PROTOCOL TITLE:	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in Participants with Immunoglobulin A (IgA) Nephropathy
PROTOCOL NUMBER:	VIS649-201
COMPOUND	VIS649
STUDY PHASE	Phase 2
SHORT TITLE:	Phase 2 Study of VIS649 for IgA Nephropathy
VERSION:	3.0
VERSION DATE:	27 January 2020
SPONSOR:	Visterra, Inc. 275 2nd Avenue Waltham, MA 02451

REGULATORY AGENCY IDENTIFIER NUMBER(S)

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APPROVAL PAGE

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

This Clinical Study Protocol has been reviewed and approved by the Sponsor in order to ensure compliance with Good Clinical Practice.

Sponsor Signatory:

PROTOCOL VERSION 3.0 SUMMARY OF CHANGES TABLE

The primary reason for this protocol amendment is to address requests made by a Health Authority.

The clinically relevant changes, ie, changes that affect the type or frequency of protocol procedures, or the addition of information to the protocol that influences clinical decision-making or consent, are itemized below:

Protocol Version 3.0 (27 January 2020)		
Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.1 Synopsis Section 1.3, Table 1, Schedule of Assessments Section 7.2 Participant Discontinuation/Withdrawal from the Study Section 8.3.5 Pregnancy	The End-of-Study (EOS) visit was changed from Month 15 (Day 450, approximately 120 days following the last dose of study intervention) to Month 16 (Day 485).	This change was made so that safety monitoring continues through the end of the relevant systemic exposure for VIS649 (through 5 half-lives of the 8 mg/kg dose, ie, 155 days following the last dose administration).
Section 1.1 Synopsis Section 3 Objectives and Endpoints Section 8.5, Table 5, Pharmacokinetic and Serum Immunoglobulin Sampling Schedule	All objectives and endpoints associated with a measurement at Month 15 were updated to Month 16, to reflect the change in the EOS visit from Month 15 to Month 16.	This revision was made to reflect the change in the timing of the EOS visit.
Section 1.1 Synopsis Section 4.1 Overall Study Design	The overall study duration was modified for each participant to account for the update in the timing of the EOS visit from Month 15 to Month 16.	This revision was made to reflect the change in the timing of the EOS visit.
Section 5.2 Exclusion Criteria	An exclusion criterion was added, stipulating that female participants who are breastfeeding cannot be enrolled in the study	Breastfeeding in this study is exclusionary for safety purposes, and at the request of a Health Authority.
Section 1.3 Schedule of Assessments, Footnote 2 Section 8.3.1 Time Period and Frequency for Collecting Adverse Events and Serious Adverse Event Information Section 8.3.3 Follow-up of Adverse Events and Serious Adverse Events	Serious adverse events (SAEs) should be followed until resolution or for a period of 30 days after the EOS, whichever is *longer*. The previous protocol version stipulated that AEs and SAEs should be followed until resolution or for a period of 30 days after the EOS, whichever is *shorter*.	This change was made to ensure adequate safety follow-up of participants who experience SAEs during the study.
Section 8.2.1 Physical Examinations	In addition to the complete physical examination to be conducted at the screening and Month 12/Early Termination visits, physical examinations should be conducted by the Investigator at the Month 16/EOS visit and at any time	This change was made to increase the level of safety monitoring during the study.

Protocol Version 3.0 (27 January 2020)		
Section # and Name	**Description of Change**	**Brief Rationale**
	during the study if clinically indicated.	
Section 8.2.3 Electrocardiograms	A mention was added that in addition to the electrocardiogram (ECG) to be conducted at screening, ECGs should be conducted by the Investigator at any time during the study if clinically indicated.	This change was made to increase the level of safety monitoring during the study.
Appendix 2 Table 8, Protocol-Required Safety Laboratory Assessments	Instead of every-3-month collection, hematology and serum chemistry testing will be performed monthly during treatment. A comprehensive serum chemistry panel will be collected at each monthly visit.	This change was made to increase safety monitoring of participants during the study.
Appendix 4, Section 10.4.2, Contraception Guidance	Definitions for contraceptive requirements during the study were updated. For female participants, highly effective methods of contraception will be required from 28 days before study intervention through at least 155 days after the last dose of study intervention, to cover the end of the relevant systemic exposure for VIS649. Highly effective methods of contraception for females are defined as methods that result in a failure rate of less than 1% per year when used consistently and correctly, and do not include double barrier methods. Criteria for considering vasectomy as a highly effective birth control method and a definition of sexual abstinence were also added. The type of male contraception in the protocol was relabeled from "highly effective" to "acceptable" per definition outlined by the Clinical Trial Facilitation Group.	Contraceptive requirements were aligned with specifications outlined in the "Recommendations related to contraception and pregnancy testing" outlined by the Clinical Trial Facilitation Group.

Protocol Version 2.0 (26 November 2019)		
Section # and Name	**Description of Change**	**Brief Rationale**
Global	The original protocol (Version 1.0) was subjected to additional review. Revisions were made and a Version 2.0 was issued.	Version 1.0 of the protocol was not submitted to an IRB and no participants were enrolled under Version 1.0 of the protocol.

Note that minor formatting changes and corrections of typographical errors are not detailed.

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1. PROTOCOL SUMMARY

1.1 Synopsis

<table>
<tr><td colspan="2">Name of Sponsor: Visterra, Inc.</td></tr>
<tr><td colspan="2">Name of Investigational Intervention: VIS649</td></tr>
<tr><td>Protocol Title:</td><td>A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Evaluate the Efficacy and Safety of VIS649 in Participants with Immunoglobulin A (IgA) Nephropathy (IgAN)</td></tr>
<tr><td>Short Title:</td><td>Phase 2 Study of VIS649 for IgA Nephropathy</td></tr>
<tr><td>Rationale:</td><td>VIS649 is a humanized immunoglobulin G_2 (IgG_2) monoclonal antibody that binds to and blocks the biological actions of the cytokine A PRoliferation Inducing Ligand (APRIL), a key factor in the production of aberrantly glycosylated IgA_1 (a-g IgA_1), which is critical to the pathogenesis of IgAN. The central mechanism for the development of IgAN is the production of a-g IgA_1. These a-g IgA_1 act as autoantigens and lead to development of autoantibodies forming circulating immune complexes which deposit in the mesangium of the glomeruli and in turn, trigger an inflammatory response and complement activation, causing damage to the kidneys.
In data from a single-ascending dose study (VIS649-101) of VIS649 in healthy participants, VIS649 reduced serum levels of IgA and a-g IgA_1. The current study will test the hypothesis that blocking the biological actions of APRIL in IgAN participants leads to reduction of serum IgA (including a-g IgA_1) levels and will reduce or halt the progression of IgAN, as measured by decrease in proteinuria.
The findings from this study will form the basis for subsequent clinical development of VIS649.</td></tr>
<tr><td>Objectives and Endpoints:</td><td>The key objectives and endpoints of the study are:
<table>
<tr><th>Primary Safety Objective</th><th>Primary Safety Endpoint</th></tr>
<tr><td>• To evaluate the safety and tolerability of monthly doses of VIS649 at each of 3 dosing levels, administered IV to IgAN participants over the course of 12 months as an add-on to SOC treatment with ACEI/ARB therapy, compared with saline placebo infusions as an add-on to SOC treatment with ACEI/ARB therapy</td><td>• AEs graded by severity, clinical laboratory tests, vital sign measurements, and physical examinations</td></tr>
</table></td></tr>
</table>

Primary Efficacy Objective	Primary Efficacy Endpoint
• To evaluate the dose response of monthly doses of VIS649 on proteinuria at each of 3 dosing levels, administered IV to IgAN participants over the course of 12 months as an add-on to SOC treatment with ACEI/ARB therapy, compared with saline placebo infusions as an add-on to SOC treatment with ACEI/ARB therapy	• Change from baseline in uPCR (measured on natural log scale from 24-hour urine collection or the intended 24-hour urine collection) at Month 12 (ie, approximately 30 days after the 12th dose is administered)
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of repeated doses of VIS649 at 3 dosing levels versus placebo on the following parameters: o uPCR at Month 9 and 16 (ie, 5 months following the final [12th] monthly dose administration) o 24-hour urine protein excretion at Months 9, 12, and 16 o ≥ 30% decline from baseline in uPCR at Months 9, 12, and 16 o Clinical remission, defined as reduction in 24-hour urine protein excretion to < 300 mg/day for at least 3 consecutive months	o Change from baseline in uPCR (measured on natural log scale from 24-hour urine collection or the intended 24-hour urine collection) at Months 9 and 16 o Change in 24-hour urine protein excretion from baseline to Months 9, 12, and 16 o Number of participants in each group achieving a ≥ 30% decline from baseline in uPCR at Months 9, 12, and 16 o Number of participants in each group achieving clinical remission
• eGFR at Months 12 and 16	• Change from baseline in eGFR at Months 12 and 16
• To evaluate the effect of repeated doses of VIS649 at each dosing level compared with placebo on the following PD parameters: IgA, IgG, and IgM concentrations	• Change from baseline in total serum IgA, IgG, and IgM concentrations at Months 9, 12, and 16
• To determine the PK profile of repeated dose of VIS649, at each dosing level	• Serum PK parameters
• To determine the PK/PD profile of VIS649, relating VIS649 PK parameters and biomarkers such as changes in IgA to changes in proteinuria and eGFR	• Correlation of VIS649 PK parameters with changes in IgA, uPCR, and eGFR
• To screen for ADA responses	• Serum ADA levels

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ADA = antidrug antibody; AE = adverse event; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; Ig = immunoglobulin; IgAN = immunoglobulin A

	nephropathy; IV = intravenous(ly); PD = pharmacodynamic; PK = pharmacokinetic; SOC = standard of care; uPCR = urinary protein/creatinine ratio.
Overall Design:	This is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety and efficacy of intravenously (IV) administered VIS649 over a 12-month treatment course in participants with IgAN. Participants will be enrolled from approximately 90 global sites in approximately 16 countries. Screening evaluations, including physical examinations, vital signs, 12-lead electrocardiogram (ECG), safety laboratory testing (serum chemistry, hematology, urinalysis, serology, hemoglobin A1c, and pregnancy), blood sampling for baseline Ig levels (IgA, IgG, and IgM), and 24-hour urine collection, will take place during the 30 days prior to the first dose of study intervention. To be eligible, participants should be on stable and maximally tolerated doses of either angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy, as per standard of care (SOC) and applicable guidelines, for at least 3 months. Participants must be on at least 50% of the maximum recommended dose of the ACEIs or ARB to be considered as having adequate renin-angiotensin-aldosterone system (RAAS) blockade. Participants who are unable to tolerate ACEI/ARB therapy may be eligible for participation in the study, if their overall management of IgAN, including blood pressure (BP) control, is as per SOC and applicable guidelines. Enrolled participants must be 18 years of age or older with an IgAN diagnosis confirmed by biopsy. It is anticipated that most biopsies resulting in a diagnosis of IgAN will have been interpreted using the MEST score - Mesangial cellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy (Cattran et al, 2009) or MEST-C scoring system (Trimarchi, Barratt et al. 2017) from the Oxford classification of IgAN. A MEST or MEST-C score finding on kidney biopsy of T2 or C2 is exclusionary for this study. If the biopsy was not reported using the Oxford classification schema, the following findings (corresponding to these Oxford classifications) are exclusionary: a) > 50% tubular atrophy, and/or b) > 25% crescents. Participants must have screening urinary protein/creatinine ratio (uPCR) ≥ 0.75 g/g or 24-hour urine protein ≥ 1.0 g/d, as measured from a 24-hour urine collection (or an intended 24-hour urine collection). Participants must have estimated glomerular filtration rate (eGFR) ≥ 45 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, Stevens et al. 2009). The study will evaluate 3 dose levels of VIS649 (2, 4, and 8 mg/kg) versus placebo. A total of 144 participants will be randomized with equal allocation (1:1:1:1) across the 4 intervention groups (approximately 36 participants per group). Randomization will be stratified first by region (Japan vs rest of world). A target of 12 or more participants are planned to be randomized in Japan; these participants will be randomized with equal allocation and without further stratification. The randomization for the rest-of-world will be stratified by screening uPCR (≤ 2.0 g/g vs > 2.0 g/g).

	VIS649 or placebo will be administered as 12 monthly IV infusions starting on Day 1/Month 0. Participants will return to the study center on Days 8 and 18, then monthly through Month 14 and on Month 16 for safety, efficacy, pharmacokinetic (PK), and/or pharmacodynamic (PD) assessments. Safety assessments will include review of adverse events (AEs) (including hypersensitivity reaction and anaphylactic reaction), physical examinations, injection site tolerability (pain, irritation, and tissue damage), clinical laboratory assessments (including biochemistry, hematology, urinalysis, and pregnancy testing), laboratory testing (including serum Ig levels and antidrug antibodies [ADAs]) vital sign measurements and use of concomitant medications. Participants will return to the study center on approximately Month 16, at least 155 days following the last dose of study intervention (Dose 12) for an end-of-study (EOS) visit, at which time final safety, PK, PD, and efficacy assessments will be performed. Participants discontinuing dosing earlier will attend an early termination visit at the time of dosing discontinuation and will be encouraged to attend the study visits as per schedule of assessments. A rollover, open-label extension study will be offered to enable access to VIS649 (there will be no placebo arm) for study participants who have completed this trial, provided that the Investigator believes that the participants might benefit, and that the site has agreed to participate in the extension study. Further details will be provided in a separate protocol.
Number of Participants:	Approximately 144 participants. A target of 12 or more participants are planned to be randomized and enrolled in Japan. The remaining participants will be enrolled at sites in the rest of world; there are no other country-specific enrollment targets.
Intervention Groups and Duration:	The study will evaluate 3 dose levels of VIS649 (2, 4, and 8 mg/kg) versus placebo. VIS649 or placebo will be administered as a single, monthly IV infusion for 12 monthly doses. VIS649 will be administered IV over 1 hour, in a single, final volume 100 mL infusion in normal saline (0.9% NaCl), followed by a 25-mL saline flush. The dose of study intervention for the duration of the study will be based on the participant's Month 0 predose weight. Placebo (0.9% NaCl) will be administered IV over 1 hour as a single 100 mL infusion, followed by a 25 mL saline flush. An unblinded pharmacist will prepare drug or placebo for infusion. Participants, the Sponsor, the Investigator, and all other site study staff will be blinded to study intervention. The total study duration for each participant (from screening to EOS) will be up to approximately 17 months (assuming up to 1 month for screening, 12 months for monthly doses [including 30 days after the 12th dose], and follow-up visits through at least 155 days after the last dose of study intervention).
Target Population:	Key inclusion criteria for eligibility into the study are the following: 1. Participant is a male or female ≥ 18 years of age at the time of signing the informed consent. 2. Participant has source-verified biopsy-confirmed IgAN.

	3. Participant has medical records showing they have been on stable and maximally tolerated doses of either ACEI or ARB, as per SOC and applicable guidelines, for at least 3 months preceding screening. Participants should be on at least 50% of the maximum recommended dose of these agents to be considered as having adequate RAAS blockade. Participants who are unable to tolerate ACEI/ARB therapy may be eligible for participation in the study, if their overall management of IgAN, including BP control, is as per SOC and applicable guidelines. 4. Participant has screening uPCR ≥ 0.75 g/g measured from a 24-hour urine sample (or an intended 24-hour urine sample) or 24-hour urine protein ≥ 1.0 g/d, as measured from 24-hour urine sample (or an intended 24-hour urine sample). The proteinuria should be stable, defined as < 25% change when compared to values from ≥ 3 months previously (if available). If previous values are not available or if the change from a prior value is > 25%, a repeat measurement of proteinuria will be done after 15 days and the participant should fulfill the above proteinuria criteria to be eligible for randomization in the study. The proteinuria should be assessed when the participant is considered to be in steady state with no recent heavy exercise, fever, or other potential issues that could impact the result. 5. Participant has eGFR ≥ 45 mL/min/1.73 m^2, calculated using the CKD-EPI formula. The eGFR should be stable, as defined by a < 25% change when compared to values from ≥ 3 months previously (if available). If previous values are not available or if the change from a prior value is > 25%, a repeat measurement of eGFR will be done after 15 days and the participant should fulfill the eGFR criteria to be eligible for randomization in the study. The eGFR should be measured when the participant is considered to be in a steady state without recent changes in volume status, medications that could impact the result (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], aminoglycosides, co-trimoxazole), or changes in dietary protein intake. 6. Participant's serum Ig values must meet the following criteria: a. IgG: ≥ 700 mg/dL b. IgM: ≥ 40 mg/dL c. IgA: ≥ 70 mg/dL Key exclusion criteria: 1. Participant has secondary forms of IgAN as defined by the treating physician (eg, Henoch-Schönlein purpura, minimal change disease with IgA deposits, infection associated IgAN, or IgAN-associated with hepatic cirrhosis). 2. Participant has co-existing chronic kidney disease, other than IgAN. 3. Participant has evidence of additional pathological findings in the kidney biopsy (eg, diabetic kidney disease, membranous nephropathy, or lupus nephritis). However, hypertensive vascular changes are acceptable.

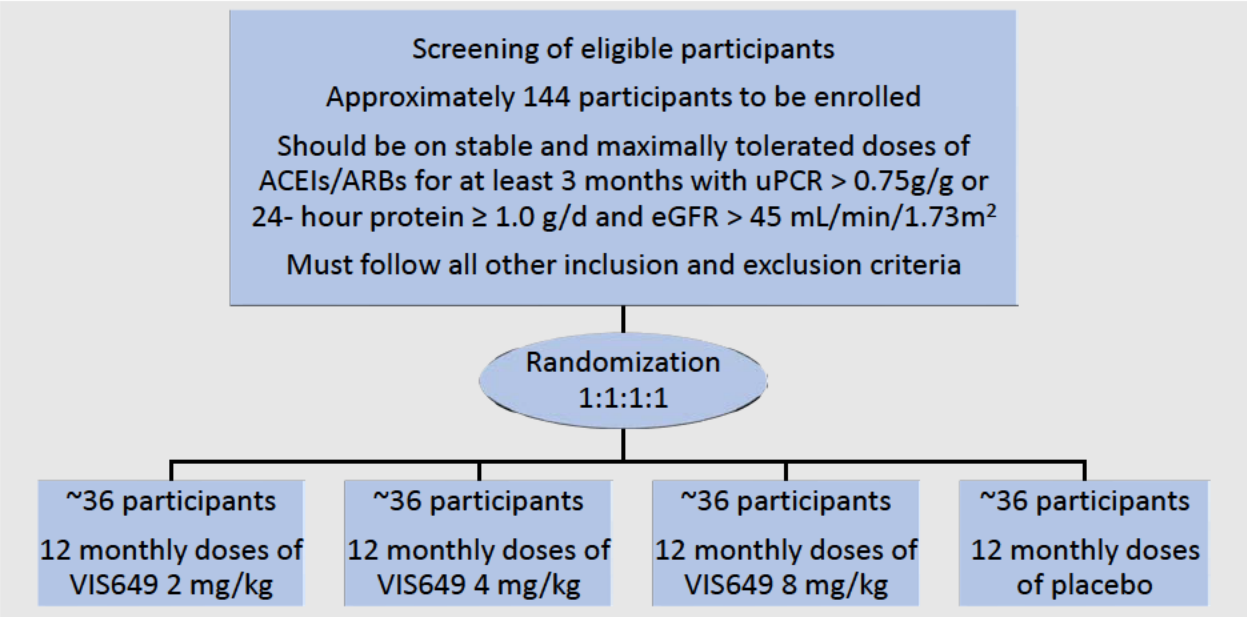
<table>
<tr><td></td><td>
4. Participant has kidney biopsy MEST or MEST-C score of T2 or C2 from the Oxford IgAN classification schema. If MEST-scoring was not performed, the presence of > 50% tubulointerstitial fibrosis, or crescents in >25% of glomeruli is exclusionary.
5. Participant has nephrotic syndrome, defined for this purpose as 24-hour urine protein > 3.5 g with concurrent hypoalbuminemia (serum albumin < 2.5 g/dL), hyperlipidemia (total cholesterol > 350 mg/dL), and edema.
6. Participant has received a solid organ transplant, including kidney.
7. Participant has received bone marrow or hematologic stem cell transplantation
8. Participant is currently receiving systemic immunosuppression (excluding topical, ophthalmic, per rectum or inhaled corticosteroids).
9. Participant has received systemic steroids within the 24 weeks prior to initial screening.
10. Participant has received treatment with 2 or more systemic immunosuppressive agents within 2 years prior to initial screening.
11. Participant has chronic infectious diseases (eg, chronic urinary tract infection; chronic sinusitis; bronchiectasis; active pulmonary or systemic tuberculosis; chronic viral hepatitis, such as hepatitis C or hepatitis B; or human immunodeficiency virus infection).
12. Participant has acute infectious disease at the time of screening. Participants may be rescreened following resolution of acute infection (such as urinary tract infection or respiratory tract infection), provided there is no evidence of an immunosuppressive condition that predisposed the participant to this infection.
13. Participant has Type 1 diabetes.
14. Participant has uncontrolled Type 2 diabetes, as evidenced by a screening hemoglobin A1c value > 8%.
15. Participant has uncontrolled BP (> 140 mm Hg systolic or > 90 mm Hg diastolic).
16. Participant has a history of a chronic autoimmune neurodegenerative disorder such as multiple sclerosis.
</td></tr>
<tr><td>Data Safety Monitoring Board:</td><td>
An independent data safety monitoring board (DSMB) will review unblinded safety data. The DSMB will meet at 5 scheduled data review meetings and as needed on an ad hoc basis. Details regarding the content and scope of safety assessments, as well as the governing of the DSMB, will be described in a separate DSMB charter.
Data safety monitoring board meetings will be scheduled as the following requirements are met:
<table>
<tr><th>Scheduled DSMB Review</th><th>Number of Participants and Treatment Exposure</th></tr>
<tr><td>DSMB review #1</td><td>Scheduled once 12 participants have been randomized and have completed at least 3 months of study dosing.</td></tr>
<tr><td>DSMB review #2</td><td>Scheduled once 24 participants have been randomized and have completed at least 3 months of study dosing.</td></tr>
</table>
</td></tr>
</table>

	<table><tr><td>DSMB review #3</td><td>Scheduled once ~25% of participants have been randomized and have completed 3 months of study dosing.</td></tr><tr><td>DSMB review #4</td><td>Scheduled once ~50% of participants have been randomized and have completed 6 months of study dosing, and ~20 participants have completed 12 months of study dosing.</td></tr><tr><td>DSMB review #5</td><td>Scheduled once ~50% of participants have been randomized and have completed 12 months of study dosing.</td></tr></table> Abbreviations: DSMB = data safety monitoring board.
Statistical Methods:	*General Considerations* All data collected will be documented using summary tables, figures, and/or data listings presented by intervention and dose group. For continuous variables, descriptive statistics (number [n]; mean; geometric mean and coefficient of variation [%CV], as appropriate; median; standard deviation; minimum; and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. As appropriate, a 95% CI will be presented. Graphical displays may be presented. *Randomization and Stratification* Participants will be randomly assigned in a 1:1:1:1 ratio to receive VIS649 at 2, 4, or 8 mg/kg, or placebo, with approximately 36 participants randomized per intervention group. Randomization will be stratified first by region (Japan vs rest of world). Japanese participants will be randomized with equal allocation and without further stratification. Randomization for the rest of world will then be stratified by screening uPCR (≤ 2.0 g/g vs > 2.0 g/g). *Interim Analyses* In addition to 5 DSMB safety reviews, 3 interim PK/Ig analyses and 2 interim efficacy analyses are planned. The interim PK/Ig analyses will provide additional data for population PK/PD modeling and will advise the study Sponsor on future study design and planning. An early interim efficacy analysis may be performed when at least 16 participants have been treated for at least 6 months and at least 50% of the 16 (or more) participants have achieved a confirmed > 30% reduction in uPCR (as determined by 2 consecutive measurements) based on review of blinded uPCR data across all study participants. In the event that this condition is met and an interim analysis is triggered, group-unblinded efficacy summaries (with individual participant treatment blinded) will be prepared by a separate, unblinded team for Sponsor review to inform future study design. A second interim efficacy analysis will be performed at the time of the fourth scheduled DSMB meeting (once 50% of randomized participants have completed 6 months of study dosing and approximately 20 participants have completed 12 months of study dosing). Group-unblinded efficacy summaries (with individual participant treatment blinded) will be prepared for Sponsor review to inform future study design. The interim efficacy analyses will not include hypothesis testing and will be for the purpose of future study design and planning. The primary efficacy endpoint, change in proteinuria levels from baseline, will be analyzed. No modifications

	to this study protocol are planned based on results of the interim analyses. Nonetheless, to account for multiple reviews of the efficacy endpoint, the type I error rate applied at the end of the study will be reduced by 0.002 for each interim efficacy review, resulting in a 2-sided end-of-study type I error rate of 0.046. *Planned analyses* The primary efficacy outcome for this study is the change from baseline in uPCR on the natural log scale at Month 12. Dose response will be explored using orthogonal contrasts. Sensitivity analysis will follow using dose as a continuous covariate. In addition, to assess the dose response over time, a Mixed Model with Repeated Measurements (MMRM), which includes fixed class-effects of treatment (intervention), visit, randomization strata, and treatment-by-visit interaction, with a fixed effect covariate of baseline uPCR on the natural log scale will be used. Secondary efficacy endpoints will be summarized using descriptive statistics. In addition, comparisons between dose groups against placebo will be performed using an Analysis of Covariance or MMRM for continuous measures and logistic regression or generalized estimating equations for categorical variables. Safety will be assessed by evaluation of AEs (including hypersensitivity reaction and anaphylactic reaction), physical examinations, injection site tolerability (pain, irritation, and tissue damage), clinical laboratory assessments (including biochemistry, hematology, urinalysis, and pregnancy testing), laboratory testing (including serum Ig levels and ADAs), vital sign measurements, and use of concomitant medications. Analysis of PK parameters will include participant data-listings of serum concentrations and summary statistics by intervention group, including mean, geometric mean, standard deviation, %CV, median, and range, as appropriate. Summary graphs including mean concentration-time profiles by group will also be presented. For the subset of participants in whom intensive PK samples are collected, serum concentration data will be analyzed by [redacted] as implemented in NONMEM or equivalent software. Additional analyses and summaries may be generated, as appropriate.

1.2 Schema

Figure 1: Study Design Schema



Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; eGFR = estimated glomerular filtration rate; uPCR = urine protein to creatinine ratio.

1.3 Schedule of Assessments

Table 1: Schedule of Assessments

Procedures	Scr[1]	Intervention Period (Study Month)																		EOS[2]
Study Month	N/A	M0				M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12/ ET[3]	M13	M14	M16
Nominal Study Day	-30[1]	D1 Pre infusion	D1 Post infusion	D8	D18	D30	D60	D90	D120	D150	D180	D210	D240	D270	D300	D330	D360	D390	D420	D485
Visit allowance (±days)		N/A	N/A	±3	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Study Visit	N/A	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Informed consent	x																			
Inclusion/exclusion criteria review	x	x																		
Medical history	x																			
Review of kidney biopsy[4]	x																			
Physical examination[5]	x																x			x
Weight	x	x									x			x			x			x
Vital signs[6]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-lead ECG	x																			
Randomization		x																		
Study intervention infusion[7]		x				x	x	x	x	x	x	x	x	x	x	x				
AE monitoring	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x			x
Concomitant medications review	x	x	x	x		x	x	x	x	x	x	x	x	x	x	x	x			x
HBV, HCV, HIV serology	x																			
Serum β-hCG (females only)	x																			
Urine β-hCG (females only)		x				x	x	x	x	x	x	x	x	x	x	x	x			x
Hemoglobin A1c	x																			
Serum chemistry[8]	x	x				x	x	x	x	x	x	x	x	x	x	x	x			x
Hematology[9]	x	x				x	x	x	x	x	x	x	x	x	x	x	x			x
Urinalysis (dipstick and microscopy)[10]	x	x		x		x	x	x	x	x	x	x	x	x	x	x	x			x
24-hour urine collection[11]	x													x			x			x
Urine sample for uPCR determination	x[12]	x		x		x	x	x	x	x	x	x	x	x[12]	x	x	x[12]			x[12]

Procedures	Scr[1]	Intervention Period (Study Month)																		EOS[2]
Study Month	N/A	M0				M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12/ ET[3]	M13	M14	M16
Nominal Study Day	-30[1]	D1 Pre infusion	D1 Post infusion	D8	D18	D30	D60	D90	D120	D150	D180	D210	D240	D270	D300	D330	D360	D390	D420	D485
Visit allowance (±days)		N/A	N/A	±3	±5	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	+7
Study Visit	N/A	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Blood sample for lymphocytes		x									x						x			x
Serum for PK[13]		x	x	x	x	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x[14]	x	x	x	x
Blood for total IgA, IgG, and IgM[13]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Blood for IgA subtypes		x						x			x			x			x			x
Serum for APRIL[14]		x	x			x	x	x[14]	x	x	x[14]	x	x	x[14]	x	x[14]	x			x
Serum for a-g IgA_1 and anti-IgA_1	x	x						x			x			x			x			x
Serum for ADA[15]		x				x	x		x		x		x			x	x			x
Blood sample for DNA[16]		x																		
Urine sample for exploratory biomarker assessments[17]		x						x			x			x			x			x
Blood for markers of complement activity		x									x						x			
Saliva samples for IgA levels		x									x						x			

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ADA = antidrug antibody; AE = adverse event; a-g IgA = aberrantly glycosylated immunoglobulin A; APRIL= A PRoliferation Inducing Ligand; ARB = angiotensin receptor blocker; β-hCG = beta-human chorionic gonadotropin; BAFF = B-cell activating factor; BP = blood pressure; D = Day; ECG = electrocardiogram; eCRF = electronic case report form; EOS = end-of-study; ET = early termination; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HR = heart rate; Ig = immunoglobulin; IgAN = immunoglobulin A nephropathy; M = Month; N/A = not applicable; PD = pharmacodynamics; PK = pharmacokinetics; RAAS = renin-angiotensin-aldosterone system; RR = respiratory rate; Scr = screening; SOC = standard of care; uACR = urinary albumin/creatinine ratio; uPCR = urinary protein/creatinine ratio.

1 All participants will undergo screening. To be eligible, participants should be on stable and maximally tolerated treatment with either ACEI or ARB, as per SOC and applicable guidelines, for at least 3 months. Participants must be on at least 50% of the maximum recommended dose of the ACEIs or ARB to be considered as having adequate RAAS blockade. Participants who are unable to tolerate ACEI/ARB therapy may be eligible for participation in the study, if their overall management of IgAN, including BP control, is as per SOC and applicable guidelines.

2 Participants must complete EOS assessments approximately 155 days after the last dose of study intervention. Participants discontinuing early will be encouraged to attend study visits as per the schedule, including the EOS visit. Adverse event and concomitant medication monitoring should be performed through the EOS visit; SAEs that are ongoing at EOS should be monitored until resolution or 30 days after the EOS, whichever is longer; AEs that are ongoing at EOS should be monitored until resolution or 30 days after the EOS.

3 Participants discontinuing early must complete ET assessments at the time of treatment discontinuation.

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

[5] A complete physical examination, including assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems will be completed at the screening, Month 12/ET visit, and Month 16/EOS visits.

[6] Vital sign measurements include BP, HR, RR, and temperature. Vital sign measurements on dosing days will be recorded within 15 (±5) minutes prior to the start of the infusion, every 15 minutes until the infusion is complete, and postinfusion at 60 minutes and 2 hours.

[7] The dose of study intervention will be based on the M0 predose weight.

[8] The comprehensive list of serum chemistry tests to be performed is provided in Appendix 2. A full serum chemistry panel will be obtained at screening and monthly . Local laboratory assessments may be performed at the Investigator's discretion throughout the study in the course of participant care (but not assessments that would potentially unblind treatment status, such as measurement of Ig levels). Any clinically significant abnormalities should be recorded in the eCRF.

[9] The comprehensive list of hematology tests to be performed is provided in Appendix 2.

[10] The comprehensive list of urinalysis tests to be performed is provided in Appendix 2. On days of 24-hour urine collections, the uPCR sample will be collected from the 24-hour urine collection and routine urinalysis will be performed on a sample freshly voided during the clinic visit.

[11] Participants will discard the first void and begin a 24-hour urine collection the day prior to the clinic visit. For all 24-hour urine collection, the following parameters will be obtained or derived: 24-hour urine volume, protein, albumin, creatinine, uPCR, and uACR.

[12] Samples should be taken from the 24-hour urine sample.

[13] Up to 60 participants (approximately 15 per cohort) may have a more intensive PK and PD sampling schedule, as described in Table 5. Study participants agreeing to participate in this more intensive PK and PD sample collection sub-study will sign an additional informed consent for this activity.

[14] Blood samples to be collected before and after study intervention infusion at all visits.

[15] Samples for ADA assessment will be collected before the start of infusion.

[16] Samples for evaluation of host genetic markers related to IgAN susceptibility loci, the APRIL/BAFF pathway, and/or immunity will be collected before the start of infusion. Participation in genetics research is optional; a separate informed consent form must be completed.

[17] On days of 24-hour urine collection, urine samples for exploratory biomarker analysis will be collected and stored from a sample freshly voided during the clinic visit. Participation in biomarker research is optional; a separate informed consent form must be completed.

2. INTRODUCTION

VIS649 is a humanized immunoglobulin G2 (IgG_2) monoclonal antibody being developed for the treatment of immunoglobulin A nephropathy (IgAN), an autoimmune glomerulonephritis characterized by the deposition of immunoglobulin A (IgA)-containing immune complexes in the kidney.

2.1 Study Rationale

Immunoglobulin A nephropathy is a chronic disease affecting the kidneys. It is clinically characterized by proteinuria, hematuria and progressive decline of glomerular filtration rate (GFR). IgAN is characterized histologically by dominant or co-dominant deposition of IgA in the kidney glomerulus (Rodrigues, Haas et al. 2017). The central mechanism for the development of IgAN is the production of aberrantly glycosylated IgA_1 (a-g IgA_1), which has been attributed to a combination of genetic and environmental factors. These a-g IgA_1 act as autoantigens and lead to development of autoantibodies forming circulating immune complexes that deposit in the mesangium of glomeruli and in turn, trigger an inflammatory response and complement activation (Kiryluk, Moldoveanu et al. 2011, Berthoux, Suzuki et al. 2012, Kiryluk, Novak et al. 2013, Kiryluk, Li et al. 2014, Kiryluk and Novak 2014). This results in episodic and cumulative kidney damage. Natural history studies indicate that IgAN may progress to end-stage renal disease (ESRD) in approximately 30% of patients, over the course of 10 years (Lai, Tang et al. 2016).

Proteinuria is an important marker of progression of renal disease in patients with IgAN. Patients with significant proteinuria (> 1.0 g/day) have a faster decline of estimated glomerular filtration rate (eGFR) and progression to ESRD, when compared to patients with lower degrees of proteinuria (< 500 mg/day). Hence, reduction in proteinuria is a crucial aspect in the management of IgAN (Reich, Troyanov et al. 2007, Nam, Kie et al. 2014, Inker, Mondal et al. 2016).

The cytokine A PRoliferation Inducing Ligand (APRIL), which belongs to the tumor necrosis factor ligand superfamily, has emerged as a key factor in the pathogenesis of IgAN through mediation of the Ig isotype switch during B-cell development, production of IgA, plasma-cell survival, and possibly specifically influencing production of a-g IgA_1 as well (Castigli, Scott et al. 2004, Varfolomeev, Kischkel et al. 2004, Endo, Nishio et al. 2007, Bossen, Cachero et al. 2008). Studies in IgAN patients have shown that elevated APRIL levels correlate with poor kidney outcomes, when compared with patients with lower APRIL levels (Han, Yang et al. 2016, Zhai, Zhu et al. 2016). A similar trend is also seen with a-g IgA_1 levels, with higher levels associated with faster and more frequent progression to kidney failure when compared to patients with lower a-g IgA_1 levels (Castigli, Scott et al. 2004, Berthoux, Suzuki et al. 2012, Zhao, Hou et al. 2012).

VIS649 is a humanized IgG_2 monoclonal antibody (mAb) that binds to and blocks the biological actions of APRIL, preventing its binding to its receptors, transmembrane activator and CAML interactor (TACI), and B-cell maturation antigen (BCMA). Blocking the biological actions of APRIL reduces the production of IgA. The hypothesis to be tested in this study is that a decrease in the production of IgA and a-g IgA_1 will diminish the formation of circulating immune

complexes and their deposition in the glomeruli, allowing injury repair and clinical improvement, as measured by reduction in proteinuria.

In data from a single-ascending dose study (VIS649-101) of VIS649 in healthy participants, VIS649 reduced serum levels of IgA and a-g IgA_1. The current study will test the hypothesis that blocking the biological actions of APRIL in IgAN participants leads to reduction of serum IgA (including a-g IgA_1) levels and will reduce or halt the progression of IgAN as measured by reduction in proteinuria (the study's primary efficacy endpoint). The current study will also assess the safety of VIS649 in participants with IgAN and collect extensive data on pharmacokinetics (PK) and pharmacodynamics (PD).

The findings from this study will form the basis for subsequent clinical development of VIS649.

2.2 Background

Immunoglobulin A nephropathy is one of the most common primary glomerular diseases and affects patients globally, with some geographical variation in incidence and prevalence (Wyatt and Julian 2013, Rodrigues, Haas et al. 2017, Schena and Nistor 2018). Clinical presentation varies from incidentally detected asymptomatic hematuria and proteinuria to rapidly progressive glomerulonephritis requiring dialysis. Immunoglobulin A nephropathy is a significant cause of chronic kidney disease (CKD) and ESRD, with 30–40% of patients reaching ESRD 20–30 years after the first clinical presentation. Immunoglobulin A nephropathy can occur in either sporadic (90–95%) or familial (5%–10%) patterns. Patients with familial IgAN might have poorer prognoses than those with sporadic disease, with an increased risk of progression to renal failure (Lai, Tang et al. 2016).

Immunoglobulin A nephropathy is diagnosed by kidney biopsy, which shows dominant or co-dominant IgA deposition on immunofluorescence. The pathogenesis of IgAN is currently thought to be a multi-hit process, the "first hit" being the production of a-g IgA_1. The primary defect is the deficiency of galactose in the hinge region of IgA_1. As a consequence, the N-acetylgalactosamine in the truncated IgA_1 hinge region glycan is exposed and acts as an autoantigen. Multiple cohort studies have shown the relationship between elevated a-g IgA_1 and IgAN, with higher a-g IgA_1 levels resulting in more rapid disease progression. The "second hit" consists of IgA and IgG autoantibody production against these a-g IgA_1. The "third hit" consists of formation of circulating immune complexes consisting of the IgG/IgA auto antibody and a-g IgA_1 antigen complex. The "fourth hit" consists of deposition of these circulating immune complexes in the mesangium of the glomeruli. These antigen-antibody complexes are nephritogenic and trigger an inflammatory response leading to infiltration of macrophages, monocytes and T cells, local release of cytokines, complement activation, and activation of the renin-angiotensin cascade. This leads to glomerular injury and tubulointerstitial fibrosis, clinically manifesting as proteinuria, hematuria, hypertension, and reduced GFR (Berthoux, Suzuki et al. 2012, Floege, Moura et al. 2014, Knoppova, Reily et al. 2016, Mestecky, Novak et al. 2016).

While proteinuria is a common manifestation of IgAN, the degree of proteinuria correlates with disease progression, with faster decline of eGFR, and progression to ESRD in patients with high-grade proteinuria (> 1.0 g/d) when compared to patients with low-grade proteinuria (< 0.5 g/d) (Reich, Troyanov et al. 2007, Nam, Kie et al. 2014, Inker, Mondal et al. 2016, Thompson, Carroll et al. 2019). Control of proteinuria is a key therapeutic target in patients with

IgAN. Measures to control proteinuria often consist of renin-angiotensin-aldosterone system (RAAS) blockade in the form of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) therapy, blood pressure (BP) control, statins to control cholesterol, smoking cessation, low-salt diet, low-protein diet, and avoidance of nephrotoxic drugs. If patients continue to have significant proteinuria despite these measures, they are usually treated with nonspecific immunosuppressive agents such as steroids, azathioprine, mycophenolate mofetil, or cyclophosphamide (Boyd, Cheung et al. 2012, KDIGO 2012, Radhakrishnan and Cattran 2012, Barbour and Feehally 2017, Rodrigues, Haas et al. 2017). These drugs, especially steroids (Pozzi, Andrulli et al. 2004, Rauen, Eitner et al. 2015, Tesar, Troyanov et al. 2015, Lv, Zhang et al. 2017), have been shown to be beneficial from a renal perspective in some studies, but their use is often complicated by significant adverse effects such as increased risk of infections, metabolic derangements, cosmetic changes, weight gain, fractures, and neuropsychiatric manifestations. Some of these agents have other significant risks such as increased risk of malignancies with prolonged administration. The significant side effects of these drugs preclude chronic use of these agents and limit their benefits in a chronic disease such as IgAN.

APRIL is a member of the tumor necrosis factor superfamily of ligands and is emerging as a key mediator in IgAN pathogenesis and disease progression based on convergence of genetic, biochemical, and clinical data. APRIL is produced by myeloid and mucosal epithelial cells. APRIL regulates B cell-mediated immune responses through several mechanisms, including class-switch recombination, principally through its 2 receptors: TACI and BCMA. APRIL is also important for plasmablast differentiation in secondary lymphoid organs. In addition, myeloid-derived APRIL mediates plasma cell survival by promoting the formation of so-called “survival niches” within the bone marrow microenvironment and mucosal compartments, leading to the establishment of a reservoir for long-lived antibody-secreting cells (Bossen, Cachero et al. 2008).

Evidence of the critical role of APRIL in IgAN includes the following: (a) serum a-g IgA_1 (autoantigen) levels are elevated in patients with IgAN and correlate with APRIL levels and disease severity; (b) genome-wide association studies link APRIL to the disease; (c) serum APRIL is elevated in patients with IgAN and higher APRIL levels among IgAN patients are associated with more rapid progression to kidney failure (Mestecky, Raska et al. 2013, Han, Yang et al. 2016, Muto, Manfroi et al. 2017).

In a mouse model of IgAN, administration of an anti-APRIL antibody similar to VIS649 led to lower IgA deposits in the kidney, lower proteinuria, and less glomerular sclerosis compared with animals administered a control antibody that does not bind APRIL. These data suggest that APRIL plays a key role in the pathogenesis of IgAN and that blocking APRIL could be an attractive approach for the treatment of IgAN (Myette, Kano et al. 2019).

VIS649 is a humanized IgG_2 mAb against the biologically active form of APRIL. VIS649 was tested in healthy human participants in a Phase 1, randomized, placebo-controlled, single-ascending dose, first-in-human study to assess the safety, tolerability, PK, and PD of VIS649 (VIS649-101). The study enrolled 51 participants in 5 sequential dosing cohorts. Participants in Cohorts 1 to 4 received 4 different dose levels of VIS649 (0.5, 2, 6, and 12 mg/kg, respectively), enrolling 9 participants per cohort (7 participants receiving VIS649 and 2 participants receiving placebo). Cohort 5 had 15 participants with 10 receiving VIS649 and 5 participants receiving placebo. Participants in Cohort 5 received 6 mg/kg of VIS649 on Day 1

and subsequently received a tetanus and diphtheria (Td) vaccine on Day 28. Blinded group data are available, including IgA levels. Preliminary data show that the total serum IgA declined by up to ~60% from normalized baseline values in these healthy participants. The vaccine response in Cohort 5 was intact, with a comparable IgG response to Td vaccine in participants receiving VIS649 and participants receiving placebo. Mean serum IgG levels declined by up to ~35% below normalized baseline values and mean IgM levels showed a marked decline of up to ~70% below the normalized baseline values. These declines in the Ig levels were reversible and the time taken to restoration of Ig levels to baseline was dependent on the dose of VIS649, with higher doses requiring a longer time period. VIS649 was very well tolerated across all dose levels and there were no serious adverse events (SAEs) attributed to VIS649. Further details can be found in the Investigator's Brochure.

The adverse risk-benefit ratio of nonspecific immunosuppressive agents precludes the chronic use of such agents and highlights the need for the development of an effective alternative that acts specifically on relevant pathophysiological factors in IgAN and is safe for chronic use.

2.3 Benefit/Risk Assessment

2.3.1 Risk Assessment

Table 2 summarizes the important potential risks that have been recognized during the conduct of VIS649 nonclinical and clinical development programs. At present, all are considered potential risks.

More detailed information about the risks and reasonably expected adverse events (AEs) of VIS649 may be found in the Investigator's Brochure.

Table 2: Summary of Potential Risks Associated with VIS649

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
IgA suppression risk	Based on the mechanism of action of VIS649, preclinical studies, and human data from healthy participants, total serum IgA levels are expected to be suppressed to nadir levels [redacted]. There is increasing recognition that selective IgA deficiency, which has typically been associated with IgA levels below the lower limit of detection [redacted], may be associated with recurrent sinopulmonary infection, allergy, autoimmunity, and gastrointestinal microbiome perturbation (Yazdani, Azizi et al. 2017, Fadlallah, El Kafsi et al. 2018). VIS649 is expected to reduce but not ablate IgA expression. Additionally, the syndrome of selective IgA deficiency is often associated with additional immunologic impairments, including T-cell disorders which are not expected to occur with VIS649 dosing.	• Serum IgA, IgG, and IgM will be measured on a monthly basis as blinded data, to be made available for routine DSMB review. The DSMB will assess unblinded safety data on a scheduled and as needed ad hoc basis, including AEs, laboratory data, and Ig data. The DSMB charter calls for assessment of the relationship of AEs to observed Ig levels (IgA, IgG and IgM) in study participants. • If needed, the DSMB charter also calls for specific risk-mitigation strategies including, but not limited to, change in inclusion/exclusion criteria, establishing criteria

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Additional information can be found in the Investigator's Brochure.	for stopping study intervention in a participant or a cohort, establishing criteria for rescue therapies such as IV Ig, and change in dosing schedule of a participant or cohort based on standardized safety laboratory and AE analysis.
IgG suppression risk	VIS649 is expected to have a moderate effect on serum IgG levels [redacted]. In the most commonly occurring disease state characterized by hypogammaglobulinemia, CVID, total IgG levels at diagnosis are typically below 250 mg/dL. CVID has been associated with recurrent otitis media, chronic sinusitis, and recurrent pneumonia, which may result in bronchiectasis (Ballow 2002, Furst 2009). The risk of these complications with VIS649 therapy is considered low, given the multifaceted immunologic dysfunction associated with CVID in comparison with the moderate (but not profound) anticipated effect of VIS649 on serum IgG. Additional information can be found in the Investigator's Brochure.	• Please see above regarding Ig and AE data monitoring under DSMB review. • To further reduce the risk of persistent clinically impactful suppression of IgG, the protocol inclusion criteria require an IgG level > 700 mg/dL at screening for enrollment [redacted]. • In a Phase 1 study of VIS649 in healthy participants, IgG responses to recall challenge with tetanus and diphtheria toxoid vaccination were comparable between recipients receiving placebo and VIS649. • In preclinical toxicology studies performed in nonhuman primates, the ability to generate a de novo humoral immune response to a novel T-cell dependent antigen (keyhole limpet hemocyanin) was not suppressed by VIS649, and peripheral blood myeloid cell line populations were unaffected.
IgM suppression risk	Based on the mechanism of action of VIS649, preclinical studies, and human data from healthy volunteers, total serum IgM is expected to be suppressed to levels approximately [redacted] below baseline.	• Please see above regarding Ig and AE data monitoring under DSMB review.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	Most patients with selective IgM deficiency are asymptomatic, but a few patients develop chronic and recurrent infections and increased risk of autoimmune diseases (Yel, Ramanuja et al. 2009, Louis and Gupta 2014, Louis, Agrawal et al. 2016, Janssen, Macken et al. 2018). Selective IgM deficiency is usually associated with other defects such as decreased T-helper cell activity, increased isotype specific suppressor T cells, increased CD8 Treg cells, and intrinsic B cell defects. VIS649 is not expected to have effects such as these on cellular immunity. Additional information can be found in the Investigator's Brochure.	
Nonspecific immunosuppression risk	There is the possibility of nonspecific immunodeficiency with potential risk of exacerbation of pre-existing latent infection or poor response to new infection. Additional information can be found in the Investigator's Brochure.	• Participants with acute or chronic infections at the time of screening are prohibited from enrollment. • Participants with underlying iatrogenic or primary immunodeficiency syndromes are prohibited from enrollment. • DSMB monitoring will include careful attention to infection-related AEs. • Concurrent treatment with systemic corticosteroids or other immunosuppressive therapy is prohibited during study conduct.
Infusion reactions (anaphylaxis, fever, chills, rigors, nausea, vomiting, pain, headache, dizziness, shortness of breath, bronchospasm, hypotension, hypertension, pruritus, rash, urticaria, angioedema, diarrhea, tachycardia, and chest pain)	There were no SAEs among participants in the Phase 1 VIS649-101 study at dose levels up to 12 mg/kg. Severe infusion reactions such as anaphylaxis have not been observed with VIS649 in humans. There was no effect of VIS649 on measured plasma cytokine concentrations in the monkey toxicology studies, and VIS649 did not stimulate significant cytokine release in an in vitro human peripheral blood lymphocyte cytokine release assay. Additional information can be found in the Investigator's Brochure.	• All VIS649 doses will be administered at the clinical site by trained personnel, and participants will be closely monitored for the occurrence of infusion reactions.
Delayed allergic reactions (SSLR [ie, urticaria,	Delayed allergic reactions to a mAb such as serum sickness (ie, urticaria, fever, general glandular enlargement, joint pains) have been	• Participants will be monitored for AEs throughout the duration of the study.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
fever, general glandular enlargement, joint pains])	reported with other mAbs and may not appear until several days or weeks after the infusion. Additional information can be found in the Investigator's Brochure.	
Injection site reactions	Injection site reactions may occur following administration of any intravenous therapy.	• All VIS649 doses will be administered at the clinical site by trained personnel, and participants will be closely monitored for injection site reactions.

Abbreviations: AE = adverse event; APRIL= A Proliferation Inducing Ligand; CVID = common variable immunodeficiency; DSMB = data safety monitoring board; Ig = immunoglobulin; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M; IV = intravenous; LLN = lower limit of normal; mAb = monoclonal antibody; PD = pharmacodynamic(s); PK = pharmacokinetic(s); SAE = serious adverse event; SSLR = serum-sickness like reaction.

2.3.2 Benefit Assessment

Immunoglobulin A nephropathy is a chronic disease with periodic flares. IgAN is a significant cause of CKD and ESRD, the clinical progression varies, with 30 – 40% of patients reaching ESRD 20 to 30 years after the first clinical presentation (Lai, Tang et al. 2016). These patients have significantly increased mortality and morbidity, with life expectancy reduced by 6 to 10 years when compared to healthy individuals. (Hastings, Bursac et al. 2017, Jarrick, Lundberg et al. 2019). There are currently no approved therapies for IgAN, and the current treatment strategies consist of 2 main approaches: nonspecific supportive treatments consisting of BP control, treatment with ACEI/ARB, smoking cessation, lipid reduction, low-salt diet, or fish oil, and immunosuppressive therapies such as steroids, cyclophosphamide, or azathioprine. The immunosuppressive therapies are usually employed in patients with a high risk of progression, as characterized by proteinuria > 1.0 g/d and declining GFR (Cheng, Zhang et al. 2009, Boyd, Cheung et al. 2012, KDIGO 2012, Radhakrishnan and Cattran 2012, Barbour and Feehally 2017, Rodrigues, Haas et al. 2017). Recent trials have shown some benefit in proteinuria reduction with steroids in these patients, thought they are at high risk for developing significant complications like infections, metabolic derangements, osteoporosis, and diabetes mellitus with these immunosuppressive agents, thus limiting the duration for which these drugs can be given to patients despite benefit from a renal perspective (Pozzi, Andrulli et al. 2004, Rauen, Eitner et al. 2015, Tesar, Troyanov et al. 2015, Lv, Zhang et al. 2017). Hence, there is a critical need for a safe and specific treatment for IgAN.

VIS649 has the potential to provide a significant advancement in the therapeutic approach to IgAN. It has a very specific mechanism of action in the form of APRIL inhibition, which plays a critical pathophysiological role in the production of a-g IgA_1 in patients with IgAN.

VIS649 has an attractive safety profile based on currently available data, including data from the first-in-human study (VIS649-101), in which no SAEs attributable to VIS649 were observed. It is anticipated that VIS649 will be used as chronic therapy and will significantly improve the outcomes in patients with IgAN when compared to intermittent therapies like steroids that are currently used to treat these patients.

2.3.3 Overall Benefit: Risk Conclusion

Given the mechanism of action of VIS649 and data from a Phase 1 single-ascending dose study (VIS649-101) in healthy participants, it is expected that participants receiving VIS649 will have a decline in Ig levels [redacted]. To mitigate the risk of IgG reduction, serum IgG thresholds for enrollment have been established so as to prevent the development of clinically significant hypogammaglobulinemia. In addition, studies in both healthy human participants and nonhuman primates have demonstrated that the ability to develop an IgG response to novel antigens and recall T-cell dependent antigen challenge is not significantly impaired. As mentioned earlier, there were no SAEs considered attributable to VIS649 in the Phase 1 single-ascending dose study (VIS649-101), and in the nonhuman primate 6-month toxicology study, the no-adverse effect level for the antibody was the highest dose evaluated.

An independent data safety monitoring board (DSMB) for this study will be reviewing all available safety data, including unblinded Ig data and AEs on a periodic and, as needed, on an ad hoc basis.

Given these encouraging preliminary data and the precautions built into the protocol, evaluation of the potential benefit of VIS649 in slowing or halting CKD progression in IgAN participants is warranted.

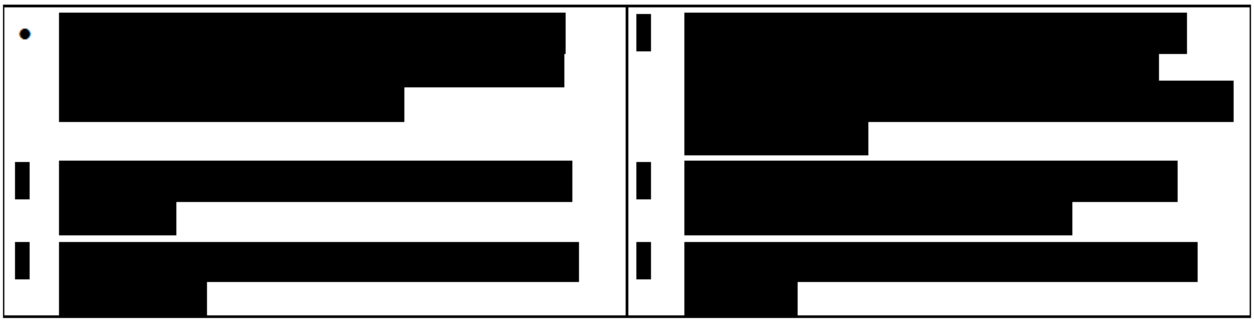
3. OBJECTIVES AND ENDPOINTS

Study objectives and endpoints are outlined in Table 3.

Table 3: Study Objectives and Endpoints

Primary Safety Objective	**Primary Safety Endpoint**
• To evaluate the safety and tolerability of monthly doses of VIS649 at each of 3 dosing levels, administered IV to IgAN participants over the course of 12 months as an add-on to SOC treatment with ACEI/ARB therapy, compared with saline placebo infusions as an add-on to SOC treatment with ACEI/ARB therapy	• AEs graded by severity, clinical laboratory tests, vital sign measurements, and physical examinations
Primary Efficacy Objective	**Primary Efficacy Endpoint**
• To evaluate the dose response of monthly doses of VIS649 on proteinuria at each of 3 dosing levels, administered IV to IgAN participants over the course of 12 months as an add-on to SOC treatment with ACEI/ARB therapy, compared with saline placebo infusions as an add-on to SOC treatment with ACEI/ARB therapy	• Change from baseline in uPCR (measured on natural log scale from 24-hour urine collection or the intended 24-hour urine collection) at Month 12 (ie, approximately 30 days after the 12th dose is administered)
Secondary Objectives	**Secondary Endpoints**
• To evaluate the effect of repeated doses of VIS649 at 3 dosing levels versus placebo on the following parameters: o uPCR at Months 9 and 16 (ie, 5 months following the final [12th] monthly dose administration) o 24-hour urine protein excretion at Months 9, 12, and 16 o ≥ 30% decline from baseline in uPCR at Months 9, 12, and 16 o Clinical remission, defined as reduction in 24-hour urine protein excretion to < 300 mg/day for at least 3 consecutive months	o Change from baseline in uPCR (measured on natural log scale from 24-hour urine collection or the intended 24-hour urine collection) at Months 9 and 16 o Change in 24-hour urine protein excretion from baseline to Months 9, 12, and 16 o Number of participants in each group achieving a ≥ 30% decline from baseline in uPCR at Months 9, 12, and 16 o Number of participants in each group achieving clinical remission
• eGFR at Months 12 and 16	• Change from baseline in eGFR at Months 12 and 16

• To evaluate the effect of repeated doses of VIS649 at each dosing level compared with placebo on the following PD parameters: IgA, IgG, and IgM concentrations	• Change from baseline in total serum IgA, IgG, and IgM concentrations at Months 9, 12, and 16
• To determine the PK profile of repeated dose of VIS649, at each dosing level • To determine the PK/PD profile of VIS649, relating VIS649 PK parameters and biomarkers such as changes in IgA to changes in proteinuria and eGFR • To screen for ADA responses	• Serum PK parameters • Correlation of VIS649 PK parameters with changes in IgA, uPCR, and eGFR • Serum ADA levels
Exploratory Objectives	**Exploratory Endpoints**
• [redacted]	[redacted]



Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ADA = antidrug antibody; AE = adverse event; a-g IgA = aberrantly glycosylated immunoglobulin A; APRIL= A Proliferation Inducing Ligand; ARB = angiotensin receptor blocker; BAFF = B-cell activating factor; eGFR = estimated glomerular filtration rate; Ig = immunoglobulin; IgAN = immunoglobulin A nephropathy; IV = intravenous(ly); MEST = Mesangial cellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy; PD = pharmacodynamic; PK = pharmacokinetic; SOC = standard of care; uACR = urinary albumin/creatinine ratio; uPCR = urinary protein/creatinine ratio.

4. STUDY DESIGN

4.1 Overall Design

This is a Phase 2 multicenter, randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety and efficacy of intravenously (IV) administered VIS649 over a 12-month treatment course in participants with IgAN.

Participants will be enrolled from approximately 90 global sites in approximately 16 countries.

Screening evaluations (including physical examinations, vital signs, 12-lead electrocardiogram [ECG], safety laboratory testing [serum chemistry, hematology, urinalysis, serology, hemoglobin A1c, and pregnancy], blood sampling for baseline Ig levels [IgA, IgG, and IgM], and 24-hour urine collection) will take place during the 30 days prior to the first dose of study intervention.

To be eligible, participants should be on stable and maximally tolerated doses of either ACEI or ARB therapy, as per standard of care (SOC) and applicable guidelines, for at least 3 months. Participants must be on at least 50% of the recommended maximum dose of the ACEI or ARB to be considered as having adequate RAAS blockade.

Participants who are unable to tolerate ACEI/ARB therapy may be eligible for participation in the study if their overall management of IgAN, including BP control, is as per SOC and applicable guidelines.

Participant education regarding temporary cessation of ACEIs/ARBs during acute illness and resumption of these drugs after resolution of the acute illness will be as per local practice and SOC and this therapy will be resumed at the dose closest to the level at the time of randomization. During the course of the study, the doses of ACEIs or ARBs should not change; however, minor changes are allowed depending on the clinical situation. Control of BP should be as per SOC and applicable guidelines. Although additional antihypertensives can be used to control BP as per the Investigator's preference and local practice, combination of ACEIs and ARBs (or direct renin inhibitors) is prohibited and addition of mineralocorticoid receptor antagonists such as spironolactone or eplerenone should be avoided.

Enrolled participants must be 18 years of age or older with an IgAN diagnosis confirmed by biopsy.

It is anticipated that most biopsies resulting in a diagnosis of IgAN will have been interpreted using the MEST score - mesangial cellularity, endocapillary proliferation, segmental sclerosis, tubular atrophy (Cattran et al, 2009) or MEST-C scoring system (Trimarchi, Barratt et al. 2017) from the Oxford classification of IgAN. Components of the MEST-C score include:

- M – Mesangial hypercellularity, defined as more than 3 mesangial cells in any mesangial area of a glomerulus; a score of M0 indicates hypercellularity in < 50% of glomeruli and a score of M1 is for hypercellularity noted in ≥ 50% of glomeruli.
- E – Endocapillary proliferation, defined as hypercellularity due to an increased number of cells within glomerular capillary lumina causing narrowing. E0 represents absence of hypercellularity; E1 is hypercellularity in any glomeruli.
- S – Segmental glomerulosclerosis, defined as adhesion or sclerosis (obliteration of capillary lumina by matrix) in part of but not the whole glomerular tuft; S0 represents

absence of segmental glomerulosclerosis; S1 is presence of segmental glomerulosclerosis in any glomerulus.

- T – Tubular atrophy/interstitial fibrosis, defined as the estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater; T0 is 0-25%; T1 is 25-50%; T2 is > 50% atrophy/interstitial fibrosis.
- C – Crescents: C0 (no crescents), C1 (crescents in < 25% of glomeruli), and C2 (crescents in ≥ 25% of glomeruli).

A MEST-C score finding on kidney biopsy of T2 or C2 is exclusionary for this study. If the biopsy was not reported using the Oxford classification schema, the following findings (corresponding to these Oxford classifications) are exclusionary: a) > 50% tubular atrophy and/or b) > 25% crescents.

Eligible participants must have sufficient proteinuria at screening, defined as urine protein to creatinine ratio (uPCR) ≥ 0.75 g/g or 24-hour urine protein ≥ 1.0 g/d, as measured from a 24-hour urine collection (or an intended 24-hour urine collection). The proteinuria should be stable, as defined by a < 25% change when compared to values from ≥ 3 months ago (if available). If previous values are not available, or if the change from a prior value is > 25%, a repeat measurement of proteinuria will be done after 15 days and the patient should fulfill the above proteinuria criteria to be eligible for randomization in the trial.

Eligible participants must have an eGFR ≥ 45 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey, Stevens et al. 2009), before dosing on Day 1. The eGFR should be stable, as defined by a < 25% change when compared to values from ≥ 3 months ago (if available). If previous values are not available or if the change from a prior value is > 25%, a repeat measurement of eGFR will be done after 15 days and the patient should fulfill the eGFR criteria to be eligible for randomization in the trial.

If the patient fulfills the proteinuria and eGFR criteria based on 2 measurements performed for each during the screening period, the second measurement (for each) will be considered as the baseline for analysis.

Participants known to have chronic infectious diseases (eg, chronic sinusitis, chronic urinary tract infections, bronchiectasis) will be excluded. Participants in countries with high prevalence of tuberculosis may undergo appropriate investigations such as chest X-ray or interferon gamma-release assay, as deemed appropriate by the Investigator, to rule out tuberculosis. Participants will be excluded from the study if they test positive for the screening serology markers listed in Table 8. Participants with a positive Hepatitis C virus (HCV) antibody test must undergo testing for HCV RNA; if HCV RNA is undetectable, the participant can be included in the study. Participants with positive HbSAg and/or positive Anti HbC antibody will be excluded.

Participants must be vaccinated as per respective national guidelines and other relevant guidelines. Participants should continue to receive annual influenza vaccine and pneumococcal vaccine, as per local guidelines.

The study will evaluate 3 dose levels of VIS649 (2, 4, and 8 mg/kg) versus placebo. A total of 144 participants will be randomized with equal allocation (1:1:1:1) across the 4 intervention groups (approximately 36 participants per group). Randomization will be stratified first by

region (Japan vs rest-of-world). A target of 12 or more participants are planned to be randomized in Japan; these participants will be randomized with equal allocation and without further stratification. The randomization for the rest-of-world will be stratified by screening uPCR (≤ 2.0 g/g vs > 2.0 g/g).

VIS649 or placebo will be administered as 12 monthly IV infusions starting on Day 1/Month 0. Participants will return to the study center on Days 8 and 18, then monthly through Month 14 and on Month 16 for safety, efficacy, PK, and/or PD assessments. Participants will be encouraged to follow the schedule of visits for their monthly infusions as close to the prescribed interval as possible. If under special circumstances, a participant is unable to visit the study center within 7 days of the scheduled infusion, they will still be able to receive the infusion within the next 7 days, and this will be recorded as a protocol deviation. However, if there is any further delay, that dose should be skipped, and the participant should receive subsequent doses as per the schedule. The participant will not receive additional doses to make up for the missed dose(s).

Safety assessments will include review of AEs (including hypersensitivity reaction and anaphylactic reaction), physical examinations, injection site tolerability (pain, irritation, and tissue damage), clinical laboratory assessments (including biochemistry, hematology, urinalysis, and pregnancy testing), laboratory testing (including serum Ig levels and antidrug antibodies [ADAs]), vital sign measurements, and use of concomitant medications.

Participants will return to the study center on Month 16, 155 days following the last dose of study intervention (Dose 12) for an end-of-study (EOS) visit, at which time final safety, PK, PD, and efficacy assessments will be performed. Participants discontinuing dosing prior to Dose 12 will attend an early termination visit at the time of dosing discontinuation and will be encouraged to attend the study visits as per schedule of assessments (Table 1).

An independent DSMB will review safety data at regular intervals (see Section 9.6).

A rollover, open-label extension study will be offered to enable access to VIS649 (there will be no placebo arm) for study participants who have completed this trial, provided that the Investigator believes that the participants might benefit, and that the site has agreed to participate in the extension study. Further details will be provided in a separate protocol.

The total study duration for each participant (from screening to EOS) will be up to 17 months (assuming up to 1 month for screening, 12 months for monthly doses [including 30 days after the 12^{th} dose], and follow-up visits up to 155 days after the last dose of study intervention.

4.2 Scientific Rationale for Study Design

This study is designed as a randomized, double-blind, placebo-controlled, multiple-dose study to evaluate the safety and efficacy of IV administered VIS649 in IgAN participants over a 12-month intervention course.

Immunoglobulin A nephropathy is a chronic, slowly progressing disease. The underlying pathogenic factor in IgAN is the formation of a-g IgA_1, which is attributed to a culmination of genetic and environmental factors in susceptible individuals. The hypoglycosylated hinge region of a-g IgA_1 presents as a novel antigen, against which IgG and IgA autoantibodies may be generated. This leads to formation of circulating IgG/a-g IgA_1 immune complexes that are

deposited (in part) in the mesangium of the glomerulus, inciting an inflammatory, nephritogenic response (Boyd, Cheung et al. 2012, Mestecky, Raska et al. 2013, Lv, Zhang et al. 2017). This manifests clinically as proteinuria, hematuria, and decline in eGFR. High grade proteinuria (> 1.0 g/d) is a critical marker of progressive IgAN and remission of proteinuria is a crucial therapeutic target in the management of IgAN (Donadio, Bergstralh et al. 2002, Reich, Troyanov et al. 2007, Nam, Kie et al. 2014, Inker, Mondal et al. 2016, Thompson, Carroll et al. 2019).

VIS649 inhibits the biological actions of APRIL and reduces the levels of IgA, a-g IgA_1 and other Ig. In patients with IgAN, it is hypothesized that this reduction in APRIL and a-g IgA_1 will reduce the deposition of circulating immunocomplexes in the glomerulus. This should lead to cessation of ongoing renal damage and lead to recovery of the damaged glomeruli, as reflected by a reduction in proteinuria.

Based on the PK/PD data from the Phase 1 single-ascending dose study (VIS649-101) and on simulation models, full therapeutic suppression of IgA through APRIL signaling inhibition will be achieved at 12 weeks, with the selected doses administered monthly. Considering the time-dependent and indirect effect of VIS649, a 12-month study intervention duration is deemed necessary to achieve therapeutic effect and assess for clinically relevant benefit of VIS649, as measured by reduction in proteinuria.

The primary efficacy endpoint will be the change from baseline in uPCR, at Month 12 (30 days after the 12^{th} dose of study intervention), as measured from a 24-hour urine collection. Studies have shown that in patients with IgAN, reduction of proteinuria leads to clinically relevant improvements like reduction in the rate of decline of eGFR and progression to ESRD.

In an analysis of data from the Toronto Glomerulonephritis Registry of 542 patients followed for a mean of 6.5 years (61% males, 50% whites, 23% Asians, with mean initial proteinuria 2.4 g/d and creatinine clearance of 77 mL/min/1.73 m^2), time-averaged proteinuria (defined as an average of the mean of the proteinuria measurements for every 6-month period) was the most important predictor of kidney function decline and risk of ESRD, independently of BP and use of renin-angiotensin blockers. If time-averaged proteinuria was maintained < 1 g/d, the 10-year risk of ESRD was 5%, versus 20% with a time-averaged proteinuria of 1–2 g/d, 40% with a time-averaged proteinuria of 2 to 3 g/d, and 60% with > 3 g/d (Reich, Troyanov et al. 2007).

This study highlights the primary importance of proteinuria reduction as a therapeutic target in the management of IgAN.

A comprehensive series of safety evaluations, including review of AEs (including hypersensitivity reaction and anaphylactic reaction), physical examinations, injection site tolerability (pain, irritation, and tissue damage), clinical laboratory assessments (including biochemistry, hematology, urinalysis, and pregnancy testing), laboratory testing (including serum Ig levels and ADAs), vital sign measurements, and use of concomitant medications will be conducted to evaluate the safety profile of VIS649.

It is expected that VIS649 will result in obvious reductions in serum IgA, IgG, and IgM, which, if visible to the site or Sponsor, would effectively unblind treatment. Therefore, unblinded Ig data will only be available to designated unblinded personnel.

The DSMB will have access to the unblinded Ig data and will be responsible for monitoring Ig and AE data periodically (see Section 9.6).

4.3 Justification for Dose

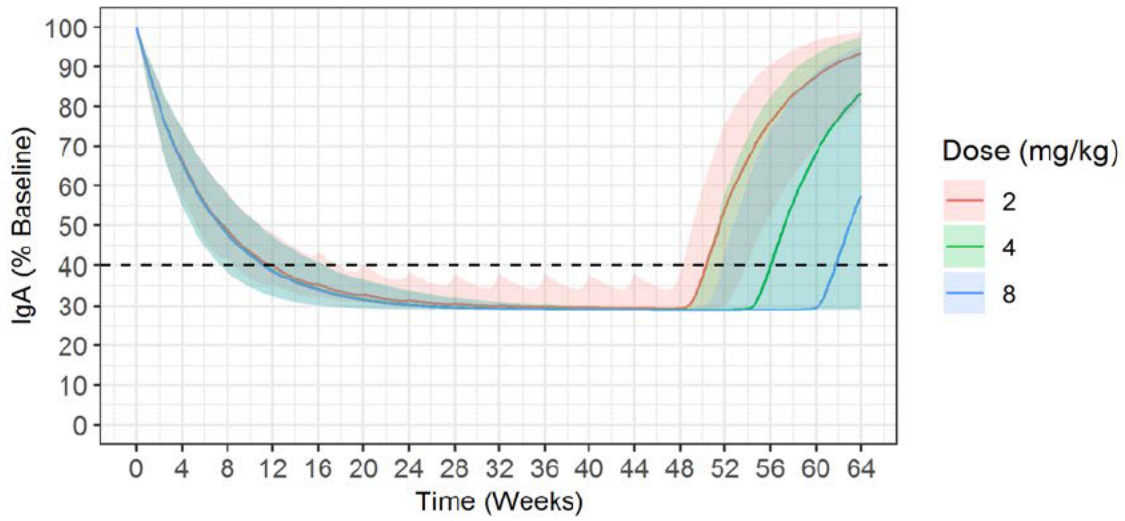
Monthly IV doses of VIS649 at 2, 4, and 8 mg/kg (and placebo) will be explored in this study.

Dose selection was informed by the totality of available nonclinical and clinical evidence, including safety margins from a 4-week and 6-month chronic toxicology study in cynomolgus monkeys and emerging data from the Phase 1 study using single doses from 0.5 to 12 mg/kg in healthy participants (VIS649-101).

Pharmacokinetic data from VIS649-101 demonstrate that there are no safety concerns when VIS649 levels are maintained above the effective concentration that inhibits APRIL and total serum IgA for ~2 and ~3 months, respectively, with single VIS649 doses of 6 and 12 mg/kg.

The anticipated pharmacologically active dose range in humans was evaluated using a PK/PD model based on data from VIS649-101. Simulation results predict that 2 mg/kg is the minimal dose that will achieve desired pharmacological activity with monthly dosing (Figure 2). Therefore, 2 mg/kg has been selected as the low dose for this study. It is possible, however, that higher APRIL levels and marked proteinuria in IgAN participants (versus healthy controls) could significantly accelerate VIS649 clearance. To mitigate this risk, 2 higher dose levels will be evaluated; 4 mg/kg and 8 mg/kg. Based on the PK/PD model simulations, VIS649 exposure after monthly 8 mg/kg doses is within the exposure range observed at 12 mg/kg in the Phase 1 single-dose study.

Figure 2: Simulated Percent Baseline Immunoglobulin A by Dose



Abbreviations: IgA = immunoglobulin A.
Note: Lines and shaded regions represent the median model prediction and model uncertainty (5th and 95th percentiles), respectively.

The results of VIS649-101 and PK/PD model simulations and the safety coverage from the 6-month toxicology study all support the planned dosing strategy for the current study.

4.4 End-of-study Definition

A participant is considered to have completed the study if he/she has completed the intervention period and EOS visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. STUDY POPULATION

Prospective approval of protocol deviations to enrollment criteria, also known as protocol waivers or exemptions, is not permitted. Rescreening is typically not permitted; possible exceptions include re-testing of samples due to issues arising during shipping/storage/handling of samples. Rescreening of a participant may also be permitted if initial participation in the study was precluded due to an acute infection or an acute illness that subsequently resolved completely, and the participant then is able to fulfill all study eligibility criteria.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant is a male or female ≥ 18 years of age at the time of signing the informed consent.
2. Participant has biopsy-confirmed IgAN.
3. Participant has medical records showing they have been on stable and maximally tolerated doses of either ACEI or ARB, as per SOC and applicable guidelines, for at least 3 months preceding screening. Participants should be on at least 50% of the maximum recommended dose of these agents to be considered as having adequate RAAS blockade. Participants who are unable to tolerate ACEI/ARB therapy may be eligible for participation in the study if their overall management of IgAN, including BP control, is as per SOC and applicable guidelines.
4. Participant has screening uPCR ≥ 0.75 g/g measured from a 24-hour urine (or an intended 24-hour urine sample) or 24-hour urine protein ≥ 1.0 g/d, as measured from 24-hour urine collection (or an intended 24-hour urine sample). The proteinuria should be stable, defined as < 25% change when compared to values from ≥ 3 months previously (if available).
    - If previous values are not available or if the change from a prior value is > 25%, a repeat measurement of proteinuria will be done after 15 days and the participant should fulfill the above proteinuria criteria to be eligible for randomization in the study.
    - The proteinuria should be assessed when the participant is considered to be in a steady state with no recent heavy exercise, fever, or other potential issues that could impact the result.
5. Participant has eGFR ≥ 45 mL/min/1.73 m^2, calculated using the CKD-EPI formula. The eGFR should be stable, as defined by a < 25% change when compared to values from ≥ 3 months previously (if available).
    - If previous values are not available or if the change from a prior value is > 25%, a repeat measurement of eGFR will be done after 15 days and the participant should fulfill the eGFR criteria to be eligible for randomization in the study.
    - The eGFR should be measured when the participant is considered to be in a steady state without recent changes in volume status, medications that could

impact the result (eg, nonsteroidal anti-inflammatory drugs [NSAIDs], aminoglycosides, co-trimoxazole), or changes in dietary protein intake.

6. Participant's serum Ig values must meet the following criteria:
   - IgG: ≥ 700 mg/dL
   - IgM: ≥ 40 mg/dL
   - IgA: ≥ 70 mg/dL
7. Female participants of childbearing potential must have a negative serum pregnancy test prior to the first dose.
8. Participant is willing to adhere to contraceptive requirements outlined in Appendix 4.
9. Participant or a legally authorized representative is able to understand the purpose and risks of the study and is willing to give voluntary written informed consent as described in Appendix 1.

5.2 Exclusion Criteria

Participants are excluded from the study if they meet any of the following criteria:

1. Participant has secondary forms of IgAN as defined by the treating physician (eg, Henoch-Schönlein purpura, minimal change disease with IgA deposits, infection associated IgAN, or IgAN-associated with hepatic cirrhosis).
2. Participant has co-existing CKD, other than IgAN.
3. Participant has evidence of additional pathological findings in the kidney biopsy (eg, diabetic kidney disease, membranous nephropathy, or lupus nephritis). However, hypertensive vascular changes are acceptable.
4. Participant has kidney biopsy 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.
5. Participant has nephrotic syndrome, defined for this purpose as 24-hour urine protein > 3.5 g with concurrent hypoalbuminemia (serum albumin < 2.5 g/dL), hyperlipidemia (total cholesterol > 350 mg/dL), and edema.
6. Participant has received a solid organ transplant, including kidney.
7. Participant has received bone marrow or hematologic stem cell transplantation.
8. Participant is currently receiving systemic immunosuppression (excluding topical, ophthalmic, per rectum, or inhaled corticosteroids).
9. Participant has received systemic steroids within the 24 weeks prior to initial screening.
10. Participant has received treatment with 2 or more systemic immunosuppressive agents within 2 years prior to initial screening.
11. Participant has chronic infectious diseases (eg, chronic urinary tract infection; chronic sinusitis; bronchiectasis; active pulmonary or systemic tuberculosis; chronic viral hepatitis, such as hepatitis C or hepatitis B; or human immunodeficiency virus infection).

12. Participant has acute infectious disease at the time of screening. Participants may be rescreened following resolution of acute infection (such as urinary tract infection or respiratory tract infection), provided there is no evidence of an immunosuppressive condition that predisposed the participant to this infection.
13. Participant has Type 1 diabetes.
14. Participant has uncontrolled Type 2 diabetes, as evidenced by a screening hemoglobin A1c value > 8%.
15. Participant has uncontrolled BP (> 140 mm Hg systolic or > 90 mm Hg diastolic), Systolic and diastolic BP should be assessed while the participant is seated or supine for at least 5 minutes in a quiet room without distractions. BP should be measured with a completely automated device. At least 3 readings should be taken and average values from these 3 readings should be calculated.
16. Participant has a history of chronic autoimmune neurodegenerative disorder such as multiple sclerosis.
17. Participant has a known allergy or intolerance to any component of the study intervention.
18. Participant is breastfeeding.
19. Participant has poorly compensated or controlled ischemic heart disease or cardiomyopathy, as judged by the Investigator.
20. Participant has chronic obstructive pulmonary disease (COPD) or asthma that has required systemic steroid therapy during the prior year. If COPD is present, severity must not exceed Global Initiative for Chronic Obstructive Lung Disease 1 (mild), defined as a forced 1-second expiratory volume (FEV_1) > 80% of predicted.
21. Participant has known cirrhosis or liver dysfunction, defined as presence of coagulopathy, platelet count < 100,000/µL or alanine aminotransferase > 3× upper limit of normal.
22. Participant has active malignancy or is receiving chemotherapy for malignancy, except for nonmelanoma skin cancers and cervical carcinoma in situ. Participants with prior malignancy who have been documented to be cancer-free for ≥ 5 years may be enrolled.
23. Participant is planning or scheduled to undergo a tonsillectomy. Prior tonsillectomy is acceptable (if greater than 6 months prior to screening).
24. Participant enrolled in another investigational drug or device study within 3 months prior to initial screening.
25. Participant with a pre-existing illness other than those listed above that, in the opinion of the Investigator, would place the participant at increased risk through participation in this study.
26. Participant is unable to comply with study protocol procedures and/or study visit schedules.

27. Participant with known or suspected alcohol or drug abuse that would compromise their safety or study participation, in the opinion of the Investigator.

5.3 Lifestyle Considerations

Lifestyle recommendations applicable to IgAN patients such as, but not limited to, BP control, low-salt diet, low-protein diet, smoking cessation, weight reduction, and avoidance of nephrotoxic drugs (eg, NSAIDs) will be followed as per local practice and guidelines.

5.4 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered into the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 Study Intervention(s) Administered

The study interventions to be administered under this protocol are detailed in Table 4.

VIS649 is for investigational use only and should only be used within the context of this study.

VIS649 will be administered as a mg/kg dosage determined by dose assigned at time of randomization. VIS649 will be administered IV over 1 hour, in a single, final volume 100 mL infusion in normal saline (0.9% NaCl), followed by a 25-mL saline flush. The dose of study intervention will be based on the Month 0 predose weight.

Placebo (0.9% NaCl) will be administered IV over 1 hour as a single 100 mL infusion, followed by a 25 mL saline flush.

Infusions should preferentially be administered to the participant's dominant arm.

Table 4: Study Interventions

Study Arm	VIS649	Placebo
Intervention Name	VIS649	Placebo
Intervention Type	Drug (IMP)	Placebo (NIMP)
Dose Formulation	Solution	NaCl (normal saline solution)
Unit Dose Strength	VIS649 is formulated at a concentration of 25 mg/mL	0.9%
Dosage Levels	2, 4, and 8 mg/kg as a single, final volume of 100 mL	N/A
Dosing Frequency	Monthly for 12 months	Monthly for 12 months
Route of Administration	1-hour IV infusion, followed by a 25-mL saline flush	1-hour IV infusion, followed by a 25-mL saline flush
Use	Experimental	Placebo-comparator
Sourcing	Provided centrally by the Sponsor	Supplies will be obtained locally
Packaging and Labeling	VIS649 will be supplied in vials containing a nominal volume of 10 mL and will be labeled according to local regulations	Per local supplies
Storage Conditions	VIS649 must be stored at a temperature between ≥ 2°C and ≤ 8°C and protected from light. Must be infused within 4 hours of reconstitution	Per package insert

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; IMP = investigational medicinal product; IV = intravenous(ly); N/A = not applicable; NIMP = noninvestigational medicinal product; SOC = standard of care.

6.2 Preparation/Handling/Storage/Accountability

The required amount of VIS649 to be dosed will be diluted in normal saline up to a maximum total volume of 100 mL; for placebo participants, 100 mL of normal saline will be prepared. The length of the IV line will be set to a maximum volume of 25 mL, so that the 25-mL saline flush following administration will ensure all VIS649/placebo has been administered.

The VIS649/placebo infusion will be administered IV using a 0.20-µm in-line filter and will be controlled by a volumetric pump. Standard, uniform-length infusion lines will be used.

In addition:

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained for study intervention during transit to and storage in the investigational pharmacy. Any deviations from Pharmacy Manual guidance are to be reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply and administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions, with access limited to the Investigator and authorized site staff.
3. The Investigator, institution, or head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

6.3 Measures to Minimize Bias: Randomization and Blinding

This study is double-blinded. An unblinded pharmacist will prepare study intervention doses for infusion. Participants, the Sponsor, the Investigator, and all other site study staff will be blinded to study intervention.

All eligible participants will be centrally assigned to randomized study intervention using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

Participants will be randomly assigned in a 1:1:1:1 allocation ratio to receive VIS649 at 2, 4, or 8 mg/kg or placebo, with approximately 36 participants randomized to each intervention group. Randomization will be stratified first by region (Japan vs rest of world). A target of 12 or more participants are planned to be randomized at Japanese sites. Japanese participants will be randomized with equal allocation and without further stratification. Randomization for the rest of world will then be stratified by screening uPCR (≤ 2.0 g/g vs > 2.0 g/g).

Each assignment will have a unique randomization number, assigned to eligible participants after the screening. Once a randomization number has been assigned via the IVRS/IWRS, it may not be reassigned.

In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is required for participant safety, the Investigator should make every effort to contact the Sponsor prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant. If a participant's intervention assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and electronic case report form (eCRF), as applicable.

Local laboratory testing such as Ig concentrations, albumin:globulin ratio (often tested as part of routine liver function panel), or serum protein electrophoresis may reveal obvious reduction in the total globulin levels in participants receiving study intervention and could effectively unblind the participant. Performing such investigations is prohibited, unless this has been discussed with the Sponsor and such investigations have been deemed necessary for clinical management of the participant.

6.4 Study Intervention Compliance

Preparation of individual doses of study intervention will be verified by a second (unblinded) member of the study site pharmacy staff.

Participants will receive study intervention at the study center directly from the Investigator or designee under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and eCRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5 Concomitant Therapy

Any medication or vaccine (including over-the-counter and prescription medicines, vitamins, herbal supplements, fish oil, and NSAIDs) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with the following:

- Reason for use
- Dates of administration, including start and end dates
- Dosage information, including dose and frequency

The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1 Concomitant Therapy to be Avoided

Participants should avoid using drugs that are contraindicated in IgAN (eg, NSAIDs, aminoglycosides, co-trimoxazole) during the study, per local practice.

During conduct of the study, administration of systemic corticosteroids or other immunosuppressive therapy (for IgAN or other conditions) is prohibited due to the risk of over immune suppression due to overlapping actions of VIS649 and other immunosuppressive agents. If the Investigator believes that treatment with such therapy is required, and the potential benefits

outweigh the possible risks, the Medical Monitor must be notified, as continued dosing with study intervention may, in this circumstance, be discontinued.

6.6 Dosing Schedule Modification

Participants will be encouraged to follow the schedule of visits for their monthly infusions as close to the prescribed interval as possible. If under special circumstances, a participant is unable to visit the study center within 7 days of the scheduled infusion, they will still be able to receive the infusion within the next 7 days, and this will be recorded as a protocol deviation. However, if there is any further delay, that dose should be skipped, and the participant should receive subsequent doses as per the schedule. The participant will not receive additional doses to make up for the missed dose(s).

There will be no other alterations from the dosing schedule outlined in Section 6.1.

6.7 Intervention after the End of the Study

A rollover, open-label extension study will be offered to enable access to VIS649 (there will be no placebo arm) for study participants who have completed this trial, provided that the Investigator believes that the participants might benefit, and that the site has agreed to participate in the extension study. Further details will be provided in a separate protocol.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 Discontinuation of Study Intervention Dosing

Participants have the right to discontinue study intervention or withdraw from the study at any time for any reason. Participants may withdraw or be withdrawn from study-related procedures and intervention for the following reasons:

- Withdrawal of consent
- Adverse event
- Protocol deviation
- Investigator decision
- Pregnancy (Appendix 4)
- Sponsor decision to terminate the study
- Lost to follow-up

In particular, study intervention should be discontinued if participants experience the following:

- Grade ≥ 3 infusion reaction such as severe anaphylaxis or cytokine release syndrome
- At the discretion of the Investigator, study intervention may be stopped if the participant has an unexplained decline in eGFR of > 30% sustained over 3 months that is not reversed after correction of all reversible factors such as volume depletion, NSAID, ACEI/ARB, other nephrotoxic drug use, or resolution of acute illness or infection.

Adverse events that are ongoing at the EOS should be monitored until resolution, stabilization, until the event is otherwise explained, the participant is lost to follow-up, or 30 days after EOS. Serious AEs that are ongoing at the EOS should be monitored until resolution, stabilization, until the event is otherwise explained, the participant is lost to follow-up, or 30 days after EOS, whichever is longer (Section 8.3.1). If the participant withdraws because of an AE, every effort must be made to perform protocol-specified safety follow-up procedures.

If study intervention dosing is definitively discontinued, participants are encouraged to continue with assessments as per the schedule of assessments. At a minimum, if study participation is terminated by the participant or Investigator, the participant should complete all early termination assessments and will be encouraged to return for the EOS assessments outlined in Table 1. The primary reason for discontinuation should be recorded in the appropriate section of the eCRF.

7.1.1 Temporary Discontinuation

Study intervention may be interrupted for up to 2 doses in participants who experience the following:

- Severe or intractable infection
- Acute severe illness or injury requiring hospitalization

7.1.2 Rechallenge

VIS649 doses may be re-initiated (at the same dose) under the following conditions:

- If study intervention was interrupted due to acute illness or infection, study intervention can be re-initiated if the participant has recovered from the acute illness or infection, as determined by the Investigator.

7.2 Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study at any time at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.

At the time of discontinuing from the study, if possible, the participant should complete all early termination (ET) assessments outlined in Table 1. The participant will be encouraged to attend an EOS visit 155 days following the last dose of study intervention. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule. The site also should ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are outlined in Table 1. Protocol waivers or exemptions are not allowed.

Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the study design requirements is essential for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. A pathology report that confirms the IgAN diagnosis will be submitted with eCRFs.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy Assessments

8.1.1 Twenty-four-hour Urine Sample Collection

Twenty-four-hour urine collection for derivation of 24-hour urine volume, protein, albumin, creatinine, uPCR, and uACR will be performed at the time points outlined in Table 1.

Participants will discard the first morning void and begin a 24-hour urine collection the day prior to the clinic visit. Care should be taken to avoid over-collection or under-collection of urine, however, if this occurs, the sample may still be used to calculate the proteinuria and uPCR. On days of 24-hour urine collection (or the intended 24-hour urine collection), the uPCR sample will be collected from the 24-hour urine collection and routine urinalysis will be performed on a sample freshly voided during the clinic visit.

8.2 Safety Assessments

8.2.1 Physical Examinations

A complete physical examination, including assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems will be completed at the screening, at the Month 12/ET visit, and at the Month 16/EOS visit. In addition, physical examinations may be conducted at any other time if considered clinically indicated by the Investigator.

8.2.2 Vital Signs

Vital sign measurements will be performed at the visits outlined in Table 1 and will include weight, temperature, pulse rate, respiratory rate, and systolic and diastolic BP. Height will be measured and recorded during screening.

Vital signs measurements on dosing days will be recorded within 15 (±5) minutes prior to the start of the infusion, every 15 minutes until the infusion is complete, and postinfusion at 60 minutes and 2 hours.

Systolic and diastolic BP and pulse measurements will be assessed while the participant is seated or supine with a completely automated device. Manual techniques will be used only if an

automated device is not available. Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (no television, cell phone, etc).

Whenever possible, vital signs should be collected before blood collection for laboratory tests and before dosing with study intervention.

8.2.3 Electrocardiograms

A single 12-lead ECG, heart rate, and measures of PR, QRS, QT, and QTc intervals will be obtained at the screening visit. Twelve-lead ECGs should also be conducted at other times during the study if considered clinically indicated by the Investigator.

Twelve-lead ECGs should be conducted after 5 minutes in recumbence or semi-recumbency.

8.2.4 Clinical Safety Laboratory Assessments

Clinical laboratory evaluations for safety will be performed by a central laboratory whenever possible, however, local laboratory tests may be utilized for more urgent safety monitoring. Before starting the study, the Investigator will provide the Sponsor (or its designee) copies of all laboratory certifications and normal ranges for all laboratory assessments to be performed by that laboratory. Local laboratory assessments to make intervention-related decisions may be performed at all visits.

A list of clinical safety laboratory tests to be performed is provided in Appendix 2 and the timing for these assessments is provided in Table 1. All protocol-required laboratory assessments must be conducted in accordance with the laboratory manual. Details of laboratory tests to be conducted for assessment of VIS649 PK, PD, exploratory biomarkers, and immunogenicity are provided in Sections 8.5, 8.6, 8.8, and 8.9, respectively.

The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal, with the exception of disease defining abnormalities such as eGFR and proteinuria considered to be a part of the natural history of IgAN, during the study or within 30 days after the last dose of study intervention should be repeated until the values return to normal, baseline, or are no longer considered clinically significant by the Investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

8.3 Adverse Events and Serious Adverse Events

Adverse event and SAE definitions are provided in Appendix 3.

All AEs (serious and nonserious) reported by the participant must be recorded on the source documents and eCRF provided by the Sponsor. Medical terminology should be used for AE

reporting. Adverse events should be reported as a single unifying diagnosis whenever possible or, in the absence of a unifying diagnosis, as individual signs or symptoms.

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 7).

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

Adverse events that are ongoing at the EOS should be monitored until resolution, stabilization, until the event is otherwise explained, the participant is lost to follow-up, or 30 days after EOS. Serious AEs that are ongoing at the EOS should be monitored until resolution, stabilization, until the event is otherwise explained, the participant is lost to follow-up, or 30 days after EOS, whichever is longer (see Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF, not the AE section.

All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek information about AEs or SAEs after conclusion of study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences. For example, participants should be asked the nonleading question: “How have you felt since your last visit?”

Exacerbation or disease progression should be reported as an AE only if there are unusual or severe clinical features that were not present, or experienced earlier, or not expected based on the course of the condition.

In addition, the Sponsor must be notified immediately by telephone, fax, or e-mail of any immediately reportable events. Immediately reportable events (IRE) include the following:

- SAEs
- Pregnancies. Although normal pregnancy is not an AE, it will mandate study intervention discontinuation and must be reported on an IRE form and the Pregnancy Surveillance Form(s) to the Sponsor. Pregnancy will only be documented on the AE eCRF if there is

an abnormality or complication. This includes pregnancy of the participant or the participant's partner

Adverse event, start date, end date, seriousness, severity, relationship to study intervention, action taken with study treatment, and outcome will be recorded on the source documents and in the eCRF. Special attention should be paid to recording hospitalization and concomitant medications.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

Nonserious AEs that are identified at any time during the study must be recorded on the AE eCRF with the current status (ongoing or resolved/recovered) noted. All nonserious events (that are not IREs) that are ongoing at the last scheduled contact will be recorded as ongoing on the eCRF. For any AE having been identified throughout the study, additional relevant medical history information may be requested by the Sponsor during analysis to further ascertain causality (including, but not limited to, information such as risk-related behavior, family history, and occupation).

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be collected from the signing of the ICF until the EOS. Adverse events that are ongoing at the EOS should be monitored until resolution, stabilization, until the event is otherwise explained, the participant is lost to follow-up, or 30 days after EOS. Serious AEs that are ongoing at the EOS should be monitored until resolution, stabilization, until the event is otherwise explained, the participant is lost to follow-up, or 30 days after EOS, whichever is longer (see Section 1.3).

Resolution means that the participant has returned to the baseline state of health and stabilized means that the Investigator does not expect any further improvement or worsening of the participant's condition. The Investigator will continue to report any significant follow-up information to the Sponsor up to the point the event has resolved or stabilized, or the participant is lost to follow-up or has died.

Further information on follow-up procedures is provided in Appendix 3.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until 155 days after the last dose of study intervention.

If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.4 Treatment of Overdose

Standard symptomatic support measures should be used in the case of excessive pharmacological effects or overdose. No antidotes are available.

8.5 Pharmacokinetics

For all participants, serial blood samples will be drawn prior to each VIS649/placebo IV infusion and at the end of each infusion in order to determine circulating serum concentrations of VIS649, as specified in Table 1 and Table 5. Up to 60 participants (approximately 15 participants in each cohort) may have a more intensive PK and PD sampling schedule, as described in Table 5. Study participants who agree to participate in this more intensive PK and PD sample collection sub-study will sign an additional informed consent for this activity.

Instructions for the collection and handling of biological samples will be provided by the Sponsor in a separate laboratory manual. The actual date and time (24-hour clock time) of each sample will be recorded.

Samples collected for analyses of serum VIS649 concentrations may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Table 5: Pharmacokinetic and Serum Immunoglobulin Sampling Schedule

Time relative to infusion	Day 1			Day 3	Day 8	Day 18
	Pre infusion (-30 min)	Post infusion (±15 min)	2h (±15 min)	48h (±1 day)	168h (±1 day)	408h (±5 days)
Month 0	PK+Ig	PK only	***PK only***[2]	***PK + Ig***[2]	PK+Ig	PK+Ig
Month 1	PK+Ig	PK only				***PK+Ig***[2]
Month 2	PK+Ig	PK only				***PK+Ig***[2]
Month 3	PK+Ig	PK only				***PK+Ig***[2]
Months 4-10	PK+Ig	PK only				
Month 11	PK+Ig	PK only	***PK only***[2]	***PK + Ig***[2]	***PK+Ig***[2]	***PK+Ig***[2]
Month 12	PK+Ig[1]					***PK+Ig***[2]
Month 13	PK+Ig[1]					***PK+Ig***[2]
Month 14	PK+Ig[1]					***PK+Ig***[2]
Month 16	PK+Ig[1]					

Abbreviations: Ig = immunoglobulin; PK = pharmacokinetics.
Note: postinfusion times are relative to the end of infusion.
[1] No infusion on this date; therefore, only 1 sample to be obtained.
[2] Additional sample collections in the PK and pharmacodynamic sample collection substudy (these visits appear in bold italics).

8.6 Pharmacodynamics

Serial blood samples will be drawn in order to determine serum IgA, IgG, and IgM concentrations as well as the following analytes for exploratory PD endpoints: [redacted] Up to 60 participants (approximately 15 participants in each cohort) will have a more intensive total serum IgA/IgM/IgG sampling schedule, as described in Table 5. Study participants who agree to participate in this more intensive sample collection sub-study will sign an additional informed consent for this activity.

It is expected that VIS649 will result in obvious reductions in serum IgA and IgM, which, if visible to site and Sponsor staff at the participant level, would effectively unblind treatment assignment. Participant level unblinded Ig data will not be available for review by the site or Sponsor staff. Unblinded Ig data will be available to the DSMB as part of the scheduled and, if required, ad hoc safety reviews (see Section 9.6). Additional PK/PD summaries will be provided at an aggregate level in accordance with planned interim analyses (see Section 9.5).

8.7 Genetics

A DNA sample will be collected to evaluate host DNA genetic markers related to IgAN susceptibility loci, the APRIL/B-cell activating factor pathway, and/or immunity in consenting participants. Blood samples will be taken on Day 1 predose. Participation in genetics research is optional; a separate ICF must be completed. Samples may be stored in de-identified fashion for a maximum of 15 years (or according to local regulations) following the last participant's last study visit.

8.8 Biomarkers

Collection of samples for other biomarker research is also part of this study. Participation is optional; a separate ICF must be obtained. Participants who do not wish to participate in the biomarker research may still participate in the study. [redacted] Other samples collected through the course of this study may be utilized for biomarker research under this informed consent.

[redacted]

Samples may be stored in de-identified fashion for a maximum of 15 years (or according to local regulations) following the last participant's last visit to enable further analysis of biomarker responses.

8.9 Immunogenicity Assessments

Antibodies to VIS649 will be evaluated in serum samples collected from all participants at the visits outlined in Table 1. Additionally, serum samples should also be collected at the ET visit for participants who discontinued study intervention or were withdrawn from the study. These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to VIS649 and the titer of confirmed positive samples will be reported. Other analyses may be performed to evaluate the stability of antibodies to VIS649 and/or further characterize the immunogenicity of VIS649.

The detection and characterization of antibodies to VIS649 will be performed using a validated assay method by or under the supervision of the Sponsor. All samples collected for detection of antibodies to VIS649 will also be evaluated for VIS649 serum concentration to enable interpretation of the antibody data. Antibodies may be further characterized and/or evaluated for their ability to neutralize VIS649 activity. Samples may be stored for a maximum of 15 years (or according to local regulations) following the last participant's last visit at a facility selected by the Sponsor to enable further analysis of immune responses to VIS649. This analysis may be provided in a separate report.

8.10 Medical Resource Utilization and Health Economics

Not applicable.

9. STATISTICAL CONSIDERATIONS

9.1 Statistical Hypothesis

The primary efficacy objective of this study is to evaluate the effect of VIS649 on proteinuria. The hypothesis that there is a VIS649-related dose response in the change from baseline in natural log uPCR at Month 12 versus placebo will be formally tested.

9.2 Sample Size Determination

The sample size for this study was calculated assuming a linear dose response in reduction of uPCR in placebo and VIS649 2, 4, and 8 mg/kg dose levels of 0%, 15%, 30%, and 45%, respectively. Applying contrasts of -3, -1, 1, and 3 for the corresponding dose levels and analyzing uPCR on the natural log scale, the result is an expected mean change from baseline of 0, -0.163, -0.357, and -0.593 for placebo and VIS649 dose levels of 2, 4, and 8 mg/kg, respectively. Using an analysis of variance model with contrasts of -3, -1, 1, and 3 for the corresponding dose levels, a standard deviation of 0.87, 80% power, a 2-sided type I error rate of 0.05, and accounting for a dropout rate of ~ 20%, the required sample size is 36 participants per group, or 144 participants overall.

9.3 Populations for Analyses

Populations for analysis in this study are defined in Table 6.

Table 6: Populations for Analysis

Population	Description
ITT	All participants who are randomized. Participants will be categorized by the intervention and dose they were randomized to receive.
mITT	All randomized participants who receive at least 1 dose of study intervention. Participants will be categorized by the intervention and dose that they were randomized to receive.
Safety	All randomized participants who receive any amount of study intervention. Participants will be analyzed according to the intervention and dose they actually received.
PK/PD	All randomized participants who have at least 1 set of PK/PD measures taken.
Biomarker	All randomized participants who consented to participation in the biomarker substudy. A separate consent process is required, as described in Section 8.8.

Abbreviations: ITT = intent-to-treat; mITT = modified intent-to-treat; PD = pharmacodynamic(s); PK = pharmacokinetic(s).

Analysis of safety parameters will be performed on the Safety population. The modified intent-to-treat (mITT) population will be the primary population for assessment of efficacy. The PK/PD population will be the primary population for PK/PD summaries. Analysis of biomarker data will be performed on the Biomarker population.

9.4 Statistical Analyses

The statistical analysis plan (SAP) will be finalized prior to database lock and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.4.1 General Considerations

All data collected will be documented using summary tables, figures, and/or participant data listings presented by intervention and dose group. For continuous variables, descriptive statistics (number [n]; mean; geometric mean and coefficient of variation [%CV], as appropriate; median; standard deviation; minimum; and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. As appropriate, a 95% CI will be presented. Graphical displays may be presented.

9.4.2 Randomization and Stratification

Approximately 144 participants will be randomly assigned in a 1:1:1:1 ratio to study intervention or placebo, such that an estimated total of 36 participants are randomized per intervention group, with enrollment from approximately 90 global clinical sites in approximately 16 countries.

Randomization will be stratified first by region (Japan vs rest of world). A target of 12 or more participants are planned to be randomized at Japanese sites. Japanese participants will be randomized with equal allocation and without further stratification. Randomization for the rest of world will be stratified by screening uPCR ($\leq$ 2.0 g/g vs > 2.0 g/g).

9.4.3 Participant Disposition

A tabulation of the disposition of participants will be presented by intervention group, including the number of participants randomized, number of participants misrandomized, participant distribution for each stratification factor, number of participants treated, number of participants in each analysis population, reasons for study intervention discontinuation, and reasons for study discontinuation.

9.4.4 Participant Demographics

Demographic data based on the Safety population will be presented by intervention group and overall. Data to be tabulated will include sex, age, race, and ethnicity.

9.4.5 Efficacy Analysis

Efficacy analyses will be performed on the mITT analysis population. [redacted]

Additional detail for analysis methods will be described in the study SAP.

9.4.5.1 Primary Endpoint

The primary efficacy outcome for this study is the change from baseline in uPCR on the natural log scale at Month 12. Dose response will be assessed using orthogonal contrasts. Sensitivity analysis will be performed using dose as a continuous covariate.

In addition, to assess the dose response over time, a Mixed Model with Repeated Measurements (MMRM), which includes fixed class-effects of treatment (intervention), visit, randomization strata, and treatment-by-visit interaction, with a fixed effect covariate of baseline uPCR on the natural log scale will be used.

9.4.5.2 Secondary Endpoint(s)

Secondary efficacy endpoints will be summarized using descriptive statistics. In addition, comparisons between dose groups against placebo and between pooled dose groups against placebo will be performed using Analysis of Covariance or MMRM for continuous measures and logistic regression or generalized estimating equations for categorical variables.

Additional detail for analysis methods will be described in the SAP.

9.4.6 Safety Analyses

Safety will be assessed by evaluation of AEs (including hypersensitivity reaction and anaphylactic reaction), physical examinations, injection site tolerability (pain, irritation, and tissue damage), clinical laboratory assessments (including biochemistry, hematology, urinalysis, and pregnancy testing), laboratory testing (including serum Ig levels and ADAs), vital sign measurements, and use of concomitant medications.

9.4.7 Other Analyses

Analyses for PK, PK/PD, and ADA are described below. Additional detail on analysis of data, including analysis of other endpoints, will be described in the SAP.

9.4.7.1 Pharmacokinetic Analyses

VIS649 serum concentrations will be listed by participant and summary statistics, including arithmetic mean, geometric mean, standard deviation, %CV, median, and ranges, as appropriate, and will be presented by intervention group. Summary graphs of mean concentration-time profiles by intervention group and ADA status will also be presented.

For the subset of participants for whom intensive PK samples are collected, serum concentration data will be analyzed [redacted] and population PK methods [redacted], as implemented in NONMEM or equivalent software, will be used. Additional analyses and summaries may be generated, as appropriate.

Various techniques may be used to explore exposure-response [redacted] and the dependent variables [redacted]. These techniques may include graphical and statistical methods, including the creation of boxplots, spaghetti plots, histograms, and a variety of linear, nonlinear, or logistic regression techniques and time-to-event methods. If appropriate, continuous independent variables will be evaluated as such and as categorical variables with participants grouped by exposure categories. Additionally, population

PK/PD modeling and simulation may be utilized to measure the dynamic relationship between drug concentration, drug effect, and drug safety.

9.4.7.2 Antidrug Antibodies

Presence vs absence of anti-VIS649 antibodies, anti-VIS649 antibody titers (including neutralizing antibody titers, if available), will be summarized by intervention group and time point using descriptive statistics.

9.5 Interim Analyses

In addition to 5 DSMB safety reviews (Section 9.6), 3 interim PK/Ig analyses and 2 interim efficacy analyses (completed to inform future study design) are planned:

- The first PK/Ig analysis will be performed once ~25% of participants have been randomized and have completed 3 months of study dosing. All the PK/Ig assessments will be performed by a separate, unblinded team. Summarized results will be made available to the Sponsor to inform future study design.
- The second PK/Ig analysis will be performed once ~20 participants have been randomized and have completed 9 months of study dosing. This analysis will be used to update previously developed population PK/PD models. Summarized results will be made available to the Sponsor to inform future study design.
- The third PK/Ig analysis will be performed once ~50% of study participants have been randomized and have completed 6 months of study dosing and ~20 participants have completed 12 months of study dosing. Summarized results will be made available to the Sponsor to inform future study design.
- An early interim efficacy analysis may be performed when at least 16 participants have been treated for at least 6 months and at least 50% of the 16 (or more) participants have achieved a confirmed > 30% reduction in uPCR (as determined by 2 consecutive measurements) based on review of blinded uPCR data across all study participants. In the event that this condition is met and an interim analysis is triggered, group-unblinded efficacy summaries (with individual participant treatment blinded) will be prepared by a separate, unblinded team for Sponsor review to inform future study design.
- A second interim efficacy analysis will be performed at the time of the fourth scheduled DSMB meeting (once 50% of randomized participants have completed 6 months of study dosing and approximately 20 participants have completed 12 months of study dosing). Group-unblinded efficacy summaries (with individual participant treatment blinded) will be prepared for Sponsor review to inform future study design.
- The interim efficacy analyses will not include hypothesis testing and will be for the purpose of future study design and planning. The primary efficacy endpoint, change in proteinuria levels from baseline, will be analyzed. No modifications to this study protocol are planned based on results of the interim analyses. Nonetheless, to account for multiple reviews of the efficacy endpoint, the type I error rate applied at the end of the study will be reduced by 0.002 for each interim efficacy review, resulting in a 2-sided end-of-study type I error rate of 0.046.

Additional details will be provided in the SAP.

9.6 Data Safety Monitoring Board

An independent DSMB will review unblinded safety data. The DSMB will meet at 5 scheduled data review meetings and on an ad hoc basis as needed. Details regarding the content and scope of safety assessments, as well as the governing of the DSMB, will be described in a separate DSMB charter. Data safety monitoring board meetings will be scheduled as the requirements in Table 7 are met.

Table 7: Scheduled Data Safety Monitoring Board Reviews

Scheduled DSMB Review	Number of Participants and Treatment Exposure
DSMB review #1	The first scheduled meeting will occur after 12 participants have been randomized and have completed at least 3 months of study dosing.
DSMB review #2	The second scheduled meeting will occur after 24 participants have been randomized and have completed at least 3 months of study dosing.
DSMB review #3	The third scheduled meeting will occur after ~25% of participants have been randomized and have completed 3 months of study dosing.
DSMB review #4	The fourth scheduled meeting will occur after ~50% of participants have been randomized and have completed 6 months of study dosing, and ~20 participants have completed 12 months of study dosing.
DSMB review #5	The fifth scheduled meeting will occur after ~50% of participants have been randomized and have completed 12 months of study dosing.

Abbreviations: DSMB = data safety monitoring board.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 Appendix 1

Regulatory, Ethical, and Study Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial Disclosure

All required information regarding financial certification or disclosure will be provided to the Sponsor for all investigators and subinvestigators in accordance with the terms of the relevant regional regulation(s).

Informed consent will be freely obtained from all participants (or their guardian or legally acceptable representative, as applicable per local laws).

Each ICF will comply with ICH GCP: Consolidated Guideline E6[1] and local regulatory requirements. The Investigator will ensure that the Sponsor reviews and authorizes any written site-specific ICF used in the study before submission to the IRB/IEC.

Investigators may discuss study availability and the possibility for entry with a potential participant without first obtaining consent. However, informed consent must be obtained and documented before initiation of any procedures that are performed solely for the purpose of determining eligibility for this study, including withdrawal from current medication(s).

Potential participants are free to refuse entry into the study, or withdraw from the study at any time, without justification, and there will be no consequences to their further care.

A separate and similar consent process will be followed for the optional blood samples for pharmacogenomic testing and future biospecimen research. Consent must be obtained before the blood sample is collected.

10.1.3 Data Protection

All information generated in this study will be considered confidential and will not be disclosed to anyone not directly concerned with the study without the Sponsor's prior written permission. Participant confidentiality requirements of the region(s) where the study is conducted will be met. However, authorized regulatory officials and Sponsor personnel (or their representatives) may be allowed full access to inspect and copy the records, consistent with local requirements. All investigational medicinal products, participant bodily fluids, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by the Sponsor.

Participants will be identified only by unique participant ID in eCRF. If further participant identification is required, participants' full names may be made known to a regulatory agency or other authorized officials if necessary, subject to local regulations.

10.1.4 Dissemination of Clinical Study Data

This study will comply with the Clinical Trials Registration and Results Information Submission rule. As such, this study will be registered at ClinicalTrials.gov, and results information from this study will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals.

10.1.5 Data Quality Assurance

The accuracy and reliability of the study data will be assured by the selection of qualified Investigators and appropriate study centers, review of protocol procedures with the Investigator and associated personnel prior to the study, and periodic monitoring visits by the Sponsor or designee.

Written instructions will be provided for the collection, preparation, and shipment of samples.

The Sponsor or its designee will review the electronic data capture system for accuracy and completeness during (on-site) monitoring visits and after transmission to the Sponsor; any discrepancies will be resolved with the Investigator or designee, as appropriate. After uploading the data into the clinical study database, they will be verified for accuracy.

In accordance with Good Clinical Research Practice Guidelines and Recommendations, the Sponsor will be entitled to audit the facilities used in the clinical and laboratory parts of the study, as well as to access all the data files pertaining to the study. Similar procedures may also be conducted by agents of any regulatory body, either as part of a national GCP compliance

program or to review the results of this study in support of a regulatory submission. The Investigator should immediately notify the Sponsor if they have been contacted by a regulatory agency concerning an upcoming inspection.

10.1.6 Source Documents

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents will include but are not limited to medical records, electronic data, screening logs, and recorded data from automated instruments. All source documents pertaining to this study will be maintained by the Investigators and made available for direct inspection by authorized persons.

Investigator(s)/institution(s) will permit study-related monitoring, audits, [IRB/IEC] review, and regulatory inspection(s) by providing direct access to source data/documents by authorized persons as defined in the ICF. In all cases, participant confidentiality must be maintained in accordance with local regulatory requirements.

10.1.7 Study and Site Start and Closure

Study site participation may be discontinued if the Sponsor or its designee, the Investigator, or the ethical review board of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP. 10.3.2.

The study will be discontinued if the Sponsor or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.8 Publication Policy

The publication policy for the study will be documented in the agreement between the Sponsor and the Investigator. Authorship for any Visterra-sponsored publications resulting from the conduct of this study will be based on International Committee of Medical Journal Editors authorship criteria (http://www.icmje.org/recommendations). According to these guidelines, one may be considered an author only if the following criteria are met:

1. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
2. Drafting the work or revising it critically for important intellectual content; AND
3. Final approval of the version to be published; AND
4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors must meet the above criteria, and all who qualify for authorship based on the above criteria should be listed as authors.

10.2 Appendix 2

Clinical Laboratory Tests

Table 8 provides a list of laboratory tests to be evaluated by the Investigator.

The tests detailed in Table 8 will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF. Local lab results will not be acceptable for qualifying a participant for the study.

Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 8: Protocol-Required Safety Laboratory Assessments

Serology (screening only)	HBsAg, anti-HBc (IgG and IgM) antibody, anti-HCV antibody, HIV.
Hematology	Hemoglobin, RBC, WBC with differential (including absolute neutrophil count), platelet count.
Serum chemistry	Comprehensive serum analyte testing will include sodium, potassium, BUN, bicarbonate (venous), creatinine, calcium, chloride, magnesium, phosphorus, albumin, glucose, AST, ALT, ALP, total bilirubin (direct bilirubin if total > ULN), total cholesterol and triglycerides. This panel of tests will be collected as described in Table 1.
Urinalysis	Color and appearance; pH, specific gravity, ketones, protein, glucose, bilirubin, nitrite, urobilinogen, blood by dipstick.
Pregnancy (females only)	Serum β-hCG (screening only); urine β-hCG (all other visits).

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; β-hCG = β -human chorionic gonadotropin; eGFR = estimated glomerular filtration rate; HBc = hepatitis B core; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RBC = red blood cell; ULN = upper limit of normal; WBC = white blood cell.
Note: eGFR will be calculated from serum creatinine by the Chronic Kidney Disease Epidemiology Collaboration formula, which is as follows:
$eGFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018$ [if female] x 1.159 [if Black]
$\kappa = 0.7$ (females) or 0.9 (males), $\alpha = -0.329$ (females) or -0.411 (males), min = indicates the minimum of S_{Cr}/κ or 1, max = indicates the maximum of S_{Cr}/κ or 1. Additional adjustment for ethnicity or race may be incorporated as warranted.
Investigators must document their review of each laboratory safety report.

Laboratory results that could unblind the study (eg, Ig) will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.3 Appendix 3

Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of Adverse Event and Adverse Reaction

Adverse Event Definition
• An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • An AE would not include information recorded as medical history at screening for preplanned procedures for which the underlying condition was known and no worsening occurred. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. • Treatment-emergent AEs (TEAEs) are defined as AEs with an onset date on or after the start of study intervention. In more detail, TEAEs are all adverse events which started after start of study intervention; or if the event was continuous from baseline and was worsening, serious, study intervention-related, or resulted in death, discontinuation, interruption or reduction of study intervention dose. • A suspected adverse reaction is any AE for which there is a reasonable possibility that the study intervention caused the AE. For the purpose of Investigational New Drug safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the study intervention and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality.

Events Meeting the Adverse Event Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease). It is the Investigator's responsibility to review the results of laboratory tests for each individual participant as they become available. This review will be documented by the Investigator's dated signature on the laboratory report. The Investigator may repeat the laboratory test or request additional tests to verify the results of the original laboratory tests. • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Adverse Event Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): The condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of Serious Adverse Event

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event Is Defined as Any Untoward Medical Occurrence That, at Any Dose:
• **Results in death**
• **Is life-threatening** The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
• **Requires inpatient hospitalization or prolongation of existing hospitalization** In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization itself should not be reported as an SAE; whenever possible the reason for the hospitalization should be reported. Hospitalizations or prolonged hospitalizations for social admissions (ie, those required for reasons of convenience or other nonmedical need) are not considered SAEs. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
• **Results in persistent disability/incapacity** The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- **Is a congenital anomaly/birth defect**

- **Other situations:**
  Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3 Recording and Follow-Up of Adverse Event and/or Serious Adverse Event

Adverse Event and Serious Adverse Event Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is not acceptable for the Investigator to send photocopies of the participant's medical records in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. Assessment of causal relationship of an AE to the study intervention is defined as follows:

- **Related**: There is a reasonable possibility of a temporal and causal relationship between study intervention and the AE.

- **Not Related**: There is no temporal or causal relationship between study intervention and the AE.

The Investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The Investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products, in his/her assessment.

For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data.

The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of Adverse Events and Serious Adverse Events

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded in the originally completed eCRF.

The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of Serious Adverse Events

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form or to the Medical Monitor by telephone.
- Contact information for SAE reporting: emai[redacted]

10.4 Appendix 4
Contraceptive Guidance and Collection of Pregnancy Information

10.4.1 Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from site personnel review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
     - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2 Contraception Guidance

Women of childbearing potential must use highly effective methods of contraception for at least 28 days prior to first study intervention through 155 days after the last dose of study intervention. Highly effective methods of contraception are defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly, and include:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation:
    - oral
    - injectable
    - implantable
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal occlusion
- vasectomized partner; note: a vasectomized partner is a highly effective birth control method provided that the partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has received medical assessment of the surgical success
- sexual abstinence; sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant

Women of childbearing potential must also have a negative serum beta human chorionic gonadotropin (β-hCG) pregnancy test at screening and a negative urine β-hCG pregnancy test prior to the first study intervention on Day 1. Female participants must also agree not to donate eggs/bank eggs for the duration of their participation in the study.

Male participants and/or his partner must use an acceptable form of contraception (ie, double-barrier, have had a vasectomy, or have a female partner of nonchildbearing potential) from date of first study dose through 155 days after the last dose of study intervention. Following the first dose of study intervention, male participants must also agree to not donate sperm through 155 days after the last dose of study intervention.

10.4.3 Collection of Pregnancy Information

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's

pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at < 22 weeks gestational age) or still birth (occurring at > 22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

10.5 Appendix 5

Abbreviations

Abbreviation	Definition
ACEI	Angiotensin-converting enzyme inhibitor
ADA	Antidrug antibody
AE	Adverse event
a-g	Aberrantly glycosylated
APRIL	A proliferation inducing ligand
ARB	Angiotensin receptor blocker
β-hCG	Beta human chorionic gonadotropin
BCMA	B-cell maturation antigen
BP	Blood pressure
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
COPD	Chronic obstructive pulmonary disease
%CV	Coefficient of variation
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
eGFR	Estimated glomerular filtration rate
EOS	End-of-study
ESRD	End-stage renal disease
ET	Early termination
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HCV	Hepatitis C virus
HRT	Hormone-replacement therapy
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IgA/G/M	Immunoglobulin A/G/M
IgAN	Immunoglobulin A nephropathy

Abbreviation	Definition
IRB	Institutional Review Board
IRE	Immediately reportable event
IV	Intravenous
IVRS/IWRS	Interactive voice/web response system
MEST-C	Mesangial cellularity, Endocapillary proliferation, Segmental sclerosis, Tubular atrophy, Crescents
mITT	Modified intent-to-treat
MMRM	Mixed Model Repeated Measurement
NSAID	Nonsteroidal anti-inflammatory drug
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
RAAS	Renin-angiotensin-aldosterone system
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	Standard of care
TACI	Transmembrane activator and CAML interactor
Td	Tetanus and diphtheria
uPCR	Urine protein to creatinine ratio
WOCBP	Woman of childbearing potential

10.6 Appendix 6

Table 9: Protocol Revision History

Document	Date
Protocol Version 3.0	27 January 2020
Protocol Version 2.0	26 November 2019
Protocol Version 1.0	28 August 2019

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