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APPLICATION NUMBER:

761434Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761434
Priority or standard	Priority
Submit date(s)	3/28/2025
Received date(s)	3/28/2025
PDUFA goal date	11/28/2025
Division/office	Division of Cardiology and Nephrology (DCN)
Review completion date	11/21/2025
Established/proper name	Sibeprenlimab-szsi
(Proposed) proprietary name	VOYXACT
Pharmacologic class	A Proliferation Inducing Ligand (APRIL) blocker
Other product name(s)	VIS649
Applicant	Otsuka Pharmaceutical Company, Ltd.
Dosage form(s)/formulation(s)	Injection
Dosing regimen	400 mg administered by subcutaneous injection once every 4 weeks
Applicant-proposed indication(s)/ population(s)	(b) (4) in adults with primary immunoglobulin A nephropathy (IgAN)
SNOMED CT code for proposed indication disease term(s)[a]	Primary immunoglobulin A nephropathy (disorder) – SCTID 68779003
Regulatory action	Accelerated approval
Approved dosage (if applicable)	400 mg
Approved indication(s)/ population(s) (if applicable)	To reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk for disease progression
SNOMED CT code for approved indication disease term(s)[a]	Primary immunoglobulin A nephropathy (disorder) – SCTID 68779003

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

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Glossary

ACEI	angiotensin-converting enzyme inhibitor
ADA	antidrug antibody
AE	adverse event
AESI	adverse event of special interest
ag-IgA	aberrantly glycosylated immunoglobulin A
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
APRIL	A-Proliferation-Inducing Ligand
ARB	angiotensin receptor blocker
AUC	area under the concentration-time curve
AUC_{tau}	area under the curve over one dosing interval
$AUC_{tau,ss}$	area under the serum concentration-time curve over one dosing interval at steady state
BCMA	B-cell maturation antigen
BLA	biologics license application
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKF	composite kidney failure
CL_{lin}	linear clearance
C_{max}	maximum serum concentration
COVID-19	coronavirus disease-2019
C_{trough}	trough serum concentration
CV%	coefficient of variation
DBL	database lock
E0	treatment response to placebo
EC_{50}	half-maximal effective concentration
EC_{80}	concentration producing 80% maximal effect
EC_{90}	concentration producing 80% maximal effect
ECL	electrochemiluminescence
eGFR	estimated glomerular filtration rate
E_{max}	maximum effect
E-R	exposure-response
F	bioavailability
FAS	full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
gddY	grouped ddY
Gd-IgA1	galactose-deficient immunoglobulin A1
GLP	good laboratory practice
GM	geometric mean
GoF	goodness-of-fit

IA	interim analysis
IAS	interim analysis set
IC_{50}	half-maximal inhibitory concentration
ICE	intercurrent event
IgA	immunoglobulin A
IgAN	immunoglobulin A nephropathy
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
iPSP	initial Pediatric Study Plan
IRT	interactive response technology
IV	intravenous
KA	absorption rate constant
KDIGO	Kidney Disease Improving Global Outcomes
LLOQ	lower limit of quantitation
LSMD	least-squares mean difference
mAb	monoclonal antibody
MEST-C	mesangial hypercellularity, endocapillary hypercellularity, segmental glomerular sclerosis, tubular atrophy and interstitial fibrosis, cellular crescents
MMRM	mixed model for repeated measures
MRHD	maximum recommended human dose
MSD	meso-scale discovery
NAb	neutralizing antibody
NF-κB	nuclear factor kappa B
NDA	new drug application
NOAEL	no-observed-adverse-effect level
OCMQ	Office of New Drugs Custom Medical Query
OLE	open-label extension
OPDC	Otsuka Pharmaceutical Development and Commercialization, Inc.
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PD	pharmacodynamic
PFS	prefilled syringe
PI	Prescribing Information
PK	pharmacokinetic
PMC	postmarketing commitment
PMR	postmarketing requirement
popPK	population pharmacokinetic
PT	preferred term
Q	distributional clearance
QC	quality control
Q4W	every 4 weeks
RD	risk difference
REMS	risk evaluation and mitigation strategy
RSE	relative standard error

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SD	standard deviation
SEE	substantial evidence of effectiveness
SF-36v2	36-Item Short-Form Survey Version 2
SGLT	sodium-glucose cotransporter-2
SGLT2i	sodium-glucose cotransporter-2 inhibitor
TACI	transmembrane activator and calcium modulator and cyclophilin ligand interactor
TEAE	treatment-emergent adverse event
uPCR	urine protein-to-creatinine ratio
uPCR-24h	urine protein-to-creatinine ratio based on 24-hour urine collections
V_2	central volume of distribution
V_3	peripheral volume of distribution
VAS	visual analog scale
V_{max}	maximal rate of nonlinear clearance
VPC	visual predictive check

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

Sibeprenlimab (sibeprenlimab-szsi, VOYXACT, VIS649) is an A-Proliferation-Inducing Ligand (APRIL) inhibitor. On March 28, 2025, the Applicant, Otsuka Pharmaceutical Company, Ltd., submitted a BLA for sibeprenlimab "(b) (4) in adults with primary immunoglobulin A nephropathy (IgAN)." The Applicant is seeking traditional approval under 21 CFR 601.

Primary IgAN is a serious kidney disease that can lead to chronic kidney disease and kidney failure. Inhibition of APRIL results in reduced levels of serum galactose-deficient immunoglobulin A1 (Gd-IgA1), which is implicated in the pathogenesis of IgAN. To date, two agents, Tarpeyo (budesonide), an oral corticosteroid given as a 9-month course of therapy, and Filspari (sparsentan), an endothelin type A receptor and angiotensin II receptor antagonist administered chronically as an oral tablet, have been granted traditional approval for the treatment of adults with primary IgAN. Budesonide is approved to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression. Although budesonide reduces the loss of kidney function during treatment, it does not change the long-term rate of decline in kidney function. Budesonide is a systemically available corticosteroid, and risks include hypercortisolism, adrenal axis suppression, immunosuppression, and other corticosteroid effects. Sparsentan is approved to slow kidney function decline in adults with IgAN who are at risk for disease progression. While sparsentan slows the rate of loss of kidney function, it does not halt progression. Sparsentan is available only through a restricted program under a risk evaluation and mitigation strategy (REMS) because of the risk of hepatotoxicity. Other risks include embryo-fetal toxicity, hypotension, acute kidney injury, hyperkalemia, fluid retention and anemia. Fabhalta (iptacopan) and Vanrafia (atrasentan) have been approved under FDA's accelerated approval pathway to reduce proteinuria in adults with IgAN at risk of rapid disease progression. For both of these therapies, the clinical benefit on slowing kidney function decline has not yet been verified. As such, there remains an unmet need for therapies that can slow the long-term rate of decline in kidney function in patients with IgAN and that have improved safety profiles.

Design of Development Program and Proteinuria as a Surrogate Endpoint

Like other development programs for the treatment of IgAN, sibeprenlimab's phase 3 trial was designed to support accelerated approval based on a prespecified interim analysis that assessed the effect on urine protein-to-creatinine ratio from a 24-hour urine collection (uPCR-24h) at 9 months. The same trial was to be used to verify the clinical benefit by demonstrating a decrease in the rate of change in eGFR over a 100-week period (i.e., a validated surrogate endpoint for progression to kidney failure). Based on the available data, the Division of Cardiology and Nephrology (the Division) accepts a substantial reduction in proteinuria as a reasonably likely surrogate endpoint for disease progression (loss of kidney function) in IgAN and as a basis for

accelerated approval (Thompson et al. 2019). To be granted accelerated approval, the magnitude of the effect on proteinuria at the interim analysis should be sufficient to provide confidence that the postmarketing phase of the trial is adequately powered to detect a treatment effect on the rate of change in eGFR. The Division has also held that available eGFR data at the time of submission of an application for accelerated approval should be assessed to provide additional confidence that the postmarketing phase of the trial is adequately powered to verify the clinical benefit.

Data Supporting Efficacy

As discussed in the body of this review, the Applicant's phase 3 trial (417-201-00007), a randomized, double-blind, placebo-controlled, multicenter trial in adults with biopsy-confirmed IgAN and proteinuria (uPCR-24h ≥0.75 g/g or urine protein ≥1.0 g/day) on background therapy with an angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB), met the primary endpoint at the interim analysis. At Month 9, compared to placebo, subjects on sibeprenlimab had a 51% (96.5% confidence interval [CI][1]: 42%, 58%, p<0.0001) greater reduction in uPCR-24h compared to baseline. In general, the treatment effect was consistent across the prespecified subgroups and stratification factors, including sex, age, race, ethnicity, geographic region, baseline proteinuria (uPCR-24h), baseline eGFR, and SGLT2i use.

Although sibeprenlimab's development program for IgAN was originally designed to support accelerated approval based on uPCR-24 h at 9 months, the Applicant is seeking traditional approval for sibeprenlimab (b) (4) in adults with primary IgAN. A key review issue was whether the available data on sibeprenlimab's effect on kidney function (i.e., effects on eGFR) were sufficient to support traditional approval (b) (4) (b) (4) (b) (4) (b) (4) As such, the review team does not believe the available data are sufficient to support traditional approval (b) (4)

Safety

Across the phase 2 and phase 3 trials, approximately 384 subjects with biopsy-proven IgAN received at least one dose of sibeprenlimab. Sibeprenlimab is an APRIL inhibitor and the risks of sibeprenlimab were generally consistent with its mechanism of action and subcutaneous route of administration. In the phase 3 trial, infections were reported in 49% of subjects treated with sibeprenlimab as compared to 45% of subjects treated with placebo and injection site reactions were reported in 24% of subjects treated with sibeprenlimab and 23% of subjects treated with placebo. The majority of infections were mild or moderate in severity and recovered or resolved without treatment interruption or discontinuation and the majority of injection site reactions were mild and resolved on the same day.

Conclusion:

The review team has concluded that the application provides substantial evidence of sibeprenlimab's effectiveness in reducing proteinuria, a reasonably likely surrogate endpoint for

[1] The confidence interval corresponds to the two-sided significance level of 0.035 for the interim analysis.

disease progression (loss of kidney function) in IgAN, and that the benefits outweigh the risks. As such, the review team recommends accelerated approval under Subpart E. Given the magnitude of the reduction in proteinuria seen in the phase 3 trial (b) (4) (b) (4) the review team recommends accelerated approval in a broad population (i.e., adults with primary IgAN at risk for disease progression) (b) (4) (b) (4)

The Signatory Authority agrees with the review team.

Other Consideration Related to Accelerated Approval

FDA's accelerated approval regulations and the Federal Food, Drug, and Cosmetic Act indicate that confirmatory trials must be completed with due diligence. As noted above, Trial 417-201-00007 is ongoing, and the primary endpoint at the final analysis in this trial will be used to verify and describe the clinical benefit. Trial 417-201-00007 is fully enrolled and is expected to complete in a timely manner following accelerated approval.

(b) (4)

Postmarketing Requirements

The Applicant will have a postmarketing requirement to conduct an adequate and well-controlled clinical trial to verify and describe the clinical benefit on slowing kidney function decline over the long-term. This requirement will be addressed by the completion of Trial 417-201-00007. The Applicant will also have a Pediatric Research Equity Act postmarketing requirement to conduct a pharmacodynamic, pharmacokinetic, safety and tolerability study in pediatric patients 2 years to 17 years of age with primary IgAN. The Applicant will also have postmarketing requirements to perform a lactation study (milk only or mother-infant pair study) in lactating women who have received sibeprenlimab to measure concentrations of sibeprenlimab and its major metabolites in breast milk, and to conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to sibeprenlimab during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant.

1.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with one adequate and well-controlled clinical investigation and confirmatory evidence.

As discussed in Section 1, the Division accepts a substantial reduction in proteinuria as a reasonably likely surrogate endpoint in IgAN and as a basis for accelerated approval. The Applicant submitted the results of a prespecified interim analysis of an adequate and well-

controlled phase 3 trial (417-201-00007) (see Table 3 for details). The review team has concluded that the trial met the primary endpoint of percent reduction in uPCR (sampled from a 24-hour urine collection) at Month 9 (Week 40) relative to baseline with a highly statistically persuasive p-value (one-sided $p<0.0001$). Compared to placebo, at Month 9, uPCR was reduced by 51% (96.5% CI: 42%, 58%) from baseline in subjects treated with sibeprenlimab. Existing data on the relationship between changes in proteinuria and disease progression suggest that the size of the treatment effect on proteinuria seen in Trial 417-201-00007 should predict clinical benefit (i.e., slow the loss of kidney function, and, with chronic use, reduce the risk of kidney failure) (see Section 2 for details).

The Applicant also provided results for Trial VIS649-201, a randomized, double-blind, placebo-controlled, phase 2 trial evaluating the efficacy and safety of sibeprenlimab 2, 4, and 8 mg/kg injected intravenously (IV) compared with placebo in adult subjects with biopsy-proven IgAN and a uPCR ≥0.75 g/g (from a 24-hour urine sample). In the 41 subjects that were treated with sibeprenlimab 4 mg/kg IV (the dose most comparable to the 400 mg subcutaneous [SC] dose evaluated in the phase 3 trial based on population pharmacokinetic [popPK] modeling), there was a 50% reduction (95% CI: 18%, 70% reduction) from baseline relative to placebo at Month 9 favoring sibeprenlimab. This trial involving a limited number of subjects and a different route of administration was considered sufficient to serve as confirmatory evidence for an effect of sibeprenlimab on uPCR reduction.

2. Benefit–Risk Assessment

2.1. Benefit–Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Primary immunoglobulin A nephropathy (IgAN) is a serious kidney disease that is estimated to affect approximately 210,000 individuals in the United States. IgAN can present at any age and has a peak incidence during the second and third decades of life. IgAN occurs with the greatest frequency in East Asians and Caucasians and is relatively rare in individuals of African ancestry. Patients typically present with proteinuria and hematuria. IgAN is associated with high morbidity and mortality; approximately 50% of patients progress to kidney failure within 30 years of diagnosis. • Primary IgAN is caused by the deposition of immune complexes containing galactose-deficient immunoglobulin A1 (Gd-IgA1) in the kidney, leading to inflammation in the kidney and eventual loss of kidney function.	Primary IgAN is a serious kidney disease that can lead to chronic kidney disease and kidney failure, resulting in the need for long-term dialysis or a kidney transplant for survival.
Current treatment options	• Current treatment strategies include blood pressure control, inhibition of the renin-angiotensin system via maximally tolerated doses of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and lifestyle modification including weight reduction, exercise, smoking cessation, and dietary sodium restriction. The sodium-glucose cotransporter-2 (SGLT2) inhibitors, dapagliflozin and empagliflozin, have been approved to reduce the risk of kidney disease progression in patients with chronic kidney disease (CKD) at risk for progression and are used in patients with IgAN to optimize supportive care.	There is unmet need for additional safe and effective treatments that can slow the long-term rate of decline in kidney function in patients with IgAN who are at risk for disease progression.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• The corticosteroid, budensonide (Tarpeyo) delayed-release capsule, is approved to reduce the loss of kidney function in adults with primary IgAN who are at risk for disease progression. Budesonide is given as a 9-month course of treatment. While budesonide reduces the loss of kidney function during treatment, it does not appear to change the rate of kidney function decline long term once patients are off of treatment. Risks of budesonide include those generally seen with corticosteriods that are systemically available (hypercorticism and adrenal axis suppression, immunosuppression, and other adverse corticosteroid effects). • Sparsentan (Filspari), an endothelin and angiotensin II receptor antagonist intended for chronic use, is approved to slow kidney function decline in adults with primary IgAN who are at risk for disease progression. While sparsentan slows the rate of loss of kidney function, it does not halt progression. Sparsentan is currently only available through a risk evaluation and mitigation strategy (REMS) due to the risk of hepatotoxicity. Other risks include embryo-fetal toxicity, hypotension, acute kidney injury, hyperkalemia, fluid retention and anemia. • Iptacopan, a factor B complement inhibitor, and atrasentan, an endothelin receptor antagonist, are both approved under the accelerated approval pathway to reduce proteinuria in adults with IgAN at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (uPCR) ≥1.5 g/g. Iptacopan is only available through a REMS due to the potential risks of serious infections caused by encapsulated bacteria. Risks of atrasentan include embyro-fetal toxicity (class risk), hepatotoxicity, fluid retention, decreased sperm counts and anemia.	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Based on regulatory precedent and currently available data, the Division accepts a substantial reduction in proteinuria as a reasonably likely surrogate endpoint for disease progression (loss of kidney function) in IgAN and as a basis for accelerated approval. • The Applicant submitted the results of their phase 3 trial (Trial 417-201-00007), a randomized, double-blind, placebo-controlled, multicenter trial in subjects with biopsy-proven IgAN, an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, and a uPCR ≥0.75 g/g on a maximized stable dose of renin-angiotensin system (RAS) inhibitor treatment. The study included two cohorts: a main cohort of 510 subjects and an exploratory cohort of 20 subjects who had an eGFR ≥20 and <30 mL/min/1.73 m^2. In the trial, subjects were randomized equally to either sibeprenlimab 400 mg or placebo every 4 weeks on top of standard of care (SOC). • The efficacy analysis was based on the first 320 subjects in Trial 417-201-0007 with an eGFR ≥30 mL/min/1.73 m^2 (main cohort) who had completed or discontinued the trial prior to the Month 9 visit. The trial met its primary endpoint of change from baseline in 24-hour uPCR at Month 9 with a statistically persuasive p-value (one-sided p<0.0001). Compared to placebo, at Month 9, uPCR was reduced 51% (96.5% CI: 42%, 58%) from baseline in subjects treated with sibeprenlimab. The treatment effect (percentage reduction between sibeprenlimab and placebo) was generally consistent across subgroups and prespecified stratification factors, including sex, age, race, ethnicity, and geographic region, baseline proteinuria (uPCR-24h), baseline eGFR (in the main cohort), and SGLT2i use. • (b) (4)	The submitted data demonstrate that sibeprenlimab reduces proteinuria in patients with IgAN. The results were highly statistically persuasive, and consistent findings across key subgroups including key demographic and baseline disease characteristics (e.g., baseline proteinuria) strengthen confidence in the results. (b) (4) However, given the magnitude of the reduction in proteinuria seen in the phase 3 trial (b) (4) accelerated approval should be granted in a broad population (i.e., adults with primary IgAN at risk for disease progression). (b) (4)

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• In the Trial 417-201-00007, there were 510 subjects (259 received sibeprenlimab and 251 received placebo) with an eGFR ≥30 mL/min/1.73 m^2 who received at least one dose of study drug (i.e., overall safety set). Serious adverse events occurred in 3.5% of subjects in the sibeprenlimab group and in 4.4% of subjects in the placebo group. Approximately 0.4% in the sibeprenlimab group and 1.6% in the placebo group discontinued study drug because of an adverse event. • Risks of sibeprenlimab observed in the Trial 417-201-00007 were generally consistent with its mechanism of action and subcutaneous administration. The most common adverse reactions (reported in ≥10% of patients treated with sibeprenlimab and at a higher incidence than placebo) reported in patients treated with sibeprenlimab and placebo, respectively, were infections (49% versus 45%) and injection site reactions (24% versus 23%). The most frequently reported infection was upper respiratory infection (15% versus 14%), and the most common injection site reaction was injection site erythema (13% versus 12%). – The majority of infections were mild or moderate in severity and recovered or resolved without treatment interruption or discontinuation. – The majority of injection site reactions were mild and resolved on the same day. No injection site reaction resulted in treatment interruprion or discontinuation.	The safety database is adequate for the safety assessment of sibeprenlimab for the treatment of IgAN. The results of safety analyses were as a whole consistent with its mechanism of action and subcutaneous route of administration. Overall, labeling is considered adequate to mitigate the potential risks and to ensure that the benefits of sibeprenlimab outweigh the risks.

2.2. Conclusions Regarding Benefit-Risk

IgAN is a serious kidney disease that can lead to chronic kidney disease (CKD) and kidney failure, resulting in the need for long-term dialysis or a kidney transplant to maintain life. The submitted data from Trial 417-201-0007 demonstrate that sibeprenlimab reduces proteinuria in subjects with primary IgAN who are at risk for progression of their disease.

Sibeprenlimab is expected to confer clinical benefit to patients by slowing CKD progression over the long-term in patients with primary IgAN, and effectiveness will be verified in the postmarket setting. Although the magnitude of the reduction in CKD progression (i.e., extent of clinical benefit) will not be described until the postmarketing confirmatory study is complete, the existing data on the relationship between changes in proteinuria and disease progression suggest that the size of the treatment effect on proteinuria seen in Trial 417-201-0007 should result in a clinically meaningful effect on the rate of loss of kidney function over the long-term.

Injection site reactions and immunosuppression were the main safety findings and can be adequately mitigated through labeling. For example, labeling will inform patients to avoid live vaccines within 30 days prior to initiating sibeprenlimab or during treatment with sibeprenlimab. Labeling will also recommend that patients be monitored for active infections and that consideration be given to interrupting sibeprenlimab if an infection occurs. Injection site reactions may be a tolerability issue for some patients who may choose to stop sibeprenlimab if sufficiently bothersome. These risks are acceptable for a therapy that is reasonably likely to slow progression of CKD, a condition with significant morbidity and mortality.

Although the data are not considered sufficient to support traditional approval, given the magnitude of the reduction in proteinuria seen in the phase 3 trial (b) (4) (b) (4) the review team recommends accelerated approval in a broad population (i.e., adults with primary IgAN at risk for disease progression) (b) (4) (b) (4)

Given the measures that will be put in place, sibeprenlimab's benefits outweigh its risks in patients with primary IgAN at risk for disease progression.

II. Interdisciplinary Assessment

3. Introduction

VOYXACT (sibeprenlimab-szsi) is an APRIL inhibitor. Sibeprenlimab binds to APRIL and blocks signaling at the B-cell maturation antigen (BCMA) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptors, resulting in reduced levels of Gd-IgA1, which is implicated in the pathogenesis of IgAN.

Disease Background

IgAN is a serious disease that is estimated to affect approximately 210,000 individuals in the United States (Swaminathan et al. 2006). Although patients with IgAN can present at any age, the peak incidence appears to be during the second and third decades of life. IgAN occurs with the greatest frequency in East Asians and Caucasians and is relatively rare in individuals of African ancestry. IgAN is associated with high morbidity and mortality; approximately 50% of patients progress to end-stage kidney disease within 30 years of diagnosis (Moriyama et al. 2014). IgAN is diagnosed by kidney biopsy; deposits containing immunoglobulin A (IgA) can be seen in the kidney mesangium using immunofluorescence.

The most common presentation of IgAN is gross hematuria (40% to 50% of cases), often accompanied by an upper respiratory infection. Approximately 30% to 40% of patients present with microscopic hematuria and subnephrotic proteinuria; less than 10% of patients present with either nephrotic syndrome or an acute, rapidly progressive glomerulonephritis.

The treatment guidelines for IgAN by Kidney Disease Improving Global Outcomes (KDIGO) were recently updated in October 2025 (KDIGO IgAN/IgAV Work Group 2025). The prior guidelines, which were published in 2021 and thus, were in effect when Trial 417-201-00007 was initiated, were published prior to the approval of drugs indicated for IgAN (KDIGO Glomerular Diseases Work Group 2021). Per the 2021 guidelines, initial treatment for IgAN included optimized supportive care, such as dietary sodium restriction, smoking cessation, weight control, control of blood pressure, and interventions to address cardiovascular risk. Angiotensin-converting enzyme inhibitors or ARBs were recommended in all patients with IgAN and proteinuria >0.5 g/day for controlling blood pressure, reducing proteinuria, and slowing the progression of renal disease (KDIGO Glomerular Diseases Work Group 2021). The sodium-glucose cotransporter-2 (SGLT2) inhibitors, dapagliflozin and empagliflozin, have been approved to reduce the risk of kidney disease progression in patients with chronic kidney disease at risk for progression and are used in patients with IgAN with persistent proteinuria despite treatment with an angiotensin-converting enzyme inhibitor or ARB to optimize supportive care (KDIGO CKD Work Group 2024). Compared to the 2021 guidelines, the 2025 guidelines now recommend treating all patients with IgAN with an ACEI or an ARB regardless of proteinuria level and to consider an SGLT2 inhibitor in patients at risk of progressive loss of kidney function. Both the 2021 and 2025 KDIGO guidelines recommend that patients consider enrollment in a clinical trial.

Treatments for IgAN are often divided into immunosuppressive treatments that are used in high-risk patients and supportive therapies, which may be used in combination with

immunosuppressant therapies and/or in lower risk patients to slow progression to kidney failure. As noted above, the 2021 KDIGO guidelines for the management of IgAN were published prior to the approval of drugs indicated for IgAN and recommended that prescribers consider immunosuppressive therapy, such as a 6-month course of systemic corticosteroids, for "high-risk" patients (defined in those guidelines as persistent proteinuria of >1 g/day despite maximal supportive care for at least 3 to 6 months) with an eGFR >30 mL/min/1.73 m^2 (KDIGO Glomerular Diseases Work Group 2021).

Since the publication of the 2021 KDIGO guidelines, two therapies have received full approval for IgAN in the United States: Tarpeyo (budesonide) and Filspari (sparsentan). Tarpeyo is an oral corticosteroid approved for a 9-month treatment duration that reduces the loss of kidney function in adults with primary IgAN who are at risk for disease progression. Filspari is intended to be used chronically and is not an immunosuppressant. Filspari, an endothelin and angiotensin II type 1 receptor antagonist, is approved to slow kidney function decline in adults with primary IgAN who are at risk for disease progression. For Tarpeyo, while the effect on kidney function that was seen during the 9-month treatment period in the phase 3 trial persisted following completion of treatment, the 9-month course of treatment did not change the long-term rate of decline in kidney function. As a systemically available oral corticosteroid, Tarpeyo has risks similar to other oral steroids including hypertension, prediabetes/diabetes mellitus, osteoporosis, peptic ulcers, and glaucoma or cataracts. The Tarpeyo label includes Warnings and Precautions for hypercortisolism and adrenal axis suppression, immunosuppression and increased risk of infection , and "Other Corticosteroid Effects." Sparsentan is not an immunosuppressant, but it is currently only available through a REMS because of the risk of hepatotoxicity. The Prescribing Information for Filspari includes the following additional Warnings and Precautions: embryo-fetal toxicity, hypotension, acute kidney injury, hyperkalemia, and fluid retention; anemia (thought to be due in part to hemodilution) is also a risk. The 2025 KDIGO guidelines have incorporated these therapies into their treatment recommendations (KDIGO IgAN/IgAV Work Group 2025).

In addition to the aforementioned therapies, iptacopan, a factor B complement inhibitor, and atrasentan, an endothelin receptor antagonist have both received accelerated approval to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a uPCR ≥1.5 g/g. Iptacopan is only available through a REMS due to the risk of serious infection caused by encapsulated bacteria. Warnings and Precautions for atrasentan include hepatotoxicity, fluid retention, and decreased sperm counts; anemia is also a risk.

Despite recent advances in the treatment of IgAN, there remains an unmet need for safe and effective treatments that can slow the loss of kidney function in patients with IgAN who are at risk for disease progression.

Regulatory History

There were numerous interactions with the Applicant over the course of the development program. See Section 12 for a summary of the regulatory history.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Adequacy of Available Data To Support Traditional Approval

3.1.2. Key Safety Review Issues

No safety findings rose to the level of a key safety review issue.

3.2. Approach to the Clinical Review

Table 3 provides an overview of the clinical trials submitted in support of the efficacy and safety of sibeprenlimab for the treatment of IgAN. This review focused on the efficacy and safety findings in Trial 417-201-00007. Supportive efficacy and safety data from phase 2 trial VIS649-201 were also reviewed.

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 to 3 for each indication.

1. Verbatim indication:

   VOYXACT is indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk for disease progression.

   This indication is approved under accelerated approval based on reduction of proteinuria. It has not been established whether VOYXACT slows kidney function decline over the long-term in patients with IgAN. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory clinical trial.

2. SEE was established with

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

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

      OR

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

   The Applicant submitted the results of a prespecified interim analysis on the treatment effect on uPCR at Week 40 compared to baseline from an adequate and well-controlled phase 3 trial (Trial 417-201-00007) in subjects with primary, biopsy-proven IgAN and proteinuria. The Applicant also provided results from a phase 2 trial (Trial VIS649-201) in subjects with primary, biopsy-proven IgAN as confirmatory evidence of effectiveness.

      OR

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

3. Complete response, if applicable

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

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

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

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

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[a] for Sibeprenlimab

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[b]	Number of Centers and Countries
Trial 417-201-00007, ongoing	Adult subjects with primary IgAN receiving stable maximally tolerated ACEI or ARB, eGFR ≥30 mL/min/1.73 m^2, uPCR ≥0.75 g/g (based on a 24-hr urine collection); included an exploratory subset of subjects with eGFR ≥20 and <30 mL/min/1.73 m^2.	Control type: Placebo Randomization: 1:1 to sibeprenlimab or placebo Blinding: Double-blind	Drug: sibeprenlimab Dosage: 400 mg subcutaneous every 4 weeks Number treated: 530 *Main Cohort:* • Sibeprenlimab: 259 • Placebo: 251 *Exploratory Cohort:* • Sibeprenlimab: 8 • Placebo: 12 Duration: 24 months	Primary: Relative change from baseline in uPCR-24h at Month 9. Secondary: • Annualized slope of eGFR estimated over the course of approximately 24 months • Mean change of eGFR from baseline at 24 months • Progression to CKF, as assessed by time to progression to CKF (time from randomization date to first occurrence of CKF) or proportion of subjects with progression to CKF	Planned: 470 Actual: 530	Centers: 242 Countries: 31

Trial Identifier (NCT#)	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[b]	Number of Centers and Countries
VIS649-201	Adult subjects with primary IgAN receiving stable maximally tolerated ACEI or ARB, eGFR ≥30 mL/min/1.73 m^2, uPCR ≥0.75 g/g (based on a 24-hr urine collection)	Control Type: Placebo Randomization: Stratified randomization Randomization Ratio: 1:1:1:1 Blinding: Double-blind	Drug (established name): Sibeprenlimab Dose: 2 mg/kg IV, 4 mg/kg IV, or 8 mg/kg IV monthly Number treated: 2 mg/kg N=38 4 mg/kg N=41 8 mg/kg N=38 Placebo N=38 Duration (quantity and units): 12 months	Primary: Change from baseline in uPCR on the natural log scale at Month 12 Secondary: • Change from baseline in uPCR on natural log scale at Months 9 and 16 • Change in 24-hour urine protein excretion from baseline to Months 9, 12, and 16 • Number of subjects in each group achieving a ≥30% decline from baseline in uPCR at Months 9, 12, and 16 • Number of subjects in each group achieving clinical remission • Change from baseline in eGFR at Months 12 and 16 • Change from baseline in total serum IgA, IgG, and IgM concentrations at Months 9, 12, and 16 • Serum PK parameters • Correlation of VIS649 PK parameters with changes in IgA, uPCR, and eGFR • Serum ADA levels	Planned: 144 Actual: 155	Centers: 100 Countries: 15

Source: Clinical Study Report and adsl.xpt
[a]Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
VIS649 refers to sibeprenlimab.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADA, antidrug antibody; ARB, angiotensin receptor blocker; CKF, composite kidney failure; eGFR, estimated glomerular filtration rate; IgAN: immunoglobulin A nephropathy; No., number; PK, pharmacokinetic; uPCR, urine protein-to-creatinine ratio

4. Patient Experience Data

The review team considered the experience and perspectives shared by patients and caregivers during an Externally Led Patient-Focused Drug-Development meeting hosted by the National Kidney Foundation and IgA Nephropathy Foundation on August 19, 2019, in its benefit-risk assessment. The National Kidney Foundation's voice-of-the-patient report for IgAN, which gathered information on the experiences and perspectives of IgAN patients, suggests that patients consider proteinuria reduction and slowing the rate of loss of kidney function as factors in deciding whether to take a new drug (Feldman et al. 2020). Furthermore, a patient-preference trial that included IgAN patients from the United States and China showed that delaying the likelihood of end-stage kidney disease was an important factor for patients when considering how likely they were to take a new treatment (Marsh et al. 2021).

With their BLA submission, the Applicant provided a review of the current published literature on the epidemiology, clinical assessment, disease course natural history, and available treatments for IgAN. The Applicant's review aggregated published qualitative, observational survey, and natural history studies, and included a review of IgAN symptom burden, patient experience with available treatments, and factors that influence a patient's decision to enter a clinical trial for IgAN. The submission also included the Applicant's literature review on an updated "conceptual model" of the patient experience with IgAN, which included key aspects such as physical and social functioning, treatment burden, and emotional and mental health for patients with the disease.

In Trial 417-207-0007, the Applicant evaluated the following exploratory endpoints: (1) change from baseline in the 36-Item Short-Form Survey Version 2 (SF-36v2) physical and mental composite scores, and (2) change from baseline in the Brief Fatigue Inventory global fatigue score. The Applicant included the results of these clinical outcomes assessments with their BLA submission (b) (4) (b) (4) These data are not discussed in this review. The clinical significance of these exploratory endpoints is unclear.

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	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☒	Patient-focused drug development meeting summary	
☒	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	Section 4; see text above Table 4.
☒	Observational survey studies	
☒	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Sibeprenlimab is a humanized immunoglobulin G2 (IgG2) monoclonal antibody that binds to APRIL and blocks its interaction with TACI and BCMA receptors, which is expected to reduce the pathogenic IgA production in diseases or conditions like IgAN through an incompletely understood mechanism. In vitro and in vivo pharmacology studies were conducted to characterize the mechanism of action and support proof of concept efficacy for the intended clinical indication, which are briefly described below.

5.1.1. In Vitro Pharmacology

Human APRIL

- Sibeprenlimab binds to human APRIL with picomolar affinity (half-maximal effective concentration [EC_{50}]=28.8pM) and blocks APRIL interactions with its receptors (TACI half-maximal inhibitory concentration [IC_{50}]=0.34nM; BCMA IC_{50}=0.18nM).
- In a binding kinetic analysis study, sibeprenlimab bound to human APRIL with a dissociation constant of 0.85 to 0.95pM.
- In cell based functional studies, sibeprenlimab showed a concentration dependent inhibition in APRIL-mediated nuclear factor kappa B (NF-κB) signaling through TACI (IC_{50} 152pM) and BCMA (IC_{50} 145pM) and B-cell proliferation (IC_{50} ~20nM).

Cross-Species Binding

- In separate replicates, sibeprenlimab bound APRIL from cynomolgus monkeys with an EC_{50}=109.8pM (versus 50.7pM for human) and rabbit with an EC_{50}=47.8pM (versus 39.0pM for human). However, sibeprenlimab did not bind to rodent APRIL. In cynomolgus monkeys, rabbits and rodents, >99%, 87% and 85% of the APRIL sequence is identical to humans, respectively. Based on the absence of rodent APRIL binding and the high sequency identity with human APRIL, the cynomolgus monkey was selected as the pharmacological relevant species suitable for toxicology assessment.

Mouse Surrogate Anti-APRIL Monoclonal Antibody

- A mouse-specific surrogate, monoclonal antibody (mAb) 4540, bound to both mouse and human APRIL with comparable receptor blocking activities (mouse APRIL: TACI IC_{50}=1.11nM, BCMA IC_{50}=1.46nM; human APRIL: TACI IC_{50}=0.65nM, BCMA IC_{50}=0.37nM), and was used for the in vivo proof-of-concept study.

5.1.2. Animal Model Data Showing Proof of Concept for Efficacy

The impact of blocking APRIL interaction with its receptors was evaluated in a grouped ddY (gddY) IgA mouse nephropathy model using the mAb 4540 mouse surrogate and in healthy cynomolgus monkeys with sibeprenlimab.

- Treatment with mAb 4540 (20 mg/kg once weekly for 4 to 8 weeks) in the gddY mouse model of IgAN suppressed serum IgA levels (>50% reduction), decreased kidney IgA, IgG, and C3 complement deposits, reduced glomerular sclerosis (~30%), and suppressed progressive proteinuria.
- In healthy cynomolgus monkeys intravenously administered 0.5 to 100 mg/kg sibeprenlimab once weekly for 4 to 26 weeks, consistent, dose-dependent reductions in serum IgA (up to ~70%), IgG (up to 50%), and immunoglobulin M (IgM) (up to 25%) levels were observed. These effects were reversed at the end of a four-month recovery period. Treatment with sibeprenlimab did not affect the humoral immune responses to novel antigens (keyhole limpet hemocyanin) in these studies.

5.2. Clinical Pharmacology/Pharmacokinetics

The clinical pharmacology review focused on the pharmacokinetics in humans (Section 5.2), assessment of dose (Section 6.1), and therapeutic individualization according to intrinsic factors (Section 8.1) and extrinsic factors (Section 8.2).

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Sibeprenlimab is an A-Proliferation-Inducing Ligand blocker.
Mechanism of action	Sibeprenlimab binds to APRIL with a dissociation constant of (K_D) of 0.95pM, which blocks signaling at the B cell maturation antigen (BCMA) and transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI) receptors.
Active moieties	Sibeprenlimab
QT prolongation	Sibeprenlimab is a monoclonal antibody, and antibodies have a low likelihood of direct ion channel interaction. A thorough QT/QTc study was not warranted.
	General Information
Bioanalysis	Human serum free sibeprenlimab concentrations were measured by a validated Meso Scale Discovery-electrochemiluminescence (MSD-ECL) immunoassay.
Healthy subjects versus patients	There is no clinically relevant difference in the pharmacokinetics of sibeprenlimab between subjects with IgAN and healthy subjects. The population pharmacokinetic (popPK) analysis found healthy subjects have a higher central volume of distribution (43.9%) and absorption rate constant (35.3%) than subjects with IgAN. However, healthy subjects have similar exposure as subjects with IgAN.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	**Table 6. Simulated Steady-State PK Exposure of 400-mg Sibeprenlimab Subcutaneously Injected Every 4 Weeks** **Parameter** / **Mean ± SD** AUC_{tau} (µg*day/mL) 2940±1760 C_{max} (µg/mL) 118±62.4 C_{trough} (µg/mL) 79.3±57.0 Source: PopPK analysis report (Report 417-24-202) Table 49. Simulated post hoc exposure for phase 3 subjects with IgAN using popPK model. Abbreviations: AUC_{tau}, area under the serum concentration-time curve over the dosing interval; C_{trough}, trough serum concentration; C_{max}, maximum (or peak) serum concentration; IgAN, immunoglobulin A nephropathy; PK, pharmacokinetic; popPK, population pharmacokinetic; SD, standard deviation

Characteristic	Drug Information
Range of effective dose(s) or exposure	4 mg/kg to 8 mg/kg monthly IV infusion (Trial VIS649-201) 400 mg SC injection every 4 weeks (Trial 417-201-00007)
Maximally tolerated dose or exposure	12 mg/kg single IV infusion over 1 hour (Trial VIS649-101), 8 mg/kg monthly IV infusion over 1 hour for 12 months (Trial VIS649-201).
Dose proportionality	**Single IV infusion (Trial VIS649-101)**: C_{max} increased in a dose proportional manner while AUCs increased more than dose proportionally (AUC_{inf} increases ~66.5x when dose increases 12x) from 0.5 mg/kg to 12 mg/kg. AUC increased approximately proportional from 6 mg/kg to 12 mg/kg. **IV infusion at steady state** (Trial VIS649-201, intense PK population at Month 11): Both C_{max} (increased 14.3x) and AUC_{tau} (increased 23.5x) increased greater than dose proportionally with increasing dose from 2 mg/kg to 8 mg/kg (4-fold). **Single SC injection** (Trial VIS649-102): Both C_{max} (increased 3.1x) and AUC_{inf} (increased 4.7x when dose increases 2x) increased in a more than dose proportional manner as dose increased from 200 mg to 400 mg, and became approximately dose proportional as dose increased from 400 to 600 mg. No dose proportionality data were available for repeated SC doses since only one repeated SC dose (i.e., 400 mg Q4W) was evaluated in the clinical program.
Accumulation	The accumulation ratio for 400 mg SC every 4 weeks dosing is not available. The accumulation ratio for 4 mg/kg monthly IV infusion is 1.93-fold.
Time to achieve steady-state	Steady-state exposure of sibeprenlimab was attained by Month 3 with monthly IV infusions. Steady state with sibeprenlimab 400 mg SC every 4 weeks dosing is reached by Week 20.
Bridge between to-be-marketed and clinical trial/study formulations	The final to-be-marketed formulation of the SC injection was used in the pivotal clinical trial.
	Absorption
Bioavailability	Based on popPK assessment, the absolute bioavailability of sibeprenlimab through SC injection using prefilled syringe is 0.92. The relative bioavailability following SC injection to the abdomen, thigh or arm are similar.
T_{max}	The median T_{max} is 8 days (Trial VIS649-201) after single SC injection of 400 mg sibeprenlimab.
Food effect (fed/fasted)	Not applicable for SC injection.
	Distribution
Volume of distribution	The popPK analysis estimated total volume of distribution for a 70 kg individual is 4 L. After a single 400 mg SC dose in healthy subjects, the mean (SD) apparent volume of distribution is 3.0 (1.5) L (Trial VIS649-102).
Plasma protein binding	Not applicable for antibody product, which does not usually bind to drug binding plasma proteins.
Drug as substrate of transporters	Not applicable for antibody product, which typically does not cross cell membranes through usual drug transporters for small molecules.

Characteristic	Drug Information
	Elimination
Mass balance results	Not conducted
Clearance	Based on popPK analysis, the estimated apparent clearance at steady state in the phase 3 subjects is 206 mL/day. After a single dose of 400 mg SC administration in healthy subjects, the mean (SD) apparent clearance is 237.3 (144.7) mL/day (Trial VIS649-102).
Half-life	Following a single 400 mg SC injection in healthy subjects, the observed elimination half-life is 9.3 days (Trial VIS649-102).
Metabolic pathway(s)	Not applicable
Primary excretion pathways (% dose)	Not applicable
	Intrinsic Factors and Specific Populations
Body weight	Based on popPK analyses, baseline body weight (range 39.7 to 238 kg) is a statistically significant covariate for clearance and distribution parameters in the popPK model but is not a statistically significant covariate in the popPK/PD (total IgA) or the E_{max} exposure-response (uPCR) model. No dose adjustment is needed for body weight.
Age	Age (range 18 to 75 years old) is not a statistically significant covariate in popPK and popPK/PD analyses. Age (range 18 to 83 years old) is a statistically significant covariate for baseline uPCR-24h in the exposure-response (ER) model but not for any drug response related parameters. No dose adjustment is needed for age.
Renal impairment	No dedicated studies have been conducted to evaluate the impact of renal impairment on the pharmacokinetics of sibeprenlimab. Renal elimination is not a major elimination pathway of sibeprenlimab. Subjects with IgAN and various eGFR values were enrolled in the pivotal phase 3 study. PopPK analysis demonstrated that eGFR was not a statistically significant covariate across the range of renal function observed in the study population (eGFR 23.7 to 244 mL/min). No dose adjustment is needed for IgAN patients with renal impairment.
Hepatic impairment	No dedicated studies have been conducted to evaluate the impact of hepatic impairment on the pharmacokinetics of sibeprenlimab. Bilirubin (range 0.1 to 2.1 mg/dL) and baseline alanine aminotransferase (range 5 to 137 U/L) were found to affect Vmax statistically significantly in the popPK analysis. However, there is minimal impact on sibeprenlimab exposures and no effect on serum IgA reduction (popPK/PD analysis) or 9-month uPCR response (ER analysis). Therefore, no dose adjustment is necessary for subjects with hepatic impairment.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	PopPK analysis found that coadministration with SGLT2 inhibitors does not affect sibeprenlimab exposure. In vitro stimulation of human whole blood with sibeprenlimab did not induce significant secretion of interleukin (IL)-1b, IL-2, IL-6, IL-8, IL-10, IL-12, interferon gamma or tumor necrosis factor alpha. Therefore, sibeprenlimab is not anticipated to affect the pharmacokinetics of concomitant drugs metabolized by CYP450 enzymes.
Inhibition/induction of transporter systems	Not applicable

Characteristic	Drug Information
	Immunogenicity
Bioanalysis	Sibeprenlimab ADA was measured by an ECL bridging immunoassay with a solid phase extraction with an acid dissociation (SPEAD) clean-up step that uses biotinylated sibeprenlimab as a capture reagent and ruthenylated sibeprenlimab as a detection reagent. An anti-idiotypic mouse monoclonal anti-sibeprenlimab antibody was used as the positive control and a pool of prescreened normal human serum samples as the negative control. A bead-based solid-phase extraction acid-dissociation sample pretreatment step followed by a competitive ligand binding format was used to detect neutralizing antibodies (NAb) against sibeprenlimab. The NAb assay has a drug tolerance issue and target interference from serum APRIL. Refer to the Office of Pharmaceutical Quality review for detailed evaluation of the immunogenicity assay ([DARRTS ID: 5674385] 2025).
Incidence	In the pivotal phase 3 study, 34.4% (88/256) of evaluable subjects treated with sibeprenlimab developed ADA, and 23.9% (21/88) of these ADA-positive subjects demonstrated neutralizing activity.
Clinical impact	PopPK analysis shows that subjects with IgAN who developed ADA has ~40% lower sibeprenlimab exposure than those who did not. The ADA-positive samples had a significantly lower C_{trough} (a reduction of 65%) as the geometric mean ratio was 0.35 and the upper bound of the 90% confidence interval was less than 1 compared to those of ADA-negative samples, indicating that ADA has negative impacts on pharmacokinetics. However, the exposure difference did not translate into differences in PD markers (IgA, APRIL). ADA-positive subjects had numerically lower reduction in uPCR-24h at 9 months than subjects with undetectable ADA over the treatment period (42% [27, 53] versus 53% [43, 61], respectively). However, both ADA-positive and ADA-negative subjects had a clinical meaningful reduction in uPCR-24h.

Source: Reviewer generated
VIS649 refers to sibeprenlimab.
Abbreviations: ADA, antidrug antibody; APRIL, A-Proliferation-Inducing Ligand; AUC_{inf}, area under the curve extrapolated to infinite time; AUC_{tau}, area under the serum concentration-time curve over the dosing interval; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; CYP450, cytochrome P450; ECL, electrochemiluminescence; eGFR, estimated glomerular filtration rate; E_{max}, maximum effect; ER, exposure-response; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IL, interleukin; IV, intravenous; Kd, dissociation constant; NAb, neutralizing antibody; PD, pharmacodynamic; PK, pharmacokinetic; popPK, population pharmacokinetic; QTc, corrected QT; SC, subcutaneous; SD, standard deviation; SGLT-2, sodium-glucose cotransporter-2; T_{max}, time of maximum serum concentration; uPCR, urine protein-to-creatinine ratio; uPCR-24h, 24-hour urine protein-to-creatinine ratio; x, times

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

6.1.1. Applicant's Proposed Dosing Regimen

The proposed dosing regimen for sibeprenlimab in the draft label is 400 mg SC injection once every 4 weeks. The dosing regimen is identical to the one used in the phase 3 trial, Trial 417-201-00007.

6.1.2. Selection of Dosing Regimen for the Phase 3 Trial

The selected dose of sibeprenlimab for the phase 3 trial was based on the results of the dose-ranging study (VIS649-201) conducted in subjects with IgAN, as well as popPK/pharmacodynamic (PD) modeling.

Trial VIS649-201, described in detail in Section 14.2.4 evaluated the efficacy (change from baseline in uPCR-24h at Month 12) of sibeprenlimab at doses of 2, 4, and 8 mg/kg administered monthly via IV infusion compared to placebo, in subjects with biopsy-confirmed IgAN who were receiving stable, maximally tolerated doses of either ACEI or ARB therapy for at least 3 months. Subjects who were on a stable dose of an SGLT2i for at least 3 months prior to screening were included in the trial.

Changes in uPCR-24h from baseline for sibeprenlimab compared to placebo following the three dosing regimens are summarized in Table 7. Percent change in uPCR-24h from baseline over time for sibeprenlimab and placebo is shown in Figure 1. The data suggest that in subjects with IgAN receiving an ACEI or ARB, doses of 2 mg/kg and above demonstrated reductions in uPCR-24h from baseline beginning at Month 9, with the 4 mg/kg group showing superior efficacy compared to the 2 mg/kg group and comparable efficacy to the 8 mg/kg group. The least-square mean change in eGFR (mL/min/1.73 m^2) from baseline over time is presented in Figure 2. The least-square mean difference (95% CI) relative to placebo in eGFR from baseline to Month 12 was +4.6 (−0.3, 9.5), +7.6 (2.8, 12.3), and +5.8 (0.9, 10.7) mL/min/1.73 m^2 for the 2, 4, and 8 mg/kg groups, respectively, with nominal statistical significance for the 4 mg/kg (p=0.002) and 8 mg/kg (p=0.02) groups.

Infections, administration reactions, and hypersensitivity are key potential risks of sibeprenlimab given its mechanism of action. The safety profile across dose levels in subjects with IgAN related to these risks was assessed using the Office of New Drugs Custom Medical Queries (OCMQs). As shown in Table 8, while there appeared to be a numerical increase in the incidence of viral infections and bacterial infections as the dose increased, the overall incidence was the same or lower than that seen with placebo in the phase 2 trial. For an evaluation of safety in the phase 3 trial, refer to Section 7.

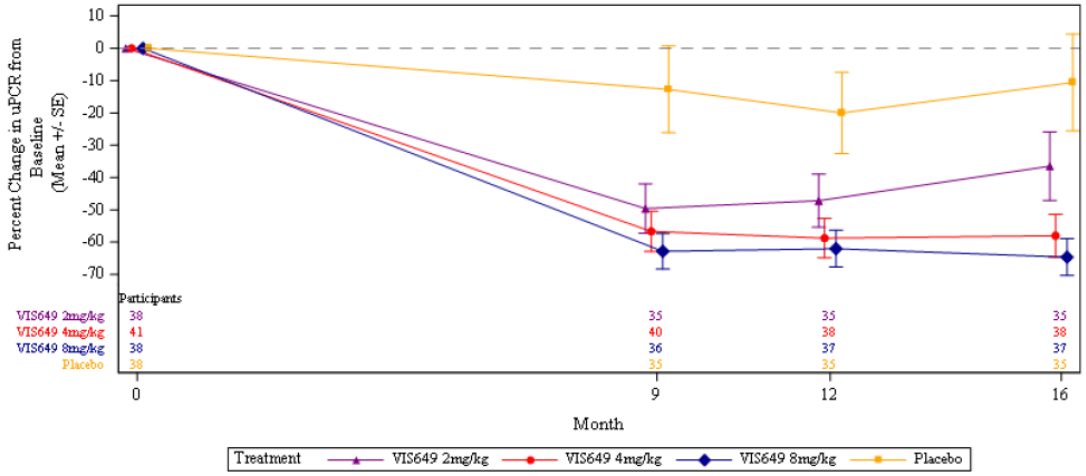
Based on the superior efficacy of 4 mg/kg compared to 2 mg/kg and the lack of additional efficacy with 8 mg/kg in subjects with IgAN, the exposure level achieved with 4 mg/kg monthly IV administration was selected as the target exposure level for phase 3.

Table 7. uPCR-24h Change From Baseline at Month 12, mITT Population, Trial VIS649-201

Categories	2 mg/kg N=38	4 mg/kg N=41	8 mg/kg N=38	Placebo N=38
Reduction of uPCR-24h from baseline (%), GM RR (95% CI)	47.2 (28.2, 61.1)	58.8 (44.8, 69.2)	62.0 (48.9, 71.8)	20.0 (−9.1, 41.4)
Treatment difference from placebo, GM RRD (95% CI)	34.0 (0.4, 56.2)	48.5 (23.2, 65.4)	52.5 (28.8, 68.4)	
p-Value (vs. placebo)	0.048	0.001	0.0004	

Source: Table 11.4.1.1.1-1 on Page 54 of trial VIS649-201 CSR
GM RR was calculated as (1-exponentiated least-squares mean)*100%. The SE of GM RR was calculated as the exponentiated (LSM)*(SE of LSM)*100%. LSM, SE, and 95% CI were estimated from MMRM with natural log scale of uPCR.
GM RRD was calculated as (1-exponentiated LSMD)*100% and the corresponding SE was calculated as the exponentiated (LSMD)*(SE of LSMD)*100%. The response variable of the MMRM was the change from baseline in uPCR on the natural log scale. The model included fixed effects of treatment, categorical visit, strata and treatment-by-visit interaction, with a fixed effect covariate of baseline uPCR on natural log scale.
Abbreviations: CSR, clinical study report; GM RR, geometric mean ratio reduction; GM RRD, geometric mean ratio reduction difference from placebo in % reduction from baseline; CI, confidence interval; LSM, least-squares mean; LSMD, least-square mean difference; mITT, modified intent-to-treat; MMRM, mixed model with repeated measurements; N, number of subjects; SE, standard error; uPCR, urine protein-to-creatinine ratio; vs, versus

Figure 1. Percent Change in uPCR-24h From Baseline Over Time: Evaluation of Overall Treatment Effect, mITT Population, Trial VIS649-201



Source: Figure 11.4.1.1.-1 on page 52 of trial VIS649-201 CSR
VIS649 refers to sibeprenlimab.
Abbreviations: CSR, clinical study report; mITT, modified intent-to-treat; uPCR, urine protein-to-creatinine ratio

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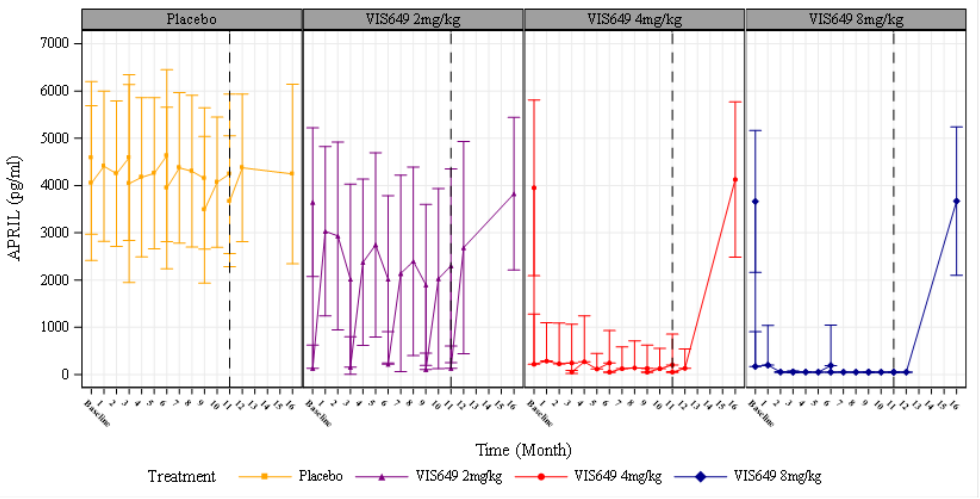
Table 8. Subjects With Adverse Events by System Organ Class and OCMQ (Narrow), Safety Population, Trial VIS649-201

SOC OCMQ(Narrow)	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)
General disorders and administration site conditions (SOC)						
Local administration reaction	1 (2.6)	1 (2.4)	2 (5.3)	4 (3.4)	2 (5.3)	−1.8 (−14.1, 4.6)
Immune system disorders (SOC)						
Anaphylactic reaction	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Hypersensitivity	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Infections and infestations (SOC)						
Nasopharyngitis	8 (21.1)	12 (29.3)	7 (18.4)	27 (23.1)	5 (13.2)	9.9 (−5.8, 21.6)
Pneumonia	1 (2.6)	0	1 (2.6)	2 (1.7)	0	1.7 (−7.6, 6.0)
Purulent material	0	1 (2.4)	1 (2.6)	2 (1.7)	0	1.7 (−7.6, 6.0)
Viral infection	13 (34.2)	15 (36.6)	17 (44.7)	45 (38.5)	17 (44.7)	−6.3 (−24.2, 11.1)
Bacterial infection	0	1 (2.4)	3 (7.9)	4 (3.4)	4 (10.5)	−7.1 (−21.0, 0.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any AE with an onset date on or after the start of the first IMP, or if event was continuing from baseline and was worsening.
Duration is 12 months of monthly doses.
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; N, number of subjects in treatment arm; n, number of subjects with adverse event; OCMQ, Office of New Drugs Custom Medical Query; PT, preferred term; SOC, system organ class

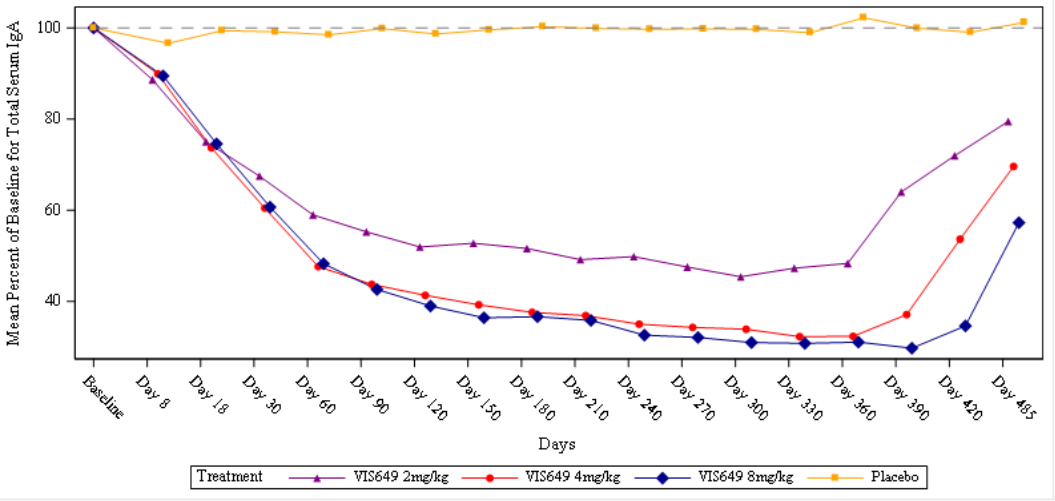
The decision to target exposure levels achieved with 4 mg/kg monthly IV administration was further supported by dose-dependent suppression of serum target (APRIL) levels and relevant pharmacodynamic marker levels (e.g., IgA). At the 2 mg/kg dose, suppression of serum APRIL levels was not maintained over the 1-month dosing interval, with only partial suppression observed at the end of each dosing period. In contrast, complete and sustained suppression of APRIL was observed in both the 4 mg/kg and 8 mg/kg treatment groups throughout each dosing interval (Figure 3). Additionally, the 4 mg/kg and 8 mg/kg doses demonstrated greater reductions in IgA levels compared to the 2 mg/kg dose (Figure 4).

Figure 3. Mean (SD) APRIL Concentration at Predose and Postdose Timepoints Over Time, PD Population, Trial VIS649-201



Source: Figure 11.5.3.3.2-1 on page 109 of trial VIS649-201 CSR
VIS649 refers to sibeprenlimab
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; CSR, clinical study report; PD, pharmacodynamic; SD, standard deviation

Figure 4. Mean Total Serum IgA Percent of Baseline Values Over Time, Trial VIS649-201



Source: Figure 11.5.3.3.1.1-1 on page 88 of trial VIS649-201 CSR
VIS649 refers to sibeprenlimab
Abbreviations: CSR, clinical study report; IgA, immunoglobulin A

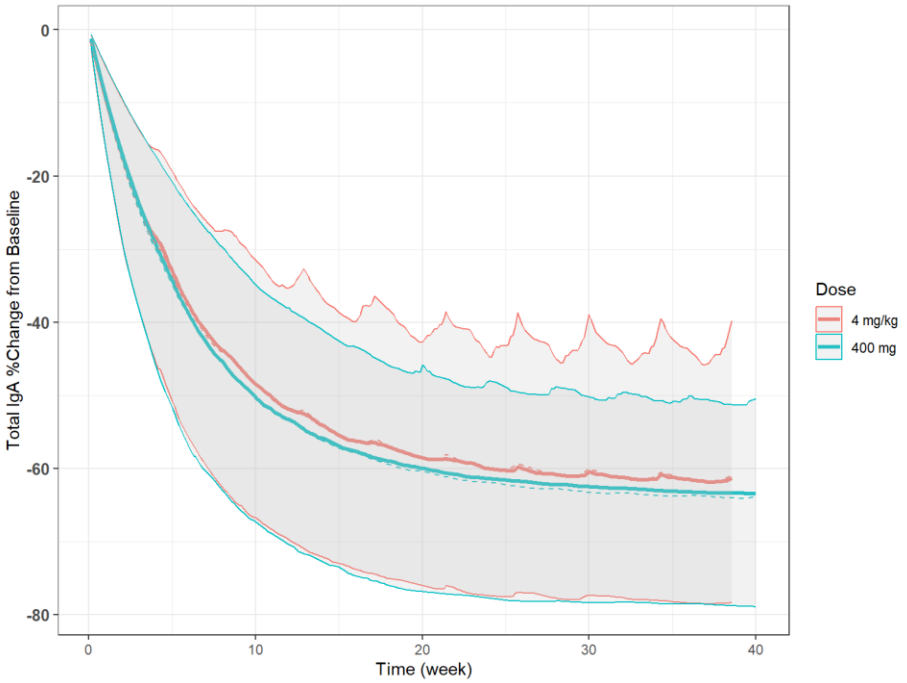
The popPK/PD model developed using data from phase 1 trials (VIS649-101, VIS649-102) and the phase 2 trial (VIS649-201) supported the evaluation of the 400 mg SC once every 4 weeks (Q4W) dose in the pivotal phase 3 trial, as this regimen achieved slightly higher area under the curve (AUC) exposures over the dosing interval (AUC_{tau}) (Table 9) and similar reductions in IgA levels compared to the 4 mg/kg IV monthly dose (Figure 5).

Table 9. Simulated Sibeprenlimab Exposures by Dosing Regimen

	4 mg/kg (N = 500)	400 mg (N = 500)
Cmax (ug/mL)		
Mean (CV%)	156 (37.5%)	128 (59.0%)
Median [Min, Max]	145 [51.9, 497]	113 [14.6, 443]
Geo. mean (Geo. CV%)	146 (37.1%)	108 (65.7%)
Ctrough (ug/mL)		
Mean (CV%)	36.0 (126.5%)	85.3 (86.5%)
Median [Min, Max]	20.5 [0.00000172, 325]	65.3 [0.00247, 394]
Geo. mean (Geo. CV%)	3.10 (322901.6%)	41.7 (713.7%)
AUCtau (ug•day/mL)		
Mean (CV%)	2030 (72.2%)	3080 (67.8%)
Median [Min, Max]	1630 [394, 11400]	2640 [146, 11900]
Geo. mean (Geo. CV%)	1620 (74.7%)	2440 (83.2%)

Source: Table 28 on page 102 of PK/PD model report 417-24-202
Note: 400 mg was administered SC every 4 weeks and 4 mg/kg was administered IV monthly.
Abbreviations: AUC_{tau}, area under the serum concentration-time curve over the dosing interval; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; CV%, coefficient of variation percentage; Geo., geometric; Max, maximum; Min, minimum; N, number of subjects with available information; PD, pharmacodynamic; PK, pharmacokinetic

Figure 5. Total IgA Concentration-Time Profile by Sibeprenlimab Dosing Regimen – Entire Simulation Time Course



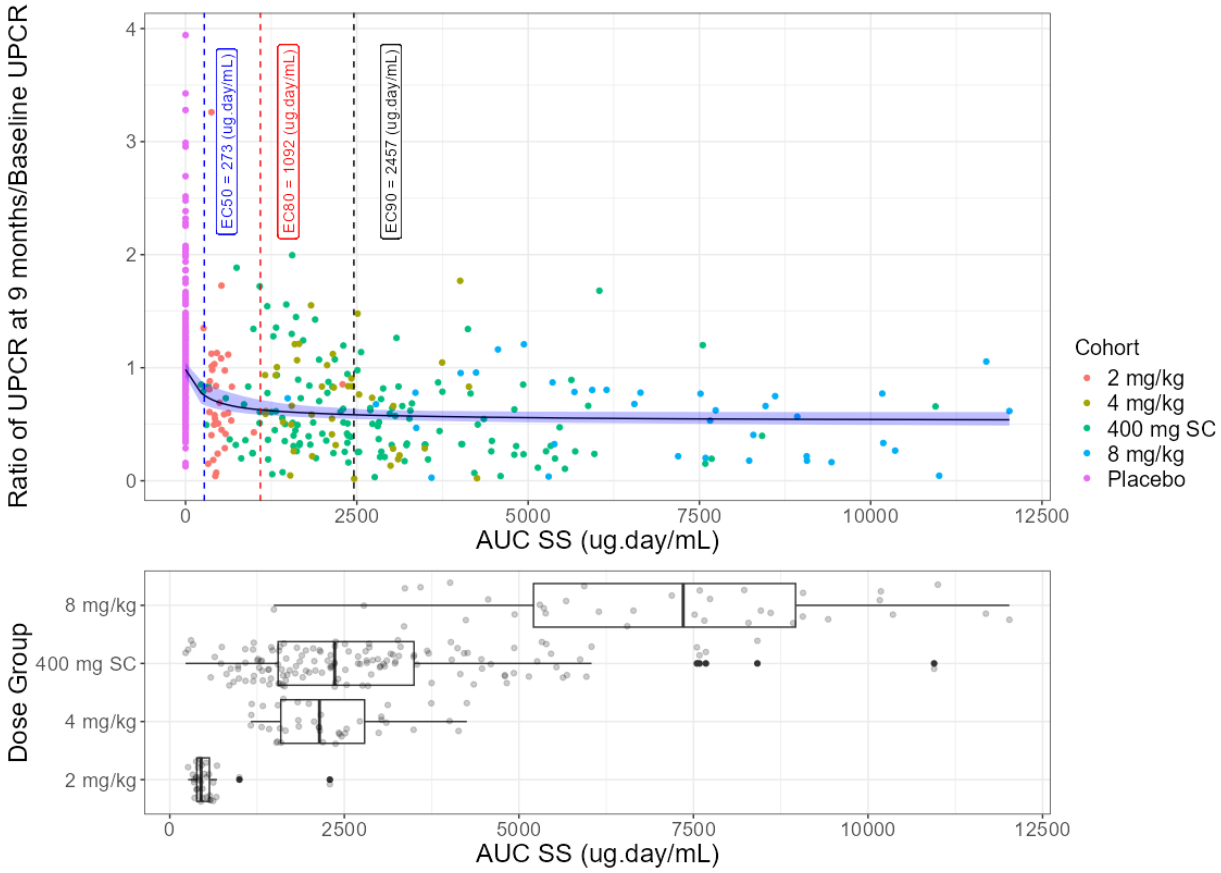
Source: Figure 25 on page 103 of PK/PD model report 417-24-202
Note: 400 mg was administered SC every 4 weeks and 4 mg/kg was administered IV monthly.
Note: The solid line is the median concentration. The dashed line is the mean concentration. The ribbon represents the 5th to 95th percentiles of observations over the concentration-time profile.
Abbreviations: IgA, immunoglobulin A, PD, pharmacodynamic; PK, pharmacokinetic

6.1.3. Dose Response

The 400 mg SC injection Q4W dosing regimen was evaluated in the randomized, double-blind, placebo-controlled phase 3 trial (417-201-00007). This dose demonstrated significantly greater reduction in uPCR-24h at Month 9 from baseline (the primary endpoint) compared with placebo (see Section 6.2).

The Applicant conducted an exposure-response (E-R) analysis using data from the phase 3 trial. The model-predicted uPCR-24h at Month 9 as a function of simulated steady-state sibeprenlimab exposure is shown in Figure 6. Administration of 400 mg SC injection Q4W resulted in exposures (as assessed using area under the serum concentration-time curve over one dosing interval at steady state [$AUC_{tau,ss}$]) near the plateau of the E-R curve for reduction in uPCR-24h. Among subjects with IgAN treated with 400 mg SC Q4W, 98.6%, 87.3%, and 46.5% of subjects achieved $AUC_{tau,ss}$ levels above the model-estimated EC_{50} (273 µg·day/mL), EC_{80} (1092 µg·day/mL), and EC_{90} (2457 µg·day/mL), respectively. These analyses further support the proposed dose of 400 mg SC injection Q4W to reduce proteinuria in adults with IgAN. See Section 14.5 for further information.

Figure 6. Relationship Between the Ratio of uPCR-24h at 9 Months/uPCR-24h at Baseline and Sibeprenlimab $AUC_{tau,ss}$ in Subjects With IgAN, Trials VIS649-201 and 417-201-00007



Source: Figure 2.7.2.3.7-1 on page 51 of Summary of Clinical Pharmacology
Note: The model predicted exposure-response relationship was overlaid with observed efficacy data in the upper panel. The blue solid line with blue shaded region represents simulated E_{max} curve and simulated 90% CI, respectively. The blue dashed vertical line represents EC_{50} (273 µg·day/mL), the red dashed line represents EC_{80} (1092 µg·day/mL), and the black dashed line represents EC_{90} (2457 µg·day/mL). Dots represent the observed uPCR-24$h_{9\ months}$/ uPCR-24$h_{Baseline}$. The $AUC_{tau,ss}$ distributions for the evaluated dose regimens in studies VIS-649-201 and 417-201-00007 are presented in the lower panel box plot.
Abbreviations: $AUC_{tau,ss}$, area under the serum concentration-time curve over the dosing interval at steady state; AUC_{ss}, area under the concentration-time curve at steady state; EC_{50}, half-maximal effective concentration; EC_{80},concentration producing 80% maximal effect; EC_{90}, concentration producing 90% maximal effect; IgAN, immunoglobulin A nephropathy; SC, subcutaneous; uPCR, urine protein-to-creatinine ratio

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Trial 417-201-00007

6.2.1.1. Design, Trial 417-201-00007

Trial 417-201-00007 is an ongoing, phase 3, randomized, double-blind, placebo-controlled trial evaluating the safety and efficacy of sibeprenlimab in subjects with biopsy-proven IgA

nephropathy at risk of progressive loss of renal function. All screened subjects in the trial were required to be on a maximally tolerated and stable dose of an ACEI and/or ARB (investigator's choice) throughout the trial; an SLGT2i was also allowed if it was initiated at least 3 months prior to screening and the dose was stable. The trial primarily enrolled subjects with a baseline eGFR ≥30 mL/min/1.73 m^2 (main cohort) but also enrolled an exploratory cohort composed of subjects with an eGFR ≥20 and <29 mL/min/1.73 m^2. This review focuses on the main cohort.

The trial is composed of a screening, treatment, and an optional single-arm, open-label extension period. After the screening period, eligible subjects were randomized 1:1 to receive either sibeprenlimab 400 mg SC Q4W or matching placebo on Day 1 for 26 doses, with the last dose occurring on Week 100. Randomization was stratified according to uPCR levels at screening (≥2 g/g versus <2 g/g), screening eGFR (30 to 44 mL/min/1.73 m^2 versus ≥45 mL/min/1.73 m^2), and SGLT2i use at randomization (yes versus no). The trial planned to enroll approximately 450 subjects in the main cohort and 20 subjects in the exploratory cohort. An unblinded interim analysis was prespecified to be conducted when the first 62.5% of randomized subjects in the main cohort had the opportunity to complete the Month 9 uPCR-24 hr evaluation.

As of March 14, 2024, the trial was fully enrolled with 510 subjects enrolled in the main cohort and 20 subjects in the exploratory cohort (see Section 15.1).

6.2.1.2. Objectives, Trial 417-201-00007

The primary objective of Trial 417-201-00007 is to compare the relative change from baseline in uPCR (based on a 24-hour collection) achieved with sibeprenlimab versus placebo in addition to standard of care, after 9 months of SC administration.

The key secondary efficacy objective is to compare the annual rate of change from baseline (slope) of eGFR achieved with sibeprenlimab versus placebo in addition to standard of care after approximately 24 months of SC administration.

6.2.1.3. Eligibility Criteria, Trial 417-201-00007

Key inclusion criteria are as follows:

- ≥18 years of age
- Source-verified biopsy-confirmed IgAN
- On a stable and maximally tolerated dose of authorized ACEI and/or ARB (per local standard of care and applicable guidelines) for at least 3 months prior to screening
  - Subjects who are on a stable dose of SGLT2i therapy for IgAN, in addition to ACEIs and/or ARBs, may participate in the trial if treatment was initiated and dose was stable for at least 3 months prior to obtaining the initial screening urine collection.
  - Subjects who are unable to tolerate ACEI and/or ARB therapy may be eligible for participation in the trial if their overall management of IgAN, including blood pressure control, is per local standard of care and applicable guidelines.

- Screening uPCR ≥0.75 g/g or urine protein excretion ≥1.0 g/day, as measured from 24-hour urine samples (geometric mean of the two 24-hour urine samples collected up to 2 weeks apart at screening) and when the subject is "considered to be in steady-state."
- An eGFR ≥30 mL/min/1.73 m^2, calculated using the 2021 CKD-EPI equation. Subjects with an eGFR of 30 to 44 mL/min/1.73 m^2 are required to have had a kidney biopsy performed within 36 months of the screening visit.
  - For the exploratory cohort only: Subject has an eGFR of 20 to 29 mL/min/1.73 m^2, calculated using the 2021 CKD-EPI equation (National Kidney Foundation 2021).

Key exclusion criteria include the following:

- Secondary forms of IgAN as determined by the treating physician (e.g., infection-associated IgAN or IgAN associated with hepatic cirrhosis) or Henoch-Schönlein purpura (IgA vasculitis).
- Coexisting chronic kidney disease, other than IgAN.
- Evidence of additional pathological findings in the kidney biopsy (e.g., diabetic kidney disease, membranous nephropathy, or lupus nephritis). However, hypertensive vascular changes are acceptable.
- Kidney biopsy with a MEST or MEST-C score of T2 or C2 from the Oxford IgAN classification schema. If MEST-scoring was not performed, the presence of >50% tubulo-interstitial fibrosis, or crescents in >25% of glomeruli is exclusionary. Note: this criterion does not apply to the exploratory cohort.
- Nephrotic syndrome, defined for this purpose as 24-hour urine protein >3.5 g/day with concurrent hypoalbuminemia (serum albumin <2.5 g/dL), hyperlipidemia (total cholesterol >350 mg/dL), and edema. Subjects with isolated nephrotic range proteinuria (>3.5 g/day) are eligible.
- History or current evidence of a serious and/or unstable cardiovascular, respiratory, gastrointestinal, hematologic, autoimmune, blood dyscrasia or other medical disorder, including psychiatric disorders, cirrhosis, or ongoing malignancy. History of minor skin cancers (not including melanoma) or surgically treated, limited cervical carcinomas (i.e., carcinoma in situ) may not be exclusionary per the discretion of the investigator.
- Body mass index <16 kg/m^2
- Serum IgG value <600 mg/dL at screening
- Received an organ transplant (i.e., solid or a bone marrow or hematologic stem cell transplantation)
- Currently receiving, or has received within 16 weeks prior to randomization, systemic immunosuppression
  - Note: Topical, ophthalmic, rectal, intra-articular, inhaled corticosteroids, and short courses (≤14 days) of oral/IV steroids are allowed
- Any chronic infectious disease (e.g., chronic urinary tract infection; chronic sinusitis; bronchiectasis; active pulmonary or systemic tuberculosis; chronic viral hepatitis, such as

hepatitis C or hepatitis B [defined as positive for hepatitis B surface antigen]; or human immunodeficiency virus infection).

- Acute infectious disease at the time of screening.
  - Note: Enrollment can be considered if the acute infection has resolved within the screening window, defined as resolution of acute clinical signs, symptoms, and related clinical laboratory parameters
- Type 1 diabetes or uncontrolled Type 2 diabetes, as evidenced by a screening hemoglobin A1c value >8%. Subjects will be excluded if their antidiabetic regimen is not stable
- Uncontrolled Hypertension (defined as systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg).

6.2.1.4. Endpoints, Trial 417-201-00007

Endpoints for the Interim Analysis

The primary efficacy endpoint for the interim analysis was the ratio of uPCR at 9 months compared with baseline, based on a 24-hour urine sample (i.e., endpoint for accelerated approval). Secondary endpoints at the time of the interim analysis were supportive (i.e., not included within the testing strategy) and included the following:

- The annualized slope of eGFR estimated over the course of approximately 12 months (Week 48),
- The mean change in eGFR from baseline at 12 months (Week 48).

Endpoints for the Confirmatory Analysis

The confirmatory endpoint to verify the clinical benefit is the rate of change in eGFR over a 100-week (approximately 2 years) period following the initiation of randomized treatment. The confirmatory analysis will include the following secondary efficacy endpoints that will be included within the testing strategy:

Key Secondary Endpoint

- Annualized slope of eGFR estimated over the course of approximately 24 months.

Secondary Endpoints

- Mean change of eGFR from baseline at 24 months.
- Time to progression to composite kidney failure (CKF) (time from the randomization date to first occurrence of CKF).
  - CKF is defined as meeting one or more of the following criteria based on observed assessments or therapy: sustained doubling of serum creatinine compared with baseline based on 2 measurements at least 4 weeks apart, sustained 40% reduction in eGFR compared with baseline based on 2 measurements at least 4 weeks apart, sustained eGFR

<15 mL/min/1.73 m^2 based on 2 measurements at least 4 weeks apart, or the requirement of renal replacement therapy (chronic dialysis for ≥4 weeks or kidney transplantation).

- Proportion of subjects with progression to CKF.

6.2.1.5. Statistical Analysis Plan, Trial 417-201-00007

The Applicant's original statistical analysis plan (SAP) for the interim analysis (IA) (database lock cutoff date September 25, 2024) was finalized on December 16, 2022. The SAP for the IA was amended three times. Amendment 3 was finalized on September 20, 2024. The changes that were made to the SAP via these amendments (see Appendix 16.1 for further details) do not raise concerns about the interpretability of the study results. An addendum to SAP amendment 3 was finalized on January 21, 2025, after the IA database lock (DBL) on September 25, 2024. This addendum documents the additional analyses conducted after the full IA unblinding, which occurred on November 18, 2024. See section 15.5 for details on the unblinding plan.

Efficacy Analysis Sets

The SAP specified the following analysis sets:

Full Analysis Set (FAS): All randomized subjects who had a baseline uPCR measured from at least one 24-hour urine sample.

IA Set: The first 62.5% of randomized subjects who had the opportunity to complete the 9-month (Week 40) uPCR-24h evaluation.

IA FAS #1: Subjects in the IA Set who had a baseline uPCR measured from at least one 24-hour urine sample.

IA FAS #2: Subjects in the IA Set who had the opportunity to complete the 12-month (Week 52) assessment and had a baseline uPCR measurement from at least one 24-hour urine sample.

IA FAS #3: Subjects in the IA Set who had the opportunity to complete the 18-month (Week 72) eGFR assessment and had a baseline eGFR measurement.

Per Protocol Set: comprises all randomized subjects who have uPCR-24h assessments at both baseline and the primary endpoint (i.e., 9 months), and who have no important protocol deviations.

Endpoints

Primary Endpoint at IA

The primary efficacy endpoint was the ratio of uPCR-24h at 9 months to uPCR-24h at baseline, denoted as $uPCR\text{-}24h_{9months}/uPCR\text{-}24h_{Baseline}$.

Two 24-hour urine samples were collected at scheduled visits. A subject's observed uPCR-24h was the geometric mean (GM) of the 2 measurements. If only one measurement was available, this measurement was used. If there was no uPCR −24h measurement, this measurement was set as missing.

Exploratory Endpoints at IA

Exploratory efficacy endpoints for eGFR:

- The annualized slope of eGFR estimated over approximately 12 months (Week 48).
- The mean change in eGFR from baseline at 12 months (Week 48).

The eGFR for each baseline and postbaseline visit will be determined using the Chronic Kidney Disease Epidemiology Collaboration formula for adults, based on serum creatinine values from the visit (Levey et al. 2009).

Analysis Visit Window

The analysis windows associated with the primary and key secondary endpoints at the interim analysis are shown in Table 10.

Table 10. Visit Windows (Study Days)

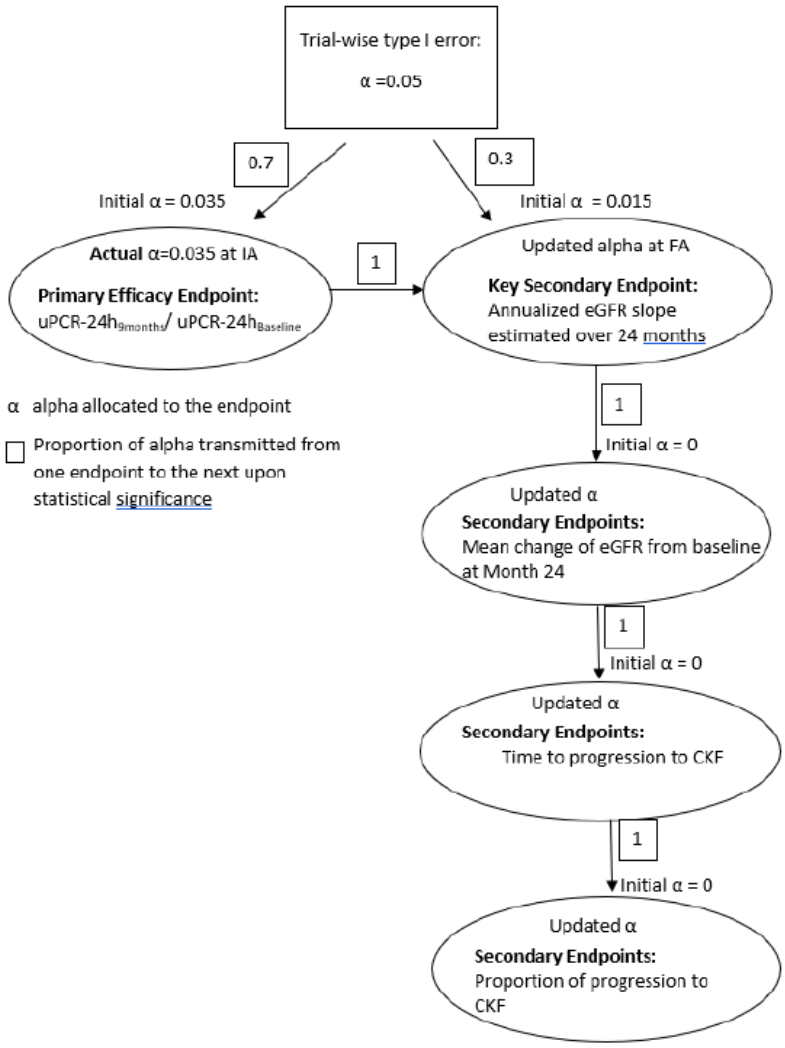
		Analysis Visit Window (Study Days)	
Analysis Visit	**Relative Target Day**	**eGFR and Safety Labs**	**24-Hour Urine**
Week 4	29	2-43	2-43
Week 40 (Month 9)	281	254-309	252-326
Week 48 (Month 12)	337	310-365	

Source: Applicant's SAP Table 16.1.1-1, Table 16.1.1-3, Table 16.1.2-2
Abbreviations: eGFR, estimated glomerular filtration rate; SAP, statistical analysis plan

Multiplicity Adjustment

To control the overall Type I error at the 0.05 level, a graphical approach was employed for handling multiplicity of multiple comparisons for primary, key secondary, and secondary endpoints. The initial alpha of 0.035 was allocated to the primary endpoint of uPCR-24h and an initial alpha of 0.015 was allocated to the key secondary endpoint of eGFR. If uPCR meets statistical criteria at the IA, the alpha will be passed to the key secondary endpoint of eGFR, which will have an updated alpha of 0.05. The key secondary endpoint and other secondary endpoints will be formally tested according to the testing procedure at the final analysis.

Figure 7. Multiple Comparison Procedure



Source: Statistical Analysis Plan, Amendment 3 Version 1.0
Abbreviations: CKF, composite kidney failure; eGFR, estimated glomerular filtration rate; FA, full analysis; IA, interim analysis; uPCR, urine protein-to-creatinine ratio

Sample Size

For the primary endpoint of uPCR-24h at Month 9, a total of 450 randomized subjects will provide at least 95% power assuming the following:

- Relative treatment difference between sibeprenlimab versus placebo is at least 30% reduction (i.e., $\log(0.70) \approx 0.36$)
- Standard deviation (SD) for the mean log change from baseline of uPCR-24h at Month 9 is 0.87.
- Two-sided alpha level is 0.05.

At the interim analysis, a total of 282 randomized subjects (62.5% information fraction) will provide at least 90% power assuming the same relative difference between the arms and the standard deviation, with 2-sided alpha of 0.035 allocated for the interim analysis. For the final

analysis of the [redacted]

- Two-sided alpha 0.015 (initially allocated)

If uPCR-24h meets statistical criteria at the interim analysis, the alpha of 0.035 will be passed to the final analysis of eGFR and in this case, the eGFR will be compared at a 2-sided alpha of 0.05. The power will be 91%.

[redacted] is based on historical data on the inter- and intrasubject SD of eGFR, the relationship between changes in urine protein and treatment effects on eGFR slope in IgAN patients and the assumed treatment effect on urine protein. Based on historical data, [redacted]

The meta-analysis describing the association of treatment effects on early change in urine protein and treatment effects on eGFR slope in IgAN patients by Inker et al. (2021) is referenced in the sample size calculation.

Primary Analysis

Analysis Method

The primary efficacy endpoint, ratio of uPCR-24h at 9 months compared with the baseline, will be analyzed using an analysis of covariance (ANCOVA) model and the IA FAS #1 dataset. The analysis will be performed on log transformed data because uPCR-24h is a right-skewed variable. The response variable will be the natural log-transformed ratio of uPCR-24h at 9 months compared with baseline, denoted as log(uPCR-24h9months/uPCR-24h$_{Baseline}$). The model included treatment group, randomization stratification factors of eGFR and SGLT2i, and log-transformed baseline uPCR-24h. Considering the collinearity between the stratification factor of uPCR-24h at randomization and the covariate of log-transformed uPCR-24h$_{Baseline}$, the stratification factor of uPCR-24h at randomization is not included in the ANCOVA model, consistent with FDA guidance. For the population level summary, the GM of the ratio of uPCR-24h at 9 months compared with baseline within each treatment will be presented, which is calculated by exponentiating the least-squares (LS) mean and its 95% CI of log-transformed data.

The treatment difference will be expressed as a GM reduction, which will be calculated as shown in Equation 1.

Equation 1. Treatment Difference

(1 – exp [LS mean difference of log-transformed uPCR-24h]) × 100%.

Source: Reviewer-generated equation
The 96.5% CI (corresponding to the two-sided significance level of 0.035 for the IA) will be calculated in a similar way.
Abbreviation: CI, confidence interval; exp, exponentiated; IA, interim analysis; LS, least-squares; uPCR-24h, urine protein-to-creatinine ratio at 24 hours

Intercurrent Events and Missing Data Handling

Intercurrent events (ICEs) of early treatment discontinuation (ICE #1) will be handled using the treatment policy strategy. Use of confounding medications/therapies (ICE #2) will be handled by the hypothetical strategy, where the subject's uPCR-24h9months will be set as missing after this ICE regardless of whether it was collected or missing.

Terminal events related to the kidney during the trial (ICE #3), including kidney transplant, chronic dialysis, or death due to kidney disease prior to the 9-month assessment of uPCR-24h, will be handled by the composite strategy. Under this strategy, first the uPCR-24h9months for a subject will be set as missing after ICE #3 regardless of whether it was collected or missing. Next, the log(uPCR-24h9months) will be imputed with the worst possible values of log(uPCR-24h9months) (observed among nonmissing data across the 2 treatment groups) plus a random error term following a normal distribution with mean of 0 and SD of s. The s is the SD of nonmissing log(uPCR $24h_{Baseline}$).

All missing data for the primary endpoint will be imputed using a multiple imputation procedure under the missing at random assumption. A fully conditional specification multiple imputation method will be used. The following covariates will be included in the imputation model:

- Baseline variables will include uPCR-24h, spot uPCR, eGFR, sex at birth, age, region, body mass index, and randomization stratification factors of SGLT2i.
- Postbaseline measurements of spot uPCR and eGFR collected up to 9 months will also be included in the multiple imputation.

Of note, during the IND phase, the Agency expressed interest in a treatment policy strategy to handle ICE #2 and indicated that if the Applicant used a different estimand, then the Applicant should also include supplementary analyses based on all observed data (i.e., a treatment policy approach).

On June 17, 2025, the Division asked the Applicant to perform the primary analysis using a treatment policy strategy to address intercurrent events related to treatment discontinuation and the use of rescue therapy, with any missing data following these intercurrent events imputed using a placebo-based multiple imputation approach. On June 24, 2025, the Applicant submitted the requested analysis, and these results were subsequently incorporated into the review.

Sensitivity Analyses

To assess the robustness of the primary analysis to the assumptions used for missing data and for handling ICEs, the following sensitivity analyses were prespecified:

- Using treatment policy strategy for handling uPCR-24h after ICE #2
- Placebo-based imputation method for ICE #2
- Using hypothetical strategy for handling uPCR-24h after ICE #1
- Using hypothetical strategy for handling uPCR-24h after ICE #3
- Two-way tipping point analysis

To assess the impact of protocol deviations:

- Repeat primary analysis on per protocol analysis set

Subgroup Analyses

Subgroup analyses for the primary endpoint will be performed for the following subgroups:

- Screening uPCR-24h based on interactive response technology (IRT) record (>2.0 g/g or ≤2.0 g/g)
- Screening eGFR based on IRT record (≥45 mL/min/1.73 m^2; 30 to 44 mL/min/1.73 m^2)
- Use of SGLT2i at randomization based on IRT record (Yes; No)
- Baseline MEST-C score
- Baseline uPCR-24h (>2.0 g/g or ≤2.0 g/g, >1.5 g/g or ≤1.5 g/g)
- Prior use of immunosuppressive drugs (including immunosuppressant therapies and systemic corticosteroids) (Yes; No)
- Prior tonsillectomy (Yes; No)
- Ethnicity (Hispanic or Latino; Not Hispanic or Latino; Other)
- Race (American Indian or Alaska Native; Asian, Black or African American; Native Hawaiian or Other Pacific Islander; White; Other)
- Region (North America; South America; Europe; East Asia; South/South-East Asia)
- Sex at birth (Male; Female)
- Age group (≤40 years; >40 years)

Exploratory Analyses

Analysis Method

The annualized slope of eGFR estimated over approximately 12 months (Week 48) will be compared between sibeprenlimab and placebo using a linear mixed-effects model with random effects without formal statistical testing. The model will be fitted with fixed effects of treatment group, time (as a continuous variable), treatment-by-time interaction, stratification factors of

uPCR-24h and SGLT2i at randomization, baseline eGFR, and random effects of intercept and time. The stratification factor of eGFR will not be included in the linear mixed-effects model to avoid the collinearity between the stratification factor of eGFR at randomization and the covariate of baseline eGFR. The within-subject correlation will be modeled using an unstructured covariance matrix. If the model does not converge, then the Toeplitz covariance structure will be used.

The mean change of eGFR from baseline at 12 months (week 48) will be analyzed using a mixed model for repeated measures (MMRM). The model will include treatment group, stratification factors of uPCR-24h and SGLT2i at randomization, visit, treatment by visit interaction, baseline eGFR, and baseline eGFR by visit interaction. No formal testing to compare eGFR change from baseline at 12 months between treatment groups will be performed.

Missing Data and Intercurrent Event Handling

The missing data and intercurrent events for the exploratory endpoints were handled in the same manner as for the primary analysis.

Sensitivity Analyses

The same sensitivity analyses will be performed for annualized slope of eGFR estimated over 12 months as for the primary analysis.

Additional sensitivity analysis: a linear spline random mixed-effect model with fixed knots at Week 8 (Month 2) and Week 12 (Month 3) will be used to estimate the acute slopes and chronic slopes before and after Week 8 and Week 12, respectively. The model will be fitted with fixed effects of treatment group, time (as a continuous variable), time2 (time after the fixed knot point, as a continuous variable), treatment-by-time interaction, treatment-by-time2 interaction, stratification factors of uPCR-24h and SGLT2i at randomization, baseline eGFR, and random effects of intercept, time, and time2.

6.2.1.6. Results of Analyses, Trial 417-201-00007

The main analyses results shown in this section are based on the main cohort interim analysis set (IAS), defined as the first 62.5% of randomized subjects who had the opportunity to complete the 9-month (Week 40) uPCR-24h evaluation. This analysis set includes subjects who either completed or were supposed to have completed the Week 40 proteinuria assessment by the interim data cutoff date of September 4, 2024.

6.2.1.6.1. Baseline Demographics and Disease Characteristics, Trial 417-201-00007

For the main cohort IA set for Trial 417-201-00007, baseline demographic characteristics (Table 11) were generally well-balanced between the two treatment groups. The majority of the subjects were Asian, followed by White, consistent with the epidemiology of IgAN (Galla 1995). Approximately 10% of the randomized subjects in the main cohort IA set were from the United States.

The baseline clinical characteristics (Table 12) and medical history (Table 13) of the subjects were similar among the sibeprenlimab and placebo groups.

Table 11. Baseline Demographics, Main Cohort IA Set, Trial 417-201-00007

Characteristics	Sibeprenlimab N=152	Placebo N=168	Total N=320
Sex, n (%)			
Female	52 (34.2)	68 (40.5)	120 (37.5)
Male	100 (65.8)	100 (59.5)	200 (62.5)
Age, years			
Mean (SD)	42.7 (12.3)	42.8 (11.6)	42.8 (11.9)
Median	42.0	43.0	42.0
IQR	34.0, 51.0	35.0, 51.0	34.0, 51.0
Min, max	18.0, 75.0	18.0, 83.0	18.0, 83.0
Age group, n (%)			
≤65 years	146 (96.1)	164 (97.6)	310 (96.9)
>65 years	6 (3.9)	4 (2.4)	10 (3.1)
Race, n (%)			
Asian	94 (61.8)	95 (56.5)	189 (59.1)
Black or African American	0	1 (0.6)	1 (0.3)
White	55 (36.2)	66 (39.3)	121 (37.8)
Other	3 (2.0)	6 (3.6)	9 (2.8)
Min, max	18.4, 58.7	16.6, 40.7	16.6, 58.7
Ethnicity, n (%)			
Hispanic or Latino	16 (10.5)	22 (13.1)	38 (11.9)
Not Hispanic or Latino	132 (86.8)	141 (83.9)	273 (85.3)
Other	4 (2.6)	5 (3.0)	9 (2.8)
Geographic region, n (%)			
East Asia	43 (28.3)	48 (28.6)	91 (28.4)
Europe	30 (19.7)	36 (21.4)	66 (20.6)
North America	22 (14.5)	21 (12.5)	43 (13.4)
South America	11 (7.2)	15 (8.9)	26 (8.1)
South/South-East Asia	46 (30.3)	48 (28.6)	94 (29.4)
Is in United States, n (%)			
United States	16 (10.5)	17 (10.1)	33 (10.3)
Non-United States	136 (89.5)	151 (89.9)	287 (87.7)

Source: Statistical reviewer's analysis; adsl.xpt, adbase.xpt
Abbreviations: IA, interim analysis; IQR, interquartile range; max, maximum; min, minimum; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation; uPCR, urine protein-to-creatinine ratio

Table 12. Baseline Clinical Characteristics, Main Cohort IA Set, Trial 417-201-00007

Characteristics	Sibeprenlimab SC 400 mg N=152	Placebo N=168	Total N=320
Baseline BMI (kg/m^2)			
Mean (SD)	28.0 (6.1)	26.7 (4.9)	27.3 (5.5)
Median	26.7	26.7	26.7
Min, max	18.4, 58.7	16.6, 40.7	16.6, 58.7
Baseline systolic blood pressure (mmHg)			
Mean (SD)	125 (11.3)	123 (11.4)	124 (11.4)
Median	125	123	124
Min, max	90, 145	97, 160	90, 160

Characteristics	Sibeprenlimab SC 400 mg N=152	Placebo N=168	Total N=320
Baseline diastolic blood pressure (mmHg)			
Mean (SD)	78 (8.1)	79 (8.0)	78 (8.0)
Median	79	79	79
Min, max	57, 95	55, 104	55, 104
Screening/baseline uPCR-24h (g/g)			
Mean (SD)	1.6 (1.1)	1.5 (0.8)	1.5 (1.0)
GM (GSD)	1.3 (1.7)	1.3 (1.6)	1.3 (1.7)
Median	1.2	1.3	1.2
Min, max	0.5, 6.7	0.5, 5.5	0.5, 6.7
Baseline uPCR-24h (g/g) groups, n (%)			
<1.5 g/g	100 (65.8)	102 (60.7)	202 (63.1)
≥1.5 g/g	52 (34.2)	66 (39.3)	118 (36.9)
Baseline uPCR-24h (g/g) groups, n (%)			
<2 g/g	123 (80.9)	137 (81.5)	260 (81.3)
≥2 g/g	29 (19.1)	31 (18.5)	60 (18.8)
Screening/baseline eGFR (mL/min/1.73 m^2)			
Mean (SD)	63.5 (24.4)	63.4 (25.3)	63.4 (24.9)
Median	57.5	60.0	59.0
Min, max	25.0, 131.0	27.0, 129.0	25.0, 131.0
Baseline eGFR (mL/min/1.73 m^2) groups, n (%)			
≤45 mL/min/1.73 m^2	40 (26.3)	47 (28.0)	87 (27.2)
>45 to ≤60 mL/min/1.73 m^2	41 (27.0)	44 (26.2)	85(26.6)
>60 mL/min/1.73 m^2	71 (46.7)	77 (45.8)	148 (46.3)
Baseline urine protein (g/24hr), GM			
Mean (SD)	2.2 (1.5)	2.0 (1.2)	2.1 (1.3)
GM (SD)	1.8 (2.2)	1.8 (1.7)	1.8 (1.9)
Median	1.8	1.7	1.7
Min, max	0.0, 8.7	0.4, 8.3	0.0, 8.7
Baseline urine protein (g/24hr) groups, n (%)			
≤2 g/24hr	88 (57.9)	103 (61.3)	191 (59.7)
>2 g/24hr	64 (42.1)	65 (38.7)	129 (40.3)
Baseline uACR-24h (mg/g)			
Mean (SD)	1145 (824.0)	1106 (658.8)	1124 (740.9)
GM (GSD)	953 (1.8)	959 (1.7)	956 (1.7)
Median	861	903	888
Min, max	271, 5424	288, 4184	271, 5424
Baseline HBA1c			
Mean (SD)	5.5 (0.52)	5.4 (0.50)	5.5 (0.51)
Median	5.4	5.4	5.4
Min, max	4, 7.3	4.5, 7.8	4, 7.8
Baseline dipstick hematuria, n (%)			
Negative	33 (21.7)	49 (29.2)	82 (25.6)
Positive	119 (78.3)	119 (70.8)	238 (74.4)
Duration of initial biopsy to randomization (years)			
Mean (SD)	2.7 (3.5)	3.5 (4.6)	3.1 (4.1)
Median	1.3	1.9	1.5
Min, max	0.1, 23.7	0.0, 34.0	0.0, 34.0

Source: Statistical reviewer's analysis; adsl.xpt, adbase.xpt
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; GM, geometric mean; GSD, geometric standard deviation; HbA1c, hemoglobin A1c; IA, interim analysis; IQR, interquartile range; max, maximum; min, minimum.; N, number of subjects; n, number of subjects in the specified category; SD, standard deviation; uACR, urine albumin/creatinine ratio; uPCR, urine protein-to-creatinine ratio

Table 13. Baseline Medication Use and Medical History - Main Cohort-IAS, Trial 417-201-00007

Characteristics	Sibeprenlimab SC 400 mg N=152	Placebo N=168	Total N=320
Prior background regimen ACEI, n (%)			
Yes	48 (31.6)	67 (39.9)	115 (35.9)
No	104 (68.4)	101 (60.1)	205 (64.1)
Prior background regimen ARB, n (%)			
Yes	106 (69.7)	103 (61.3)	209 (65.3)
No	46 (30.3)	65 (38.7)	111 (34.7)
Prior background regimen SGLT2i, n (%)			
Yes	56 (36.8)	72 (42.9)	128 (40.0)
No	96 (63.2)	96 (57.1)	192 (60.0)
Prior use of immunosuppressive drugs, n (%)			
Yes	6 (3.9)	6 (3.6)	12 (3.8)
No	146 (96.1)	162 (96.4)	308 (96.3)
Relevant medical history, n (%)			
Hypertension	106 (70)	108 (64)	214 (67)
Type 2 diabetes mellitus	13 (9)	10 (6)	23 (7)

Source: Statistical Reviewer adsl.xpt, adbase.xpt. adlb.xpt admh.xpt
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; IAS, interim analysis set; N, number of subjects in treatment arm; n, number of subjects with given characteristic; SGLT2i, sodium-glucose cotransporter 2 inhibitor

6.2.1.6.2. Subject Disposition, Trial 417-201-00007

The disposition for all screened subjects is shown in Table 14. The study was fully enrolled at the date of data cut-off. As shown in Table 14, 901 subjects were screened, and of these, 530 subjects were randomized into the study; 510 subjects were randomized to the main cohort and 20 subjects were randomized to the exploratory cohort. Among the 320 randomized subjects included in the IAS, 4.6% of subjects in the sibeprenlimab arm and 4.8% of subjects in the placebo arm discontinued the treatment prior to 9 months. The proportion of subjects who discontinued the study prior to 9 months was similar in both groups; 3.9% in the sibeprenlimab arm and 3.6% in the placebo arm. As of the data cutoff, 7.7% of subjects in the IAS randomized to placebo discontinued treatment compared to 5.9% of subjects randomized to sibeprenlimab, and 4.8% of subjects in the placebo group discontinued from the study compared to 4.6% in the sibeprenlimab group.

Table 14. Subject Disposition, Main Cohort, IAS, Trial 417-201-00007

Disposition Category	Sibeprenlimab n (%)	Placebo n (%)	Total n (%)
No. subjects screened			901
No. screening failures			371
No. subjects randomized			510
No. subjects in IAS			320
Subjects randomized, IAS	152 (100)	168 (100)	320 (100)
IAFAS#1	152 (100)	168 (100)	320 (100)
Per protocol population	92 (60.5)	101 (60.1)	193 (60.3)
Safety population	152 (100)	168 (100)	320 (100)

Disposition Category	Sibeprenlimab n (%)	Placebo n (%)	Total n (%)
Discontinued treatment (before data cutoff)	9 (5.9)	13 (7.7)	22 (6.3)
Adverse event	1 (0.7)	1 (0.6)	2 (0.6)
Progressive disease	0 (0.0)	2 (1.2)	2 (0.6)
Required prohibited medication	0 (0.0)	3 (1.8)	3 (0.9)
Protocol-specific withdrawal criterion met	1 (0.7)	0 (0.0)	1 (0.3)
Subject decision	5 (3.3)	4 (2.4)	9 (2.8)
Physician decision	1 (0.7)	2 (1.2)	3 (0.9)
Other	1 (0.7)	1 (0.6)	2 (0.6)
Discontinued treatment prior to 9 months	7 (4.6)	8 (4.8)	15 (4.7)
Discontinued study (before data cutoff)	7 (4.6)	8 (4.8)	15 (4.7)
Withdrawal by subject	6 (3.9)	6 (3.6)	12 (3.8)
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.7)	2 (1.2)	3 (0.9)
Discontinued study prior to 9 months	6 (3.9)	6 (3.6)	12 (3.8)

Source: Clinical Study Report Table 10.1.1-1, Table 10.1.1-2, and Table CT-2.2. Verified by Statistical Reviewer.
Percentage (%) is calculated based on the number of subjects from the Interim Analysis Set in Main Cohort.
Abbreviations: IAS, interim analysis set; IAFAS, Interim Analysis Full Analysis Set; mITT, modified intent-to-treat; n, number of subjects in specified category; No., number of

Of the randomized subjects in the IAS, the proportion of subjects with available uPCR-24h data at Month 9 (Week 40) was similar in the placebo group (95.8%) and the sibeprenlimab group (95.4%) (Table 15). The majority of subjects with missing Week 40 uPCR-24h data had discontinued treatment early.

Table 15. Subjects With uPCR Data at Week 40, IAS

Disposition Category	Sibeprenlimab N=152 n (%)	Placebo N=168 n (%)
Valid 40-week value	145 (95.4)	161 (95.8)
Received 40 weeks of treatment	144 (94.7)	158 (94.0)
Discontinued treatment early	1 (0.7)	3 (1.8)
Missing 40-week value	7 (4.6)	7 (4.2)
Received 40 weeks of treatment	1 (0.7)	2 (1.2)
Discontinued treatment early	6 (4.0)	5 (3.0)

Source: Statistical reviewer's analysis
Abbreviation: IAS, interim analysis set; N, number of subjects; n, number of subjects in specified category; uPCR, urine protein-to-creatinine ratio

6.2.1.6.3. Primary Efficacy Endpoint, IAS, Trial 417-201-00007

The primary efficacy endpoint at the interim analysis was the ratio of uPCR-24h at 9 months compared with baseline. At Month 9 (Week 40), subjects who were randomized to sibeprenlimab achieved a 49.7% (95% CI [%]: 43.4, 55.3) reduction in uPCR-24h compared with a 2.2% increase (95% CI [%]: −14.0, 8.4) in subjects who were randomized to placebo. This corresponded to a statistically significant reduction at the prespecified significance level of 0.035 (2-sided) in uPCR-24h of 50.8% (96.5% CI [%]: 42.4, 57.9, $p<0.0001$) in the sibeprenlimab group compared with the placebo group (Table 16). The primary analysis was conducted using IA FAS #1 data set, which consisted of subjects in the IAS who had a baseline uPCR measured from at least one 24-hour urine sample and was identical to the IAS.

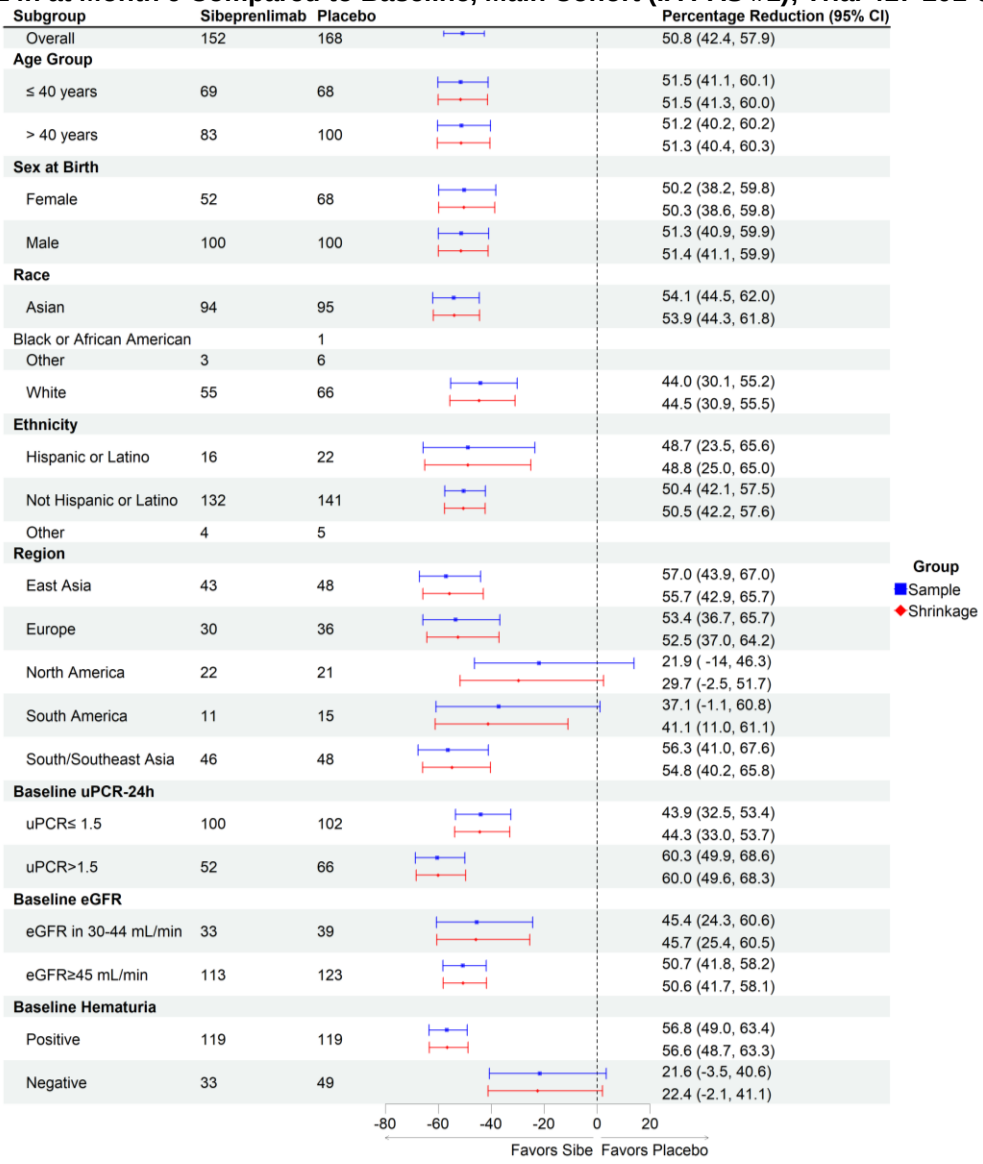
Table 16. Analysis of 24-Hour uPCR at Month 9 Compared to Baseline: ANCOVA, Main Cohort (IA FAS #1), Trial 417-201-00007

			Treatment Effect vs. Placebo		
Treatment	Ratio of GM (95% CI)	Corresponding % Reduction[a] (95% CI) (%)	Ratio of GM Ratio (96.5% CI[c])	Corresponding % Reduction[b] (96.5% CI[c]) (%)	p-Value
Sibeprenlimab (N=152)	0.50 (0.45, 0.57)	49.7 (43.4, 55.3)	0.49 (0.42, 0.58)	50.8 (42.4, 57.9)	<0.0001
Placebo (N=168)	1.02 (0.92, 1.14)	−2.2 (−14.0, 8.4)			

Source: Statistical reviewer's analysis.
uPCR-24h at Month 9 compared to baseline was defined as ($uPCR\text{-}24h_{9months}/uPCR\text{-}24h_{Baseline}$).
In this analysis, both ICE#1 and ICE #2 were handled using the treatment strategy. Missing uPCR values after ICE#1 and ICE #2 in the sibeprenlimab group were imputed using a placebo-based approach, while all other missing uPCR values were imputed under the assumption of MAR. Estimates from each imputed data set (100) were combined using Rubin's rule.
[a]Calculated as (1 - GM of uPCR-24h ratio estimated from ANCOVA model)*100%.
[b]Calculated as (1 - ratio of GM of uPCR-24h ratio for sibeprenlimab 400 mg over placebo estimated from ANCOVA model)*100%.
[c]Corresponding to the two-sided significance level of 0.035 for the IA.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; GM, geometric mean; IA, interim analysis; IA FAS, Interim Analysis Full Analysis Set; ICE, intercurrent event; MAR, missing at random; N, number of subjects; uPCR, urine protein-to-creatinine ratio; uPCR-24h, urine protein-to-creatinine ratio at 24-hour urine collection

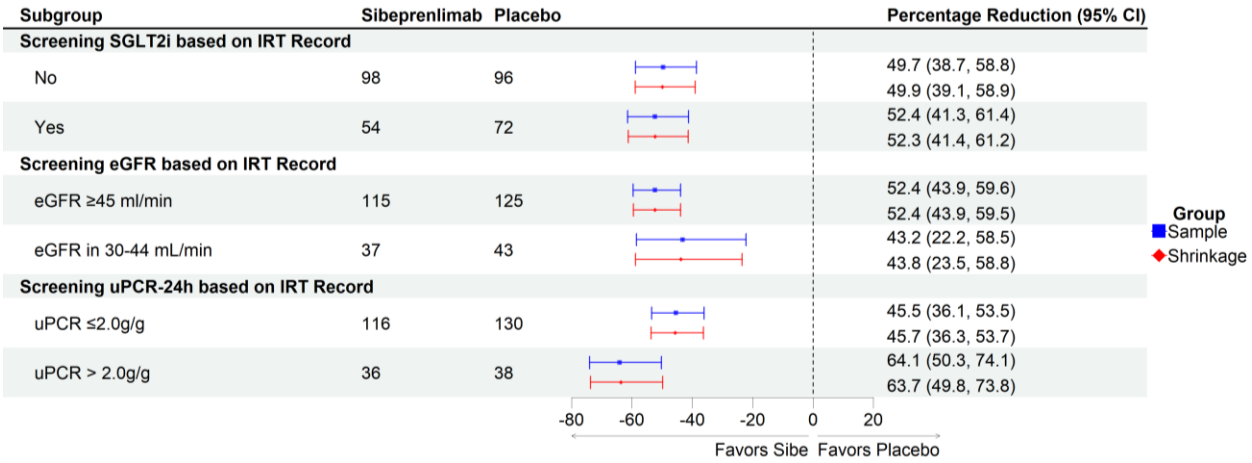
Results were generally consistent across demographic subgroups (age, sex, race, ethnicity, region) and baseline characteristics except for the North America regional subgroup and the negative baseline hematuria subgroup (Figure 8), which had numerically smaller point estimates and wider confidence intervals that crossed the reference line at zero, indicating a degree of uncertainty in the treatment effect. These findings could be due to the smaller sample sizes in these subgroups or they could be due to chance. However, it is possible that the subgroup without hematuria at baseline had less active glomerular inflammation and therefore was less responsive to sibeprenlimab given its mechanism of action. Similar subgroup analyses should be conducted when the ongoing study is completed. The treatment effect was otherwise consistent across subgroups defined by baseline disease and medical history (Figure 10), baseline proteinuria and eGFR levels (Figure 9), and stratification factors, including SGLT2i use (Figure 9).

Figure 8. Forest Plot for Demographic and Baseline Characteristics Subgroup Analysis of uPCR-24h at Month 9 Compared to Baseline, Main Cohort (IA FAS #1), Trial 417-201-00007



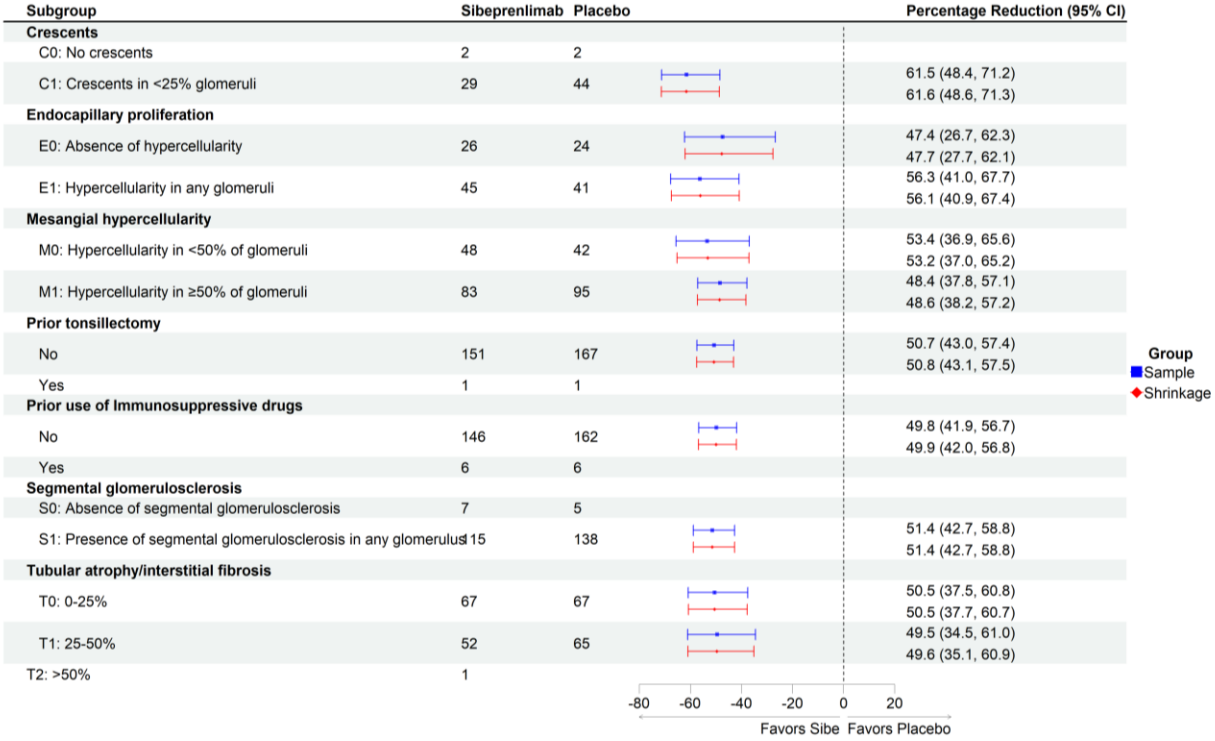
Source: Statistical reviewer's analysis.
The subgroup analyses used the same ANCOVA analysis as was used for the primary analysis. The imputed datasets created for the primary endpoint were utilized for subgroup analyses; data observed after treatment discontinuation and initiation of rescue therapy were used in the analyses (treatment policy strategy).
There are typically some random highs and random lows in sample estimates of subgroup treatment effects due to small sample sizes and large variability for some subgroups. Therefore, we also derived shrinkage estimates (presented in red) of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. This approach leads to improved precision and lower variability, shown with narrower confidence intervals, most notably in subgroups with a smaller sample size. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in the underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. A set of fairly noninfluential priors {$\mu \sim n$ (0, 100), $\tau 2 \sim \text{cauchy}$ (0, 2.5, lower =$1^{e\text{-}12}$)] was used to derive shrinkage estimates for all subgroups.
The dot indicates the percentage reduction calculated as (−1)*(1- GM of uPCR ratio estimated from ANCOVA model)*100% and the bar indicates the 95% CI.
Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; IA, interim analysis; FAS, full analysis set; Sibe, sibeprenlimab; GM, geometric mean; uPCR, urine protein-to-creatinine ratio; uPCR24h, urine protein-to-creatinine ratio at 24-hour urine collection

Figure 9. Forest Plot for Stratification Factors Subgroup Analysis of uPCR-24h at Month 9 Compared to Baseline, Main Cohort (IA FAS #1), Trial 417-201-00007



Source: Statistical reviewer's analysis
Abbreviations: eGFR, estimated glomerular filtration rate; IA FAS, interim analysis full analysis set; SGLT2i,SGLT-2, sodium-glucose cotransporter-2; uPCR, urine protein-to-creatinine ratio; uPCR-24h, urine protein-to-creatinine ratio based on 24-hour urine collection

Figure 10. Forest Plot for Baseline Disease and Medical History Subgroup Analysis of uPCR-24h at Month 9 Compared to Baseline, Main Cohort (IA FAS #1), Trial 417-201-00007



Source: Statistical reviewer's analysis.
Abbreviation: CI, confidence interval; GM, geometric mean; IA FAS, Interim Analysis Full Analysis Set; Sibe, sibeprenlimab; uPCR, urine protein-to-creatinine ratio; uPCR-24h, urine protein-to-creatinine ratio based on 24- hour urine collection

Overall, sibeprenlimab demonstrated a statistically significant reduction in uPCR-24h at 9 months compared with placebo and results appeared to be consistent across evaluated subgroups.

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7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Sibeprenlimab was well tolerated in studies of durations up to 6 months in cynomolgus monkeys who were administered sibeprenlimab by the SC or IV routes at doses up to 100 mg/kg given once every 2 weeks. No significant nonclinical safety issues were identified in those studies, including risk of infection. The highest doses tested provide at least a 10-fold clinical exposure margin at the maximum recommended human dose (MRHD).

In an enhanced pre- and postnatal development study designed to assess the safety of sibeprenlimab during pregnancy, the single dose tested (101 mg/kg/day) in cynomolgus monkeys did not identify any reproductive hazard, including infection. The dose provides a 10-fold clinical exposure margin to the MRHD. A summary of the developmental and reproductive toxicology studies that support product labeling is included in Section 8.4 of this review.

Genetic toxicology and carcinogenicity studies were not conducted as they were not deemed to be scientifically justified for assessment of the risks for sibeprenlimab.

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

Sibeprenlimab is a humanized IgG2 mAb that selectively inhibits APRIL. Potential safety concerns include infections and increased immunosuppressive effects when initiating sibeprenlimab either before or after immunosuppressive therapy based on its mechanism of action as an APRIL inhibitor; and injection site reactions due to its subcutaneous administration.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

There is no postmarking experience with sibeprenlimab as the drug has not yet been marketed in any country.

7.4. FDA Approach to the Safety Review

The safety review of sibeprenlimab 400 mg once every 4 weeks focused mainly on the data from the pivotal phase 3 trial, Trial 417-201-00007, collected up to the data cutoff date of September 4, 2024. Safety analyses for Trial 417-201-00007 used the overall safety set (510 total subjects; 259 sibeprenlimab, 251 placebo) from the main cohort. The overall safety set included all randomized subjects who received at least one dose or part of a dose of the investigational medicinal product (IMP) and was analyzed according to the treatment received. Safety analyses for the subpopulation of the study subjects who completed the 9-month (Week 40) uPCR-24h evaluation by the data cutoff date of September 4, 2024 (IA safety set: 320 total subjects; 152 sibeprenlimab, 168 placebo) were also conducted and compared with the safety results from the overall safety set. An additional 20 subjects were included in an exploratory cohort (subjects with IgAN who had an eGFR of 20 to 29 mL/min/1.73 m^2 [Stage 4 CKD]). Safety analyses for the exploratory cohort were also reviewed and compared with the safety results from the overall safety set of the main cohort. The safety review also included analyses from the phase 2 trial, Trial VIS649-201 (see Section 17). Due to differences in the design of the double-blind trials (Trial 417-201-00007 and Trial VIS649-201), including the different sibeprenlimab doses, routes of administration (IV or SC), and duration of treatment, the double-blind trial data are presented for each trial separately.

FDA's safety review included an evaluation of data quality and integrity, as well as adverse events (AEs) and laboratory findings. There were no concerns regarding data quality, conduct of the studies with respect to assessment of safety, or the Applicant's characterization of AEs.

All AE analyses were based on treatment-emergent adverse events (TEAEs), defined as AEs starting after the first IMP dose or for AEs present before the first IMP dose, those that increased in severity after the first IMP dose. AEs were primarily analyzed by Medical Dictionary for Regulatory Activities (version 27.0) preferred terms (PTs, same as the Applicant's analyses) and by pooling similar PTs using OCMQs (version 2.1). AEs were presented as the number and percentage of subjects with the AE and as the absolute risk difference (RD), which was calculated as the difference in the percentage of subjects with AEs between sibeprenlimab and

placebo groups: negative RD values indicate a lower risk in the sibeprenlimab group and positive RD values indicate a higher risk.

To further evaluate the potential risks of infections, injection site reactions, and hypersensitivity reactions (i.e., adverse events of special interest [AESIs]), the Applicant also conducted analyses using the pooled safety data from Trial 417-201-00007 (the IA safety set) and all doses evaluated in Trial VIS649-201 (155 total subjects: 117 sibeprenlimab, 38 placebo) in addition to the individual safety data from these trials. This double-blind pool included subjects who received any dose of treatment and combined different sibeprenlimab doses and routes of administration. To account for some of the study differences, the Applicant stratified by study and limited the comparison to the first 9 months of the double-blind period for both studies. These analyses were verified by the FDA review team and are presented in Section 7.6.1.6. Given differences in the design of the studies included in these pooled datasets, these datasets were only used by the FDA review team to explore the potential risks of infections and hypersensitivity reactions. In addition to the pooled analyses, the FDA review team also evaluated these potential risks as part of their review of the individual safety data for Trials 417-201-00007 and VIS649-201, as described above. These data are presented in Sections 7.6.1.5 and 17.2.5

The statistical software R was used for safety analyses.

7.5. Adequacy of the Clinical Safety Database

Sibeprenlimab was administered to approximately 800 subjects in six completed or ongoing clinical trials (Table 3). In Trial 417-201-00007, median duration of exposure was approximately 44 weeks and 48 weeks for the sibeprenlimab and placebo groups, respectively (Table 23). There were over 250 subjects who had exposure to sibeprenlimab longer than 6 months in Trial 417-201-00007, ninety-nine of whom had exposure to sibeprenlimab of at least 52 weeks.

Table 23. Duration of Exposure, Main Cohort, Overall Safety Set[a], Trial 417-201-00007

Parameter	Sibeprenlimab N=259	Placebo N=251
Duration of treatment, weeks		
Mean (SD)	47.3 (17.9)	50.8 (19)
Median (Q1, Q3)	44 (32.7, 60.1)	48 (34.8, 61.5)
Min, max	4, 96.1	8, 104.9
Total exposure (person years)	235	244
Subjects treated, by duration, n (%)		
<12 weeks	3 (1.2)	1 (0.4)
≥12 weeks	256 (98.8)	250 (99.6)
≥24 weeks	252 (97.3)	246 (98.0)
≥40 weeks	146 (56.4)	162 (64.5)
≥52 weeks	99 (38.2)	115 (45.8)
≥72 weeks	30 (11.6)	37 (14.7)
≥100 weeks	0	4 (1.6)

Source: adex.xpt and adsl.xpt; Software: R
[a]The overall safety set includes all randomized subjects who received at least 1 dose or part of a dose of the IMP and analyzed according to the treatment received.
Abbreviations: IMP, investigational medicinal product; max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

In Trial VIS649-201, the median duration of exposure was approximately 359 days in the sibeprenlimab group; exposure was balanced between the sibeprenlimab and placebo groups. See Section 17, **Error! Reference source not found.** for the exposure table for the Trial VIS649-201. In combination with Trial VIS649-201, the safety exposure to sibeprenlimab in Trial 417-201-00007 is considered adequate both in terms of the number of subjects exposed to the trial drug and the duration of exposure to support the safety evaluation in subjects with IgAN for the purposes of approval.

7.6. Safety Results

7.6.1. Safety Results, Trial 417-201-00007

Safety analyses conducted in the exploratory cohort and in the 9-month IA safety set of Trial 417-201-00007 did not reveal additional safety concerns and are not presented in this review.

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial 417-201-00007

The overall incidence of TEAEs was lower in the sibeprenlimab group compared to the placebo group in Trial 417-201-00007 (Table 24). Most adverse events were mild or moderate in severity. There were no important imbalances in the incidence of treatment-emergent serious adverse events (SAEs), SAEs requiring hospitalization, or TEAEs leading to study drug discontinuation between treatment groups in Trial 417-201-00007.

Table 24. Overview of Treatment-Emergent Adverse Events[a], Main Cohort, Overall Safety Set[b], Trial 417-201-00007

Event Category	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[c]
SAE	9 (3.5)	11 (4.4)	−0.9 (−4.6, 2.6)
SAEs with fatal outcome	0	0	0.0 (−1.5, 1.5)
Life-threatening SAEs	0	2 (0.8)	−0.8 (−2.9, 0.7)
SAEs requiring hospitalization	7 (2.7)	7 (2.8)	−0.1 (−3.3, 3.0)
SAEs resulting in substantial disruption of normal life functions	0	2 (0.8)	−0.8 (−2.9, 0.7)
Other	2 (0.8)	4 (1.6)	−0.8 (−3.3, 1.4)
AE leading to permanent discontinuation of study drug	1 (0.4)	4 (1.6)	−1.2 (−3.7, 0.7)
AE leading to dose modification of study drug	17 (6.6)	14 (5.6)	1.0 (−3.3, 5.3)
AE leading to interruption of study drug	17 (6.6)	14 (5.6)	1.0 (−3.3, 5.3)
AE leading to reduction of study drug	0	0	0.0 (−1.5, 1.5)
AE leading to dose delay of study drug	0	0	0.0 (−1.5, 1.5)

Event Category	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[c]
Any AE[d]	192 (74.1)	206 (82.1)	−7.9 (−15.1, −0.8)[e]
Severe and worse	4 (1.5)	9 (3.6)	−2.0 (−5.3, 0.8)
Moderate	63 (24.3)	54 (21.5)	2.8 (−4.5, 10.1)
Mild	125 (48.3)	143 (57.0)	−8.7 (−17.3, −0.0)[e]

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
[d]Severity as assessed by the investigator.
[e]95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Trial 417-201-00007

No deaths were observed in Trial 417-201-00007 by the cutoff date.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial 417-201-00007

The results of analyses of SAEs based on individual PTs (Table 25) and narrow OCMQs (see Section 17, **Error! Reference source not found.**) were consistent for the sibeprenlimab versus placebo groups in Trial 417-201-00007, and none of the SAEs had a RD >1%.

The number of subjects with SAEs was low in both treatment groups. With the exception of coronavirus disease-2019 (COVID-19, which was reported in 2 of 259 subjects [0.8%] in the sibeprenlimab group) and nephropathy (which was reported in 2 of 251 subjects [0.8%] in the placebo group), no SAE was reported in more than one subject and there was no imbalance in the incidence of SAEs between treatment groups.

The narratives for the SAEs of pharyngeal abscess, perianal/anal abscess, COVID-19, and gastroenteritis are provided in Section 7.6.1.6.1. It is possible that sibeprenlimab played a role in these events by increasing the subject's susceptibility to infections.

Table 25. Subjects With Serious Treatment-Emergent Adverse Events[a] by System Organ Class and Preferred Term, Showing Preferred Term With Risk Difference >0%, Main Cohort, Overall Safety Set[b], Trial 417-201-00007

System Organ Class Preferred Term[c]	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[d]
Any SAE	9 (3.5)	11 (4.4)	−0.9 (−4.6, 2.6)
Cardiac disorders (SOC)	1 (0.4)	0	0.4 (−1.1, 2.2)
Atrioventricular block complete	1 (0.4)	0	0.4 (−1.1, 2.2)
Gastrointestinal disorders (SOC)	1 (0.4)	0	0.4 (−1.1, 2.2)
Diarrhoea	1 (0.4)	0	0.4 (−1.1, 2.2)

System Organ Class Preferred Term[c]	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[d]
Infections and infestations (SOC)	3 (1.2)	3 (1.2)	0.0 (−2.4, 2.3)
COVID-19	2 (0.8)	0	0.8 (−0.7, 2.8)
Anal abscess	1 (0.4)	0	0.4 (−1.1, 2.2)
Gastroenteritis	1 (0.4)	0	0.4 (−1.1, 2.2)
Pharyngeal abscess	1 (0.4)	0	0.4 (−1.1, 2.2)
Injury, poisoning and procedural complications (SOC)	1 (0.4)	0	0.4 (−1.1, 2.2)
Compression fracture	1 (0.4)	0	0.4 (−1.1, 2.2)
Musculoskeletal and connective tissue disorders (SOC)	1 (0.4)	0	0.4 (−1.1, 2.2)
Osteoarthritis	1 (0.4)	0	0.4 (−1.1, 2.2)
Spinal stenosis	1 (0.4)	0	0.4 (−1.1, 2.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.4)	2 (0.8)	−0.4 (−2.5, 1.4)
Renal cell carcinoma	1 (0.4)	0	0.4 (−1.1, 2.2)
Nervous system disorders (SOC)	1 (0.4)	0	0.4 (−1.1, 2.2)
Transient ischaemic attack	1 (0.4)	0	0.4 (−1.1, 2.2)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. 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. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Coded as MedDRA preferred terms.
[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease-2019; IMP, investigational medical product; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Trial 417-201-00007

There was no imbalance in the incidence of TEAEs leading to study drug discontinuation between treatment groups in Trial 417-201-00007 (Table 26). In the sibeprenlimab group, the only TEAE leading to treatment discontinuation was chromaturia. The narrative is provided below. The investigator assessed the event as moderate in severity and related to study drug. Based on the narrative, it is unclear whether sibeprenlimab played a role in the event.

Subject (b) (6) a 30-year-old White male with biopsy-proven, primary IgAN, experienced a nonserious TEAE of chromaturia on Day 82 that led to permanent study drug discontinuation. The subject received the last dose of sibeprenlimab on Day 57. No concomitant medications were taken within 14 days before the onset of the event. Amoxicillin was administered 3 days after the start of the event. The event resolved on Day 98. No labs were reported around the time of the event. Baseline laboratory values were as follows: serum creatinine 1.14 mg/dL, eGFR 89 mL/min/1.73 m^2, and urinalysis with 15 to 39 erythrocytes/HPF and 0 to 3 leukocytes/HPF. On Day 114, clinical laboratory test results showed stable serum creatinine (1 mg/dL) and eGFR (104 mL/min/1.73 m^2), and urinalysis with 9 to14 erythrocytes/HPF (normal range: 0 to 5/HPF), and no leukocytes (0 to 3/HPF).

The subject had experienced a mild muscle strain on Day 17. The event was reported as ongoing at the time of this report and no changes were made to the study treatment.

Table 26. Subjects With Adverse Events[a] Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Main Cohort, Overall Safety Set[b], Trial 417-201-00007

System Organ Class Preferred Term[c]	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[d]
Any AE leading to discontinuation	1 (0.4)	4 (1.6)	−1.2 (−3.7, 0.7)
Renal and urinary disorders (SOC)	1 (0.4)	3 (1.2)	−0.8 (−3.1, 1.1)
Chromaturia	1 (0.4)	0	0.4 (−1.1, 2.2)
Renal impairment	0	1 (0.4)	−0.4 (−2.2, 1.1)
Nephropathy	0	2 (0.8)	−0.8 (−2.9, 0.7)
Skin and subcutaneous tissue disorders (SOC)	0	1 (0.4)	−0.4 (-2.2, 1.1)
Rash	0	1 (0.4)	−0.4 (−2.2, 1.1)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Coded as MedDRA preferred terms.
[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Trial 417-201-00007

The results of analyses of TEAEs based on individual PTs (Table 27) and narrow OCMQs (Table 28) were consistent for the sibeprenlimab versus placebo groups in Trial 417-201-00007.

The most common TEAEs in the sibeprenlimab group (affecting ≥10% of subjects) were upper respiratory tract infections, nasopharyngitis, injection site erythema, and injection site pain (Table 27). The TEAEs by narrow OCMQs with a RD ≥1.5% for sibeprenlimab compared to placebo were bacterial infection, nasopharyngitis, and erythema (Table 28). The point estimate of the RD for all the TEAEs related to infections and injection site reactions was small and associated with wide confidence intervals that included zero.

Table 27. Subjects With Common Treatment-Emergent Adverse Events[a] Occurring at ≥3.5% Frequency With Risk Difference >0%, Main Cohort, Overall Safety Set[b], Trial 417-201-00007

Preferred Term[c]	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[d]
Any AE	192 (74.1)	206 (82.1)	−7.9 (−15.1, −0.8)[e]
COVID-19	25 (9.7)	17 (6.8)	2.9 (−2.0, 7.8)
Nasopharyngitis	32 (12.4)	25 (10.0)	2.4 (−3.2, 8.0)
Abdominal pain	6 (2.3)	0	2.3 (0.8, 5.0)[e]
Influenza	21 (8.1)	16 (6.4)	1.7 (−2.9, 6.4)
Alanine aminotransferase increased	4 (1.5)	0	1.5 (0.0, 3.9)[e]
Tachycardia	4 (1.5)	0	1.5 (0.0, 3.9)[e]
Injection site induration	12 (4.6)	8 (3.2)	1.4 (−2.1, 5.1)
Pyrexia	14 (5.4)	10 (4.0)	1.4 (−2.4, 5.4)
Injection site erythema	34 (13.1)	30 (12.0)	1.2 (−4.7, 7.0)
Injection site swelling	16 (6.2)	13 (5.2)	1.0 (−-3.2, 5.2)

Preferred Term[c]	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[d]
Back pain	17 (6.6)	14 (5.6)	1.0 (−3.3, 5.3)
Injection site pain	26 (10.0)	23 (9.2)	0.9 (−4.4, 6.1)
Upper respiratory tract infection	38 (14.7)	35 (13.9)	0.7 (−5.4, 6.9)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Coded as MedDRA preferred terms.
[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
[e]95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease 2019; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 28. Subjects With Treatment-Emergent Adverse Events[a] by System Organ Class and OCMQ (Narrow), Showing OCMQ With Risk Difference ≥1.5%, Main Cohort, Overall Safety Set[b], Trial 417-201-00007

System Organ Class OCMQ (Narrow)	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[c]
Infections and infestations (SOC)			
Bacterial infection	29 (11.2)	23 (9.2)	2.0 (−3.3, 7.4)
Nasopharyngitis	73 (28.2)	67 (26.7)	1.5 (−6.3, 9.2)
Skin and subcutaneous tissue disorders (SOC)			
Erythema	37 (14.3)	32 (12.7)	1.5 (−4.5, 7.5)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, Office of New Drugs Custom Medical Query; IMP, investigational medical product; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

7.6.1.6. Adverse Events of Special Interest

The Applicant identified AESIs for sibeprenlimab based on its mechanism of action as an APRIL inhibitor and on the method of administration (i.e., subcutaneous injection). These AESIs included infections, injection site reactions, and hypersensitivity. As stated in Section 7.4 FDA Approach to the Safety Review, the Applicant used the pooled safety data from the first 9 months of the double-blind treatment periods of Trial 417-201-00007 (of the IA safety set) and Trial VIS649-201 for subjects who received any amount of treatment (i.e., double-blind pool of 475 subjects) to evaluate these AESIs. The FDA review team also used these pooled datasets to evaluate the potential risks of infections and hypersensitivity reactions with sibeprenlimab.

7.6.1.6.1. Infections

Given its mechanism of action, sibeprenlimab has the potential to increase a subject's susceptibility to infections. In the main cohort of Trial 417-201-00007 (overall safety set), the

incidence of bacterial infection, nasopharyngitis, and viral infection (OCMQs) was numerically higher in subjects treated with sibeprenlimab compared to those treated with placebo (RD of 2.0, 1.5, and 1.0, respectively; Table 28).The most common infections were upper respiratory tract infections, nasopharyngitis, COVID-19, and influenza (Table 27). The majority of infections were mild or moderate in severity and recovered or resolved without treatment interruption or discontinuation.

The narratives for SAEs of pharyngeal abscess, perianal abscess, COVID-19, and gastroenteritis in Trial 417-201-00007 are described below. It is possible that sibeprenlimab played a role in these events by increasing the subject's susceptibility to infections. The SAE of gastroenteritis occurred in the setting of a COVID-19 infection; gastrointestinal symptoms are common in COVID-19 infections.

Subject (b) (6) a 39-year-old White male with biopsy-proven, primary IgAN, was hospitalized on Day 139 due to odynophagia. Computed tomography (CT) of the neck with biphasic IV contrast showed pharyngeal abscess. No recent or untreated dental infection was reported. Clinical laboratory test results included neutrophils of 13.4 × 10^3/μL (normal range: 2 to 7 × 10^3/μL) and total leukocytes of 16.3 × 10^3/μL (normal range: 4 to 10 × 10^3/μL). On Day 140, surgery was performed to open the pharyngeal abscess. Bacteriological culture revealed the growth of normal mucocutaneous flora. The subject was discharged from the hospital on Day 142. Treatments administered during the hospitalization and following discharge included amoxicillin/clavulanate potassium, methylprednisolone, amoxicillin, clavulanic acid, omeprazole, and prednisone. The event resolved on Day 149. As a result of this event, sibeprenlimab administration was interrupted after the dose on Day 116 and restarted on Day 169. The subject had received sibeprenlimab on Day 416.

On Day 428, the subject went to emergency care due to pain in the perianal region and fever. Upon arrival, the subject's vital signs included blood pressure of 120/93 mm Hg, body temperature of 38.5°C, and pulse of 110 beats per minute. Upon physical examination, a perianal drainage scar was noted on the left posterolateral side. During rectal examination, the left posterolateral side was painful to palpation but there were no fluctuating areas, bulges, internal fistula orifices, or external fistula. The subject was diagnosed with a perianal abscess. As the abscess did not require drainage, the subject was treated with antibiotics and discharged a few hours later. On Day 431, the subject returned to the hospital because he was still experiencing pain in the perianal region and fever. A CT scan was performed and showed an abscess on the posterior wall of the anal canal. Clinical laboratory test results included neutrophils of 10.7 × 10^3/μL (normal range: 2 to 7 × 10^3/μL) and leukocytes of 13.1 × 10^3/μL (normal range: 4 to 10 × 10^3/μL). On Day 432, surgery was performed. The subject also tested positive for influenza A virus. The abscess was treated with amoxicillin/clavulanate potassium and clindamycin. As a result of the event, the dose was not changed. On Day 433, leucocytes were in normal range (5 × 10^3/μL) and the subject was discharged.

Subject (b) (6) a 72-year-old Asian female with biopsy-proven, primary IgAN and relevant medical history of vertigo, developed a fever of 38°C on Day 91. The following day on Day 92, the subject tested positive for SARS-CoV-2 on an antigen test during a visit to the trial site clinic (reported as a nonserious TEAE of COVID-19). Given the potential risk of COVID-19 aggravation, a decision was made to hospitalize the subject the same day. On Day 93, the subject reportedly felt unsteady and had a fall, suffering a laceration to her head that

was sutured. On Day 94, the subject's body temperature was 36°C. The event resolved on Day 96 and the subject was discharged from the hospital on the same day. No oxygen was administered during the hospitalization. She was treated with remdesivir and paracetamol. As a result of this event, the sibeprenlimab administration was interrupted after the dose on Day 64 and restarted on Day 113.

Subject (b) (6) a 30-year-old White female with biopsy-proven, primary IgAN, called the investigator on Day 218 to report that she was experiencing severe nausea, vomiting, and diarrhea since Day 216 (reported as nonserious gastroenteritis, but the investigator assessed the gastroenteritis event as serious [medically significant]) and had not consumed any food or drink since Day 217. Earlier (date not specified), the subject had visited an urgent care facility, where tests for COVID-19 and influenza were negative, and ondansetron (as needed) was prescribed. The subject also mentioned that she had not urinated since early in the morning on Day 218 and had a blood pressure reading of 90/60 mm Hg. Due to the subject's inability to tolerate oral medication, the investigator advised the subject to seek emergency room treatment for IV fluid administration. At the emergency department, a repeat COVID-19 test yielded a positive result. The emergency department physician reported that the subject was tachycardic and hypotensive upon arrival (vital signs not reported), necessitating IV fluid administration. Following treatment, the subject's nausea had improved, and blood pressure had stabilized to approximately 113/80 mm Hg. The subject was also diagnosed with 2 nonserious events of urinary tract infection and acute kidney injury the same day (Day 218). The urinary tract infection resolved within a single day, while the acute kidney injury was reported as ongoing at the time of this report. The subject received supportive care. The subject had received sibeprenlimab on Day 204. As a result of the event, the dose was not changed. The events of gastroenteritis and COVID-19 were resolved on Days 220 and 224, respectively.

In Trial VIS649-201, the incidence of nasopharyngitis (OCMQ) was numerically higher and the incidence of bacterial infection and viral infection (OCMQs) was numerically lower in subjects treated with sibeprenlimab compared to those treated with placebo (TablesTable 29, 30, and 31).

In the double-blind pool, the overall incidence of nasopharyngitis and viral infection (OCMQs) was numerically higher in subjects treated with sibeprenlimab compared to those treated with placebo (Tables 30 and 31**)**, and there were no important imbalances in the incidence of bacterial infection (OCMQ) between treatment groups (Table 29).

Table 29. Adverse Events[a] Assessment of Bacterial Infection OND Custom Medical Query (Narrow) Showing Preferred Term That Occurred in More Than One Subject, 9-Month Interim Analysis Safety Set[b], Trial 417-201-0007, Trial VIS649-201, and Double-Blind Pool

	Trial 417-201-00007		Trial VIS649-201		Double-Blind Pool		
OCMQ (Narrow) Preferred Term[c]	Sibeprenlimab N=152 n (%)	Placebo N=168 n (%)	Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Sibeprenlimab N=269 n (%)	Placebo N=206 n (%)	Risk Difference % (95% CI)[d]
Bacterial infection (OCMQ)	16 (10.5)	13 (7.7)	2 (1.7)	2 (5.3)	18 (6.7)	15 (7.3)	−0.6 (−5.6, 4.0)
Helicobacter infection	2 (1.3)	0	0	0	2 (0.7)	0	0.7 (−1.1, 2.7)
Cellulitis	1 (0.7)	1 (0.6)	0	1 (2.6)	1 (0.4)	2 (1.0)	−0.6 (−3.1, 1.2)
Urinary tract infection	3 (2.0)	3 (1.8)	0	1 (2.6)	3 (1.1)	4 (1.9)	−0.8 (−3.9, 1.6)
Folliculitis	0	2 (1.2)	0	0	0	2 (1.0)	−1.0 (−3.5, 0.4)
Cystitis	0	3 (1.8)	0	0	0	3 (1.5)	−1.5 (−4.2, −0.0)*
Maximum severity							
Death	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Life-threatening	0	1 (0.6)	0	0	0	1 (0.5)	−0.5 (−2.7, 0.9)
Severe	0	1 (0.6)	1 (0.9)	0	1 (0.4)	1 (0.5)	−0.1 (−2.4, 1.6)
Moderate	6 (3.9)	2 (1.2)	0	1 (2.6)	6 (2.2)	3 (1.5)	0.8 (−2.2, 3.5)
Mild	10 (6.6)	9 (5.4)	1 (0.9)	1 (2.6)	11 (4.1)	10 (4.9)	−0.8 (−5.0, 3.0)
Serious	1 (0.7)	2 (1.2)	0	0	1 (0.4)	2 (1.0)	−0.6 (−3.1, 1.2)
Deaths	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Resulting in discontinuation	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Relatedness[e]	3 (2.0)	0	0	0	3 (1.1)	0	1.1 (−0.7, 3.2)

Source: adae.xpt; Software: R

[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0

[b]Treatment duration for Trial 417-201-00007 is 104 weeks, 26 doses administered once every 4 weeks. Trial VIS649-201 duration is 12 months of monthly doses. Only data in the first 9 months of double-blind treatment from both trials are included.

[c]Coded as MedDRA preferred terms.

[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.

[e]Relatedness is determined by the investigator.

[f]95% confidence interval excludes zero.

Table only shows AEs that occurred in more than one subject in any treatment group.

Abbreviations: AE, adverse event; CI, confidence interval; nOCMQ, narrow Office of New Drugs Custom Medical Query; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 30. Adverse Events[a] Assessment of Nasopharyngitis OND Custom Medical Query (Narrow) Showing Preferred Term That Occurred in More Than One Subject, 9-Month Interim Analysis Safety Set[b], Trial 417-201-0007, Trial VIS649-201, and Double-Blind Pool

	Trial 417-201-00007		Trial VIS649-201		Double-Blind Pool		
OCMQ (Narrow) Preferred Term[c]	Sibeprenlimab N=152 n (%)	Placebo N=168 n (%)	Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Sibeprenlimab N=269 n (%)	Placebo N=206 n (%)	Risk Difference % (95% CI)[d]
Nasopharyngitis (OCMQ)	41 (27.0)	34 (20.2)	15 (12.8)	3 (7.9)	56 (20.8)	37 (18.0)	2.9 (−4.5, 9.9)
Nasopharyngitis	16 (10.5)	9 (5.4)	9 (7.7)	2 (5.3)	25 (9.3)	11 (5.3)	4.0 (−0.9, 8.7)
Pharyngitis	3 (2.0)	2 (1.2)	3 (2.6)	0	6 (2.2)	2 (1.0)	1.3 (−1.5, 4.0)
Upper respiratory tract infection	24 (15.8)	20 (11.9)	3 (2.6)	0	27 (10.0)	20 (9.7)	0.3 (−5.4, 5.7)
Rhinitis	2 (1.3)	2 (1.2)	0	0	2 (0.7)	2 (1.0)	−0.2 (−2.8, 1.8)
Rhinitis allergic	0	1 (0.6)	0	1 (2.6)	0	2 (1.0)	−1.0 (−3.5, 0.4)
Maximum severity							
Death	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Life-threatening	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Severe	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Moderate	3 (2.0)	3 (1.8)	0	0	3 (1.1)	3 (1.5)	−0.3 (−3.2, 2.0)
Mild	38 (25.0)	31 (18.5)	15 (12.8)	3 (7.9)	53 (19.7)	34 (16.5)	3.2 (−3.9, 10.1)
Serious	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Deaths	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Resulting in discontinuation	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Relatedness[e]	5 (3.3)	2 (1.2)	2 (1.7)	0	7 (2.6)	2 (1.0)	1.6 (−1.1, 4.4)

Source: adae.xpt; Software: R

[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0

[b] Treatment duration for Trial 417-201-00007 is 104 weeks, 26 doses administered once every 4 weeks. Trial VIS649-201 duration is 12 months of monthly doses. Only data in the first 9 months of double-blind treatment from both trials are included.

[c]Coded as MedDRA preferred terms.

[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.

[e]Relatedness is determined by the investigator.

Table only shows AEs that occurred in more than one subject in any treatment group.

Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; nOCMQ, narrow OND custom Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 31. Adverse Events[a] Assessment of Viral Infection OND Custom Medical Query (Narrow) Showing Preferred Term That Occurred in More Than One Subject, 9-Month Interim Analysis Safety Set[b], Trial 417-201-0007, Trial VIS649-201, and Double-Blind Pool

	Trial 417-201-00007		Trial VIS649-201		Double-Blind Pool		
OCMQ (Narrow) Preferred Term[c]	Sibeprenlimab N=152 n (%)	Placebo N=168 n (%)	Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Sibeprenlimab N=269 n (%)	Placebo N=206 n (%)	Risk Difference % (95% CI)[d]
Viral infection (OCMQ)	28 (18.4)	20 (11.9)	20 (17.1)	10 (26.3)	48 (17.8)	30 (14.6)	3.3 (−3.6, 9.9)
COVID-19	17 (11.2)	7 (4.2)	16 (13.7)	10 (26.3)	33 (12.3)	17 (8.3)	4.0 (−1.7, 9.5)
Herpes zoster	1 (0.7)	3 (1.8)	1 (0.9)	0	2 (0.7)	3 (1.5)	−0.7 (−3.5, 1.4)
Influenza	11 (7.2)	8 (4.8)	1 (0.9)	0	12 (4.5)	8 (3.9)	0.6 (−3.5, 4.3)
SARS-CoV-2 test positive	1 (0.7)	1 (0.6)	1 (0.9)	0	2 (0.7)	1 (0.5)	0.3 (−2.0, 2.2)
Maximum severity							
Death	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Life-threatening	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Severe	0	1 (0.6)	2 (1.7)	0	2 (0.7)	1 (0.5)	0.3 (−2.0, 2.2)
Moderate	8 (5.3)	6 (3.6)	1 (0.9)	0	9 (3.3)	6 (2.9)	0.4 (−3.2, 3.8)
Mild	20 (13.2)	13 (7.7)	17 (14.5)	10 (26.3)	37 (13.8)	23 (11.2)	2.6 (−3.6, 8.5)
Serious	1 (0.7)	1 (0.6)	1 (0.9)	0	2 (0.7)	1 (0.5)	0.3 (−2.0, 2.2)
Deaths	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Resulting in discontinuation	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Relatedness[e]	1 (0.7)	2 (1.2)	0	0	1 (0.4)	2 (1.0)	−0.6 (−3.1, 1.2)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Treatment duration for Trial 417-201-00007 is 104 weeks, 26 doses administered once every 4 weeks. Trial VIS649-201 duration is 12 months of monthly doses. Only data in the first 9 months of double-blind treatment from both trials are included.
[c]Coded as MedDRA preferred terms.
[d] Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
[e]Relatedness is determined by the investigator.
Table only shows AEs that occurred in more than one subject in any treatment group.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; nOCMQ, narrow OND custom Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Given its mechanism of action, sibeprenlimab is expected to decrease immunoglobulin levels. As expected, a higher proportion of subjects in the sibeprenlimab group had postbaseline immunoglobulin levels below the lower limit of normal compared with those in the placebo group in the individual studies and the double-blind pool (Table 32). The protocol for Trial 417-201-00007 did not include discontinuation criteria based on low immunoglobulin levels and no subjects discontinued sibeprenlimab due to low immunoglobulin levels in Trial 417-201-00007. For details on sibeprelimab's pharmacodynamic effects on IgA, see Section 6.1.

Table 32. Subjects With IgA, IgM, and IgG Values Below the Lower Limit of Normal, 9-Month Interim Analysis Safety Set[a], Trial 417-201-0007, Trial VIS649-201, and Double-Blind Pool

	Trial 417-201-00007		Trial VIS649-201		Double-Blind Pool	
Immunoglobulin Antibodies[b]	Sibeprenlimab N=152 n/Ne (%)	Placebo N=168 n/Ne (%)	Sibeprenlimab N=117 n/Ne (%)	Placebo N=38 n/Ne (%)	Sibeprenlimab N=269 n/Ne (%)	Placebo N=206 n/Ne (%)
IgA < LLN (<70 mg/dL)	37/152 (24.3)	0/167 (0)	18/117 (15.4)	0/38 (0)	55/269 (20.4)	0/205 (0)
IgM < LLN (<40 mg/dL)	126/144 (87.5)	5/160 (3.1)	98/116 (84.5)	1/36 (2.8)	224/260 (86.2)	6/196 (3.1)
IgG < LLN (<600 mg/dL)	57/152 (37.5)	3/164 (1.8)	36/117 (30.8)	0/38 (0)	93/269 (34.6)	3/202 (1.5)

Source: Summary of Clinical Safety, Table 2.7.4.4.4-1
[a]Trial 417-201-00007 duration is 104 weeks, 26 doses administered once every 4 weeks. Trial VIS649-201 duration is 12 months of monthly doses. Only data in the first 9 months of double-blind treatment from both trials are included.
[b]The subjects' IgA, IgM, and IgG values were ≥ the LLN at baseline.
Abbreviations: Ig, immunoglobulin antibodies (IgA, IgM, and IgG); IV, intravenous; LLN, lower limit of normal; n, number of subjects with ≥1 postbaseline Ig value < the LLN; Ne, total number of subjects with baseline IgG values ≥ the LLN

7.6.1.6.2. Injection/Infusion Site Reactions

As noted above, injection site reactions are expected risks of sibeprenlimab based on the method of administration (i.e., subcutaneous injection). The clinical protocol for Trial 417-201-00007 did not include administration of prophylactic medications (e.g., topical anesthetics, antihistamines, corticosteroids) to mitigate the risk of injection site reactions. The protocol included prespecified timepoints for assessments and grading of injection site reactions. The protocol did not include specific discontinuation criteria based on the severity of injection site reactions. In Trial 417-201-00007, the incidence of injection site reactions (OCMQs) was numerically higher in subjects treated with sibeprenlimab compared to those treated with placebo (Tables 27, 28, and 33). The most common injection site reactions were injection site erythema, injection site pain, injection site swelling, and injection site induration. The majority of injection site reactions were mild in severity and resolved on the same day as treatment administration. There were no life threatening or severe local administration reactions reported, and none resulted in treatment interruption or discontinuation.

The narrative for injection site hypersensitivity from the Trial 417-201-00007 is provided below. Based on the narrative, both injection site reactions occurred on the same day as sibeprenlimab administration and, hence, appear to be related to sibeprenlimab.

Subject (b) (6) a 27-year-old White male with biopsy-proven, primary IgAN, experienced a mild, nonserious TEAE of injection site reaction on Day 203 after sibeprenlimab administration which resolved in 2 days without treatment discontinuation or interruption. The subject also had a mild, nonserious local allergic reaction at the injection site on Day 223 after sibeprenlimab administration which resolved in 4 days without treatment discontinuation or interruption.

In Trial VIS649-201, sibeprenlimab was administered via IV infusion and hence, these local administration reactions were reported as infusion site reactions. The incidence of infusion site reaction was low, and there were no important imbalances between treatment groups in Trial VIS649-201 (Table 33).

As noted above, given differences in the method of administration of sibeprenlimab between Trials 417-201-00007 and VIS649-201, assessments of pooled data were not performed by FDA.

Table 33. Adverse Events[a] Assessment of Local Administration Reaction OND Custom Medical Query (Narrow), 9-Month Interim Analysis Safety Set[b], Trial 417-201-0007 and Trial VIS649-201

	Trial 417-201-00007		Trial VIS649-201	
OCMQ (Narrow) Preferred Term[c]	Sibeprenlimab N=152 n (%)	Placebo N=168 n (%)	Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)
Local administration reaction (OCMQ)	39 (25.7)	40 (23.8)	3 (2.6)	2 (5.3)
Injection site swelling	11 (7.2)	8 (4.8)	0	0
Injection site pain	18 (11.8)	15 (8.9)	1 (0.9)	0
Injection site induration	7 (4.6)	6 (3.6)	0	0
Injection site reaction	5 (3.3)	6 (3.6)	0	0
Injection site pruritus	0	3 (1.8)	0	0
Injection site erythema	17 (11.2)	23 (13.7)	0	0

OCMQ (Narrow) Preferred Term[c]	Trial 417-201-00007 Sibeprenlimab N=152 n (%)	Trial 417-201-00007 Placebo N=168 n (%)	Trial VIS649-201 Sibeprenlimab N=117 n (%)	Trial VIS649-201 Placebo N=38 n (%)
Maximum severity				
Death	0	0	0	0
Life-threatening	0	0	0	0
Severe	0	0	0	0
Moderate	3 (2.0)	1 (0.6)	1 (0.9)	0
Mild	36 (23.7)	39 (23.2)	2 (1.7)	2 (5.3)
Serious	0	0	0	0
Deaths	0	0	0	0
Resulting in discontinuation	0	0	0	0
Relatedness[d]	32 (21.1)	37 (22.0)	1 (0.9)	1 (2.6)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Treatment duration for Trial 417-201-00007 is 104 weeks, 26 doses administered once every 4 weeks. Trial VIS649-201 duration is 12 months of monthly doses.
[c]Coded as MedDRA preferred terms.
[d]Relatedness is determined by the investigator.
Table only shows AEs that occurred in more than one subject in any treatment group.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; nOCMQ, narrow Office of New Drugs Custom Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.6.3. Hypersensitivity

As noted above, hypersensitivity is a known risk of sibeprenlimab. There was no important imbalance in the incidence of hypersensitivity-related PTs (OCMQ) between subjects treated with sibeprenlimab and those administered placebo in the double-blind pool (Table 34).

Out of three hypersensitivity-related TEAEs reported in the sibeprenlimab group, two events (PTs of allergic cough and injection site hypersensitivity) were mild in severity; one subject in Trial VIS649-201 had an anaphylactic reaction. No hypersensitivity-related TEAEs resulted in treatment discontinuation.

The narrative for the SAE of anaphylactic reaction from Trial VIS649-201 is described below. Based on the narrative, the anaphylactic reaction was likely due to the magnetic resonance imaging gadolinium-based contrast agent and not sibeprenlimab.

Subject (b) (6) is a 39-year-old Asian male with biopsy-proven, primary IgAN and key medical history of hypertension, drug hypersensitivity, food allergy, and pancreatic neoplasm. On Day 65, the subject was administered 14 mL of gadolinium IV for a magnetic resonance imaging of the upper abdomen; 5 minutes later, the subject experienced dyspnea and a rash. The subject was administered 1 mg adrenaline intramuscularly and referred to the emergency room with a diagnosis of an anaphylactic reaction where he was treated with epinephrine, fenoterol hydrobromide/ipratropium bromide, chlorphenamine, dexamethasone, and saline solution (sodium chloride). The subject's blood pressure was 147/97 mm Hg and oxygen saturation was 99% to 100%. Concomitant medications taken by the subject up to 14 days before the onset of the event included carvedilol, losartan, manidipine hydrochloride, and doxazosin. On Day 66, the event of anaphylactic reaction was resolved, and the subject was discharged from the emergency room. There were no changes made to the study treatment. The subject received sibeprenlimab through Day 331.

Table 34. Adverse Events[a] Assessment of Hypersensitivity OND Custom Medical Query (Narrow), 9-Month Interim Analysis Safety Set[b], Trial 417-201-0007, Trial VIS649-201, and Double-Blind Pool

	Trial 417-201-00007		Trial VIS649-201		Double-Blind Pool		
OCMQ (Narrow) Preferred Term[c]	Sibeprenlimab N=152 n (%)	Placebo N=168 n (%)	Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Sibeprenlimab N=269 n (%)	Placebo N=206 n (%)	Risk Difference % (95% CI)[d]
Hypersensitivity (OCMQ)	2 (1.3)	1 (0.6)	1 (0.9)	0	3 (1.1)	1 (0.5)	0.6 (−1.7, 2.8)
Allergic cough	1 (0.7)	0	0	0	1 (0.4)	0	0.4 (−1.5, 2.1)
Anaphylactic reaction	0	0	1 (0.9)	0	1 (0.4)	0	0.4 (−1.5, 2.1)
Injection site hypersensitivity	1 (0.7)	0	0	0	1 (0.4)	0	0.4 (−1.5, 2.1)
Drug hypersensitivity	0	1 (0.6)	0	0	0	1 (0.5)	-0.5 (−2.7, 0.9)
Maximum severity							
Death	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Life-threatening	0	0	1 (0.9)	0	1 (0.4)	0	0.4 (−1.5, 2.1)
Severe	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Moderate	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Mild	2 (1.3)	1 (0.6)	0	0	2 (0.7)	1 (0.5)	0.3 (−2.0, 2.2)
Serious	0	0	1 (0.9)	0	1 (0.4)	0	0.4 (−1.5, 2.1)
Deaths	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Resulting in discontinuation	0	0	0	0	0	0	0.0 (−1.8, 1.4)
Relatedness[e]	1 (0.7)	0	0	0	1 (0.4)	0	0.4 (−1.5, 2.1)

Source: adae.xpt; Software: R

[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0

[b]Treatment duration for Trial 417-201-00007 is 104 weeks, 26 doses administered once every 4 weeks. Trial VIS649-201 duration is 12 months of monthly doses. Only data in the first 9 months of double-blind treatment from both trials are included.

[c]Coded as MedDRA preferred terms.

[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.

[e]Relatedness is determined by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; nOCMQ, narrow Office of New Drugs Custom Medical Query; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.7. Laboratory Findings, Trial 417-201-00007

Analyses of immunoglobulins are described in Section 7.6.1.6.1. Analyses of biochemistry, hematology, lipids, and liver laboratory data did not reveal findings of interest or concern.

7.6.1.8. Vital-Sign Analyses, Trial 417-201-00007

Analyses of vital signs data did not reveal any findings of interest or concern. There were no significant differences between arms in mean or median vital signs (i.e., systolic blood pressure, diastolic blood pressure, heart rate and temperature) over time.

7.6.1.9. Subgroup Analyses, Trial 417-201-00007

In general, subgroup analyses of TEAEs did not suggest that sibeprenlimab was associated with a greater risk among the subgroups that were examined (Table 35). The number of subjects ≥65 years of age in Trial 417-201-00007 was small and, as such, the interpretation of the findings in this subgroup is limited.

Table 35. Overview of Treatment-Emergent Adverse Events[a] by Demographic Subgroup, Main Cohort, Overall Safety Set[b], Trial 417-201-00007

Characteristic	Sibeprenlimab N=259 n/N_s (%)	Placebo N=251 n/N_s (%)	Risk Difference % (95% CI)[c]
Sex, n (%)			
Female	81/103 (78.6)	92/107 (86.0)	−7.3 (−17.9, 3.0)
Male	111/156 (71.2)	114/144 (79.2)	−8.0 (−17.7, 1.8)
Age group 65, years, n (%)			
<65	183/250 (73.2)	202/244 (82.8)	−9.6 (−16.8, −2.3)[d]
≥65	9/9 (100)	4/7 (57.1)	42.9 (4.2, 75.7)[d]
Race, n (%)			
American Indian or Alaska Native	0/0 (NA)	1/1 (100)	NA
Asian	113/159 (71.1)	112/142 (78.9)	−7.8 (−17.5, 2.1)
Black or African American	1/1 (100)	3/3 (100)	0.0 (−83.7, 63.1)
White	72/91 (79.1)	82/96 (85.4)	−6.3 (−17.5, 4.8)
Other	6/8 (75.0)	8/9 (88.9)	−13.9 (−52.3, 26.1)
Ethnicity, n (%)			
Hispanic or Latino	20/26 (76.9)	26/32 (81.2)	−4.3 (−26.5, 16.8)
Not Hispanic or Latino	165/224 (73.7)	171/209 (81.8)	−8.2 (−15.9, -0.3)[d]
Other	7/9 (77.8)	8/9 (88.9)	−11.1 (−47.8, 27.8)
Unknown	0/0 (NA)	1/1 (100)	NA
Is in United States, n (%)			
United States	22/26 (84.6)	18/23 (78.3)	6.4 (−16.1, 29.6)
Non-United States	170/233 (73.0)	188/228 (82.5)	−9.5 (−17.0, −1.9)[d]

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
[d]95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; IMP, investigational medical product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.7. Key Safety Review Issues

No safety findings rose to the level of a key safety review issue.

8. Therapeutic Individualization

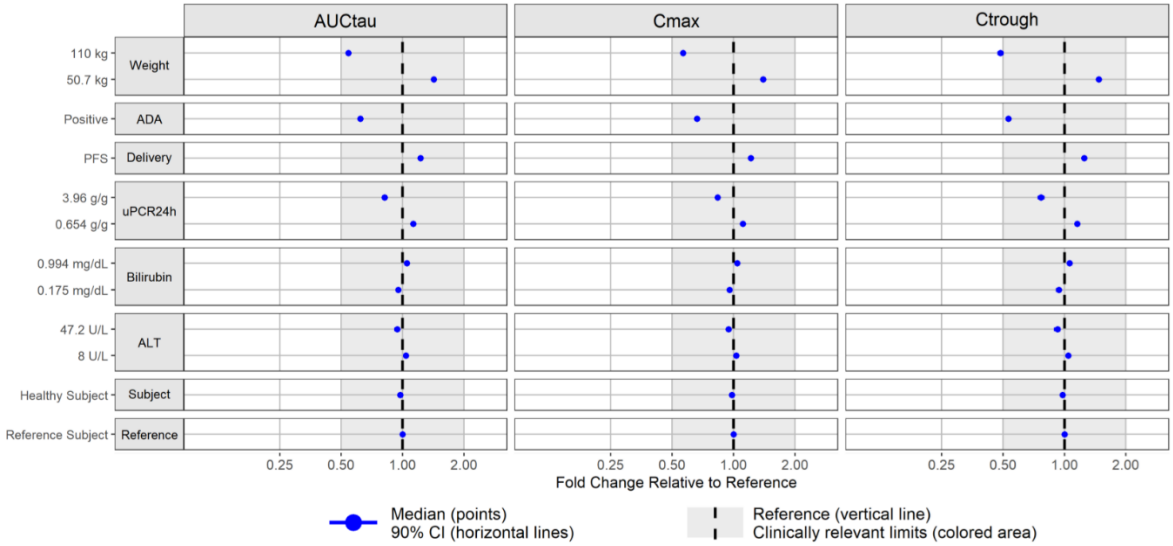
8.1. Intrinsic Factors

Based on population PK analyses, intrinsic factors including age (18 to 75 years), sex, and race were not found to meaningfully influence the pharmacokinetics of sibeprenlimab.

The final popPK model included the following as statistically significant covariates: body weight effect on linear clearance (CL_{lin})/distributional clearance (Q)/maximal rate of nonlinear clearance (V_{max}) and central volume of distribution (V_2)/peripheral volume of distribution (V_3), subject level antidrug antibody (ADA)-positive status for subjects with IgAN on CL_{lin}, healthy subject effect on V_2 and absorption rate constant (KA), method of delivery (prefilled syringe [PFS]) effect on subcutaneous bioavailability (F), baseline bilirubin and baseline alanine aminotransferase (ALT) effect on V_{max}, and baseline uPCR-24h effect on CL_{lin}. The univariate influence of each of these covariates on sibeprenlimab steady-state exposure (AUC_{tau}, maximum serum concentration [C_{max}], and trough serum concentration [C_{trough}]) in subjects with IgAN following the 10th Q4W dose of 400 mg SC injection in the phase 3 trial is presented in Figure 13.

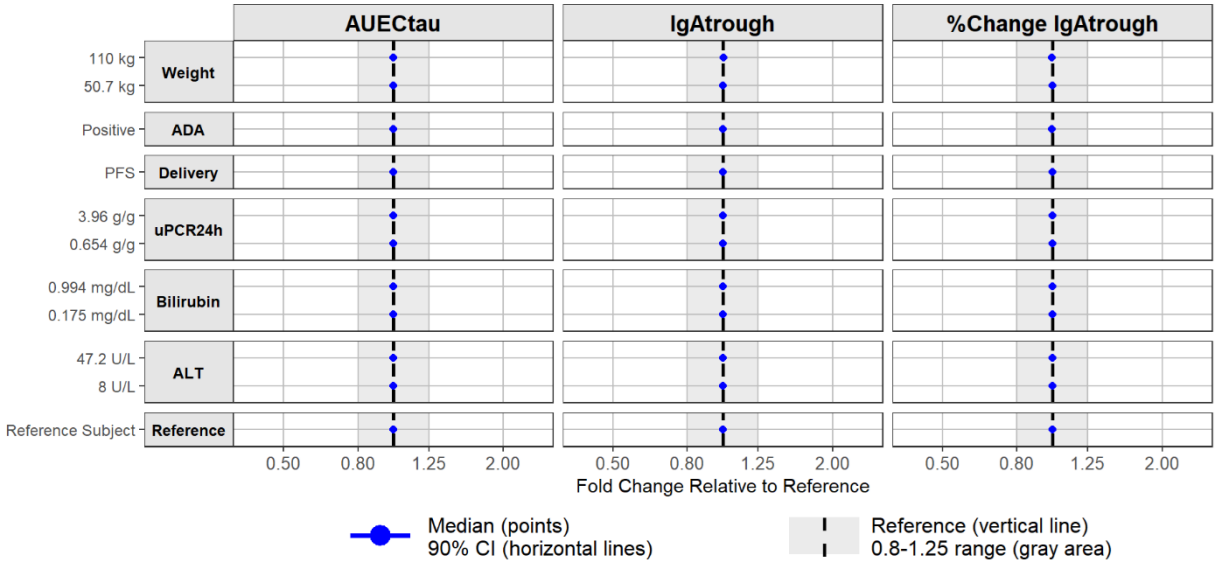
Of these covariates, only body weight and subject-level ADA status were predicted to affect the simulated steady-state pharmacokinetic (PK) exposures by more than 20% (Figure 13). None of these covariates were identified as statistically significant covariates in the popPK/PD (IgA) model or the E-R model (uPCR-24h at Month 9), indicating no clinically meaningful impact of these covariates on the PD marker of IgA or the efficacy endpoint of uPCR-24h at Month 9. Hence, dose adjustment is not needed for intrinsic factors. The impact of these covariates on IgA and uPCR-24h is depicted in Figure 14 and Figure 15, respectively.

Figure 13. Effect of Statistically Significant Covariates on Sibeprenlimab Steady-State Exposure (AUC_{tau}, C_{max} and C_{trough}) in Subjects With IgAN Following 10 Doses of 400 mg Administered Subcutaneously Q4W



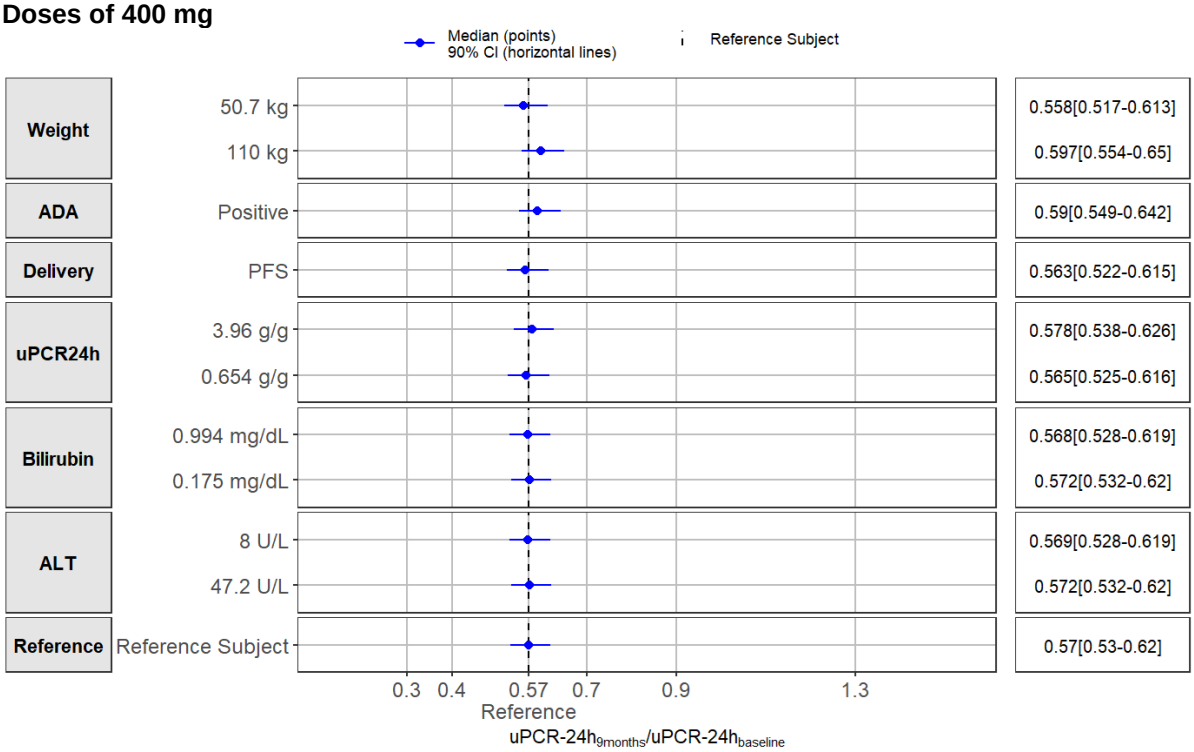
Source: Figure 23 on Page 96 of popPK/PD report 417-24-202
Dots represent the median. Reference virtual subject: body weight of 70 kg, baseline bilirubin of 0.41 mg/dL, baseline ALT of 16 U/L, baseline uPCR-24h of 1.29 g/g, ADA-negative IgAN patient receiving sibeprenlimab from a vial.
Abbreviations: ADA, antidrug antibody; ALT, alanine transaminase; AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; IgAN, Immunoglobulin A nephropathy; PFS, prefilled syringe; popPK/PD, population pharmacokinetic/pharmacodynamic; Q4W, every 4 weeks; uPCR, urine protein creatinine ratio

Figure 14. Effect of Statistically Significant Covariates Identified From the PopPK Model on IgA Responses ($AUEC_{tau}$, IgA_{trough}, and Percent Change of IgA_{trough}) in Subjects With IgAN Following 10 Doses of 400 mg Administered Subcutaneous Q4W



Source: Figure 24 on Page 99 of popPK/PD report 417-24-202
Dots represent the median. Reference subject: 70-kg, ADA-negative IgAN patient following administration with a vial, baseline bilirubin 0.41 mg/dL, baseline ALT 16 U/L, and baseline uPCR-24h 1.29 g/g.
Abbreviations: ADA, antidrug antibody; ALT, alanine aminotransferase; $AUEC_{tau}$, area under the curve of percent change of IgA from baseline versus time over the dosing interval; CI, confidence interval; IgA, immunoglobulin A; IgAN, Immunoglobulin A nephropathy; IgA_{trough}, trough concentration of IgA; PFS, prefilled syringe; PopPK, population pharmacokinetic; Q4W, every 4 weeks; uPCR-24h, urine protein-to-creatinine ratio based on 24-hour urine collection

Figure 15. Effect of Statistically Significant Covariates Identified From the PopPK Model on uPCR-24h at Month 9/uPCR-24h at Baseline in Subjects With IgAN Following Q4W Subcutaneous Doses of 400 mg



Source: Figure 1 on Page 12 of E-R report 417-24-203
Dots represent median with lines representing the 90% CI based on parameter uncertainty of the E-R model.
Reference subject: 70 kg, ADA-negative IgAN subject following 400 mg SC Q4W administration with a vial, baseline bilirubin 0.41 mg/dL, baseline ALT 16 U/L, and baseline uPCR-24h 1.29 g/g.
Abbreviations: ADA, antidrug antibody; AUC, area under the serum concentration-time curve; CI, confidence interval; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; E-R, exposure-response; PFS, prefilled syringe; PopPK, population pharmacokinetic; uPCR24h, urine protein-to-creatinine ratio based on 24-hour urine collection

Body Weight

Among the significant covariates in the final popPK model, body weight had the most pronounced effect. An increase in baseline body weight causes an increase in CL_{lin}, Q, V_{max}, V_2, and V_3. Compared to a subject weighing 70 kg (body weight for a typical subject), a subject weighing 110 kg (the 95th percentile) has 43%, 51%, and 46% lower steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively, and a subject weighing 50.7 kg (the 5th percentile) has 40%, 47%, and 42% higher steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively, following Q4W administration of 400 mg SC injections. However, the changes in pharmacokinetics did not translate into clinically significant effects on pharmacodynamics (IgA), efficacy, or safety.

In the phase 2 trial (VIS649-201), subjects who received the 8 mg/kg IV dose had 2.2- to 3.4-fold higher exposure compared to those receiving the 400 mg SC dose in the phase 3 trial. This higher exposure did not raise safety concerns, although the sample size for safety evaluation was limited. Sibeprenlimab was well tolerated across the 2- to 8-mg/kg dose levels in the phase 2 trial.

Based on popPK/PD analysis, subjects with IgAN across different body weight groups (5^{th} and 95th percentiles of baseline body weight) demonstrated comparable IgA reductions (Figure 14). Furthermore, in the exposure-efficacy response analysis, the simulated uPCR-24h at Month 9/

uPCR-24h at baseline responses were largely overlapping across these body weight groups (Figure 14 and Figure 15). An analysis of the observed data in the phase 3 trial (417-201-00007) also showed a similar reduction in uPCR-24h at Month 9 across weight quartiles as presented in Table 36.

These results indicate that, although body weight could significantly affect sibeprenlimab exposure, the change in pharmacokinetics does not translate into clinically significant changes in efficacy or safety. Therefore, the current fixed dosing regimen for sibeprenlimab (400 mg SC Q4W) is reasonable; the dose does not need to be adjusted based on body weight.

Table 36. Summary of uPCR-24h Response (i.e., uPCR-24h at Month 9/uPCR-24h at Baseline) by Body Weight Quartile in Subjects With IgAN Receiving Active Treatment (400 mg SC Q4W) in Trial 417-201-00007

Body Weight (kg)	N	uPCR-24h9 months /uPCR-24hBaseline Geo-Mean ± Geo-SD
43.80 – 65.12	35	0.42 ± 1.92
65.13 – 76.50	36	0.42 ± 2.46
76.51 – 88.95	35	0.55 ± 2.1
88.96 – 238.0	36	0.51 ± 2.14

Source: Table 7 on Page 28 of E-R report 417-24-203
Abbreviations: Geo-mean, geometric mean; Geo-SD, geometric standard deviation; IgAN, immunoglobulin A nephropathy; N, number of subjects with available information; Q4W, every 4 weeks; SD, standard deviation; uPCR, urine protein creatinine ratio; uPCR-24h, urine protein-to-creatinine ratio based on 24-hour urine collection; uPCR-24h9 months, uPCR-24h at Month 9; uPCR-$24h_{baseline}$, uPCR-24h at baseline

Effects of Renal and Hepatic Impairment

Sibeprenlimab is a monoclonal antibody and as such, the exposure of sibeprenlimab is not expected to be affected by renal impairment. Although a dedicated pharmacokinetics study in subjects with renal impairment was not conducted, sibeprenlimab pharmacokinetics has been evaluated in subjects with IgAN representing a range from severe renal impairment to normal renal function categories (eGFR 23.7 to 244 mL/min/1.73 m²). In the popPK dataset, there were 14 subjects with severe renal impairment, 267 subjects with moderate renal impairment, 223 subjects with mild renal impairment, and 151 subjects with normal renal function. PopPK analysis did not identify eGFR as a significant covariate affecting sibeprenlimab pharmacokinetics. Therefore, no dose adjustment is needed for IgAN subjects with renal impairment.

A dedicated PK study in subjects with hepatic impairment was not conducted. Hepatic function parameters including baseline bilirubin (range 0.1 to 2.1 mg/dL), ALT (range 5 to 137 U/L), aspartate aminotransferase (range 8 to 280 U/L), and albumin (range 2.9 to 5.4 g/dL) were evaluated as covariates for all PK parameters in the popPK model. PopPK analysis showed no statistically significant associations between baseline levels of albumin or aspartate aminotransferase and any PK parameters (CL_{lin} or V_{max}) of sibeprenlimab. Although baseline bilirubin and ALT levels were found to affect V_{max} statistically significantly in the covariate analysis, there was minimal impact on sibeprenlimab exposures (Figure 13) and no effect on serum IgA reduction (Figure 14) or uPCR-24h at Month 9 (Figure 15). This finding is consistent with the mechanistic understanding of the elimination and distribution of sibeprenlimab as an

antibody drug. Therefore, no dose adjustment is needed for subjects with IgAN with hepatic impairment.

Effects of Antidrug Antibody

As of the September 4, 2024, interim analysis data cutoff date, in the ongoing pivotal phase 3 Trial 417-201-00007, 34.4% (88/256) of evaluable subjects treated with sibeprenlimab developed an ADA, and 23.9% (21/88) of these ADA-positive subjects demonstrated neutralizing activity. Based on FDA's review, the ADA assay is acceptable while the drug or target (APRIL) may interfere with the neutralizing antibody (NAb) assay. Therefore, only effects of ADA on pharmacokinetics, pharmacodynamics, and efficacy are described below. Covariate screening was attempted for NAb status and time dependent NAb in popPK and popPK/PD (IgA) models (data from all clinical studies), as well as subject level NAb status in the exposure-response model (uPCR-24h, data from pivotal phase 3 studies only). However, due to the bioanalytical issues identified for the NAb assay, no definitive conclusion can be drawn from these analyses.

Based on data available at the time of the preplanned interim analysis of the pivotal Trial 417-201-00007, sibeprenlimab mean predose serum concentrations in ADA-positive subjects were approximately 40% lower than those in ADA-negative subjects. Based on popPK analysis, a similar decrease in C_{trough} of sibeprenlimab was predicted (47% reduction) in ADA-positive subjects compared to ADA-negative subjects. Additional popPK simulations showed decreases of 34% and 38% in C_{max} and AUC_{tau}, respectively, in ADA-positive subjects compared to ADA-negative subjects.

In Trial 417-201-00007, total IgA, serum APRIL, and Gd-IgA1 versus time profiles were similar between ADA-positive and ADA-negative subjects. Furthermore, popPK/PD analysis showed that immunogenicity was not a statistically significant covariate affecting IgA response.

At the time of the preplanned interim analysis of Trial 417-201-00007, the estimated percent reduction in uPCR-24h at Month 9 compared with baseline by ANCOVA for ADA-positive and ADA-negative subjects was 41.6% (95% CI: 26.7, 53.4) and 52.7% (95% CI: 42.6, 61.0], respectively. Furthermore, ADA status was not identified as a statistically significant covariate in the exposure-response model.

Simulations were conducted to assess the impact of reduced exposure in ADA-positive subjects on 9-month uPCR-24h (Figure 13) and serum IgA responses (Figure 14) In these analyses, ADA status did not appear to affect the reduction in 9-month uPCR-24h or serum IgA responses.

These results suggest that despite lower sibeprenlimab exposures due to ADA status, there is no clinically relevant effect on serum IgA levels or uPCR-24h responses.

Disease Characteristics

Baseline APRIL level (the binding target) and uPCR-24h (proteinuria may affect the elimination of the antibody drug) were evaluated in the covariate analysis of the popPK model.

PopPK analysis did not identify baseline APRIL as a significant covariate on any of the PK parameters. Baseline uPCR-24h was found to have a statistically significant impact on the clearance of sibeprenlimab. The 95th percentile (3.96 g/g) of uPCR-24h generated decreases of 17%, 23%, and 19% for steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively, when compared to

the reference subject (Figure 13). However, the slightly lowered sibeprenlimab exposures resulting from higher baseline uPCR-24h levels had no clinically meaningful impact on IgA (Figure 14) or uPCR-24h at Month 9 (Figure 14) or uPCR-24h at Month 9 (Figure 15).

8.2. Extrinsic Factors

Effects of Injection Site and Method of Delivery

In the clinical pharmacology trials (VIS649-102 and 417-201-00005), sibeprenlimab was administered from vials via SC injection in the abdomen. In the phase 3 trial (417-201-00007), subjects with IgAN rotated injection sites (arm, thigh, or abdomen) and received sibeprenlimab using either vials or PFS (introduced later). On average [SD], each subject received more injections from PFS than from vials (8.0 [2.6] versus 5.7 [3.7] injections, respectively) in the phase 3 trial.

The effect of injection sites (arm, thigh, or abdomen) and methods of delivery (PFS or vial) on KA and F was evaluated in the popPK analysis. The analysis results showed that injection site was not a statistically significant covariate for the absorption parameters, suggesting similar exposure levels of sibeprenlimab irrespective of injection site (abdomen, arm, or thigh). These results indicate that sibeprenlimab can be administered to the abdomen, arm, or thigh with no dose adjustment required.

Method of delivery was found to be a statistically significant covariate affecting F. The absolute bioavailability of SC administration via PFS was estimated to be 0.919, representing a 12.6% increase compared to sibeprenlimab delivered from vials, which had an absolute bioavailability of 0.816. This increased bioavailability results in higher exposures, with increases of 21%, 25%, and 22% for steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively, relative to vials. However, simulations of the method of delivery effect indicate that the slightly increased exposure of PFS compared to vials would not be expected to affect serum IgA (Figure 14) and uPCR-24h at Month 9 (Figure 15). These results suggest that there are no clinically relevant differences between delivery from vials or PFS.

Effect of Concomitant Medications

No dedicated clinical drug-drug interaction trials were conducted. The impact of coadministered SGLT2 inhibitors on sibeprenlimab pharmacokinetics was assessed through popPK analysis, and no effect on the pharmacokinetics of sibeprenlimab was identified.

In addition, sibeprenlimab is not a proinflammatory cytokine therapeutic protein nor a cytokine modulator; therefore, it is not anticipated to affect the pharmacokinetics of concomitant drugs metabolized by cytochrome P450 enzymes.

8.3. Plans for Pediatric Drug Development

The marketing application triggers the Pediatric Research Equity Act as a new active ingredient, indication, dosage form, dosing regimen, and route of administration. The Applicant submitted their agreed-upon Agreed Initial Pediatric Study Plan (iPSP) with their application.

There are no approved therapies for the treatment of pediatric patients with IgAN. Because the product is ready for accelerated approval in adults with IgAN, the FDA will issue a postmarketing requirement (PMR) for a deferred trial in pediatric subjects 2 years to less than 18 years of age with primary IgAN. A partial waiver will be granted for pediatric patients' birth to less than 2 years of age because IgAN rarely occurs in that age group; hence, trials would be impossible or highly impracticable. Based on the available data in adult and pediatric IgAN, the Division agrees that, in general, a pediatric extrapolation approach for IgAN using uPCR as a pharmacodynamic biomarker to extrapolate efficacy from adult to pediatric patients with primary IgAN at high risk of disease progression is appropriate.

The following PMR, agreed upon with the Pediatric Review Committee, will be issued at the time of accelerated approval:

- Conduct a pharmacodynamic, pharmacokinetic, safety and tolerability study in pediatric patients 2 years to 17 years of age with primary immunoglobulin A nephropathy. The pharmacodynamic assessment should be based on effects on proteinuria.
  - Final protocol submission: 05/2026
  - Study initiation: 01/2027
  - Study completion: 07/2031
  - Final report submission: 12/2031

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

Nonclinical data supporting labeling language are shown in Table 37 by labeling section.

Table 37. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	In an enhanced prenatal and postnatal development toxicity study, subcutaneous administration of sibeprenlimab once every 2 weeks to pregnant cynomolgus monkeys from gestation Day 20 through delivery did not result in any adverse effects on embryofetal or postnatal development at one tested dose of 101 mg/kg which provides approximately 10-fold clinical exposure at the MRHD based on AUC.
8.2 Lactation	Not applicable.
8.3 Females and Males of Reproductive Potential	Not applicable.
13.1 Impairment of Fertility	In cynomolgus monkeys intravenously administered sibeprenlimab doses of 25, 50, or 100 mg/kg once every 2 weeks for 26 weeks, no sibeprenlimab-related adverse effects on female menstrual cycle frequency and lengths, testicular volume, sperm analysis of motility, concentration, and count, or male and female reproductive organs were observed at doses up to 100 mg/kg, which provides approximately 13-fold clinical exposure at the MRHD based on AUC.

Source: Reviewers table
Abbreviations: AUC, area under the concentration versus time curve over a dosing interval; MRHD, maximum recommended human dose

Pregnancy

The use of sibeprenlimab is also anticipated in females of reproductive potential. Monoclonal antibodies, such as sibeprenlimab, are transported across the placenta in a linear fashion as pregnancy progresses and was demonstrated to occur with sibeprenlimab in animals; therefore, sibeprenlimab may be present in infants exposed *in utero*, with a potential risk to the fetus due to exposure to a drug that is not indicated for fetal treatment. However, there are currently no available data on sibeprenlimab use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage or other adverse maternal or fetal outcomes.

To better understand this risk, a descriptive pregnancy safety study is needed to collect prospective and retrospective data in women exposed to sibeprenlimab during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant, with infant outcomes assessed through at least the first year of life. This approach is preferred over a pregnancy exposure registry study when a drug is expected to be used in a small population. Given that IgAN is an uncommon disease, the available study population is likely to be small. With a descriptive pregnancy safety study, there will be a systematic approach to collect pregnancy outcome data that may be used to evaluate the safety of the drug when used during pregnancy.

Thus, the following PMR will be issued at the time of accelerated approval:

- Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to sibeprenlimab-szsi during pregnancy to assess risk of pregnancy and maternal complications, and adverse effects on the developing fetus, neonate, and infant. Assess infant outcomes through at least the first year of life. The minimum number of patients will be specified in the protocol.
  - Final Protocol Submission: 07/2027
  - Study Completion: 01/2036
  - Final Report Submission: 12/2036

Lactation

There is anticipated use of sibeprenlimab in females of reproductive potential including lactating women. Endogenous maternal IgG and monoclonal antibodies are transferred into human milk. However, there are currently no data on the presence of sibeprenlimab in human milk, the effects of sibeprenlimab on the breastfed infant, or the effects of sibeprenlimab on milk production. The effects of local gastrointestinal exposure of sibeprenlimab in the breastfed infant are also unknown. Thus, a clinical lactation study is needed to assess the degree to which sibeprenlimab is transferred into human milk and to assess the potential effects on the breastfed infant.

The following PMR will be issued at the time of accelerated approval:

- Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received sibeprenlimab-szsi to measure concentrations of sibeprenlimab-szsi and its major metabolites in breast milk using a validated assay. Assess the effects on the breastfed infant, if available, based on study population.
  - Final Protocol Submission: 05/2027
  - Study Completion: 10/2029
  - Final Report Submission: 10/2030

9. Product Quality

Approval With PMC

The Office of Pharmaceutical Quality (OPQ) recommends approval of BLA 761434 for VOYXACT (sibeprenlimab-szsi) manufactured by Otsuka Pharmaceutical Company, Ltd. The data submitted in this application are adequate to support the conclusion that the manufacture of VOYXACT (sibeprenlimab-szsi) is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. The chemistry, manufacturing, and controls postmarketing commitments (PMCs) listed below will be included in the action letter.

- **PMC 4907-2:** Conduct a Low Endotoxin Recovery hold time study, with at least 3 batches of sibeprenlimab drug product, at temperatures that reflect the relevant temperatures of the drug product manufacturing process (b) (4) for a duration greater than the proposed hold times during the manufacturing process.
  - Final report submission: August 31, 2026
- **PMC 4907-3:** Implement and qualify bioburden testing, with appropriate limits (b) (4) (b) (4)
  - Final report submission: August 31, 2026
- **PMC 4907-4:** Conduct bioburden method qualification for sibeprenlimab drug substance and associated in-process samples using two additional drug substance batches.
  - Final report submission: December 31, 2025

9.1. Device or Combination Product Considerations

Device constituent parts of the combination product are approvable.

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

The Applicant has adequately disclosed financial arrangements with clinical investigators (see Section 25 for details), and Trial 417-201-00007 appears to have been conducted in compliance with United States regulations pertaining to Good Clinical Practice (GCP). The number of subjects in each site was relatively small (≤10 subjects) compared to the overall trial population and there were no sites that strongly biased efficacy results. One principal investigator, Dr. Seokwoo Park (clinical site #110), was inspected because the clinical site enrolled a relatively large number of subjects (n=9). Dr. Park has never been inspected before. The Office of Scientific Investigations (OSI) was asked to verify the major efficacy data, specifically uPCR at Day 1 (baseline) and Month 9, and serum creatinine and eGFR data at Day 1 (baseline), Month 12, and Month 24. OSI was also asked to conduct a clinical inspection of the Applicant, Otsuka Pharmaceutical Development and Commercialization, Inc. (OPDC), to ensure that “blinding

procedures and firewalls that were previously discussed with the Agency have been implemented appropriately at the time of the interim analysis to support accelerated approval and to minimize potential impacts on trial integrity to support completion of the final confirmatory analysis to support full approval."

In their Clinical Inspection Summary letter (dated October 27, 2025), for Site #110, OSI reported that "No significant GCP deficiencies or regulatory violations were observed. The sponsor's monitoring appeared adequate. The study records showed complete CI financial disclosure, adequate reporting of adverse events and protocol deviations, and acceptable drug accountability. The major efficacy and adverse event data were verifiable." For the Applicant, OSI reported "No significant regulatory violations were observed. The findings at this sponsor inspection were consistent with those observed at the CI inspection (Site 110). The sponsor's oversight of the study including CI site monitoring appears to have been adequate to assure subject safety and study data quality."

OSI concludes that "Based on the inspection findings, the study appears to have been conducted in observance of GCP principles and in compliance with FDA regulations. The data reported by the clinical investigator (CI) and submitted by the sponsor appear to be acceptable in support of this BLA."

11. Advisory Committee Summary

Because the Application did not raise significant or controversial issues that would benefit from outside expertise or public discussion, an Advisory Committee Meeting was not held for this Application.

III. Additional Analyses and Information

12. Summary of Regulatory History

There were two INDs submitted for sibeprenlimab (VIS649) (IND 135282 and IND 158899):

- IND 135282 (b) (4)

  On May 3, 2017, the Applicant (Visterra, Inc.) submitted a Pre-IND meeting request for the treatment of IgAN and on September 13, 2018, an IND was opened with a phase 1 protocol, (b) (4)

  On November 17, 2021, an end of phase 2 meeting was held to obtain feedback on the phase 3 trial design and the clinical and nonclinical data packages.

  On October 26, 2021, OPDC obtained all rights to IND 135282.

- IND 158899 (SC formulation)

  On January 26, 2022, OPDC opened a new IND for VIS649. The opening IND included two studies:

  - **Trial 417-201-00007**, entitled, "A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy"
  - **Trial 417-201-00012**, entitled, "A Phase 2/3, Multicenter, Open-label Trial to Evaluate the Long-term Safety, Tolerability, and Efficacy of Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy"

Key Regulatory History (IND 158899)

- On February 8, 2024, breakthrough therapy designation for the treatment of biopsy-confirmed IgAN was granted.
- The iPSP was submitted on January 26, 2022, with the IND. It was reviewed by the Pediatric Review Committee and a No Agreement Letter was issued on August 5, 2022. On June 6, 2023, the Applicant submitted a meeting request to obtain Agency feedback on proposed revisions to their iPSP; the Agency issued written responses on August 18, 2023. On September 13, 2024, the Applicant submitted a revised Agreed iPSP and on October 19, 2024, the Agency issued an Agreed iPSP for the treatment of biopsy confirmed IgAN. The Agreed iPSP included a plan to request a partial waiver in children <2 years old on the grounds that studies are impossible or highly impractical and a deferral in children ≥2 to ≤17 years of age until additional data to support safety and effectiveness had been collected from the phase 3 program in adults.
- On April 22, 2024, the Applicant submitted a Type B Pre-BLA meeting request to discuss the content and format of a BLA Application and on June 17, 2024, the meeting was canceled by the Applicant after receiving the Division's preliminary responses.

- On November 18, 2024, the Applicant discussed their topline results with the Agency via video conference.
- On January 21, 2025, OPQ issued their written responses to the Applicant's November 22, 2024, meeting request to discuss the chemistry, manufacturing, and controls of VIS649 for inclusion in their BLA submission.

13. Pharmacology Toxicology

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

13.1.1. Pharmacology

Primary Pharmacology

In Vitro Primary Pharmacology Studies

In the sibeprenlimab discovery program (Study # 2017-022-R0), CD-1 mice were immunized with stabilized trimeric human APRIL and hybridomas were screened to ensure target specificity, which led to selection of lead candidate mAb 2419 that showed APRIL binding in the picomolar range (EC_{50}=112pM) and dual receptor blocking activity (TACI IC_{50}=0.74nM, BCMA IC_{50}=0.22nM). Epitope mapping using mouse-human APRIL chimeras identified binding residues at the receptor binding site, with functional activity confirmed through NF-κB signaling inhibition assays.

The humanization program tested 143 variable heavy/variable light combinations through complementary determining regions grafting onto human germline frameworks and successfully converted the mouse antibody to sibeprenlimab, a fully humanized IgG2κ antibody that retained potency while achieving >85% germline identity. X-ray crystallography confirmed that sibeprenlimab binds a quaternary epitope spanning two APRIL monomers, overlapping the high-affinity receptor binding site domain shared by TACI and BCMA.

Studies for sibeprenlimab binding affinity and functional activity are summarized in Table 38 below. Sibeprenlimab binds to human APRIL (EC_{50} of 28.8pM and dissociation constant of 0.95pM) and blocks APRIL-receptor interactions with both BCMA (IC_{50}=0.18nM) and TACI (IC_{50}=0.34nM) receptors, inhibiting B-cell mediated immune responses including NF-κB activation and cell proliferation and viability.

In cross-species comparison studies, binding affinity for APRIL was comparable between cynomolgus monkeys, rabbits, and humans whereas binding to APRIL could not be detected in rodents (mouse or rat). Given >99% homology with human APRIL and comparable binding affinity, the cynomolgus monkey was considered a pharmacological relevant species for safety evaluation. However, while comparable binding affinity in the rabbit was established, the species proved to be unsuitable for toxicology assessment due to strong immunogenicity (antidrug antibodies [ADA]) to sibeprenlimab.

Table 38. Sibeprenlimab In Vitro Pharmacodynamic Studies

Study Title (Number) and Methods	Summary Results
Binding and Specificity Studies	
In vitro binding and blocking activities of VIS649 (2017-026-R0) Methods: Indirect enzyme-linked immunosorbent assay (ELISA) (0.5 µg/mL APRIL coating), competition ELISA with TACI/BCMA-Fc (1 µg/mL), sibeprenlimab titration.	Sibeprenlimab binds to human APRIL with an EC_{50} of 28.8pM. Sibeprenlimab blocked TACI and BCMA receptors with an IC_{50} of 0.34nM and 0.18nM, respectively.
Comparative binding of VIS649 to human versus cynomolgus APRIL (2017-023-R0) Methods: Capture ELISA with FLAG-ACR-APRIL constructs, 0.5 µg/mL APRIL 12-point sibeprenlimab titration from 1 µg/mL	Comparable binding with only ~2-fold difference observed between human and cynomolgus monkey APRIL (EC_{50}: 50.7pM, human versus 109.8pM, cynomolgus monkey).
Comparative binding of VIS649 to human versus rabbit APRIL (2017-024-R0) Methods: Similar to study # 2017-023-R0, 8-point sibeprenlimab titration, included mouse and rat APRIL testing	Comparable binding was observed between human and rabbit APRIL (EC_{50}: 39.0pM human versus 47.8pM rabbit) No detectable binding to mouse or rat APRIL was observed.
Assessment of VIS649-APRIL binding (375-8888-004) Methods: Biacore T200 kinetic analysis at ~30 RU and ~100 RU ligand densities; APRIL concentrations 0-6000pM; 300s association, 3h dissociation	High binding affinity (Equilibration dissociation constant (K_D) =0.85-0.95pM) High association rate (*ka* =2.37-2.63×10^7) Low dissociation rate (*kd* =2.24-2.25×10^{-5}) No avidity contribution observed
In vitro characterization of mAb 4540 (2017-028-R0) Methods: Cross-reactive mAb 4540 binding to human/mouse APRIL by ELISA; receptor blocking assays with TACI-Fc and BCMA-Fc	The mouse surrogate, mAb 4540, demonstrated potent binding to both human and mouse APRIL, with effective blocking of APRIL-receptor interactions across both species. Blocking potency for mAb 4540 against human APRIL: IC_{50} of 0.65nM (TACI) and 0.37nM (BCMA), comparable to the blocking potency of sibeprenlimab in humans. Blocking potency for mAb 4540 through mouse APRIL: IC_{50} of 1.11nM (TACI) and 1.46nM (BCMA).
Functional Activity	
Inhibition of APRIL-receptor mediated NF-κB cellular signaling by VIS649 (2017-013-R0) Methods: NFκB reporter cell assay using TACI/BCMA transfected cells, 50 ng/ml APRIL, varying sibeprenlimab concentrations, 24-hour incubation	Sibeprenlimab showed a concentration dependent inhibition in APRIL-mediated NFκB signaling through both TACI (IC_{50} 152pM) and BCMA (IC_{50} 145pM) receptors.
Inhibition of mouse B cell proliferation by VIS649 (R2017-025-R0) Methods: Mouse B cell isolation, resazurin viability assay, 1 µg/mL APRIL, 5.5 µg/mL anti-IgM, 72-hour incubation	Sibeprenlimab showed complete inhibition of APRIL-mediated B cell proliferation with IC_{50} approximately 20nM (3 µg/mL)

Study Title (Number) and Methods	Summary Results
VIS649 inhibition of primary mouse B cell proliferation and viability (R2017-038-R0) Methods: CFSE proliferation assay, ATP viability assay, 0-100 ng/ml APRIL 10 µg/ml anti-IgM, 3 to 5-day incubation	Sibeprenlimab inhibited APRIL-mediated proliferation with IC_{50} ~1 ng/ml. Sibeprenlimab completely neutralized APRIL-mediated effects at concentrations ≥5nM (0.73 µg/mL).

Source: Applicant's study reports
VIS649 refers to sibeprenlimab
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; ATP, adenosine triphosphate; BCMA, B-cell maturation antigen; CFSE, carboxyfluorescein succinimidyl ester; EC_{50}, half-maximal effective concentration; ELISA, enzyme linked immunosorbent assay; IC_{50}, sibeprenlimab concentration at which 50% maximal inhibition occurs; IgM, immunoglobulin M; K_a, association rate constant; K_d, dissociation rate constant; mAb, monoclonal antibody; NFκB, nuclear factor kappa B; TACI, transmembrane activator and CAML interactor

Proof-of-Concept In Vivo Studies (Table 39)

Due to lack of binding to rodent APRIL, direct effects of sibeprenlimab were assessed in rodent models using a mouse surrogate antibody (mAb 4540). In a mouse gddY IgA nephropathy model, mAb 4540 demonstrated potent efficacy in suppressing IgA levels, reducing kidney deposits, and preventing proteinuria progression (Table 39 below). The pharmacological effects of sibeprenlimab on IgA were tested in normal cynomolgus monkeys in which IV or SC administration of sibeprenlimab reduced IgA levels by up to 70% when compared to the control.

Table 39. Sibeprenlimab In Vivo Pharmacodynamic Studies

Study Title (Study #)	Findings
Preclinical Efficacy	
Evaluation of anti-APRIL antibody treatment in C57/BL6 Mice (2016-061-R0) Methods: 15 male C57/BL6 mice, 3 groups (n=5); mAb 4540 (mouse surrogate), isotype control; 20 mg/kg weekly i.p. for 8 weeks	• >50% reduction in serum IgA levels observed within 2 weeks after dosing initiation. • Effect sustained through treatment and 18 days post discontinuation. • No significant effects on serum IgG levels. • IgM effects inconclusive due to variability.
Anti-APRIL efficacy in gddY IgA nephropathy model (2017-051-R0) Methods: Pilot Study (mAb 4540-20 mg/kg weekly, 4 weeks) and follow-up second study (10 mg/kg weekly, 8 weeks with recovery group); female gddY mice	• >50% reduction in serum IgA and kidney IgA deposits • >80% reduction in kidney IgG deposits • ~50% reduction in C3 • ~30% reduction in glomerular sclerosis • Proteinuria suppression; effects reversible upon discontinuation

Study Title (Study #)	Findings
VIS649 pharmacodynamics in rabbits and cynomolgus monkeys (2018-007-R0) Methods: Four studies: rabbits (5-25 mg/kg, IV, once weekly for 4-week), cynomolgus monkeys (25 mg/kg, IV, once weekly for 8 weeks), dose-range (0.5-25 mg/kg, IV, once weekly for 4-weeks, GLP toxicity (25-100 mg/kg, IV, once weekly for 6-months)	• No pharmacodynamic effects (reduction in IgA levels) in rabbits were observed as robust rabbit ADAs reduced sibeprenlimab exposure to below quantification. • ~70% maximal IgA reduction in monkeys at ≥10 mg/kg • ~50% IgA reduction in monkeys at 0.5 to 2.5 mg/kg

Source: Applicant's study reports
VIS649 refers to sibeprenlimab.
Abbreviations: ADA, antidrug antibody; APRIL, A-Proliferation-Inducing Ligand; C3, complement component 3; gddY, grouped Deutschland, Denken, Yoken strain; GLP, Good Laboratory Practice; IgA, immunoglobulin A; IgG, immunoglobulin G; i.p., intraperitoneal; IV, intravenous; mAb, monoclonal antibody; n, number of subjects with an assessment available at the relevant time point

Established Pharmacological Class

Sibeprenlimab is a first-in-class drug that recognizes a critical quaternary epitope spanning the APRIL trimer interface with significant overlap to TACI and BCMA binding sites. Crystal structure analyses showed that each Fab molecule crosslinked two APRIL monomers with a 1247 Ų interface area. It bound to human APRIL with picomolar affinity and inhibited APRIL-mediated NF-κB activation through TACI (IC_{50} 152 pM) and BCMA (IC_{50} 145 pM) receptors, with a blockade of APRIL-induced B-cell proliferation and viability.

Based on nonclinical pharmacology studies discussed above, the mechanistic characterization supports selecting "APRIL blocker" as the established pharmacological class for sibeprenlimab.

Secondary Pharmacology (Table 40)

Sibeprenlimab demonstrated selective binding to APRIL with no detectable cross reactivity to other tumor necrosis factor superfamily cytokines including B-cell-activating factor.

Sibeprenlimab showed the expected IgG2 binding profile with weak FcγR1A and stronger FcγR2A engagement and demonstrated no antibody-dependent cell-mediated cytotoxicity activity against target cells despite robust binding to membrane localized APRIL, predicting an absence of cytotoxic liability.

Table 40. Sibeprenlimab Secondary Pharmacodynamic Studies

Study Title (Study #)	Findings
Evaluation of VIS649 cross reactivity to TNF superfamily related cytokines (2017-027-R0) Methods: VIS649 at 10 µg/mL tested against 8 TNFSF cytokines by ELISA; cytokines coated at 0.5 µg/mL	• Exclusive binding to human APRIL was observed. • No cross-reactivity to BAFF (trimeric or oligomeric), nor binding to other TNFSF members, were observed. • Results confirmed that sibeprenlimab has high specificity to APRIL.
VIS649 and VIS624 antibody target specificity screen (RP251 and RP363) Methods: VIS649 (sibeprenlimab) (10 µg/mL) was screened against 4542 human membrane proteins	• Although PDGFRA binding potential was initially identified for sibeprenlimab, a follow-up FACS analysis (study #RP363) ruled out PDGFRA interaction.
A tissue Cross reactivity study of fluoresceinated VIS649 in normal human tissues (20136678) Methods: Immunohistochemistry study using VIS649-FITC at 5 µg/mL and 0.5 µg/mL on normal human tissue panels from ≥3 donors per tissue	• No cross-reactivity was detected for sibeprenlimab in normal human tissues, likely due to low endogenous APRIL expression. • Strong binding to APRIL-transfected cells (positive control) at both concentrations was detected.
VIS649 Fc gamma receptor and C1q binding study (2017-014-R0) Methods: Octet FcγR binding assays (1 µM-10nM VIS649), C1q ELISA and Octet assays (5.0 µg/mL-5.0 ng/mL), human and cynomolgus receptors	• Sibeprenlimab exhibited a canonical IgG2 binding profile with minimal FcγRI/III binding and low binding to FcγRII which may not activate immune response. • C1q binding was significantly lower compared to the IgG1 control, indicating sibeprenlimab is expected to elicit minimal effector functions.
Evaluation of potential ADCC activity of VIS649 following binding to cell surface associated APRIL (2017-052-R0) Methods: Flow cytometry binding studies using U266 myeloma cells with recombinant APRIL (up to 1 µg/mL) and VIS649 (0-50 µg/mL). ADCC assessment using Promega reporter bioassay with VIS649-IgG2, VIS649-IgG1, and anti-CD138 control (up to 20 µg/mL) over 16 hours.	• Sibeprenlimab demonstrated robust, APRIL-dependent binding to U266 cells with ~90% binding at 10 µg/mL. • No measurable ADCC activity was detected for sibeprenlimab at any tested concentrations (up to 20 µg/mL) • An IgG1 variant of sibeprenlimab showed modest ADCC activity only in the presence of APRIL. • Results of this study confirmed that the IgG2 format of sibeprenlimab successfully minimized effector functions while maintaining target binding.
Evaluation of VIS649 induced cytokine release in human whole blood (Study #3001556) Methods: 24-hour whole blood stimulation from 10 donors; VIS649 at 10, 100, 500 µg/mL (soluble) and equivalent concentrations (wet-coated); 8-cytokine Luminex analysis	• No induction of IL-1β, IL-2, IL-10, IL-12(p70), IFN-γ was observed in either format. • Minimal IL-6 secretion at 10-100 µg/mL (soluble) observed was within historical negative control range. • Minimal dose-dependent IL-8 release at 100-500 µg/mL (wet coated). • All cytokine levels listed above were comparable to negative control antibody adalimumab.

Source: Applicant's study reports
VIS649 refers to sibeprenlimab
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; ADCC, antibody-dependent cellular cytotoxicity; BAFF, B-cell activating factor; C1q, complement component 1q; CD, cluster of differentiation; ELISA, enzyme linked immunosorbent assay; FACS, Fluorescence Activated Cell Sorting; FcγR, Fc gamma receptor; FITC, Fluorescein Isothiocyanate; IgG, immunoglobulin G; IFN-γ, interferon gamma; IL, interleukin; PDGFRA, platelet-derived growth factor receptor alpha; TNFSF, tumor necrosis factor alpha super family

Safety Pharmacology

Standalone safety pharmacology studies were not conducted for sibeprenlimab; instead, safety pharmacology parameters were incorporated into good laboratory practice (GLP) repeat-dose toxicology studies in cynomolgus monkeys, where animals received 0 to 100 mg/kg/dose sibeprenlimab via slow bolus IV injection either once weekly for 4 weeks or once every 2 weeks for 6-months. No adverse effects related to sibeprenlimab were observed in qualitative neurological assessments, and there were no significant effects on heart rate, blood pressure, electrocardiogram parameters, or on respiratory function at any dose levels tested. See Section 13.1.3 for more information.

13.1.2. Pharmacokinetic/Toxicokinetic Studies

Absorption

Pharmacokinetic studies were conducted in transgenic Tg32 mice expressing human FcRn and cynomolgus monkeys; the results are summarized in Table 41.

In Tg32 mice, a single 5 mg/kg IV dose produced the expected biphasic concentration-time curve with a predicted human half-life of 17.5 days.

In cynomolgus monkeys, IV administration (0.5 to 100 mg/kg) showed rapid peak concentrations with nonlinear elimination below 40 µg/mL, dose related increases in concentrations, and approximately 2-fold accumulation with weekly dosing. Subcutaneous administration demonstrated dose-related increases in exposure with approximately 70% bioavailability compared to IV administration, with steady-state achieved by Day 29.

Table 41. Sibeprenlimab In Vivo Pharmacodynamic Studies

Study Title (Study #)	Findings
VIS649 pharmacokinetic and allometric scaling study (2017-018-R0)	• Tg32 homozygous mice dosed with sibeprenlimab at 5 mg/kg IV showed biphasic elimination with C_{max} of 78 µg/mL, AUC of 8,570 hr*µg/mL, and terminal half-life of 238 hours (9.9 days). Allometric scaling using 0.93 exponent for clearance predicted human half-life of 17.5 days (range: 9 to 35 days based on 2-fold accuracy of clearance estimation).
A dose range finding study of VIS649 by intravenous injection in cynomolgus monkeys (20122380)	• Sibeprenlimab demonstrated nonlinear pharmacokinetics across 0.5 to 10 mg/kg doses with dose proportional increase in C_{max} and greater than dose proportional increase in AUC. • Following single doses, mean half-life ranged from 1.05 days (0.5 mg/kg) to 6.19 days (10 mg/kg). After the fourth weekly dose on day 22, mean half-life at 10 mg/kg was 4.86 days and the steady-state had not yet been reached by week 4.

Study Title (Study #)	Findings
Population pharmacokinetic and pharmacodynamic analysis for VIS649 in non-human primates (multiple studies: 2016-2453, 20122380, 20122384)	• Final population PK model was two-compartment with parallel linear and nonlinear clearance; a rapid concentration-dependent elimination was observed at <40 µg/mL. • Human simulations predicted that 0.5 mg/kg sibeprenlimab may result in minimal IgA reduction (86.1% baseline, ~14% reduction) while 20 mg/kg may result in ~60% IgA reduction (40.2% baseline) at 41.5 days. • Linear half-life in humans was predicted to be 18 days at an IC_{50} of 0.0925 µg/mL.

Source: Applicant's study reports
VIS649 refers to sibeprenlimab
Abbreviations: AUC, area under the curve; C_{max}, maximum (or peak) serum concentration; IgA, immunoglobulin A; IV, intravenous; PK, pharmacokinetic; Tg32, human neonatal Fc receptor transgenic strain

Distribution

Distribution studies were conducted as part of GLP repeat-dose toxicity studies in cynomolgus monkeys using immunohistochemistry to detect human IgG. Sibeprenlimab was detected intravascularly and extravascularly around small vessels in most tissues examined, with distribution patterns correlating with physiologic distribution of endogenous monkey IgG. The antibody was found extracellularly and/or intracytoplasmic in lymphoid tissues including gut-associated lymphoid tissues, spleen, mesenteric lymph nodes, tonsil, and bone marrow, consistent with expected distribution for a monoclonal antibody targeting immune system components (Study #20122394).

Metabolism and Excretion

No formal metabolism or excretion studies were conducted with sibeprenlimab, as the pharmacokinetic properties and clearance mechanisms of monoclonal antibody therapeutics are well understood.

13.1.3. Toxicology

13.1.3.1. General Toxicology

Good laboratory practice studies up to 6-months in cynomolgus monkeys established a comprehensive safety profile. A 26-week IV study (25 to 100 mg/kg biweekly) showed no adverse effects at the highest dose of 100 mg/kg/dose. A 26-week study with SC dosing (25 to 100.5 mg/kg biweekly) demonstrated a similar safety profile and with ~70% bioavailability compared to the IV route of administration. All studies showed the anticipated pharmacological effect, i.e., decreases in immunoglobulin levels (particularly IgA) that were reversible and not associated with any adverse effects on clinical chemistry or histopathology.

Based on the AUC exposures at the highest doses tested in monkeys with IV and SC dosing for 6 months, these studies established 13-fold and 10-fold safety margins, respectively, for clinical exposures at the MRHD of 400 mg (Table 42).

Table 42. General Toxicology Summary Table

Study (6 Months, Monkey)	NOAEL (mg/kg/Dose)	Nonclinical Exposure (AUC µM*hr/mL)	Margins to Clinical Exposure at MRHD[a] (Multiples)	Basis for NOAEL
IV	100	457,000	13X	No treatment-related significant adverse findings up to the highest dose tested.
SC	100.5	345,000	10X	

Source: Reviewers table
[a]The human $AUC_{0 \text{ to } 28SS}$ of 2,940 µg*day/mL =70,560 µg*hr/mL. The $AUC_{0 \text{ to } 336 \text{ hr}}$ ($AUC_{0 \text{ to } 14 \text{ days}}$) on last day of the dosing period from the monkey studies was for a time interval of 14 days. To compare the human AUC with a time interval of 28 days, the animal AUCs were adjusted by multiplying a factor of two (28 days/14 days =2), i.e., 2 x $AUC_{0 \text{ to } 14 \text{ days}}$.
Abbreviations: AUC, area under the curve; IV, intravenous; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; SC, subcutaneous; X, times

Monkeys

Monkey toxicology studies using both IV and SC routes were conducted with durations up to 26 weeks. The following discussion focused on the pivotal GLP-compliant toxicity studies.

Study Title/Study Number: A 6-Month Study of VIS649 by Intravenous Injection in Cynomolgus Monkeys With a 4-Month Recovery Period / 20122394

Key Study Findings

- Dose independent sibeprenlimab related decreases in serum immunoglobulins (IgA, IgG, IgM) were observed and resolved at the end of recovery period, which is consistent with the expected pharmacological effect.
- No sibeprenlimab related toxicities were observed up to the high dose tested.
- No sibeprenlimab-related effects on female menstrual cycles, testicular volume, sperm motility, concentration, or count were observed up to the high dose tested.
- The no-observed-adverse-effect level (NOAEL) was established at the high dose of 100 mg/kg/2-week, corresponding to Day 85 sibeprenlimab $AUC_{0 \text{ to } 336 \text{ hr}}$ of 463,000 µg*hr/mL for males and 451,000 µg*hr/mL for females, which provides approximately 13-fold human exposures at the MRHD of 400 mg based on combined male and female AUC.

Study Details

Table 43. Cynomolgus Monkey 6-Month Study Information

Study Features and Methods	Details
GLP compliance	Yes
Study design	6-month repeat dose toxicity study with 4-month recovery period; four groups (control and three dose levels)
Dose and frequency of dosing	0, 25, 50, 100 mg/kg/dose; IV injection once every 2 weeks for 6 months (13 total doses)
Route of administration	Intravenous (IV) slow bolus injection; 100 mg/kg group switched to 1-hour IV infusion from Day 57 onwards
Formulation/vehicle	0.9% NaCl – sterile (0.9% sodium chloride injection, USP)
Species/strain	Cynomolgus monkeys / *Macaca fascicularis*

Study Features and Methods	Details
Number/sex/group	Main study: Three males and Three females per group. Recovery study: Two males and Two females per group
Age (Day 1)	Male animals: 5.2 to 12.5 years Female animals: 4.5 to 7.4 years
Deviation from study protocol affecting interpretation of result:	No deviations affecting overall study integrity or interpretation of results were reported

Source: Reviewers table
Abbreviations: GLP, good laboratory practice; IV, intravenous; NaCl, sodium chloride; USP, United States Pharmacopeia

Table 44. Cynomolgus Monkey 6-Month Study Observations and Results

Endpoints With Notable Observations	Major Findings
Mortality	Two unscheduled deaths: Animal 3005 (fight related injuries, Day 278); Animal 4103 (suspected infusion reaction, euthanized Day 155) These were not considered test article related.
Clinical signs	No sibeprenlimab-related clinical observations; postdose reactions in Animal 4103 (vomiting, pallor, decreased activity)
Electrocardiogram (ECG)	ECGs were recorded at pretreatment and Week 4 postdose, while body temperature, blood pressure, heart rate, respiratory rate, and neurological function were evaluated pretreatment and prior to necropsy. Animals were temporarily restrained but not sedated for most measurements. No sibeprenlimab related effects were observed across any parameters. All ECGs, cardiovascular measurements, body temperature, respiratory rate, and neurological examinations were normal for the species.
Clinical chemistry	Sibeprenlimab-related mild to moderate decreases in globulins (0.66x to 0.83x for males, 0.69x to 0.82x for females) at ≥25 mg/kg/dose. The changes were consistent with the primary pharmacology of sibeprenlimab and were small in magnitude and were not considered adverse.
Histopathology: Adequate batter: Yes	No direct sibeprenlimab-related microscopic findings; immune complex (granular) deposits containing sibeprenlimab, monkey IgG, IgM, C3, and sC5b-9 in Animal 4103; no clear differences in immunoglobulin-positive cells between groups.
Other Evaluations	
Menstrual cycles, testicular measurements, and semen evaluation	No sibeprenlimab related effects on female menstrual cycles, testicular volume, sperm motility, concentration, or count.
Immunoglobulin evaluation	No clear differences between control and sibeprenlimab treated animals in tissue immunoglobulin-positive cells.
Serum immunoglobulins analysis (IgA, IgM, IgG)	Sibeprenlimab related dose-independent reductions in all immunoglobulins were observed and resolved at the end of recovery period.
Lymphocyte or monocyte subsets	No sibeprenlimab related changes in lymphocyte or monocyte subsets.
T-cell dependent antibody response	All animals produced primary and secondary anti-KLH responses; a trend toward increased IgG responses in sibeprenlimab-treated animals was observed.
Bioanalytical analysis	Dose proportional exposure; sustained/increased exposure on Days 85 and 169 versus Day 1.

Endpoints With Notable Observations	Major Findings
Antitherapeutic antibody analysis	Only one monkey (male #4103) at dose of 100 mg/kg/dose showed a confirmed ADA positive result during treatment, which was associated with exposure to sibeprenlimab that was undetectable (below the limit of quantification). This animal was euthanized (Day 155) for potential postdose reactions after subsequent dosing. No impact of ADAs on overall exposure and TK profile was observed in the surviving animals.
Endpoints without notable observations	Body weight, ophthalmoscopy, hematology, clinical chemistry, urinalysis, gross pathology, and organ weights.

Source: Reviewers table
Abbreviations: ADA, antidrug antibody; C3, complement component 3; ECG, electrocardiogram; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; KLH, keyhole limpet hemocyanin; sC5b-9, soluble C5b-9; TK, toxicokinetic; x, times

Study Title/Study Number: A 26-Week Study of VIS649 by Subcutaneous Injection in Cynomolgus Monkeys With a 13-Week Recovery Period/20174164

Key Study Findings

- Dose independent reductions in total serum immunoglobulins (IgA: 66.6 to 70.3% reduction, IgG: 31.5 to 43.1% reduction, IgM: 19.2 to 25.2% reduction) consistent with the expected pharmacology of sibeprenlimab. Partial recovery of IgA levels and full recovery of IgG and IgM levels observed during the 13-week recovery period.
- ADAs were observed in 20% of male and female monkeys in the 25 and 50 mg/kg/dose groups, but not in the highest dose groups. No effect on exposure was observed.
- No sibeprenlimab related toxicities were observed at any dose levels. The NOAEL was 100.5 mg/kg/dose (highest dose tested), corresponding to Day 85 sibeprenlimab AUC0 to 336 of 352,000 and 338,000 hr*µg/mL for males and females, respectively, which provides approximately 10-fold human exposure at the MRHD of 400 mg based on combined male and female AUC.

Study Details

Table 45. Cynomolgus Monkey 26-Week Study Information

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 25, 50, 100.5 mg/kg/dose; subcutaneous injection once every 2 weeks for 26 weeks (total of 13 doses)
Route of administration	Subcutaneous injection into scapular and mid-dorsal areas
Formulation/vehicle	(b) (4) mM histidine (b) (4) mM glutamic acid (b) (4) mM arginine, (b) (4) mM sorbitol, (b) (4) % PS80, pH 6.2
Species/strain	Cynomolgus monkeys/*Macaca fascicularis*

Study Features and Methods	Details
Number/sex/group	Main study: Three males and three females per group Recovery study: Two males and two females per group
Age	~2 years, 5 months to 4 years, 5 months
Deviation from study protocol affecting interpretation of results	No deviations affecting overall study integrity or interpretation of results were reported

Source: Reviewers table
Abbreviation: GLP, good laboratory practice; PS80, polysorbate 80

Table 46. Cynomolgus Monkey 26-Week Study Observations and Results

Endpoints With Notable Observations	Major Findings
Mortality	One early euthanasia (Day 43) in 100.5 mg/kg male due to stress related factors, unrelated to test article.
Clinical chemistry	Mild to moderate dose-independent decreases in globulins at ≥25 mg/kg/dose on Days 57, 90, and 172; recovery observed by Day 274 except in one animal. These reversible changes were consistent with the primary pharmacology of sibeprenlimab and were small in magnitude and were not considered adverse.
Histopathology adequate batter: Yes	No sibeprenlimab-related microscopic findings; early euthanasia animal showed stress-related changes unrelated to test article.
Other Evaluations	
Serum immunoglobulins analysis (IgA, IgM, IgG)	Dose independent reductions: IgA (66.6 to 70.3% reduction), IgG (31.5 to 43.1% reduction), IgM (19.2 to 25.2% reduction); partial recovery during recovery period.
Bioanalytical analysis	T_{max} observed between 24 to 144 hours; dose related increase in exposure; slight accumulation over time; ADA-positive animals showed decreased exposure.
Antitherapeutic antibody analysis	Immunogenic response to ADAs was observed in 20% (one animal in each group) of animals at 25 and 50 mg/kg/dose and correlated with the decrease of sibeprenlimab serum concentration and exposure in these animals, but not in the 100.5 mg/kg/dose groups. As the ADAs were observed predominantly during the recovery period in the 25 and 50 mg/kg/day groups, there was no impact on the exposure and TK parameters.
Endpoints without notable observations	Body weight, ophthalmoscopy, hematology, urinalysis, gross pathology, and organ weights.

Source: Reviewers table
VIS649 refers to sibeprenlimab
Abbreviations: ADA, antidrug antibody; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; TK, toxicokinetic

Rabbits

Study Title/Study #: A Pilot 4-Week Repeat Dose Intravenous Toxicity, Pharmacokinetics, Pharmacodynamics, and Immunogenicity Study of Monoclonal Antibody VIS649 in New Zealand White Rabbits Followed by a 4-Week Recovery Period/15208.01.01

Administration of sibeprenlimab 5 and 25 mg/kg IV weekly for 4 weeks to New Zealand white rabbits resulted in severe species-specific immunogenicity including ADA formation, immune complex mediated infusion reactions and mortality, which precluded meaningful safety assessment and led to the conclusion that the rabbit is not suitable for toxicology evaluation.

13.1.3.2. Genetic Toxicology and Carcinogenicity

Genotoxicity studies were not conducted for sibeprenlimab, a monoclonal antibody, which lacks the ability to directly interact with DNA.

A carcinogenicity risk assessment was submitted by the applicant, which was reviewed under the IND. Rodent carcinogenicity studies were deemed not to be warranted to establish an adequate assessment of carcinogenicity risk for sibeprenlimab.

13.1.3.3. Reproductive Toxicology

Reproductive parameters were assessed in sexually mature cynomolgus monkeys during the 26-week IV toxicity study (listed above in the 6-month IV study in cynomolgus monkeys with a 4-month recovery period / Study #20122394), which showed no effects on female menstrual cycles, male testicular volume, or semen parameters at doses up to 100 mg/kg, IV, once every 2 weeks.

The potential maternal and developmental effect on pregnant cynomolgus monkeys and their offspring was evaluated in an enhanced pre- and postnatal development study. No treatment-related adverse effects were observed. The single 100.65 mg/kg dose employed in the study provided a 10-fold clinical exposure margin to the MRHD, based on AUC (Table 47).

Table 47. Reproductive Toxicity Summary Table

Study	NOAEL (mg/kg/Dose)	Nonclinical Exposure (AUC in µM*hr/mL)	Margins to Clinical Exposure at MRHD[1] (Multiples)	Basis for NOAEL
ePPND/ SC, monkey	100.65	334,000	9.5X	No treatment-related significant adverse findings.

Source: Reviewers table
[1]The human $AUC_{0 \text{ to } 28SS}$ of 2940 µg*day/mL =70,560 µg*hr/mL. The $AUC_{0 \text{ to } 336 \text{ hr}}$ (AUC0 to 14 days) on last day of the dosing period from the monkey studies was for a time interval of 14 days. To compare the human AUC with a time interval of 28 days, the animal AUCs were adjusted by multiplying a factor of two (28 days/14 days =2), i.e., 2 x $AUC_{0 \text{ to } 14 \text{ days}}$.
Abbreviations: AUC, area under the curve; ePPND, enhanced pre/postnatal development; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; SC, subcutaneous; X, times

Monkeys

Study Title/Study Number: An Enhanced Pre- and Postnatal Developmental Toxicity Study of VIS649 Administered Biweekly (Every 2 Weeks) by Subcutaneous Injection in Pregnant Cynomolgus Monkeys With a 6-Month Postnatal Evaluation/20268962

Key Findings

- Maternal safety outcomes: No adverse effects were observed on maternal health, gestation length, or fetal/infant loss rates throughout the study period.
- Developmental safety: Infant development proceeded normally with no adverse effects detected during the 6-month postnatal monitoring period.
- Placental transfer: Sibeprenlimab demonstrated placental crossing capability, with infant drug concentrations measuring 3.7-fold higher than maternal levels at postpartum Day 28.

- Immune function assessment: All infants showed normal immune responses when challenged with keyhole limpet hemocyanin immunization, indicating preserved immune system development and function.
- The study established a NOAEL of 100.65 mg/kg/once every two-weeks for both maternal and developmental endpoints.

Table 48. Study Information

Study Features and Methods	Details
Dose and frequency of dosing	Zero (control), 100.65 mg/kg (sibeprenlimab); biweekly (every 2 weeks), dosing from GD20 to 22 to parturition (~11 doses); 6-month postnatal evaluation
Route of administration	Subcutaneous (SC)
Formulation/vehicle	(b) (4) mM histidine (b) (4) mM glutamic acid, (b) (4) mM arginine, (b) (4) mM sorbitol, (b) (4) % PS80, pH 6.2
Species/strain	Cynomolgus Monkeys / *Macaca fascicularis*
Number/sex/group	16 pregnant females/group
Study design	Standard (only one dose level was selected, which was the highest dose used in general toxicology studies).
Deviation from study protocol affecting interpretation of results	No deviations affecting overall study integrity or interpretation of results were reported.

Source: Reviewers table
Abbreviations: GD, gestation day; PS80, polysorbate 80

Table 49. Observations and Results

Categories	Maternal	Offspring
Mortality	• No mortality was observed.	Unscheduled deaths • Two infants (one each in control and treated groups) were not considered treatment related.
Pregnancy and developmental outcomes	• No sibeprenlimab-related changes in gestation length, fetal loss rates, or infant loss rates. • No developmental changes observed in aborted fetuses from either control or treated group.	• NA
Clinical pathology: hematology and coagulation	• Mild, reversible decreases in globulins (−18.61% to −24.10%) and total protein (−10.65% to −11.11%) with increased albumin/globulin ratio was observed at 100.65 mg/kg, which were fully reversed by PPD 183±2.	• No treatment related effects were observed

Categories	Maternal	Offspring
Pathology Findings		
Gross pathology	• Placenta: No sibeprenlimab-related placental changes identified in 19 evaluated placentas (9 controls, 10 treated); minimal to mild intraplacental hematomas occurred in both groups were considered incidental. • Fetal losses: No sibeprenlimab-related changes were identified in morphometric measurements, body weights, or organ evaluations of aborted/stillborn fetuses; observed differences attributed to normal biological variability and birthing process effects.	<u>Two unscheduled terminated infants:</u> • No sibeprenlimab-related changes observed; individual differences attributed to gestational age variations and normal biological variability. <u>Terminal necropsy findings:</u> • Infant measurements and body weights: No sibeprenlimab-related changes were observed. • External and visceral evaluations: No sibeprenlimab-related findings were observed. • Heart and skeletal evaluations: No sibeprenlimab-related cardiac or skeletal findings were observed. The vertebral variations in both groups were considered incidental.
Bioanalytical and Immunotoxicology Evaluations		
Toxicokinetic evaluation	• Sibeprenlimab was detected in all treated animals with no quantifiable levels in controls; mean T_{max} - 61.5 to 87.4 hours. • Minimal accumulation - 1.7-fold and 1.8-fold increases in C_{max} and $AUC_{0\text{-}144\ hrs}$ on GD 77 compared to Day 21 • Steady-state achieved by GD 77 as GD 133 exposure values were comparable to GD 77.	• Infant sibeprenlimab concentrations were approximately 3.7-fold and 140-fold higher relative to their matching dams on PPD 28 and PPD 91, respectively, due to slower clearance in infants.
Antitherapeutic antibody analysis	• Pre parturition: Low and similar ADA incidence between groups (4 of 59 samples positive, including 2 controls); one confirmed ADA-positive treated animal showed dramatically reduced systemic exposure (approximately 3% of ADA-negative animals). • Post parturition: ADA incidence increased to 50% by PPD 183 in treated dams despite dosing cessation, though impact on exposure could not be determined as sibeprenlimab level was mostly unquantifiable at those time points.	• No ADA detected in any infants from treated dams.

Categories	Maternal	Offspring
Serum immunoglobulins analysis (IgA, IgM, IgG)	• Sibeprenlimab related reductions in total serum immunoglobulin levels (IgA, IgG, and IgM) observed in treated adult females at GD 77 and GD 133 at 100.65 mg/kg, with IgA showing the greatest reduction followed by IgG and IgM.	• NA
T-cell dependent antibody response	• NA	• All infants from both groups demonstrated normal immune responses with no Sibeprenlimab-related changes in anti-KLH antibody responses after primary (PND140) and secondary (PND161) immunizations.

Source: Reviewers table
Abbreviations: ADA, antidrug antibody; AUC, area under the curve; C_{max}, maximum drug concentration; GD, gestation day; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; KLH, keyhole limpet hemocyanin; NA, not applicable; PND, postnatal development; PPD, post parturition day; T_{max}, time of maximum serum concentration

Local Tolerance

Subcutaneous administration of sibeprenlimab resulted in no injection site edema, erythema, or adverse pathological findings. indicating that sibeprenlimab via the SC route of administration is well tolerated in monkeys.

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

Not applicable.

14. Clinical Pharmacology

14.1. In Vitro Studies

The in vitro metabolism and excretion of sibeprenlimab was not investigated. As an IgG2 mAb, sibeprenlimab is expected to be degraded by proteolytic enzymes into small peptides and amino acids via catabolic pathways.

14.2. In Vivo Studies

Clinical studies providing clinical pharmacology information for sibeprenlimab are summarized in Table 50.

The proposed to-be-marketed drug product for SC administration is 400 mg (200 mg/mL, 2 mL) sibeprenlimab in a PFS. The to-be-marketed formulation in the PFS presentation was used in the pivotal phase 3 trial (417-201-00007).

Table 50. Summary of Clinical Studies

Study/Trial	Design/Primary Objectives	Drug Product/ Formulation	Dose and Regimen
VIS649-101	Phase 1, randomized, placebo-controlled, single ascending-dose; healthy subjects; evaluate safety and tolerability	(b) (4) mg in Vial ((b) (4) mg/mL sibeprenlimab in (b) (4) mM histidine, (b) (4) (b) (4) mM sorbitol, (b) (4) % polysorbate 80, pH 6.2)	IV infusion[a], single dose: 0.5, 2.0, 6.0, 12.0 mg/kg or placebo; cohort 5: 6.0 mg/mL sibeprenlimab on Day 1 in one arm and a single intramuscular injection of TENIVAC vaccine on Day 28 into the opposite arm.
VIS649-102	Phase 1, sequential, open-label; single ascending-dose, healthy subjects; characterize the SC PK profile, and evaluate safety and tolerability	400 mg in Vial (200 mg/mL sibeprenlimab in (b) (4) mM (b) (4) histidine, (b) (4) mM (b) (4) arginine, (b) (4) mM (b) (4) glutamic acid, (b) (4) mM sorbitol, (b) (4) % (w/v) polysorbate 80, pH 6.2.)	SC injection, single dose: 200 mg (1mL SC injection), 400 mg (two 1 mL injections), 400 mg (2 mL SC injection), 600 mg (one 2 mL SC injection and one 1 mL SC injection)
417-201-00005	Phase 1, sequential, open-label; single SC dose; Chinese healthy subjects; characterize the SC PK profile, and evaluate safety and tolerability in Chinese subjects	400 mg in Vial	SC injection, single dose: 200 mg (1mL SC injection), 400 mg (2 mL SC injection), 600 mg (one 2 mL SC injection and one 1 mL SC injection)
VIS649-201	Phase 2, randomized, double-blinded, placebo-controlled; subjects with IgAN on stable or maximally tolerated doses of either ACEI or ARB, with uPCR ≥0.75 g/g, eGFR ≥45 mL/min/1.73 m^2 (eGFR ≥30 mL/min/ 1.73 m^2 under certain conditions), immunoglobin G (IgG) ≥700 mg/dL, immunoglobin M (IgM) ≥37 mg/dL, and immunoglobin A (IgA) ≥70 mg/dL; evaluate dose response on proteinuria	(b) (4) mg in Vial	IV infusion[a], every month for 12 months: 2 mg/kg, 4 mg/kg and 8 mg/kg monthly, versus placebo.

Study/Trial	Design/Primary Objectives	Drug Product/ Formulation	Dose and Regimen
417-201-0007	Pivotal phase 3 (ongoing), randomized, double-blinded, placebo-controlled, subjects with IgAN on stable or maximally tolerated doses of either ACEI or ARB, with uPCR ≥0.75 g/g or urine protein ≥1.0 g/day, and eGFR ≥30 mL/min/1.73m^2 in the main cohort, and eGFR of 20-29 mL/min/1.73 m^2 in the exploratory cohort; Evaluate efficacy as measured by ratio of uPCR-24h at 9 months compared with baseline	400 mg in Vial and 400 mg in PFS (same formulation as Vial)	SC injection Q4W for 26 doses: 400 mg versus placebo.
417-201-00012	Phase 2/3 (ongoing), open-label, subjects with IgAN rollover from phase 2 trial (VIS649-201) and phase 3 trial (417-201-00007); Evaluate the long-term safety and tolerability	400 mg in Vial and 400 mg in PFS So far, PFS has not be introduced	SC injection Q4W for 26 weeks.
PopPK, PK/PD and Exposure-Efficacy Response Analyses			
417-24-202	PopPK: Describe sibeprenlimab pharmacokinetics following IV and SC administration; identify and quantify significant covariate effect; support the dosing regimen based on simulations		All dosing regimens studied in Trials VIS649-101, VIS649-102, 417-201-00005, VIS649-201, and 417-201-00007
	PopPK/PD: Describe sibeprenlimab PK-IgA relationship; identify and quantify significant covariate effect; support the dosing regimen based on simulations		All dosing regimens and the placebo studied in Trials VIS649-201 and 417-201-00007
417-24-203	Exposure-efficacy response analysis: Evaluate the relationship between sibeprenlimab exposure and change in uPCR-24h from baseline at 9 months; identify and quantify significant covariate effect; support the dosing regimen based on simulations		All dosing regimens and the placebo studied in Trials VIS649-201 and 417-201-00007

Source: Table 2.7.2.1-1 page 14 of Summary of Clinical Pharmacology, CSR for Trials VIS649-101, VIS649-102, 417-201-00005, VIS649-201, 417-201-00007, and 417-201-00012
[a]The amount of sibeprenlimab was diluted to a final volume of 100 mL in 0.9% sodium chloride and administered as a single infusion over 1 hour.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; eGFR, estimated glomerular filtration rate; IA, interim analysis; IgA, immunoglobulin A; IgAN, immunoglobulin A nephropathy; IV, intravenous; PD, pharmacodynamic; PFS, prefilled syringe; PK, pharmacokinetic; PopPK, population PK; NaCl, sodium chloride; SC, subcutaneous; uPCR, urine protein-to-creatinine ratio; Q4W, every 4 weeks

14.2.1. Trial VIS649-101 (Single Ascending-Dose Study of IV Administration in Healthy Subjects)

Title

A Phase 1, Randomized, Placebo-Controlled, Single Ascending-Dose First-in-Human Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of VIS649 Administered Intravenously in Healthy Subjects

Study Design

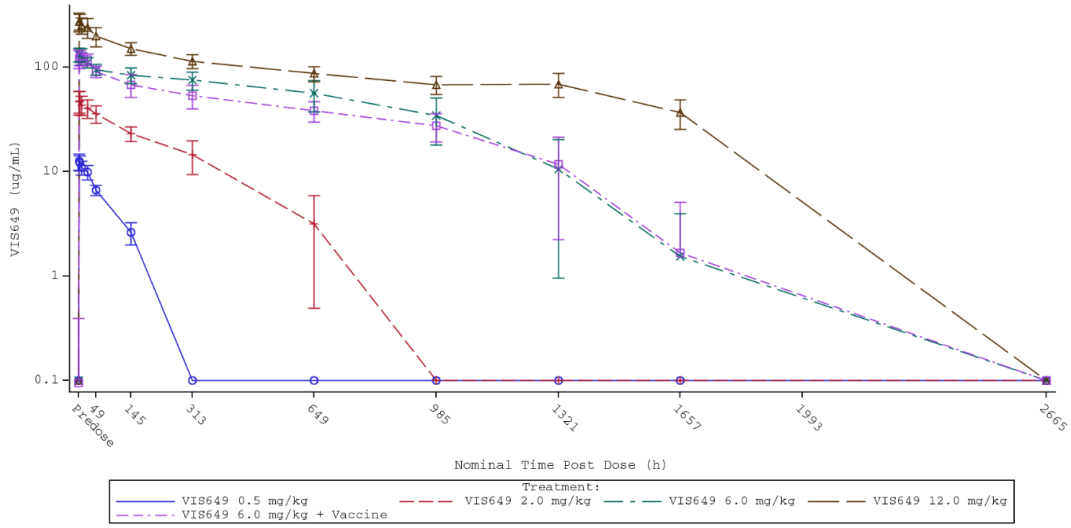
This study was conducted in five sequential dosing cohorts evaluating sibeprenlimab at 0.5, 2.0, 6.0, and 12.0 mg/kg versus placebo, plus a fifth cohort combining 6.0 mg/kg with TENIVAC vaccine. Cohorts 1 to 4 enrolled nine subjects each (seven active [four Japanese], two placebo [one Japanese]) using sentinel dosing with the first two subjects dosed at least 24 hours before the remainder. Cohort 5 enrolled 15 non-Japanese subjects randomized 10:5 to active treatment or placebo plus vaccine.

A single IV dose was administered on Day 1 after a light meal. PK sampling occurred pre-infusion, at the end of infusion, and at 2, 8, and 24 hours postinfusion, with additional samples collected on Days 2, 3, 7, 14, 28, 42, 56, 70, and 112. Serum IgA was measured on Days 3, 7, 14, 21, 28, 35, 42, 49, 56, 70, 84, 112, and Weeks 20 and 24. APRIL and aberrantly glycosylated immunoglobulin A (ag-IgA) were assessed at baseline and on Days 7, 28, 56, 84, and 112. Lymphocyte populations (cohorts 1 to 4 only) were evaluated at baseline, Days 28 and 112, and Weeks 20 and 24. ADA samples were collected at baseline and Weeks 4, 8, 16, 20, and 24.

PK Results

Sibeprenlimab serum concentrations decreased slowly with higher dose levels (6.0 and 12.0 mg/kg) appearing to plateau from approximately 13 to 55 days post administration, respectively (Figure 16). Beyond this time, concentrations decreased more rapidly, consistent with observations from early time points for lower dose levels (0.5 and 2.0 mg/kg). The increased elimination rates at approximately 13- and 55-days post administration for the 6.0 and 12.0 mg/kg dose levels appeared to be concentration dependent. Elimination was consistent when sibeprenlimab was administered at 6.0 mg/kg alone or co-administered with TENIVAC vaccine.

Figure 16. Mean (± Standard Deviation) for Serum Sibeprenlimab Concentration Time Data (Semi Log Scale), Pharmacokinetic Population



Source: Figure 18 on Page 127 of CSR for VIS649-101
VIS649 refers to sibeprenlimab
Abbreviation: CSR, clinical study report

The summarized serum sibeprenlimab PK parameters by treatment are presented in Table 51. Arithmetic mean C_{max} increased in an approximately dose-proportional manner across 0.5 to 12.0 mg/kg dose levels with low variability (coefficient of variation [CV%] 15 to 24%). AUCs increased in a more than dose proportional manner across 0.5 to 12 mg/kg with low variability (15 to 29%). Total clearance decreased with dose from 31.5 mL/h (0.5 mg/kg) to 4.51 mL/h (12.0 mg/kg), and half-life increased from approximately 61 hours (0.5 mg/kg) to 670 hours (12.0 mg/kg). Volume of distribution appeared dose-independent, ranging from 2183 to 4122 mL across dose levels. Sibeprenlimab 6.0 mg/kg administered alone or coadministered with TENIVAC vaccine demonstrated similar PK parameters.

Table 51. Summary of Pharmacokinetic Parameters of Sibeprenlimab by Treatment, Combined Ethnicities, Pharmacokinetic Population

Categories	Sibeprenlimab 0.5 mg/kg (n=7)	Sibeprenlimab 2.0 mg/kg (n=7)	Sibeprenlimab 6.0 mg/kg (n=7)	Sibeprenlimab 12.0 mg/kg (n=7)	Sibeprenlimab 6.0 mg/kg + Vaccine (n=10)
C_{max} (µg/mL)	12.45 (16.8%)	47.42 (24.2%)	134.5 (16.4%)	278.8 (18.0%)	129.3 (15.7%)
$AUC_{0\text{-last}}$ (µg*h/mL)	876 (15.2%)	10210 (26.1%)	70020 (32.9%)	148000 (12.3%)	49800 (47.8%)
$AUC_{0\text{-inf}}$ (µg*h/mL)	1103 (17.0%)	11300 (27.3%)	71930 (30.4%)	184500 (19.1%)	54610 (40.5%)
$T_{1/2}$ (h)	60.59 (7.1%)	171.60 (22.6%)	219.70 (35.9%)	653.5 (23.2%)	328.3 (33.3%)
T_{max} (h)[a]	1.14 (1.12, 3.11)	3.05 (1.15, 3.09)	3.04 (1.13, 3.16)	1.15 (1.11, 9.11)	3.05 (1.14, 25.11)

Categories	Sibeprenlimab 0.5 mg/kg (n=7)	Sibeprenlimab 2.0 mg/kg (n=7)	Sibeprenlimab 6.0 mg/kg (n=7)	Sibeprenlimab 12.0 mg/kg (n=7)	Sibeprenlimab 6.0 mg/kg + Vaccine (n=10)
CL (mL/h)	31.20 (13.9%)	11.46 (22.2%)	5.77 (39.5%)	4.31 (35.0%)	8.09 (39.5%)
V_d (mL)	2727 (12.9%)	2837 (11.7%)	1828 (72.5%)	4060 (18.8%)	3834 (21.2%)

Source: Reconstructed from Table 21 on Page 132-133 of VIS649-101 CSR
[a] T_{max} was presented as median (min, max), others as geometric mean (cv%)
Abbreviations: Abbreviations: $AUC_{0\text{-last}}$, area under the concentration-time curve from predose (time 0) to the last quantifiable concentration; $AUC_{0\text{-inf}}$, area under the concentration-time curve from predose (time 0) extrapolated to infinite time; CL, clearance; C_{max}, maximum serum concentration; CSR, clinical study report; n, number of subjects in the specified category; T_{max}, time of maximum serum concentration; $T_{½}$, terminal elimination half-life; V_d, volume of distribution

PD Results

Following sibeprenlimab dosing, dose dependent reduction in serum IgA levels was observed. Maximum mean (median) percent reduction ranged from −19.8% (−20.3%) in the 0.5 mg/kg group to −57.2% (−57.4%) in the 12.0 mg/kg group, with dose dependent time to nadirs occurring between Week 3 (0.5 mg/kg) and Week 12 (12.0 mg/kg). Serum IgA suppression was reversible with dose dependent recovery times: at 16 to 24 weeks postdose, mean (median) percent changes were −2.2% (−3.2%), −23.4% (−26.1%), −21.5% (−17.7%), and −33.3% (−31.4%) for the 0.5, 2.0, 6.0, and 12.0 mg/kg groups, respectively. Similar dose dependent and reversible reductions were observed for serum IgM, IgG, and ag-IgA.

Mean serum APRIL levels (target) decreased from baseline to/below 50 pg/mL (lower limit of quantification) at Day 7 for all dose levels. Time to APRIL recovery demonstrated dose dependent responses: recovery to predose levels occurred by Day 28 (0.5 mg/kg), Day 56 (2.0 mg/kg), Day 84 (6.0 mg/kg), and Day 112 (12.0 mg/kg).

Summary

- After a single IV infusion over approximately 1 hour, sibeprenlimab C_{max} increased in an approximately dose-proportional manner while AUCs increased in a more than dose proportional manner across the 0.5 to 12 mg/kg dose levels. Total clearance decreased with dose across the 0.5 to 12.0 mg/kg dose levels and was concentration dependent with higher clearance at lower concentrations. Volume of distribution did not appear to be dose dependent. These results indicated that sibeprenlimab exhibited nonlinear pharmacokinetics, which may result from target-mediated elimination at lower concentrations which is saturated at higher concentrations.
- After a single IV infusion, sibeprenlimab was able to decrease serum APRIL (target) to undetectable levels (i.e., <50 pg/mL). The inhibition duration was dose dependent. At dose levels higher than 2 mg/kg, APRIL levels maintained undetectable for at least 4 weeks. At dose levels higher than 6 mg/kg, APRIL levels maintained undetectable for 6 weeks.
- Accordingly, serum IgA, IgG, IgM, and ag-IgA reduction and recovery were also dose dependent. Except for the 0.5 mg/kg dose, all other dose levels (i.e., 2 mg/kg, 6 mg/kg, and 12 mg/kg) showed significant reduction in serum PD biomarker levels at Week 4 with dose dependent recovery.

14.2.2. Trial VIS649-102 (Single Ascending-Dose Study of SC Administration in Healthy Subjects)

Title

A Sequential Treatment, Phase 1, Open-Label Study to Assess the Pharmacokinetics, Safety and Tolerability, and Pharmacodynamics of VIS649 Solution Administered Subcutaneously in Healthy Male and Female Participants Aged 18 to 55 Years

Study Design

The study was conducted in four sequential dosing cohorts. The treatments for cohort 1 to 4 were 200 mg sibeprenlimab as one 1 mL SC injection, 400 mg sibeprenlimab as two 1 mL SC injections, 400 mg sibeprenlimab as one 2 mL SC injection and 600 mg sibeprenlimab as one 1 mL and one 2 mL SC injections. Each cohort enrolled 12 subjects. On Day 1, a single dose of sibeprenlimab was administered SC in the morning approximately 30 minutes after a light meal. The SC injection site for all subjects was abdomen.

Blood samples for PK analysis were collected predose, at 4, 8 and 24 hours, and on Days 3, 5, 7, 9, 14 (Week 2), 28 (Week 4), 42 (Week 6), 56 (Week 8), 70 (Week 10), 84 (Week 12), and 112 (Week 16) postdose. Pharmacodynamic samples for total IgA, IgG, IgM, and APRIL were collected at baseline, and on Days 3, 7, 14 (Week 2), 28 (Week 4), 42 (Week 6), 56 (Week 8), 70 (Week 10), 84 (Week 12), and 112 (Week 16) postdose. ADA samples were collected at predose, Days 28 (Week 4), 56 (Week 8) and 112 (Week 16) postdose.

PK Results

The PK parameters of sibeprenlimab after a single SC dose are summarized in Table 52.

Following single SC doses of 200 mg (one injection), 400 mg (two injections), 400 mg (one injection), and 600 mg (two injections), sibeprenlimab elimination rate displayed concentration dependent increases with decreasing concentration, indicating nonlinear pharmacokinetics similar to IV administration.

Dose proportional exposure increases were observed from 400 mg to 600 mg, while greater than dose-proportional increases occurred from 200 mg to 400 mg doses. Apparent clearance and apparent volume of distribution were similar at 400 mg and 600 mg doses but significantly lower than those at 200 mg. Time to maximum concentration was variable (minimum 4.0 hours, maximum 648.5 hours) with median values ranging from approximately 144 hours (200 mg) to 252 hours (600 mg). Mean half-life was similar across cohorts (189 to 231 hours). PK exposure was comparable between the two 400 mg cohorts, though intersubject variability was higher with 2×1 mL injections (CV% 42.8% to 48.7%) compared to a single 2 mL injection (CV% 26.1% to 32.0%).

Table 52. Descriptive Statistics for Serum Sibeprenlimab Pharmacokinetic Concentrations (µg/mL) Over Time, Pharmacokinetic Analysis Set

Statistic	Cohort 1 (200 mg, 1 Injection) N=12)	Cohort 2 (400 mg, 2 Injections) (N=12)	Cohort 3 (400 mg, 1 Injection) (N=12)	Cohort 2 and 3 (400 mg) (N=24)	Cohort 4 (600 mg, 2 Injections) (N=12)
C_{max} (µg/mL)					
n	12	12	12	24	12
Geo mean	18.16	55.09	56.78	55.93	77.15
CV%	39%	64%	28%	47.10%	26.90%
$AUC_{0\text{-}28d}$ (µg*h/mL)					
n	5	11	11	22	12
Geo mean	8555	32053	30490	31262	41067
CV%	41.90%	45.60%	22.50%	34.80%	30.40%
$AUC_{0\text{-}last}$ (*µg*h/mL)					
n	12	12	12	24	12
Geo mean	6890	38486	37820	38152	66770
CV%	48.00%	110.2	44.20%	77%	47.70%
$AUC_{0\text{-}inf}$ (µg*h/mL)					
n	5	5	9	14	10
Geo mean	10153	55557	41698	46198	69437
CV%	48.10%	91.40%	29.00%	54.10%	48.50%
$T_{1/2}$ (h)					
n	5	5	9	14	10
Geo mean	225.3	204.6	210.2	208.2	186.2
CV%	26%	57%	36%	42%	17%
T_{max} (h)					
n	12	12	12	24	12
median	143.97	191.58	191.72	191.72	251.77
min, max	92.2,192.2	4.0, 288.6	95.3, 192	4.0, 288.6	47.8, 648.5
CL/F (mL/h)					
n	5	5	9	14	10
Geo mean	19.7	7.2	9.6	8.7	8.6
CV%	48%	91%	29%	54%	49%
Vd/F (mL)					
n	5	5	9	14	10
Geo mean	6403	2125	2910	2601	2322
CV%	29%	83%	44%	59%	43%

Source: reconstructed from Table 14.2.3 on page 135-139 of VIS649-102 CSR
Abbreviations: $AUC_{0\text{-}28d}$, area under the concentration-curve from time zero to Day 28, $AUC_{0\text{-}inf}$, area under the concentration-curve from time zero extrapolated to infinite time. $AUC_{0\text{-}last}$, area under the concentration-curve from time zero to the last quantifiable concentration; CL/F, apparent clearance; C_{max}, maximum serum concentration; CSR, clinical study report; CV%, coefficient of variation; Geo mean, geometric mean; max, maximum; min, minimum; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; $t_{1/2}$, apparent terminal elimination half-life. T_{max}, time of maximum serum concentration

PD Results

Following a single SC administration, serum IgA reduction from baseline and recovery were dose dependent, with 200 mg cohort having lower reduction and earlier recovery than other cohorts. According to serum IgG and IgM levels, the maximum decrease was similar across cohorts while a dose dependent recovery was observed.

All dose cohorts reduced serum APRIL to undetectable levels for up to 14 days. Recovery of serum APRIL was dose dependent: recovery to predose levels was observed by Day 42 for

Cohort 1 (200 mg, one injection), Day 112 for Cohort 2 (400 mg, two injections), Day 84 for Cohort 3 (400 mg, one injection), and Day 112 for Cohort 4 (600 mg, two injections).

Summary

- Following a single SC administration, sibeprenlimab C_{max} and AUC increased in a greater than dose-proportional manner from 200 mg to 400 mg. Sibeprenlimab exposures increased approximately dose-proportionally from 400 mg to 600 mg.
- Apparent clearance and apparent volume of distribution were lower at 400 mg and 600 mg than at 200 mg.
- Subjects receiving 400 mg VIS649 doses by two SC injections (Cohort 2) or one SC injection (Cohort 3) had similar pharmacokinetics, though with relatively higher intersubject variability with two SC injections.
- Following a single SC administration of sibeprenlimab, the maximum reduction in serum IgA from baseline was dose dependent, while the maximum reduction in serum IgG, IgM, and APRIL was similar across doses. Time to return to baseline for PD markers was dose dependent, with faster recovery at the lowest dose (200 mg) than other dose cohorts.

14.2.3. Trial 417-201-00005 (Single Dose SC in Chinese Healthy Subjects)

Title

A Randomized, Open-Label, Phase 1 Trial to Assess the Pharmacokinetics, Safety and Tolerability, and Pharmacodynamics of Sibeprenlimab Solution Administered Subcutaneously in Chinese Healthy Subjects

Study Design

The trial had three treatment arms: Arm 1 (200 mg, one 1 mL SC injection), Arm 2 (400 mg, one 2 mL SC injection), and Arm 3 (600 mg, one 1 mL and one 2 mL SC injection). Eight subjects were enrolled and randomized into each arm.

Blood samples for PK analysis were collected on Day 1 (predose, 4 hours postdose, and 8 hours postdose), Day 2 (24 hours postdose), and on Days 3, 5, 7, 9, 14, 28, 42, 56, 70, and 84 without specified time points for these later collections. Blood samples for IgA, IgM, IgG, and APRIL were collected at baseline and on Days 3, 7, 14, 28, 42, 56, 70, and 84. ADA samples were collected at predose and on Days 28, 56, and 84.

PK Results

A summary of sibeprenlimab PK parameters following single SC administration at doses of 200, 400, and 600 mg in Chinese healthy subjects is presented in Table 53. Summary of PK parameters including apparent terminal elimination half-life, AUC_{inf}, apparent clearance, and apparent terminal volume of distribution is not shown due to inadequate terminal phase data within subjects.

Table 53. Mean (SD) of Sibeprenlimab Serum Pharmacokinetic Parameters Following Single Subcutaneous Administration of 200 to 600 mg Sibeprenlimab to Chinese Healthy Subjects

Sibeprenlimab PK Parameter (Unit)	200 mg (n=8)	400 mg (n=8)	600 mg (n=8)
C_{max} (µg/mL)	25.8 (7.85)	58.2 (14.9)	82.4 (26.0)
t_{max} (h)[a]	142.87 (94.50-190.83)	142.67 (94.65-310.95)	166.58 (47.23-310.85)
AUC_t (µg·h/mL)	11500 (4380)	36600 (11700)	67500 (17100)
C_{max}/dose ([µg/mL]/mg)	0.128 (0.0392)	0.145 (0.0374)	0.137 (0.0431)
AUC_t/dose ([µg·h/mL]/mg)	57.7 (21.9)	91.4 (29.2)	112 (28.5)

Source: Table 11.5.2.4.1-1 on page 46 of 417-201-00005 CSR
[a]Values are median (minimum-maximum)
Abbreviations: AUC, area under the concentration-time curve; AUC_t, from time zero to time t; $AUC_{t/dose}$, dose normalized AUC_t. C_{max}, maximum serum concentration; CSR, clinical study report; n, number of subjects with an assessment available at the relevant time point; PK, pharmacokinetic; SD, standard deviation; T_{max}, time of maximum serum concentration

PD Results

Following sibeprenlimab SC administration in Chinese healthy subjects, serum levels of APRIL, IgA, IgM, and to a less extent, IgG, decreased in a dose dependent and reversible manner.

14.2.4. Trial VIS649-201 (Phase 2, Dose Ranging, IV Infusion)

Title

A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in subjects with Immunoglobulin A (IgA) Nephropathy

Study Design

This study evaluated sibeprenlimab at 2, 4, and 8 mg/kg versus placebo administered as monthly IV infusions for 12 doses. Subjects were randomized 1:1:1:1 (approximately 36 per group) with stratification by region (Japan versus rest-of-world) and screening uPCR (≤2.0 g/g versus >2.0 g/g for rest-of-world). Subjects were ≥18 years with biopsy-confirmed IgAN.

Sibeprenlimab or placebo was administered over 1 hour in 100 mL normal saline followed by 25 mL saline flush, with dosing based on Month 0 predose weight. PK samples were collected pre- and postinfusion at each administration, Days 8 and 18 post first infusion, and Months 13, 14, and 16. Total IgA, IgG, and IgM samples were collected at baseline, Days 8 and 18, predose at monthly visits through Month 11, and at Months 12, 13, 14, and 16. ADA samples were collected prior to first infusion and on Days 30, 60, 120, 180, 240, 330, 360, and 485.

A subset of 32 subjects (6, 10, 8, and 8 in the 2, 4, 8 mg/kg, and placebo groups, respectively) underwent intensive PK/PD sampling with additional collections at 2 and 48 hours post first infusion, 408 hours post-2nd, 3rd, and 4th infusions, and 2, 48, 168, and 408 hours post last infusion, plus Day 18 of Months 12, 13, and 14.

PK Results

Subjects with predose sibeprenlimab concentrations >5% of C_{max} and one subject with a protocol deviation affecting their first dose were excluded from noncompartmental analysis. Terminal slope dependent parameters were excluded if $\%AUC_{ext}$ >20% or adjusted R^2<0.8.

Overall PK Population

Most subjects in the 2 mg/kg group had concentrations below the lower limit of quantitation (LLOQ) at predose sampling due to increased concentration dependent elimination from target-mediated drug disposition. The 4 and 8 mg/kg groups-maintained concentrations above LLOQ in most subjects. Steady-state was reached at approximately Months 3, 5, and 7 for the 2, 4, and 8 mg/kg groups, respectively, with the 2 mg/kg group reaching steady-state faster due to more rapid elimination at lower concentrations.

Intensive PK Population

Following the last dose at Month 11, concentration dependent elimination was observed across all doses when concentrations approached 10 μg/mL, occurring at approximately 1, 2, and 3 months post last dose for the 2, 4, and 8 mg/kg groups, respectively. After first infusion, mean C_{max} increased dose-proportionally while AUC_{0-30} increased greater than dose-proportionally. At Month 11, C_{max}, C_{trough}, and AUC_{tau} all increased greater than dose-proportionally. Mean apparent terminal elimination half-life increased with dose (8.82, 10.67, and 14.85 days, respectively), accumulation ratios increased with dose (1.27, 2.01, and 4.41, respectively), and clearance at steady-state decreased with increasing dose, consistent with concentration dependent elimination. Overall, sibeprenlimab exhibited nonlinear pharmacokinetics with greater than dose proportional increases in steady-state exposure.

PD Results

Total serum IgA showed dose dependent reductions compared to placebo. At 4 mg/kg, approximately 59% reduction was achieved by Month 4 and maintained through Month 12 (68% reduction). The 4 and 8 mg/kg doses showed greater IgA reduction than 2 mg/kg. Post-treatment, the 8 mg/kg group demonstrated longer lasting suppression through Month 14, trending toward baseline by Month 16.

Similarly, sibeprenlimab produced dose dependent IgG and IgM reductions. At doses ≥4 mg/kg, approximately 30% IgG and 70% IgM reductions were achieved by Month 4 and maintained through Month 12, showing greater reductions than 2 mg/kg. The 8 mg/kg group demonstrated longer-lasting post-treatment suppression through Month 14.

Sibeprenlimab demonstrated dose dependent APRIL suppression. The 2 mg/kg dose achieved partial suppression with levels approaching baseline at each dosing interval's end, while 4-and 8 mg/kg produced near complete, sustained suppression. APRIL levels returned to baseline by Month 16 following treatment discontinuation, confirming reversible suppression.

All sibeprenlimab groups achieved maximal Gd-IgA1 reduction by Month 3, maintained through Month 12. The 2 mg/kg group showed approximately 50% reduction while 4 and 8 mg/kg groups achieved approximately 60% reduction. Gd-IgA1 levels recovered to near baseline by Month 16 following treatment discontinuation, with reduction patterns closely paralleling total IgA1 reductions.

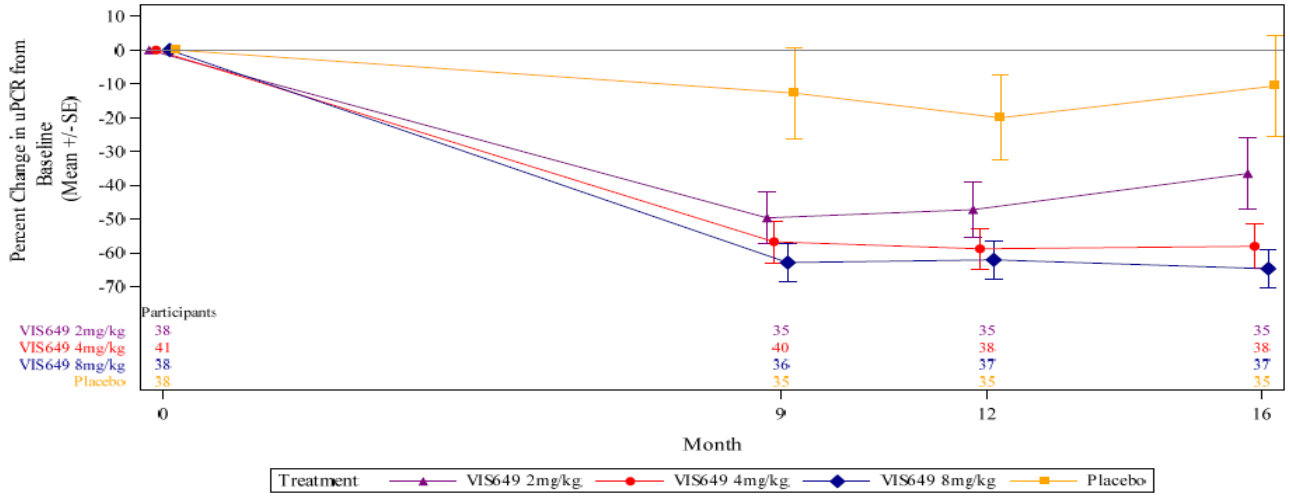
Efficacy

The mean (± standard error) percent change from baseline in 24-hour uPCR over time, evaluation of overall treatment effect using an MMRM, is presented in Figure 17. Sibeprenlimab demonstrated dose dependent reductions in 24-hour uPCR from baseline at Month 12: 47.2% (2 mg/kg), 58.8% (4 mg/kg), and 62.0% (8 mg/kg), all nominally statistically significant versus placebo (p=0.048, 0.001, and 0.0004, respectively). Similar trends were observed for spot uPCR measurements. Month 12 uPCR reductions were maintained through Month 16 in the 4 and 8 mg/kg groups, while the 2 mg/kg group began returning toward baseline by Month 16.

Sibeprenlimab also demonstrated dose dependent reductions in 24-hour urine protein excretion. After 12 months, the pooled sibeprenlimab doses achieved 58.3% reduction from baseline versus 18.8% for placebo, with dose group reductions of 49.5% (2 mg/kg), 57.8% (4 mg/kg), and 65.5% (8 mg/kg). Month 12 reductions were sustained through Month 16 in the 4-and 8 mg/kg groups.

The least-squares mean change in eGFR (mL/min/1.73 m^2) from baseline over time is presented in Figure 18. Sibeprenlimab preserved kidney function compared to placebo over 12 months. While placebo showed eGFR decline of −7.4 mL/min/1.73 m^2, sibeprenlimab groups showed minimal changes: −2.7 (2 mg/kg), +0.2 (4 mg/kg), and −1.5 mL/min/1.73 m^2 (8 mg/kg). Least-squares mean differences versus placebo were +4.6, +7.6, and +5.8 mL/min/1.73 m^2 for the 2, 4, and 8 mg/kg groups, respectively, with nominal statistical significance for 4 mg/kg (p=0.002) and 8 mg/kg (p=0.02) groups. Annualized eGFR slope analysis confirmed attenuated decline for all sibeprenlimab doses, with nominal statistical significance for the 4 and 8 mg/kg groups.

Figure 17. uPCR-24h Percent Change in uPCR From Baseline Over Time: Evaluation of Overall Treatment Effect Using MMRM, mITT Population, Trial VIS649-201



Source: Figure 14.2.1.2 on Page 3183 of VIS649-201 CSR
VIS649 refers to sibeprenlimab
Abbreviations: mITT, modified intent-to-treat; MMRM, mixed model with repeated measures; uPCR, urine protein-to-creatinine ratio; SE, standard error

The pharmacokinetics, pharmacodynamics, and efficacy data support further evaluation of a dose level that provides similar exposure to 4 mg/kg IV monthly administration in the phase 3 trial. Refer to Section 6.1 for detailed evaluation of dose selection.

14.2.5. Trial 417-201-00007

Title

A Phase 3, Multicenter, Randomized, Double-Blind, Placebo-controlled Trial to Evaluate the Efficacy and Safety of Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy

Study Design

This ongoing phase 3, multicenter, randomized, double-blind, placebo-controlled trial evaluates safety, efficacy, pharmacodynamics, pharmacokinetics, and immunogenicity of SC sibeprenlimab in IgAN subjects. Refer to Section 6.2.1 for detailed information.

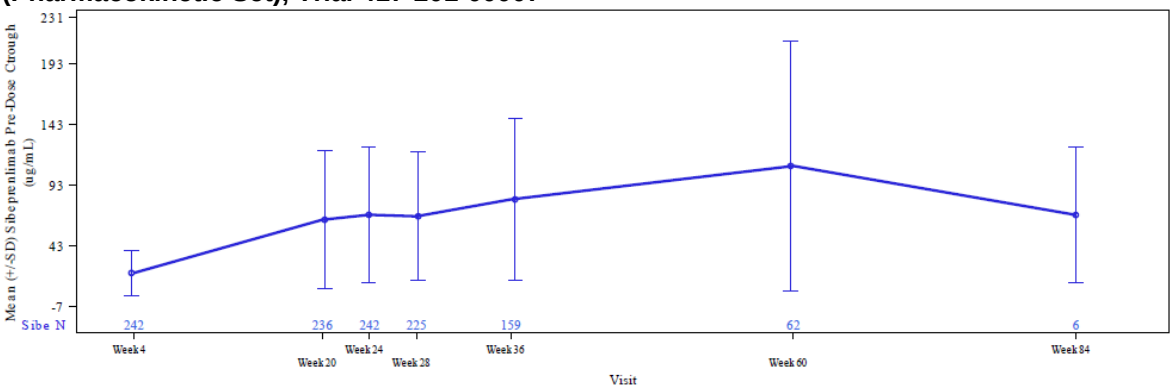
Eligible subjects were randomized 1:1 to sibeprenlimab 400 mg Q4W or placebo (approximately 225 per group). An additional exploratory cohort enrolled up to 20 subjects with eGFR 20 to 30 mL/min/1.73 m^2. Exploratory cohort data were excluded from popPK/PD analysis but included in E-R analysis.

PK samples were collected predose at Doses 2, 6, 7, 8, 10, 16, and 22 (Weeks 4, 20, 24, 28, 36, 60, 84) with postdose samples 8 to 12 days after Doses 2, 6, and 8 (Weeks 5, 21, 29). Blood samples for total IgA, IgG, IgM, APRIL, Gd-IgA1, anti-IgA1 autoantibody, and IgA-containing circulating immune complexes were collected predose on Day 1 and at Weeks 4, 8, 12, 24, 36, 48, 60, 72, 84, 96, and 112. ADA samples were collected at the same timepoints.

PK Results

The mean C_{trough} values of sibeprenlimab across treatment visits are presented in Figure 19. Steady-state was reached by Week 20 based on comparable C_{trough} values at Weeks 20, 24, and 28. The trial is ongoing and data beyond Week 36 are limited.

Figure 19. Mean (SD) Sibeprenlimab Predose (C_{trough}) Concentration (µg/mL) by Visit, Main Cohort (Pharmacokinetic Set), Trial 417-201-00007



Source: Figure 11.5.2.1.2-1 on Page 146 of 417-201-00007 CSR.
Abbreviations: CSR, clinical study report; C_{trough}, trough serum concentration; SD, standard deviation

PD Results

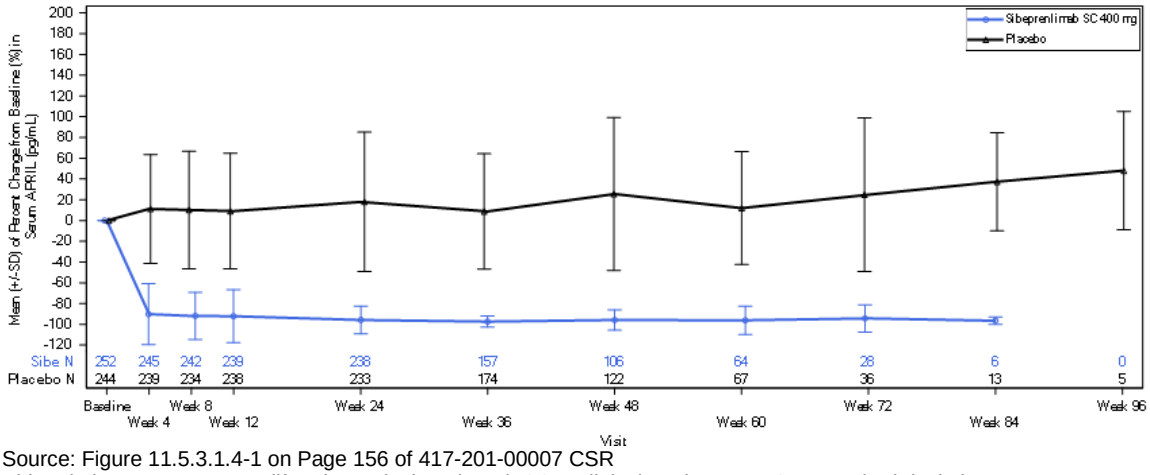
As shown in Figure 20, sibeprenlimab almost completely suppressed mean APRIL concentrations (reduction of 90.2%) by Week 4 and maintained the reduction through Week 84 in the small subset of subjects with data out to Week 84 (reduction of 96.5%). Minimal changes in APRIL concentrations were observed in the placebo group throughout the treatment period.

In the sibeprenlimab group, all immunoglobulin subtypes showed greatest decreases at Week 48:

- IgA: Decreased by 38.0% at Week 4, 62.2% at Week 24, and 68.8% at Week 48
- IgM: Decreased by 41.2% at Week 4, 70.4% at Week 24, and 74.5% at Week 48
- IgG: Decreased by 16.2% at Week 4, 32.1% at Week 24, and 35.0% at Week 48, with levels maintained thereafter
- Gd-IgA1: Decreased by 44.6% at Week 4, 63.6% at Week 24, and 67.1% at Week 48

Fewer samples were available at later time points for most parameters except IgG.

Figure 20. Mean (± SD) of Percent Change From Baseline in APRIL (pg/mL) by Visit, Main Cohort (Pharmacodynamic Set), Trial 417-201-00007



Source: Figure 11.5.3.1.4-1 on Page 156 of 417-201-00007 CSR
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; CSR, clinical study report; SD, standard deviation

14.2.6. Trial 417-201-00012

Title

Phase 2/3, Multicenter, Open-Label Trial to Evaluate the Long-Term Safety, Tolerability, and Efficacy of Sibeprenlimab Administered Subcutaneously in Subjects with Immunoglobulin A Nephropathy

Study Design

This is an ongoing, phase 2/3, multicenter, open-label trial to evaluate the long-term safety, tolerability, and efficacy of sibeprenlimab 400 mg administered SC Q4W. A total of 26 doses are planned to be administered, with Dose 1 administered on Day 1 and Dose 26 administered at Week 100. The trial population will only include subjects from Trials 417-201-00007 and VIS649-201. As of the interim analysis data cutoff date of September 4, 2024, only data from subjects who rolled over from Trial VIS649-201 (a total of 121 subjects) were analyzed.

Blood samples for PK analysis were collected as follows: Dose 1: predose sample at Day 1; Dose 3: one sample predose (Week 8) and one sample 8 to 12 days postdose (Week 9); Dose 6: one sample predose (Week 20); Dose 9: one sample predose (Week 32), Dose 17: one sample predose (Week 64), Dose 23: one sample predose (Week 88), and at Week 104 and Week 112 in the post-treatment follow-up period.

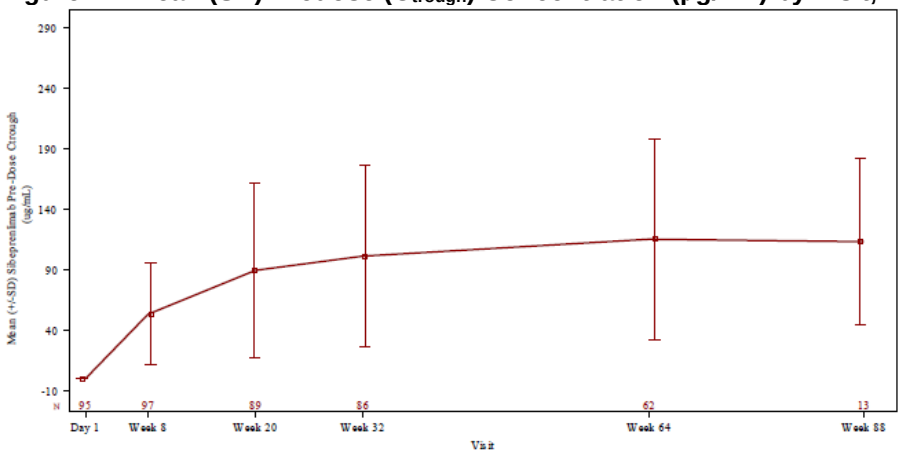
Blood samples for total IgA, IgG, IgM, APRIL, and ADA were collected predose on Day 1 and at Weeks 8, 20, 32, 44, 52, 64, 76, 88, 100, and 112.

PK Results

Following completion of Trial VIS649-201, there was a mean gap of approximately 7 months (not including the mandatory 4-month washout period from Trial VIS649-201) before subjects received their first 400 mg SC dose in this trial. During this interval, sibeprenlimab concentrations declined to below the LLOQ (100 ng/mL) in most subjects (74 of 76) who had previously received IV sibeprenlimab. Mean sibeprenlimab serum concentrations at Week 9

(110.3 µg/mL), measured 1-week after the Week 8 dose, exceeded the corresponding mean predose concentration at Week 8 (53.2 µg/mL). With 400 mg SC injection of sibeprenlimab Q4W, mean trough concentrations gradually increased and approached steady-state by Week 32 (Figure 21).

Figure 21. Mean (SD) Predose (C_{trough}) Concentration (µg/mL) by Visit, PK Set, Trial 417-201-00012



Source: Figure 11.5.2.3-1 on Page 80 of 417-201-00012 CSR
Abbreviations: CSR, clinical study report; C_{trough}, trough serum concentration ; PK, pharmacokinetic; SD, standard deviation

PD Results

PD biomarker (IgA, IgG, IgM, Gd-IgA1, and APRIL) levels in the prior sibeprenlimab IV group returned to baseline levels comparable to the placebo group following the approximately 7-month gap between trials.

Treatment Effects on PD Markers With SC Sibeprenlimab 400 mg Q4W

- IgA: Decreased by 58.6% at Week 20, with further reduction to 68.7% by Week 64. Levels began recovering toward baseline 12 weeks after treatment discontinuation.
- IgG: Achieved a 36.9% reduction by Week 52, which was maintained through Week 88. Recovery toward baseline was observed 12 weeks post-treatment.
- IgM: Showed the most pronounced reduction at 68.4% by Week 20, which was sustained through Week 100. Recovery began 12 weeks after treatment cessation.
- Gd-IgA1: Demonstrated a 64.5% reduction by Week 32, with further reduction to 76.4% at Week 100. Levels increased toward baseline 12 weeks post-treatment.
- APRIL: Exhibited near-complete suppression (−94.0%) by Week 8 that was maintained throughout treatment. Recovery was evident 12 weeks after the last dose, with levels increasing 24.8% above baseline.

The recovery data were only generated from three subjects.

14.3. Bioanalytical Method Validation and Performance

PK (free sibeprenlimab) and PD (APRIL) assays were initially validated (b) (4) (b) (4) then transferred (b) (4) with independent full validations and cross-validation. (b) (4) analyzed samples from subjects outside China; (b) (4) analyzed samples from Chinese subjects. Trial 417-201-00005 (Chinese subjects only) used (b) (4) Trial 417-201-00007 (global enrollment) used both laboratories; other studies (VIS649-101, VIS649-102, VIS649-201, 417-201-00012) used (b) (4) (b) (4) IgA, IgG, IgM were analyzed by central laboratories (b) (4) using Clinical Laboratory Improvement Amendments-certified assays but were not reviewed as they did not provide substantial evidence for benefit-risk assessment.

14.3.1. PK Bioanalytical Method

Serum free sibeprenlimab was measured by a meso-scale discovery-electrochemiluminescence (MSD-ECL) immunoassay, validated over 100-100,000 ng/mL (b) (4) (method TM.2154, validation report 13258.101218.2) and 100 to 50,000 ng/mL (anchored to 100,000 ng/mL) (b) (4) (method (b) (4)-2449) with minimum required dilution 1:5. Mouse anti-sibeprenlimab antibody clone 1H4 (anti paratopic) is coated onto MSD high-bind plates, sibeprenlimab in standards/quality controls (QCs)/samples are captured, then bound to ruthenium-labeled anti-sibeprenlimab. Concentrations are back-calculated from nonlinear regression.

Cross-validation tested 45 QC samples at (b) (4) (15 each at low, mid, high levels) and 27 QC samples at (b) (4) (9 each level). Percent differences were 18.5% (high), 9.0% (mid), and 8.5% (low), meeting <20% acceptance criteria.

The method performance during validation and sample analysis for method TM.2154 (b) (4) (b) (4) and (b) (4)-2449 (b) (4) are summarized in Table 54 and Table 55, respectively.

Table 54. Summary of Method Performance Using Method TM.2154

Parameter	Result/Summary
Summary of method performance during method validation (Report 13258.101218.2)	
Analyte	Free sibeprenlimab (VIS649)
Matrix	Human serum
Materials used for standard calibration curve, quality controls (QCs) and concentration	VIS649, Lot # 0000499526 (Primary Stock Concentration 23.9 mg/mL), (b) (4) At least six prescreened human serum lots
Minimum required dilutions (MRDs)	1:5
Source and lot of reagents	Critical reagents used: Mouse antiVIS649 Antibody (Clone 1H4), Lot # 308359, Visterra; Ruthenylated antiVIS649 antibody (RU-a-VIS649), Lot # SS88955, (b) (4) Recombinant Human APRIL/TNFSF13, Lot # TCF1018031, (b) (4)

Parameter	Result/Summary	
Validation parameters	Method validation summary	
Standard calibration curve properties, performance during accuracy and precision runs	range	100 to 100,000 ng/mL
	Regression model, weighting	4-parameter logistic, $1/y^2$
	Cumulative accuracy (%RE) from LLOQ to ULOQ	−3.80% to 8.80%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤7.67%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs	−13.5% to −1.94%
	Interbatch %CV	≤15.2%
	Intrabatch pooled precision	≤7.90%
	Total error (TE)	≤26.3% (LLOQ)
Selectivity and matrix effect	Matrix factor: 10 lots were tested in normal human serum. %RE −19.6% to −1.8% for QCL and −16.0% to 1.87% for QCH	
Interference & specificity	No interference in QCL samples fortified with up to 10.0 ng/mL of APRIL. No interference in QCM and QCH samples fortified with up to 20.0 ng/mL of APRIL.	
Hemolysis effect	No discernable effect observed. 5 lots were tested. %RE −12.4% to 1.00% for QCL and −5.20% to 4.40% for QCH. 1 lot for QCL outside acceptance criteria	
Lipemic effect	No discernable effect observed. 5 lots were tested. %RE −9.80% to 1.00% for QCL and −12.5% to −4.67% for QCH. 1 lot for QCL outside acceptance criteria	
Dilution linearity and hook effect	Maximum dilution: 32-fold; No hook effect observed	
Bench top/process stability	67 hours at ambient	
Freeze-thaw stability	Eight cycles (−80°C, nominal)	
Long term storage	1103 days at −80°C; 333 days at −20°C	
Parallelism	N/A	
Carry over	N/A	
Method performance in Trial VIS649-101 (Report number 13269.012119)		
Assay passing rate	28 runs passed over a total of 28 runs (100%)	
Standard curve performance	• Cumulative bias range: −3.00% to 6.00% • Cumulative precision: ≤5.63% CV	
QC performance	Excluding values outside acceptance range • Cumulative bias range: −7.19% to 1.47% • Cumulative precision: ≤9.21% CV Including values outside acceptance range • Cumulative bias range: −7.50% to 2.00% • Cumulative precision: ≤9.21% CV	
Method reproducibility	ISR was performed in 10.4% of study samples (50 out of 482), and 98% of the samples met the prespecified criteria (48 out of 49).	
Study sample analysis/ stability	Study samples were stored 322 days at −80°C Nominal. The LTS of 1103 days at −80°C Nominal covers the sample storage.	
Method performance in Trial VIS649-102 (Report number 17253.070121)		
Assay passing rate	17 runs passed over a total of 17 runs (100%)	
Standard curve performance	• Cumulative bias range: −2.40% to 3.00% • Cumulative precision: ≤7.19% CV	

Parameter	Result/Summary
QC performance	Excluding values outside acceptance range • Cumulative bias range: −2.27% to 18.0% • Cumulative precision: ≤5.87% CV Including values outside acceptance range • Cumulative bias range: −11.4% to 6.67% • Cumulative precision: ≤36.8% CV
Method reproducibility	ISR was performed in 10.7% of study samples (76 out of 707), and 100% of the samples met the prespecified criteria (76 out of 76).
Study sample analysis/ stability	Study samples were stored 156 days at −80°C nominal. The LTS of 1103 days at −80°C nominal covers the sample storage.
Method performance in Trial VIS649-201 (Report number 17493.190221)	
Assay passing rate	112 runs passed over a total of 130 runs (86%)
Standard curve performance	• Cumulative bias range: −2.20% to 4.40% • Cumulative precision: ≤7.12%
QC performance	Excluding values outside acceptance range • Cumulative bias range: −5.60% to 5.33% • Cumulative precision: ≤8.00% CV Including values outside acceptance range • Cumulative bias range: −5.57% to 7.81% • Cumulative precision: ≤142% CV
Method reproducibility	ISR was performed in 10% of 1st 1000 and 6.1% of the remaining study samples (331 out of 4774), and 85.4% of the samples met the prespecified criteria (280 out of 328).
Study sample analysis/stability	Study samples were stored 845 days at −80°C Nominal. The LTS of 1103 days at −80°C nominal covers the sample storage.
Method Performance in Trial 417-201-00007 (Report number 21153.150323)	
Assay passing rate	51 runs passed over a total of 60 runs (85.0%)
Standard curve performance	• Cumulative bias range: −1.50 to 4.00% • Cumulative precision: ≤8.58% CV
QC performance	Excluding values outside acceptance range • Cumulative bias range: −3.20 to 7.00% • Cumulative precision: ≤11.6% CV Including values outside acceptance range • Cumulative bias range: −3.20% to 16.0% • Cumulative precision: ≤125% CV
Method reproducibility	ISR was performed in 10% of 1st 1000 and 4.1% of the remaining study samples (33 out of 803), and 82.1% (101 out of 123) of the samples met the prespecified criteria. Additional analysis is ongoing.
Study sample analysis/stability	Study samples were stored 859 days at −80°C nominal. The LTS of 1103 days at −80°C nominal covers the sample storage.

Parameter	Result/Summary
Method performance in Trial 417-201-00012 (Report number 22253.161123)	
Assay passing rate	20 runs passed over a total of 23 runs (87%)
Standard curve performance	• Cumulative bias range: −2.70% to 3.60% • Cumulative precision: ≤8.12% CV
QC performance	Excluding values outside acceptance range • Cumulative bias range: −12.1% to 5.33% • Cumulative precision: ≤10.2% CV Including values outside acceptance range • Cumulative bias range: −5.90% to 8.00% • Cumulative precision: ≤16.4% CV
Method reproducibility	ISR was performed in 9.4% of study samples (52 out of 554), and 73.1% of the samples met the prespecified criteria (38 out of 52). Additional analysis is on-going.
Study sample analysis/stability	Study samples were stored 902 days at −80°C Nominal. The LTS of 1103 days at −80°C Nominal covers the sample storage.

Source: Table 2.7.1.5.2-1 on Page 16 to 21 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
VIS649 refers to sibeprenlimab
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; CV, coefficient of variation; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; LTS, long term storage; MRD, minimum required dilution; N/A, not available; QC, quality control; QCH, quality control high; QCL, quality control low; QCM, quality control mid; RE, relative error; TE, total error; ULOQ, upper limit of quantitation

Table 55. Summary of Method Performance Using Method (b) (4)-2449

Parameter	Result/Summary	
Summary of method performance during method validation (Report (b) (4) D18-R4531)		
Analyte	Free sibeprenlimab (VIS649)	
Matrix	Human serum	
Materials used for standard calibration curve, quality controls (QCs) and concentration	VIS649 drug product, Lot # 191B20-02 (primary stock concentration 205.5 mg/mL), Visterra pooled human serum	
Minimum required dilutions (MRDs)	1:5	
Source and lot of reagents	Mouse antiVIS649 antibody, Clone 1H4, Lot # 308359, 1.05 mg/mL, Visterra RU-a-VIS649, Lot # CR163105-024, 1 mg/mL, Visterra	
Validation parameters	Method validation summary	
Standard calibration curve properties, performance during accuracy and precision runs	range	100 ng/mL to 50,000 ng/mL (100,000 ng/mL anchor)
	Regression model, weighting	4-parameter logistic, $1/y^2$
	Cumulative accuracy (%RE) from LLOQ to ULOQ	−3.5% to 3.8%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤7.0%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs	−6.7% to 0.0%
	Interbatch %CV	≤9.5%
	Total Error (TE)	≤15.0%
Selectivity and matrix effect	Matrix Factor: 10 lots of healthy human serum. %bias −16.7% to 14.6%	
Interference and specificity	No interference up to 2,500 pg/mL recombinant human APRIL.	

Parameter	Result/Summary
Hemolysis effect	Significant interference observed at 5% hemolysis. Bias −30.8% to −10.4% No significant interference observed at 2% hemolysis. Bias −24.2% to 3.7%
Lipemic effect	No significant interference observed at ≥500 mg/dL triglycerides Bias −17.3% to 10.8%
Dilution linearity and hook effect	There was no hook effect when VIS649 concentration was up to 2,000,000 ng/mL The validated largest dilution factor in human serum is 8000.
Bench top/process stability	Stable up to 71 hours at room temperature and 2°C - 8°C
Freeze thaw stability	7 cycles from −80°C to room temperature
Long term storage	575 days at −80°C
Parallelism	N/A
Carry over	N/A
Method performance in Trial 417-201-00005 (Report number (b) (4) D18-R4612)	
Assay passing rate	9 runs passed over a total of 9 runs (100.0%)
Standard curve performance	• Cumulative bias range: −4.6% to 4.3% • Cumulative precision: ≤5.4% CV
QC performance	• Cumulative bias range: −2.0% to 0.5% • Cumulative precision: ≤5.5% CV
Method reproducibility	ISR was performed in 10.7% of study samples, and 100.0% of the samples met the prespecified criteria.
Study sample analysis/ stability	Study samples were stored 197 days at −80°C Nominal. The established LTS of 575 days at −80°C Nominal covers the sample storage.
Method performance in Trial 417-201-00012 (Report number (b) (4) D18-R5014)	
Assay passing rate	10 runs passed over a total of 10 runs (100.0%)
Standard curve performance	• Cumulative bias range: −2.2% to 9.2% • Cumulative precision: ≤18.3% CV
QC performance	• Cumulative bias range: −2.5% to 5.2% • Cumulative precision: ≤10.9% CV
Method reproducibility	ISR is planned but was not completed in time for the interim analysis.
Study sample analysis/ stability	Study samples were stored 407 days at −80°C Nominal. The established LTS of 575 days at −80°C Nominal covers the sample storage.

Source: Table 2.7.1.5.3-1 on Page 22 to 24 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
VIS649 refers to sibeprenlimab
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; CV, coefficient of variation; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; LTS, long term storage; N/A, not available; QC, quality control; RE, relative error; TE, total error; ULOQ, upper limit of quantitation

14.3.2. Bioanalytical Method for Serum APRIL Levels

The bioanalytical method for serum APRIL level detection was validated over 50.0 to 50,000 pg/mL using an ECL assay with minimum required dilution 1:10. Briefly, anti-recombinant-human-APRIL antibody is coated onto an MSD high-bind plate (ECL capable) and free APRIL that is present in standards/QCs/samples are captured onto the coated plate, and then bound to biotinylated anti-recombinant-human-APRIL antibody, followed by a streptavidin

sulfotag as the detection reagent. The assay plate is then read using an MSD ECL plate reader. The concentration of free APRIL is back calculated from the nonlinear regression of the standards. The method performance during validation and sample analysis for method TM.2174 (b) (4) and (b) (4)-2451 (b) (4) are summarized in Table 56 and Table 57, respectively.

Table 56. Summary of Method Performance Using Method TM.2174

Parameter	Result/Summary	
Summary of method performance during method validation (Report 12938.050318.1)		
Analyte	APRIL (TNFSF13)	
Matrix	Human serum	
Materials used for standard calibration curve, quality controls (QCs) and concentration	rhAPRIL (TNFSF13), Lot # TCF1018031, (b) (4) 100 µg/mL reconstituted, Calibration standards were prepared using APRIL in buffer. QC samples were prepared for APRIL in human serum (at least 6 prescreened human serum lots were pooled) and in buffer	
Minimum required dilutions (MRDs)	1:10	
Source and lot of reagents	Critical reagents used: Anti-recombinant human APRIL, Lot# B174406, (b) (4) Biotinylated anti-recombinant Human APRIL, Lot# B181875, (b) (4) Streptavidin Sulfotag, Lot# W0017855S & Lot# W0018126S, (b) (4).	
Validation parameters	Method validation summary	
Standard calibration curve properties, performance during accuracy and precision runs	range	50 to 50,000 pg/mL
	Regression model, weighting	4-parameter logistic, 1/ y^2
	Cumulative accuracy (%RE) from LLOQ to ULOQ	−1.50% to 2.00%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤3.59%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs	−15.2% to 0.0229%
	Interbatch %CV	≤16.2%
	Total error (TE)	≤20.7%
Selectivity and matrix effect	Matrix Factor: 10 lots were tested in normal human serum at the blank (unspiked), LLOQ (50.0 pg/mL) and QCH (37500 pg/mL) concentrations. %RE: −23.8 to −3.31% for LLOQ and −19.5 to 4.35% for QCH, 1 lot for LLOQ outside acceptance criteria No matrix effect observed	
Interference and specificity	VIS649 interference observed at all levels tested.	
Hemolysis effect	No discernable effect observed. 5 lots were tested. %RE: −13.0% to −9.96% for QCL and −17.1% to −10.7% for QCH	
Lipemic effect	No discernable effect observed. 5 lots were tested. %RE: −13.4% to 4.20% for QCL and −16.5% to 0.00% for QCH	

Parameter	Result/Summary
Dilution linearity & hook effect	N/A
Bench-top/process stability	APRIL (TNFSF13): 24 hours at Ambient
Freeze-Thaw stability	APRIL (TNFSF13): 4 cycles (−80°C, Nominal)
Long Term Storage	619 days at −80°C
Parallelism	N/A
Carry over	N/A
Method performance in Trial VIS649-101 (Report number 13268.030319)	
Assay passing rate	14 runs passed over a total of 14 runs (100%)
Standard curve performance	• Cumulative bias range: −1.00% to 2.80% • Cumulative precision: ≤6.41% CV
QC performance	Excluding values outside acceptance range • Cumulative bias range: −3.47% to −1.48% • Cumulative precision: ≤6.19% CV Including values outside acceptance range • Cumulative bias range: −4.00% to −1.48% • Cumulative precision: ≤7.91% CV
Method reproducibility	ISR was performed in 10.2% of study samples (30 out of 294), and 96.7% of the samples met the prespecified criteria (29 out of 30).
Study sample analysis/ stability	Standard/QCs were prepared fresh on day of assay. Study samples were stored 137 days at −80°C Nominal. The LTS of 619 days at −80°C Nominal covers the sample storage
Method performance in Trial VIS649-102 (Report number 17255.070121)	
Assay passing rate	10 runs passed over a total of 14 runs (71.4%)
Standard curve performance	• Cumulative bias range: −2.25% to 3.80% • Cumulative precision: ≤7.45% CV
QC performance	Excluding values outside acceptance range • Cumulative bias range: −5.99% to 8.89% • Cumulative precision: ≤7.73% CV Including values outside acceptance range • Cumulative bias range: −5.99% to 10.3% • Cumulative precision: ≤8.50% CV
Method reproducibility	The ISR was performed in 10.4% of study samples (50 out of 480), and 82.0% of the samples met the prespecified criteria (41 out of 50).
Study sample analysis/ stability	Standard/QCs were prepared fresh on day of assay. Study samples were stored 147 days at −80°C Nominal. The LTS of 619 days at −80°C Nominal covers the sample storage.

Parameter	Result/Summary
Method performance in Trial VIS649-201 (Report number 17513.230221)	
Assay passing rate	53 runs passed over a total of 55 runs (96.4%)
Standard curve performance	• Cumulative bias range: −1.50% to 2.60 • Cumulative precision: ≤7.12% CV
QC performance	Excluding values outside acceptance range • Cumulative bias range: −5.39% to −1.60% • Cumulative precision: ≤9.30% CV Including values outside acceptance range • Cumulative bias range: −5.39% to −1.60% • Cumulative precision: ≤14.7% CV
Method reproducibility	ISR was performed in 10% of 1st 1000 and 5.1% of the remaining study samples (194 out of 2830), and 97.4% of the samples met the prespecified criteria (189 out of 194).
Study sample analysis/stability	Standard/QCs were prepared fresh on day of assay. Study samples were stored 1169 days at −80°C Nominal. The LTS of 619 days at −80°C Nominal covers the sample storage, except for 20 samples. Data was reported for the 20 samples. LTS is on-going.
Method Performance in Trial 417-201-00007 (Report number 21312.210423)	
Assay passing rate	54 runs passed over a total of 73 runs (74.0%)
Standard curve performance	• Cumulative bias range: −0.80% to 2.00% • Cumulative precision: ≤7.74% CV
QC performance	Excluding Values Outside Acceptance Range • Cumulative bias range: −9.00% to −1.33% • Cumulative precision: ≤9.12% CV Including Values Outside Acceptance Range • Cumulative bias range: −9.00% to 7.33% • Cumulative precision: ≤83.9% CV
Method reproducibility	ISR was not performed.
Study sample analysis/stability	Standard/QCs were prepared fresh on day of assay. Study samples were stored 562 days at −80°C Nominal. The LTS of 619 days at −80°C Nominal covers the sample storage.
Method performance in Trial 417-201-00012 (Report number 22256.161123)	
Assay passing rate	12 runs passed over a total of 14 runs (85.7%)
Standard curve performance	• Cumulative bias range: −1.20% to 3.00% • Cumulative precision: ≤7.15% CV
QC performance	• Cumulative bias range: −4.50% to 2.67% • Cumulative precision: 6.82% CV
Method reproducibility	ISR was not performed.
Study sample analysis/stability	Standard/QCs were prepared fresh on day of assay. Study samples were stored 693 days at −80°C Nominal. The LTS of 619 days at −80°C Nominal covers the sample storage, except for 5 samples. Data was reported for the 5 samples. LTS is on-going.

Source: Table 2.7.1.5.6-1 on Page 28 to 33 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; CV, coefficient of variation; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; LTS, long term storage; MRD, minimum required dilution; MSD, material safety datasheet; N/A, not available; QC, quality control; QCH, quality control high; QCL, quality control low; rh, recombinant; RE, relative error; TE, total error; TNSF13, tumor necrosis factor ligand superfamily member 13; ULOQ, upper limit of quantitation

Table 57. Summary of Method Performance Using Method (b) (4)-2451

Parameter	Result	
Summary of method performance during method validation (Report (b) (4) D18-R4533)		
Analyte	Free sibeprenlimab (VIS649)	
Matrix	Human serum	
Materials used for standard calibration curve, quality controls (QCs) and concentration	rhAPRIL/TNFSF13, Lot # TCF1522031, (b) (4) Calibration standards were prepared using APRIL in buffer, QC samples were prepared for APRIL in human serum.	
Minimum required dilutions (MRDs)	1:10	
Source and lot of reagents	Anti-recombinant Human APRIL, Lot# B341048, (b) (4) Biotinylated Anti-recombinant Human APRIL, Lot# B366012, (b) (4) Streptavidin Sulfotag, Lot# W0021065S, Meso Scale Discovery	
Validation parameters	Method validation summary	
Standard calibration curve properties, performance during accuracy and precision runs	range	50 to 50,000 pg/mL
	Regression model, weighting	4-parameter logistic, $1/y^2$
	Cumulative accuracy (%RE) from LLOQ to ULOQ	−1.7% to 2.9%
	Cumulative precision (%CV) from LLOQ to ULOQ	≤11.2%
Performance of QCs during accuracy and precision runs	Cumulative accuracy (%RE) in 5 QCs	−0.7% to 3.9%
	Inter batch %CV	≤10.7%
	Total error (TE)	≤14.6%
Selectivity and matrix effect	Matrix Factor: 6 individual human serum spiked with rhAPRIL/TNFSF13, tested by using serial dilution starting at the original followed by 4 additional levels (1:4, 1:16, 1:64, 1:256) in Assay Diluent %RE: −6.0% to 17.6% All results passed and met the acceptance criteria in the study protocol, so the method has no matrix effect in nominal healthy human serum	
Interference and specificity	VIS649 Interference: not tested	
Hemolysis effect	Not tested	
Lipemic effect	Not tested	
Dilution linearity and hook effect	Dilution linearity up to 256-fold No hook effect observed up to 500,000 pg/mL	
Bench-top/process stability	24 hours 7 minutes at room temperature 24 hours 7 minutes at 2-8°C	
Freeze-Thaw stability	Five cycles (−80°C, Nominal)	
Long Term Storage	362 days at −80°C	
Parallelism	N/A	
Carry over	N/A	

Parameter	Result
Method performance in Trial 417-201-00005 (Report number (b) (4) D18-R4614)	
Parameter	Summary
Assay passing rate	Four runs passed over a total of 5 runs (80.0%)
Standard curve performance	• Cumulative bias range: −2.7 to 5.1% • Cumulative precision: ≤8.3% CV
QC performance	• Cumulative bias range: −3.7% to 2.5% • Cumulative precision: ≤8.2% CV
Method reproducibility	ISR was not performed.
Study sample analysis/ stability	Study samples were stored 156 days at −80°C Nominal. The LTS of 362 days at −80°C Nominal covers the sample storage.
Method Performance in Trial 417-201-00012 (Report number (b) (4) D18-R5016)	
Parameter	Summary
Assay passing rate	10 runs passed over a total of 13 runs (85.7%)
Standard curve performance	• Cumulative bias range: −0.7 to 1.4% • Cumulative precision: ≤6.5% CV
QC performance	• Cumulative bias range: −4.8% to 3.3% • Cumulative precision: ≤11.4% CV
Method reproducibility	ISR was not performed.
Study sample analysis/ stability	Standard/QCs were prepared fresh on day of assay. Study samples were stored 445 days at −80°C Nominal. The LTS of 362 days at −80°C Nominal which does not cover the sample storage. LTS is ongoing.

Source: Table 2.7.1.5.7-1 on Page 23 to 35 of Summary of Biopharmaceutic Studies and Associated Analytical Methods
Abbreviations: APRIL, A-Proliferation-Inducing Ligand; CV, coefficient of variation; ISR, incurred sample reanalysis; LLOQ, lower limit of quantitation; LTS, long term storage; MRD, minimum required dilution; N/A, not available; QC, quality control; rh, recombinant; RE, relative error; TE, total error; TNSF13, tumor necrosis factor ligand superfamily member 13; ULOQ, upper limit of quantitation

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

Immunogenicity was assessed in all sibeprenlimab clinical trials, including three phase 2/3 trials in subjects with IgAN (Trials 417-201-00007, VIS649-201, and 417-201-00012) and three phase 1 trials in healthy subjects (Trials VIS649-101, VIS649-102, and 417-201-00005). Due to different routes of administration (IV versus SC), dosing regimens, and drug exposure durations, pooled immunogenicity analyses were not conducted.

According to the Office of Pharmaceutical Quality review, the ADA assay demonstrated drug tolerance of 750 µg/mL and target (APRIL) tolerance of 50 µg/mL {[DARRTS ID: 5674385], 2025 #11}. The NAb assay demonstrated drug tolerance of 10 µg/mL at 300 ng/mL positive control (PC), 30 µg/mL at 800 ng/mL PC, 100 µg/mL at 3,200 ng/mL PC, and target (APRIL) tolerance of 10 ng/mL. Per the Office of Pharmaceutical Quality review, the ADA assay has no drug or target tolerance issues while drug and target concentration in clinical trials may have interfered with the NAb assay. Therefore, ADA assessments for clinical trials were reliable while NAb assessments were not.

For NAb assay drug tolerance, a notable number of ADA-positive samples demonstrated trough sibeprenlimab concentrations that exceeded tolerable drug concentrations at various PC cut

points (refer to Figures CF-IR3-4.1, CF-IR3-5.1, CF-IR3-6.1 in the Applicant's response to IR Q1-3). Higher drug concentrations exceeding drug tolerance cut points may result in NAb false-negative results. Considering these interferences and the small sample sizes for NAb-negative and -positive subjects, no definitive conclusion can be drawn regarding NAb incidence and its effects on pharmacokinetics, pharmacodynamics, efficacy, and safety. Preliminary results are presented but should be interpreted with caution. Since this submission is for accelerated approval with interim data, and because samples for pharmacokinetics, pharmacodynamics, and ADA will be collected until the end of the pivotal trial and throughout the extension trial, this topic will be revisited after completion of the confirmatory phase of the trial when more data are available.

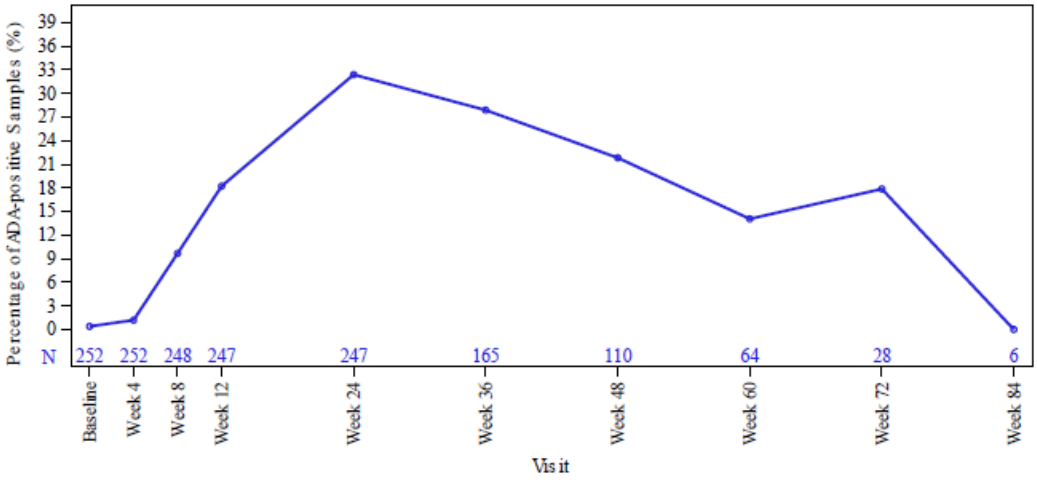
For VIS-649-201 and 417-201-00007 trials, the immunogenicity set includes all randomized subjects who received at least 1 dose of IMP, excluding placebo, and have at least 1 evaluable ADA measurement.

For 417-201-00012 trial, the immunogenicity set includes all enrolled subjects who received at least 1 dose of IMP and have at least 1 evaluable ADA measurement.

ADA Incidence in Pivotal Phase 3 Trial

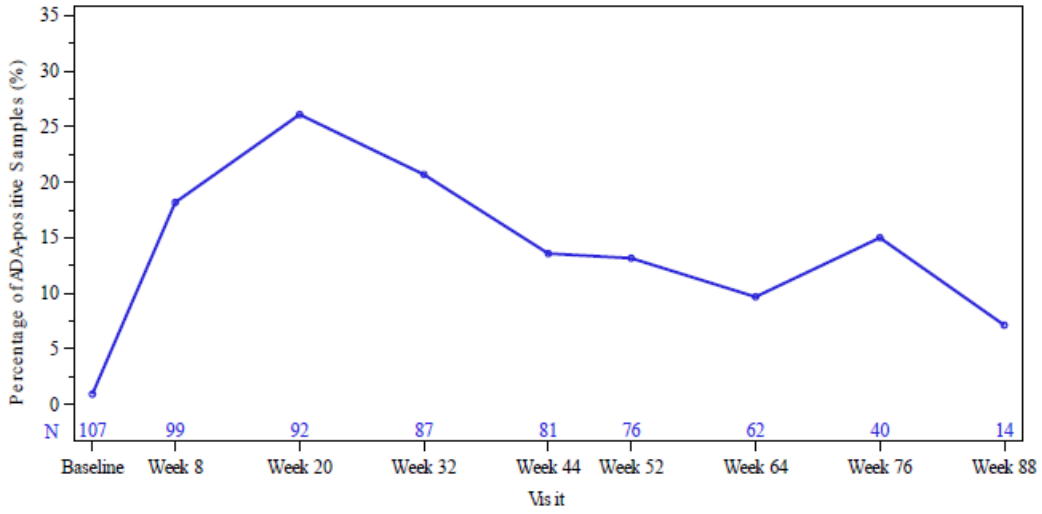
As of the September 4, 2024, interim analysis data cutoff date, in the ongoing pivotal Trial 417-201-00007, 34.4% (88/256) of evaluable subjects treated with sibeprenlimab developed ADA, and 23.9% (21/88) of these ADA-positive subjects demonstrated neutralizing activity. The peak ADA incidence occurred between Week 20 (Day 141) and Month 6 (Day 180) (Figure 22 and Figure 23). Two subjects with postdose ADA-positive results were reported as ADA-negative by the Applicant due to missing baseline ADA values. The FDA reviewers classified these two subjects as treatment-emergent ADA-positive. This classification difference resulted in an ADA incidence of 88/256 (34.4%) per FDA assessment versus 86/257 (33.5%) per the Applicant's analysis. One subject who only had baseline ADA status was excluded from the FDA reviewers' analysis.

Figure 22. Percentage of ADA-Positive Samples by Visit, Trial 417-201-00007



Source: Figure 4.5.1.3.-1 on Page 77 of Integrated Summary of Immunogenicity
Abbreviations: ADA, antidrug antibody

Figure 23. Percentage of ADA-Positive Samples by Visit, Trial 417-201-00012



Source: Figure 4.5.3.3.-1 on Page 100 of Integrated Summary of Immunogenicity
Abbreviations: ADA, antidrug antibody

ADA/NAb Status on Pharmacokinetics, Pharmacodynamics, Efficacy and Safety

The evaluation of immunogenicity effects on pharmacokinetics, pharmacodynamics, efficacy, and safety focused on results from the pivotal phase 3 trial (417-201-00007) and open-label extension trial (417-201-00012, interim analysis with subjects rolled over from phase 2 trial VIS649-201) because the population and dosing regimen were most relevant. Data from phase 2 trial (VIS649-201) served as supportive evidence only, as the dosing regimen (body weight-based IV infusion monthly) differs from the proposed to be marketed regimen (flat SC dose Q4W). Immunogenicity effects in phase 1 studies (VIS649-101: single-dose IV; VIS649-102: single-dose SC; 417-201-00005: single-dose SC in healthy Chinese subjects) were not summarized because ADA effects after single doses are not expected to onset immediately, and ADA titer and incidence may increase after multiple doses.

As stated in Section 8, population PK/PD and exposure-efficacy response relationship analyses using data from trials VIS649-201, 417-201-00007, and 417-201-00012 showed that ADA-positive subjects have approximately 40% lower sibeprenlimab exposure. However, this decreased exposure did not appear to translate into a clinically meaningful effect on pharmacodynamics or proteinuria compared to placebo.

As noted, due to NAb assay drug and target tolerance issues, NAb effects on pharmacokinetics, pharmacodynamics, efficacy, and safety presented in this review should be interpreted with caution.

Immunogenicity findings in each of the clinical trials conducted in subjects with IgAN, including effects on pharmacokinetics, pharmacodynamics, efficacy, and safety, are summarized below.

Trial 417-201-00007

The IA cut-off date was September 4, 2024. A total of 320 subjects (152 sibeprenlimab, 168 placebo) were included in the IA Set for efficacy evaluations. For pharmacokinetics, pharmacodynamics, and safety evaluations, all enrolled subjects with at least one evaluable ADA sample were included.

ADA prevalence at baseline was 0.4%, which is within expectation due to the ADA assay cut point assignment method. For all post-treatment visits, 86 subjects (33.5%) had at least one ADA-positive result while 171 subjects (66.5%) remained ADA-negative; 19 subjects (8.1%) were NAb-positive at one or more visits. For analysis of ADA titer relationships to clinical endpoints, ADA titer groups were defined as low ≤16, medium >16 and ≤128, and high >128. ADA incidence in the low, medium, and high titer groups was 34.9%, 44.2%, and 19.8%, respectively.

Effect on Pharmacokinetics

Based on data available at the preplanned IA, sibeprenlimab mean predose serum concentrations (C_{trough}) in ADA-positive subjects were approximately 40% lower than those in ADA-negative subjects (Table 58), though C_{trough} variability largely overlapped between groups. PopPK modeling and simulation predicted a similar C_{trough} decrease (47% reduction) in ADA-positive versus ADA-negative subjects (Figure 13). Additional popPK simulations showed decreases of 34% and 38% in C_{max} and AUC_{tau}, respectively, in ADA-positive versus ADA-negative subjects (Figure 13, Section 8).

NAb effect on C_{trough} is not clear due to limited sample size and potential drug interference on the NAb assay (Table 59).

Table 58. Summary of Sibeprenlimab Predose C_{trough} by Visit and by ADA Category, Trial 417-201-00007

Visit	ADA Negative		ADA Positive		Percent Decrease[a]
	n	Mean C_{trough}, µg/mL (SD)	n	Mean C_{trough}, µg/mL (SD)	
Week 4	163	23.0 (19.7)	79	16.4 (14.1)	28.7
Week 20	158	74.7 (58.9)	78	44.1 (45.8)	41.0
Week 24	162	79.7 (59.2)	80	46.1 (37.5)	42.2
Week 28	149	77.6 (54.6)	76	47.3 (41.8)	39.0
Week 36	105	94.4 (73.6)	54	55.6 (38.9)	41.1
Week 60	42	133.3 (114.2)	20	57.1 (36.7)	57.2
Week 84	2	105.1 (45.2)	4	50.2 (56.5)	52.2

[a] % lower = 100 - (Mean C_{trough} ADA positive / Mean C_{trough} ADA negative)*100)
Source: Table 4.5.1.4-1 on Page 78 of Integrated Summary of Immunogenicity
Abbreviations: ADA, antidrug antibody; C_{trough}, trough serum concentration; n, number of subjects with an assessment available at the relevant time point; SD, standard deviation

Table 59. Summary of Sibeprenlimab Predose C_{trough} by Visit and by NAb Category, Trial 417-201-00007

	ADA-Negative		ADA-Positive					
			NAb-Negative			NAb-Positive		
Visit	n	Mean C_{trough}, µg/mL (SD)	n	Mean C_{trough}, µg/mL (SD)	% Decrease	n	Mean C_{trough}, µg/mL (SD)	% Decrease
Week 4	163	23.0 (19.7)	41	15.0 (14.8)	34.8	17	17.6 (14.4)	23.5
Week 20	158	74.7 (58.9)	42	49.6 (47.5)	33.6	16	24.2 (22.4)	67.6
Week 24	162	79.7 (59.2)	43	50.8 (32.5)	45.1	17	29.3 (20.7)	63.2
Week 28	149	77.6 (54.6)	42	47.5 (33.1)	38.8	18	48.6 (58.0)	37.3

Visit	ADA-Negative		ADA-Positive					
			NAb-Negative			NAb-Positive		
	n	Mean C_{trough}, µg/mL (SD)	n	Mean C_{trough}, µg/mL (SD)	% Decrease	n	Mean C_{trough}, µg/mL (SD)	% Decrease
Week 37	105	94.4 (73.6)	34	66.7 (42.6)	29.3	11	34.0 (19.0)	64.0
Week 60	42	133.3 (114.2)	10	68.2 (43.2)	48.8	9	47.8 (27.4)	64.1
Week 84	2	105.1 (45.2)	3	27.6 (41.6)	73.7	1	118.0 (n.e.)	-12.3

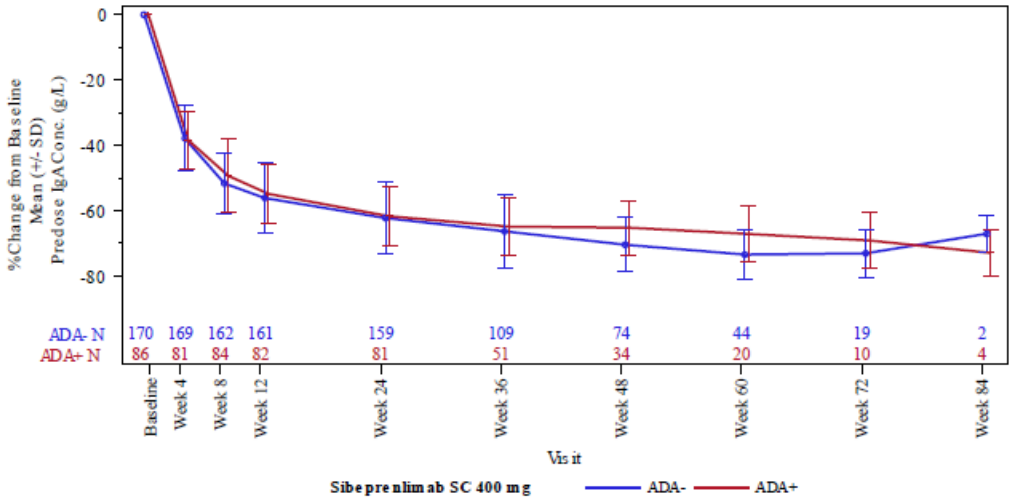
Source: reconstructed from Table CT-15.1.2.1 on page 2748-2754 of 417-201-00007 CSR
Values less than lower limit of quantification (LLOQ) were considered as 0. Percent decrease was relative to mean C_{trough} ADA-negative.
Abbreviations: ADA, antidrug antibody; CSR, clinical study report; C_{trough}, trough serum concentration; NAb, neutralizing antibody; n.e., not estimable; SD, standard deviation

Effect on Pharmacodynamics

At Week 24, when ADA prevalence peaked at 32.4% with maximum mean ADA titer of 170 (SD 526), antidrug antibody status did not meaningfully impact PD responses. The percent change from baseline in mean (SD) serum total IgA was −62.3% (11.2) for ADA-negative subjects compared with −61.7% (9.1) for ADA-positive subjects and −58.1% (10.1) for NAb-positive subjects.

Mean serum total IgA concentration profiles over time were similar across all groups regardless of ADA status Figure 24 NAb status, or ADA titer level. Comparable trends were observed for other PD parameters including APRIL and Gd-IgA1.

Figure 24. Percent Change From Baseline of Predose IgA Concentration by Visit and by ADA Category, Trial 417-201-00007



Source: Figure 4.5.1.5-1 on Page 80 of the integrated summary of immunogenicity
Abbreviations: ADA, antidrug antibody, ADA-, ADA-negative; ADA+, ADA-positive; IgA, immunoglobulin A; N, total number of subjects in the relevant analysis set; SC, subcutaneous; SD, standard deviation

Effect on Efficacy

The incomplete dataset at the time of the IA precludes a reliable interpretation of the relationship between ADA/NAb status and efficacy; this will be evaluated further upon completion of Trial 417-201-00007.

ANCOVA analysis of uPCR-24h reduction at Month 9 showed 41.6% (95% CI: 26.7, 53.4) in ADA-positive subjects versus 52.7% (95% CI: 42.6, 61.0) in ADA-negative subjects with

overlapping confidence intervals (Table 60). While the reduction in uPCR-24h at Month 9 was numerically greater in ADA-negative subjects, these results should be interpreted with caution given the small sample size at the time of the IA. Regardless of ADA status, sibeprenlimab-treated subjects experienced clinically meaningful uPCR-24h reduction versus placebo. Insufficient subjects were available for NAb status or ADA titer category analysis at the interim timepoint.

Table 60. ANCOVA Analysis of uPCR-24h at Baseline and at Month 9 by ADA Category, Immunogenicity Set, and IA Full Analysis Set #1, Trial 417-201-00007

ADA Category	N[a]	Ratio of GM (95% CI)	Corresponding % Reduction[b] (95% CI)
ADA negative	102	0.473 (0.390, 0.574)	52.7 (42.6, 61.0)
ADA positive	49	0.584 (0.466, 0.733)	41.6 (26.7, 53.4)

Source: Table 4.5.1.6-1 on Page 80 of the integrated summary of immunogenicity
[a] Number of subjects who were in both IA Full Analyses Set #1 and Immunogenicity Set
[b] Calculated as (1-GM of uPCR ratio estimated from ANCOVA odel)*100%
Abbreviations: ANCOVA, analysis of covariance; ADA, antidrug antibody; CI, confidence interval; GM, geometric mean; IA, interim analysis; N, total number of subjects in the relevant analysis set; uPCR, urine protein-to-creatinine ratio

(b) (4)

Effect on Safety

Neither ADA status (Table 62) nor ADA titer category (Table 63) influenced the frequency of any TEAEs or of hypersensitivity TEAEs.

Table 62. Number of Subjects With Any TEAEs and Hypersensitivity TEAEs by ADA Category Main Cohort, Immunogenicity Set, Trial 417-201-00007

System Organ Class/ Preferred Term	ADA Negative (N = 171) n (%)	ADA Positive (N = 86) n (%)
Any TEAE	127 (74.3%)	64 (74.4%)
Any hypersensitivity TEAE	12 (7.0%)	2 (2.3%)
Eye disorders	1 (0.6%)	0
Swelling of eyelid	1 (0.6%)	0
General disorders and administration site conditions	1 (0.6%)	0
Injection site hypersensitivity	1 (0.6%)	0
Respiratory, thoracic, and mediastinal disorders	2 (1.2%)	0
Rhinitis allergic	2 (1.2%)	0
Skin and subcutaneous tissue disorders	8 (4.7%)	2 (2.3%)
Dermatitis	1 (0.6%)	0
Dermatitis allergic	1 (0.6%)	0
Dermatitis contact	1 (0.6%)	0
Eczema	2 (1.2%)	2 (2.3%)
Rash	2 (1.2%)	0
Rash erythematous	1 (0.6%)	0

Source: Table 4.5.1.7-1 on Page 85 of the integrated summary of immunogenicity
Abbreviations: ADA, antidrug antibody; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; TEAE, treatment-emergent adverse event

Table 63. Number of Subjects With Any TEAEs and Hypersensitivity TEAEs by ADA Titer Group, Immunogenicity Set, Trial 417-201-00007

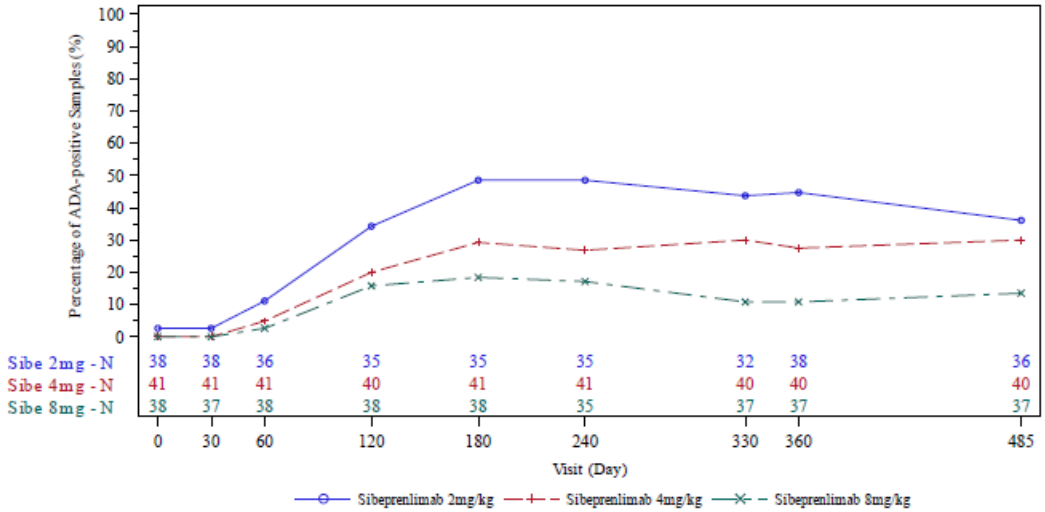
System Organ Class/ Preferred Term	ADA Negative (N = 171) n (%)	ADA Titer Group		
		Low (N = 30) n (%)	Medium (N = 38) n (%)	High (N = 17) n (%)
Any TEAE	127 (74.3%)	22 (73.3%)	28 (73.7%)	14 (82.4%)
Any hypersensitivity TEAE	12 (7.0%)	0	0	2 (11.8%)
Eye disorders	1 (0.6%)	0	0	0
Swelling of eyelid	1 (0.6%)	0	0	0
General disorders and administration site conditions	1 (0.6%)	0	0	0
Injection site hypersensitivity	1 (0.6%)	0	0	0
Respiratory, thoracic, and mediastinal disorders	2 (1.2%)	0	0	0
Rhinitis allergic	2 (1.2%)	0	0	0
Skin and subcutaneous tissue disorders	8 (4.7%)	0	0	2 (11.8%)
Dermatitis	1 (0.6%)	0	0	0
Dermatitis allergic	1 (0.6%)	0	0	0
Dermatitis contact	1 (0.6%)	0	0	0
Eczema	2 (1.2%)	0	0	2 (11.8%)
Rash	2 (1.2%)	0	0	0
Rash erythematous	1 (0.6%)	0	0	0

Source: Adapted from Table 4.5.1.7-2 on Page 86 of the integrated summary of immunogenicity
ADA titer groups – low (≤16), medium (>16 to ≤128), high (>128)
Abbreviations: ADA, antidrug antibody; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; TEAE, treatment-emergent adverse event

Trial VIS649-201

All 155 subjects were included in the Immunogenicity Set (117 sibeprenlimab, 38 placebo). ADA prevalence versus time is presented in Figure 25. ADA prevalence peaked at Month 6 (Day 180: 47.2%, 29.3%, 18.4% for 2, 4, 8 mg/kg respectively) then remained consistent through Day 485. ADA incidence through Month 16 decreased with increasing dose: 50.0% (2 mg/kg), 39.0% (4 mg/kg), 23.7% (8 mg/kg), suggesting higher doses may more effectively clear ADA via immune complex formation.

Figure 25. Percentage of ADA-Positive Samples by Visit Day, Immunogenicity Set, Trial VIS649-201



Source: Figure 4.5.2.2-1 on Page 88 of the integrated summary of immunogenicity
Abbreviations: ADA, antidrug antibody; N, total number of subjects in the relevant analysis set; Sibe, sibeprenlimab

Effect on Pharmacokinetics, Pharmacodynamics, Efficacy and Safety (Trial VIS649-201)

For the 4 and 8 mg/kg groups, mean C_{trough} values in ADA-positive subjects were lower than ADA-negative subjects; however, the reduction in magnitude was within the range for intersubject variability (reflected by SD values) (Table 64).

ADA-positive status did not influence percent change from baseline in mean serum total IgA compared to ADA-negative subjects during IV treatment with 2, 4, or 8 mg/kg sibeprenlimab every 30 days.

In ADA-negative subjects, the estimated percent reduction in uPCR-24h at Month 9 was 46.6% (2 mg/kg), 42.8% (4 mg/kg), and 53.8% (8 mg/kg). ADA-positive subjects showed similar or higher reductions: 44.3% (2 mg/kg), 61.0% (4 mg/kg), and 62.7% (8 mg/kg) (Table 65). ADA status did not negatively impact efficacy, consistent with the absence of an impact on serum total IgA reduction.

For combined sibeprenlimab groups, ADA-positive subjects had similar percentages of any TEAEs and hypersensitivity TEAEs compared to ADA-negative subjects (Table 66). Subjects with higher ADA titers (≥400) showed no clinically significant safety findings, with TEAE profile similar to the overall trial profile.

Table 64. Summary of Sibeprenlimab Predose C_{trough} by Visit and by ADA Category, Immunogenicity Set, Trial VIS649-201

Visit	ADA-Negative		ADA-Positive		
	n	Mean C_{trough}, µg/mL (SD)	n	Mean C_{trough}, µg/mL (SD)	% Decrease[a]
Dose cohort = VIS649 4 mg/kg IV (N=41)					
Day 30	24	13.94 (10.11)	16	8.12 (5.34)	41.8
Day 60	25	23.06 (12.70)	16	11.68 (8.30)	49.3
Day 90	25	31.82 (18.12)	16	25.87 (29.41)	18.7
Day 120	24	38.79 (32.81)	16	40.87 (70.51)	-5.4
Day 150	24	35.95 (25.32)	16	68.39 (177.67)	-90.2
Day 180	25	39.08 (26.49)	16	28.16 (30.24)	27.9
Day 210	25	55.05 (39.94)	16	37.48 (51.66)	31.9
Day 240	25	48.36 (30.02)	16	32.74 (31.01)	32.3
Day 270	24	55.61 (42.81)	16	40.03 (28.35)	28.0
Day 300	24	56.03 (41.11)	16	38.43 (26.80)	31.4
Day 330	24	57.38 (44.92)	16	30.95 (24.48)	46.1
Dose cohort = VIS649 8 mg/kg IV (N=38)					
Day 30	28	49.99 (19.39)	9	38.59 (22.63)	22.8
Day 60	29	84.38 (33.55)	9	73.98 (42.99)	12.3
Day 90	29	111.60 (41.91)	9	89.88 (77.75)	19.5
Day 120	29	139.07 (44.93)	9	96.72 (77.84)	30.5
Day 150	27	154.70 (71.71)	8	116.71 (61.35)	24.6
Day 180	29	153.90 (76.19)	9	120.16 (86.37)	21.9
Day 210	29	183.40 (94.65)	8	120.87 (93.21)	34.1
Day 240	26	175.14 (99.28)	9	145.85 (129.41)	16.7
Day 270	28	314.34 (752.33)	9	131.48 (81.91)	58.2
Day 300	28	206.96 (108.02)	9	127.81 (67.64)	38.2
Day 330	28	184.74 (88.30)	9	138.99 (90.65)	24.8

Source: reconstructed Table 4.5.2.3-1 on Page 91 of the integrated summary of immunogenicity.
VIS649 refers to sibeprenlimab
[a]% decrease =100 - (mean C_{trough} ADA-positive / mean C_{trough} ADA-negative) *100)
Abbreviations: ADA, antidrug antibody; C_{trough}, trough serum concentration; IV, intravenous; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; SD, standard deviation

Table 65. Analysis of uPCR-24h at Month 9 Compared to Baseline by ADA Category (ADA-Negative vs. ADA-Positive Subjects), ANCOVA, Immunogenicity Set, Trial VIS649-201

ADA Category	Sibeprenlimab Dose Level	N	Ratio of GM (95% CI)	Corresponding % Reduction[a] (95% CI) (%)
ADA negative participants	2 mg/kg	19	0.557 (0.335, 0.925)	44.3 (7.5, 66.5)
	4 mg/kg	25	0.567 (0.377, 0.852)	43.3 (14.8, 62.3)
	8 mg/kg	29	0.430 (0.298, 0.621)	57.0 (37.9, 70.2)
ADA positive participants	2 mg/kg	19	0.590 (0.386, 0.901)	41.0 (9.9, 61.4)
	4 mg/kg	16	0.372 (0.211, 0.656)	62.8 (34.4, 78.9)
	8 mg/kg	9	0.388 (0.158, 0.954)	61.2 (4.6, 84.2)

Source: Table 4.5.2.5-1 on Page 95 of the integrated summary of immunogenicity
[a]Calculated as (1-GM of uPCR ratio estimated from ANCOVA model)*100
Abbreviations: ADA, antidrug antibody; ANCOVA, analysis of covariance; CI, confidence interval; GM, geometric mean; N, total number of subjects in the relevant analysis set; uPCR, urine protein-to-creatinine ratio at 24-hour urine collection; vs., versus

Table 66. Number of Subjects With Any TEAEs and Hypersensitivity TEAEs by ADA Category, Immunogenicity Set, Trial VIS649-201

System Organ Class/ Preferred Term	Sibeprenlimab Treatment Group			All Sibeprenlimab (N = 117) n (%)[a]
	2 mg/kg (N = 38) n (%)[a]	4 mg/kg (N = 41) n (%)[a]	8 mg/kg (N = 38) n (%)[a]	
ADA negative participants	**19 (100.0)**	**25 (100.0)**	**29 (100.0)**	**73 (100.0)**
Any TEAE	13 (68.4)	19 (76.0)	26 (89.7)	58 (79.5)
Any hypersensitivity TEAE	2 (10.5)	4 (16.0)	1 (3.4)	7 (9.6)
Immune system disorders	0	1 (4.0)	0	1 (1.4)
Anaphylactic reaction	0	1 (4.0)	0	1 (1.4)
Skin and subcutaneous tissue disorders	2 (10.5)	3 (12.0)	1 (3.4)	6 (8.2)
Dermatitis	0	1 (4.0)	0	1 (1.4)
Eczema	0	2 (8.0)	0	2 (2.7)
Rash	1 (5.3)	1 (4.0)	1 (3.4)	3 (4.1)
Rash erythematous	0	1 (4.0)	0	1 (1.4)
Rash maculo-papular	1 (5.3)	0	0	1 (1.4)
ADA positive participants	**19 (100.0)**	**16 (100.0)**	**9 (100.0)**	**44 (100.0)**
Any TEAE	15 (78.9)	14 (87.5)	5 (55.6)	34 (77.3)
Any hypersensitivity TEAE	1 (5.3)	1 (6.3)	1 (11.1)	3 (6.8)
General disorders and administration site conditions	0	0	1 (11.1)	1 (2.3)
Swelling face	0	0	1 (11.1)	1 (2.3)
Injury, poisoning and procedural complications	1 (5.3)	0	0	1 (2.3)
Infusion related reaction	1 (5.3)	0	0	1 (2.3)
Respiratory, thoracic, and mediastinal disorders	0	1 (6.3)	0	1 (2.3)
Rhinitis allergic	0	1 (6.3)	0	1 (2.3)

Source: Table 4.5.2.6-1 on Page 97 of the integrated summary of immunogenicity
[a]Percentage calculated as (number of events)/(total number of subjects in respective ADA category).
Abbreviations: ADA, antidrug antibody; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; TEAE, treatment-emergent adverse event

Trial 417-201-00012

The results for open-label extension (OLE) Trial 417-201-00012 are based on an IA (data cutoff date: September 4, 2024) of the ongoing trial. A total of 121 subjects were enrolled at the time of the IA and 107 were included in the Immunogenicity Set.

Analyses examined ADA/NAb response dynamics and clinical parameter relationships for all subjects rolling over from the phase 2 Trial VIS649-201, regardless of previous treatment (sibeprenlimab 2, 4, or 8 mg/kg IV or placebo). This combined analysis approach was used because treatment-emergent ADA/NAb response profiles were similar in OLE Trial 417-201-00012, despite approximately 20% of previous sibeprenlimab recipients being ADA-positive at Trial 417-201-00012 baseline (Table 67).

Relative to baseline ADA status in Trial VIS649-201, OLE Trial 417-201-00012 showed 31.8% ADA incidence and 11.2% NAb incidence among 107 Immunogenicity Set subjects at the IA (Table 68).

Titer groups were defined as low ≤16, medium >16 to ≤64, and high >64 (calculated as 33rd and 66th percentiles of maximum subject titer). The highest incidence was observed in the low titer group (47.1%), followed by the high group (29.4%), then the medium group (14.7%). Peak ADA prevalence was 26.1% at Week 20, declining to 13.2% at Week 52 and zero at Week 100;

however, as shown in Table 67, sample sizes at later timepoints are limited because the trial is ongoing. A similar pattern was observed for NAb.

Table 67. Summary of Sample ADA Status by Visit, Immunogenicity Set, Trial 417-201-00012

Visit	ADA Category	Prior Treatment With Sibeprenlimab n %[b]	Prior Treatment With Placebo n %[b]	Total n %[b]
Baseline	Total[a]	86	21	107
	Negative	85 (98.84)	21 (100.00)	106 (99.07)
	Positive	1 (1.16)	0	1 (0.93)
Week 8	Total[a]	78	21	99
	Negative	61 (78.21)	20 (95.24)	81 (81.82)
	Positive	17 (21.79)	1 (4.76)	18 (18.18)
Week 20	Total[a]	74	18	92
	Negative	54 (72.97)	14 (77.78)	68 (73.91)
	Positive	20 (27.03)	4 (22.22)	24 (26.09)
Week 32	Total[a]	72	15	87
	Negative	57 (79.17)	12 (80.00)	69 (79.31)
	Positive	15 (20.83)	3 (20.00)	18 (20.69)
Week 44	Total[a]	68	13	81
	Negative	60 (88.24)	10 (76.92)	70 (86.42)
	Positive	8 (11.76)	3 (23.08)	11 (13.58)
Week 52	Total[a]	62	14	76
	Negative	55 (88.71)	11 (78.57)	66 (86.84)
	Positive	7 (11.29)	3 (21.43)	10 (13.16)
Week 64	Total[a]	52	10	62
	Negative	48 (92.31)	8 (80.00)	56 (90.32)
	Positive	4 (7.69)	2 (20.00)	6 (9.68)
Week 76	Total[a]	33	7	40
	Negative	28 (84.85)	6 (85.71)	34 (85.00)
	Positive	5 (15.15)	1 (14.29)	6 (15.00)
Week 88	Total[a]	11	3	14
	Negative	11 (100.00)	2 (66.67)	13 (92.86)
	Positive	0	1 (33.33)	1 (7.14)
Week 100	Total[a]	8	0	8
	Negative	8 (100.00)	0	8 (100.00)
	Positive	0	0	0
Week 104 / follow-up	Total[a]	7	0	7
	Negative	7 (100.00)	0	7 (100.00)
	Positive	0	0	0
Week 112 / end-of-trial	Total[a]	3	0	3
	Negative	3 (100.00)	0	3 (100.00)
	Positive	0	0	0

Source: Table CT-14.1.1 on Page 1624-1626 on 417-201-00012 CSR
[a]Number of subjects with nonmissing ADA results.
[b]% 100*n/Total[a].
For subjects prior treated with sibeprenlimab, ADA baseline samples in the parent trial were used as baseline. For subjects prior treated with placebo, the OLE baseline is used, instead of parent baseline.
Abbreviations: ADA, antidrug antibody; CSR, clinical study report; n, number of subjects with an assessment available at the relevant time point; OLE, open-label extension

Table 68. Summary of Subject Level ADA and NAb Status, Immunogenicity Set, Trial 417-201-00012

Participant-level ADA/NAb status	Sibeprenlimab SC 400 mg	
	N	n (%)
ADA negative participants	107	73 (68.2)
ADA positive participants	107	34 (31.8)
Baseline ADA positive participants[a]	107	1 (0.9)
NAb negative participants	107	21 (19.6)
NAb positive participants	107	12 (11.2)
ADA positive participants		
NAb negative participants	34	21 (61.8)
NAb positive participants	34	12 (35.3)
Persistent ADA participants	34	20 (58.8)
Transient ADA participants	34	10 (29.4)
ADA titer group		
Low (≤ 16)	34	16 (47.1)
Medium (> 16 and ≤ 64)	34	5 (14.7)
High (> 64)	34	10 (29.4)

Source: Table 4.5.3.3-1 on Page 100 of integrated summary of immunogenicity
[a]For subjects that were treated with sibeprenlimab in Trial VIS649-201, ADA baseline samples in the VIS649-201 were used as baseline. For subjects that were treated with placebo in Trial VIS649-201, ADA baseline samples in the OLE were used in baseline Data include only subjects who rolled over from Trial VIS649-201.
% of NAb positive and NAb negative subjects were calculated based on the total number of evaluable subjects.
Abbreviations: ADA, antidrug antibody; NAb, neutralizing antibody; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; OLE, open-label extension; SC, subcutaneous

Effect on Pharmacokinetics

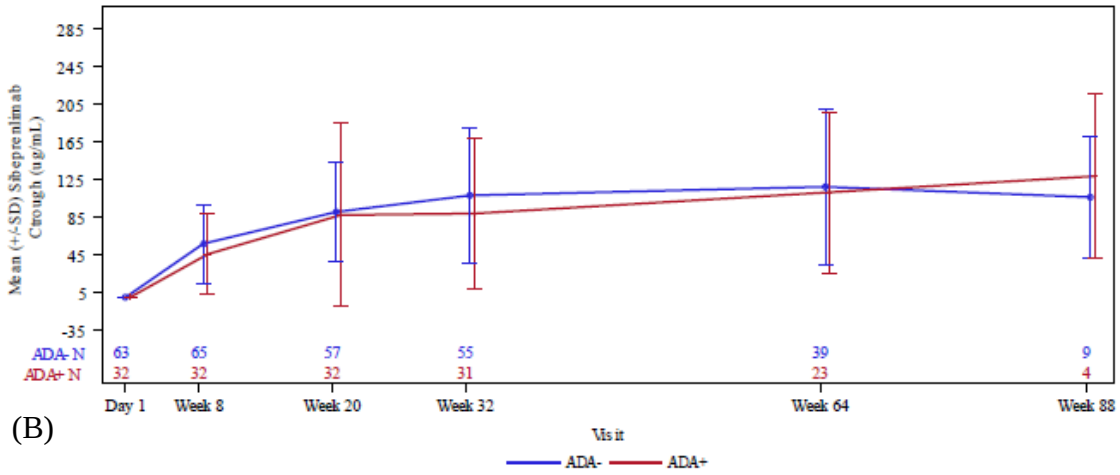
Mean C_{trough} value comparison by visit and ADA status/ADA and NAb status/ADA titer groups are presented in Figure 26.

Mean C_{trough} of sibeprenlimab in ADA-positive subjects were similar to that in ADA-negative subjects at all visits through Week 88. Subjects who were ADA-positive but NAb-negative, or in low/medium ADA titer groups, had similar mean exposure to the ADA-negative subgroup. In NAb-positive subjects, mean C_{trough} levels at Week 20 (maximum ADA prevalence timepoint) were 50.8% lower than those in ADA-negative subjects. The high ADA titer group showed 60.0% lower C_{trough} levels than the ADA-negative subgroup. NAb-positive and high ADA titer subgroups demonstrated a similar magnitude of mean C_{trough} reduction.

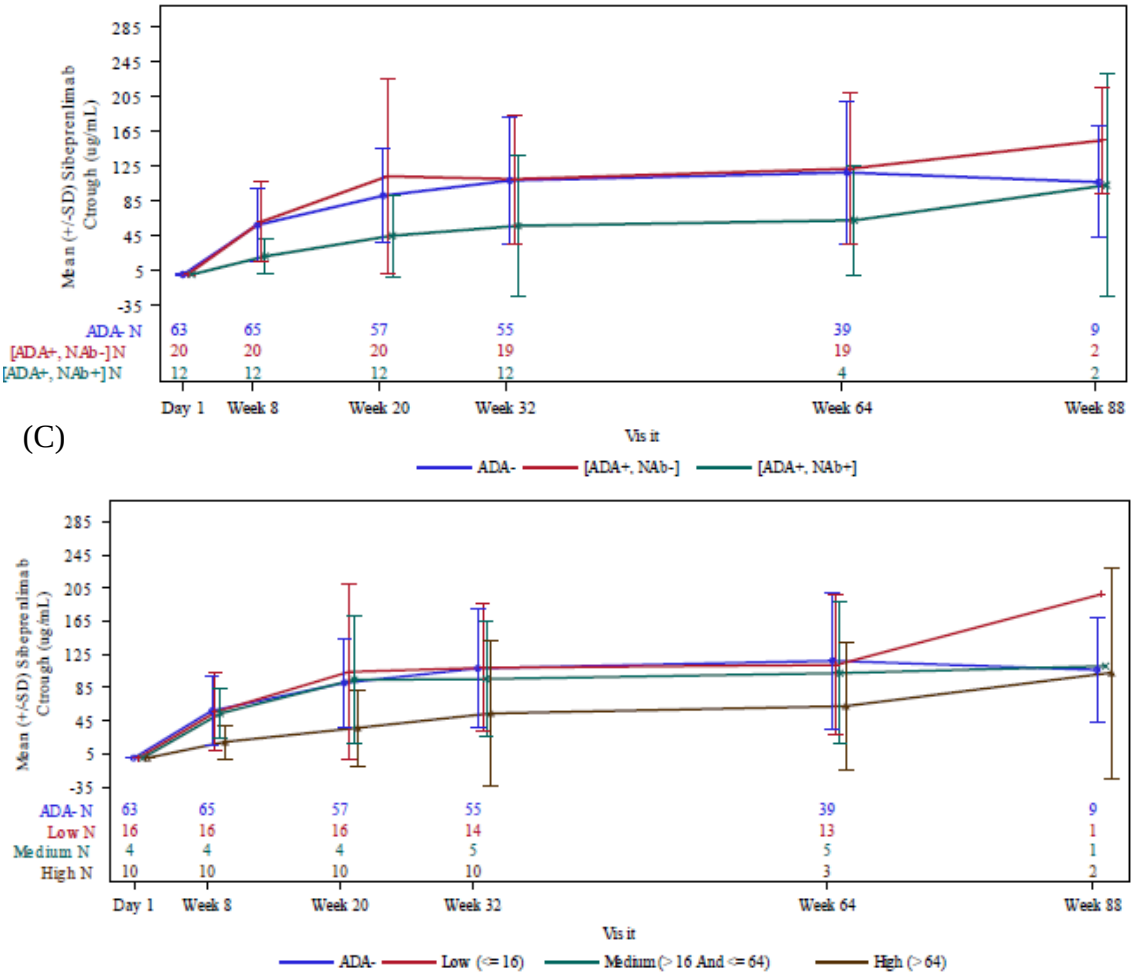
The NAb-positive subgroup represented 12/107 subjects (11.2%), while the high ADA titer group comprised 10/107 subjects (9.3%). All 10 high ADA titer subjects were NAb-positive and classified as having persistent ADA. Therefore, ADA/NAb appeared to reduce exposure in a relatively small proportion (approximately 10%) of sibeprenlimab treated subjects.

Figure 26. Sibeprenlimab Predose C_{trough} by Visit and by ADA Category, ADA and NAb Category, ADA Titer Groups, Immunogenicity Set, Trial 417-201-00012

(A)



(B)



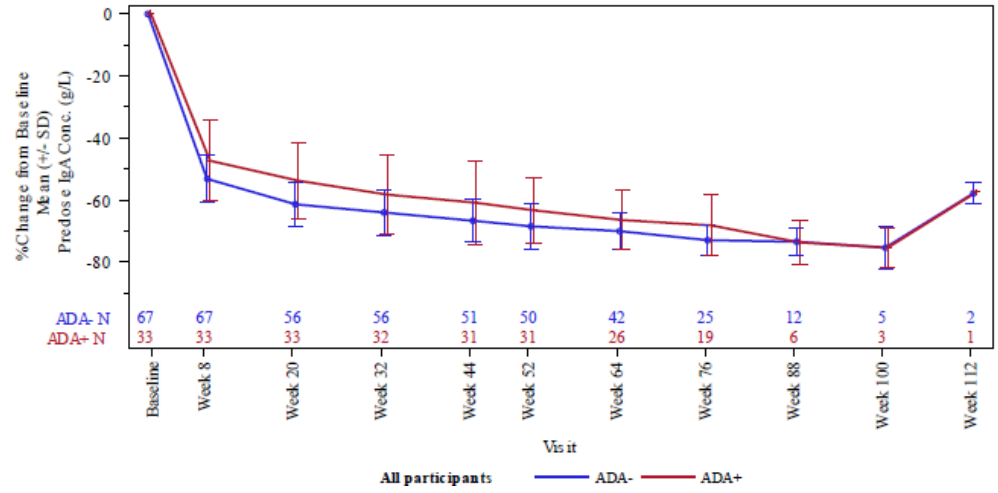
Source: Figures 4.5.3.4-1, 4.5.3.4-2 and 4.5.3.4-3 on Page 104-105 of integrated summary of immunogenicity
Panel A is sibeprenlimab predose C_{trough} by visit and by ADA category; Panel B is sibeprenlimab predose C_{trough} by visit and by ADA and NAb category; and Panel C is sibeprenlimab predose C_{trough} by visit and by ADA titer groups.
Abbreviations: ADA, antidrug antibody; ADA+, ADA-positive; ADA-, ADA-negative; C_{trough}, trough serum concentration; NAb, neutralizing antibody; NAb+, NAb-positive; NAb-, NAb-negative; N, total number of subjects in the relevant analysis set; SD, standard deviation

Effects on Pharmacodynamics

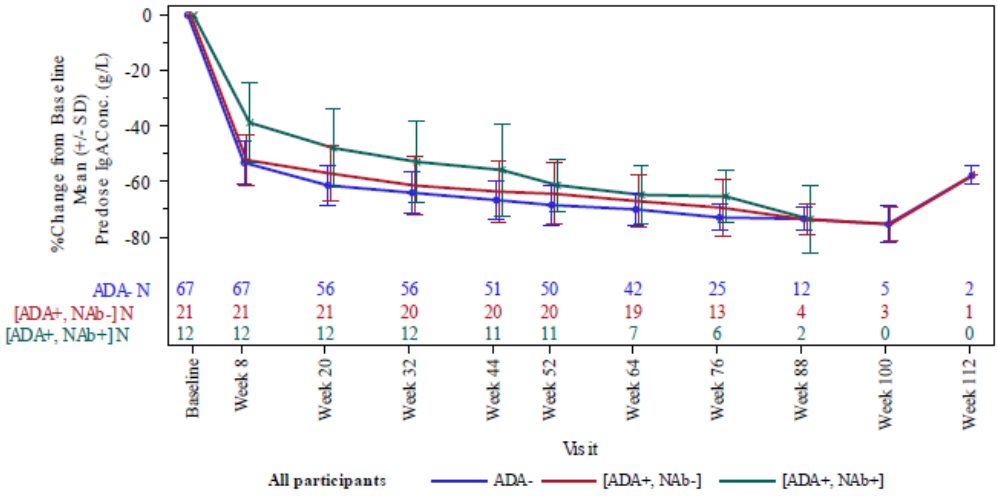
The percent changes from baseline in predose IgA concentration by visit and by ADA status/ADA and NAb status/ADA titer groups are presented Figure 27. Overall, lower mean sibeprenlimab C_{trough} levels in NAb-positive and high ADA titer subgroups were associated with a relatively modest difference in PD response at Week 20 based on the point estimate, although the confidence intervals were overlapping. At Week 20 (post-treatment visit with highest ADA prevalence), the mean percent change from baseline in serum total IgA concentration (SD) was −53.8% (12.3) in ADA-positive subjects compared to −61.4% (7.1) in ADA-negative subjects. This difference appeared to reflect a lower mean percent change of −47.9% (14.2) in the NAb-positive subgroup. No trend was observed by titer group: −53.9% (9.3), −58.7% (9.6), and −48.2% (15.7) for the low, medium, and high titer groups, respectively.

Figure 27. Percent Change From Baseline of Predose IgA Concentration by Visit and by ADA Category (Panel A), ADA and NAb Category (Panel B), ADA Titer Groups (Panel C), Immunogenicity Set, Trial 417-201-00012

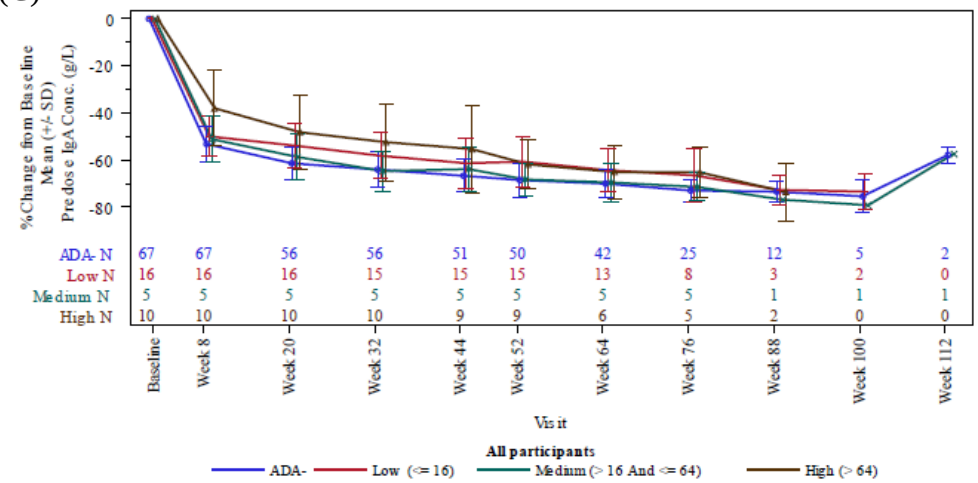
(A)



(B)



(C)



Source: Figures 4.5.3.5-1, 4.5.3.5-2 and 4.5.3.5-3 on Page 106-108 of integrated summary of immunogenicity
Abbreviations: ADA, antidrug antibody; ADA+, ADA-positive; ADA-, ADA-negative; IgA, immunoglobulin A; NAb, neutralizing antibody; NAb+, NAb-positive; NAb-, NAb-negative; N, total number of subjects in the relevant analysis set; SD, standard deviation

Effect on Efficacy

The geometric means of uPCR-24h at baseline and at Week 52 summarized by ADA/NAb category and ADA titer groups are presented in Table 69 and Table 70, respectively.

The relative geometric mean of uPCR-24h at Week 52 compared with baseline was similar in magnitude across the different ADA/NAb category and ADA titer subgroups.

(b) (4)

Given the small sample size of the subgroup analysis and the relatively high intersubject variability, no definitive conclusion can be drawn from these data. The NAb assay bioanalytic drug tolerance issues add another level of uncertainty. As stated above, this assessment will be revisited when the full dataset is available.

Table 69. Geometric Mean of uPCR-24h at Baseline and at Week 52 (Month 12) by ADA/NAb Category, Immunogenicity Set, Trial 417-201-00012

Statistic	ADA Negative	ADA Positive	ADA Positive/ NAb Negative	ADA Positive/ NAb Positive
uPCR-24h (g/g) at Baseline				
N	52	31	20	11
GM	0.84	0.76	0.58	1.23
GSD[a]	2.685	2.873	3.216	1.815
95% CI[b])	(0.64, 1.11)	(0.51, 1.12)	(0.34, 1.01)	(0.82, 1.83)
uPCR-24h (g/g) at Week 52 (Month 12)				
N	50	30	19	11
GM	0.59	0.62	0.48	1.00
GSD	2.704	2.604	2.797	1.837
95% CI	(0.44, 0.78)	(0.44, 0.89)	(0.29, 0.78)	(0.66, 1.50)
uPCR-24h (g/g) at Week 52 (Month 12) Compared to Baseline[c]				
N	50	30	19	11
GM	0.73	0.81	0.80	0.81
GSD	1.819	1.799	1.747	1.941
95% CI	(0.61, 0.86)	(0.65, 1.00)	(0.61, 1.05)	(0.52, 1.27)

Source: Table 4.5.3.6-1 on Page 109 of integrated summary of immunogenicity
[a]Calculated as exponential of SD of log scaled data.
[b]Calculated as exponential (log scaled mean ±1.96* log scaled SE of data).
[c]24-hour uPCR compared to baseline is defined as ($uPCR/uPCR_{baseline}$).
Data includes only subjects who rolled over from Trial VIS649-201.
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GM, geometric mean; GSD, Geometric standard deviation; N, total number of subjects in the relevant analysis set; NAb, neutralizing antibody; SD, standard deviation; SE, standard error; uPCR, urine protein-to-creatinine ratio

Table 70. Geometric Mean of uPCR-24h at Baseline and at Week 52 (Month 12) by ADA Titer Group, Immunogenicity Set, Trial 417-201-00012

Statistic	ADA Negative	Low ADA Titer (≤ 16)	Medium ADA Titer (> 16 and ≤ 64)	High ADA Titer (> 64)
uPCR-24h (g/g) at Baseline				
N	52	15	5	9
GM	0.84	0.53	0.98	1.22
GSD[a]	2.685	3.342	2.461	1.898
95% CI[b]	(0.64, 1.11)	(0.27, 1.04)	(0.32, 2.99)	(0.75, 2.00)
uPCR-24h (g/g) at Week 52 (Month 12)				
N	50	15	4	9
GM	0.59	0.45	0.92	1.04
GSD	2.704	2.690	2.902	1.949
95% CI	(0.44, 0.78)	(0.26, 0.79)	(0.17, 4.99)	(0.62, 1.73)
uPCR-24h (g/g) at Week 52 (Month 12) compared to baseline[c]				
N	50	15	4	9
GM	0.73	0.86	0.76	0.85
GSD	1.819	1.734	1.361	2.070
95% CI	(0.61, 0.86)	(0.63, 1.16)	(0.46, 1.24)	(0.48, 1.48)

Source: Table 4.5.3.6-2 on Page 109 and 110 of integrated summary of immunogenicity.
[a]Calculated as exponential of standard deviation of log-scaled data.
[b]Calculated as exponential (log-scaled mean +/- 1.96*log-scaled standard error of data).
[c]uPCR-24h compared to baseline is defined as ($uPCR/uPCR_{baseline}$).
Data includes only subjects who rolled over from Trial VIS649-201.
Abbreviations: ADA, antidrug antibody; CI, confidence interval; GM, geometric mean; GSD, Geometric standard deviation; N, total number of subjects in the relevant analysis set; NAb, neutralizing antibody; SD, standard deviation; SE, standard error; uPCR, urine protein-to-creatinine ratio

(b) (4)

(b) (4)

Effect on Safety

The proportions of ADA-negative versus ADA-positive subjects reporting any TEAE or hypersensitivity TEAE are summarized in Table 73. A review of this listing did not reveal a temporal association between the ADA titer onset and the hypersensitivity TEAE onset. In the ADA-negative subgroup, 54/73 subjects (74.0%) reported any TEAE, compared with 28/34 subjects (82.4%) in the ADA-positive subgroup. Hypersensitivity TEAEs were reported at a lower incidence in ADA-negative subjects (5/73 [6.8%]) compared to ADA-positive subjects (7/34 [20.6%]). However, no temporal association was observed between ADA titer onset and hypersensitivity TEAE onset. Due to the limited sample size and ongoing status of trial 417-201-00012, the immunogenicity effect on safety, particularly hypersensitivity reactions, should be reassessed when the full study report is submitted. TEAEs and hypersensitivity TEAEs reported for ADA-positive subjects are summarized by ADA titer group in Table 74. ADA titer group did not appear to influence hypersensitivity TEAE frequency in ADA-positive subjects. Assessment of subjects with higher ADA titers (≥64) revealed no clinically significant safety findings.

Table 73. Number of Subjects With Any TEAE and Hypersensitivity TEAE by ADA Category, Immunogenicity Set, Trial 417-201-00012

System Organ Class/ Preferred Term	ADA Negative (N=73) n (%)	ADA Positive (N=34) n (%)
Any TEAE	54 (74.0)	28 (82.4)
Any Hypersensitivity TEAE	5 (6.8)	7 (20.6)
Immune system disorders	1 (1.4)	0
Drug hypersensitivity	1 (1.4)	0
Respiratory, thoracic, and mediastinal disorders	1 (1.4)	3 (8.8)
Rhinitis allergic	1 (1.4)	3 (8.8)
Skin and subcutaneous tissue disorders	3 (4.1)	5 (14.7)
Dermatitis allergic	1 (1.4)	0
Dermatitis	0	1 (2.9)
Eczema	1 (1.4)	0
Rash erythematous	1 (1.4)	0
Rash	0	1 (2.9)
Rash popular	0	1 (2.9)
Urticaria	0	2 (5.9)

Source: Table 4.5.3.7-2 on Page 112 of integrated summary of immunogenicity
Data includes only subjects who rolled over from Trial VIS649-201.
Abbreviations: ADA, antidrug antibody; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; TEAE, treatment-emergent adverse event

Table 74. Number of Subjects With Any TEAE and Hypersensitivity TEAE by ADA Titer Group, Immunogenicity Set, Trial 417-201-00012

System Organ Class/ Preferred Term	ADANegative (N = 73) n (%)	ADA Titer Group		
		Low (N = 16) n (%)	Medium (N = 5) n (%)	High (N = 10) n (%)
Any TEAE	54 (74.0)	14 (87.5)	3 (60.0)	9 (90.0)
Any Hypersensitivity TEAE	5 (6.8)	4 (25.0)	1 (20.0)	2 (20.0)
Immune system disorders	1 (1.4)	0	0	0
Drug hypersensitivity	1 (1.4)	0	0	0
Respiratory, thoracic, and mediastinal disorders	1 (1.4)	2 (12.5)	1 (20.0)	0
Rhinitis allergic	1 (1.4)	2 (12.5)	1 (20.0)	0
Skin and subcutaneous tissue disorders	3 (4.1)	3 (18.8)	0	2 (20.0)
Dermatitis allergic	1 (1.4)	0	0	0
Dermatitis	0	0	0	1 (10.0)
Eczema	1 (1.4)	0	0	0
Rash erythematous	0	0	0	0
Rash	0	1 (6.3)	0	0
Rash popular	0	1 (6.3)	0	0
Urticaria	0	1 (6.3)	1 (6.3)	1 (10.0)

Source: Table 4.5.3.7-3 on Page 113 of integrated summary of immunogenicity.
ADA titer groups: low (≤16), medium (>16 - ≤64), high (>64) Includes only subjects who rolled over from Trial VIS649-201.
Abbreviations: ADA, antidrug antibody; N, total number of subjects in the relevant analysis set; n, number of subjects with an assessment available at the relevant time point; TEAE, treatment-emergent adverse event

14.5. Pharmacometrics Assessment

Review Summary (Pharmacometrics)

Is the proposed dosing regimen appropriate to chronically treat IgAN in adults who are at risk of disease progression to reduce proteinuria?

The Office of Clinical Pharmacology review team agrees with the proposed dosage of sibeprenlimab 400 mg every 4 weeks subcutaneously (400 mg Q4W SC) in adults with IgAN who are at risk of disease progression to reduce proteinuria. The rationale for the proposed dosage regimen is described below.

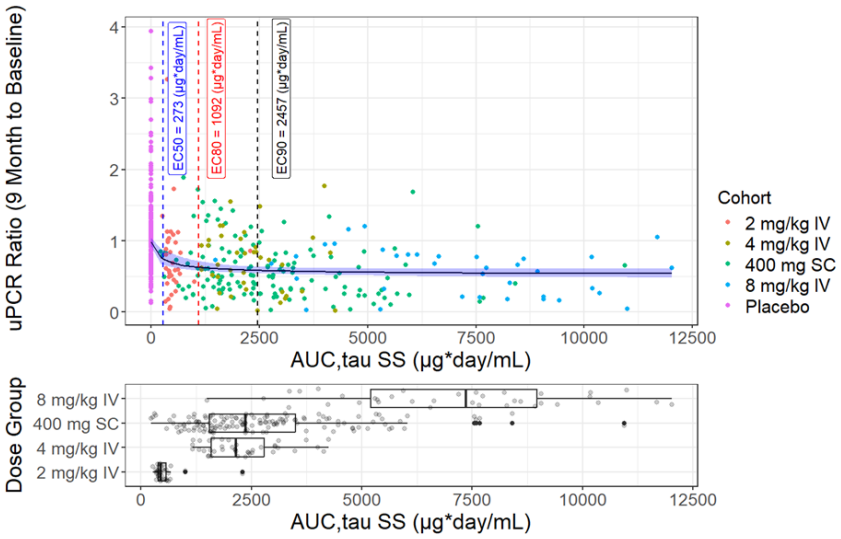
To describe the pharmacokinetics of sibeprenlimab and support the proposed dosage, the Applicant performed popPK, PK/PD, and E-R assessments based on data collected from healthy subjects and the target patient population. Briefly, the previously developed popPK model, based on 3 Phase 1 clinical studies, was reassessed and optimized, and popPK model parameters were re-estimated using 6740 measurable sibeprenlimab concentrations from 477 subjects obtained from a total of five ongoing and completed clinical studies. The PK/PD model was reassessed using the data obtained from the ongoing phase 3 clinical trials.

The final popPK model was then used to derive individual level model parameters and simulate PK exposure metrics (C_{max}, C_{trough}, AUC) at steady-state for the dosing-interval to compare the 4 mg/kg IV every 28 days dose used in the phase 2 trial with the proposed 400 mg SC Q4W dose. Further, the simulated PK exposure metrics were also used in E-R analyses. While the PK/PD model was used to describe the relationship between sibeprenlimab concentration and serum IgA level over time, the E-R analysis characterized the relationship between sibeprenlimab PK exposure and the efficacy endpoint (i.e., the ratio between uPCR (urine protein-creatinine ratio) over 24h at 9 months) compared to uPCR-24h at baseline).

The 400 mg Q4W SC dose appeared to show similar PK exposure as that of the 4 mg/kg every 28 days IV dose in the popPK simulation (Figure 28). The proposed 400 mg Q4W SC and 4 mg/kg every 28 days IV doses also resulted in a similar reduction from baseline in IgA level (biomarker) in the PK/PD model simulation over the simulated treatment time (Figure 29). Simulations conducted based on the final E-R model indicated a consistent reduction in the ratio of uPCR-24h over 9 months compared to baseline upon treatment with sibeprenlimab 400 mg SC Q4W (Figure 28).

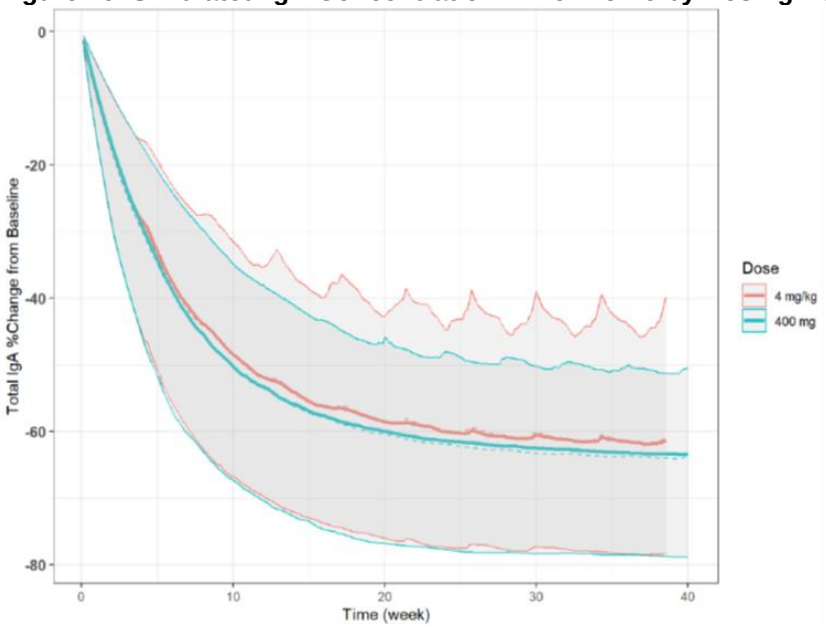
As summarized above, based on the results from the popPK, PK/PD and E-R analyses, the proposed dosage of 400 mg Q4W SC appears to be supported for use in the treatment of subjects with IgAN.

Figure 28. Model-Predicted Exposure Comparisons and E-R Relationship Overlaid With Observed Data



Source: Reproduced by Reviewer
Blue line and shaded area represent the model fit and 90% confidence interval to the data. Dots represents observed data.
Abbreviations: $AUC_{tau,ss}$, area under the concentration-time curve at steady-state; EC_{50}, half-maximal effective concentration; EC_{80}, concentration producing 80% maximal effect; EC_{90}, concentration producing 90% maximal effect; E-R, exposure-response; IV, intravenous; SC, subcutaneous; uPCR, urine protein-creatinine ratio

Figure 29. Simulated IgA Concentration Time Profile by Dosing Regimen



Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Figure 25: Page 103
Abbreviations: IgA, immunoglobulin A; M&S, modeling and simulation

Are there intrinsic and extrinsic factors that impact the pharmacokinetics of sibeprenlimab?

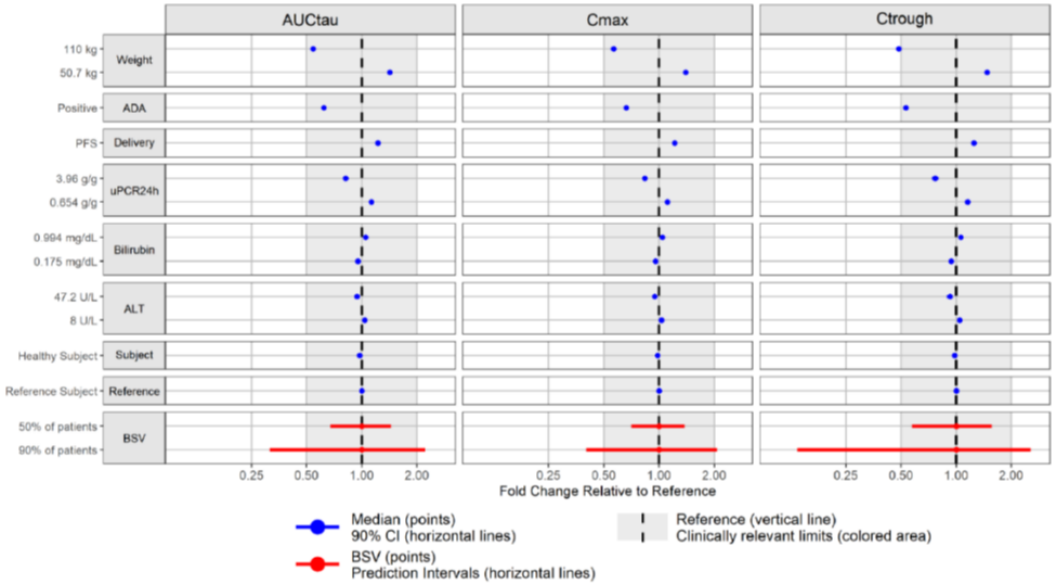
The selected final popPK model of sibeprenlimab included the following covariate effects: effect of baseline body weight on CL_{lin}, Q, V_{max} and V_2, V_3, subject-level ADA-positive for subjects

with IgAN on CL_{lin}, healthy subject effect on V_2 and KA, method of delivery (PFS) effect on F, baseline bilirubin and baseline ALT on V_{max}, and baseline uPCR-24h on CL_{lin}.

The impact of the identified covariates was evaluated on the PK exposure metrics generated after 400 mg SC every 4 weeks for 10 doses. The results, expressed as a ratio based on a fold change in each exposure metric relative to a reference subject, are shown in the forest plot (Figure 30). Compared to a subject weighing 70 kg (body weight for a typical subject), baseline body weight for a subject weighing 110 kg (the 95th percentile) was associated with a 43%, 51%, and 46% decrease in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively. However, in a subject weighing 50.7 kg (the 5th percentile), body weight was associated with a 40%, 47%, and 42% increase in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively (Figure 31). Compared to ADA-negative subjects with IgAN subjects, ADA-positive subjects with IgAN were predicted to show 33%, 47%, and 38% decrease in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively. The PFS method of delivery was associated with a 21%, 25%, and 22% increase whereas the 95th percentile (3.96 g/g) of baseline uPCR-24h showed a 17%, 23%, and 19% decrease in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively, when compared to the reference subject.

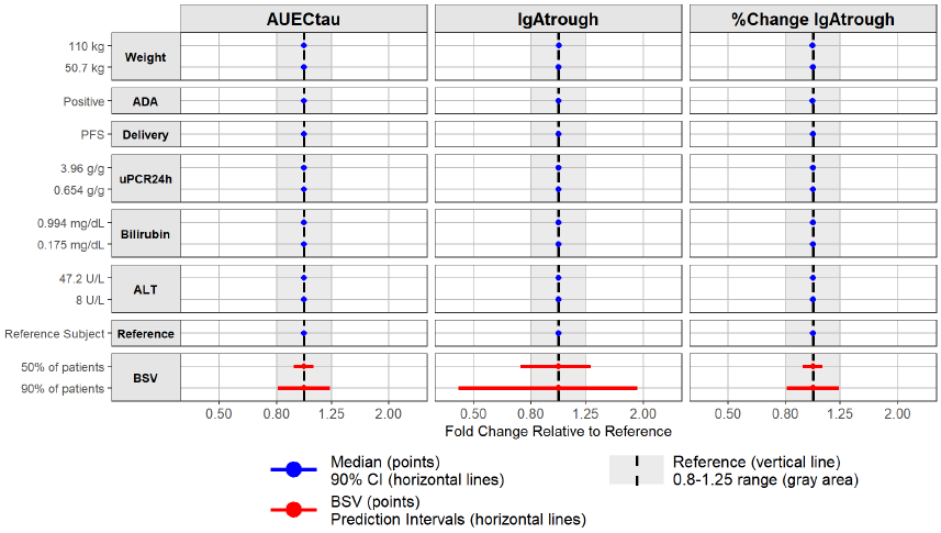
However, the percent differences observed above did not appear to have any clinically significant impact based on IgA (Figure 32) and 9-month uPCR-24h responses. Therefore, no dose adjustments are recommended.

Figure 30. Impact of Identified Covariates on Steady-State PK Exposures



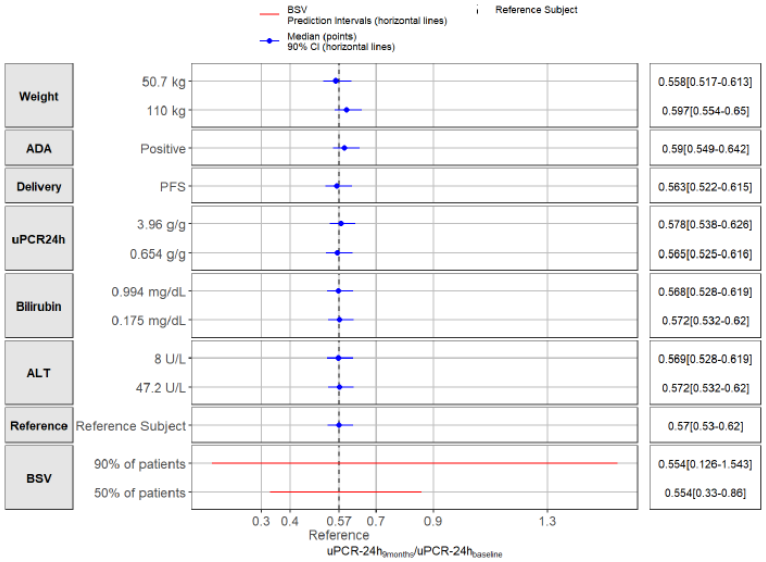
Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Figure 23: Page 96
Dots represent the median with lines representing the 90% CI. Reference subject: 70-kg, ADA-negative IgAN patient following administration with a vial, baseline bilirubin 0.41 mg/dL, baseline ALT 16 U/L, and baseline uPCR-24h 1.29 g/g.
Abbreviations: ADA, antidrug antibody; ALT, alanine aminotransferase; AUC_{tau}, area under the serum concentration-time curve over the dosing interval; BSV, between-subject variability; CI, confidence interval; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; M&S, modeling and simulation; PFS, prefilled syringe; PK, pharmacokinetic; Q4W, every 4 weeks; uPCR-24h, 24-hour urine protein-creatinine ratio

Figure 31. Effect of Covariates Identified From the PopPK Model on IgA Responses ($AUEC_{tau}$, IgA_{trough}, and Percent Change of IgA_{trough})



Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Figure 24: Page 99
Dots represent the median with lines representing the 90% CI. Reference subject: 70-kg, ADA-negative IgAN patient following administration with a vial, baseline bilirubin 0.41 mg/dL, baseline ALT 16 U/L, and baseline uPCR-24h 1.29 g/g.
Abbreviations: $AUEC_{tau}$, area under the curve of percent change of IgA from baseline versus time over the dosing interval; ALT, alanine aminotransferase; BSV, between-subject variability; CI, confidence interval; IgA, immunoglobulin A; IgA_{trough}, trough concentration of IgA; M&S, modeling and simulation; Q4W, every 4 weeks; uPCR-24h, 24-hour urine protein-to-creatinine ratio

Figure 32. Effect of Covariates Identified From the PopPK Model on the Efficacy Endpoint (uPCR-24h 9 Months/$uPCR\text{-}24h_{Baseline}$)



Source: Applicant's M&S Report (VIS649), Figure 10: Page 41
Dots represent the median with lines representing the 90% CI based on parameter uncertainty of the E-R model.
Reference subject: 70 kg, ADA-IgAN subject following 400 mg SC Q4W administration with a vial, baseline bilirubin 0.41 mg/dL, baseline ALT 16 U/L, and baseline uPCR-24h 1.29 g/g.
Abbreviations: ADA, antidrug antibody; AUC, area under the serum concentration-time curve; BSV, between subject variability; CI, confidence interval; C_{max}, maximum serum concentration; C_{trough}, trough serum concentration; PFS, prefilled syringe; uPCR24h, 24-hour urine protein-to-creatinine ratio

14.5.1. Executive Summary

This section discusses the Applicant's popPK, PK/PD and E-R analyses of sibeprenlimab (M&S Report# *OTSU-PMX-VIS649-6130 & VIS 649*).

Pharmacometrics analyses were conducted to support the proposed indication in patients with IgAN. To achieve this goal, popPK, PK/PD and E-R analyses were conducted. The assessment of risk with each modeling method is summarized in Table 75.

Table 75. Assessment of Model Risk

Elements	Details
Question of interest	Is the proposed dosing regimen appropriate to chronically treat IgAN in adults who are at risk of disease progression to reduce proteinuria?
Context of use	Simulations were conducted based on the: PopPK model to derive exposures for the proposed dose, PK/PD model to illustrate dose bridging between 400 mg every 4 weeks SC and 4 mg/kg every 30 days IV and E-R model to support the efficacy of the proposed dosage regimen in the target population.
Model influence	Moderate: Observed PK and efficacy data are available in the target patient population from phase 1 to 3 clinical studies. However, in the current application, safety data are not included. Therefore, modeling and simulations, in combination with clinical and nonclinical evaluations will be applied to support the efficacy but not safety of the proposed dosing in the target patient population.
Decision consequence	Moderate: Incorrect predictions of exposure could lead to incorrect dosage which could impact safety or effectiveness.
Model risk	Moderate: By combining model influence and decision consequence.

Source: Reviewer's Analysis
Abbreviations: eGFR, estimated glomerular filtration rate; E-R, exposure-response; IgAN, immunoglobulin A nephropathy; IV, intravenous; PD, pharmacodynamic; PK, pharmacokinetic; PopPK, population PK; SC, subcutaneous

In line with the anticipated model risk in deriving the sibeprenlimab dose in IgAN patients, the following evaluation and criteria were considered in the review (Table 76).

Table 76. Evaluation and Criteria Considered in Pharmacometrics Review

Methodology	Objective	Model Evaluation	Section
Exposure-response analysis	To characterize the relationship between exposure and the efficacy endpoint (uPCR[a]).	Standard evaluation	14.5.1.2
Population PK and PK/PD analyses	To simulate sibeprenlimab and immunoglobin A concentrations at steady-state for PK/PD and E-R analyses.	Standard evaluation	14.5.1.1

Source: Reviewer's Analysis
[a]Ratio of uPCR-24h 9months compared to uPCR-24h$_{baseline}$
Abbreviations: E-R, exposure-response; PD, pharmacodynamic; PK, pharmacokinetic; uPCR-24h, 24-hour urine protein-to-creatinine ratio

The pharmacometrics analyses support the following:

- The E-R analysis supports the Applicant's proposed dose (sibeprenlimab at 400 mg SC Q4W) for the treatment of patients with IgAN.
- Based on population PK and PK/PD modeling and simulation analyses, the proposed dosage plan (400 mg SC Q4W) produced comparable exposures and reduction in IgA over the treatment period as that of 4 mg/kg IV dose.

14.5.1.1. Applicant's Analysis

Population PK and PK/PD Analyses

Objectives

- Characterize population PK and PK/PD models to describe sibeprenlimab pharmacokinetics and pharmacodynamics following IV and SC administration in healthy adults and adults with IgAN.
- Support the recommended sibeprenlimab dosing regimen based on simulations from the PK and PK-IgA model framework.

Data

The popPK analysis included data from 5 clinical studies (VIS649-101, VIS649-102, 417-201-00005, VIS649-201, and 417-201-00007) conducted in healthy subjects and subjects with IgAN. Table 77 (A and B) shows the demographic and baseline characteristics of the subjects included in the analysis.

Table 77. Summary of Subjects Demographic and Baseline Characteristics

(A) Continuous Variables

Covariate	Healthy Subjects (N = 110)	Subjects With IgAN (N = 367)	Overall (N = 477)
Baseline weight (kg)			
Mean (SD)	67.8 (12.6)	77.0 (20.7)	74.9 (19.6)
Median [Min, Max]	65.8 [39.7, 103]	74.0 [40.2, 238]	71.7 [39.7, 238]
Age (years)			
Mean (SD)	30.7 (9.76)	42.0 (12.1)	39.4 (12.6)
Median [Min, Max]	28.0 [18.0, 54.0]	41.0 [18.0, 75.0]	39.0 [18.0, 75.0]
Baseline albumin (g/dL)			
Mean (SD)	4.31 (0.551)	4.19 (0.367)	4.22 (0.419)
Median [Min, Max]	4.30 [3.10, 5.35]	4.20 [2.90, 5.10]	4.20 [2.90, 5.35]
Baseline APRIL level (pg/mL)			
Mean (SD)	4570 (1310)	3900 (3130)	4060 (2820)
Median [Min, Max]	4380 [1860, 8650]	3430 [228, 49900]	3790 [228, 49900]
Missing	0 (0%)	5 (1.4%)	5 (1.0%)
Baseline aspartate aminotransferase (U/L)			
Mean (SD)	18.0 (6.29)	22.3 (17.5)	21.3 (15.7)
Median [Min, Max]	17.0 [9.00, 47.0]	20.0 [8.00, 280]	19.0 [8.00, 280]
Baseline alanine aminotransferase (U/L)			
Mean (SD)	17.0 (9.47)	22.3 (15.3)	21.0 (14.4)
Median [Min, Max]	14.0 [6.00, 54.0]	17.0 [5.00, 137]	16.0 [5.00, 137]
Baseline bilirubin (mg/dL)			
Mean (SD)	0.554 (0.248)	0.426 (0.269)	0.456 (0.270)
Median [Min, Max]	0.500 [0.175, 1.52]	0.351 [0.0877, 2.10]	0.409 [0.0877, 2.10]
Baseline eGFR (mL/min)			
Mean (SD)	113 (16.4)	70.9 (27.9)	80.6 (31.2)
Median [Min, Max]	112 [75.1, 154]	66.2 [23.7, 244]	78.2 [23.7, 244]
Baseline uPCR-24h (g/g)			
Mean (SD)	NA (NA)	1.64 (1.07)	1.64 (1.07)
Median [Min, Max]	NA [NA, NA]	1.29 [0.490, 7.77]	1.29 [0.490, 7.77]
Missing	110 (100%)	0 (0%)	110 (23.1%)

(B) Categorical Variables

	Healthy Subjects (N = 110)	Subjects With IgAN (N = 367)	Overall (N = 477)
Sex at birth			
Male	48 (43.6%)	225 (61.3%)	273 (57.2%)
Female	62 (56.4%)	142 (38.7%)	204 (42.8%)
Race			
Caucasian	26 (23.6%)	116 (31.6%)	142 (29.8%)
Black or African American	17 (15.5%)	2 (0.5%)	19 (4.0%)
American Indian or Alaskan Native	0 (0%)	1 (0.3%)	1 (0.2%)
Asian	56 (50.9%)	239 (65.1%)	295 (61.8%)
Other	11 (10.0%)	9 (2.5%)	20 (4.2%)
Subject ADA status			
ADA positive subject	41 (37.3%)	129 (35.1%)	170 (35.6%)
ADA negative subject	69 (62.7%)	238 (64.9%)	307 (64.4%)
Subject NAb status			
NAb positive subject	0 (0%)	41 (11.2%)	41 (8.6%)
NAb negative subject	110 (100%)	305 (83.1%)	415 (87.0%)
Not reportable all the time	0 (0%)	21 (5.7%)	21 (4.4%)
Concomitant medication[a]			
Yes	0 (0%)	104 (28.3%)	104 (21.8%)
No	110 (100%)	263 (71.7%)	373 (78.2%)
Health status			
Healthy subject	110 (100%)	0 (0%)	110 (23.1%)
IgAN subject	0 (0%)	367 (100%)	367 (76.9%)
Ethnicity (Japanese versus non-Japanese)			
Japanese	21 (19.1%)	33 (9.0%)	54 (11.3%)
Non-Japanese	89 (80.9%)	334 (91.0%)	423 (88.7%)
Ethnicity (Chinese versus non-Chinese)			
Mainland Chinese	24 (21.8%)	18 (4.9%)	42 (8.8%)
Non-Chinese	86 (78.2%)	349 (95.1%)	435 (91.2%)
Ethnicity (Eastern Asian versus non-Eastern Asian)			
Eastern Asian	24 (21.8%)	106 (28.9%)	130 (27.3%)
Non-Eastern Asian	86 (78.2%)	261 (71.1%)	347 (72.7%)
Ethnicity (Hispanic or Latino)			
Hispanic or Latino	6 (5.5%)	32 (8.7%)	38 (8.0%)
Not Hispanic or Latino	56 (50.9%)	325 (88.6%)	381 (79.9%)
Other	48 (43.6%)	10 (2.7%)	58 (12.2%)
Baseline renal impairment			
Normal	102 (92.7%)	81 (22.1%)	183 (38.4%)
Mild	8 (7.3%)	136 (37.1%)	144 (30.2%)
Moderate	0 (0%)	141 (38.4%)	141 (29.6%)
Severe	0 (0%)	9 (2.5%)	9 (1.9%)

Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Tables 7 & 8: Page 49-50 & 52-3, respectively
[a] Concomitant medication is Yes if the subject had taken any concomitant medications throughout the study.
Numeric columns are formatted as count (% of total). SGLT-2 inhibitors include dapagliflozin, empagliflozin, dapagliflozin propanediol monohydrate, canagliflozin, ertugliflozin, bexagliflozin, and ipragliflozin.
Abbreviations: ADA, antidrug antibody; APRIL, A-Proliferation-Inducing Ligand; eGFR, estimated glomerular filtration rate; IgAN, immunoglobulin A nephropathy; Max, maximum; Min, minimum; M&S, modeling and simulation; N, number of subjects with available information; NA, not available; NAb, neutralizing antibody; SGLT-2, sodium-glucose cotransporter-2; SD, standard deviation; uPCR-24h, 24-hour urine protein-to-creatinine ratio

Methods

Previously, based on data obtained from the three phase 1 clinical studies, a popPK model of sibeprenlimab was developed. A two-compartment model structure with first-order absorption with lag time and a linear and Michaelis-Menten approximated nonlinear elimination fitted the data. In the present application, after initial exploratory investigations, the previously developed popPK model was updated with the addition of new data from phase 2 (VIS649-201) and phase 3 (417-201-00007) clinical studies and retained with minor refinements. Baseline body weight was included as a covariate on CL_{lin} and volume parameters as fixed or estimated allometric exponents, because baseline body weight was a predictor for CL_{lin} and volume for antibodies. Other relevant covariates were also investigated on the popPK parameters. A stepwise covariate model building strategy was implemented with the parameter-covariate relationships that were statistically significant in a univariate covariate screening. The covariate selection was performed using a forward addition process (at 0.01 significance level) followed by backward elimination (at 0.001 significance level). Statistically significant covariates were further evaluated for clinical relevance based on simulations.

Previously, based on data from three phase 1 studies, an indirect response PK/PD model of sibeprenlimab concentration dependent inhibition of IgA production using the first-order elimination rate of IgA (K_{out}) was also developed. Serum total IgA was the PD endpoint. In the present application, the previous PK/PD model was reassessed and refined with the addition of new data from the phase 2 (VIS649-201) and 3 (417-201-00007) studies in IgAN patients. Individual post hoc parameters of the current final popPK model were used to predict sibeprenlimab concentrations. The covariate effects were investigated on the PK/PD parameters.

The popPK and PK/PD models were assessed based on trends in goodness-of-fit (GoF) plots as well as for the precision of parameter estimates such that the relative standard errors (RSEs) of the fixed and random effects were accepted if the RSE is less than 30% and 50%, respectively. The predictive ability of the final model was evaluated based on the agreement between the observed and simulated data distributions according to visual predictive checks (VPCs).

The final popPK and PK/PD models were used to simulate sibeprenlimab concentrations and IgA profiles following the 400 mg SC every 4 weeks dosing regimen and 4 mg/kg IV monthly (30 days) dosing regimens using a total of 500 resampled subjects from a pooled population of IgAN patient population obtained from the phases 2 and 3 studies. In the popPK simulation, the reference subject was simulated 1000 times with randomly assigned between-subject variability from the final PK model with the median exposure of those 1000 replicates chosen as the comparator. The simulations were used to compare different dose regimens in terms of pharmacokinetics and pharmacodynamics measured by inhibitory effect of sibeprenlimab on serum IgA as well as to evaluate the impact of covariates on PK exposures.

Results

The final PK-evaluable dataset used in the current analysis contained 477 subjects with 5813 quantifiable PK observations. Consistent with the prior model of sibeprenlimab, the two-compartment structure with linear and nonlinear elimination (Michaelis-Menten approximation) was selected. SC absorption was described by a first-order process with absorption with lag time, and F was estimated. After the stepwise covariate modeling of the evaluated covariates, the

following covariates were found to have a significant effect: uPCR-24h on CL_{lin}, baseline ALT and bilirubin on V_{max}, health status on V_2 and KA and method of delivery on F.

The selected final popPK model included: effect of body weight on CL_{lin}/Q /V_{max} and V_2 /V_3, subject-level ADA-positive for subjects with IgAN on CL_{lin}, healthy subject effect on V_2 and KA, method of delivery (PFS) effect on F, baseline bilirubin and baseline ALT on V_{max}, and baseline uPCR-24h on CL_{lin}. This model was largely similar to the previously developed popPK model for sibeprenlimab.

The parameter estimates for the final model with corresponding precision estimates (%RSE), are provided in Table 78.

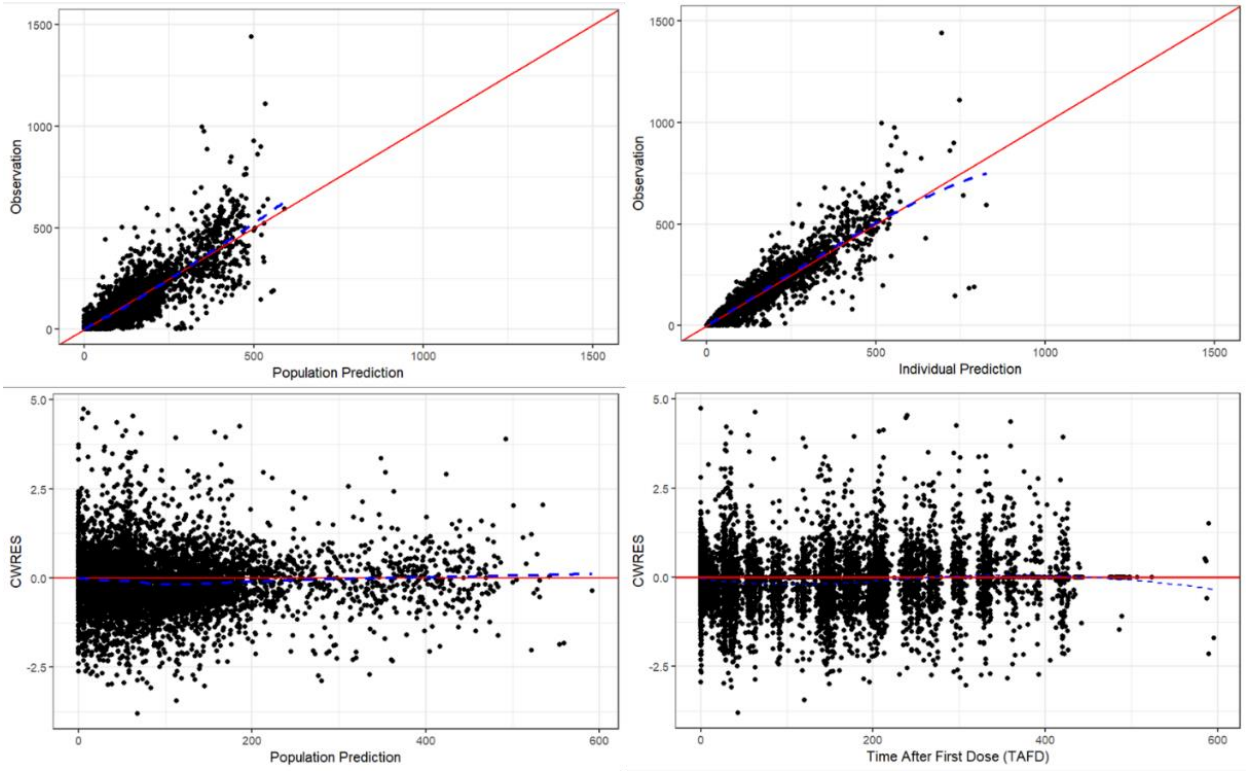
Table 78. Parameter Estimates of the Final Population PK Model of Sibeprenlimab

Parameters	Estimates	RSE%	95% CI	Shrinkage
Typical values				
CL_{lin} (mL/day)	48.5	2.61	46.1, 51.0	NA
Q (mL/day)	623	3.50	580, 665	NA
V2 (mL)	2524	1.43	2453, 2595	NA
V3 (mL)	1511	1.52	1466, 1556	NA
Vmax (ug/day)	5156	1.61	4993, 5319	NA
Km (ug/mL)	0.186	6.79	0.161, 0.211	NA
F (%)	0.816	0.209	0.813, 0.819	NA
KA (1/day)	0.170	1.15	0.166, 0.174	NA
ALAG (day)	0.0889	0.789	0.0875, 0.0902	NA
Covariate effects				
Weight on CL_{lin}, Q, and Vmax	0.661	1.49	0.642, 0.680	NA
Weight on V2 and V3	0.574	5.27	0.515, 0.633	NA
Subject-level ADA-positive on CL_{lin} for IgAN subjects only	0.665	3.26	0.622, 0.707	NA
uPCR-24h on CL_{lin}	0.202	9.01	0.166, 0.237	NA
PFS on F	0.126	2.60	0.119, 0.132	NA
Healthy subject on KA	0.439	14.7	0.312, 0.565	NA
Healthy subject on V2	0.353	20.6	0.210, 0.496	NA
ALT on Vmax	0.0685	26.8	0.0325, 0.105	NA
Bilirubin on Vmax	-0.0720	25.6	-0.108, -0.0358	NA
Between-subject variability[a]				
On CL_{lin}	63.1	0.875	62.1, 64.2	25.9%
On Vmax	30.5	0.394	30.2, 30.7	24.5%
On V2	28.0	0.0630	28.0, 28.0	42.4%
On KA	54.3	0.930	53.3, 55.3	27.6%
On ALAG	31.6	0.942	31.0, 32.2	53.8%
On V3	47.7	1.90	45.9, 49.5	43.7%
Residual error				
Proportional error (%)	31.0	0.348	30.8, 31.2	13.8%
Additive error (ug/mL)	0.0412	5.46	0.0368, 0.0456	13.8%

Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Table 17: Page 68-9
[a]Estimates shown are CV%.
Abbreviations: ADA, antidrug antibody; ALAG, absorption lag time; CI, confidence interval; CL_{lin}, linear clearance; CV%, coefficient of variation percentage; F, subcutaneous bioavailability; KA, absorption rate constant; K_m, concentration at which 50% maximal nonlinear elimination occurs; M&S, modeling and simulation; NA, not applicable; PFS, prefilled syringe; PK, pharmacokinetic; Q, distributional clearance; RSE%, relative standard error percentage; SC, subcutaneous; V_2, central volume of distribution; V_3, peripheral volume of distribution; V_{max}, maximal rate of nonlinear clearance

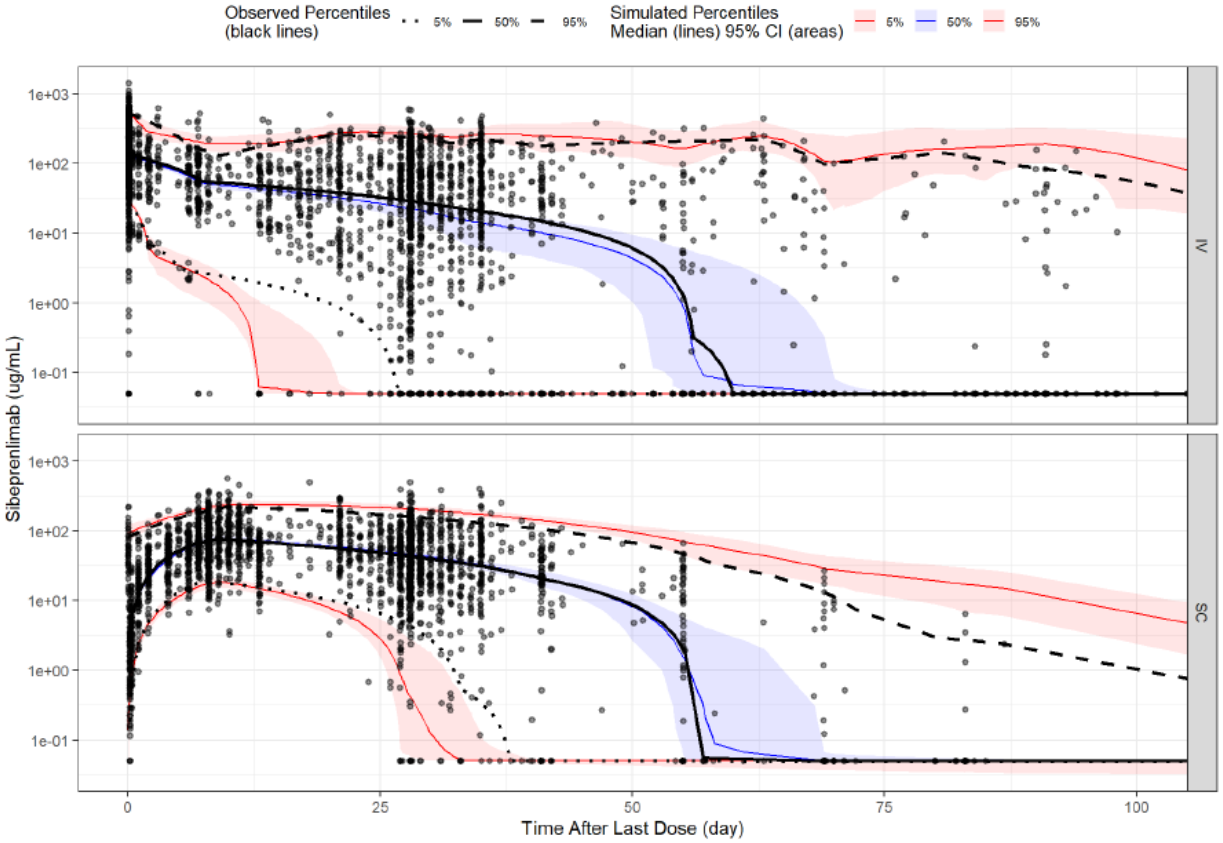
The GoF and the VPC plots of the final popPK model are shown in Figure 33 and Figure 34, respectively. Based on these plots, the selected final PK model appears to describe the current data adequately.

Figure 33. Goodness-of-Fit Plots of the Final Population PK Model for Sibeprenlimab



Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; PK, pharmacokinetic

Figure 34. Visual Predictive Check Stratified by Route of Administration of the Final PopPK Model



Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Figure 11: Page 77
Abbreviations: CI, confidence interval; IV, intravenous; M&S, modeling and simulation; PopPK, population pharmacokinetic; SC, subcutaneous

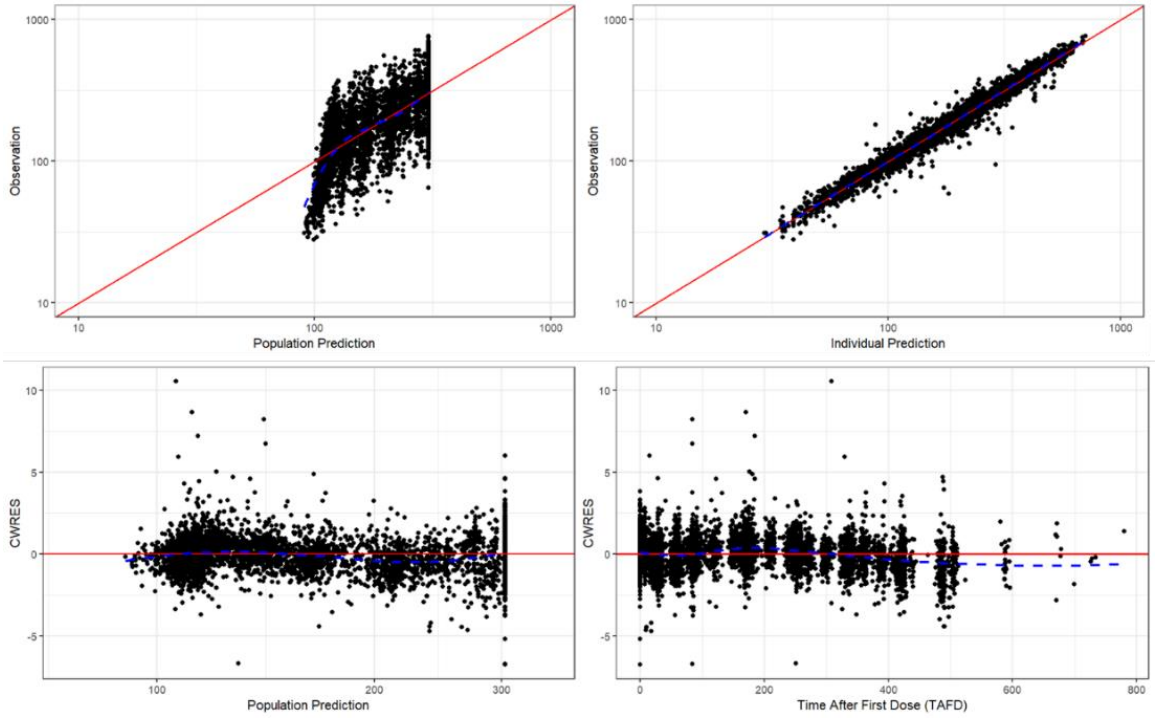
Consistent with the prior PK/PD base model, the indirect response model was selected and described the present sibeprenlimab concentration and IgA data. Using this base PK/PD model, among the tested covariates**,** the only significant covariate that was retained in the final model was the effect of baseline IgA on I_{max}. The parameter estimates of the final PK/PD model are presented in Table 79. The GoF and VPC plots of the final PK/PD model are shown in Figure 35 and Figure 36, respectively. Based on the diagnostic plots, the selected final PK/PD model appears to sufficiently characterize the current sibeprenlimab concentration and IgA data. The estimated parameter-covariate relationship indicated an inverse association, where higher baseline IgA levels correspond to a slight reduction in I_{max} (Figure 37).

Table 79. Parameter Estimates of the Final PK/PD Model

Parameter	Model Estimate	Bootstrap Median	Bootstrap 95% CI
Typical values			
Kout (1/day)	0.0224	0.0224	0.0213, 0.0235
Imax	0.640	0.640	0.629, 0.651
IC50 (µg/mL)	0.230	0.237	0.0446, 0.691
BASE (mg/dL)	303	303	295, 311
Covariate effects			
Effect of BIGA on Imax	-0.0798	-0.0795	-0.118, -0.0432
Between-subject variability (CV%)			
On Kout	35.5	35.3	31.3, 39.7
On BASE	36.1	36.1	34.0, 38.4
On Imax	12.7	12.6	11.2, 14.1
Residual error			
Proportional error (%)	5.81	5.68	2.95, 9.33
Additive error (µg/mL)	0.0875	0.0872	0.0776, 0.0954

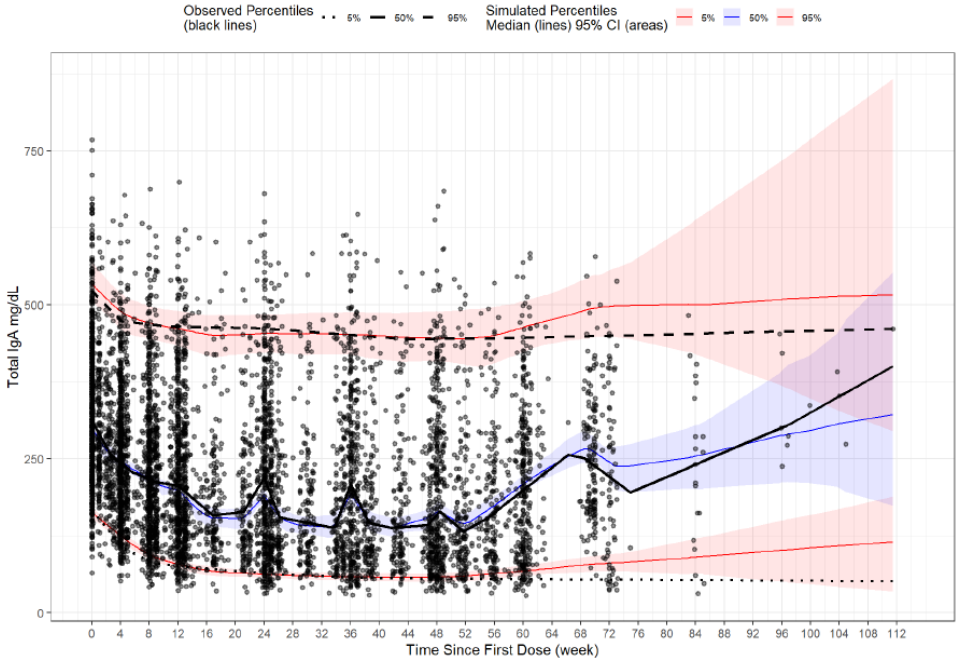
Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Table 25: Page 92-3
Abbreviations: BASE, estimated baseline IgA; BIGA, observed baseline IgA; CI, confidence interval; CV%, coefficient of variation percentage; IC_{50}, sibeprenlimab concentration at which 50% maximal inhibition occurs; IgA, immunoglobulin A; I_{max}, maximal inhibition; K_{out}, first-order elimination rate of IgA; M&S, modeling and simulation; PD, pharmacodynamic; PK, pharmacokinetic

Figure 35. Goodness-of-Fit Plots of the Final PK/PD Model for Sibeprenlimab



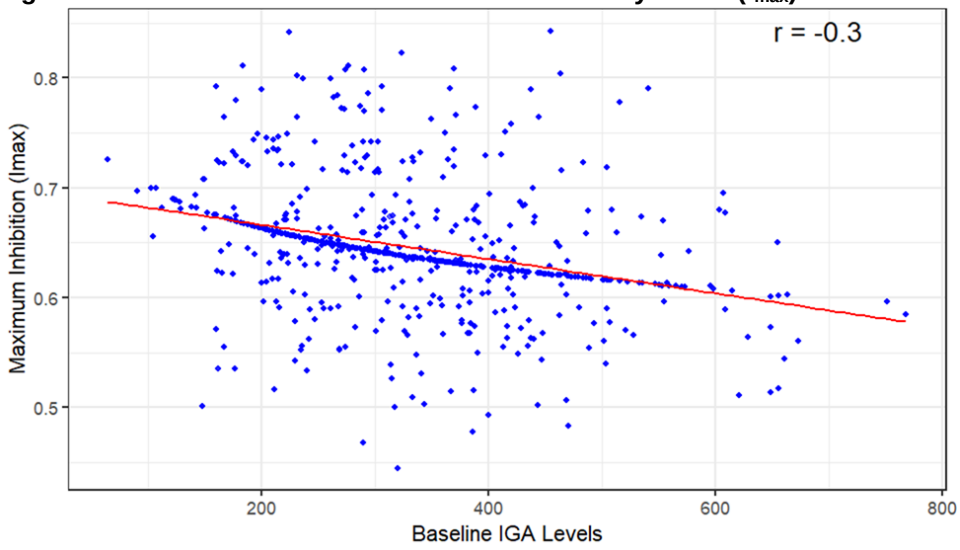
Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; PD, pharmacodynamic; PK, pharmacokinetic

Figure 36. Visual Predictive Check of the Final PK/PD Model



Source: Applicant's M&S Report (OTSU-PMX-VIS649-6130), Figure 21: Page 93
Abbreviations: IgA, immunoglobulin A; M&S, modeling and simulation; PD, pharmacodynamic; PK, pharmacokinetic

Figure 37. Correlation Between Maximum Inhibitory Effect (I_{max}) vs. Baseline IgA level



Source: Reviewer's analysis
Abbreviations: IgA, immunoglobulin A; I_{max}, maximum inhibition; vs., versus

Based on the final popPK model, simulations were conducted to evaluate the isolated effects of identified covariates on steady-state sibeprenlimab exposure metrics (AUC_{tau}, C_{max}, and C_{trough}) following 400 mg subcutaneous every 4 weeks for 10 doses. Each significant covariate was tested at extreme values (5^{th} and 95^{th} percentiles for continuous variables and nontypical values for categorical variables) while all other covariates were held at typical values for the IgAN patient population. Forest plots (Figure 31) illustrate the fold change in exposure metrics expressed as ratios relative to a reference subject (70-kg, ADA-negative IgAN patient with vial

administration, baseline bilirubin 0.41 mg/dL, ALT 16 U/L, and uPCR-24h 1.29 g/g). Forest plots (Figure 31) illustrate the fold change in exposure metrics expressed as ratios relative to a reference subject (70-kg, ADA-negative IgAN patient with vial administration, baseline bilirubin 0.41 mg/dL, ALT 16 U/L, and uPCR-24h 1.29 g/g). The reference subject was simulated 1000 times with randomly assigned between-subject variability from the final pharmacokinetic model, with the median exposure of those replicates serving as the comparator for evaluating covariate effects within a 0.5 to 2-fold range of reference exposure.

Of the notable effects, compared to a subject weighing 70 kg (body weight for a typical subject), baseline body weight was associated with a 43%, 51%, and 46% decrease in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively in a subject weighing 110 kg (the 95th percentile). However, in a subject weighing 50.7 kg (the 5th percentile), body weight was associated with a 40%, 47%, and 42% increase in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively **(**Figure 31**)**. Compared to ADA-negative IgAN patients, ADA-positive IgAN patients were predicted to show 33%, 47%, and 38% decreases in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively. The effect of PFS method of delivery was associated with a 21%, 25%, and 22% increase whereas the 95th percentile (3.96 g/g) of baseline uPCR-24h showed a 17%, 23%, and 19% decrease in steady-state C_{max}, C_{trough}, and AUC_{tau}, respectively, when compared to the reference subject.

Using 500 resampled IgAN subjects from Trials VIS649-201 and 417-201-00007, simulations were also performed with the final popPK and PK/PD models to compare the simulated PK exposures (C_{max}, C_{trough}, and AUC_{tau}) and IgA profiles over the entire treatment courses between 400 mg SC every 4 weeks for 10 doses versus 4 mg/kg IV every month (30 days) for nine doses. The simulated steady-state C_{max}, C_{trough} and AUC_{tau} were generally comparable between the two dosing regimens (Figure 28). Further, the median curve and the 5th to 95th percentile range of the simulated IgA percent change from baseline of both regimens largely overlap (Figure 29).

Conclusions

While the pharmacokinetics of sibeprenlimab following IV and SC administration were characterized by a two-compartment PK model with first-order absorption (for SC) with lag time and linear and nonlinear (Michaelis-Menten approximated) eliminations, the pharmacodynamics (serum IgA level) of sibeprenlimab were characterized by an indirect response PK/PD model with sibeprenlimab concentration dependent inhibition of IgA production. Baseline body weight, ADA-positive status in subjects with IgAN, baseline uPCR-24h, PFS, baseline ALT, and baseline bilirubin had a statistically significant impact on PK parameters of sibeprenlimab. In a IgAN subject with a baseline body weight of 110 kg (95th percentile), body weight resulted a decrease in PK exposures ranging from 43% to 51% but an increase in PK exposures ranging from 40% to 47% for 50.7 kg (5th percentile) of body weight, compared to a typical 70 kg IgAN subject. Baseline IgA on I_{max} was the only significant covariate in the PK/PD model. Higher I_{max} was associated with lower baseline IgA. PK and PK/PD simulation results in the IgAN patient population showed comparable PK exposures and simulated IgA concentration-time profiles between 400 mg SC every 4 weeks and 4 mg/kg IV monthly dosing regimens.

The GoF plots of the final popPK model (Figure 33) generally indicate that there is a concurrence between the observed and predicted sibeprenlimab concentrations; as shown by the blue loess lines, the data appear to be distributed nearly equally along the lines of identity on the observed versus population as well as individual predicted concentrations. This is generally evident since conditional weighted residual versus population prediction plot points scattered

randomly around zero without any notable trend, suggesting that the model is neither biased toward over- nor underpredicting concentrations at different concentration levels. Further, the VPC plots (Figure 34), which were created based on simulation replicates of the observed data, also indicate that the median, 5th and 95th percentiles of the observed versus predicted concentrations appear in alignment, reaffirming that the model captures both the central tendency (median) and the magnitude of the variability (5th and 95th percentiles) of the observed data. All parameters of fixed, random and covariate effects were estimated with acceptable precision (relative standard errors were <30%). The shrinkages on most interindividual variabilities terms were <30% (Table 78) and thus deemed acceptable although the interindividual variability on volume terms appears above the threshold of 30%.

Similarly, the GoF plots of the final PK/PD model show agreement between observations and predictions both at the population and individual level (Figure 35). Based on the VPC plot (Figure 36), the model also describes the central tendency (median) and variabilities (5th and 95th percentiles) of the data. The model parameters were accurately estimated based on the concordance with bootstrap results (Table 79).

Overall, the selected final popPK and PK/PD models are considered acceptable to describe the observed data and can be used in simulations and subsequent exposure-response analyses.

14.5.1.2. E-R Analysis

Background

In the current E-R analyses, the Applicant assessed the E-R (efficacy) in a full dataset based on placebo and three IV dose levels of sibeprenlimab from a completed phase 2 study (Trial VIS649-201) and partial dataset from the ongoing phase 3 study (Trial 417-201-00007) in which the 400 mg SC every 28 days dosing regimen was used in IgAN patients. The steady-state PK exposure metrics used in the E-R relationship analysis were AUC_{tau} (area under the concentration-time curve), average concentration, and C_{trough} (trough serum concentration), derived based on the final popPK model. The primary efficacy endpoint was a ratio between uPCR-24h$_{9months}$ and uPCR-24h$_{baseline}$.

Objectives

To characterize the relationship between sibeprenlimab PK exposure and the efficacy endpoint (ratio of uPCR-24h9months compared to uPCR-24hbaseline), identify and quantify significant covariate effects on the relationship between PK exposure and the efficacy endpoint, and simulate to support the recommended dosing regimen.

Data

The analysis included data from two clinical studies (Trial VIS649-201, a phase 2 study, and Trial 417-201-00007, a phase 3 study).

Method

A nonlinear mixed effects modeling approach was utilized to characterize the relationship between the efficacy endpoint (ratio of uPCR-24h9months compared to uPCR-24h$_{baseline}$) and PK exposures of sibeprenlimab. Linear and saturable base models with an exponential error model

were evaluated. A stepwise covariate model building strategy was performed to assess the covariates of interest. Goodness-of-fit and VPC plots were used to evaluate the predictive ability of the final E-R model.

Using the final popPK model, simulations were performed to simulate PK profiles for 400 mg SC every 4 weeks through 40 weeks (10 total doses) for the typical subjects of interest. Using the E-R model, 1000 parameter vectors were drawn from the variance–covariance matrix. Model-estimated 9-month to baseline ratio of 24 hr-uPCR with their associated 90% CIs were calculated for the 400 mg SC every 4 weeks dosing regimen for 10 total doses for the typical patient reference as well as typical patients at extreme values (5^{th} and 95^{th} percentiles).

Results

Of the total 665 IgAN subjects, the E-R efficacy analysis was conducted on a dataset containing 446 subjects. Two hundred fifty-three (253) subjects were treated with sibeprenlimab while 193 subjects received placebo. Among the evaluated models, the maximum effect (E_{max}) model resulted in the best fit to the E-R data, therefore it was selected as the base model structure for further model development. The base E_{max}-model structure for $AUC_{tau,ss}$ as an example is displayed mathematically below.

Equation 2. Base E_{max}-Model Structure for $AUC_{tau,ss}$

$$uPCR_{ratio} = E0 + (Emax \times \frac{AUC_{tau,ss}}{AUC_{tau,ss} + EC50})$$

Source: Applicant's M&S Report (VIS649), Page 34
VIS649 refers to sibeprenlimab
Abbreviation: $AUC_{tau,ss}$, area under the time-concentration curve in steady-state; E0, uPCR ratio upon placebo treatment; E_{max}, maximum effect attainable and EC_{50}, sibeprenlimab $AUC_{tau,ss}$ at which 50% of the maximum effect is obtained

The final E-R model included age effect and interindividual variability on treatment response to placebo (E0) parameter. The final model parameter estimates are provided in Table 80. E_{max} and E0 were estimated with good precision (RSE <15%), the age effect on the E0 estimate was with reasonable precision (RSE <30%), however, the EC_{50} for all three models was estimated with poor precision (RSE ranging 78% to 123%). Among the PK exposure metrics, $AUC_{tau,ss}$ resulted in the lowest RSE (78%) in the EC_{50}, and therefore is considered to be the preferred PK exposure metric for the final E-R model.

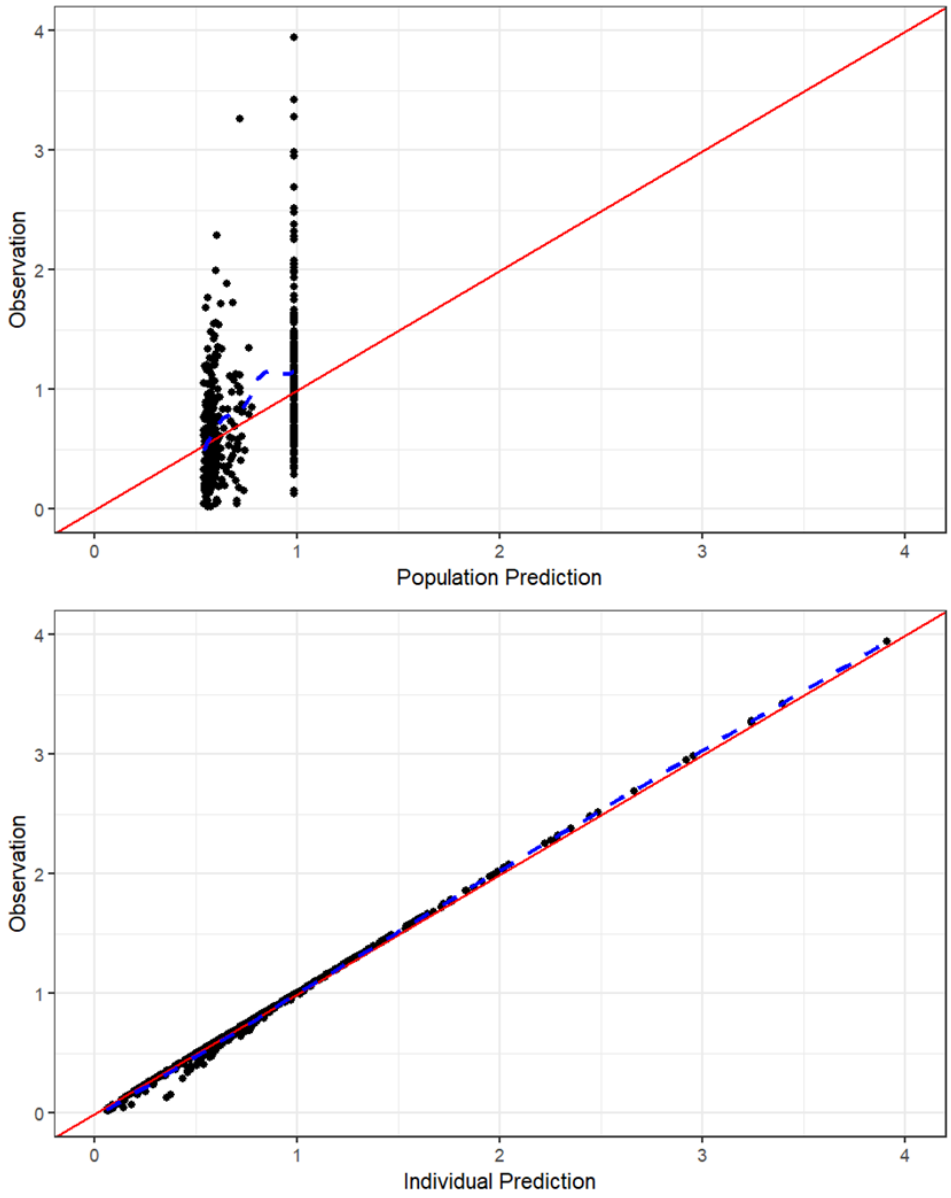
The GoF and VPC plots of the final E-R model, are shown in Figure 38 and Figure 39 respectively.

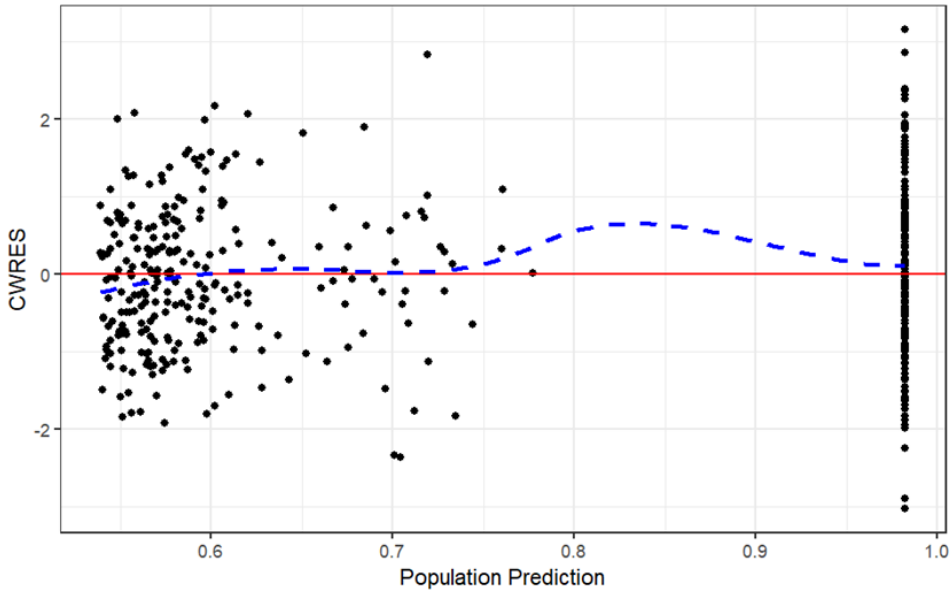
Table 80. Parameter Estimates of the Final E-R Model

Parameter	$AUC_{tau,ss}$ Model	$C_{avg,ss}$ Model	$C_{trough,ss}$ Model
E_{max} (RSE%)	−0.4534 (12.5)	−0.4524 (12.8)	−0.393 (9.6)
EC_{50} (RSE%)	273.4 (78.4)[a]	9.261 (84)	0.0032 (123)
E0 (RSE%)	0.982 (3.7)	0.982 (3.7)	0.976 (3.6)
Age effect on E0 (RSE%)	−0.26 (29)	−0.26 (29)	−0.27 (28)
IIV E0 (CV%)	42 (6.1)	42 (6.2)	42 (5.6)
OFV	−301	−301	−299

Source: Modified by the Reviewer, Applicant's M&S Report (VIS649), Table 12: Page 35
[a]Exponentiated values after being estimated in the log domain during model development.
Abbreviations: $AUC_{tau,ss}$, area under the concentration-time curve at steady-state; $C_{avg,ss}$, average concentration at steady-state; $C_{trough,ss}$, trough serum concentration at steady-state; E0, response with no dose; EC_{50}, half-maximal effective concentration; E_{max}, maximum effect; IIV, interindividual variability; M&S, modeling and simulation; OFV, objective function value; RSE, relative standard error

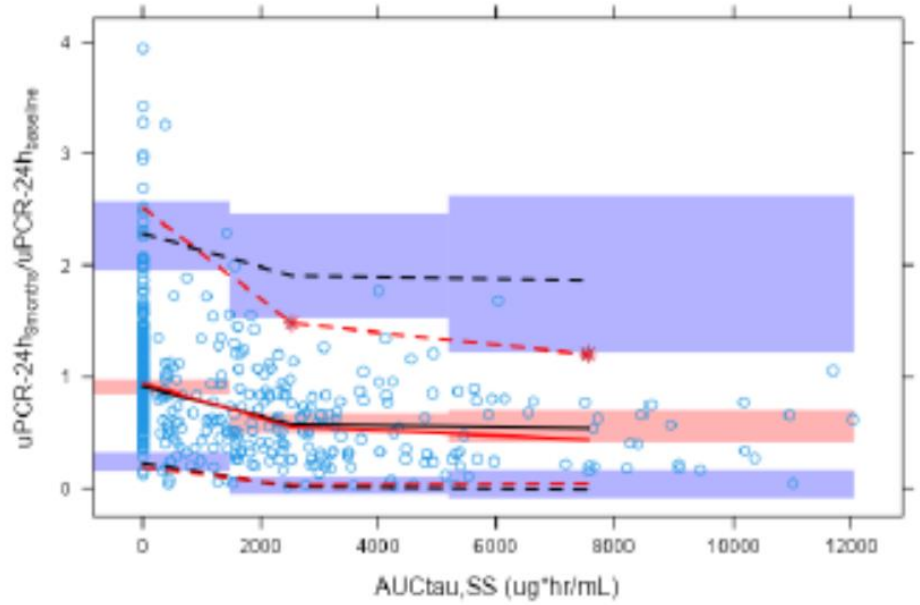
Figure 38. Goodness-of-Fit Plot of the Final E-R (E_{max}) Model





Source: Reviewer's analysis
Abbreviations: CWRES, conditional weighted residuals; E_{max}, maximum effect; E-R, exposure-response

Figure 39. Visual Predictive Check of E_{max} Model Using $AUC_{tau,ss}$ as Exposure Metric



Source: Applicant's M&S Report (VIS649), Figure 9: Page 38
Blue open circles are observed data points; the red solid line is the observed median; the red dashed lines are the observed 5th percentile and 95th percentiles. The red-shaded region is the 95% prediction interval of the simulated median, and blue-shaded regions are the 95% prediction interval of the simulated 5th and 95th percentiles. The black lines represent the median of the simulated data.
Abbreviations: $AUC_{tau,ss}$, area under the concentration-time curve at steady-state; E_{max}, maximum effect; M&S, modeling and simulation; uPCR, urine protein-creatinine ratio

Simulations were conducted to assess the impact of relevant covariate effects on the efficacy endpoint following treatment with sibeprenlimab 400 mg SC Q4W using the final popPK and the E-R models with AUC_{tau},ss as the exposure metric. None of the covariates, including body weight or ADA status, resulted in a meaningful change in the ratio (>0.025 change in the ratio).

As displayed in Figure 28, the top-panel represents the observed data of both clinical studies included in the E-R analysis overlaid on the model-predicted curve. The final E-R model estimated an EC_{50} of 273 µg·day/mL, EC_{80} of 1092 µg·day/mL, and EC_{90} of 2457 µg·day/mL. These estimates correspond to the $AUC_{tau,ss}$ levels above which 50%, 80%, and 90% of the maximum effect on uPCR-24h is achieved, respectively.

The exposure distribution shown in the lower-panel demonstrates that the majority of patients across dose groups achieved $AUC_{tau,ss}$ levels above the EC_{80} threshold. Furthermore, comparison of the exposure ranges indicates that the 400 mg SC dose achieved comparable exposures to the 4 mg/kg IV doses, with both regimens showing similar 9-month uPCR-24h responses as evidenced by the overlapping data points in the goodness-of-fit plot (Figure 28).

Conclusions

An E_{max} model was chosen as a base model as it describes the E-R relationship between sibeprenlimab exposure and the efficacy endpoint. Among PK exposure metrics, AUC_{ss} fitted the data with the lowest RSE% on model parameters and was therefore chosen as the exposure metric in the model. Of the evaluated covariates, age was the only covariate identified on E0; however, it did not result in a meaningful impact on the efficacy endpoint. Therefore, no covariate was added on the base-model structure. Simulations conducted based on the final E-R model indicated a consistent reduction in the ratio of uPCR-24h over 9 months compared to uPCR-24h from the baseline upon treatment with sibeprenlimab 400 mg SC Q4W and support the use of this dose for the treatment of subjects with IgAN.

Figure 38 of the E-R model indicates that the observed versus predicted drug effects both at the population and individual level show mutual agreement. Additionally, the conditional weighted residual plot illustrates that the predicted drug effect is largely scattered randomly around the line of identity, reinforcing the appropriateness of the final E-R model. Further, based on the VPC plots, the final E-R model describes both the central tendency and the variability of the observed data **(**Figure 39**)**, suggesting that the selected final E-R model is acceptable for simulation purposes. A 400 mg SC dose achieved comparable PK exposures and similar responses to the 4 mg/kg IV dose while lower (2 mg/kg IV) or higher (8 mg/kg IV) dose levels did not offer additional efficacy benefit **(**Figure 28**).**

Overall, the E-R analysis supports the use of 400 mg SC Q4W dose for the treatment of patients with IgAN.

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

15.1. Important Trial Dates

Trial 417-201-0007 is currently ongoing; the first subject, first visit, occurred on March 15, 2022. The preplanned IA data cutoff, which was scheduled to occur when at least 62.5% of

randomized subjects in the main cohort have had the opportunity to complete the Month 9 uPCR 24-hour evaluation, occurred on September 4, 2024. As of March 14, 2024, the trial is fully enrolled with 510 subjects in the main trial population and 20 subjects in the exploratory cohort.

15.2. Protocol Amendments

The original protocol was amended globally four times. An overview of key changes in each amendment is provided in Table 81 below. Of note, Amendment 1 was the first protocol submitted to IND 158899.

Table 81. Overview of Protocol Amendments, Trial 417-201-00007

Amendment No. Date	Summary of Significant Changes
Amendment 1 January 3, 2022	• Added a secondary objective/endpoint to analyze eGFR at 12 months. • Removed secondary objective to assess progression of chronic kidney disease. • Added exploratory cohort with an eGFR of 20 to 30 mL/min/1.73 m^2.
Amendment 2 February 16, 2023	• Clarified inclusion/exclusion criteria, language, schedule of assessments. • Added text requiring consultation with medical monitor to discuss need for subject treatment discontinuation if rescue medication is deemed necessary. • Deleted text describing evaluation of AEs using Common Terminology Criteria for Adverse Events
Amendment 3 February 8, 2024	• Added two composite kidney failure secondary efficacy endpoints. • Updated text for handling of missing data, handling of intercurrent events, and efficacy/safety analyses (see Section 16.1 SAP Amendment Number 2 for details).

Source: Reviewer
Abbreviations: AE, adverse event; eGFR, estimated glomerular filtration rate; No., number; SAP, statistical analysis plan

15.3. Trial Administrative Structure

Data Safety Monitoring Board

The trial has an external independent data safety monitoring board (DSMB). The membership and responsibilities are defined by a written charter. The DSMB's responsibilities include safeguarding the interests of clinical research subjects, assessing ongoing safety and efficacy of the study interventions, monitoring overall trial conduct, and making recommendations to the Applicant for future conduct of the trial. Open sessions included Sponsor representatives, DSMB members, and the unblinded DSMB support team ((b) (4), a contract research organization), and consisted of a review of the trial, update on recruitment status, discontinuations, protocol violations, and a blinded safety update, including review of any serious adverse events (SAEs). Closed sessions included only DSMB members and a statistician and project manager from a contract research organization (CRO), (b) (4) (b) (4) and consisted of reviewing unblinded results. The closed-session meeting minutes are not made available to any members of the blinded trial team from the CRO or Applicant. After each meeting, the committee makes recommendations regarding continuation, modification, suspension, or termination of the trial. However, all decisions regarding the conduct of the trial are made by the Applicant.

The committee has met approximately every 6 months, and the Applicant has submitted meeting minutes for six completed DMC meetings. See Table 95 for a summary of the meeting minutes.

See Section 15.5 for information on the administrative structure as relates to preparing the NDA submission and/or blinding related issues.

Independent Statistician

An independent statistician from (b) (4) was responsible for preparation of DSMB reports (in the format of tables, figures, listings). This independent statistician was a nonvoting member of the DSMB.

Institutional Review Board/Independent Ethics Committee

The trial is being conducted in accordance with the International Council of Harmonisation (ICH) Good Clinical Practice (GCP) Consolidated Guideline, and the applicable local laws and regulatory requirements of the countries in which the trial is conducted. The trial is only being conducted at sites where the governing Institutional Review Board (IRB) or Independent Ethics Committee (IEC) have reviewed and approved the protocol, any amendments, and the informed consent form (ICF) prior to the start of the trial or implementation of the protocol or protocol amendment at that trial site and/or country.

15.4. Trial Assessments

The trial's full schedule of assessments is depicted in Table 82 and Table 83 below. In brief, the treatment period starts on Day 1 (first day of study drug administration) and extends until Week 112, and study drug was administered every four weeks. The study collected two 24-hour urine collections (within two weeks of each other) at the Screening, Week 40, Week 52, and "Follow-up" visits for determining the reported 24-hr uPCR from that visit (calculated as the geometric mean of the two uPCRs at the visit). The uPCR results from the Screening and Week 40 visits were used for the primary efficacy endpoint. Spot urine samples (from a first morning void) were collected every four to eight weeks to assess spot uPCR. The study analyzed serum chemistries, including serum creatinine levels to calculate eGFR, during Screening and every four to eight weeks throughout the trial. All serum samples were processed at a central laboratory.

Table 82. Schedule of Assessments – Screening through Week 48

Period	Scr	Intervention Period															
Trial Week	-	-	W4	W5	W8	W12	W16	W20	W21	W24	W28	W29	W32	W36	W40	W44	W48
Trial Day	D−60 to D−1	D1	D29	D37	D57	D85	D113	D141	D149	D169	D197	D205	D225	D253	D281	D309	D337
Visit allowance (days)	NA	NA[a]	± 7	+4	± 7	± 7	± 7	± 7	+ 4	± 7	± 7	+ 4	± 7	± 7	± 7	± 7	± 7
Dose Number	-	#1	#2	-	#3	#4	#5	#6	-	#7	#8	-	#9	#10	#11	#12	#13
PROCEDURES																	
Informed consent	X																
Inclusion/exclusion criteria review	X																
Medical history[b]	X																
Demographic information	X																
Review of kidney biopsy[c]	X																
Optional kidney biopsy collection	X[d]														X[e]		
Hemoglobin A1c	X																
Viral serology	X																
Pregnancy test (subjects of childbearing potential only)[f]	X	X[g]															
FSH (perimenopausal and postmenopausal subjects only)	X																
Height and weight[h]	X	X			X					X				X			X
Randomization		X															
IMP administration[i]		X	X		X	X	X	X		X	X		X	X	X	X	X
Assessment of injection site[j]		X	X		X	X	X	X		X	X		X	X	X	X	X
Pain VAS[j]		X	X		X	X	X	X		X	X		X	X	X	X	X
Vital signs[k]	X	X	X		X	X	X	X		X	X		X	X	X	X	X

Period	Scr	Intervention Period															
Trial Week	-	-	W4	W5	W8	W12	W16	W20	W21	W24	W28	W29	W32	W36	W40	W44	W48
Trial Day	D−60 to D−1	D1	D29	D37	D57	D85	D113	D141	D149	D169	D197	D205	D225	D253	D281	D309	D337
Visit allowance (days)	NA	NA[a]	± 7	+4	± 7	± 7	± 7	± 7	+ 4	± 7	± 7	+ 4	± 7	± 7	± 7	± 7	± 7
Dose Number	-	#1	#2	-	#3	#4	#5	#6	-	#7	#8	-	#9	#10	#11	#12	#13
12-lead ECG	X																
Physical examination[l]	X	X			X					X							X
AE monitoring[m]	X																
Concomitant medications review	X																
Serum chemistry	X	X[g]	X		X		X			X			X		X		X
Hematology	X	X[g]	X		X		X			X			X		X		X
Urinalysis (dipstick and microscopy)	X	X[g]	X		X		X			X			X		X		X
24-hour urine collection (creatinine, protein, and albumin)[n]	X (× 2)														X (× 2)		
Spot urine sample for uPCR determination[o]		X[g]	X		X	X		X		X	X		X	X	X		X
Blood sample for PK[p]			X	X				X	X	X	X	X		X			
Blood sample for total IgA, IgG, and IgM[q]	X	X	X		X	X				X				X			X
Blood sample for APRIL[q]		X	X		X	X				X				X			X
Blood sample for g-d IgA1 and anti-IgA1 autoantibody[q]		X	X		X	X				X				X			X
Blood sample for IgA-containing circulating immune complexes[q]		X	X		X	X				X				X			X

Period	Scr	Intervention Period															Notes
Trial Week	-	-	W4	W5	W8	W12	W16	W20	W21	W24	W28	W29	W32	W36	W40	W44	W48	
Trial Day	D−60 to D−1	D1	D29	D37	D57	D85	D113	D141	D149	D169	D197	D205	D225	D253	D281	D309	D337	
Visit allowance (days)	NA	NA[a]	± 7	+4	± 7	± 7	± 7	± 7	+ 4	± 7	± 7	+ 4	± 7	± 7	± 7	± 7	± 7	
Dose Number	-	#1	#2	-	#3	#4	#5	#6	-	#7	#8	-	#9	#10	#11	#12	#13	
Blood sample for markers of complement activation[q]		X								X								Section 8.3
Blood sample for ADA[q]		X	X		X	X				X				X			X	Section 8.11.1
Future biospecimen research (optional)[r]		X[r]																Section 8.6
Urine and blood sample for exploratory assessments[q]		X			X			X					X			X		Section 8.5
SF-36v2		X		X		X				X					X			Section 8.10.1
Brief Fatigue Inventory		X		X		X				X					X			Section 8.10.2

ADA = anti-drug antibody; AE = adverse event; anti-IgA1 = anti-immunoglobulin A1; APRIL = A Proliferation Inducing Ligand; D = day; ECG = electrocardiogram; EDC = electronic data capture; FSH = follicle stimulating hormone; g-d IgA1 = galactose deficient immunoglobulin A1; Ig = immunoglobulin (IgA, IgG, and IgM); IgAN = immunoglobulin A nephropathy; IMP = investigational medicinal product; NA = not applicable; PK = pharmacokinetics; Scr = screening; SF-36v2 = 36-Item Short-Form Survey Version 2; uPCR = urine protein/creatinine ratio; VAS = visual analog scale; W = week.

Note: The screening and Day 1 visit will be performed at the trial site clinic. All other visits may be completed remotely using mobile health per the discretion of the investigator and subject.

[a]The visit allowance for Day 1 is "not applicable" unless otherwise specified.

[b]Vaccinations received within 1 year prior to the signing of informed consent through the end of the trial and historical kidney biopsy results will be recorded in EDC.

[c]A biopsy diagnostic of IgAN must have been performed and source-verified documentation must be available.

[d]Pre-baseline optional biopsy or assessment of tissue from a recently performed biopsy (ie, obtained 1 year prior to randomization with no exposure to immunosuppressants).

[e]Optional follow-up biopsy can be performed at any time between 9- and 12-months postbaseline.

[f]Serum pregnancy tests will be performed at all scheduled time points. Additional pregnancy tests (ie, serum or urine) may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the trial.

[g]Visit window allowance of −3 days.

[h]Height will be performed at screening only. The body mass index will be calculated based on the weight and height information.

[i]Investigational medicinal product will be administered in the abdomen, thigh, or upper arm. For all subjects, Dose 1 (Day 1), Dose 2 (Week 4), Dose 3 (Week 8), Dose 4 (Week 12), Dose 5 (Week 16), and Dose 7 (Week 24) will be injected SC in the abdomen. Dose 6 (Week 20) and Dose 8 (Week 28) will be rotated to either the thigh or upper arm based on assignment at randomization so that each subject has at least 1 IMP administration in each of the SC injection sites. From Dose 9 (Week 32) onwards, subjects will be allowed to select which injection site they prefer for the IMP administration.

[j]The assessment of the injection site and VAS should be performed within approximately 10 minutes after IMP administration. If an injection site reaction is observed at a later time, an assessment of the injection site should be completed.

[k]On dosing days, vital signs (blood pressure, pulse, respiratory rate, and temperature) will be measured within 1 hour predose.

[l]A full physical examination will be performed at screening and Day 1; however, a symptom directed physical examination may be performed on Day 1 if a full physical examination has been performed within 1 week of the visit. Symptom-directed physical examinations will be performed at all other visits.

[m]In the event of any severe event or serious adverse event which is suspected by the investigator to be an immunogenicity related clinical condition, such as injection site reaction, cytokine release syndrome, or delayed allergic reaction (eg, serum sickness), additional ADA and PK samples may be collected for further evaluation. Additional details will be provided in the operations manual.

[n]Two 24-hour urine collections will be collected at each time point (up to 2 weeks apart). Each 24-hour urine collection should start after the first void upon awakening and every complete urine void is to be collected for a 24-hour period. The 24-hour urine collections must occur within the 7-day window allowed for the scheduled visit (as applicable).

[o]The uPCR sample will be collected from the first morning void.

[p]Blood samples to be collected as follows: Dose 2: 1 sample predose (Week 4) and 1 sample 8 to 12 days postdose (Week 5), Dose 6: 1 sample predose (Week 20) and 1 sample 8 to 12 days postdose (Week 21), Dose 7: 1 sample predose (Week 24), Dose 8: 1 sample predose (Week 28) and 1 sample 8 to 12 days postdose (Week 29), Dose 10: 1 sample predose (Week 36). Predose samples are to be collected within 120 minutes prior to the administration of IMP. If the visit preceding a postdose PK-only visit is early or delayed, the PK postdose visit should be adjusted accordingly.

[q]On dosing days, sample(s) to be collected predose (within 120 minutes prior to dosing). ADA samples may be used to measure drug concentration as needed in order to ensure the accuracy of the ADA results.

[r]The optional sample for future biospecimen research may be collected from all consenting subjects at a later visit if not collected on Day 1 (−3 days).

From Protocol 417-201-00007, Amendment 4, dated August 15, 2024

Table 83. Schedule of Assessments – Week 52 through End-of-Trial

Period	Intervention Period													Post-treatment Follow-up	End-of-Trial	Notes
Trial Week	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104/ ED[a]	W112[b]	
Nominal Trial Day	D365	D393	D421	D449	D477	D505	D533	D561	D589	D617	D645	D673	D701	D729	D785	
Visit allowance (days)	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+ 7	
Dose	#14	#15	#16	#17	#18	#19	#20	#21	#22	#23	#24	#25	#26	-	-	
PROCEDURES																
Pregnancy test (subjects of childbearing potential only)[c]	X														X	
IMP administration	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 6.1
Assessment of injection site[d]	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 8.7.5.1
Pain VAS[d]	X	X	X	X	X	X	X	X	X	X	X	X	X			Section 8.7.5.2
Weight			X		X			X			X		X		X	
Physical examination[e]						X							X		X	Section 8.7.2
Vital signs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X		X	Section 8.7.3
AE monitoring[g]	X															Section 8.8
Concomitant medications review	X															Section 6.5
Optional kidney biopsy collection														X		Section 8.3
Serum chemistry	X	X		X		X		X		X		X		X	X	Section 8.7.1
Hematology		X		X		X		X		X		X		X	X	Section 8.7.1
Urinalysis (dipstick and microscopy)		X		X		X		X		X		X		X	X	Section 8.7.1
24-hour urine collection (creatinine, protein, and albumin)[h]	X (× 2)													X (× 2)		Section 8.1
Spot urine sample for uPCR determination[i]	X	X		X		X		X		X		X		X	X	Section 8.1

Period	Intervention Period													Post-treatment Follow-up	End-of-Trial	Notes
Trial Week	W52	W56	W60	W64	W68	W72	W76	W80	W84	W88	W92	W96	W100	W104/ ED[a]	W112[b]	
Nominal Trial Day	D365	D393	D421	D449	D477	D505	D533	D561	D589	D617	D645	D673	D701	D729	D785	
Visit allowance (days)	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	± 7	+ 7	
Dose	#14	#15	#16	#17	#18	#19	#20	#21	#22	#23	#24	#25	#26	-	-	
Blood sample for PK[j]			X						X						X	Section 8.2
Blood sample for total IgA, IgG, and IgM[j]			X			X			X			X			X	Section 8.3
Blood sample for APRIL[j]			X			X			X			X			X	Section 8.3
Blood sample for g-d IgA1 and anti-IgA1 autoantibody[j]			X			X			X			X			X	Section 8.3
Blood sample for markers of complement activation[j]	X					X								X		Section 8.3
Blood sample for ADA[j]			X			X			X			X		X	X	Section 8.11.1
Urine and blood sample for exploratory assessments[j]	X			X					X				X		X	Section 8.5
SF-36v2	X					X								X	X	Section 8.10.1
Brief Fatigue Inventory	X					X								X	X	Section 8.10.2

ADA = anti-drug antibody; AE = adverse event; anti-IgA1 = anti-immunoglobulin A1; APRIL = A Proliferation Inducing Ligand; D = day; ED = early discontinuation; g-d IgA1 = galactose deficient immunoglobulin A1; Ig = immunoglobulin (IgA, IgG, and IgM); IMP = investigational medicinal product; PK = pharmacokinetics; SF-36v2 = 36 Item Short-Form Survey Version 2; uPCR = urine protein/creatinine ratio; VAS = visual analog scale; W = week.

Note: Visits may be completed remotely using mobile health per the discretion of the investigator and subject.

[a]Subjects discontinuing prior to Dose 26 will complete the early discontinuation visit (assessments at Week 104) at the time of treatment discontinuation. Subjects will be encouraged to continue all planned trial visits through the end-of-trial after treatment discontinuation. Subjects who discontinue treatment and are unable to follow the assessment schedule for the remaining visits will continue to be followed until Week 100 and complete the end-of-trial visit (Week 112), if possible, during a regular scheduled subject visit, a telehealth visit, or by telephone contact.

[b]Subjects who complete trial treatment (at least 20 of 26 doses) and the end-of-trial visit (Week 112) will have the opportunity to enter into the rollover open-label extension trial (417-201-00012), if the trial has been approved by the country specific regulatory authority. Assessments performed at any time

after completion of the treatment phase (ie, beginning at Week 104) may be used for screening assessments in the open-label extension trial (417-201-00012), assuming they are performed within the noted screening window.

[c]Serum pregnancy tests will be performed at all scheduled time points. Additional pregnancy tests (ie, serum or urine) may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the trial.

[d]The assessment of the injection site and VAS should be performed within approximately 10 minutes after IMP administration. If an injection site reaction is observed at a later time, an assessment of the injection site should be completed.

[e]Symptom-directed physical examinations will be performed.

[f]On dosing days, vital signs (blood pressure, pulse, respiratory rate, and temperature) will be measured within 1 hour predose.

[g]In the event of any severe event or serious adverse event which is suspected by the investigator to be an immunogenicity related clinical condition, such as injection site reaction, cytokine release syndrome, delayed allergic reaction (eg, serum sickness), or anaphylaxis, additional ADA and PK samples may be collected for further evaluation. Additional details will be provided in the operations manual.

[h]Two 24-hour urine collections will be collected at each time point (up to 2 weeks apart). Each 24-hour urine collection should start after the first void upon awakening and every complete urine void is to be collected for a 24-hour period. The 24-hour urine collections must occur within the 7-day window allowed for the scheduled visit (as applicable).

[i]The uPCR sample will be collected from the first morning void.

[j]On dosing days, sample(s) to be collected predose (within 120 minutes prior to dosing). ADA samples may be used to measure drug concentration as needed in order to ensure the accuracy of the ADA results.

From Protocol 417-201-00007, Amendment 4, dated August 15, 2024

15.5. Trial Procedures

Randomization

Eligible subjects for the double-blind, placebo-controlled portion of the trial were randomized on Day 1 through an interactive response technology system in a 1:1 ratio to sibeprenlimab or placebo. Randomization was stratified by screening uPCR-24h (≤2.0 g/g vs. >2.0 g/g), screening eGFR (30-44 mL/min/1.73 m^2 vs. ≥45 mL/min/1.73 m^2), and SGLT2i use at the time of randomization (yes or no).

Blinding and Unblinding

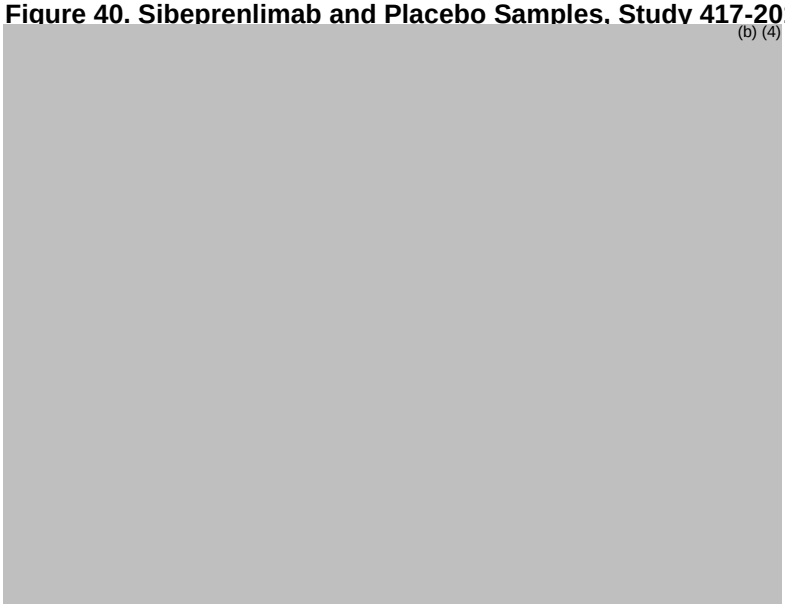
Blinding

To maintain the integrity of the trial, study subjects and investigators were to remain blinded to treatment assignment until the final analysis at the end of the trial.

Study drug was supplied by the Applicant or designated agent either as vials or pre-filled syringes (PFS) (Figure 40) to the investigators and the persons designated by the investigator(s) or institutions(s) and was injected by healthcare personnel.

Figure 40. Sibeprenlimab and Placebo Samples, Study 417-201-00007

(b) (4)



Source: FDA
Left: Sibeprenlimab 200 mg/mL pre-filled syringe (Med ID: 321828)
Right: Placebo solution pre-filled syringe (Med ID: 301449)
Abbreviations: FDA, Food and Drug Administration

Unblinding

At the time of the primary endpoint analysis (e.g., IA, after the first 62.5% of randomized subjects who had the opportunity to complete the Week 40 uPCR evaluation based on a 24-hour urine collection), designated Applicant personnel and designees were unblinded to aggregate data. Details regarding unblinding were specified by the Applicant in their document, Unblinding Procedure at Interim Analysis, Version 2.0 (dated August 15, 2024). The unblinding procedure specified three levels of unblinding as follows:

- **Fully Unblinded**, i.e., those who are unblinded at the subject level:
    - A small group required to conduct statistical analyses, write subject level narratives, or review subject level listings to support a regulatory submission.
- **Unblinded at summary or aggregate level**, i.e., those who will have no access to individual treatment assignment but can access summary tables or figures of the IA results:
    - A group of sponsor personnel required to conduct quality checks, write, review, and compile submission documents or make program-level decisions.
- **No unblinding to subject- or summary-level data:**
    - The majority of sponsor personnel not involved in the aforementioned activities.

An external independent statistics group prepared a topline report of the unblinded efficacy results of the primary endpoint for the DSMB. The DSMB conducted an unblinded efficacy review of the IA to determine whether or not the prespecified statistical criteria were met and reported recommendations to the Applicant's senior leadership designee (no later than 24 hours after the DSMB closed session, as described in the DSMB charter). Once advised by senior leadership to proceed, this small, predefined group of the Applicant's personnel, also known as the core unblinded team – summary-level data, were unblinded to the interim data to conduct the prespecified analyses (as per the SAP), as well as to support development of the interim clinical

study report and marketing application submissions. Once unblinded, this prespecified group was not further involved in the conduct of trial activities or clinical decisions related to the trial.

The following table describes the level of access to the interim results, whether the team has access to summary level or patient level information.

Table 84. Level of Access to Interim Results, Trial 417-201-00007

Team	Composition	Level of Access	Responsibilities
Blinded Team	Biostatistics, CM, CSO, DM, GCD, GPV, GRA, PS&AM, SP External: CRO, DSMB, Central Lab	No access	These team members will remain blinded to summary- and subject-level data and will be responsible for the ongoing conduct of the phase 3 trial.
Core Unblinded Team – Subject-Level Data	Internal: Biostatistics, CM, DM, GCD, GPV, Medical Writing, SP External: DSMB vendor, DSMB, CRO	Subject-level data	Manages access to unblinded subject-level data, produce datasets, subject narratives, and perform analyses The external DSMB vendor will produce initial unblinded topline results report The external DSMB will review all unblinded efficacy and safety results at the interim analysis
Core Unblinded Team – Summary-Level Data	CMO, SVP Global R&D Evidence, VP Nephrology, VP GPV, VP D&A, GCD, Biostatistics, GRA, Medical Writing	Summary-level data	Reviews initial unblinded results report once released by DSMB, and support FDA review of topline data.
Core Unblinded Leadership Team	CMO, SVP Global R&D Evidence, VP Nephrology, VP Data & Analytics	Summary-level data	Evaluates data for initial go-to-file recommendation. Supports FDA review of topline results.
Unblinded Decision-Making Team	CEO, CMO, EVP Global Pharmaceutical Strategy, SVP Global R&D Evidence, VP & General Counsel, VP Investor Relations, VP Nephrology, VP EP&TM, VP D&A, Legal IP	Summary-level data	Following FDA review of topline results, unblinded decision-making team will review available information to inform Otsuka business decisions and public disclosures.
Executive Team	Otsuka ELT	Summary-level data	Executive team to initiate public and financial disclosures.
Board of Directors	Otsuka BoD	Summary-level data	BoD will be advised of study results shortly prior to and in conjunction with the timing of the public release of information.
Expanded Unblinded Team – Subject-Level Data	Core Unblinded Team (Subject-Level) as defined in table above, EP&TM (Clinical Pharmacology, Quantitative Pharmacology, Bioanalytics), Medical and Real-World Data Analytics, Regulatory Operations, Medical Writing External Vendors or Consultants	Subject-level data	Supports subject-level data interpretation and presentation for marketing applications and relevant health authority interactions following topline meeting with FDA.
Expanded Unblinded Team – Summary-Level Data	Core Unblinded Team (Summary-Level) as defined in table above, VP EP&TM, GRA, Clinical Management, GPV, Medical Writing, Labeling, Regulatory Operations, EP&TM, PS&AM External Vendors or Consultants	Summary-level data	Supports summary-level data interpretation and presentation for marketing applications and relevant health authority interactions following topline meeting with FDA.
Unblinded Labeling Team	Labeling, GCD, GRA, Biostatistics, EP&TM, GPV, Commercial, Legal, PS&AM	Summary-level data	Creates draft label.
Market Access and HEOR	Global Market Access, GVRWE, Medical & Real-World Data Analytics External Vendors or Consultants	Summary-level data	Generates, interprets, and presents summary-level data for HTA applications and relevant post-hoc analyses.
Publications Team	Unblinded Core Team (Summary-Level), Global Medical Affairs, Scientific Communication, Legal IP, Corporate Communications	Summary-level data	Drafts, compiles, and presents abstracts, publications, scientific communications based on IA. Note: no eGFR outcomes will be conveyed.

BoD = Board of Directors; CEO = Chief Executive Officer; CM = Clinical Management; CMO = Chief Medical Officer; CRO = Clinical Research Organization; CSO = Clinical Supplies Operations; D&A = Data and Analytics; DM = Data Management; DSMB = Data Safety Monitoring Board; ELT = Executive Leadership Team; EP&TM = Early Phase & Translational Medicine; EVP = Executive Vice President; FDA = Food & Drug Administration; GCD = Global Clinical Development: GPV = Global Pharmacovigilance; GRA = Global Regulatory Affairs; GVRWE = Global Value and Real-World Evidence; HTA = Health Technology Application; IP = Intellectual Property; PS&AM = Portfolio Strategy & Asset Management; SP = Statistical Programming; SVP = Senior Vice President; VP = Vice President.

Source: Table 3-2 of Unblinding Procedure at Interim Analysis, Version 2.0 (dated August 15, 2024)

Dosing

Subjects were dosed with sibeprenlimab 400 mg SC Q4W or matching placebo up to Week 100 (total of 26 doses). Up to two study drug administration interruptions due to medical/surgical or

other reasons were allowed and can be reinitiated as determined by the investigator. If a subject missed >2 consecutive study drug doses, the investigator was instructed to consult with the medical monitor to determine if the subject should discontinue treatment.

Treatment Discontinuation

A subject could discontinue treatment for the following reasons:

- Adverse event
    - Subject decides to discontinue because of annoyance or discomfort due to a nonserious AE which is not otherwise determined to be an undue hazard.
    - Continuing treatment places the subject at undue risk as determined by the investigator (e.g., a safety concern that is possibly, probably, or likely related to study treatment) including SAEs or other potentially treatment-related safety concerns or AEs.
- Pregnancy
- Progressive disease
    - This includes subjects who develop ESKD, defined as an eGFR < 15 mL/min/1.73 m^2 and/or the need for renal replacement therapy. For other clinical situations, the investigator was instructed to discuss the situation with the Sponsor and/or medical monitor.
- Use of protocol prohibited medications (described under Concomitant Medications below)
- Subject withdrawal
- Physician decision
- Other

Compliance

Study treatment was administered by trained healthcare personnel who recorded the date, time, and volume of administered study drug product as well as the injection site. Any deviations from planned dosing procedures were documented.

Concomitant Medications

All medications and therapies taken by the subject from 3 months prior to the signing of informed consent through the end of the trial were documented. For medications related to IgAN treatment (e.g., ACEIs, ARBs, SGLT2i), up to a 1-year history was collected.

The protocol prohibited the following medications/therapies within 16 weeks prior to randomization and for the full course of the trial:

- Nephrotoxic medications contraindicated in IgAN (e.g., chronic NSAIDs [> 1 week], aminoglycosides) are exclusionary. Chronic use of medications that raise serum creatinine but are not believed to be nephrotoxic is permitted if the medication is well-tolerated and at a stable dose for at least 3 months prior to randomization (e.g., fenofibrates).
- Systemic corticosteroid immunosuppressive therapy for IgAN or other conditions (note: topical, ophthalmic, rectal, intra-articular, inhaled corticosteroids, and short courses [≤ 14 days] of oral/IV steroids were allowed).

- Other immunosuppressive therapy such as, but not limited to mycophenolate mofetil, anti-tumor necrosis factor inhibitors, rituximab, hydroxychloroquine, etc.
- Traditional Chinese medicine, Ayurvedic medications, and herbal supplements.

In addition, the initiation of SGLT2i therapy, endothelin receptor antagonists, glucagon-like peptide-1 (GLP-1) receptor agonists, mineralocorticoid receptor antagonists, fish oil, traditional Chinese medication, ayurvedic medications, and herbal medications within 3 months of screening or at any subsequent time point during the trial was prohibited.

Adverse Events of Special Interest

There were no adverse events of special interest specified in the protocol.

Clinical Outcomes of Interest

In addition to the uPCR primary efficacy endpoint and eGFR key secondary efficacy endpoint, other clinical outcomes of interest included progression to chronic to kidney failure, defined as a sustained doubling of serum creatinine compared to baseline, sustained 40% reduction in eGFR compared to baseline, and eGFR <15 mL/min/1.73 m^2 (all based on two laboratory measurements at least 4 weeks apart) or the requirement of renal replacement therapy (chronic dialysis for ≥4 weeks or kidney transplantation).

Measures to Prevent Missing Data

Subjects who discontinued treatment prior to Dose 26 were encouraged to continue all planned trial visits through the end-of trial after treatment discontinuation. Investigators were instructed to meet and discuss with the subject to comprehensively determine the desire for treatment discontinuation/withdrawal from the trial; for reasons due to trial burden on a subject's life, the investigator was encouraged to determine if the subject could continue participation in the trial if modifications to his/her treatment and/or schedule of assessments could be accommodated.

For subjects who are "lost to follow-up", the protocol specified the trial site would make 3 documented attempts to contact the subject by telephone and in the event the site is unable to reach the subject by telephone, the site will attempt to contact the subject via certified mail or an alternate similar method, where appropriate, before deeming the subject "lost to follow-up."

For all subjects who were "lost to follow-up," the Applicant will take reasonable action to ascertain vital status, including obtaining acceptable documentation (e.g., death certificate, medical records, public records, statement by a family member or primary care physician).

16. Efficacy

16.1. SAP Amendments

SAP Amendments

The SAP underwent three amendments, and one postdatabase lock SAP addendum was submitted on September 23, 2024 (see details below). Amendment 1 was submitted after all subjects were randomized (**Error! Reference source not found.Error! Reference source not found.**). Amendments 2 and 3 primarily incorporated changes to align with protocol amendments and provide methodological clarifications. Key modifications are summarized below:

Amendment 1

General Revisions

- Updated the handling strategy for ICE#3 in the primary efficacy endpoint analysis.
- Updated the primary sensitivity tipping point analysis to reflect a two-way approach per FDA's feedback.
- Updated the handling strategy for ICE#3 in the key secondary efficacy endpoint analysis.
- Updated the key secondary sensitivity analysis to use the hypothetical strategy for handling ICE #3.
- Updated the key secondary sensitivity tipping point analysis to incorporate FDA's comments.
- Moved the MMRM analysis to estimate eGFR change from baseline over 24 months and eGFR AUC analysis from supplementary analyses to additional analyses of eGFR in Section 9.2.3 of SAP.
- Changed the endpoints regarding the progression to CKF from exploratory to secondary to align with protocol amendment 2 and added the corresponding analysis methods.
- Updated the wording in Section 15 of the SAP regarding sample size re-estimation to incorporate the VIS649-201 results.

Amendment 2

SAP Amendment 2 updated the SAP to align with protocol amendment 3 and incorporate feedback from the FDA. Notable changes are highlighted below:

General Revisions

- IA #2 was removed, and the initial alphas allocated to the primary efficacy endpoint of uPCR-24h and the key secondary efficacy endpoint of eGFR were updated. Although the

power was re-evaluated due to the updated alpha for the primary efficacy endpoint of uPCR-24h, the sample size remained the same.

- Analyses for prohibited medication or therapies were added to support the ICE #2 handling strategy.
- The ICE #2 handling strategy for the primary efficacy endpoint of uPCR-24h was updated to a hypothetical strategy.
- The imputation method for ICE #3 handling was updated.
- The ICE #2 handling strategy for the key secondary efficacy endpoint of eGFR was updated to a hypothetical strategy per FDA's feedback.
- The mean change of eGFR from baseline at 24 months was updated as one of the key secondary endpoints and the MMRM model was used for the analysis of change from baseline in eGFR at 24 months. In addition, the mean change of eGFR from baseline at 12 months was updated as one of the exploratory endpoints.
- To align with a protocol amendment, the eGFR AUC analysis was updated as one of the exploratory endpoints.
- To align with a protocol amendment, the clinical remission was updated as proteinuric remission and was updated as exploratory endpoints per FDA's comments.
- The annualized slope of eGFR estimated over the course of approximately 12 months was updated as an exploratory endpoint.
- The criteria for CKF were updated per FDA's comments.
- The MMRM analysis for the spot uPCR was added.
- The forest plots were added for the subgroup analyses.
- The treatment exposure analyses were added for subgroup analyses.
- The section for type 1 error control was updated to align with the updated alpha split strategy.
- The analysis windows for efficacy parameters, safety parameters, and patient-reported outcome were updated.

Amendment 3

SAP Amendment 3 provided clarifications on the determination process for prohibited and confounding medications, along with minor clarifications for handling ICE #2 for eGFR. The amendment also removed Tables 16.1.2-3 from SAP Amendment 2, which previously documented window mapping for injection site reaction, visual analog scale (VAS) score, SF-36v2, and Brief Fatigue Inventory, since injection site reactions were assessed on the same day as IMP administration and therefore require no additional window mapping. The mapping algorithms for VAS score, SF-36v2, and Brief Fatigue Inventory—accounting for restricted timing of VAS collection after each subcutaneous administration and repeated measurements—

were to be documented in the Analysis Data Model specifications prior to Applicant unblinding. Notable changes are highlighted below:

General Revisions

- The list of prohibited medications in Appendix 3 was updated.

SAP Postdatabase Lock Addendum

This addendum to the Trial 417-201-00007 SAP Amendment 3 documents the additional analyses conducted after the IA DBL, which occurred on September 25, 2024, and unblinding, which occurred on November 18, 2024. These post-DBL analyses were conducted to address regulatory feedback received after IA unblinding as well as to provide further clarifications on SAP Amendment 3. These analyses were based on the data from the IA DBL. The data sets, statistical methodologies, data analysis algorithms, and conventions remain consistent with SAP Amendment 3. This addendum does not raise concern regarding trial integrity.

Postdatabase Lock Analyses

- In addition to summarizing the background standard of care regimens administered prior to the first dose of IMP described in the SAP Amendment 3 Section 8.5.1, the background standard of care regimens administered during the scheduled 24-month treatment period and the 3-month follow-up period were also summarized.
- After DBL and prior to IA unblinding, a few new prohibited medications were found in the database due to the updates on concomitant medications between the prior-DBL and post-DBL database. Subsequently, the detailed prohibited medication list of medications was updated and resigned off.
- During the topline results meeting on November 18, 2024, the Division recommended that the Applicant include in their BLA submission (b) (4) (b) (4) To address the Division's requests, the Applicant provided the results from the preplanned eGFR analyses and additional exploratory analyses of eGFR to evaluate the treatment effect of sibeprenlimab on stabilization of eGFR. The following analyses were conducted by the Applicant:

(b) (4)

  - Composite kidney failure analysis: Clarifications on progression to composite kidney failure criteria, including sustained doubling of serum creatinine, 40% eGFR reduction, eGFR <15 mL/min/1.73 m², or need for renal replacement therapy, analyzed using stratified log-rank tests and Cox proportional hazards regression.

- Additional exploratory analyses: Hematuria shift tables, urine protein assessments, and subgroup analyses by baseline uPCR-24h categories to evaluate treatment effect robustness.

(b) (4)

Table 85. SAP Changes, Trial 417-201-00007

SAP Version (Approved Date)	Date Submitted (Sequence Number)	Number of Subjects Enrolled at Time of Change
417-201-00007 SAP (December 16, 2022)	December 22, 2022 (SN0014)	29 (16 main cohort)
SAP amendment 1 (November 13, 2023)	April 08, 2024 (SN0051)	530 (510 main cohort)
SAP amendment 2 (August 16, 2024)	August 19, 2024 (SN0070)	530 (510 main cohort)
SAP amendment 3 (September 20, 2024)	September 23, 2024 (SN0077)	530 (510 main cohort)
SAP postdatabase lock addendum (January 21, 2025)		530 (510 main cohort)

Source: Applicant's Appendix 16.1.9
Database lock occurred on September 25, 2024
eCTD link to study report and statistical methods documentation:
\\CDSESUB1\evsprod\BLA761434\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\iga-nephropathy\5351-stud-rep-contr\417-201-00007
Abbreviations: SAP, statistical analysis plan; SN, sequence number

(b) (4)

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(b) (4)

17. Clinical Safety

17.1. Safety Results, Trial 417-201-00007

17.1.1. Treatment-Emergent Adverse Events, Trial 417-201-00007

In Trial 417-201-00007, the incidence of Applicant-defined AESI of infections (includes all PTs from Infections and Infestations System Organ Class) was numerically higher in subjects treated with sibeprenlimab compared to those treated with placebo (49% versus 45%, respectively; (**Error! Reference source not found.**).

Table 86. Subjects With Treatment-Emergent Adverse Events[a] by System Organ Class and Preferred Term, Showing Preferred Term With Risk Difference >2%, Main Cohort, Overall Safety Set[b], Trial 417-201-00007

System Organ Class Preferred Term[c]	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[d]
Any AE	192 (74.1)	206 (82.1)	−7.9 (−15.1, -0.8)[e]
Gastrointestinal disorders (SOC)	53 (20.5)	55 (21.9)	−1.4 (−8.6, 5.7)
Abdominal pain	6 (2.3)	0	2.3 (0.8, 5.0)[e]
Infections and infestations (SOC)	127 (49.0)	113 (45.0)	4.0 (−4.7, 12.6)
COVID-19	25 (9.7)	17 (6.8)	2.9 (−2.0, 7.8)
Nasopharyngitis	32 (12.4)	25 (10.0)	2.4 (−3.2, 8.0)
Sinusitis	8 (3.1)	2 (0.8)	2.3 (−0.1, 5.3)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. MedDRA, version 27.0
[b] Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Coded as MedDRA preferred terms.
[d]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
[e]95% confidence interval excludes zero.
Abbreviations: AE, adverse event; CI, confidence interval; incl, including; COVID-19, coronavirus disease-2019; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SARS, severe acute respiratory syndrome; SOC, system organ class

17.1.2. Serious Treatment-Emergent Adverse Events, Trial 417-201-00007

Table 87. Subjects With Serious Treatment-Emergent Adverse Events[a] by System Organ Class and OND Custom Medical Query (Narrow) Showing OND Custom Medical Query With Risk Difference >0%, Main Cohort (Overall Safety Set)[b], Trial 417-201-00007

System Organ Class OCMQ (Narrow)	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[c]
Cardiac disorders (SOC)			
Cardiac conduction disturbance	1 (0.4)	0	0.4 (−1.1, 2.2)
Gastrointestinal disorders (SOC)			
Diarrhea	1 (0.4)	0	0.4 (−1.1, 2.2)
Infections and infestations (SOC)			
Purulent material	1 (0.4)	0	0.4 (−1.1, 2.2)
Viral infection	2 (0.8)	1 (0.4)	0.4 (−1.5, 2.4)
Musculoskeletal and connective tissue disorders (SOC)			
Arthritis	1 (0.4)	0	0.4 (−1.1, 2.2)
Fracture	1 (0.4)	0	0.4 (−1.1, 2.2)
Nervous system disorders (SOC)			
Stroke and TIA	1 (0.4)	0	0.4 (−1.1, 2.2)

System Organ Class OCMQ (Narrow)	Sibeprenlimab N=259 n (%)	Placebo N=251 n (%)	Risk Difference % (95% CI)[c]
Vascular disorders (SOC)			
Thrombosis	1 (0.4)	0	0.4 (−1.1, 2.2)
Thrombosis arterial	1 (0.4)	0	0.4 (−1.1, 2.2)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose. 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. MedDRA, version 27.0
[b]Median duration of exposure is 44 weeks and 48 weeks in sibeprenlimab and placebo groups, respectively.
[c]Risk difference (with 95% confidence interval) is shown between sibeprenlimab and placebo.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; OCMQ, Office of New Drugs Custom Medical Query; IMP, investigational medicinal product; incl, including; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class; TIA, transient ischemic attack

17.2. Trial VIS649-201

17.2.1. Duration of Exposure, Trial VIS649-201

Table 88. Duration of Exposure, Overall Safety Seta, Trial VIS649-201

Parameter	Sibeprenlimab 2 mg/kg N=38	Sibeprenlimab 4 mg/kg N=41	Sibeprenlimab 8 mg/kg N=38	Total Sibeprenlimab N=117	Placebo N=38
Duration of treatment, days					
Mean (SD)	338.2 (68.5)	351.3 (42.1)	356.7 (24.6)	348.8 (48.6)	343.3 (68)
Median (Q1, Q3)	359 (354, 362.5)	360 (358, 361)	359 (358.2, 363)	359 (358, 363)	361 (358.2, 365)
Min, max	58, 369	113, 367	212, 374	58, 374	30, 373
Total exposure (person years)	246	276	260	782	250
Subjects treated, by duration, n (%)					
<30 days	0	0	0	0	0
≥30 to <120 days	1 (2.6)	1 (2.4)	0	2 (1.7)	1 (2.6)
≥120 to <210 days	2 (5.3)	0	0	2 (1.7)	1 (2.6)
≥210 to <300 days	0	1 (2.4)	1 (2.6)	2 (1.7)	1 (2.6)
≥300 to <360 days	22 (57.9)	18 (43.9)	20 (52.6)	60 (51.3)	11 (28.9)
≥360 to <400 days	13 (34.2)	21 (51.2)	17 (44.7)	51 (43.6)	24 (63.2)
≥400 days	0	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R
[a] The overall safety set includes all randomized subjects who received at least 1 dose or part of a dose of the IMP and analyzed according to the treatment received. Duration is 12 months of monthly doses.
Abbreviations: IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

17.2.2. Overview of Treatment-Emergent Adverse Events Summary, Trial VIS649-201

There were no important imbalances in the incidence of SAEs, SAEs requiring hospitalization, or TEAEs leading to study drug discontinuation between treatment groups in Trial VIS649-201 (Table 89). The incidence of TEAEs and TEAEs leading to dose interruption of study drug was numerically higher in subjects treated with sibeprenlimab compared to those treated with placebo.

Table 89. Overview of Treatment-Emergent Adverse Events[a], Overall Safety Set[b], Trial VIS649-201

Event Category	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[c]
SAE	2 (5.3)	2 (4.9)	1 (2.6)	5 (4.3)	2 (5.3)	−1.0 (−13.3, 5.7)
SAEs with fatal outcome	0	0	0	0	1 (2.6)	−2.6 (−13.5, 0.6)
Life-threatening SAEs	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
SAEs requiring hospitalization	2 (5.3)	1 (2.4)	1 (2.6)	4 (3.4)	2 (5.3)	−1.8 (−14.1, 4.6)
SAEs resulting in substantial disruption of normal life functions	0	1 (2.4)	0	1 (0.9)	1 (2.6)	−1.8 (−12.7, 2.5)
Other	0	0	1 (2.6)	1 (0.9)	1 (2.6)	−1.8 (−12.7, 2.5)
AE leading to permanent discontinuation of study drug	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
AE leading to dose modification of study drug	5 (13.2)	1 (2.4)	3 (7.9)	9 (7.7)	0	7.7 (−1.7, 14.0)
AE leading to interruption of study drug	5 (13.2)	1 (2.4)	3 (7.9)	9 (7.7)	0	7.7 (−1.7, 14.0)
AE leading to reduction of study drug	0	0	0	0	0	0.0 (−9.2, 3.2)
AE leading to dose	0	0	0	0	0	0.0 (−9.2, 3.2)

Event Category	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[c]
delay of study drug						
Any AE[d]	28 (73.7)	33 (80.5)	31 (81.6)	92 (78.6)	27 (71.1)	7.6 (−7.1, 24.9)
Severe and worse	2 (5.3)	3 (7.3)	1 (2.6)	6 (5.1)	1 (2.6)	2.5 (−8.7, 8.8)
Moderate	7 (18.4)	8 (19.5)	8 (21.1)	23 (19.7)	3 (7.9)	11.8 (−2.4, 21.9)
Mild	19 (50.0)	22 (53.7)	22 (57.9)	63 (53.8)	23 (60.5)	−6.7 (−23.6, 11.6)

Source: adae.xpt; Software: R
[a] Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose.
[b] Duration is 12 months of monthly doses.
[c] Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
[d] Severity as assessed by the investigator.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

17.2.3. Deaths, Trial VIS649-201

In Trial VIS649-201, there was one death in the placebo group (Table 90). The subject's concurrent chronic obstructive pulmonary disease, cor-pulmonale, smoking, and morbid obesity were considered risk factors for this event.

Table 90. Listing of All Individual Subject Deaths, Overall Safety Set[a], Trial VIS649-201

Trial Arm	Subject ID	Age	Sex	Dosage	Dosing Duration (Days)	Trial Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
Placebo	VIS649201-(b) (6)	46	M	NA	92	175	Respiratory failure	Type 2 respiratory failure leading to death

Source: adae.xpt; Software: R
[a] Duration is 12 months of monthly doses.
Abbreviations: AE, adverse event; ID, identifier; M, male; NA, not applicable

17.2.4. Serious Treatment-Emergent Adverse Events, Trial VIS649-201

In Trial VIS649-201, the number of subjects with SAEs was low in both treatment groups (Table 91); no SAE was reported in more than one subject.

Table 91. Subjects With Serious Adverse Events[a] by System Organ Class and Preferred Term, Showing Preferred Term With Risk Difference >0%, Overall Safety Set[b], Trial VIS649-201

System Organ Class Preferred Term	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[c]
Any SAE	2 (5.3)	2 (4.9)	1 (2.6)	5 (4.3)	2 (5.3)	−1.0 (−13.3, 5.7)
Hepatobiliary disorders (SOC)	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Portal vein thrombosis	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Immune system disorders (SOC)	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Anaphylactic reaction	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Infections and infestations (SOC)	1 (2.6)	0	0	1 (0.9)	1 (2.6)	−1.8 (−12.7, 2.5)
COVID-19	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Nervous system disorders (SOC)	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Migraine	0	1 (2.4)	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	1 (2.6)	1 (0.9)	1 (2.6)	−1.8 (−12.7, 2.5)
Pulmonary embolism	0	0	1 (2.6)	1 (0.9)	0	0.9 (−8.4, 4.7)

Source: adae.xpt; Software: R

[a] Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP. dose but increased in severity after the first IMP dose. 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.

[b] Duration is 12 months of monthly doses.

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

Abbreviations: AE, adverse event; CI, confidence interval; COVID-19, coronavirus disease-2019; IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

17.2.5. Treatment-Emergent Adverse Events Leading to Discontinuation, Trial VIS649-201

In Trial VIS649-201, in the sibeprenlimab 2 mg/kg group, one subject reported TEAEs of portal vein thrombosis, hepatic cirrhosis, and hepatic encephalopathy that led to treatment discontinuation (Table 92). The event of portal vein thrombosis is unlikely to be related to the trial intervention, considering the abdominal CT finding of liver cirrhosis and the short period of time between the start date of trial intervention and event onset. In addition, the subject's concurrent conditions of chronic liver disorder and being a smoker are considered strong confounders for the event. The narrative is described below.

Subject (b) (6) a 71-year-old Asian male with IgAN and relevant medical history of liver disease and smoking (seven cigarettes a day for the past 53 years), reported to an outpatient clinic on Day 44 after having diarrhea for 4 days. On physical examination, the subject's lower abdomen was mildly tender. The following day on Day 45, an abdominal CT scan was performed which revealed portal vein thrombosis.

On Day 48, an enhanced abdominal CT scan demonstrated thrombosis at the main trunk and branches of the portal vein. The mesentery fatty tissue of the descending colon and rectum had high intensity, suggesting congestion due to portal hypertension. Liver cirrhosis was also detected with uneven liver margins and a shunt between the spleen and kidney. An esophagogastroduodenoscopy revealed mild esophageal varix. The subject was diagnosed with liver cirrhosis, which was reported as a TEAE, and was admitted to hospital the same day. A follow-up enhanced abdominal CT scan revealed mild reduction of portal vein thrombosis, and the subject was discharged from the hospital on Day 59.

On Day 85, the subject was unable to respond to the questions from trial site staff and a TEAE of hepatic encephalopathy was reported the same day. On Day 91, the subject fell while going to the toilet and was hospitalized. The subject was noted to have high ammonia levels and was diagnosed with hepatic encephalopathy. Following an injection of aminoleban, the subject's condition improved, and he returned home.

The event of portal vein thrombosis was resolved on Day 142. Corrective treatments administered for the event of portal vein thrombosis included Seirogan (citrus aurantium peel, creosote, glycyrrhiza spp. root, phellodendron spp. bark, and Uncaria Gambir leaf with twig), berberine chloride hydrate, bifidobacterium, Solace TF (calcium chloride dihydrate, potassium chloride, sodium acetate trihydrate, and sodium chloride), glucose, levofloxacin, Clostridium Butyricum, omeprazole sodium, pyridoxine hydrochloride/thiamine disulfide phosphate, Soldem 3AG (glucose, potassium chloride, sodium chloride, and sodium lactate), danaparoid sodium, Veen-d (calcium chloride dihydrate, glucose, potassium chloride, sodium acetate, and sodium chloride), vonoprazan fumarate, and apixaban.

The last dose of sibeprenlimab was on Day 29 and the subject was withdrawn from the trial due to an AE (not reported) on Day 190.

Table 92. Subjects With Adverse Events[a] Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Overall Safety Set[b], Trial VIS649-201

System Organ Class Preferred Term	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[c]
Any AE leading to discontinuation	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Hepatobiliary disorders (SOC)	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Hepatic cirrhosis	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Portal vein thrombosis	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Nervous system disorders (SOC)	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)
Hepatic encephalopathy	1 (2.6)	0	0	1 (0.9)	0	0.9 (−8.4, 4.7)

Source: adae.xpt; Software: R
[a] Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose.
[b] Duration is 12 months of monthly doses.
[c] Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

17.2.6. Treatment-Emergent Adverse Events, Trial VIS649-201

In Trial VIS649-201, the results of analyses of TEAEs based on individual PTs (Table 93) and narrow OCMQs (Table 94) were consistent for the sibeprenlimab and placebo groups. The most common TEAEs in the sibeprenlimab group with a RD >0% were nasopharyngitis and upper respiratory tract infections (Table 93). Most adverse events were mild or moderate in severity.

Table 93. Subjects With Common Adverse Events[a] Occurring at ≥5% Frequency With Risk Difference >0%, Overall Safety Set[b], Trial VIS649-201

Preferred Term[c]	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[d]
Any AE	28 (73.7)	33 (80.5)	31 (81.6)	92 (78.6)	27 (71.1)	7.6 (−7.1, 24.9)
Upper respiratory tract infection	3 (7.9)	5 (12.2)	2 (5.3)	10 (8.5)	0	8.5 (−0.9, 15.0)
Nasopharyngitis	4 (10.5)	5 (12.2)	6 (15.8)	15 (12.8)	3 (7.9)	4.9 (−8.9, 14.2)
Bronchitis	2 (5.3)	1 (2.4)	1 (2.6)	4 (3.4)	0	3.4 (−5.9, 8.5)
Cough	2 (5.3)	2 (4.9)	0	4 (3.4)	0	3.4 (−5.9, 8.5)
Hypertension	4 (10.5)	3 (7.3)	0	7 (6.0)	1 (2.6)	3.4 (−7.9, 9.9)

Preferred Term[c]	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[d]
SARS-CoV-2 test positive	0	0	3 (7.9)	3 (2.6)	0	2.6 (−6.7, 7.3)
Diarrhoea	0	4 (9.8)	2 (5.3)	6 (5.1)	1 (2.6)	2.5 (−8.7, 8.8)
Muscle spasms	1 (2.6)	4 (9.8)	1 (2.6)	6 (5.1)	1 (2.6)	2.5 (−8.7, 8.8)
Contusion	2 (5.3)	0	0	2 (1.7)	0	1.7 (−7.6, 6.0)
Diverticulum	0	0	2 (5.3)	2 (1.7)	0	1.7 (−7.6, 6.0)
Oedema peripheral	4 (10.5)	1 (2.4)	0	5 (4.3)	1 (2.6)	1.6 (−9.5, 7.6)
Pain in extremity	1 (2.6)	4 (9.8)	0	5 (4.3)	1 (2.6)	1.6 (−9.5, 7.6)
Pain	2 (5.3)	0	2 (5.3)	4 (3.4)	1 (2.6)	0.8 (−10.3, 6.5)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose.
[b]Duration is 12 months of monthly doses.
[c]Coded as MedDRA preferred terms.
[d]Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medicinal product; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2

17.2.6.1. OND Custom Medical Queries, Trial VIS649-201

Table 94. Subjects With Adverse Events[a] by System Organ Class and OCMQ (Narrow), Showing OCMQ With Risk Difference ≥2%, Overall Safety Set[b], Trial VIS649-201

System Organ Class OCMQ (Narrow)	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[c]
Cardiac disorders (SOC)						
Systemic hypertension	4 (10.5)	3 (7.3)	1 (2.6)	8 (6.8)	1 (2.6)	4.2 (-7.1, 11.0)
Gastrointestinal disorders (SOC)						
Abdominal pain	0	3 (7.3)	1 (2.6)	4 (3.4)	0	3.4 (-5.9, 8.5)
Diarrhea	0	4 (9.8)	3 (7.9)	7 (6.0)	1 (2.6)	3.4 (-7.9, 9.9)
General disorders and administration site conditions (SOC)						
Fatigue	0	3 (7.3)	0	3 (2.6)	0	2.6 (-6.7, 7.3)
Infections and infestations (SOC)						
Nasopharyngitis	8 (21.1)	12 (29.3)	7 (18.4)	27 (23.1)	5 (13.2)	9.9 (-5.8, 21.6)

System Organ Class OCMQ (Narrow)	Sibeprenlimab 2 mg/kg N=38 n (%)	Sibeprenlimab 4 mg/kg N=41 n (%)	Sibeprenlimab 8 mg/kg N=38 n (%)	Total Sibeprenlimab N=117 n (%)	Placebo N=38 n (%)	Total Sibeprenlimab vs. Placebo Risk Difference % (95% CI)[c]
Musculoskeletal and connective tissue disorders (SOC)						
Arthralgia	1 (2.6)	2 (4.9)	0	3 (2.6)	0	2.6 (-6.7, 7.3)
Gout	2 (5.3)	1 (2.4)	0	3 (2.6)	0	2.6 (-6.7, 7.3)
Respiratory, thoracic and mediastinal disorders (SOC)						
Cough	2 (5.3)	2 (4.9)	0	4 (3.4)	0	3.4 (-5.9, 8.5)
Skin and subcutaneous tissue disorders (SOC)						
Pruritus	2 (5.3)	1 (2.4)	0	3 (2.6)	0	2.6 (-6.7, 7.3)
Vascular disorders (SOC)						
Thrombosis	2 (5.3)	0	1 (2.6)	3 (2.6)	0	2.6 (-6.7, 7.3)
Thrombosis venous	2 (5.3)	0	1 (2.6)	3 (2.6)	0	2.6 (-6.7, 7.3)

Source: adae.xpt; Software: R
[a]Treatment-emergent adverse events defined as AEs started after the first IMP dose or if AEs present before the first IMP dose but increased in severity after the first IMP dose.
[b]Duration is 12 months of monthly doses.
[c]Risk difference (with 95% confidence interval) is shown between total treatment and comparator.
Each OCMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some OCMQs may contain PTs from more than one SOC.
Some preferred terms are not included in any OCMQ. Those preferred terms are not shown or counted in this table.
Abbreviations: AE, adverse event; CI, confidence interval; IMP, investigational medicinal product; OCMQ, Office of New Drugs Custom Medical Query; IMP, investigational medicinal product; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

Not applicable.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A high-level summary of key DSMB meeting discussions is provided in the table below.

Table 95. Data Safety Monitoring Board Meeting Discussions, Study 417-201-00007

Date	Number of Patients Enrolled	Meeting Type	Issue/Description
November 22, 2022	22	Open	No substantial issues raised. One DSMB member requested information on immunoglobulins; the topic was deferred to a closed session.
July 13, 2023	155	Closed	Immunoglobulin data presented, too early to identify any trends. No significant safety concerns identified to date.
December 14, 2023	N/A	Open	DSMB recommended trial could continue with no modifications. One subject mis-stratified due to human error. Reviewed a case of pharyngeal abscess. Removed language in a safety report that sibeprenlimab "… (b) (4) (b) (4)"
July 31, 2024	N/A	Open	DSMB recommended trial could continue without modification.
October 18, 2024	N/A	Open	Discussed scope of interim analysis and related procedures with the DSMB.
December 18, 2024	N/A	Open	DSMB recommended trial could continue without modification.

23. Labeling: Key Changes

This Prescribing Information (PI) section includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI (Table 96). The PI was reviewed to ensure that the 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 96. Key Labeling Changes and Considerations

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
BOXED WARNING	Not applicable.
1 INDICATIONS AND USAGE	As discussed in Sections 1.1 and 6.3, the available data are not adequate to support traditional approval, and the BLA will be approved under the accelerated approval pathway. Thus, the Applicant's proposed indication was revised to the following: "to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk for disease progression" and language was added to note that the indication is approved under accelerated approval based on the reduction of proteinuria. Language was also added noting that it has not been established whether VOYXACT slows kidney function decline over the long-term in patients with IgAN.
2 DOSAGE AND ADMINISTRATION	This section was revised to include instructions to allow the prefilled syringe to come to room temperature prior to injection, as well as proper storage and disposal once removed from refrigeration.
4 CONTRAINDICATIONS	Text was modified to specify the contraindication in patients with a "serious" hypersensitivity to the product or any of the excipients.
5 WARNINGS AND PRECAUTIONS	The Applicant-proposed Warnings and Precautions (W&P) for immunosuppression and increased risk of infections were consolidated into one W&P and text was revised. Language regarding the risk of coadministration of live vaccines was revised to state that live vaccinations are not recommended within 30 days prior to initiation or during treatment. Text was added to note that there are no data on secondary transmission of infection from persons receiving live vaccine to VOYXACT treated patients. The Applicant-proposed W&P (b) (4) was removed as the contraindication is sufficient to describe the potential risk.
6 ADVERSE REACTIONS	The Applicant's proposed (b) (4) (b) (4) was removed and replaced by text. Relevant text (b) (4) was removed and added to the W&P.
7 DRUG INTERACTIONS	Not applicable.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	The Pregnancy subsection was revised to include information on placental transfer of mAbs and a descriptive pregnancy safety study. The Lactation subsection was revised to note that endogenous maternal IgG and mAbs are transferred to human milk. A (b) (4) was removed, as (b) (4).
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	N/A

Full PI Sections[a]	Rationale for Major Changes to Finalized PI[b] Compared to Applicant's Draft PI
12 CLINICAL PHARMACOLOGY	Section 12.1, Mechanism of Action (MOA), was revised to focus on established MOA and to avoid speculative language. Language regarding differences in ADA-associated pharmacokinetic changes was revised to note that the presence of ADA did not have a clinically significant effect on the incidence or severity of adverse reactions and that there is insufficient data to assess whether ADA-associated PK changes reduce effectiveness.
13 NONCLINICAL TOXICOLOGY	Revisions for clarity were made in this section.
14 CLINICAL STUDIES	This section was revised to reflect the review findings (see Section 6).
17 PATIENT COUNSELING INFORMATION	Text noting the descriptive pregnancy safety study was added.
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	Revisions were made to these sections for clarity. Instructions were added to the How Supplied Storage and Handling section to note that VOYXACT should not be used if it has been stored at room temperature for 7 days or longer.

Source: FDA Reviewer
[a]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.
[b]For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
VOYXACT denotes sibeprenlimab
Abbreviation(s): ADA, antidrug antibody; BLA, biologics license application; IgAN, immunoglobulin A nephropathy; mAb, monoclonal antibody; MOA, mechanism of action; N/A, not available; NDA, new drug application; PI, Prescribing Information; PK, pharmacokinetic; W&P, warnings and precautions

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
- Carton and container labeling

24. Postmarketing Requirements and Commitments

The BLA will be approved under the accelerated approval regulations, 21 CFR 601. The Applicant will have a PMR to conduct an adequate and well-controlled clinical trial to verify and describe the clinical benefit. This requirement will be addressed by the completion of Trial 417-201-00007.

The Applicant will also have a PMR for a descriptive pregnancy safety study and a lactation study as discussed in Section 8.4 and a Pediatric Research Equity Act PMR as discussed in Section 8.3.

See the Approval letter for the agreed-upon milestone dates for these PMRs.

Product Quality PMCs issued by OPQ are described in Section 9.

25. Financial Disclosure

Table 97. Covered Clinical Studies: Trial 417-201-00007

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1311 (318 principal investigators, 993 sub-investigators)		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
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: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 1 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): 9 sub-investigators		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: CFR, code of federal regulations; FDA, Food and Drug Administration

As noted in the table above, there were 9 sub-investigators without an FDA Form 3454. The Applicant states the following to support due diligence: “Multiple attempts at contact were unable to obtain this financial disclosure, but the subinvestigators would not have had a material impact on the outcome of the trial, due to a limited number of subjects.”

26. References

26.1. Literature

Galla, JH, 1995, IgA Nephropathy, Kidney Int, 47(2):377-387, https://www.ncbi.nlm.nih.gov/pubmed/7723227.

Inker, LA, HJL Heerspink, H Tighiouart, J Chaudhari, S Miao, U Diva, A Mercer, GB Appel, JV Donadio, J Floege, PKT Li, BD Maes, F Locatelli, M Praga, FP Schena, AS Levey, and T Greene, 2021, Association of Treatment Effects on Early Change in Urine Protein and Treatment Effects on GFR Slope in IgA Nephropathy: An Individual Participant Meta-Analysis, Am J Kidney Dis, 78(3):340-349 e341, https://www.ncbi.nlm.nih.gov/pubmed/33775708.

KDIGO CKD Work Group, 2024, KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, Kidney Int, 105(4s):S117-s314, https://www.ncbi.nlm.nih.gov/pubmed/38490803.

KDIGO Glomerular Diseases Work Group, 2021, KDIGO 2021 Clinical Practice Guideline for the Management of Glomerular Diseases, Kidney Int, 100(4s):S1-s276, https://www.ncbi.nlm.nih.gov/pubmed/34556256.

KDIGO IgAN/IgAV Work Group, 2025, KDIGO 2025 Clinical Practice Guideline for the Management of Immunoglobulin A Nephropathy (IgAN) and Immunoglobulin A Vasculitis (IgAV), Kidney Int, 108(4S):S1-S71, https://www.ncbi.nlm.nih.gov/pubmed/40975564.

Levey, AS, LA Stevens, CH Schmid, YL Zhang, AF Castro, 3rd, HI Feldman, JW Kusek, P Eggers, F Van Lente, T Greene, J Coresh, and CKD-EPI, 2009, A New Equation to Estimate Glomerular Filtration Rate, Ann Intern Med, 150(9):604-612, https://www.ncbi.nlm.nih.gov/pubmed/19414839.

Marsh, K, KA Ho, R Lo, N Zaour, AT George, and NS Cook, 2021, Assessing Patient Preferences in Rare Diseases: Direct Preference Elicitation in the Rare Chronic Kidney Disease, Immunoglobulin A Nephropathy, Patient, 14(6):837-847, https://www.ncbi.nlm.nih.gov/pubmed/34008165.

Moriyama, T, K Tanaka, C Iwasaki, Y Oshima, A Ochi, H Kataoka, M Itabashi, T Takei, K Uchida, and K Nitta, 2014, Prognosis in IgA Nephropathy: 30-Year Analysis of 1,012 Patients at a Single Center in Japan, PLoS One, 9(3):e91756, https://www.ncbi.nlm.nih.gov/pubmed/24658533.

Swaminathan, S, N Leung, DJ Lager, LJ Melton, 3rd, EJ Bergstralh, A Rohlinger, and FC Fervenza, 2006, Changing Incidence of Glomerular Disease in Olmsted County, Minnesota: a 30-Year Renal Biopsy Study, Clin J Am Soc Nephrol, 1(3):483-487, https://www.ncbi.nlm.nih.gov/pubmed/17699249.

Thompson, A, K Carroll, AI L, J Floege, V Perkovic, S Boyer-Suavet, WM R, IS J, J Barratt, DC Cattran, SG B, A Kausz, WM A, HN Reich, HR B, M West, and PH Nachman, 2019, Proteinuria Reduction as a Surrogate End Point in Trials of IgA Nephropathy, Clin J Am Soc Nephrol, 14(3):469-481, https://www.ncbi.nlm.nih.gov/pubmed/30635299.

Zou, B, J Cai, GG Koch, H Zhou, and F Zou, 2017, A Model-Based Conditional Power Assessment for Decision Making in Randomized Controlled Trial Studies, Stat Med, 36(30):4765-4776, https://www.ncbi.nlm.nih.gov/pubmed/28868630.

26.2. Guidance for Industry

FDA Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019), Food and Drug Administration (FDA), https://www.fda.gov/media/133660/download.

FDA Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998), Food and Drug Administration (FDA), https://www.fda.gov/media/71655/download.

FDA Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023), Food and Drug Administration (FDA), https://www.fda.gov/media/172166/download.

26.3. Other

[DARRTS ID: 5674385], 2025, OPQ BLA Executive Summary: BLA 761434 VOYXACT (sibeprenlimab-szsi). Food and Drug Administration (FDA): Office of Pharmaceutical Quality (OPQ), https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af807e12e1.

Feldman, DL, EM White, BJ Julian, P Canetta, B Schneider, J McCann, J Valentine, and S Kim, 2020, Voice of the Patient: Report on the Externally Led Patient-Focused Drug Development Meeting on IgA Nephropathy. accessed 4/1/2025, https://www.igan.org/wp-content/uploads/2021/01/VOP_IgAN_12-7-20__FNL.pdf

National Kidney Foundation, 2021, CKD-EPI Creatinine Equation (2021). https://www.kidney.org/ckd-epi-creatinine-equation-2021-0.

27. Review Team

Table 98. Reviewers of Integrated Assessment

Role	Names
Regulatory project manager	Anna Park
Nonclinical reviewer	Srinivasa Raju Datla
Nonclinical team leader	Jean Wu (secondary); Calvin Lee Elmore (tertiary)
OCP reviewer(s)	Dong Guo
OCP team leader(s)	Hebing Liu (secondary); Jayabharathi Vaidyanathan (tertiary)
Clinical reviewer	Austin Hu
Clinical team leader	Rekha Kambhampati
Biometrics reviewer	Sapna Thakur
Biometrics team leader	Dali Zhou (secondary); Mark Rothmann (tertiary)
Cross-discipline team leader	Rekha Kambhampati
Division director (pharm/tox)	Calvin Lee Elmore
Division director (OCP)	Jaya Vaidyanathan
Division director (OB)	Mark Rothmann
Division director (clinical)	Aliza Thompson
Office director (or designated signatory authority)	Hylton Joffe

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 99. Additional Reviewers of Application

Office or Discipline	Names
OPQA: DP/DS	Dilip Devineni/ Nailing Zhang
OPQA: Immunogenicity	Davinna Ligons/ Nailing Zhang
OPMA: DP/ DS Process/Facilities	Maria Gutierrez-Hoffman/ Madushini Dharmasena
OPMA: DP/ DS Microbiology	Maria Gutierrez-Hoffman/ Madushini Dharmasena
OPQA Labeling	Vicky Borders-Hemphill
CDRH: Device	Sangeetha Rajesh/ Shruti Mistry
ATL:	Nailing Zhang/ Maria Gutierrez-Lugo
OPQ RPBM:	Shazma Aftab
OPDP	Koung U. Lee/ Susannah O'Donnell
Pt Labeling	Susan Redwood/ Barbara Fuller
OSI	Suyoung (Tina) Chang/ Phillip Kronstein
OSE/DMEPA	IIa Srivastava/ Millie Shah
OSE/DRM	Cristen Lambert/ Yasmeen Abou-Sayeed
OSE DPV	Sandeep Devabhakthuni/ Daniel Woronow
CDSA	Christian Cao
OSE RPM	Monique Killen/ Darrell Lyons
OSE HF	IIa Srivastava/ Millie Shah/ Tri Bui Nguyen
DPMH	Katherine Kratz/Miriam Dinatale
DPMH RPM	Kerri-Ann Jennings/ George Greeley

Abbreviations: ATL, Application Technical Lead; CDRH, Center for Devices and Radiological Health; CDSA, Controlled Drugs and Substance Act; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management, DRM, Division of Risk Management; DPV, Division pf Pharmacovigilance; HF, human factors engineering; OPQA: DP, Office of Pharmaceutical Quality Assessment: Drug Product; OPQA: DS, OPQA: Drug Substance; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; Pt, patient; RPM, Regulatory Project Manager

27.1. Reviewer Signatures

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 Associate Director	Christine Garnett OCHEN DCN	Sections: 7.1-7.7	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Christine Garnett

Digitally signed by Christine Garnett

Date: 11/21/2025 2:52 PM EST
GUID: 20251121195249

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	Rekha Kambhampati OCHEN DCN	Sections: 1, 2, 3, 6.2, 7, 10, 11, 15, 17-25	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Rekha Kambhampati

Digitally signed by Rekha Kambhampati

Date: 11/21/2025 2:52 PM EST
GUID: 20251121195249

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	Michael Monteleone OCHEN DCN	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Michael Monteleone**			**Digitally signed by Michael Monteleone** **Date: 11/21/2025 2:54 PM EST** **GUID: 20251121195430**	

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	Michael Monteleone OCHEN DCN	Sections: 23	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Michael Monteleone**			**Digitally signed by Michael Monteleone** **Date: 11/21/2025 2:54 PM EST** **GUID: 20251121195454**	

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	Vishnu Sharma OCP DPM	Sections: Section 6.1 and Section 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Vishnu Sharma**			**Digitally signed by Vishnu Sharma** **Date: 11/21/2025 2:57 PM EST** **GUID: 2025112119577**	

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	Srinivasa Datla OCHEN DPTCHEN	Sections: 5.1, 5.2, 7.1, 8.4, 13	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Srinivasa Datla**			**Digitally signed by Srinivasa Datla** **Date: 11/21/2025 2:59 PM EST** **GUID: 20251121195953**	

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	Anna Park ORO DROCHEN	Sections: 12	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Anna Park			**Digitally signed by Anna Park** **Date: 11/21/2025 3:00 PM EST** **GUID: 2025112120043**	

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	Calvin Elmore OCHEN DPTCHEN	Sections: 5.1, 7.1, 8.4, 13	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Calvin Elmore			**Digitally signed by Calvin Elmore** **Date: 11/21/2025 3:04 PM EST** **GUID: 202511212048**	

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	Abiy Eyakem OCP DPM	Sections: 5,6,8,14	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Abiy Eyakem			**Digitally signed by Abiy Eyakem** **Date: 11/21/2025 3:04 PM EST** **GUID: 2025112120450**	

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	Dali Zhou OB DBII	Sections: 6.2.1.4, 6.2.1.5, 6.2.1.6, 6.3, 16	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dali Zhou			**Digitally signed by Dali Zhou** **Date: 11/21/2025 3:06 PM EST** **GUID: 2025112120641**	

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	Sapna Thakur OB DBII	Sections: 6.2.1.4, 6.2.1.5, 6.2.1.6, 6.3, 16	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sapna Thakur			**Digitally signed by Sapna Thakur** **Date: 11/21/2025 3:06 PM EST** **GUID: 2025112120653**	

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	Nailing Zhang OPQAIII DPQAXV	Sections: 9 Product Quality	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Nailing Zhang			**Digitally signed by Nailing Zhang** **Date: 11/21/2025 3:08 PM EST** **GUID: 2025112120835**	

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	Dilip Devineni OPQAIII DPQAXV	Sections: Section 9	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dilip Devineni			**Digitally signed by Dilip Devineni** **Date: 11/21/2025 3:08 PM EST** **GUID: 2025112120856**	

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	Jean Wu OCHEN DPTCHEN	Sections: 5.1, 5.2 (partial), 7.1, 8.4, 13	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jean Wu			**Digitally signed by Jean Wu** **Date: 11/21/2025 3:15 PM EST** **GUID: 2025112120151**	

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	Julie Van Der Waag ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Julie Van Der Waag			**Digitally signed by Julie Van Der Waag** **Date: 11/21/2025 3:21 PM EST** **GUID: 20251121202139**	

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	Dong Guo OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dong Guo			**Digitally signed by Dong Guo** **Date: 11/21/2025 3:32 PM EST** **GUID: 20251121203234**	

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	Tejas Patel OCHEN DCN	Sections: 1, 7, 17	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Tejas Patel			**Digitally signed by Tejas Patel** **Date: 11/21/2025 3:41 PM EST** **GUID: 20251121204157**	

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	Austin Hu OCHEN DCN	Sections: 2. 3. 6, 12, 15, 22	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Austin Hu			**Digitally signed by Austin Hu** **Date: 11/21/2025 3:55 PM EST** **GUID: 20251121205553**	

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 Reviewer	Austin Hu OCHEN DCN	Sections: 2, 3, 6, 12, 15, 22, 25	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Austin Hu			**Digitally signed by Austin Hu** **Date: 11/21/2025 3:57 PM EST** **GUID: 20251121205751**	

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 Tertiary Reviewer	Hao Zhu OCP DPM	Sections: 6.1, 14.5	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Hao Zhu			**Digitally signed by Hao Zhu** **Date: 11/21/2025 4:00 PM EST** **GUID: 20251121121045**	

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 Tertiary Reviewer	Mark Rothmann OB DBII	Sections: 6.2.1.4, 6.2.1.5, 6.2.1.6, 6.3, 16	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ✓ Not applicable.	
Signature: Mark Rothmann			**Digitally signed by Mark Rothmann** **Date: 11/22/2025 10:17 AM EST** **GUID: 2025112215179**	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Jayabharathi Vaidyanathan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jayabharathi Vaidyanathan			**Digitally signed by Jayabharathi Vaidyanathan** **Date: 11/24/2025 8:03 AM EST** **GUID: 2025112413322**	

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	Hebing Liu OCP DCEP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ✓ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: **Hebing Liu**			**Digitally signed by Hebing Liu** **Date: 11/24/2025 9:23 AM EST** **GUID: 20251124142332**	

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/

REKHA KAMBHAMPATI
11/21/2025 02:53:31 PM

ALIZA M THOMPSON
11/24/2025 03:36:06 PM

HYLTON V JOFFE
11/25/2025 11:02:11 AM