Week 16.

EASI-75 Response: To detect a difference of 30%, assuming EASI-75 response for nemolizumab 49% and placebo 19% at Week 16.

To ensure sufficient exposure with nemolizumab and to ensure sufficient size of the safety database, the sample size is increased to 750 subjects in total with randomization ratio 2:1. This sample size will provide more than 99% power to detect the treatment difference for both co-primary endpoints at 2.5% significance level.

Figure 1. Study Visit Schema (Synopsis)

Source: Page 20 of the protocol (Version 8) for ARCADIA

Abbreviations: BL, baseline; q4wk, every 4 weeks; q8wk, every 8 weeks; R, randomization; RR, re-randomization of responders; W, week

16. Efficacy

16.1. Different Approaches for Handling Missing Data

Table 83 and Table 84 present the results for the primary efficacy endpoints by the various imputation methods in ARCADIA 1 and ARCADIA 2, respectively. The results for both endpoints were generally similar across the primary analysis and the sensitivity analyses in both trials.

Table 83. Comparison of Approaches for Handling Missing Data – ARCADIA 1 (ITT¹)

	Nemolizumab (N=620)	Placebo (N=321)	Adjusted Difference (97.5% CI) ²	Adjusted Difference (95% CI) ²	p-Value ²
IGA Score of 0 or 1 at Week 16					
NRI (Primary) ³	36%	25%	12% (5%, 18%)	12% (5%, 18%)	0.0003
MI-MAR ⁴	38%	25%	13% (6%, 20%)	13% (7%, 19%)	<0.0001
LOCF ⁵	39%	27%	12% (5%, 20%)	12% (6%, 18%)	0.0002
OC ⁶	39%	26%	13% (6%, 20%)	13% (7%, 20%)	<0.0001
EASI-75 at Week 16					
NRI (Primary) ³	44%	29%	15% (8%, 22%)	15% (8%, 22%)	<0.0001
MI-MAR ⁴	45%	30%	15% (8%, 23%)	15% (9%, 22%)	<0.0001
LOCF ⁵	45%	30%	16% (9%, 23%)	16% (10%, 22%)	<0.0001
OC ⁶	48%	31%	17% (10%, 25%)	17% (11%, 24%)	<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADEFF.xpt, ADEFFMI.xpt

¹ ITT population: all randomized subjects. Except for the 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factor of baseline disease severity (IGA; moderate: IGA = 3; severe: IGA = 4).

³ Missing data imputed using NRI.

⁴ Missing data imputed using MI-MAR.

⁵ Missing data imputed using LOCF.

⁶ For this OC analysis, all observed data even after use of rescue therapy is used without imputation of missing data.

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, 75% improvement in the Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intent to treat; LOCF, last observation carried forward; MI, multiple imputation, MAR, assuming missing at random; N, number of patients in treatment arm; NRI, non-responder imputation; OC, observed case; PP-NRS, Peak Pruritus Numerical Rating

Table 84. Comparison of Approaches for Handling Missing Data – ARCADIA 2 (ITT¹)

	Nemolizumab (N=522)	Placebo (N=265)	Adjusted Difference (97.5% CI) ²	Adjusted Difference (95% CI) ²	p-Value ²
IGA Score of 0 or 1 at Week 16					
NRI (Primary) ³	38%	26%	12% (5%, 20%)	12% (5%, 20%)	0.0008
MI-MAR ⁴	40%	28%	12% (5%, 20%)	12% (6%, 19%)	0.0004
LOCF ⁵	39%	27%	12% (5%, 20%)	12% (6%, 19%)	0.0008
OC ⁶	41%	28%	13% (5%, 22%)	13% (6%, 21%)	0.0005
EASI-75 at Week 16					
NRI (Primary) ³	44%	29%	15% (8%, 22%)	15% (8%, 22%)	<0.0001
MI-MAR ⁴	43%	31%	13% (5%, 21%)	13% (6%, 20%)	0.0005
LOCF ⁵	44%	33%	11% (3%, 19%)	11% (4%, 18%)	0.0025
OC ⁶	47%	33%	14% (6%, 22%)	14% (7%, 21%)	0.0004

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADEFF.xpt, ADEFFMI.xpt

¹ ITT population: all randomized subjects. Except for the 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factor of baseline disease severity (IGA; moderate: IGA = 3; severe: IGA = 4).

³ Missing data imputed using NRI.

⁴ Missing data imputed using MI-MAR.

⁵ Missing data imputed using LOCF.

⁶ For this OC analysis, all observed data even after use of rescue therapy is used without imputation of missing data.

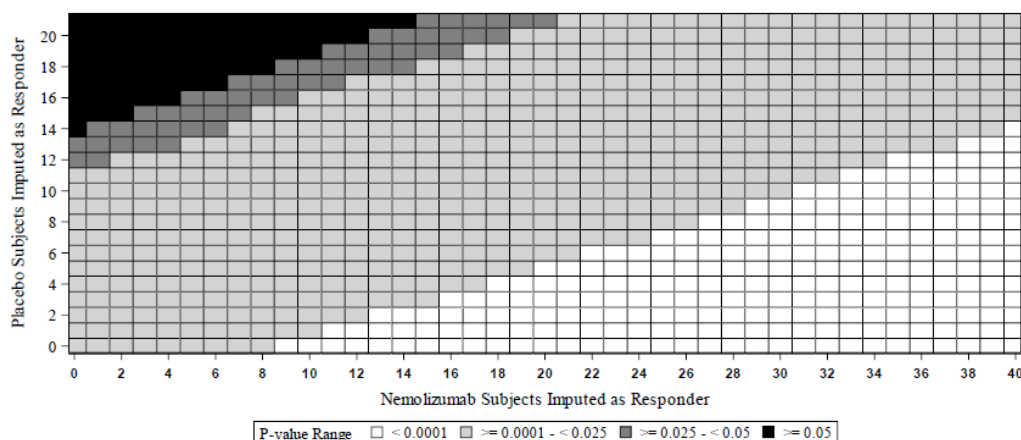
Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, 75% improvement in the Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intent to treat; LOCF, last observation carried forward; MI, multiple imputation, MAR, assuming missing at random; N, number of patients in treatment arm; NRI, non-responder imputation; OC, observed case; PP-NRS, Peak Pruritus Numerical Rating

The Applicant also conducted tipping point analyses for the co-primary efficacy endpoints. For ARCADIA 1, the results for the primary endpoint of IGA success at Week 16 remained statistically significant even under the worst-case scenario (strata-adjusted p-value = 0.0203), where all subjects on the nemolizumab arm with missing data at Week 16 are imputed as non-responders and all such subjects on the placebo arm are imputed as responders. For ARCADIA 2, the results for the primary efficacy endpoint of IGA success tip 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 ([Figure 31](#))

The tipping point analysis results for the primary efficacy endpoint of EASI-75 closely mirrored those for the primary efficacy endpoint of IGA success. For ARCADIA 1, the results remained statistically significant even under the worst-case scenario (strata-adjusted p-value of 0.0012), i.e., most unfavorable to nemolizumab. However, for ARCADIA 2, the results for the primary efficacy endpoint of EASI-75 tip when a high proportion of 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 ([Figure 32](#)).

Figure 31. Applicant's Tipping Point Analysis for the Primary Efficacy Endpoint of IGA Success at Week 16 – ARCADIA 2 (ITT¹)

Population: Full Population; Statistics: Adjusted p-value



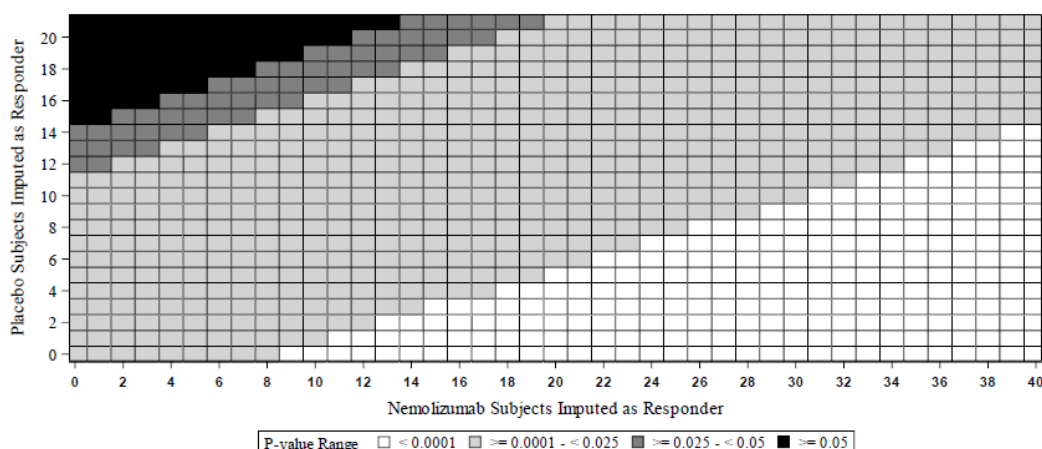
Source: Figure 14.2.1.1.6 in Clinical Study Report for ARCADIA 2.

¹ ITT population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders.

Abbreviations: IGA; Investigator's Global Assessment; ITT, intent-to-treat

Figure 32. Applicant's Tipping Point Analysis for the Primary Efficacy Endpoint of $\geq 75\%$ Reduction in Eczema Area and Severity Index Score From Baseline at Week 16 – ARCADIA 2 (ITT¹)

Population: Full Population; Statistics: Adjusted p-value



Source: Figure 14.2.1.2.6 in Clinical Study Report for ARCADIA 2.

¹ ITT population: all randomized subjects. Subjects who received rescue therapy were imputed as non-responders.

Abbreviations: ITT, intent-to-treat

Table 85 and Table 86 present the analysis results for the key secondary efficacy endpoints with extended bounds based on the ITT population and the Severe Baseline PP-NRS population, respectively. The results for these analyses generally had higher response rates than those without the extended bounds due to the Applicant's prespecified method for missing data handling (i.e., non-responder imputation).

Table 85. Results for the Key Secondary Efficacy Endpoints With Extended Bounds¹ – ARCADIA 1 and ARCADIA 2 (ITT²)

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
≥4-point reduction in PP-NRS (Week 16)	265 (43%)	57 (18%)	214 (41%)	48 (18%)
Adjusted difference (97.5% CI) ³		25% (18%, 31%)		23% (16%, 30%)
Adjusted difference (95% CI) ³		25% (19%, 31%)		23% (17%, 29%)
p-value ³		< 0.0001		< 0.0001
PP-NRS < 2 (Week 16)	190 (31%)	36 (11%)	148 (28%)	30 (11%)
Adjusted Difference (97.5% CI) ³		19% (14%, 25%)		17% (11%, 23%)
Adjusted Difference (95% CI) ³		19% (14%, 24%)		17% (12%, 23%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in SD-NRS (Week 16)	235 (38%)	64 (20%)	175 (34%)	43 (16%)
Adjusted difference (97.5% CI) ³		18% (11%, 25%)		18% (11%, 24%)
Adjusted difference (95% CI) ³		18% (12%, 24%)		18% (12%, 23%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 4)	170 (27%)	21 (7%)	136 (26%)	14 (5%)
Adjusted difference (97.5% CI) ³		21% (16%, 26%)		21% (16%, 26%)
Adjusted difference (95% CI) ³		21% (16%, 25%)		21% (16%, 25%)
p-value ³		< 0.0001		< 0.0001
PP-NRS < 2 (Week 4)	99 (16%)	12 (4%)	83 (16%)	7 (3%)
Adjusted difference (97.5% CI) ³		12% (8%, 16%)		13% (9%, 17%)
Adjusted difference (95% CI) ³		12% (9%, 16%)		13% (10%, 17%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 2)	110 (18%)	10 (3%)	88 (17%)	5 (2%)
Adjusted difference (97.5% CI) ³		15% (11%, 19%)		15% (11%, 19%)
Adjusted difference (95% CI) ³		15% (11%, 18%)		15% (11%, 19%)
p-value ³		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 1)	29 (5%)	4 (1%)	35 (7%)	1 (0%)
Adjusted difference (97.5% CI) ³		3% (1%, 6%)		6% (4%, 9%)
Adjusted difference (95% CI) ³		3% (1%, 6%)		6% (4%, 9%)
p-value ³		0.0064		< 0.0001

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
EASI-75 & ≥4-point reduction in PP-NRS (Week 16)	147 (24%)	36 (11%)	120 (23%)	26 (10%)
Adjusted difference (97.5% CI) ³		13% (7%, 18%)		13% (8%, 19%)
Adjusted difference (95% CI) ³		13% (8%, 17%)		13% (8%, 19%)
p-value ³		< 0.0001		< 0.0001
IGA Success & ≥4-point reduction in PP-NRS (Week 16)	122 (20%)	30 (9%)	107 (20%)	23 (9%)
Adjusted difference (97.5% CI) ³		11% (5%, 16%)		12% (7%, 18%)
Adjusted difference (95% CI) ³		11% (6%, 15%)		12% (7%, 17%)
p-value ³		< 0.0001		< 0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt; Software: SAS, R

¹ The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS and SD-NRS, see the footnote of Table 8.2 in Section 8.4 of the Statistical Analysis Plan.

² ITT population: all randomized subjects. Except for the OC analysis, subjects who received rescue therapy were imputed as non-responders.

³ Adjusted difference in proportions is the weighted average of the treatment differences across the randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, at least 75% reduction in Eczema Area and Severity Index score from baseline; 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

Table 86. Results for the Key Secondary Efficacy Endpoints With Extended Bounds¹ – ARCADIA 1 and ARCADIA 2 (Severe Baseline PP-NRS Population²)

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=372)	Placebo (N=193)	Nemolizumab (N=280)	Placebo (N=151)
≥4-point reduction in PP-NRS (Week 16)	179 (48%)	37 (19%)	144 (51%)	35 (23%)
Adjusted difference (97.5% CI) ³		29% (20%, 38%)		28% (18%, 38%)
Adjusted difference (95% CI) ³		29% (22%, 37%)		28% (19%, 37%)
p-value		< 0.0001		< 0.0001
PP-NRS <2 (Week 16)	103 (28%)	13 (7%)	76 (27%)	14 (9%)
Adjusted difference (97.5% CI) ³		21% (14%, 27%)		18% (10%, 26%)
Adjusted difference (95% CI) ³		21% (15%, 27%)		18% (11%, 25%)
p-value		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 4)	115 (31%)	14 (7%)	89 (32%)	12 (8%)
Adjusted difference (97.5% CI) ³		24% (17%, 31%)		24% (16%, 32%)
Adjusted difference (95% CI) ³		24% (18%, 30%)		24% (17%, 31%)
p-value		< 0.0001		< 0.0001

Endpoint	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=372)	Placebo (N=193)	Nemolizumab (N=280)	Placebo (N=151)
PP-NRS <2 (Week 4)	47 (13%)	5 (3%)	29 (10%)	2 (1%)
Adjusted difference (97.5% CI) ³		10% (6%, 15%)		9% (4%, 14%)
Adjusted difference (95% CI) ³		10% (6%, 14%)		9% (5%, 13%)
p-value		< 0.0001		0.0006
≥4-point reduction in PP-NRS (Week 2)	82 (22%)	7 (4%)	56 (20%)	4 (3%)
Adjusted difference (97.5% CI) ³		19% (13%, 24%)		17% (11%, 23%)
Adjusted difference (95% CI) ³		19% (14%, 24%)		17% (12%, 23%)
p-value		< 0.0001		< 0.0001
≥4-point reduction in PP-NRS (Week 1)	25 (7%)	4 (2%)	25 (9%)	1 (1%)
Adjusted difference (97.5% CI) ³		5% (1%, 8%)		8% (4%, 12%)
Adjusted difference (95% CI) ³		5% (1%, 8%)		8% (5%, 12%)
p-value		0.019		0.0006
EASI-75 & ≥4-point reduction in PP-NRS (Week 16)	99 (27%)	23 (12%)	81 (29%)	18 (12%)
Adjusted difference (97.5% CI) ³		15% (7%, 22%)		17% (9%, 26%)
Adjusted difference (95% CI) ³		15% (8%, 21%)		17% (10%, 25%)
p-value		< 0.0001		< 0.0001
IGA 0/1 & ≥4-point reduction in PP-NRS (Week 16)	80 (22%)	19 (10%)	72 (26%)	17 (11%)
Adjusted difference (97.5% CI) ³		11% (5%, 18%)		14% (6%, 23%)
Adjusted difference (95% CI) ³		11% (6%, 17%)		14% (7%, 22%)
p-value		0.0007		0.0004

Source: Statistical Reviewer's Analysis; adsl.xpt, adef.xpt; Software: SAS, R

¹ The Applicant's original analysis allowed for extensions to the bounds for calculating the weekly average score for the PP-NRS, see the footnote of Table 8.2 in Section 8.4 of the Statistical Analysis Plan.

² Severe Baseline PP-NRS population: all randomized subjects with baseline PP-NRS ≥ 7. 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factor of baseline disease severity (IGA; moderate: IGA = 3; severe: IGA = 4).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, at least 75% reduction in Eczema Area and Severity Index score from baseline; IGA, Investigator's Global Assessment, N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 87 through Table 94 present the results for the sensitivity analyses for the key secondary efficacy endpoints 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). The results for these sensitivity analyses are generally similar to the results for the corresponding main analyses.

Table 87. Sensitivity Analyses for the Key Secondary 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 – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sensitivity Analysis #1: ≥ 2 Diary Assessments in 7-Day Period ≥ 4 -point improvement on the PP-NRS from baseline to Week 16	257 (41%)	56 (17%)	214 (41%)	44 (17%)
Adjusted difference (97.5% CI) ²		24% (17%, 30%)		25% (18%, 32%)
Adjusted difference (95% CI) ²		24% (18%, 30%)		25% (19%, 31%)
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	235 (38%)	52 (16%)	200 (38%)	42 (16%)
Adjusted difference (97.5% CI) ²		22% (15%, 28%)		23% (16%, 30%)
Adjusted difference (95% CI) ²		22% (16%, 27%)		23% (17%, 29%)
p-value ²		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adeff.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 88. Sensitivity Analyses for the Key Secondary Endpoint of PP-NRS <2 at Week 16 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT1)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sensitivity Analysis #1: ≥2 Diary Assessments in 7-Day Period				
PP-NRS < 2 at Week 16	181 (29%)	34 (11%)	146 (28%)	27 (10%)
Adjusted difference (97.5% CI) ²		19% (13%, 24%)		18% (12%, 24%)
Adjusted difference (95% CI) ²		19% (14%, 23%)		18% (13%, 23%)
p-value ⁴		<0.0001		<0.0001
Sensitivity Analysis #2: ≥3 Diary Assessments in 7-Day Period				
PP-NRS < 2 at Week 16	166 (27%)	31 (10%)	136 (26%)	26 (10%)
Adjusted difference (97.5% CI) ²		17% (12%, 23%)		16% (10%, 22%)
Adjusted difference (95% CI) ²		17% (12%, 22%)		16% (11%, 21%)
p-value ²		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 89. Sensitivity Analyses for the Key Secondary Endpoint of ≥ 4 -Point Improvement on the PP-NRS From Baseline to Week 4 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sensitivity Analysis #1: ≥ 2 Diary Assessments in 7-Day Period ≥ 4 -point improvement on the PP-NRS from baseline to Week 4	175 (28%)	21 (7%)	143 (27%)	15 (6%)
Adjusted difference (97.5% CI) ²		22% (17%, 28%)		22% (17%, 28%)
Adjusted difference (95% CI) ²		22% (17%, 26%)		22% (17%, 27%)
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 4	175 (28%)	21 (7%)	143 (27%)	15 (6%)
Adjusted difference (97.5% CI) ²		22% (17%, 27%)		22% (17%, 27%)
Adjusted difference (95% CI) ²		22% (17%, 26%)		22% (17%, 27%)
p-value ²		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 90. Sensitivity Analyses for the Key Secondary Endpoint of PP-NRS < 2 at Week 4 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sensitivity Analysis #1: ≥2 Diary Assessments in 7-Day Period				
PP-NRS <2 at Week 4	105 (17%)	12 (4%)	89 (17%)	7 (3%)
Adjusted difference (97.5% CI) ²		13% (9%, 17%)		14% (10%, 18%)
Adjusted difference (95% CI) ²		13% (9%, 17%)		14% (10%, 19%)
p-value ⁴		<0.0001		<0.0001
Sensitivity Analysis #2: ≥3 Diary Assessments in 7-Day Period				
PP-NRS <2 at Week 4	103 (17%)	12 (4%)	88 (17%)	7 (3%)
Adjusted difference (97.5% CI) ²		13% (9%, 17%)		14% (10%, 18%)
Adjusted difference (95% CI) ²		13% (9%, 16%)		14% (10%, 18%)
p-value ²		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adeff.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 91. Sensitivity Analyses for the Key Secondary Endpoint of ≥ 4 -Point Improvement on the PP-NRS From Baseline to Week 2 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=620)	Placebo (N=321)
Sensitivity Analysis #1: ≥ 2 Diary Assessments in 7-Day Period ≥ 4 -point improvement on the PP-NRS from baseline to Week 2	115 (19%)	10 (3%)	93 (18%)	7 (3%)
Adjusted difference (97.5% CI) ²		15% (11%, 19%)		15% (11%, 20%)
Adjusted difference (95% CI) ²		15% (12%, 19%)		15% (11%, 19%)
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 2	112 (18%)	10 (3%)	89 (17%)	6 (2%)
Adjusted difference (97.5% CI) ²		15% (11%, 19%)		15% (11%, 19%)
Adjusted difference (95% CI) ²		15% (11%, 18%)		15% (11%, 19%)
p-value ²		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 92. Sensitivity Analyses for the Key Secondary Endpoint of ≥ 4 -Point Improvement on the PP-NRS From Baseline to Week 1 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sensitivity Analysis #1: ≥ 2 Diary Assessments in 7-Day Period ≥ 4 -point improvement on the PP-NRS from baseline to Week 1	30 (5%)	5 (2%)	37 (7%)	2 (1%)
Adjusted difference (97.5% CI) ²		3% (1%, 6%)		6% (4%, 9%)
Adjusted difference (95% CI) ²		3% (1%, 5%)		6% (4%, 9%)
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 1	29 (5%)	5 (2%)	36 (7%)	1 (0%)
Adjusted difference (97.5% CI) ²		3% (1%, 6%)		7% (4%, 9%)
Adjusted difference (95% CI) ²		3% (1%, 5%)		7% (4%, 9%)
p-value ²		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 93. Sensitivity Analyses for the Key Secondary Endpoint of Achievement of EASI-75 at Week 16 and ≥ 4 -Point Improvement on the PP-NRS From Baseline to Week 16 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=522)	Placebo (N=265)
Sensitivity Analysis #1: ≥ 2 Diary Assessments in 7-Day Period				
EASI-75 and ≥ 4 -point improvement on the PP-NRS from baseline to Week 16	138 (22%)	35 (11%)	120 (23%)	23 (9%)
Adjusted difference (97.5% CI) ²		11% (6%, 17%)		15% (9%, 20%)
Adjusted difference (95% CI) ²		11% (7%, 16%)		15% (10%, 20%)
p-value ⁴		<0.0001		<0.0001
Sensitivity Analysis #2: ≥ 3 Diary Assessments in 7-Day Period				
EASI-75 and ≥ 4 -point improvement on the PP-NRS from baseline to Week 16	126 (20%)	32 (10%)	114 (22%)	21 (8%)
Adjusted difference (97.5% CI) ²		10% (5%, 16%)		14% (9%, 20%)
Adjusted difference (95% CI) ²		10% (6%, 15%)		14% (9%, 19%)
p-value ⁴		<0.0001		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adef.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥ 7 ; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; EASI-75, at least 75% reduction in Eczema Area and Severity Index score from baseline; IGA, Investigator's Global Assessment; ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 94. Sensitivity Analyses for the Key Secondary Endpoint of Achievement of IGA 0/1 at Week 16 and ≥ 4 -Point Improvement on the PP-NRS From Baseline to Week 16 Based on the Number of Diary Assessments in the 7-Day Period – ARCADIA 1 and ARCADIA 2 (ITT¹)

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=620)	Placebo (N=321)
Sensitivity Analysis #1: ≥ 2 Diary Assessments in 7-Day Period				
IGA 0/1 and ≥ 4 -point improvement on the PP-NRS from baseline to Week 16	114 (18%)	30 (9%)	105 (20%)	21 (8%)
Adjusted difference (97.5% CI) ²		9% (4%, 14%)		12% (7%, 18%)
Adjusted difference (95% CI) ²		9% (5%, 14%)		12% (8%, 17%)
p-value ⁴		0.0003		<0.0001

	ARCADIA 1		ARCADIA 2	
	Nemolizumab (N=620)	Placebo (N=321)	Nemolizumab (N=620)	Placebo (N=321)
Sensitivity Analysis #2: ≥3 Diary Assessments in 7-Day Period				
IGA 0/1 and ≥4-point improvement on the PP-NRS from baseline to Week 16	105 (17%)	27 (8%)	101 (19%)	19 (7%)
Adjusted difference (97.5% CI) ²		9% (4%, 14%)		12% (7%, 18%)
Adjusted difference (95% CI) ²		9% (4%, 13%)		12% (8%, 17%)
p-value ²		0.0004		<0.0001

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); adsl.xpt, adefx.xpt

¹ 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 randomization strata (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]) using CMH weights. Two-sided 97.5% and 95% CIs are based on the normal approximation to the weighted average. P-value is based on the CMH test stratified by the randomization stratification factors (i.e., baseline disease severity [IGA; moderate: IGA = 3; severe: IGA = 4] and PP-NRS severity [PP-NRS ≥7; PP-NRS <7]).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment, ITT, intent to treat; N, number of patients in treatment arm; PP-NRS, Peak Pruritus Numeric Rating Scale

16.2. Findings in Special/Subgroup Populations

Table 95. Results for IGA Success at Week 16 by Region, Age, Sex, Race, Ethnicity, Baseline IGA Score, and PP-NRS Stratification Factor – ARCADIA 1 and ARCADIA (ITT¹)

IGA Success	ARCADIA 1		ARCADIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Region				
Europe				
IGA success	43.35%	29.27%	38.32%	29.95%
Risk difference (95% CI)		14.48% (5.77%, 23.19%)		8.9% (0.95%, 16.85%)
Asia Pacific				
IGA success	20.41%	5.77%	0%	0%
Risk difference (95% CI)		14.32% (4.48%, 24.16%)		-
North America				
IGA success	31.07%	26.67%	38.93%	15.62%
Risk difference (95% CI)		5.17% (-5.33%, 15.67%)		24.48% (12.36%, 36.6%)
Age group				
12-17 years				
IGA success	55.29%	32.65%	42.86%	36.59%
Risk difference (95% CI)		17.62% (0.3%, 34.93%)		7.92% (-10.55%, 26.38%)
18-64 years				
IGA success	32.41%	21.62%	36.08%	23.79%
Risk difference (95% CI)		11.55% (5.15%, 17.94%)		13.16% (5.79%, 20.54%)
≥65 years				
IGA success	34.38%	53.85%	41.86%	27.78%
Risk difference (95% CI)		-18.09% (-49.18%, 13%)		12.62% (-13.21%, 38.45%)
Sex				
Female				
IGA success	47.47%	27.78%	44.44%	30.15%
Risk difference (95% CI)		19.4% (10.12%, 28.67%)		14.78% (5.12%, 24.44%)
Male				
IGA success	24.77%	22.03%	30.56%	21.71%
Risk difference (95% CI)		3.8% (-3.82%, 11.42%)		9.41% (0.49%, 18.33%)

IGA Success	ARCADIA 1		ARCADIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Race				
White				
IGA success	41.46%	28.69%	39.52%	29.52%
Risk difference (95% CI)		13.51% (6.33%, 20.7%)		10.17% (2.84%, 17.5%)
Other				
IGA success	0%	0%	50%	-
Risk difference (95% CI)		-	-	-
Asian				
IGA success	17.95%	7.84%	17.14%	5.56%
Risk difference (95% CI)		9.81% (-0.33%, 19.95%)		14.72% (-1.48%, 30.91%)
Multiple				
IGA success	20%	0%	-	-
Risk difference (95% CI)		-	-	-
Black or African American				
IGA success	30.56%	27.78%	32%	5%
Risk difference (95% CI)		9.33% (-19.13%, 37.8%)		29.74% (7.34%, 52.15%)
American Indian or Alaska Native				
IGA success	0%	0%	0%	-
Risk difference (95% CI)		-		-
Native Hawaiian or other Pacific Islander				
IGA success	0%	-	100%	-
Risk difference (95% CI)		-		-
Ethnicity				
Not Hispanic or Latino				
IGA success	33.88%	21.53%	37.07%	27.05%
Risk difference (95% CI)		12.74% (6.67%, 18.81%)		10.45% (3.45%, 17.45%)
Hispanic or Latino				
IGA success	51.56%	53.12%	52.27%	15.79%
Risk difference (95% CI)		0.49% (-21%, 21.98%)		43.91% (20.47%, 67.36%)
Not reported				
IGA success	50%	0%	16.67%	0%
Risk difference (95% CI)		-		10.2% (-9.75%, 30.16%)

IGA Success	ARCADIA 1		ARCADIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Baseline IGA				
3 = moderate				
IGA success	41.42%	27.78%	42.09%	31.55%
Risk difference (95% CI)		13.66% (6.29%, 21.02%)		10.53% (2.12%, 18.93%)
4 = severe				
GA success	21.86%	16.09%	28.57%	12.82%
Risk difference (95% CI)		5.93% (-3.85%, 15.71%)		15.98% (5.88%, 26.08%)
PP-NRS Stratification Factor				
≥7				
IGA success	35.47%	21.43%	36.71%	21.95%
Risk difference (95% CI)		14.29% (7.11%, 21.48%)		14.92% (6.73%, 23.11%)
<7				
IGA success	35.98%	30.63%	39.32%	32.67%
Risk difference (95% CI)		6.21% (-4.33%, 16.75%)		7.79% (-3.34%, 18.92%)

Source: Statistical Reviewer Analysis; adsl.xpt, adefx.xpt; Software: R, SAS
IGA Success was defined as the achievement of IGA score of 0 ('clear') or 1 ('almost clear') plus at least a 2-grades reduction from Baseline.
The risk difference, 95% confidence interval, and p-value are obtained from the CMH method stratified by randomization stratification factors (i.e., IGA severity and PP-NRS severity).
Analyses were based on the ITT population.
Abbreviations: CI, Confidence Interval; CMH, Cochran-Mantel-Haenszel; IGA, Investigator's Global Assessment; ITT, intent-to-treat; PP-NRS, Peak Pruritus Numeric Rating Scale

Table 96. Results for EASI-75 at Week 16 by Region, Age, Sex, Race, Ethnicity, Baseline IGA Score, and PP-NRS Stratification Factor – ARCADIA 1 and ARCADIA 2 (ITT¹)

Score, and PP-NRS Stratification Factor – ARCADIA 1 and ARCADIA 2 (PP)				
EASI-75	ARCADIA 1		ARCADIA 2	
Region	Nemolizumab	Placebo	Nemolizumab	Placebo
Europe				
EASI-75	50.63%	34.76%	44.36%	32.49%
Risk difference (95% CI)	16.28% (7.29%, 25.26%)		12.35% (4.24%, 20.47%)	
Asia Pacific				
EASI-75	30.61%	15.38%	10%	0%
Risk difference (95% CI)	14.48% (1.22%, 27.73%)		8.82% (-9.05%, 26.7%)	
North America				
EASI-75	38.83%	26.67%	38.17%	25%
Risk difference (95% CI)	12.97% (2.33%, 23.61%)		14.32% (1.15%, 27.49%)	
Age group				
12-17 years				
EASI-75	57.65%	42.86%	49.45%	43.9%
Risk difference (95% CI)	11.61% (-6.34%, 29.56%)		6.54% (-12.03%, 25.11%)	
18-64 years				
EASI-75	40.79%	25.1%	40.1%	26.79%
Risk difference (95% CI)	16.27% (9.59%, 22.95%)		14.13% (6.61%, 21.66%)	
≥65 years				
EASI-75	50%	66.67%	45.95%	40%
Risk difference (95% CI)	-18.93% (-55.49%, 17.63%)		2.97% (-27.98%, 33.92%)	
Sex				
Female				
EASI-75	53.87%	28.47%	48.52%	30.88%
Risk difference (95% CI)	25.31% (15.99%, 34.62%)		18.1% (8.41%, 27.79%)	
Male				
EASI-75	34.06%	29.38%	35.32%	29.46%
Risk difference (95% CI)	5.41% (-2.99%, 13.81%)		6.67% (-2.96%, 16.3%)	

EASI-75	ARCADIA 1		ARCADIA 2	
	Nemolizumab	Placebo	Nemolizumab	Placebo
Race				
White				
EASI-75	48.56%	32.38%	44.32%	32.6%
Risk difference (95% CI)	16.96% (9.59%, 24.33%)		11.9% (4.41%, 19.4%)	
Other				
EASI-75	0%	0%	50%	-
Risk difference (95% CI)	-		-	
Asian				
EASI-75	29.06%	11.76%	22.86%	22.22%
Risk difference (95% CI)	15.88% (3.65%, 28.1%)		3.39% (-19.87%, 26.64%)	
Multiple				
EASI-75	30%	50%	-	-
Risk difference (95% CI)	-36.84% (-91.77%, 18.08%)		-	
Black or African American				
EASI-75	36.11%	33.33%	28%	10%
Risk difference (95% CI)	9.43% (-20.95%, 39.81%)		18.68% (-3.51%, 40.87%)	
American Indian or Alaska Native				
EASI-75	50%	0%	100%	-
Risk difference (95% CI)	50% (-69.3%, 100%)		-	
Native Hawaiian or other Pacific Islander				
EASI-75	0%	-	0%	-
Risk difference (95% CI)	-		-	
Ethnicity				
Not Hispanic or Latino				
EASI-75	42.21%	27.08%	41.38%	30.74%
Risk difference (95% CI)	15.32% (8.85%, 21.79%)		11.09% (3.88%, 18.31)	
Hispanic or Latino				
EASI-75	56.25%	46.88%	54.55%	21.05%
Risk difference (95% CI)	11.26% (-10.23%, 32.76%)		41.04% (16.08%, 66%)	
Not Reported				
EASI-75	50%	0%	33.33%	50%
Risk difference (95% CI)	-		-30.61% (-85.98%, 24.76%)	

		ARCADIA 1		ARCADIA 2	
EASI-75	Nemolizumab	Placebo	Nemolizumab	Placebo	
Baseline IGA					
3 = moderate					
EASI-75	48.51%	32.05%	46.89%	36.36%	
Risk difference (95% CI)	16.49% (8.9%, 24.07%)		10.51% (1.89%, 19.13%)		
4 = severe					
EASI-75	31.69%	20.69%	32.14%	15.38%	
Risk difference (95% CI)	10.82% (-0.01%, 21.64%)		17.01% (6.34%, 27.68%)		
PP-NRS Stratification					
Factor					
≥7					
EASI-75	41.63%	23.81%	41.14%	25%	
Risk difference (95% CI)	18.09% (10.66%, 25.51%)		16.32% (7.84%, 24.8%)		
<7					
EASI-75	47.2%	38.74%	43.69%	38.61%	
Risk difference (95% CI)	8.87% (-2.35%, 20.1%)		6.34% (-5.08%, 17.76%)		

Source: Statistical Reviewer Analysis; adsl.xpt, adef.xpt; Software: R, SAS

EASI-75 was defined as ≥ 75% improvement in EASI from Baseline.

The risk difference, 95% confidence interval, and p-value are obtained from the CMH method stratified by randomization stratification factors (i.e., IGA severity and PP-NRS severity).

Analyses were based on the ITT population.

Abbreviations: CI, Confidence Interval; CMH, Cochran-Mantel-Haenszel; EASI, Eczema Area and Severity Index; IGA, Investigator's Global Assessment; ITT, intent-to-treat; PP-NRS, Peak Pruritus Numeric Rating Scale

17. Clinical Safety

Refer to the Safety Section (Sec. [7](#)) of the IAMA review.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action / Drug Resistance

Refer to the CMC Section of the review for information regarding the mechanism of action (MoA) for NEMLUVIO. Drug Resistance based on the MoA is not applicable to NEMLUVIO.

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 moderate to severe atopic dermatitis (AD) from Studies SPR.118161 (NCT03985943) and SPR.118169 (NCT03989349).

Three clinical investigators (Drs. Trullenque, Kalowska, and Reich) 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 December 13, 2023 (Table 97). 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 97. Key Labeling Changes and Considerations

Full PI Sections ¹	Rationale for Major Changes to the PI ² Conveyed to the Applicant on October 18, 2024, Compared to Applicant's Draft PI
1 INDICATIONS AND USAGE	The Applicant proposed indicating NEMLUVIO for the treatment of adults and pediatric patients 12 years of age and older with moderate-to-severe atopic dermatitis when the disease is not adequately controlled with topical prescription therapies. The scope of the indication was modified to indicate NEMLUVIO in combination with topical corticosteroids and/or calcineurin inhibitors. The Phase 3 trials (ARCADIA 1 and ARCADIA 2) were not designed as monotherapy trials; both trials required all subjects to receive standardized background topical therapy with a medium-potency topical corticosteroid (TCS) for the body and a low-potency TCS or topical calcineurin inhibitor (TCI) for sensitive areas (face, neck, intertriginous areas, etc.) beginning over a run-in period of at least 2 weeks before baseline and for continued use as needed throughout the study. The proposed change is consistent with the recommendation of the draft guidance for industry: <i>Indications and Usage Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (July 2018), Section II.A.1: 1. <i>Scope of an Indication Relative to the Population Studied</i>.
	Removed the claim, (b) (4) ”
	Removed the information concerning (b) (4) (b) (4)
2 DOSAGE AND ADMINISTRATION	The abbreviations (b) (4) were deleted because these abbreviations can be misinterpreted and pose risk of medication dosing errors. Refer to the DMEPA labeling review in DARRTS for additional information. The route of administration (“subcutaneous” injection) and additional details regarding the patient population (“adults and pediatric” patients) were added. The following instructions were added this section for consistency with the NEMLUVIO labeling approved under BLA 761390 and the draft guidance for industry: <i>Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (January 2023): In pediatric patients 12 years of age and older, administer NEMLUVIO by or under the supervision of a trained adult or caregiver. NEMLUVIO is supplied in a single-dose prefilled dual-chamber pen with white powder in one chamber and a clear diluent in the other chamber. NEMLUVIO must be reconstituted prior to administration. Following reconstitution, each prefilled pen delivers 30 mg/0.49 mL as a clear and colorless to slightly yellow solution. Discard any unused portions after administration.

Full PI Sections ¹	Rationale for Major Changes to the PI ² Conveyed to the Applicant on October 18, 2024, Compared to Applicant's Draft PI
4 CONTRAINDICATIONS	No major changes
5 WARNINGS AND PRECAUTIONS	Subsection 5.1 Hypersensitivity was modified for consistency with the NEMLUVIO labeling approved under BLA 761390. Subsection 5.2
6 ADVERSE REACTIONS	The abbreviations (b) (4) were deleted because these abbreviations can be misinterpreted and pose risk of medication dosing errors. Refer to the DMEPA labeling review in DARRTS for additional information. Under subsection 6.1 Clinical Trials Experience, (b) (4) was removed (b) (4). Refer to the Clinical section for the rationale for this change. The following ARs were added to Table 1. Refer to the Clinical section for the rationale for this change: Headache* (incl. migraine), Arthralgia, and Myalgia. Herpes Zoster was added to the list of specific adverse reactions. During the initial treatment period herpes zoster infections were reported in 5 subjects (0.4%) treated with NEMLUVIO (including 1 case of ophthalmic herpes zoster) and no subjects receiving placebo. Cases of herpes zoster were mild to moderate in severity and did not lead to discontinuation of treatment. Refer to the Clinical section for the rationale for this change.
7 DRUG INTERACTIONS	(b) (4)
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Subsections 8.1 Pregnancy and 8.2 Lactation were modified per the recommendations of the Nonclinical and DPMH review teams and for consistency with the NEMLUVIO labeling approved under BLA 761390. Additionally, DPMH recommended a revision to the language in 8.1 Pregnancy, under Clinical Considerations, which typically describes the potential risk of poor immune response to infections and delayed live attenuated vaccine administration to infants exposed to monoclonal antibodies in utero. DPMH held a public workshop in July 2024 regarding "Evaluating Immunosuppressive Effects of In Utero Exposure to Drug and Biologic Products". The stimulation for this workshop were postmarketing cases where infants exposed in utero to infliximab subsequently contracted BCG-vaccine derived infection, concerns for infant immunosuppression based on animal data with other mABs, as well as ongoing discussions about how to properly assess this risk in postmarketing studies. Over the course of the workshop, experts determined that there was lack of clinical evidence to support delaying routine vaccinations (specifically rotavirus vaccine for US populations). They recommended evaluating each drug and each vaccine upon its own evidence rather than a global statement in all monoclonal antibody labeling regarding delay of live attenuated

Full PI Sections ¹	Rationale for Major Changes to the PI ² Conveyed to the Applicant on October 18, 2024, Compared to Applicant's Draft PI
	vaccination. DPMH Peds and MHT leadership have reached consensus on revisions to this subsection 8.1, Clinical Considerations language to de-emphasize risk following vaccination and convey potential concern for serious infections. Note below the recommended language revision to apply to monoclonal antibody product labeling when there have been no reports of immunosuppression in infants (most cases). 8.1 Pregnancy <u>Clinical Considerations</u> <i>Fetal/Neonatal adverse reactions</i> Transport of endogenous IgG antibodies across the placenta increases as pregnancy progresses, and peaks during the third trimester. It is unclear whether [chemical name] may interfere with an infant's immune response to infections. Therefore, monitoring for the development of serious infection during the first XX months of life in infants exposed in utero is recommended. Refer to the Nonclinical section and the DPMH review in DARRTS for additional information. In subsection 8.4 Pediatric Use the language in the indication statement was modified to incorporate changes that are proposed under Section 1 Indications and Usage. This is consistent with the recommendations of the guidance for industry: <i>Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling</i> (March 2019). In subsection 8.5 Geriatric Use the language was modified for consistency with the recommendations on page 55 of the Labeling Review Tool and in the draft guidance for industry: <i>Geriatric Information in Human Prescription Drug and Biological Product Labeling</i> (September 2020).
10 OVERDOSAGE	No major changes
12 CLINICAL PHARMACOLOGY	This section was modified according to the recommendations of the Clinical Pharmacology review team and the guidance for industry: <i>Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format</i> (December 2016), and for consistency with the NEMLUVIO labeling approved under BLA 761390. Refer to the Clinical Pharmacology section for additional details.
13 NONCLINICAL TOXICOLOGY	This section was modified according to the recommendations of the Nonclinical review team and for consistency with the NEMLUVIO labeling approved under BLA 761390. Refer to the Nonclinical section for additional details.
14 CLINICAL STUDIES	The abbreviations (b) (4) were deleted because these abbreviations can be misinterpreted and pose risk of medication dosing errors. Refer to the DMEPA labeling review in DARRTS for additional information.

Full PI Sections ¹	Rationale for Major Changes to the PI ² Conveyed to the Applicant on October 18, 2024, Compared to Applicant's Draft PI
	A description of the Peak Pruritus Numeric Rating Scale (PP-NRS), a key secondary outcome in Trials ARCADIA 1 and 2, was included. The efficacy results were modified according to the recommendations of the Biostatistics and COA review teams and for consistency with the NEMLUVIO labeling approved under BLA 761390. Refer to the Biostatistics section and the COA review in DARRTS for additional details.
17 PATIENT COUNSELING INFORMATION	No major changes
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	(b) (4)

Source: [Please provide a source for this table.]

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.

Abbreviation(s): AR, adverse reaction; COA, Clinical Outcome Assessment; DDI, 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; TCS, topical corticosteroids; TCI, topical calcineurin inhibitor

23.1. Approved Labeling Types

Upon approval of this [application/efficacy supplement], 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

Clinical studies were conducted in subjects ≥12 years of age. Because AD is a new indication for nemolizumab-ilto, this BLA is required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients, under the Pediatric Research Equity Act (21 U.S.C. 355c).

On 8/2/2021, the Division agreed to the Amended Agreed initial Pediatric Study Plan (v. 6) submitted by the sponsor on 7/1/2021, which included the following:

- Partial waiver to conduct studies in pediatric patients less than 6 months of age (studies are impossible or highly impractical)
- Deferral of Phase 3 clinical trials in pediatric patients ages 6 months to < 12 years.

The following 2 postmarketing requirements were agreed to by the FDA and the Applicant, and will be issued with the following milestones:

Postmarketing Requirement -1

A single arm, open-label phase 2/3 PK/safety study in subjects (between 2 to < 12 years of age) with moderate-to-severe AD who are inadequately controlled by topical therapy for a minimum duration of 52 weeks (Study SPR.118126).

Postmarketing Requirement-1 Schedule Milestones

- Final Protocol Submission: 11/2020 (Submitted)
- Study/Trial Completion 04/2025
- Final Report Submission: 10/2025

Postmarketing Requirement-2

A single arm, open-label phase 2/3 PK/safety study in subjects (between 6 months < 2 years of age) with moderate-to-severe AD who are inadequately controlled by topical therapy for a minimum duration of 52 weeks (Study SPR.118130).

Postmarketing Requirement-2 Schedule Milestones

- Final Protocol Submission: 07/2025
- Study/Trial Completion: 11/2027
- Final Report Submission: 05/2028

Product quality postmarketing commitments are detailed in Section [9](#).

25. Financial Disclosure

Table 98. Covered Clinical Studies: [SPR.118161 (ARCADIA 1)]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 177		
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:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

Table 99. Covered Clinical Studies: [SPR.118169 (ARCADIA 2)]

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 136		
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:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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Weston, WL, 2021, Patient education: Eczema (atopic dermatitis) (Beyondthe Basics), www.uptodate.com.

27. Review Team

Table 100. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Howard F. Van Horn III, PharmD, MBA
Chief Project Management Staff	LCDR Susan Rhee, PharmD
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	Hamid Tabatabai, MD
Biometrics reviewer	Daeyoung Lim, PhD, Andraca-Carrera, Eugenio
Biometrics secondary reviewer	Matthew Guerra, PhD
Cross-discipline team leader	Hamid Tabatabai, 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)	Jill Lindstrom, MD

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 101. 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	Montherson Saint Juste, David Foss, Jim Dvorsky
DMPP	Maria Nguyen, Marcia Williams
ADL	Matthew White
OSI	Stephanie Coquia Michelle Fedowitz
OSE/DEPI	Xi Wang, Benjamin Booth
OSE/DMEPA	Madhuri Patel, PharmD, Yevgeniya Kogan
OSE/DMEPA/HF	Lisa Huang, Oluwamurewa Oguntimein, PhD
OSE/DRISK	Donella Fitzgerald, Jacqueline Sheppard
OSE/DPV	Jonn Bailey, Melissa Reyes, Jamie Klucken
OSE	Wana Manitpisitkul, SRPM
DPMH	Kristie Baisden, Tamara Johnson, Didi Nwokorie, Mona Khurana, Heather Buck, Rosemary Addy
DCOA	Yasmin Choudhry, Selena Daniels
Pharmacometrics	Da Zhang, Youwei Bi
Clinical Data Scientist	Merve Kasap, DeAngelo McKinley
CDRH	Colleen Lawrimore, Shruti Mistry
DNII	Kevan E. VanLandingham, Phil Sheridan
Medical Editor	Noah Whiteman, Sahar Leazer
Other	

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; DMPP, Division of Medical Policy Programs; ADL, Associate Director of Labeling; 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; DPV, Division of Pharmacovigilance; HF, Human Factors; DPMH, Division of Pediatrics and Maternal Health; DCOA, Division of Clinical Outcomes Assessment; CDRH, Center for Device and Radiological Health; DNII, Division of Neurology II

27.1. Reviewer Signatures

Table 27-102 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 Discipline Primary Reviewer	Hamid Tabatabai OII DDD	Sections: 1.2, 2, 3, 4, 7, 8.3, 10, 11, 17, 18, 19, 20, 21, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hamid Tabatabai Digitally signed by Hamid Tabatabai Date: 12/12/2024 4:38 PM EST GUID: 20241212213841				

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: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew White Digitally signed by Matthew White Date: 12/12/2024 4:42 PM EST GUID: 20241212214251				

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: 12	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Susan Rhee Digitally signed by Susan Rhee Date: 12/12/2024 4:44 PM EST GUID: 20241212214422				

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: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Andrew Goodwin Digitally signed by Andrew Goodwin Date: 12/12/2024 4:44 PM EST GUID: 20241212214445				

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 Primary Reviewer	Jacek Cieslak OPQAIII DPQAXVI	Sections: 8 - 12	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jacek Cieslak Digitally signed by Jacek Cieslak Date: 12/12/2024 4:45 PM EST GUID: 2024121221457				

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: 8 - 12	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jacek Cieslak Digitally signed by Jacek Cieslak Date: 12/12/2024 4:46 PM EST GUID: 20241212214613				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Youwei Bi OCP DPM	Sections: 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Youwei Bi Digitally signed by Youwei Bi Date: 12/12/2024 4:46 PM EST GUID: 20241212214617				

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, 7.1, 8.4.1, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Barbara Hill Digitally signed by Barbara Hill Date: 12/12/2024 4:54 PM EST GUID: 20241212215453				

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: 4., 6.3.1.	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Yasmin Choudhry Digitally signed by Yasmin Choudhry Date: 12/12/2024 5:16 PM EST GUID: 20241212221659				

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	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Nisha Kwatra Digitally signed by Nisha Kwatra Date: 12/12/2024 5:24 PM EST GUID: 20241212222435				

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: 4., 6.3.	Based on my assessment of the application: ☐ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Yasmin Choudhry Digitally signed by Yasmin Choudhry Date: 12/12/2024 5:26 PM EST GUID: 2024121222267				

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 Secondary Reviewer	Selena Daniels ODES DCOA	Sections: 4, 6.2.4, 6.2.5, 6.3.1,	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Selena Daniels Digitally signed by Selena Daniels Date: 12/12/2024 6:20 PM EST GUID: 20241212232059				

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	Matthew Guerra OB DBIII	Sections: Section 6, 15, and 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Matthew Guerra Digitally signed by Matthew Guerra Date: 12/12/2024 7:24 PM EST GUID: 2024121302424				

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, 8, 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Approvable from Clinical Pharmacology.
Signature: Chinmay Shukla Digitally signed by Chinmay Shukla Date: 12/12/2024 8:29 PM EST GUID: 2024121312937				

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, 8.4.1, 13	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jianyong Wang Digitally signed by Jianyong Wang Date: 12/12/2024 11:39 PM EST GUID: 2024121343953				

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	Howard Van Horn ORO DROII	Sections: 12	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Howard Van Horn Digitally signed by Howard Van Horn Date: 12/13/2024 7:25 AM EST GUID: 2024121312258				

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	Daeyoung Lim OB DBIII	Sections: Sections 6, 15, and 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Daeyoung Lim Digitally signed by Daeyoung Lim Date: 12/13/2024 8:09 AM EST GUID: 2024121313925				

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: all	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jill Lindstrom Digitally signed by Jill Lindstrom Date: 12/13/2024 8:23 AM EST GUID: 20241213132336				

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, 3, 4, 7, 8.3, 10, 11, 17, 18, 19, 20, 21, 24, 25, 26	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hamid Tabatabai Digitally signed by Hamid Tabatabai Date: 12/13/2024 9:54 AM EST GUID: 20241213145419				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Da Zhang OCP DPM	Sections: 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Da Zhang Digitally signed by Da Zhang Date: 12/13/2024 10:26 AM EST GUID: 20241213152649				

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
12/13/2024 10:32:11 AM

JILL A LINDSTROM
12/13/2024 10:52:02 AM