1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis

Vertex Study Number: VX19-147-101

IND Number: [redacted]

EudraCT Number: 2020-000185-42

Date of Protocol: 05 March 2020 (Version 2.0)

Replaces Version 1.0 (dated 10 October 2019)

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862, USA

Summary of Changes to the Protocol

The previous version of this protocol (Version 1.0, dated 10 October 2019) was amended to create the current version (Version 2.0, dated 05 March 2020).

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 10 October 2019	Original version
Version 2.0, 05 March 2020	Current version

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Modified the upper threshold of the inclusion criterion for estimated glomerular filtration rate from ≥30 mL/min/1.73 m^2 to ≥45 mL/min/1.73 m^2 to include subjects with less severe kidney disease.	Sections 2 and 8.1
Removed the requirement for kidney biopsy to be done within 18 months before screening. This timeframe was intended to ensure preserved renal function, which is no longer needed because the eligible eGFR was increased to ≥45 mL/min/1.73 m^2.	Section 8.1
Specified the doses to be used are 15 mg once daily (qd) (Treatment Period 1) and 45 mg qd (Treatment Period 2).	Sections 2, 9.1, 9.1.2.1, 9.3.1, 9.3.3, 9.6, and 10.3
Added an optional cohort of subjects (Cohort 2) who represent a broader population of FSGS patients than the population in version 1.0. Enrollment of Cohort 1 will be prioritized over enrollment of Cohort 2.	Sections 2, 3, 8, 9.1, 9.1.2.1, and 12
The FSGS Patient-reported Outcome (PRO) assessment and endpoint were removed because the PRO form is not available to the sponsor.	Sections 2, 7, 9.3, 9.3.4, 11.5, and 12.3.5; Table 3-2
The visit names for Part B were modified to reflect the time of the visit relative to the last dose of study drug.	Table 3-3
The Part B requirement to collect a confirmatory UPCR sample after the level returns to baseline was removed because Part B is optional and the requirement is an unnecessary burden for subjects.	Table 3-3
The blood pharmacokinetic (PK) sample was removed from the Safety Follow-up Visit (28 days after the last dose of study drug) because it is not needed for analysis.	Table 3-3
Clarified that the Postdose PK Sampling Visit is not required for subjects who complete an ETT Visit.	Table 3-3
The visit window for the Part A Week 13 Visit was changed from ± 2 days to -2 days to ensure that the efficacy samples for the primary endpoint are collected while the subject is on treatment.	Table 3-2
Added 1 additional UPCR sample during Week 9 (for a total of 2 samples) to provide a more accurate measurement at this timepoint.	Table 3-2; Sections 11.3 and 11.6.2
Clarified the timing of visit windows.	Table 3-2 and Table 3-3
Clarified in several sections that Part B is optional.	Sections 2 and 9.1
Short form-36 (SF-36) was added at the Safety Follow-up Visit and as an exploratory endpoint for Part B to assess the sensitivity of this tool to changes in treatment (i.e., baseline, during treatment, and off treatment).	Table 3-3; Sections 2 and 7.2
Added a visit window for the Treatment Period Day 15 Visit of ±2 days to allow flexibility in visit scheduling.	Table 3-2

Change and Rationale	Affected Sections
Modified the requirement for the 3 urine samples collected during screening and Week 13 to be collected on separate days within a 7-day period, instead of requiring at least 1 day between 3 separate collections. This will allow additional operational flexibility without changing the intent of the assessment. The corresponding eligibility criteria were also updated.	Table 3-1 and Table 3-2; Sections 8.1, 9.3.4.1, 11.3, 11.6.2, and 12.3.3
Urine PK was removed from the secondary endpoints because urine PK will not be collected.	Sections 2 and 7
Added rationale for the study duration and dose based on clinical and nonclinical data.	Sections 5 and 9.3
Added an additional exclusion criterion: "Hypersensitivity to investigational medicinal product or to any of its excipients".	Section 8.2
Added exclusion of hemoglobin <10 g/dL to exclude subjects with clinically significant anemia.	Section 8.2
Lowered the eligible blood pressure threshold from 180/110 to 160/100. Requiring subjects to have better controlled blood pressure reduces the likelihood of changes to blood pressure medications during the study that could confound the study results.	Section 8.2
Revised the heading of "Eligibility Adjudication" to "Eligibility Review" to more accurately reflect the process.	Sections 8.1 and 9.3.6
Specified that subjects who discontinue study drug before completing Part A will not complete further Part A Visits. These subjects will not continue to Part B.	Table 3-2; Sections 2 and 9.1.2.3
Removed the option to participate in Part B for subjects who have proteinuria levels in Part A that are at or greater than baseline before the end of Part A. These subjects cannot be followed for return to baseline Part B, because they have already reached that status.	Section 9.1.3
Added neprilysin inhibitor, sodium-glucose co-transporter-2 inhibitor, and corticosteroids (applies to Cohort 2 only) as additional medications that are commonly used in this population and that should not be planned for stopping, starting, or having dosing changes during study participation.	Sections 8.1 and 9.4
Based on Institutional Review Board feedback, guidance was added for concomitant medication use if it becomes clinically necessary to alter a subject's antihypertensive regimen during the study. Changes to an antihypertensive medication dose or addition of a new antihypertensive medication are recommended before changes are made to any angiotensin converting enzyme inhibitor, angiotensin receptor blocker, neprilysin inhibitor, or renin inhibitor.	Section 9.4
Removed the study restriction for concomitant use of sensitive CYP3A substrates, based on Study VX18-147-001 data showing that VX-147 45 mg q24h does not result in clinically meaningful CYP3A inhibition or induction.	Section 9.5
Reduced the restriction for corticosteroid use before the first dose of investigational product from 12 weeks to 4 weeks, because this is a sufficient washout period for corticosteroid effects on proteinuria.	Section 9.5
Specified that, if local regulations or site practice do not allow telemedicine, all visits will be conducted at the site.	Section 9.3.5
Added rituximab to the list of restricted medications because this medication is used for FSGS treatment and concomitant or recent use could affect interpretation of the results of this study.	Section 9.5
Removed the requirement to fast before and after dosing, based on data from Study VX18-147-001 showing no food effect.	Section 9.6
Added blood smears to the safety laboratory panel to more completely assess hematology.	Table 11-2

Change and Rationale	Affected Sections
Added instructions for the investigator to deliver the *APOL1* genotype result to the subject. Vertex will ensure the subject can obtain the services of a genetic counselor, if desired. Sites will be responsible for managing the corresponding logistics.	Section 11.4
Removed electronic consent as an option, because this method will not be used.	Section 8.1, 11.6.5.2, and 13.1.1.1; Table 3-1, Table 3-2, and Table 3-3
Streamlined statistical analysis section as details will be included in a separate statistical analysis plan.	Section 12
Added the option for interim analysis to support program planning.	Section 12.3.6
Updated the table for reporting of AE severity to match the table in Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.	Section 13.1.1.4
Specified that the lipid profile will only be measured at the Day 1, Week 3, Week 13, ETT, and Safety Follow-up Visits because these are visits that require overnight fasting before the serum chemistry blood draw and will provide a more robust assessment of safety compared to non-fasted samples.	Table 11-2
Specified that the baseline value used to determine when a subject in Part B has returned to baseline will be the average of the 2 screening values used to determine eligibility.	Section 9.1.3; Table 3-3

Typographical and administrative changes were also made to improve the clarity of the document.

2 PROTOCOL SYNOPSIS

Title A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis

Brief Title Phase 2a Study of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis

Clinical Phase and Clinical Study Type Phase 2a pharmacodynamics (PD), safety, and pharmacokinetics (PK)

Objectives

Part A (Treatment Period)

Primary

- To evaluate the ability of VX-147 to reduce proteinuria

Secondary

- To evaluate the safety and tolerability of VX-147
- To characterize the PK of VX-147

Part B (Optional Off-treatment Follow-up Period)

Exploratory

- To evaluate the change in proteinuria after stopping administration of VX-147

Endpoints

Part A (Treatment Period)

Primary

- Percent change from baseline in urine protein to creatinine ratio (UPCR) at Week 13

Secondary

- Safety and tolerability based on adverse events (AEs), clinical laboratory values (i.e., hematology, serum chemistry, urinalysis, coagulation studies), standard 12-lead ECGs, and vital signs
- Plasma PK of VX-147

Exploratory

- Percent change from baseline in UPCR over time during the Treatment Period
- Percent change from baseline in urine albumin-to-creatinine ratio (UACR) at Week 13
- Percent change from baseline in UACR over time during the Treatment Period
- Change from baseline in patient-reported outcome (PRO) Short Form Health Survey 36 (SF-36) over time during the Treatment Period

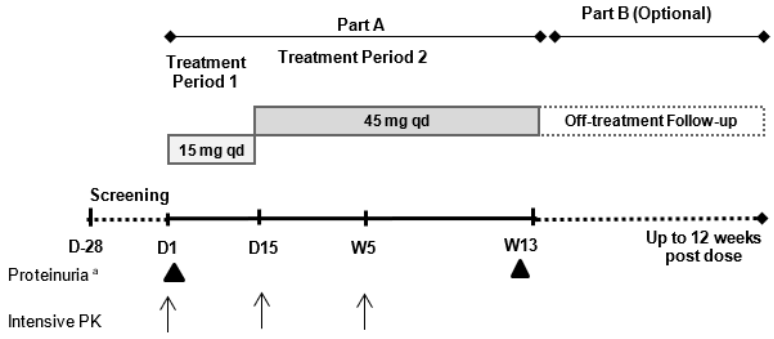
Part B (Optional Off-treatment Follow-up Period)

Exploratory

- Percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period
- Change from baseline in SF-36 over time during the Off-treatment Follow-up Period

Number of Subjects	Approximately 10 subjects in Cohort 1 and approximately 10 subjects in optional Cohort 2
Study Population	Male and female subjects 18 to 60 years old with 2 apolipoprotein L1 (*APOL1*) risk alleles (*G1/G1*, *G1/G2*, or *G2/G2* genotype) who have APOL1-mediated focal segmental glomerulosclerosis (FSGS), UPCR ≥3 g/g and < 10 g/g (Cohort 1) or ≥ 2 g/g and < 10 g/g (Cohort 2), and estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2
Investigational Drug	Active substance: VX-147 Activity: APOL1-inhibitor Strength and route of administration: 15 mg tablets for oral administration
Study Duration	Excluding the Screening Period, each subject will participate in the study for approximately 13 weeks of treatment in Part A. Subjects may choose to participate in an off-treatment observation for up to 12 weeks in Part B (optional). All subjects will complete a Safety Follow-up Visit (SFUV) at 28 (± 7) days after the last dose of study drug.
Study Design	This is a single-arm, open-label, 2-part study. In Part A, subjects will receive VX-147 at a dosage of 15 mg qd for 2 weeks and VX-147 at a dosage of 45 mg qd for 11 weeks. Part A will be enrolled in 2 cohorts: Cohort 1 and an optional Cohort 2. Cohort 1 includes approximately 10 subjects with UPCR ≥3 g/g and <10 g/g who are not taking systemic corticosteroid or other immunosuppressants. Cohort 2 includes approximately 10 subjects with UPCR ≥2 g/g and <10 g/g, and these subjects are permitted to take a stable low dose of systemic corticosteroid. Enrollment of Cohort 1 will be prioritized over enrollment of Cohort 2; this will be managed through the interactive web response system (IWRS). Each site will be required to enroll a subject in Cohort 1 before the same site can enroll in Cohort 2. After completing Part A, subjects will be followed for up to 12 weeks in Part B (optional) for evaluation of proteinuria off treatment if they consent to do so. If a subject prematurely discontinues study drug in Part A, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. After completing the ETT Visit, subjects will not complete further Part A Visits; these subjects will come in for a SFUV and will not continue to Part B. All subjects are required to complete a SFUV at 28 (± 7) days after the last dose of study drug. The SFUV may occur while a subject is participating in Part B.

Figure 2-1 VX19-147-101 Study Design



D: Day; PK: pharmacokinetics; qd: once daily; UPCR: urine protein to creatinine ratio; W: Week

Notes: The figure is not drawn to scale. After completing Part A, subjects will be followed monthly for up to 12 weeks or until UPCR returns to baseline, whichever occurs first. All subjects will be required to complete a SFUV at 28 (± 7) days after the last dose of study drug.

[a] Proteinuria will be assessed at multiple timepoints throughout the Treatment Period and Off-treatment Follow-up. Triangles represent timepoints for the primary analysis.

Assessments

Efficacy: UPCR

Safety: AEs; clinical laboratory assessments; ECGs; vital signs; and physical examinations

PK: VX-147 plasma concentrations

Exploratory: UACR, SF-36, biomarker blood and urine samples

Statistical Analyses

Efficacy

Analyses will be done separately for Cohort 1 and Cohort 2. The primary endpoint is percent change from baseline in UPCR at Week 13. In all analyses of UPCR related data, the Week 13 UPCR value will be calculated as the average of the available UPCR measurements (maximum 3) taken during Week 13, and the baseline value will be the average of the 3 UPCR values from the urine samples collected for this purpose during screening.

The percent change from baseline in UPCR at Week 13 will be analyzed by first log-transforming the UPCR data before analyses to reduce skewness, and calculating the change from baseline in log-transformed values. The geometric mean percent change (GMPC) from baseline in UPCR will be estimated along with the corresponding 2-sided 80% CI. The GMPC from baseline and associated confidence limits will be calculated by back-transforming the estimated simple mean of change from baseline in log-transformed data.

Safety

The safety analyses will be descriptive only.

Pharmacokinetics

Noncompartmental analyses will be performed, and summary statistics will be provided for VX-147 PK parameters. Additional analysis including population PK modeling will be performed to further characterize the PK and exposure-response relationships.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments for Cohort 1 and Cohort 2 are in Table 3-1 through Table 3-3. All visits will be scheduled relative to the Day 1 Visit.

Subjects may choose to complete all screening assessments within the 28-day Screening Period or they may choose a 2-step screening process and first complete only the *APOL1* genotype assessment at any time before Day -1 (including before Day -28), followed by the rest of the screening assessments during the 28-day Screening Period. The informed consent form (ICF) will outline the screening options. Additional information is provided in Section 9.1.1. Informed consent must be completed before any assessments are done at the Screening Visit. The SF-36 must be completed before any other assessment when they are required. Other assessments may be performed in any order when more than 1 assessment is required at a particular time point, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise.

Table 3-1 Study VX19-147-101: Screening

Event/Assessment	Optional Genotype Screening Visit (Before Day -1)	Screening Period (Day -28 to Day -1)	Comments
Subject visit		X	Activities may be performed by a home health visit or in the clinic, unless otherwise noted (Section 9.3.5). The complete physical exam must be done in a clinic (Section 11.6.3).
Informed consent	X	X	
Demographics		X	
Medical history		X	
Medications review		X	Section 9.4
Standard 12-lead ECG		X	To be performed in triplicate after the subject has been supine for at least 5 minutes. When ECGs, vital signs, and blood draws coincide, they should be performed in said order. (Section 11.6.4).
Vital signs		X	Vital signs will be collected after the subject has rested for at least 5 minutes. Blood pressure must be collected in triplicate. (Section 11.6.3).
Height and weight		X	Weight and height will be measured with shoes off with light weight clothing (no outerwear). BMI will be calculated using height and weight (Section 11.1).
Complete physical examination		X	Cannot be done by home health nurse and must be done in a clinic (Section 11.6.3).
Serum FSH (suspected postmenopausal female subjects only)		X	A blood sample will be collected (Section 11.6.2).
Serum β-hCG (all female subjects)		X	A blood sample will be collected (Section 11.6.2).
Serum chemistry		X	A blood sample will be collected (Section 11.6.2).

Table 3-1 Study VX19-147-101: Screening

Event/Assessment	Optional Genotype Screening Visit (Before Day -1)	Screening Period (Day -28 to Day -1)	Comments
Hematology		X	A blood sample will be collected (Section 11.6.2).
Coagulation		X	A blood sample will be collected (Section 11.6.2).
Serology (HIV-1 and HIV-2 Antibodies)		X	A blood sample will be collected (Section 11.6.2).
Hepatitis B surface antigen		X	A blood sample will be collected (Section 11.6.2).
HCV nucleic acid test		X	A blood sample will be collected (Section 11.6.2).
Confirmation of *APOL1* genotype	X	X	A genotyping sample will be collected if a result is not available using a Vertex-approved clinical study assay (Section 9.1.1).
Urine sample		X (3 samples)	Collected after signing the informed consent for use in efficacy, biomarker, and safety analyses (Sections 11.3 and 11.6.2). The first morning void will be collected for 3 independent samples, which are collected on 3 separate days within a 7-day period. The third sample must be collected by Day -5 to allow confirmation that UPCR values meet eligibility criteria (Section 8.1).
Adverse events		Continuous from signing of ICF through SFUV	For subjects undergoing a 2-step screening process, AEs will not be collected during the time between a subject undergoing genotype screening and the start of the Screening Visit. Additional information about AE reporting is provided in Section 11.6.1.

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Subject visit	X	X	X	X	X	X	X	X	All visits may be performed by a home health visit or in the clinic at the discretion of the investigator (Section 9.3.5). All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window.
SF-36	X				X		X	X	To be completed before all other study assessments (Section 11.5.4).
Standard 12-lead ECG	X	X	X	X	X	X	X	X	Complete predose after SF-36 and before other assessments. The subject should be supine for at least 5 minutes before the start of ECG. When ECGs, vital signs, and blood draws coincide, they should be performed in said order. On Day 1 and Day 15, an ECG (Section 11.6.4) will also be collected 2 (± 1) hours postdose.
Vital signs	X	X	X	X	X	X	X	X	Complete before the assessments listed in rows below. The subject should rest for at least 5 minutes before the start of vital sign collection and they should be seated during the assessment (Section 11.6.3).
Weight	X	X	X	X	X	X	X	X	Weight will be measured with shoes off and light weight clothing (no outerwear) (Section 11.1).

[a] All assessments will be performed before dosing unless noted otherwise.

[b] If the subject prematurely discontinues study treatment during the Treatment Period, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the SFUV, and a separate SFUV will not be required. After the ETT Visit, subjects will not complete further Part A Visits; these subjects will not continue to Part B (Table 3-3).

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Abbreviated Physical examination	X	X	X	X	X	X	X	X	In addition to the scheduled visits, symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.6.3).
Serum chemistry	X Fasted	X	X	X Fasted	X	X	X Fasted	X Fasted	A blood sample will be collected predose after an overnight fast on indicated days. All other days do not require fasting. (Section 11.6.2).
Hematology	X	X	X	X	X	X	X	X	A blood sample will be collected (Section 11.6.2).
Coagulation	X	X	X	X	X	X	X	X	A blood sample will be collected (Section 11.6.2).
RNA sample	X	X	X	X	X	X	X	X	A blood sample will be collected for use in exploratory biomarker analysis (Section 11.5.3).
Optional DNA sample	X								This optional sample will be collected for use in exploratory biomarker analysis (Section 11.5.3).
Biomarker blood sample	X	X	X	X	X	X	X	X	Section 11.5.1.
VX-147 PK blood sample	intensive	predose	intensive	predose	intensive	predose	X	X	A blood sample will be collected (Section 11.2.1). **Intensive PK sampling** *Day 1, Day 15, Week 5*: predose (within 60 min before dosing) and 0.25, 0.5, 1, 2, 4 and 12 hours postdose **Post treatment samples (Week 13 and ETT):** A single sample collected anytime during the Visit.

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Urine sample	X[c]	X	X	X	X	X (3 samples)	X (3 samples)	X	The first morning urine void (predose) will be collected and used for efficacy, safety, and biomarker analyses (Sections 11.3 and 11.6.2). During Week 9 and Week 13, 3 samples will be collected on 3 separate days within a 7-day period. If the subject forgets to collect the first morning void on the day of the visit, they may provide this sample predose on a different day within the visit window.
β-hCG (urine)	X				X	X	X	X	All female subjects of childbearing potential (Sections 11.6.2 and 11.6.5). This can be collected in the same sample as the urine sample for efficacy, safety, and biomarker analysis.
VX-147 dosing	X								The last dose of Treatment Period 1 will be Day 14. The first dose of Treatment Period 2 will be on Day 15 after all predose assessments are completed. The last day of dosing will occur the day before the Week 13 visit. The first dose in each period must be administered under the supervision of site medical staff or a home health nurse. Subjects will be monitored for 4 hours after receiving the first dose of each Treatment Period. (Section 9.6).
Adverse events	Continuous from signing of ICF through SFUV								Section 11.6.1.
Medications review	Continuous from signing of ICF through SFUV								Section 9.4

[c] Day 1 urinalysis will be for safety and biomarker assessments. Efficacy assessments will not be done.

Table 3-3 Study VX19-147-101: Postdose PK Sampling, Safety Follow-up Visit, and Part B Off-treatment Follow-up Period

Event/Assessment	Postdose PK Sampling (Approximately 48 hours after the last dose of study drug)[a]	SFUV 28 (± 7) Days After Last Dose of Study Drug[b]	Part B: Optional Off-treatment Follow-up Visits [c] (Part B Week 4[b], 8, and 12)	Comments
Subject visit	X	X	X (until UPCR returns to the baseline level)[d]	The visit may be performed by a home health visit or in the clinic at the discretion of the investigator (Section 9.3.5). For each visit, at least 1 interaction with the subject and investigator will occur by phone, video, or in the clinic (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window.
SF-36		X		To be completed before all other study assessments (Section 11.5.4).
Standard 12-lead ECG		X		Complete after SF-36 and before other assessments after subject has been supine for at least 5 minutes. ECGs (Section 11.6.4), vital signs, and blood draws should be performed in said order.
Vital signs		X		Complete before other assessments listed below after subject has been at rest for at least 5 minutes; they should be seated during the assessment (Section 11.6.3).

[a] The postdose PK sampling visit is required for all subjects, with the exception of those who complete an ETT Visit.
[b] The SFUV and Part B Week 4 Off-treatment Follow-up Visit may occur on the same day, provided the visit windows are met for both visits.
[c] Visit windows for Part B are as follows: Week 4 Visit (Day 120 ± 2 weeks), Week 8 Visit (Day 148 ± 2 weeks), Week 12 Visit (Day 176 ± 2 weeks).
[d] For the purpose of this assessment, baseline UPCR is defined as the average of the last 3 screening assessments ± 10%. If a subject has not achieved ≥90% of baseline UPCR by the Part B Week 12 Visit, the Part B Week 12 Visit will be the last study visit.

Table 3-3 Study VX19-147-101: Postdose PK Sampling, Safety Follow-up Visit, and Part B Off-treatment Follow-up Period

Event/Assessment	Postdose PK Sampling (Approximately 48 hours after the last dose of study drug)[a]	SFUV 28 (± 7) Days After Last Dose of Study Drug[b]	Part B: Optional Off-treatment Follow-up Visits [c] (Part B Week 4[b], 8, and 12)	Comments
Weight		X		Weight will be measured with shoes off and light weight closing (no outerwear). (Section 11.1).
Abbreviated physical examination		X		In addition to the scheduled visits, symptom-targeted physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.6.3).
Serum chemistry		X Fasted		A blood sample will be collected following an overnight fast (Section 11.6.2).
Hematology		X		A blood sample will be collected (Section 11.6.2)
Coagulation		X		A blood sample will be collected (Section 11.6.2)
VX-147 PK Sampling	X			A blood sample will be collected (Section 11.2.1).
Urine sample		X	X	The first morning urine void will be collected and used for efficacy, safety, and biomarker analyses (Sections 11.3 and 11.6.2).
β-hCG (urine)		X		All female subjects of childbearing potential (Section 11.6.2). This can be collected in the same sample as the other urine sample.
Adverse events	Continuous from signing of ICF through SFUV		NA	Section 11.6.1
Medications review	Continuous from signing of ICF through SFUV		NA	Section 9.4

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
ACE	angiotensin converting enzyme
ADL	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine transaminase
APOL1	apolipoprotein L1
ARB	angiotensin receptor blocker
AST	aspartate transaminase
AUC_{τ}	AUC during a dosing interval
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
bpm	beats per minute
CAKUT	congenital anomaly of the kidney or urinary tract
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration
CYP	cytochrome P450
DNA	deoxyribonucleic acid
ECG	electrocardiogram
EDC	electronic data capture
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
ETT	Early Termination of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FSGS	focal segmental glomerulosclerosis
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMPC	Geometric Mean Percent Change
GPS	Global Patient Safety
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HIV-2	human immunodeficiency virus-2
HR	heart rate

Abbreviation	Definition
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IWRS	interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
PC	publication committee
PD	pharmacodynamics
PE	physical examination
PK	pharmacokinetic, pharmacokinetics
PR	PR interval, segment
PRO	patient-reported outcome
PT	Preferred Term
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTcF	QT interval corrected by Fridericia's formula
RNA	ribonucleic acid
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SF-36	Short Form Health Survey 36
SI	SI units (International System of Units)
SOC	System Organ Class
SRA	serum resistant associated-protein
SUSARs	suspected, unexpected, serious adverse reactions
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal
UPCR	urine protein to creatinine ratio
V_{ss}/F	apparent volume of distribution at steady-state
WHO-DD	World Health Organization-Drug Dictionary

5 INTRODUCTION

Focal segmental glomerulosclerosis (FSGS) is a rare kidney disease with an estimated global incidence of 0.2 to 1.1/100,000/year.[1] FSGS is caused by damage to podocytes, which are part of the glomerular filtration barrier, resulting in proteinuria.[2] Patients with nephrotic-range proteinuria (i.e., protein to creatinine ratio >3 g/g) are at a higher risk of developing end-stage kidney disease (ESKD) and developing proteinuria-related complications, such as infections or thromboembolic events. There is no well-standardized treatment regimen for FSGS. Current therapeutic options for patients with FSGS who have nephrotic-range proteinuria include high-dose corticosteroids, which induce remission of proteinuria in a minority of patients.[2]

FSGS can be divided into different subgroups based on the underlying etiology. One homogeneous subgroup of FSGS is characterized by the presence of 2 independent common sequence variants in the apolipoprotein L1 (*APOL1*) gene termed *G1* and *G2*, which are referred to as the "*APOL1* risk alleles." *G1* encodes a correlated pair of non-synonymous amino acid changes (S342G and I384M), *G2* encodes a 2 amino acid deletion (N388del:Y389del) near the C-terminus of the protein, and *G0* is the ancestral (low risk) allele.[3,4]

The *APOL1* gene is expressed in multiple organs in humans, including the liver and kidney.[5,6] The biologic function of APOL1 is to protect against parasitic infection (*Trypanosoma brucei brucei [T. b. brucei])*.[7] APOL1 is endocytosed by *T. b. brucei* and transported to lysosomes, where it inserts into the lysosomal membrane and forms pores that lead to parasite swelling and death.[8] While the ability to lyse *T. b. brucei* is shared by all 3 *APOL1* variants (*G0*, *G1*, and *G2*), *APOL1 G1* and *G2* variants confer additional protection against parasite species that have evolved a serum resistant associated-protein (SRA) which inhibits *APOL1 G0*; these species cause sleeping sickness. *G1* and *G2* variants evade inhibition by SRA and *G1* confers additional protection against *T. b. gambiense* (which causes West African sleeping sickness), and *G2* confers additional protection against *T. b. rhodesiense* (which causes East African sleeping sickness).[9]

In the kidney, APOL1 is expressed in podocytes, endothelial cells (including glomerular endothelial cells), and some tubular cells.[6, 10] Podocyte-specific expression of *APOL1 G1* or *G2* (but not *G0*) in transgenic mice induces structural and functional changes, including albuminuria, decreased kidney function, podocyte abnormalities, and glomerulosclerosis.[11] Consistent with these data, *G1* and *G2* variants of *APOL1* play a causative role in inducing FSGS and accelerating its progression in humans. Individuals with 2 *APOL1* risk alleles (i.e., homozygous or compound heterozygous for the *APOL1 G1* or *APOL1 G2* alleles) have increased risk of developing FSGS with an odds ratio of 10 to 17, and they are at risk for rapid decline in kidney function if they develop FSGS.[3, 4, 12] Thus, inhibition of APOL1 could have a positive impact in individuals who harbor 2 *APOL1* risk alleles.

VX-147 is a small molecule that inhibits APOL1-induced cell death and inhibits the biological function of APOL1, i.e., APOL1-induced lysis of *T. b. brucei*. These nonclinical data suggest that VX-147 has the potential to reduce proteinuria and reverse APOL1-induced podocyte lesions in patients with APOL1-mediated FSGS. Therefore, VX-147 is being developed to treat individuals with FSGS who also have 2 *APOL1* risk alleles and nephrotic-range proteinuria.

This study is a Phase 2a proof-of-concept study designed to assess the efficacy effects, safety, and pharmacokinetics (PK) of VX-147 in subjects with APOL1-mediated FSGS.

Additional information about the first-in-human (FIH) study (VX18-147-001; Study 001) and nonclinical studies is available in the Investigator's Brochure.

6 STUDY OBJECTIVES

6.1 Part A (Treatment Period)

6.1.1 Primary Objective

- To evaluate the ability of VX-147 to reduce proteinuria

6.1.2 Secondary Objectives

- To evaluate the safety and tolerability of VX-147
- To characterize the PK of VX-147

6.2 Part B

6.2.1 Exploratory Objective

- To evaluate the change proteinuria after stopping administration of VX-147

7 STUDY ENDPOINTS

7.1 Part A

7.1.1 Primary Endpoints

- Percent change from baseline in urine protein to creatinine ratio (UPCR) at Week 13

7.1.2 Secondary Endpoints

- Safety and tolerability based on adverse events (AEs), clinical laboratory values (i.e., hematology, serum chemistry, urinalysis, coagulation studies), standard 12-lead ECGs, and vital signs
- Plasma PK of VX-147

7.1.3 Exploratory Endpoints

- Percent change from baseline in UPCR over time during the Treatment Period
- Percent change from baseline in urine albumin to creatinine ratio (UACR) at Week 13
- Percent change from baseline in UACR over time during the Treatment Period
- Change from baseline in patient-reported outcome (PRO) Short Form Health Survey 36 (SF-36) over time during the treatment period

7.2 Part B (Optional Off-treatment Follow-up Period)

7.2.1 Exploratory Endpoints

- Percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period
- Change from baseline in SF-36 over time during the Off-treatment Follow-up Period

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible.

8.1 Inclusion Criteria

The following criteria are applicable for Cohort 1 and Cohort 2:

1. Willing to sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions (Section 9.5), laboratory tests, contraceptive guidelines (Section 11.6.5), and other study procedures.
3. An *APOL1* genotype of *G1/G1, G2/G2,* or *G1/G2* obtained with a Vertex-approved clinical study assay.
4. Between the ages of 18 and 60 years, inclusive.
5. Body mass index (BMI) of 18.0 to 40.0 kg/m^2, inclusive, and a total body weight >50 kg.
6. FSGS diagnosed by kidney biopsy, with the exception of the tip variant, as confirmed through the eligibility review process.
7. Estimated glomerular filtration rate (eGFR) ≥45 mL/min/1.73 m^2 based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13, 14]

The following criteria are applicable for Cohort 1:

8. A UPCR ratio of ≥3 g/g and <10 g/g in the first morning void on 3 measurements collected on at least 3 separate days within a 7-day period, during the Screening Period. All 3 measurements must meet this criterion.
9. There should be no plan to start, stop, or modify dosing for an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), neprilysin inhibitor, sodium-glucose co-transporter-2 inhibitor, or renin inhibitor during the Treatment Period or Follow-up Period.

The following criteria are applicable for Cohort 2:

10. A UPCR ratio of ≥ 2 g/g and <10 g/g in the first morning void on 3 measurements collected on at least 3 separate days within a 7-day period, during the Screening Period. All 3 measurements must meet this criterion.
11. There should be no plan to start, stop, or modify dosing for an ACE inhibitor, ARB, neprilysin inhibitor, sodium-glucose co-transporter-2 inhibitor, renin inhibitor, or systemic corticosteroids during the Treatment Period or Follow-up Period.

8.2 Exclusion Criteria

The following criteria are applicable for Cohort 1 and Cohort 2:

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:
   - Solid organ or bone marrow transplantation
   - Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ (each being disease-free for the last 5 years)
   - Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator
   - Clinically significant liver disease
   - Ongoing alcohol or drug abuse as determined by the investigator
   - Any condition possibly affecting drug absorption (e.g., gastrectomy, gastrointestinal tract surgery except appendectomy and cholecystectomy)
   - Stroke or myocardial infarction within 6 months before Day 1
2. Evidence of non-APOL1-mediated FSGS. This includes but is not limited to the following:
   - FSGS occurring concomitantly to administration of drugs known to induce FSGS, including but not limited to lithium, interferon, and bisphosphonates (e.g., pamidronate), or FSGS occurring in a subject using intravenous illicit drugs at the time of diagnosis.
   - Evidence of another underlying kidney disease that can cause FSGS, including evidence of congenital anomaly of the kidney or urinary tract (CAKUT) on renal ultrasound, history of CAKUT, history of nephrectomy.
   - FSGS occurring in a subject with known sickle cell disease.
   - Known genetic mutation other than *APOL1 G1* or *G2* that is associated with FSGS.
   - Positive serology for human immunodeficiency virus-1 (HIV-1) or human immunodeficiency virus-2 (HIV-2).
3. Evidence of kidney disease other than FSGS on kidney biopsy, as assessed by the eligibility review process.
4. Kidney biopsy showing the tip variant of FSGS, as assessed by the eligibility review process.
5. Any of the following abnormal laboratory values at screening:
   - Serum albumin <1 g/dL
   - Total bilirubin ≥1.5 × upper limit of normal (ULN)
   - Aspartate transaminase (AST) or alanine transaminase (ALT) ≥2 × ULN
   - Potassium above the ULN
   - Hemoglobin <10 g/dL.

6. Positive for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) antibody during screening.
7. Risk factors for Torsade de Pointes (e.g., familial long QT syndrome, chronic hypokalemia, heart failure) or concomitant medications that prolong the QT/QTc interval or any history of cardiac disorders that, in the opinion of the investigator, might put the subject at risk or may confound the results of the study.
8. Any clinically significant ECG abnormality (as determined by the investigator) or median QTcF of triplicate standard 12 ECGs >450 msec at screening.
9. Screening blood pressure ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), based on the average of 3 measurements.
10. Pregnant or nursing female subjects.
11. Subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.6.5.1.
12. Plan to travel to countries where sleeping sickness is endemic, from the Screening Visit through 1 week after the last dose of study drug.
13. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.
14. Hypersensitivity to investigational medicinal product or to any of its excipients.

The following criterion is applicable for Cohort 1

15. Use of the substances or activities as indicated in Section 9.5 during the specified times, including but not limited to ongoing treatment with corticosteroids (any dose level) or another immunosuppressive drug.

The following criterion is applicable for Cohort 2

16. Use of the substances or activities as indicated in Section 9.5 during the specified times, including but not limited to ongoing treatment with high doses of corticosteroids (>10 mg/day of prednisone or prednisone equivalent) or another immunosuppressive drug.

9 STUDY IMPLEMENTATION

9.1 Study Design

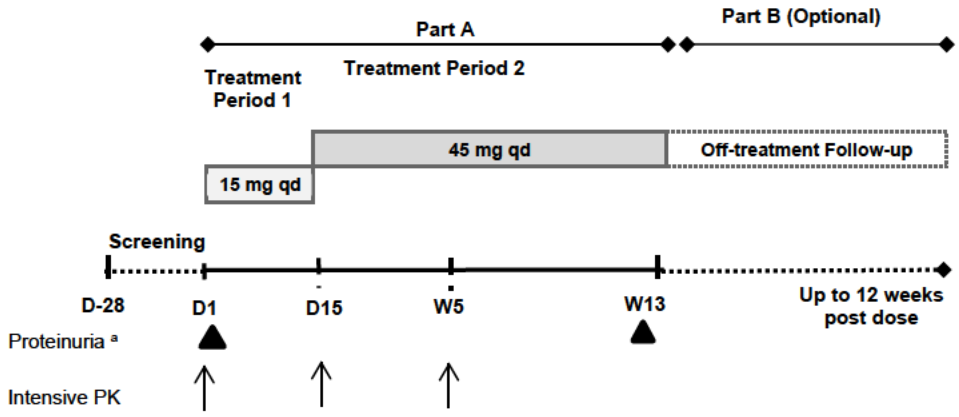
This is a single-arm, open-label, 2-part study. In Part A, all subjects will receive VX-147 at a dosage of 15 mg qd for 2 weeks and VX-147 at a dosage of 45 mg qd for 11 weeks. Part A will be enrolled in 2 cohorts: Cohort 1 and an optional Cohort 2. Cohort 1 includes approximately 10 subjects with UPCR ≥ 3 g/g and < 10 g/g who are not taking systemic corticosteroids or other immunosuppressants. The optional Cohort 2 includes approximately 10 subjects with UPCR ≥ 2 g/g and < 10 g/g, and these subjects are permitted to have a stable low dose of systemic corticosteroid.

Enrollment of Cohort 1 will be prioritized over enrollment of Cohort 2; this will be managed through the interactive web response system (IWRS). Each site will be required to enroll a subject in Cohort 1 before the same site can enroll Cohort 2.

In Optional Part B, subjects will be followed for up to 12 weeks for evaluation of proteinuria off-treatment (Section 9.1.3).

All subjects will complete a Safety Follow-up Visit (SFUV) at 28 (± 7) days after the last dose of study drug.

Figure 9-1 VX19-147-101 Study Design



D: Day; PK: pharmacokinetics; qd: once daily; UPCR: urine protein to creatinine ratio; W: Week
Notes: The figure is not drawn to scale. After completing Part A, subjects will be followed monthly for up to 12 weeks or until UPCR returns to baseline, whichever occurs first. All subjects will be required to complete a SFUV at 28 (± 7) days after the last dose of study drug.
[a] Proteinuria will be assessed at multiple timepoints throughout the Treatment Period and Off-treatment Follow-up. Triangles represent timepoints for the primary analysis.

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1. Subjects may choose to complete all screening assessments within the 28-day Screening Period or they may choose a 2-step screening process and first complete only the *APOL1* genotype assessment at any time before Day -1 (including before Day -28), followed by the rest of the screening assessments during the 28-day Screening Period. The ICF will outline the screening options. *APOL1* genotype results must be obtained using a Vertex-approved clinical study assay. If genotype results are available in the medical records and a Vertex-approved clinical study assay was used, the genotype assessment does not need to be done.

With the exception of genotyping, all screening assessments will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent from each subject before conducting any study-related procedure.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.5).

9.1.1.1 Repetition of Screening Assessments

Repetition of any individual screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence of a laboratory error (e.g., hemolysis of sample) or equipment failure, or if the investigator believes the result is not consistent with the subject's current status.

9.1.1.2 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1),
- Unexpected operational or logistic delays, or

If more than 42 days have elapsed from screening before first dose of study drug, all screening assessments need to be repeated.

9.1.1.3 Rescreening

Individuals who do not meet the eligibility criteria for participation upon initial screening can be rescreened up to 3 times. All screening tests should be repeated to determine eligibility except for *APOL1* genotyping, confirmation of biopsy-proven APOL1-mediated FSGS by the eligibility review process (Section 9.3.6), and follicle-stimulating hormone (FSH).

Rescreened participants will keep the same subject identification number assigned during the initial screening process. The rescreening period will start from the date of the first assessment of the rescreen.

9.1.2 Part A

9.1.2.1 Treatment Period

Subjects will be enrolled in Cohort 1 and optional Cohort 2. Treatment Period assessments are listed in Table 3-2. During Treatment Period 1, subjects will receive VX-147 at a dosage of 15 mg qd for 2 weeks. During Treatment Period 2, subjects will receive VX-147 at a dosage of 45 mg qd for 11 weeks. Dosing details are in Section 9.6.

9.1.2.2 Safety Follow-up

Subjects will have a SFUV 28 (± 7) days after the last dose of study drug. SFUV assessments are listed in Table 3-3.

9.1.2.3 Early Termination of Treatment or Early Discontinuation

If a subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the SFUV, approximately 28 (± 7) days after their last dose of study drug. The assessments performed at the SFUV are listed in Table 3-3.

If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the SFUV, and a separate SFUV will not be required.

After the ETT Visit, subjects will not complete further Part A Visits; these subjects will not continue to Part B.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent.

9.1.3 Part B

Participation in Part B is optional. After the last Part A Visit, subjects will be followed off-treatment at a visit scheduled every 4 weeks (± 2 weeks) to assess the change in proteinuria after stopping administration of VX-147 (Table 3-3). Part B visits will continue until the UPCR level reaches baseline levels or 3 months after the last dose of study drug, whichever occurs first. For the purpose of this assessment, baseline UPCR is defined as the average of the last 3 screening assessments ± 10%. If a subject has not achieved ≥90% of baseline UPCR by the Part B Week 12 Visit, the Part B Week 12 Visit will be the last study visit.

Subjects will not be allowed to participate in Part B if (1) their UPCR level during Part A remained ≥ baseline or (2) their UPCR level reached baseline (as defined above) before the Part A Week 13 Visit and remained at that level through the Week 13 Visit.

The SFUV and Part B Week 4 Off-treatment Follow-up Visit may occur on the same day, provided the visit windows for both visits are met.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects will receive VX-147.

9.2.1 Replacement Subjects

Subjects may be replaced at the discretion of Vertex.

9.3 Rationale for Study Elements

9.3.1 Study Design

The study will be single-arm and open-label. All subjects will receive VX-147 for a total of 13 weeks. A placebo arm was not included because FSGS is a rare, severe disease with a very low likelihood of spontaneous remission.[15-17] This is the first study targeting the APOL1 pathway in patients with FSGS, so the duration required for proteinuria levels to reach nadir is unknown. Clinical practice guidelines[18] for other therapies indicate that ≥4 months of therapy may be required for patients with nephrotic-range proteinuria to achieve complete remission (defined as UPCR <0.3 g/g). The duration of 13 weeks for this study was selected to allow the maximum treatment time supported by nonclinical data.

This is the first study in patients with FSGS, therefore subjects will receive 2 dose levels of VX-147 to characterize PK of VX-147 at 2 dose levels in this population. As shown in Figure 9-1, the 15 mg qd dose will be administered for 2 weeks and the 45 mg qd dose will be administered for 11 weeks. The 2-week duration for the 15 mg qd dose was selected based on an exposure-response model suggesting that a measurable decrease in proteinuria may be observed after 2 weeks of dosing. The 11-week additional duration for the 45 mg qd dose, provides a total of 13 weeks continuous dosing, which is the longest observation period supported by available nonclinical data.

9.3.2 Study Population

The study will enroll male and female subjects, aged 18 to 60 years old, with biopsy proven FSGS, 2 *APOL1*-risk alleles, and nephrotic-range proteinuria. These patients have need for new treatments, because patients with FSGS and nephrotic-range proteinuria have rapid progression to kidney failure, with mean renal survival less than 10 years.[15, 16, 19-21] The presence of FSGS on biopsy will be confirmed by an independent, external expert (Section 9.3.6) to determine eligibility.

9.3.3 Study Drug Dose

The administration of once daily doses of 15 mg and 45 mg were selected on the totality of clinical safety, tolerability, and PK from the FIH study (Study 001); as well as toxicology and non-clinical pharmacodynamic (PD) data.

In Study 001, single ascending oral doses of VX-147 up to 50 mg and multiple ascending doses of VX-147 up to 45 mg once daily for 14 days were evaluated. The doses were well-tolerated and no clinically significant safety concerns were identified. In this study, a low dose of 15 mg once daily is selected to characterize the PK in FSGS patients and to assess any measurable decrease in proteinuria. Based on an exposure-response model, the exposures from the 15 mg dose are expected to result in approximately 90% inhibition in the in vitro ion flux model. This level of inhibition may result in a measurable decrease in proteinuria after 2 weeks of dosing.

A high dose of 45 mg once daily is selected to maximize the probability of reduction in proteinuria over the 11-week dosing period. Based on the exposure-response model referenced above, exposures from this dose are expected to result in over 96% inhibition in the in vitro ion flux model. VX-147 exposure from the 2 doses are expected to be well differentiated based on data from the FIH healthy subject study (Study 001). Thus, the doses selected will provide an adequate assessment of the dose-response relationship and safety profile of VX-147 in the exposure range of interest.

Additional information about FIH and nonclinical data are available in the Investigator's Brochure.

9.3.4 Study Assessments

All efficacy, safety, and PK assessments are common assessments for clinical studies, with the exception of those described below.

9.3.4.1 UPCR

Percent change from baseline in UPCR at Week 13 was chosen as the primary endpoint because proteinuria is a characteristic feature of FSGS and 1 of its main prognostic factors. Urine samples will be collected for UPCR using the first morning void, which is standardly used in clinical practice to determine accurate urine protein levels. As UPCR is variable within an individual, 3 samples will be taken during screening, Week 9, and Week 13; and the average of the 3 values will be used to determine baseline, Week 9, and end-of-treatment UPCR values.

9.3.4.2 SF-36

Change in SF-36 from baseline over the study treatment period will be assessed as an exploratory outcome. SF-36 is a patient-reported generic measure of health status. It has been

previously used to evaluate health-related quality of life in patients with chronic kidney disease, including FSGS.[22,23]

9.3.5 Use of Telemedicine for Study Visits

Telemedicine may be used for a number of study visits as detailed in Table 3-2 and Table 3-3. These visits will include home health nurse visits to the subject's home to complete assessments. All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, in order to check-in and collect AEs. Subjects and investigators may choose to conduct individual visits in the clinic or through use of home health. Periodic phone or telemedicine video visits may also be done to allow the investigator and subject to communicate directly; these visits may be done face-to-face in the clinic at the discretion of the investigator.

If local regulations or site practice do not allow telemedicine, all visits will be conducted at the site.

9.3.6 Eligibility Review

An independent, external expert with appropriate clinical and scientific background will evaluate the histopathological eligibility criteria to ensure that the subjects meet the study's definition of FSGS. Details of the process will be included in a separate procedure manual.

9.4 Prior and Concomitant Medications

Information about all prior and concomitant medications, including the subject's FSGS medications, other medications, and herbal and naturopathic remedies administered from 28 days before the Screening Visit through the SFUV, if applicable, will be recorded in each subject's source documents. For subjects who are screened but not subsequently randomized, details of prior medication will only be documented in the subjects' source documents.

Subjects in Cohort 1 and Cohort 2 who are taking ACE inhibitors, ARB, neprilysin inhibitor, sodium-glucose co-transporter-2 inhibitor, or a renin inhibitor must remain on a stable medication regimen at least 28 days before the Screening Visit through the Week 13 or ETT (if applicable) Visit. Subjects in Cohort 2 who are taking systemic corticosteroids must remain on a stable low dose (i.e., ≤ 10 mg/day of prednisone or prednisone equivalent) from at least 28 days before the Screening Visit through the Week 13 or ETT (if applicable) Visit. During the Off-Treatment Period, every effort should be made to avoid starting, stopping, or modifying doses of these medications. If it becomes clinically necessary to alter a subject's antihypertensive regimen during the study, changes to an antihypertensive medication dose or addition of a new antihypertensive medication are recommended before changes are made to any ACE inhibitor, ARB, neprilysin inhibitor, or renin inhibitor.

9.5 Study Restrictions

Study restrictions are summarized in Table 9-1. A nonexhaustive list of medications is provided in the Study Reference Manual.

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	Start	**Stop**
Moderate and strong CYP3A4 inhibitors or inducers, including consumption of herbal medications (e.g., St. John's Wort)	None allowed within 14 days before the first dose of the study drug	Completion of Safety Follow-up Visit assessments
Systemic corticosteroids (applicable to Cohort 1 only)	None allowed within 4 weeks before the first dose of the study drug	Completion of the last study assessment
Immunosuppressants	None allowed within 12 weeks before the first dose of study drug	Completion of the last study assessment
Rituximab	None allowed within 6 months before the first dose of study drug	Completion of the last study assessment
Other investigational drugs or devices	28 days before first dose of study drug, 5 half-lives before first dose of study drug dose, or time determined by local requirements (whichever is longer)	Completion of the last study assessment
Creatine or creatine-containing dietary supplements	7 days before first dose of study drug	Completion of Safety Follow-up Visit assessments
Grapefruit, grapefruit juice, pomelos, orange marmalade, Seville/blood oranges	7 days before first dose of study drug	Until last PK sample is taken

[a] See Section 9.4 for guidance on concomitant medications.

9.6 Administration

VX-147 will be administered as 15 mg tablets, orally, as shown in Table 3-2.

Study drug will be administered according to the following guidelines:

- The first dose in each period must be administered under the supervision of site medical staff or a home health nurse. Subjects will be monitored for 4 hours after receiving the first dose of each Treatment Period
- On days of scheduled visits, the dose of study drug will be administered after predose assessments have been completed.
- Study drug will be taken at approximately the same time on each dosing occasion. For example, subjects that administer VX-147 dose at 8AM on Day 1 should administer all subsequent doses at 08:00AM ± 2 hours.
- Study drug may be taken with or without food.

- Subjects will swallow the study drug whole, with a full glass of water and will not chew it before swallowing.
- On days of intensive PK sampling, the date, dose taken, and time of study drug administration will be recorded for the 2 doses before PK sample collection and on the morning of PK sample collection.
- Subjects will be instructed to bring all used and unused materials associated with the study drug to the site or the nurse will take these materials at each study visit; study drug will be dispensed at each visit, as appropriate.

Missed Doses

If a subject misses a dose and recalls the missed dose within 6 hours, the subject should take his/her dose according to the guidance above. If more than 6 hours have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose. An example is provided below:

- If the morning dose of study drug should have been taken at approximately 08:00AM, and the subject remembers at 12:00PM that he/she forgot to take his/her dose, he/she should take the dose as soon as possible. If they remember after 2:00PM that they forgot to take the morning dose, they should skip that dose and resume the normal schedule the next day.

Additional information is provided in the Pharmacy Manual.

9.7 Dose Modification

No dose modifications are allowed. Treatment may be interrupted as outlined in Section 9.8. If any unacceptable toxicity arises in the opinion of the investigator, individual subjects may discontinue dosing. The Vertex medical monitor must be notified immediately.

9.8 Study Drug Interruption

Study drug may be interrupted for safety concerns by the investigator. The Vertex medical monitor should be notified of an interruption of study drug and of the resumption of study drug after such interruption.

9.9 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

Subjects who discontinue study treatment early should complete the ETT and SFUV, as noted in Sections 9.1.2.2 and 9.1.2.3.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a SFUV, if applicable (see Section 9.1.2.3), and follow up with the subject regarding any unresolved AEs.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period(s) may be replaced at Vertex's discretion.

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

10.2 Packaging and Labeling

Vertex will supply the 15-mg VX-147 tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for VX-147 will be in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for in the drug accountability forms as instructed by Vertex.

Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Dosing Form/ Route	Dosage	How Supplied
VX-147	Tablet/ oral	15-mg	Supplied as 15-mg tablets
VX-147	Tablet/ oral	45-mg	Supplied as 3 × 15-mg tablets

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information about the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. A central pharmacy will be used for subjects opting to have home health visits. Subjects will be instructed to return all used and unused materials associated with

the study drug to the home health nurse or site. These materials will be retained at the site or central pharmacy according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site or central pharmacy uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site or in the subject's home at required study visits. At each visit, site personnel/home health care nurses will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should consider discontinuing the subject from the study

10.7 Blinding and Unblinding

This is an open-label study.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1 through Table 3-3.

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight.

Medical history will be elicited from each subject and extracted from medical records during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history will include a complete review of systems, past medical and surgical histories, and any allergies.

Height and weight will be measured with shoes off with light weight clothing (no outerwear). BMI will be calculated from weight and height.

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of VX-147. Metabolites of VX-147 may be analyzed, if necessary. These samples may also be used for further evaluation of

the bioanalytical method, evaluation of unbound concentration of VX-147, and for exploratory analyses that provide information on the metabolic pathways used by or affected by VX-147; these results may not be included in the clinical study report.

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. Samples collected outside of these acceptable windows will be considered protocol deviations.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	Up to 60 minutes before dose
From 0.25 up to ≤4 hours after study drug dosing	± 15 minutes
> 4 hours after study drug dosing	± 120 minutes
48 hours after study drug dosing	± 180 minutes

For each visit with a PK blood draw, a record of study drug administration will be collected. The collection date and exact time that each PK blood sample is drawn will also be recorded.

Samples from the PK sampling will be kept frozen by Vertex or its designee until all analyses have been completed and then disposed of according to Vertex or designee standard operating procedures.

11.2.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of samples and further procedures for processing and handling of samples for PK analysis will be in a separate document.

11.2.3 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.3 Urine Sampling for UPCR, UACR, and Safety Laboratory Panel

Urine will be collected from the first morning void (predose) for use in efficacy and safety analyses. Efficacy analyses will include UPCR and UACR, as calculated from protein, albumin, and creatinine measured in the urine lab panel (Table 11-2). Safety assessments will include the urine laboratory parameters in Section 11.6.2. During the Week 9 and Week 13 Visits, when 3 samples are collected on 3 separate days within a 7-day period, the third sample collected will be used for the safety lab and biomarker assessments; all 3 samples will be used for UPCR and UACR.

If the subject does not remember to collect their first morning void on the scheduled visit day, the subject may provide the sample on another day within the visit window.

Details about the collection and processing of urine samples will be provided in the Laboratory Manual.

11.4 APOL1 Genotyping

A blood sample will be collected for determining APOL1 genotype during screening. This sample is not required if a genotype result is available from a previous Vertex study using a Vertex-approved clinical study assay.

The results of the genotyping test will be provided to the investigator. The investigator will inform the subject of the *APOL1* genotype. Vertex will ensure that subjects can obtain the services of a genetic counselor, if desired. The site will be responsible for managing the corresponding logistics.

11.5 Exploratory Assessments

These data will be used for internal exploratory purposes. Detailed procedures for the collection of blood, urine, and pharmacogenomic samples, as well as additional procedures for processing and handling samples will be provided in a separate document.

11.5.1 Blood Biomarker Samples

Blood samples will be collected for potential exploratory evaluation of correlations between blood markers (e.g., proteins, peptides, lipids, endogenous metabolites, etc.) with PK and AEs observed in the study. The samples may also be used for the evaluation of safety biomarkers.

11.5.2 Urine Biomarker Samples

Urine samples will be collected from the first morning void for potential exploratory evaluation of correlations between urine markers with PK, treatment response, and AEs observed in the study. At the Week 13 Visit, only the last on-treatment urine sample will be used for urine biomarker analysis. Additional details will be provided in the Laboratory Manual.

11.5.3 Pharmacogenomic Samples

RNA and optional DNA samples will be collected for potential exploratory evaluation of correlations between DNA and RNA markers with PK, treatment response, and AEs observed in the study. The RNA sample may be considered optional if so required by an IRB/IEC reviewing this study on behalf of a participating institution.

11.5.4 SF-36

Subjects will complete the SF-36 ePRO (if available) in their native language (if validated translations are available) before all other study assessments at each scheduled time point. If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. The questionnaire provides information about functional health and wellbeing, as well as 2 psychometrically based physical and mental health summary measures.

11.6 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and physical examinations (PEs).

11.6.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.6.2 Clinical Laboratory Assessments

The safety laboratory test panels are shown in Table 11-2. For purposes of study conduct, blood and urine samples will be analyzed at a central laboratory, with the exception of urine pregnancy tests, as described below.

Urine samples for safety laboratory assessments may be collected at the same time as the urine samples for efficacy and biomarker assessments (See Section 11.3). At the Week 9 and Week 13 Visit, only the third urine sample will be used for urinalysis and biomarker assessments, with the exception of urine protein, creatinine, and albumin, which will be assessed for all 3 samples collected during this visit.

On days when overnight fasts are required (see Table 3-2 and Table 3-3), subjects will abstain from food and beverages for 8 hours before the start of the visit. During this period, water may be consumed up to 1 hour before study drug administration.

Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

Table 11-2 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[b]	Hematocrit	Nitrite
Creatinine	Erythrocytes	Urine protein[c]
Creatine kinase	Mean corpuscular volume	Urine creatinine[c]
Sodium	Platelets	Urine albumin[c]
Potassium	Reticulocytes	Urine blood
Calcium	Leukocytes	
Chloride	Differential (absolute and percent):	
Magnesium	Eosinophils	Urine ketones
Bicarbonate	Basophils	Urine glucose
Phosphate	Neutrophils	Urobilinogen
Total bilirubin, direct bilirubin	Lymphocytes	Urine pH
Alkaline phosphatase	Monocytes	Specific gravity
Aspartate transaminase	Blood smear[e]	
Alanine transaminase	**Coagulation**	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Gamma-glutamyl transferase	Prothrombin time International Normalized Ratio	
Protein		
Albumin		
Cholesterol[d]		
Triglycerides[d]		
Low-density lipoprotein-direct[d]		
High-density lipoprotein[d]		

[a] For the Day 1 predose sample, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.
[b] If blood urea nitrogen cannot be measured, urea may be substituted.
[c] eGFR will be calculated using the CKD-EPI equation, and AKI will be determined using KDIGO criteria.[24] Urine protein, creatinine, and albumin measurements will be used for PD and safety.
[d] Lipid profile will only be measured at the visits with fasting: Day 1, Week 3, Week 13, ETT, and SFUV.
[e] A blood smear will be collected on Day 1, Week 13, and the ETT Visit.

Additional Tests at Screening: The following additional tests will be performed during screening to assess eligibility:

- *Serum beta-human chorionic gonadotropin (β-hCG) for all subjects*: Serum samples will be analyzed for β-hCG at the central laboratory.
- *Follicle-stimulating Hormone (Screening Period only):* Blood sample for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be within the postmenopausal reference range of the performing laboratory to be considered postmenopausal.
- *APOL1*: A blood sample will be collected to determine *APOL1* genotype, if required per Table 3-1.
- *HIV-1 and HIV-2 antibodies:* A blood sample will be collected for serology.
- *Hepatitis B surface antigen:* A blood sample will be collected for serology.

- *Hepatitis C nucleic acid test:* A blood sample will be collected for nucleic acid testing.

Pregnancy Testing for Female Subjects of Childbearing Potential (Section 11.6.5):

- Urine pregnancy tests will either be performed and analyzed at the site or, when there is no clinic visit scheduled, at home using a home kit provided by the site/home health nurse. The urine pregnancy test on Day 1 must be negative before the first dose of study drug. Additional pregnancy tests may be required according to local regulations and/or requirements.

If a urine pregnancy test is positive, all study drug dosing will stop and the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.6.5.2 will be followed.

Additional Evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

11.6.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening and select study visits. At other visits, symptom-directed PEs and symptom-directed vital signs assessments can be performed at the discretion of the investigator or healthcare provider.

A PE includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The abbreviated PE will include an assessment of the following body systems: cardiovascular system; respiratory system; skin; and abdomen.

Vital signs include blood pressure (systolic and diastolic), oral temperature, pulse rate, and respiration rate. The subject will be instructed to rest for at least 5 minutes before vital signs are assessed.

11.6.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position

A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the SFUV will be recorded as AEs.

If study sites cannot use QTcF they should discuss alternatives with the medical monitor.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a confirmed QTcF value above the threshold value will discontinue dosing.

11.6.5 Contraception and Pregnancy

The effects of VX-147 on conception, pregnancy, and lactation in humans are not known. Refer to the VX-147 Investigator's Brochure for additional details.

11.6.5.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below:

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
  - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
  - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy
    Note: All other females (including females with tubal ligations and females who do not have a documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy) will be considered to be of childbearing potential.
- Same sex relationships.

For subjects for whom the contraception requirement is not waived:

For male subjects with female partners of childbearing potential, in addition to wearing a condom, study participation requires a commitment from the subject that at least 1 allowed method of contraception (in addition to a condom) will be used as a couple. Refer to Table 11-3 for allowed methods of contraception.

For female subjects with childbearing potential, study participation requires a commitment from the subject that at least 1 allowed method of contraception is used as a couple. Allowed methods of contraception are listed in Table 11-3.

Methods of contraception must be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug.

Table 11-3 Allowed Methods of Contraception

Method	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Documented tubal ligation 4 weeks or more previously	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug	Yes	Yes [a]
Oral, patch, implanted, or injected hormonal contraceptives, if used consistently and correctly for at least 60 days before the first dose of study drug	Yes [b]	No [c]

[a] Non-hormonal releasing IUD only
[b] Female (Non-study) Partners only
[c] The effects of VX-147 on the PK of hormonal contraceptives are not known. Thus, hormonal contraception is NOT an acceptable method of contraception for female subjects.

Additional notes:

- Male subjects must use a condom to avoid exposing a potential fetus to study drug via the seminal fluid. The female condom is not an acceptable method due to the increased risk of tearing when the female and male condoms are used at the same time.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- Male subjects must not donate sperm from the first study drug dose until 90 days after the last dose of study drug.
- Female subjects of childbearing potential should not plan to become pregnant during the study or within 90 days after the last dose of study drug. For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug.
- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or designee on an individual basis.

11.6.5.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

If a female subject, or the female partner of a male subject, becomes pregnant while participating in the study, the study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex Global Patient Safety (GPS) within 24 hours of the site's

knowledge of the subject's (or partner's) pregnancy, and send the Pregnancy Information Collection Form to Vertex GPS.

A subject (or their partner, if relevant) who becomes pregnant while on study will be followed until the end of the pregnancy. The infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF will be provided to explain these follow-up activities. Pregnancy itself is not an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned final analyses for efficacy, safety, and clinical pharmacology. Efficacy and safety statistical analysis details will be provided in the statistical analysis plan (SAP) for this study, and clinical pharmacologic analysis details will be provided in the clinical pharmacology analysis plan (CPAP), both of which will be finalized before last subject last visit for the treatment period (Part A).

The primary endpoint analysis will occur after all subjects in Cohort 1 have completed the SFUV, and all related data have been locked.

An additional analysis for Part A will occur after all subjects in Cohort 2 have completed the SFUV and the related data have been locked.

The final analysis for the study will occur after all subjects have completed their last required visit of the study (Part A or Part B, as applicable) and the database has been locked.

12.1 Sample Size and Power

The sample size was not calculated based on power assumptions, because this is an estimation study. The primary endpoint is percent change from baseline in UPCR at Week 13. Assuming an SD of 0.672 (in log scale),[25] a sample size of 10 subjects will provide a precision of 0.294 (in log scale) for the estimation of the Geometric Mean Percent Change (GMPC) from baseline in UPCR. The precision of the estimate corresponds to the half width of its 80% CI, in log scale. Table 12-1 displays the expected size of the 80% CIs for the GMPC at various values of the observed GMPC.

Table 12-1 Two-sided 80% Confidence Interval for GMPC from Baseline in UPCR

Number of Subjects Completing	Assumption for SD in Log Scale	Observed GMPC (corresponding percent reduction from baseline)			
		0.5 (-50%)	0.6 (-40%)	0.7 (-30%)	0.8 (-20%)
10	0.672	0.37, 0.67 (-63%, -33%)	0.45, 0.81 (-55%, -19%)	0.52, 0.94 (-48%, -6%)	0.60, 1.07 (-40%, 7%)

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), Safety Set, and Follow-up Set.

The **All Subjects Set** will include all subjects who were enrolled in the study. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

The **FAS** will include all subjects who received at least 1 dose of study drug in the Treatment Period and at least 1 post-baseline efficacy assessment. The FAS will be used for all efficacy analyses in the Treatment Period, unless otherwise specified.

The **Follow-up Set** will include all subjects who entered the Off-treatment Follow-up Period (Part B) and have at least 1 efficacy assessment in that period. The Follow-up Set will be used for all efficacy analyses in the Follow-up Period, unless otherwise specified.

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be to summarize subject demographics and baseline characteristics, and used for all safety analyses, unless otherwise specified.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of efficacy, safety and PK endpoints of the study. Statistical analysis details will be provided in the SAP.

12.3.1 General Considerations

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP. Unless otherwise specified, minimum and maximum values will be reported with the same precision as the units of the raw data. The mean, median, and SD will be reported to 1 additional decimal place. Any values that require a transformation to standard units (metric or International System [SI]) will be converted with the appropriate precision.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit). For ECGs, baseline will be defined as the most recent pretreatment measurement (or the average of triplicate measurements, if the most recent pretreatment measurement is obtained in triplicate) before the first dose of study drug in the Treatment Period (i.e., the Day 1 visit). For UPCR (and UACR) data baseline value will be the average of UPCR (UACR) values from the 3 urine samples collected during screening for the purpose of assessing eligibility.

Change (absolute change) from baseline will be calculated as Post-baseline value − Baseline value.

Treatment-emergent (TE) Period will include the time from the first dose of study drug in the Treatment Period to either (1) the SFUV, (2) ETT Visit if it replaces the SFUV, or (3) the date of the last dose + 28 days for subjects who do not have a SFUV. The TE Period will be used for safety analyses unless specified otherwise.

The analysis visit windows for protocol-defined visits will be described in the SAP.

The rules for handling missing data due to treatment or study discontinuation will be described in the SAP.

Data will be analyzed separately for the Treatment Period (Part A) and the Off-treatment Follow-up Period (Part B), unless specified otherwise.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category in the Treatment Period (e.g., included in the All Subjects Set, included in the Safety Set, completed Treatment Period, completed SFUV, and discontinued treatment or study with a breakdown of the reasons for discontinuation) will be summarized.

The number and percentage of subjects in each disposition category in the Off-treatment Follow-up Period (e.g., included in the Follow-up Set, completed Follow-up Period, and discontinued study/Follow-up Period with a breakdown of the reasons for discontinuation) will be summarized.

12.3.2.2 Demographics and Baseline Characteristics

Demographics, background (e.g. medical history), and baseline characteristics will be summarized using descriptive summary statistics.

The following demographics and baseline characteristics will be summarized based on the Safety Set and will include (but not limited to): sex, race, age, weight, height, BMI, UPCR, UACR, and eGFR.

12.3.2.3 Prior and Concomitant Medications

Medications used will be coded using the World Health Organization-Drug Dictionary (WHO-DD) and categorized as the following:

Prior medication: any medication that started before the date of the first dose of study drug, regardless of when the medication ended

Concomitant medication: medication continued or newly received on or after the date of the first dose of study drug through the end of the TE Period

A given medication may be classified as prior, concomitant, or both prior and concomitant.

If a medication start date is on or after the first dose date of study drug, then the medication will be categorized as concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the first dose date of study drug, then the medication will be categorized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started before the first dose of study drug and continued after the first dose will be categorized as prior medication and separately as concomitant medication.

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, or concomitantly, it will be considered in both categories of prior and concomitant medication.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by Preferred Name based on the Safety Set.

Details for imputing missing or partial start and/or stop dates of medication will be in the SAP.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug will be summarized for the Safety Set in terms of duration of treatment a subject received (in days), defined as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Study drug compliance based on study drug exposure, will be summarized for the Safety Set, and will be calculated as: 100 × [1 – (total number of days of any study drug interruption)/(duration of study drug exposure in days)].

12.3.2.5 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The rules for identifying an IPD will be described in the SAP.

IPDs will be provided in an individual subject data listing.

12.3.3 Efficacy Analysis

Analyses will be done separately for Cohort 1 and Cohort 2.

12.3.3.1 Analysis of Primary Variables

The primary efficacy endpoint is percent change from baseline in UPCR at Week 13. The Week 13 UPCR value will be calculated as the average of the available UPCR measurements (maximum 3) taken during Week 13. The baseline value will be the average of the 3 UPCR values from the urine samples collected during screening.

The percent change from baseline in UPCR at Week 13 will be analyzed by first log-transforming the UPCR data before analyses to reduce skewness, and calculating the change from baseline in log-transformed values. The GMPC from baseline in UPCR will be estimated along with the corresponding 2-sided 80% CI. The GMPC from baseline and associated confidence limits will be calculated by back-transforming the estimated simple mean of change from baseline in log-transformed data.

Sensitivity analyses for handling missing data due to treatment or study discontinuation will be described in the SAP.

12.3.3.2 Analysis of Other Variables

In all exploratory analyses of UPCR and UACR related data, the Week 9 and Week 13 UPCR/UACR value will be calculated as the average of the available UPCR/UACR measurements (maximum 3) taken during Week 9 or Week 13, and the baseline value will be the average of the 3 UPCR/UACR values from the urine samples collected for this purpose during screening.

The percent change from baseline in UPCR over time during the Treatment period is an exploratory efficacy endpoint. Similar to the primary endpoint analysis, UPCR data will be log-transformed and change from baseline at each planned visit, up to Week 13, will be analyzed using the log-transformed UPCR values. The GMPC from baseline and associated 2-sided 80% CI at each planned visit will be calculated by back-transforming the corresponding estimated simple mean and CI from the log-transformed data.

Other exploratory efficacy endpoints include percent change from baseline in urinary albumin-to-creatinine ratio (UACR) at Week 13, and percent change from baseline in UACR over time during the Treatment period. Analysis of these 2 endpoints will be similar to that performed for the corresponding UPCR endpoints.

Off-treatment Follow-up Period (Part B): The exploratory endpoint of percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period will be analyzed similarly to the primary efficacy endpoint.

Additional details of these analyses will be provided in the SAP.

12.3.4 Safety Analysis

All safety analyses will be based on data from the TE Period for all subjects in the Safety Set.

The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis)
- Standard 12-lead ECG outcomes
- Vital signs

Only a descriptive analysis of safety will be performed.

All safety data will be presented in individual subject data listings.

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs or TEAEs, defined as follows:

Pretreatment AE: any AE that started before the first dose date of study drug

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug through the end of the TE Period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs.

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation
- Serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event).

When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

In addition, a listing of individual subject level AE data for TEAEs leading to treatment discontinuation, serious adverse events (SAEs), and deaths will be provided separately. All AEs, including pretreatment AEs, will be in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

For treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized in SI units by visit.

The number and percentage of subjects with at least 1 laboratory event outside threshold criteria for the event during the TE Period will be summarized, including a shift of the event from baseline to post-baseline. The threshold criteria will be in the SAP.

Results of urinalysis and the urine/serum pregnancy test will be in individual subject data listings only.

In addition, a listing of individual subject hematology, chemistry, and coagulation values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.

12.3.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided by visit and time point, as applicable, for the following ECG measurements: RR (msec), heart rate (HR; beats per minute [bpm]), PR (msec), QRS duration (msec), QT (msec), and QT corrected for HR intervals (QTcF [msec]).

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. The threshold analysis criteria will be provided in the SAP.

Clinically significant abnormal findings will be reported as AEs.

Additional ECG analyses may be described in the SAP.

12.3.4.4 Vital Signs

For treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by visit: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (bpm), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 event outside the threshold criteria for a vital sign during the TE Period will be summarized. The threshold analysis criteria will be provided in the SAP.

Clinically significant abnormal findings in vital signs will be reported as AEs.

Additional vital signs analyses may be described in the SAP.

12.3.4.5 Physical Examination

PE findings will be presented in individual subject data listings only.

12.3.4.6 Other Safety Analysis

Change from baseline in weight will be summarized by visit.

12.3.5 Other Analyses

Analysis of the exploratory endpoints for SF-36 will be provided in the SAP.

12.3.6 Interim and Independent Data Monitoring Committee Analyses

Interim analyses may be done at the discretion of the sponsor to allow for regulatory interactions and clinical development planning. There is no independent Data Monitoring Committee for this study.

12.4 Clinical Pharmacology Analysis

The following systemic exposure parameters will be estimated using noncompartmental and population PK analysis: AUCτ during a dosing interval, C_{max} and C_{trough} will be estimated for all subjects who provide adequate number of PK samples:

- on Day 1 after single administration of the lower dose;
- at Week 2 after the first administration of the higher dose;
- at Week 5 after multiple administrations of the higher dose.

In addition, observed C_{trough} will be reported at Weeks 1, 3, 9, and 13. Based on availability of data after the last administration of the higher dose, half-life will be reported after multiple administrations of the higher dose.

12.4.1 Pharmacokinetic Analysis

Mean and/or median plasma concentrations versus time will be plotted on log and linear scales. The PK parameters (C_{max}, C_{trough}, AUC_{τ}, and other parameters as needed) of VX-147 estimated by noncompartmental analysis will be listed and summarized using summary statistics. Ongoing analyses of plasma concentrations of VX-147 may be conducted before database lock.

Details of the analyses will be in the CPAP.

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of VX-147 will be performed using the nonlinear mixed-effects modeling approach. Population and individual PK parameters: clearance after oral administration (CL/F) and apparent volume of distribution at steady state (Vss/F) will be estimated and the influence of various covariates (such as age, gender, and body weight) on these parameters will be investigated in an exploratory way. If deemed necessary, data may be pooled with data from other studies with VX-147 in order to improve the parameter estimates from the model.

Plasma concentration – response relationship (PD markers and AEs, if any) will be explored. A more detailed description of the methodology to be followed will be in either the CPAP or the population PK/PD analysis plan. Listings of VX-147 plasma concentration data will be in the bioanalytical report. The population PK analysis will be in a stand-alone report.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a SFUV: through the SFUV
- For enrolled subjects who do not have a SFUV, the earliest of
  - 28 days after the last dose of study drug, or
  - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.2.3)

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed February 2020). The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Description
Mild (Grade 1)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Severe (Grade 3)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Life-threatening (Grade 4)	Life-threatening consequences, urgent intervention indicated
Death (Grade 5)	Death related to AE

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories in Table 13-2.

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record).

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/resolved	Resolution of an AE with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an AE with residual signs or symptoms

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Not recovered/not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific

event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious", which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent and assent (where applicable) through the SFUV, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after the SFUV and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours of identification**.

For SAEs that occur after obtaining informed consent and assent (where applicable) through the SFUV, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

[redacted]

For technical issues related to submitting the form, contact telephone: [redacted]

SAEs that occur after the SFUV and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report the outcome to Vertex using the SAE Form.

13.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, IECs, and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance

with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject, before study participation. The method of obtaining and documenting the informed consent and assent (if applicable) and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers will be limited to the site and the study physician and will not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE Forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.7 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

13.2.8 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure,

validated, web-based electronic data capture (EDC) application. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP Guidelines. On-site checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application is sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to them, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.6 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

13.7 Publications and Clinical Study Report

13.7.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[26]

Publication Planning: Vertex staff along with the lead principal investigators (PIs), the steering committee (SC), and/or the publication committee (PC) will work together to develop a publication plan.

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria[27]:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
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 conditions 1, 2, 3, and 4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Contributions such as medical writing, enrollment of subjects, acquisition of funding, collection of data, or general supervision of the research group, alone, do not justify authorship.

Contributors: Contributors who meet fewer than all 4 of International Committee of Medical Journal Editors (ICMJE) criteria for authorship will not be listed as authors, but their contribution will be acknowledged and specified either as a group (e.g., “study investigators”) or individually (e.g., “served as scientific advisor”).

Publication Review: As required by a separate clinical study agreement, Vertex must have the opportunity to review all publications, including any manuscripts, abstracts, oral/slide presentations, and book chapters regarding this study before submission to congresses or journals for consideration.

13.7.2 Clinical Study Report

A clinical study report (CSR), written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCES

1 McGrogan A, Franssen C, de Vries C. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrology Dialysis Transplantation. 2011;26(2):414-30.

2 D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365(25):2398-411.

3 Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 2011;22(11):2129-37.

4 Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841-5.

5 Shukha K, Mueller JL, Chung RT, Curry MP, Friedman DJ, Pollak MR, et al. Most ApoL1 is secreted by the liver. J Am Soc Nephrol. 2017;28(4):1079-83.

6 Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. J Am Soc Nephrol. 2011;22(11):2119-28.

7 Vanhamme L, Paturiaux-Hanocq F, Poelvoorde P, Nolan DP, Lins L, Van Den Abbeele J, et al. Apolipoprotein L-I is the trypanosome lytic factor of human serum. Nature. 2003;422(6927):83-7.

8 Perez-Morga D. Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. Science. 2005;309(5733):469-72.

9 Cooper A, Ilboudo H, Alibu VP, Ravel S, Enyaru J, Weir W, et al. APOL1 renal risk variants have contrasting resistance and susceptibility associations with African trypanosomiasis. Elife. 2017;6:e25461.

10 Ma L, Chou JW, Snipes JA, Bharadwaj MS, Craddock AL, Cheng D, et al. APOL1 renal-risk variants induce mitochondrial dysfunction. J Am Soc Nephrol. 2017;28(4):1093-105.

11 Beckerman P, Bi-Karchin J, Park ASD, Qiu C, Dummer PD, Soomro I, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. Nat Med. 2017;23(4):429-38.

12 Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet. 2010;128(3):345-50.

13 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.

14 Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. New England Journal of Medicine. 2012;367(1):20-29.

15 Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol. 2004;15(8):2169-77.

16 Stirling CM, Mathieson P, Boulton-Jones JM, Feehally J, Jayne D, Murray HM, et al. Treatment and outcome of adult patients with primary focal segmental glomerulosclerosis in five UK renal units. QJM. 2005;98(6):443-9.

17 Cattran DC, Rao P. Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis. 1998;32(1):72-9.
18 (KDIGO) KDIGO. 2012 Clinical Practice Guideline for the Evaluation and Management of Glomerulonephritis. Kidney Int. 2012;2(2):15-16.
19 Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am J Kidney Dis. 1994;23(6):773-83.
20 Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry G. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16(4):1061-8.
21 Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. Am J Kidney Dis. 1995;25(4):534-42.
22 Gipson DS, Trachtman H, Kaskel FJ, Radeva MK, Gassman J, Greene TH, et al. Clinical trials treating focal segmental glomerulosclerosis should measure patient quality of life. Kidney International. 2011;79(6):678-85.
23 Komers R, Gipson DS, Nelson P, Adler S, Srivastava T, Derebail VK, et al. Efficacy and Safety of Sparsentan Compared With Irbesartan in Patients With Primary Focal Segmental Glomerulosclerosis: Randomized, Controlled Trial Design (DUET). Kidney International Reports. 2017;2(4):654-64.
24 Kidney Disease: Improving Global Outcomes (KDIGO) Working Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplement. 2012;2(1)
25 Trachtman H, Nelson P, Adler S, Campbell KN, Chaudhuri A, Derebail VK, et al. DUET: A Phase 2 Study Evaluating the Efficacy and Safety of Sparsentan in Patients with FSGS. Journal of the American Society of Nephrology. 2018;29(11):2745-54.
26 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med. 2015;163(6):461-4.
27 (ICMJE) ICoMJE. International Committee of Medical Journal Editors (ICMJE). Recommendations for conduct, reporting, editing, and publication of scholarly work in medical journals. [Internet]. Available from: http://www.icmje.org/recommendations. Accessed 06 September.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-147-101	Version #: 2.0	Version Date: 05 March 2020
Study Title: A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis		

This clinical study protocol has been reviewed and approved by the sponsor.

[redacted]

15.2 Investigator Signature Page

Protocol #: VX19-147-101	Version #: 2.0	Version Date: 05 March 2020
Study Title: A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis		

I have read Protocol VX19-147-101, Version 2.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-147 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date

1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Clinical Study Protocol

A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis

Vertex Study Number: VX19-147-101

IND Number: [redacted]

EudraCT Number: 2020-000185-42

Date of Protocol: 26 July 2021 (Version 6.0)

Replaces Version 5.0 (dated 09 April 2021)

Vertex Pharmaceuticals Incorporated
50 Northern Avenue
Boston, MA 02210-1862, USA

Summary of Changes to the Protocol

The previous version of this protocol (Version 5.0, dated 09 April 2021) was amended to create the current version (Version 6.0, 26 July 2021).

Protocol History	
Version and Date of Protocol	**Comments**
Version 1.0, 10 October 2019	Original version
Version 2.0, 05 March 2020	Specified the doses to be used; added optional Cohort 2; modified the schedule of assessments and eligibility criteria.
Version 3.0, 23 September 2020	Added an option for telemedicine and home health nurse visits to be used during to the Screening Visit; amended the eligibility criteria; several administrative and minor changes.
Version 4.0, 11 December 2020	Amended the eligibility criteria; specified that both cohorts will be analyzed for the primary endpoint; several administrative and minor changes.
Version 5.0, 09 April 2021	Modified the eligibility criteria for estimated glomerulofiltration rate (eGFR) and UPCR; updated the study restrictions to allow concomitant use of cyclosporine.
Version 6.0, 26 July 2021	Current version

Key changes in the current version of the protocol are summarized below.

Change and Rationale	**Affected Sections**
Specified that Cohort 1 will enroll “up to 10 subjects” and not “approximately 10 subjects.” This change clarifies that enrollment may be stopped before 10 subjects are enrolled.	Sections 2, 9.1, and 12.1

2 PROTOCOL SYNOPSIS

Title A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis

Brief Title Phase 2a Study of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis

Clinical Phase and Clinical Study Type Phase 2a pharmacodynamics (PD), safety, and pharmacokinetics (PK)

Objectives

Part A (Treatment Period)

Primary

- To evaluate the ability of VX-147 to reduce proteinuria

Secondary

- To evaluate the safety and tolerability of VX-147
- To characterize the PK of VX-147

Part B (Optional Off-treatment Follow-up Period)

Exploratory

- To evaluate the change in proteinuria after stopping administration of VX-147

Endpoints

Part A (Treatment Period)

Primary

- Percent change from baseline in urine protein to creatinine ratio (UPCR) at Week 13

Secondary

- Safety and tolerability based on adverse events (AEs), clinical laboratory values (i.e., hematology, serum chemistry, urinalysis, coagulation studies), standard 12-lead ECGs, and vital signs
- Plasma PK of VX-147

Exploratory

- Percent change from baseline in UPCR over time during the Treatment Period
- Percent change from baseline in urine albumin-to-creatinine ratio (UACR) at Week 13
- Percent change from baseline in UACR over time during the Treatment Period
- Change from baseline in patient-reported outcome (PRO) Short Form Health Survey 36 (SF-36) over time during the Treatment Period
- Change from baseline in SF-36 at 4 weeks after the last dose (Safety Follow-up Visit [SFUV])

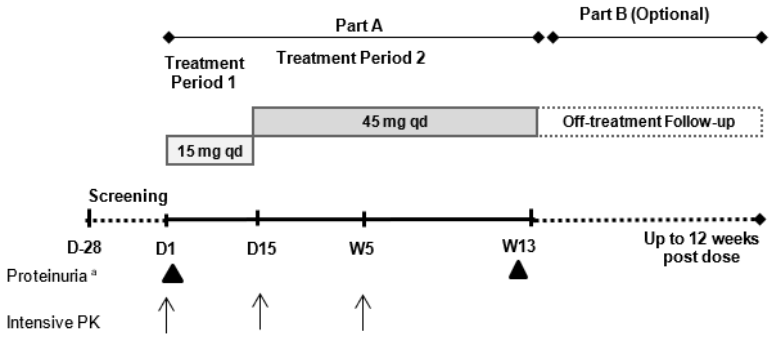
Part B (Optional Off-treatment Follow-up Period)

Exploratory

- Percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period

Number of Subjects	Up to 10 subjects in Cohort 1 and approximately 10 subjects in optional Cohort 2
Study Population	Male and female subjects 18 to 65 years old with 2 apolipoprotein L1 (*APOL1*) risk alleles (*G1/G1*, *G1/G2*, or *G2/G2* genotype) who have APOL1-mediated focal segmental glomerulosclerosis (FSGS), UPCR ≥3 g/g and < 10 g/g (Cohort 1) or ≥ 0.8 g/g and < 2.7 g/g (Cohort 2), and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 (Cohort 1 and Cohort 2)
Investigational Drug	Active substance: VX-147 Activity: APOL1-inhibitor Strength and route of administration: 15 mg tablets for oral administration
Study Duration	Excluding the Screening Period, each subject will participate in the study for approximately 13 weeks of treatment in Part A. Subjects may choose to participate in an off-treatment observation for up to 12 weeks in Part B (optional). All subjects will complete a SFUV at 28 (± 7) days after the last dose of study drug.
Study Design	This is a single-arm, open-label, 2-part study. In Part A, subjects will receive VX-147 at a dosage of 15 mg once daily (qd) for 2 weeks and VX-147 at a dosage of 45 mg qd for 11 weeks. Part A will be enrolled in 2 cohorts: Cohort 1 and optional Cohort 2. Cohort 1 includes up to 10 subjects with UPCR approximately ≥3 g/g and <10 g/g and eGFR approximately ≥30 mL/min/1.73 m^2. Optional Cohort 2 includes approximately 10 subjects with UPCR approximately ≥0.8 g/g and <2.7 g/g and eGFR approximately ≥30 mL/min/1.73 m^2. Subjects in Cohort 1 and Cohort 2 are permitted to take a stable low dose of systemic corticosteroid (prednisone ≤ 10 mg per day or prednisone equivalent) and/or an allowed immunosuppressant (i.e., tacrolimus, mycophenolate, or cyclosporine). Enrollment of Cohort 1 and Cohort 2 will be managed through the interactive web response system (IWRS). After completing Part A, subjects will be followed for up to 12 weeks in Part B (optional) for evaluation of proteinuria off treatment if they consent to do so. If a subject prematurely discontinues study drug in Part A, an Early Treatment Termination (ETT) Visit should be scheduled as soon as possible after the decision to terminate study drug treatment. After completing the ETT Visit, subjects will not complete further Part A Visits; these subjects will come in for a SFUV and will not continue to Part B. All subjects are required to complete a SFUV at 28 (± 7) days after the last dose of study drug. The SFUV may occur while a subject is participating in Part B.

Figure 2-1 VX19-147-101 Study Design



D: Day; PK: pharmacokinetics; qd: once daily; UPCR: urine protein to creatinine ratio; W: Week

Notes: The figure is not drawn to scale. After completing Part A, subjects will be followed monthly for up to 12 weeks or until UPCR returns to baseline, whichever occurs first. All subjects will be required to complete a SFUV at 28 (± 7) days after the last dose of study drug.

[a] Proteinuria will be assessed at multiple timepoints throughout the Treatment Period and Off-treatment Follow-up. Triangles represent timepoints for the primary analysis.

Assessments

Efficacy: UPCR

Safety: AEs; clinical laboratory assessments; ECGs; vital signs; and physical examinations

PK: VX-147 plasma concentrations

Exploratory: UACR, SF-36, biomarker blood and urine samples

Statistical Analyses

Efficacy

Analyses will be done separately for Cohort 1 and Cohort 2, as well as combined. The primary endpoint is percent change from baseline in UPCR at Week 13. In all analyses of UPCR related data, the Week 13 UPCR value will be calculated as the average of the available UPCR measurements (maximum 3) taken during Week 13, and the baseline value will be the average of the 3 UPCR values from the urine samples collected for this purpose during screening.

The percent change from baseline in UPCR at Week 13 will be analyzed by first log-transforming the UPCR data before analyses to reduce skewness and calculating the change from baseline in log-transformed values. The geometric mean percent change (GMPC) from baseline in UPCR will be estimated along with the corresponding 2-sided 80% CI. The GMPC from baseline and associated confidence limits will be calculated by back-transforming the estimated simple mean of change from baseline in log-transformed data.

Safety

The safety analyses will be descriptive only.

Pharmacokinetics

Noncompartmental analyses will be performed, and summary statistics will be provided for VX-147 PK parameters. Additional analysis including population PK modeling will be performed to further characterize the PK and exposure-response relationships.

3 SCHEDULE OF ASSESSMENTS

Schedules of assessments for Cohort 1 and Cohort 2 are in Table 3-1 through Table 3-3. All visits will be scheduled relative to the Day 1 Visit.

Subjects may choose to complete all screening assessments within the 28-day Screening Period or they may choose a 2-step screening process and first complete only the *APOL1* genotype assessment at any time before Day -1 (including before Day -28), followed by the rest of the screening assessments during the 28-day Screening Period. The informed consent form (ICF) will outline the screening options. Additional information is provided in Section 9.1.1. Informed consent must be completed before any assessments are done at the Screening Visit. The SF-36 must be completed before any other assessment when they are required. Other assessments may be performed in any order when more than 1 assessment is required at a particular time point, unless noted otherwise. All assessments will be performed before dosing, unless noted otherwise.

Table 3-1 Study VX19-147-101: Screening

Event/Assessment	Optional Genotype Screening Visit (Before Day -1)	Screening Period (Day -28 to Day -1)	Comments
Subject visit	X	X	Activities may be performed by a home health visit or in the clinic, unless otherwise noted (Section 9.3.5). The complete physical exam must be done by the investigator (Section 11.6.3). The Screening Visit should occur in the clinic if possible, but home health may be used if extenuating circumstances prevent a clinic visit (Section 9.1.1).
Informed consent	X	X	Informed consent must be obtained before any study-related procedures. It may be obtained in person or remotely, and it may be collected before the first visit (Section 13.2.2).
Demographics		X	
Medical history		X	
Medications review		X	Section 9.4
Standard 12-lead ECG		X	To be performed in triplicate after the subject has been supine for at least 5 minutes. When ECGs, vital signs, and blood draws coincide, they should be performed in said order. (Section 11.6.4).
Vital signs		X	Vital signs will be collected after the subject has rested for at least 5 minutes. Blood pressure must be collected in triplicate. (Section 11.6.3).
Height and weight		X	Weight and height will be measured with shoes off with light weight clothing (no outerwear). BMI will be calculated using height and weight (Section 11.1).
Physical examination		X	A complete exam will be done if the visit occurs in the clinic. If the visit occurs using a home health nurse, an abbreviated exam will be done (Section 11.6.3).

Table 3-1 Study VX19-147-101: Screening

Event/Assessment	Optional Genotype Screening Visit (Before Day -1)	Screening Period (Day -28 to Day -1)	Comments
Serum FSH (suspected postmenopausal female subjects only)		X	A blood sample will be collected (Section 11.6.2).
Serum β-hCG (all female subjects)		X	A blood sample will be collected (Section 11.6.2).
Serum chemistry		X	A blood sample will be collected (Section 11.6.2).
Hematology		X	A blood sample will be collected (Section 11.6.2).
Coagulation		X	A blood sample will be collected (Section 11.6.2).
Serology (HIV-1 and HIV-2 Antibodies)		X	A blood sample will be collected (Section 11.6.2).
Hepatitis B surface antigen		X	A blood sample will be collected (Section 11.6.2).
HCV test		X	A blood sample will be collected (Section 11.6.2).
Confirmation of *APOL1* genotype	X	X	A genotyping sample will be collected if a result is not available using a Vertex-approved clinical study assay (Section 9.1.1).
Urine sample		X (3 samples)	Collected after signing the informed consent for use in efficacy, biomarker, and safety analyses (Sections 11.3 and 11.6.2). The first morning void will be collected for 3 independent samples, which are collected on 3 separate days within a 7-day period. The third sample must be collected by Day -5 to allow confirmation that UPCR values meet eligibility criteria (Section 8.1). Refer to sample handling guidelines to ensure samples are submitted appropriately for analysis.
Adverse events	Continuous from signing of ICF through SFUV		For subjects undergoing a 2-step screening process, AEs related to phlebotomy will be collected for up to 24 hours after the blood collection; AEs will not be collected during the time between a subject undergoing genotype screening and the start of the Screening Visit. Additional information about AE reporting is provided in Section 11.6.1.

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Subject visit	X	X	X	X	X	X	X	X	All visits may be performed by a home health visit or in the clinic at the discretion of the investigator (Section 9.3.5). All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window.
SF-36	X				X		X	X	To be completed before all other study assessments (Section 11.5.3).
Standard 12-lead ECG	X	X	X	X	X	X	X	X	Complete predose after SF-36 and before other assessments. The subject should be supine for at least 5 minutes before the start of ECG. When ECGs, vital signs, and blood draws coincide, they should be performed in said order. On Day 1 and Day 15, an ECG (Section 11.6.4) will also be collected 2 (± 1) hours postdose.
Vital signs	X	X	X	X	X	X	X	X	Complete before the assessments listed in rows below. The subject should rest for at least 5 minutes before the start of vital sign collection and they should be seated during the assessment (Section 11.6.3). Blood pressure will be collected in triplicate.
Weight	X	X	X	X	X	X	X	X	Weight will be measured with shoes off and light weight clothing (no outerwear) (Section 11.1).

[a] All assessments will be performed before dosing unless noted otherwise.

[b] If the subject prematurely discontinues study treatment during the Treatment Period, an ETT Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the SFUV, and a separate SFUV will not be required. After the ETT Visit, subjects will not complete further Part A Visits; these subjects will not continue to Part B (Table 3-3).

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Abbreviated Physical examination	X	X	X	X	X	X	X	X	In addition to the scheduled visits, symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.6.3).
Serum chemistry	X Fasted	X	X	X Fasted	X	X	X Fasted	X Fasted	A blood sample will be collected predose after an overnight fast on indicated days. All other days do not require fasting. (Section 11.6.2).
Hematology	X	X	X	X	X	X	X	X	A blood sample will be collected (Section 11.6.2).
Coagulation	X	X	X	X	X	X	X	X	A blood sample will be collected (Section 11.6.2).
Biomarker blood sample	X	X	X	X	X	X	X	X	Section 11.5.1.
VX-147 PK blood sample	intensive	predose	intensive	predose	intensive	predose	X	X	A blood sample will be collected (Section 11.2.1). **Intensive PK sampling** *Day 1, Day 15, Week 5*: predose (within 60 min before dosing) and 0.25, 0.5, 1, 2, 4 and 12 hours postdose **Post treatment samples (Week 13 and ETT):** A single sample collected anytime during the Visit.

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Urine sample	X[c]	X	X	X	X (3 samples)	X (3 samples)	X (3 samples)	X	The first morning urine void (predose) will be collected and used for efficacy, safety, and biomarker analyses (Sections 11.3 and 11.6.2). During Week 5, Week 9, and Week 13, 3 samples will be collected on 3 separate days within a 7-day period. If the subject forgets to collect the first morning void on the day of the visit, they may provide this sample predose on a different day within the visit window. Refer to sample handling guidelines to ensure samples are submitted appropriately for analysis.
β-hCG (urine)	X				X	X	X	X	All female subjects of childbearing potential (Sections 11.6.2 and 11.6.5). This can be collected in the same sample as the urine sample for efficacy, safety, and biomarker analysis.
VX-147 dosing	X								The last dose of Treatment Period 1 will be Day 14. The first dose of Treatment Period 2 will be on Day 15 after all predose assessments are completed. The last day of dosing will occur the day before the Week 13 visit. The first dose in each period must be administered under the supervision of site medical staff or a home health nurse. Subjects will be monitored for 4 hours after receiving the first dose of each Treatment Period. (Section 9.6).

[c] Day 1 urinalysis will be for safety and biomarker assessments. Efficacy assessments will not be done.

Table 3-2 Study VX19-147-101: Part A Treatment Period 1, Treatment Period 2, and Early Termination of Treatment Visit

Event/ Assessment[a]	Treatment Period 1		Treatment Period 2					Early Termination of Treatment Visit[b]	Comments
	Day 1 Visit	Week 1 Visit	Day 15 Visit	Week 3 Visit	Week 5 Visit	Week 9 Visit	Week 13 Visit		
	Window: Day 1 (±0 days)	Window: Day 8 (±1 day)	Window: Day 15 (±2 days)	Window: Day 22 (±2 days)	Window: Day 36 (±2 days)	Window: Day 64 (±2 days)	Window: Day 92 (-2 days)		
Adverse events	Continuous from signing of ICF through SFUV								Section 11.6.1.
Medications review	Continuous from signing of ICF through SFUV								Section 9.4.

Table 3-3 Study VX19-147-101: Postdose PK Sampling, Safety Follow-up Visit, and Part B Off-treatment Follow-up Period

Event/Assessment	Postdose PK Sampling (Approximately 48 hours after the last dose of study drug)[a]	SFUV 28 (± 7) Days After Last Dose of Study Drug[b]	Part B: Optional Off-treatment Follow-up Visits [c] (Part B Week 4[b], 8, and 12)	Comments
Subject visit	X	X	X (until UPCR returns to ≥90% of baseline level)	The visit may be performed by a home health visit or in the clinic at the discretion of the investigator (Section 9.3.5). For each visit, at least 1 interaction with the subject and investigator will occur by phone, video, or in the clinic (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, which can be outside the visit window. See Section 9.1.3 for details about determining the last visit for Part B.
SF-36		X		To be completed before all other study assessments (Section 11.5.3).
Standard 12-lead ECG		X		Complete after SF-36 and before other assessments after subject has been supine for at least 5 minutes. ECGs (Section 11.6.4), vital signs, and blood draws should be performed in said order.
Vital signs		X		Complete before other assessments listed below after subject has been at rest for at least 5 minutes; they should be seated during the assessment (Section 11.6.3). Blood pressure will be collected in triplicate.

[a] The postdose PK sampling visit is required for all subjects, with the exception of those who complete an ETT Visit.
[b] The SFUV and Part B Week 4 Off-treatment Follow-up Visit may occur on the same day, provided the visit windows are met for both visits.
[c] Visit windows for Part B are as follows: Week 4 Visit (Day 120 ± 2 weeks), Week 8 Visit (Day 148 ± 2 weeks), Week 12 Visit (Day 176 ± 2 weeks).

Table 3-3 Study VX19-147-101: Postdose PK Sampling, Safety Follow-up Visit, and Part B Off-treatment Follow-up Period

Event/Assessment	Postdose PK Sampling (Approximately 48 hours after the last dose of study drug)[a]	SFUV 28 (± 7) Days After Last Dose of Study Drug[b]	Part B: Optional Off-treatment Follow-up Visits [c] (Part B Week 4[b], 8, and 12)	Comments
Weight		X		Weight will be measured with shoes off and light weight closing (no outerwear). (Section 11.1).
Abbreviated physical examination		X		In addition to the scheduled visits, symptom-directed physical examinations will occur at any time during the study if triggered by AEs or if deemed necessary by the investigator (Section 11.6.3).
Serum chemistry		X Fasted		A blood sample will be collected following an overnight fast (Section 11.6.2).
Hematology		X		A blood sample will be collected (Section 11.6.2)
Coagulation		X		A blood sample will be collected (Section 11.6.2)
VX-147 PK Sampling	X			A blood sample will be collected (Section 11.2.1).
Urine sample		X	X	The first morning urine void will be collected and used for efficacy, safety, and biomarker analyses (Sections 11.3 and 11.6.2). Refer to sample handling guidelines to ensure samples are collected and submitted appropriately for analysis.
β-hCG (urine)		X		All female subjects of childbearing potential (Section 11.6.2). This can be collected in the same sample as the other urine sample.
Adverse events	Continuous from signing of ICF through SFUV		NA	Section 11.6.1
Medications review	Continuous from signing of ICF through SFUV or last off-treatment follow-up visit, whichever is later			May be collected via telemedicine (Section 9.4)

4 TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations

Abbreviation	Definition
ACE	angiotensin converting enzyme
ADL	activities of daily living
AE	adverse event
AKI	acute kidney injury
ALT	alanine transaminase
APOL1	apolipoprotein L1
ARB	angiotensin receptor blocker
AST	aspartate transaminase
$AUC_{0-\infty}$	AUC from the time of dosing extrapolated to infinity
AUC_{τ}	AUC during a dosing interval
β-hCG	beta-human chorionic gonadotropin
BMI	body mass index
bpm	beats per minute
CAKUT	congenital anomaly of the kidney or urinary tract
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL/F	apparent clearance
C_{max}	maximum observed concentration
CPAP	clinical pharmacology analysis plan
CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	predose concentration
CV	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
ECG	Electrocardiogram
EDC	electronic data capture
EE	ethinyl estradiol
EENT	eyes, ears, nose, and throat
eGFR	estimated glomerular filtration rate
ESKD	end-stage kidney disease
ETT	Early Termination of Treatment
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIH	first-in-human
FSGS	focal segmental glomerulosclerosis
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMPC	Geometric Mean Percent Change
GMR	geometric mean ratio
GPS	Global Patient Safety
HBsAg	hepatitis B surface antigen

Abbreviation	Definition
HCV	hepatitis C virus
HIV-1	human immunodeficiency virus-1
HIV-2	human immunodeficiency virus-2
HR	heart rate
ICF	informed consent form
ICH	International Council for Harmonization
ICMJE	International Committee of Medical Journal Editors
IEC	independent ethics committee
IPD	important protocol deviation
IRB	institutional review board
IWRS	interactive web response system
LN	levonorgestrel
MedDRA	Medical Dictionary for Regulatory Activities
NA	not applicable
PC	publication committee
PD	Pharmacodynamics
PE	physical examination
P-gp	P-glycoprotein
PI	principal investigator
PK	pharmacokinetic, pharmacokinetics
PR	PR interval, segment
PRO	patient-reported outcome
PT	Preferred Term
QRS	the portion of an ECG comprising the Q, R, and S waves, together representing ventricular depolarization
QT	QT interval
QTcF	QT interval corrected by Fridericia's formula
RR	interval from the onset of 1 QRS complex to the next
SAE	serious adverse event
SAP	statistical analysis plan
SC	steering committee
SD	standard deviation
SF-36	Short Form Health Survey 36
SFUV	Safety Follow-up Visit
SGLT2	sodium-glucose co-transporter-2
SI	SI units (International System of Units)
SOC	System Organ Class
SRA	serum resistant associated-protein
SUSARs	suspected, unexpected, serious adverse reactions
TE	Treatment-emergent
TEAE	treatment-emergent adverse event
UACR	urine albumin to creatinine ratio
ULN	upper limit of normal

Abbreviation	Definition
UPCR	urine protein to creatinine ratio
V_{ss}/F	apparent volume of distribution at steady-state
WHO-DD	World Health Organization-Drug Dictionary

5 INTRODUCTION

5.1 FSGS Background

Focal segmental glomerulosclerosis (FSGS) is a rare kidney disease with an estimated global incidence of 0.2 to 1.1/100,000/year.[1] FSGS is caused by damage to podocytes, which are part of the glomerular filtration barrier, resulting in proteinuria.[2] Patients with nephrotic-range proteinuria (i.e., protein to creatinine ratio >3 g/g) are at a higher risk of developing end-stage kidney disease (ESKD) and developing proteinuria-related complications, such as infections or thromboembolic events. There is no well-standardized treatment regimen for FSGS. Current therapeutic options for patients with FSGS who have nephrotic-range proteinuria include high-dose corticosteroids, which induce remission of proteinuria in a minority of patients.[2]

FSGS can be divided into different subgroups based on the underlying etiology. One homogeneous subgroup of FSGS is characterized by the presence of 2 independent common sequence variants in the apolipoprotein L1 (*APOL1*) gene termed *G1* and *G2*, which are referred to as the "*APOL1* risk alleles." *G1* encodes a correlated pair of non-synonymous amino acid changes (S342G and I384M), *G2* encodes a 2 amino acid deletion (N388del:Y389del) near the C-terminus of the protein, and *G0* is the ancestral (low risk) allele.[3,4]

The *APOL1* gene is expressed in multiple organs in humans, including the liver and kidney.[5,6] The biologic function of APOL1 is to protect against parasitic infection (*Trypanosoma brucei brucei [T. b. brucei]*).[7] APOL1 is endocytosed by *T. b. brucei* and transported to lysosomes, where it inserts into the lysosomal membrane and forms pores that lead to parasite swelling and death.[8] While the ability to lyse *T. b. brucei* is shared by all 3 *APOL1* variants (*G0*, *G1*, and *G2*), *APOL1 G1* and *G2* variants confer additional protection against parasite species that have evolved a serum resistant associated-protein (SRA) which inhibits *APOL1 G0*; these species cause sleeping sickness. *G1* and *G2* variants evade inhibition by SRA and *G1* confers additional protection against *T. b. gambiense* (which causes West African sleeping sickness), and *G2* confers additional protection against *T. b. rhodesiense* (which causes East African sleeping sickness).[9]

In the kidney, APOL1 is expressed in podocytes, endothelial cells (including glomerular endothelial cells), and some tubular cells.[6, 10] Podocyte-specific expression of *APOL1 G1* or *G2* (but not *G0*) in transgenic mice induces structural and functional changes, including albuminuria, decreased kidney function, podocyte abnormalities, and glomerulosclerosis.[11] Consistent with these data, *G1* and *G2* variants of *APOL1* play a causative role in inducing FSGS and accelerating its progression in humans. Individuals with 2 *APOL1* risk alleles (i.e., homozygous or compound heterozygous for the *APOL1 G1* or *APOL1 G2* alleles) have increased risk of developing FSGS with an odds ratio of 10 to 17, and they are at risk for rapid decline in kidney function if they develop FSGS.[3, 4, 12] Thus, inhibition of APOL1 could have a positive impact in individuals who harbor 2 *APOL1* risk alleles.

This study is a Phase 2a proof-of-concept study designed to assess the efficacy effects, safety, and pharmacokinetics (PK) of VX-147 in subjects with APOL1-mediated FSGS.

5.2 VX-147 Background

VX-147 is a small molecule that inhibits APOL1-induced cell death and inhibits the biological function of APOL1, i.e., APOL1-induced lysis of *T. b. brucei*. These nonclinical data suggest that VX-147 has the potential to reduce proteinuria and reverse APOL1-induced podocyte

lesions in patients with APOL1-mediated FSGS. Therefore, VX-147 is being developed to treat individuals with FSGS who also have 2 *APOL1* risk alleles and nephrotic-range proteinuria.

In vitro studies indicated VX-147 is a weak inducer of CYP3A4; however, in a previous clinical study (VX18-147-001; Study 001) an interaction with midazolam, a sensitive substrate of CY3A4, indicated that VX-147 has minimal inhibitory effect. To characterize the CYP3A4-mediated PK interaction between VX-147 and combined oral contraceptives containing the steroids, ethinyl estradiol (EE, 30 µg)/levonorgestrel (LN, 150 µg), a dedicated drug-drug interaction (DDI) study was conducted, Study VX19-147-004 (Study 004; analysis complete; CSR in preparation). The effect of multiple doses of 45 mg VX-147 was assessed on the steady-state PK of LN and EE. The study design was an open label, 2-period, fixed-sequence crossover study in 17 healthy female adult subjects. Steady-state plasma levels of EE and LN did not decrease in the presence of daily doses of 45 mg VX-147. There were minor (~20%) increases in $AUC_{0\text{-}24h,ss}$ of both EE and LN. Geometric mean ratio (GMR) of $AUC_{0\text{-}24h}$ for EE at steady state was 1.20 (90% confidence interval [CI] of 1.14, 1.27) and that for LN was 1.20 (1.14, 1.27). The steady state C_{max} of EE and LN also increased with a GMR (90% CI) of 1.23 (1.10, 1.38) for EE and 1.08 (1.00, 1.17) for LN. VX-147 was safe and well tolerated in this study, and there were no discontinuations. There were no serious adverse events (SAEs), and all AEs were mild in severity. Based on these results the magnitude of these interactions are not deemed clinically significant; therefore, coadministration of VX-147 and combined oral contraceptives containing EE and LN is unlikely to result in contraceptive failure.

In vitro studies indicated VX-147 is substrate for CYP3A4 and P-gp. Therefore, it is anticipated that drugs that inhibit or induce CYP3A4 and P-gp could have an impact on the PK of VX-147. A dedicated DDI study (Study VX19-147-005; analysis complete; clinical study report [CSR] in preparation) was done to evaluate the effect of rifampin, a strong CYP3A and P-gp inducer, and itraconazole, a strong CYP3A4 and P-gp inhibitor, on single dose PK of VX-147 in an open-label, fixed-sequence, crossover, DDI study in 28 healthy male and female subjects (14 subjects in the itraconazole group and 14 subjects in the rifampin group). Administration of rifampin resulted in a significant decrease in VX-147 exposure: $AUC_{0\text{-}\infty}$ GMR (90% CI) 0.154 (0.139, 0.170) and C_{max} GMR (90% CI) 0.552 (0.498, 0.612) relative to VX-147 administration alone. These results indicate that strong CYP3A4 inducers have the potential to significantly decrease VX-147 exposure. Administration of itraconazole resulted in a smaller change (approximately 2-fold) compared to rifampin. VX-147 $AUC_{0\text{-}\infty}$ increased with a GMR (90% CI) of 1.98 (1.79, 2.19), while C_{max} increased slightly, GMR of 1.14 (1.07, 1.20) compared to VX-147 administration alone. VX-147 was safe and well tolerated in this study. There were SAEs, and all AEs were mild or moderate in severity. One subject discontinued study drug due to an AE (mild AE of urticaria during dosing with itraconazole alone; considered possibly related). These results indicate that strong CYP3A4 inhibitors are unlikely to cause a significant increase (>2-fold) in VX-147 exposure, and that a moderate CYP3A4 inhibitor, such as cyclosporine, is expected to result in a less than 2-fold increase in $AUC_{0\text{-}24h,ss}$. Hence, cyclosporine administration is anticipated to be safe if co-administered with a 45 mg qd dose of VX-147.

Preliminary, blinded safety data are available from VX20-147-008 (Study 008), in which 36 healthy subjects received single-ascending doses of VX-147 (90 to 165 mg) or placebo, and 58 healthy subjects received multiple-ascending doses of VX-147 (60 to 120 mg daily doses) or placebo for up to 14 days. VX-147 was generally safe and well tolerated at all doses evaluated.

There were no serious adverse events (SAEs), and all AEs were mild or moderate in severity. Two subjects discontinued due to AEs. Of these, one subject (60 mg qd or placebo) discontinued on Day 7 due to a mild AE of tachycardia and another subject (90 mg qd or placebo) discontinued due to a moderate AE of COVID-19 infection. Both were reported by the investigator to be not related.

In Study 008, the highest dose of 120 mg qd for 14 days was generally safe and well tolerated. Preliminary PK analysis demonstrated that the mean (CV%) $AUC_{0\text{-}24h,ss}$ achieved at this dose was 50.1 (27.5%) µg*h/mL, providing an approximately 3.8-fold exposure margin over the 45 mg qd clinical dose with a mean (CV%) $AUC_{0\text{-}24h,ss}$ of 13.3 (21.5%) µg*h/mL (Study 001). A moderate CYP3A4 inhibitor, such as cyclosporine, is expected to result in a less than 2-fold increase in $AUC_{0\text{-}24h,ss}$.

Additional information about the first-in-human (FIH) study (Study 001) and nonclinical studies is available in the Investigator's Brochure.

6 STUDY OBJECTIVES

6.1 Part A (Treatment Period)

6.1.1 Primary Objective

- To evaluate the ability of VX-147 to reduce proteinuria

6.1.2 Secondary Objectives

- To evaluate the safety and tolerability of VX-147
- To characterize the PK of VX-147

6.2 Part B

6.2.1 Exploratory Objective

- To evaluate the change proteinuria after stopping administration of VX-147

7 STUDY ENDPOINTS

7.1 Part A

7.1.1 Primary Endpoints

- Percent change from baseline in urine protein to creatinine ratio (UPCR) at Week 13

7.1.2 Secondary Endpoints

- Safety and tolerability based on adverse events (AEs), clinical laboratory values (i.e., hematology, serum chemistry, urinalysis, coagulation studies), standard 12-lead ECGs, and vital signs
- Plasma PK of VX-147

7.1.3 Exploratory Endpoints

- Percent change from baseline in UPCR over time during the Treatment Period

- Percent change from baseline in urine albumin to creatinine ratio (UACR) at Week 13
- Percent change from baseline in UACR over time during the Treatment Period
- Change from baseline in patient-reported outcome (PRO) Short Form Health Survey 36 (SF-36) over time during the treatment period
- Change from baseline in SF-36 at 4 weeks after the last dose (Safety Follow-up Visit [SFUV])

7.2 Part B (Optional Off-treatment Follow-up Period)

7.2.1 Exploratory Endpoints

- Percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period

8 STUDY POPULATION

Eligibility will be reviewed and documented by an appropriately qualified member of the investigator's team before subjects are enrolled.

Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be eligible.

8.1 Inclusion Criteria

The following criteria are applicable for Cohort 1 and Cohort 2:

1. Willing to sign and date an informed consent form (ICF).
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions (Section 9.59.4), laboratory tests, contraceptive guidelines (Section 11.6.5), and other study procedures.
3. An *APOL1* genotype of *G1/G1, G2/G2,* or *G1/G2* obtained with a Vertex-approved clinical study assay.
4. Between the ages of 18 and 65 years, inclusive.
5. Body mass index (BMI) of 18.0 to 40.0 kg/m^2, inclusive, and a total body weight >50 kg.
6. FSGS diagnosed by kidney biopsy, with the exception of the tip variant, as confirmed through the eligibility review process.
7. There should be no plan to start, stop, or modify dosing for an angiotensin converting enzyme (ACE) inhibitor, angiotensin receptor blocker (ARB), neprilysin inhibitor, sodium-glucose co-transporter-2 (SGLT2) inhibitor, renin inhibitor, systemic corticosteroids, tacrolimus, mycophenolate, or cyclosporine from 28 days before Screening through the Follow-up Period.
8. Subjects who are on low-dose corticosteroids (prednisone ≤ 10 mg per day or prednisone equivalent) or on an allowed immunosuppressant (i.e. tacrolimus, mycophenolate, or cyclosporine) must be on a stable dose for 28 days before screening.
9. Estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 (±10%) based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[13, 14]

10. Subjects with eGFR ≥30 (±10%) to <40 mL/min/1.73 m^2 must have tubulointerstitial fibrosis ≤50% or described as no, mild, or moderate on their kidney biopsy.

The following criterion is applicable for Cohort 1:

11. A UPCR ratio of ≥3 g/g (±10%) and <10 g/g in the first morning void on 3 measurements collected on at least 3 separate days within a 7-day period, during the Screening Period. The average of the 3 measurements must meet this criterion.

The following criterion is applicable for Cohort 2:

12. A UPCR ratio of ≥0.8 g/g (±10%) and <2.7 g/g in the first morning void on 3 measurements collected on at least 3 separate days within a 7-day period, during the Screening Period. The average of the 3 measurements must meet this criterion.

8.2 Exclusion Criteria

The following criteria are applicable for Cohort 1 and Cohort 2:

1. History of any illness or any clinical condition that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug(s) to the subject. This includes, but is not limited to, the following:

- Solid organ or bone marrow transplantation
- Cancer, except for squamous cell skin cancer, basal cell skin cancer, and Stage 0 cervical carcinoma in situ
- Clinically significant and active bacterial, viral, fungal, or parasitic infection as determined by the investigator
- Clinically significant liver disease
- Ongoing alcohol or drug abuse as determined by the investigator
- Any condition possibly affecting drug absorption (e.g., gastrectomy, gastrointestinal tract surgery except appendectomy and cholecystectomy)
- Stroke or myocardial infarction within 6 months before Day 1

2. Evidence of non-APOL1-mediated FSGS. This includes but is not limited to the following:

- FSGS occurring concomitantly to administration of drugs known to induce FSGS, including but not limited to lithium, interferon, and bisphosphonates (e.g., pamidronate), or FSGS occurring in a subject using intravenous illicit drugs at the time of diagnosis.
- Evidence of another underlying kidney disease that can cause FSGS, including evidence of congenital anomaly of the kidney or urinary tract (CAKUT) on renal ultrasound, history of CAKUT, history of nephrectomy.
- FSGS occurring in a subject with known sickle cell disease.
- Known genetic mutation other than *APOL1 G1* or *G2* that is associated with FSGS.
- Positive serology for human immunodeficiency virus-1 (HIV-1) or human immunodeficiency virus-2 (HIV-2).

3. Evidence of kidney disease other than FSGS on kidney biopsy, as assessed by the eligibility review process.
4. Kidney biopsy showing the tip variant of FSGS, as assessed by the eligibility review process.
5. Abnormal laboratory values at screening that present a risk to subject safety in the opinion of the investigator, or any of the following abnormal laboratory values at screening:

- Total bilirubin ≥1.5 × upper limit of normal (ULN)
- Aspartate transaminase (AST) or alanine transaminase (ALT) ≥2 × ULN
- Serum albumin <1 g/dL
    - Hemoglobin <10 g/dL.

6. Positive for hepatitis B surface antigen (HBsAg) or hepatitis C virus (HCV) nucleic acid during screening.
7. Risk factors for Torsade de Pointes (e.g., familial long QT syndrome, chronic hypokalemia, heart failure) or concomitant medications that prolong the QT/QTc interval or any history of cardiac disorders that, in the opinion of the investigator, might put the subject at risk or may confound the results of the study.
8. Any clinically significant ECG abnormality (as determined by the investigator) or median QTcF of triplicate standard 12 ECGs >450 msec at screening.
9. Screening blood pressure ≥160 mm Hg (systolic) or ≥100 mm Hg (diastolic), based on the average of 3 measurements.
10. Pregnant or nursing female subjects.
11. Subjects of reproductive potential who are not willing to follow the contraception requirements outlined in Section 11.6.5.1.
12. Plan to travel to countries where sleeping sickness is endemic, from the Screening Visit through 1 week after the last dose of study drug.
13. Subject, or close relative of the subject, is the investigator or a subinvestigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site.
14. Hypersensitivity to investigational medicinal product or to any of its excipients.
15. Use of the substances or activities as indicated in Section 9.5 during the specified times, including but not limited to ongoing treatment with high doses of corticosteroids (>10 mg/day of prednisone or prednisone equivalent) or an immunosuppressive drug other than tacrolimus, mycophenolate, or cyclosporine.

9 STUDY IMPLEMENTATION

9.1 Study Design

This is a single-arm, open-label, 2-part study. In Part A, all subjects will receive VX-147 at a dosage of 15 mg qd for 2 weeks and VX-147 at a dosage of 45 mg qd for 11 weeks. Part A will be enrolled in 2 cohorts: Cohort 1 and an optional Cohort 2. Cohort 1 includes up to 10 subjects

with UPCR approximately ≥ 3 g/g and < 10 g/g and eGFR approximately ≥30 mL/min/1.73 m^2. Optional Cohort 2 includes approximately 10 subjects with UPCR approximately ≥ 0.8 g/g and <2.7 g/g and eGFR approximately ≥30 mL/min/1.73 m^2.

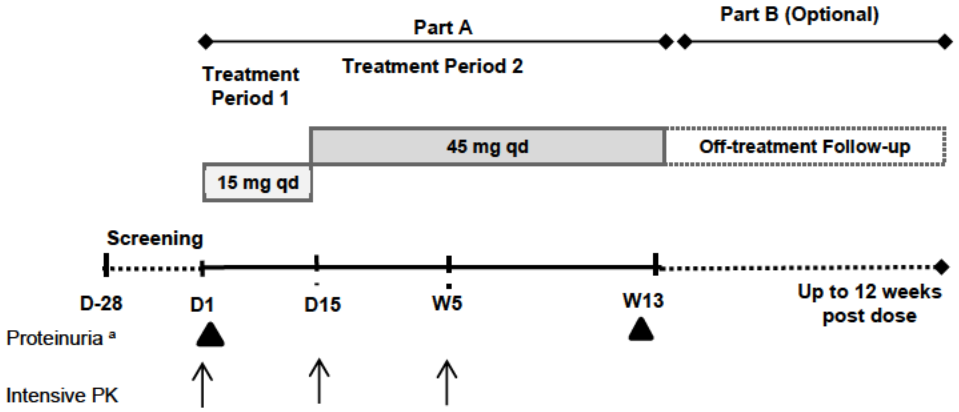
Subjects in Cohort 1 and Cohort 2 are permitted to take a stable low dose of systemic corticosteroid (prednisone ≤ 10 mg per day or prednisone equivalent) and/or an allowed immunosuppressant (i.e., tacrolimus, mycophenolate, or cyclosporine).

Enrollment of Cohort 1 and Cohort 2 will be managed through the interactive web response system (IWRS).

In Optional Part B, subjects will be followed for up to 12 weeks for evaluation of proteinuria off-treatment (Section 9.1.3).

All subjects will complete a SFUV at 28 (± 7) days after the last dose of study drug.

Figure 9-1 VX19-147-101 Study Design



D: Day; PK: pharmacokinetics; qd: once daily; UPCR: urine protein to creatinine ratio; W: Week
Notes: The figure is not drawn to scale. After completing Part A, subjects will be followed monthly for up to 12 weeks or until UPCR returns to baseline, whichever occurs first. All subjects will be required to complete a SFUV at 28 (± 7) days after the last dose of study drug.

[a] Proteinuria will be assessed at multiple timepoints throughout the Treatment Period and Off-treatment Follow-up. Triangles represent timepoints for the primary analysis.

9.1.1 Screening

Screening Visit assessments are listed in Table 3-1. Subjects may choose to complete all screening assessments within the 28-day Screening Period or they may choose a 2-step screening process and first complete only the *APOL1* genotype assessment at any time before Day -1 (including before Day -28), followed by the rest of the screening assessments during the 28-day Screening Period. The ICF will outline the screening options. *APOL1* genotype results must be obtained using a Vertex-approved clinical study assay. If genotype results are available in the medical records and a Vertex-approved clinical study assay was used, the genotype assessment does not need to be done.

With the exception of genotyping, all screening assessments will occur within 28 days before administration of study drug. The investigator (or an appropriate authorized designee at the study site) will obtain informed consent in person or remotely (Section 13.2.2) from each subject before conducting any study-related procedure.

The Screening Visit and informed consent should occur in the clinic if possible. If the subject is unable or unwilling to visit the clinic for screening due to extenuating circumstances, the Screening visit may occur using a home health nurse. Remote informed consent may be obtained before the home health visit.

To prepare for study participation, subjects will be instructed on the study restrictions (Section 9.5).

9.1.1.1 Repetition of Screening Assessments

Screening assessments may be repeated once per screening to establish study eligibility. If repeat values of the individual assessment(s) are within the eligibility criteria and completed within the screening window, then the subject is eligible for the study.

Additional repetition of any individual screening assessment that did not meet eligibility criteria is not permitted, unless there is clear evidence of a laboratory error (e.g., hemolysis of sample) or equipment failure, or if the investigator believes the result is not consistent with the subject's current medical condition.

9.1.1.2 Extension of Screening Period Window

A subject may have the Screening Period window extended by 2 weeks for the following reasons:

- Repetition of the Screening Period assessments (Section 9.1.1.1),
- Unexpected operational or logistic delays, or

If more than 42 days have elapsed from screening before first dose of study drug, all screening assessments need to be repeated.

9.1.1.3 Rescreening

Individuals who do not meet the eligibility criteria for participation upon initial screening can be rescreened up to 3 times. All screening tests should be repeated to determine eligibility except for *APOL1* genotyping, confirmation of biopsy-proven APOL1-mediated FSGS by the eligibility review process (Section 9.3.6), and follicle-stimulating hormone (FSH).

Rescreened participants will keep the same subject identification number assigned during the initial screening process. The rescreening period will start from the date of the first assessment of the rescreen. Rescreening assessments may be done in the clinic or using home health. If home health is used for rescreening, abbreviated PE may be done.

9.1.2 Part A

9.1.2.1 Treatment Period

Subjects will be enrolled in Cohort 1 and optional Cohort 2. Treatment Period assessments are listed in Table 3-2. During Treatment Period 1, subjects will receive VX-147 at a dosage

of 15 mg qd for 2 weeks. During Treatment Period 2, subjects will receive VX-147 at a dosage of 45 mg qd for 11 weeks. Dosing details are in Section 9.6.

9.1.2.2 Safety Follow-up

Subjects will have a SFUV 28 (± 7) days after the last dose of study drug. SFUV assessments are listed in Table 3-3.

9.1.2.3 Early Termination of Treatment or Early Discontinuation

If a subject prematurely discontinues study treatment, an Early Termination of Treatment (ETT) Visit should be scheduled as soon as possible after the subject decides to terminate study treatment. Subjects who prematurely discontinue treatment will also be required to complete the SFUV, approximately 28 (± 7) days after their last dose of study drug. The assessments performed at the SFUV are listed in Table 3-3.

If the ETT Visit occurs 3 weeks or later following the last dose of study drug, then the ETT Visit will replace the SFUV, and a separate SFUV will not be required.

After the ETT Visit, subjects will not complete further Part A Visits; these subjects will not continue to Part B.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue to use any data and samples collected before such withdrawal of consent.

9.1.3 Part B

Participation in Part B is optional. After the last Part A Visit, subjects will be followed off-treatment at a visit scheduled every 4 weeks (± 2 weeks) to assess the change in proteinuria after stopping administration of VX-147 (Table 3-3). Part B visits will continue until the UPCR level reaches ≥90% of baseline levels or 3 months after the last dose of study drug, whichever occurs first. If a subject has not achieved ≥90% of baseline UPCR by the Part B Week 12 Visit, the Part B Week 12 Visit will be the last study visit.

Subjects will not be allowed to participate in Part B if (1) their UPCR level during Part A remained ≥90% of baseline or (2) their UPCR level reached ≥90% of baseline before the Part A Week 13 Visit and remained at that level through the Week 13 Visit.

The SFUV and Part B Week 4 Off-treatment Follow-up Visit may occur on the same day, provided the visit windows for both visits are met.

9.2 Method of Assigning Subjects to Treatment Groups

This is an open-label study. All subjects will receive VX-147.

9.2.1 Replacement Subjects

Subjects may be replaced at the discretion of Vertex.

9.3 Rationale for Study Elements

9.3.1 Study Design

The study will be single-arm and open-label. All subjects will receive VX-147 for a total of 13 weeks. A placebo arm was not included because FSGS is a rare, severe disease with a very low likelihood of spontaneous remission.[15-17] This is the first study targeting the APOL1 pathway

in patients with FSGS, so the duration required for proteinuria levels to reach nadir is unknown. Clinical practice guidelines[18] for other therapies indicate that ≥4 months of therapy may be required for patients with nephrotic-range proteinuria to achieve complete remission (defined as UPCR <0.3 g/g). The duration of 13 weeks for this study was selected to allow the maximum treatment time supported by nonclinical data.

This is the first study in patients with FSGS, therefore subjects will receive 2 dose levels of VX-147 to characterize PK of VX-147 at 2 dose levels in this population. As shown in Figure 9-1, the 15 mg qd dose will be administered for 2 weeks and the 45 mg qd dose will be administered for 11 weeks. The 2-week duration for the 15 mg qd dose was selected based on an exposure-response model suggesting that a measurable decrease in proteinuria may be observed after 2 weeks of dosing. The 11-week additional duration for the 45 mg qd dose, provides a total of 13 weeks continuous dosing, which is the longest observation period supported by available nonclinical data.

9.3.2 Study Population

The study will enroll male and female subjects, aged 18 to 65 years old, with biopsy proven FSGS, 2 *APOL1*-risk alleles, and nephrotic-range proteinuria. These patients have need for new treatments, because patients with FSGS and nephrotic-range proteinuria have rapid progression to kidney failure, with mean renal survival less than 10 years.[15, 16, 19-21] The presence of FSGS on biopsy will be confirmed by an independent, external expert (Section 9.3.6) to determine eligibility.

9.3.3 Study Drug Dose

The administration of once daily doses of 15 mg and 45 mg were selected on the totality of clinical safety, tolerability, and PK from the FIH study (Study 001); as well as toxicology and non-clinical pharmacodynamic (PD) data.

In Study 001, single ascending oral doses of VX-147 up to 50 mg and multiple ascending doses of VX-147 up to 45 mg once daily for 14 days were evaluated. The doses were well-tolerated and no clinically significant safety concerns were identified. In this study, a low dose of 15 mg once daily is selected to characterize the PK in FSGS patients and to assess any measurable decrease in proteinuria. Based on an exposure-response model, the exposures from the 15 mg dose are expected to result in approximately 90% inhibition in the in vitro ion flux model. This level of inhibition may result in a measurable decrease in proteinuria after 2 weeks of dosing.

A high dose of 45 mg once daily is selected to maximize the probability of reduction in proteinuria over the 11-week dosing period. Based on the exposure-response model referenced above, exposures from this dose are expected to result in over 96% inhibition in the in vitro ion flux model. VX-147 exposure from the 2 doses are expected to be well differentiated based on data from the FIH healthy subject study (Study 001). Thus, the doses selected will provide an adequate assessment of the dose-response relationship and safety profile of VX-147 in the exposure range of interest.

Additional information about FIH and nonclinical data are available in the Investigator's Brochure.

9.3.4 Study Assessments

All efficacy, safety, and PK assessments are common assessments for clinical studies, with the exception of those described below.

9.3.4.1 UPCR

Percent change from baseline in UPCR at Week 13 was chosen as the primary endpoint because proteinuria is a characteristic feature of FSGS and 1 of its main prognostic factors. Urine samples will be collected for UPCR using the first morning void, which is standardly used in clinical practice to determine accurate urine protein levels. As UPCR is variable within an individual, 3 samples will be taken during screening, Week 5, Week 9, and Week 13; and the average of the 3 values will be used to determine baseline, Week 5, Week 9, and end-of-treatment UPCR values, respectively.

9.3.4.2 SF-36

Change in SF-36 from baseline over the study treatment period will be assessed as an exploratory outcome. SF-36 is a patient-reported generic measure of health status. It has been previously used to evaluate health-related quality of life in patients with chronic kidney disease, including FSGS.[22,23]

9.3.5 Use of Telemedicine for Study Visits

Telemedicine may be used for a number of study visits as detailed in Table 3-1 through Table 3-3. These visits will include home health nurse visits to the subject's home to complete assessments. All visits must have a consultation between the subject and investigator (i.e., in person, phone, or telemedicine video conference) within 1 business day after the home health visit, in order to check-in and collect AEs. Subjects and investigators may choose to conduct individual visits in the clinic or through use of home health. Periodic phone or telemedicine video visits may also be done to allow the investigator and subject to communicate directly; these visits may be done face-to-face in the clinic at the discretion of the investigator.

If local regulations or site practice do not allow telemedicine, all visits will be conducted at the site.

9.3.6 Eligibility Review

An independent, external expert with appropriate clinical and scientific background will evaluate the histopathological eligibility criteria to ensure that the subjects meet the study's definition of FSGS. Details of the process will be included in a separate procedure manual.

9.4 Prior and Concomitant Medications

Information about all prior and concomitant medications, including the subject's FSGS medications, other medications, and herbal and naturopathic remedies administered from 28 days before the Screening Visit through the SFUV or last off-treatment Follow-up Visit in Part B, whichever is later, will be recorded in each subject's source documents. For subjects who are screened but not subsequently enrolled, details of prior medication will only be documented in the subjects' source documents.

Subjects in Cohort 1 and Cohort 2 who are taking low dose systemic corticosteroids (i.e., ≤ 10 mg/day of prednisone or prednisone equivalent), ACE inhibitors, ARB, neprilysin inhibitor, SGLT2 inhibitor, a renin inhibitor, or certain immunosuppressants (tacrolimus, mycophenolate,

or cyclosporine) must remain on a stable medication regimen at least 28 days before the Screening Visit through the Week 13 or ETT (if applicable) Visit. Subjects in Cohorts 1 and 2 who are taking systemic corticosteroids must remain on a stable low dose from at least 28 days before the Screening Visit through the Week 13 or ETT (if applicable) Visit. Use of higher doses of corticosteroids are permitted to treat urgent comorbid medical conditions. During the Part B Off-Treatment Period, every effort should be made to avoid starting, stopping, or modifying doses of these medications. If it becomes clinically necessary to alter a subject's antihypertensive regimen during the study, changes to an antihypertensive medication dose or addition of a new antihypertensive medication are recommended before changes are made to any ACE inhibitor, ARB, neprilysin inhibitor, or renin inhibitor.

9.5 Study Restrictions

Study restrictions are summarized in Table 9-1. A nonexhaustive list of medications is provided in the Study Reference Manual.

Table 9-1 Study Restrictions

Restricted Medication/Food/Activity[a]	Timing of Restriction	
	Start	**Stop**
Moderate and strong CYP3A4 inhibitors or inducers, including consumption of herbal medications (e.g., St. John's Wort)	None allowed within 14 days before the first dose of the study drug	Completion of Safety Follow-up Visit assessments
Nonpermitted Immunosuppressants *Note: This includes all immunosuppressants except tacrolimus, mycophenolate, and cyclosporine, which are permitted.*	None allowed within 12 weeks before the first dose of study drug	Completion of the last study assessment
Rituximab	None allowed within 6 months before the first dose of study drug	Completion of the last study assessment
Other investigational drugs or devices	28 days before first dose of study drug, 5 half-lives before first dose of study drug dose, or time determined by local requirements (whichever is longer)	Completion of the last study assessment
Creatine or creatine-containing dietary supplements	7 days before first dose of study drug	Completion of Safety Follow-up Visit assessments
Grapefruit, grapefruit juice, pomelos, orange marmalade, Seville/blood oranges	7 days before first dose of study drug	Until last PK sample is taken

[a] See Section 9.4 for guidance on concomitant medications.

9.6 Administration

VX-147 will be administered as 15 mg tablets, orally, as shown in Table 3-2.

Study drug will be administered according to the following guidelines:

- The first dose in each period must be administered under the supervision of site medical staff or a home health nurse. Subjects will be monitored for 4 hours after receiving the first dose of each Treatment Period
- On days of scheduled visits, the dose of study drug will be administered after predose assessments have been completed.
- Study drug will be taken at approximately the same time on each dosing occasion. For example, subjects that administer VX-147 dose at 8AM on Day 1 should administer all subsequent doses at 08:00AM ± 2 hours.
- Study drug may be taken with or without food.
- Subjects will swallow the study drug whole, with a full glass of water and will not chew it before swallowing.
- On days of intensive PK sampling, the date, dose taken, and time of study drug administration will be recorded for the 2 doses before PK sample collection and on the morning of PK sample collection.
- Subjects will be instructed to bring all used and unused materials associated with the study drug to the site or the nurse will take these materials at each study visit; study drug will be dispensed at each visit, as appropriate.

Missed Doses

If a subject misses a dose and recalls the missed dose within 6 hours, the subject should take his/her dose according to the guidance above. If more than 6 hours have elapsed after his/her usual dosing time, the subject should skip that dose and resume his/her normal schedule for the following dose. An example is provided below:

- If the morning dose of study drug should have been taken at approximately 08:00AM, and the subject remembers at 12:00PM that he/she forgot to take his/her dose, he/she should take the dose as soon as possible. If they remember after 2:00PM that they forgot to take the morning dose, they should skip that dose and resume the normal schedule the next day.

Additional information is provided in the Pharmacy Manual.

9.7 Dose Modification

No dose modifications are allowed. Treatment may be interrupted as outlined in Section 9.8. If any unacceptable toxicity arises in the opinion of the investigator, individual subjects may discontinue dosing. The Vertex medical monitor must be notified immediately.

9.8 Study Drug Interruption

Study drug may be interrupted for safety concerns by the investigator. The Vertex medical monitor should be notified of an interruption of study drug and of the resumption of study drug after such interruption.

9.9 Removal of Subjects

Subjects may withdraw from the study at any time at their own request. Subjects may be withdrawn from study drug treatment at any time at the discretion of the investigator or Vertex

for safety, behavior, noncompliance with study procedures, or administrative reasons. A subject who withdraws from study drug treatment will continue to be followed unless the subject withdraws consent.

Subjects who discontinue study treatment early should complete the ETT and SFUV, as noted in Sections 9.1.2.2 and 9.1.2.3.

If a subject does not return for a scheduled visit, reasonable effort will be made to contact the subject. In any circumstance, reasonable effort will be made to document subject outcome. The investigator will inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a SFUV, if applicable (see Section 9.1.2.3), and follow up with the subject regarding any unresolved AEs.

If a subject withdraws consent for the study, no further assessments will be performed. Vertex may retain and continue using the study data and samples after the study ends and may use the samples and information in the development of the study compound, for other drugs and diagnostics, in publications and presentations, and for education purposes. If a subject withdraws from the study, the study data and samples collected will remain part of the study. A subject will not be able to request the withdrawal of his/her information from the study data. A subject may request destruction of the samples collected from him/her during the study as long as those samples can be identified as his/her samples.

9.10 Replacement of Subjects

Subjects who withdraw or are withdrawn for nonsafety reasons during the study drug treatment period(s) may be replaced at Vertex's discretion.

10 STUDY DRUG INFORMATION AND MANAGEMENT

10.1 Preparation and Dispensing

Study drug may be dispensed only under the supervision of the investigator or an authorized designee and only for administration to the study subjects.

10.2 Packaging and Labeling

Vertex will supply the 15-mg VX-147 tablets. Study drug labeling will be in compliance with applicable local and national regulations. Additional details about packaging, labeling, and dispensing for VX-147 will be in the Pharmacy Manual.

10.3 Study Drug Supply, Storage, and Handling

The investigator, or an authorized designee (e.g., a licensed pharmacist), will ensure that all investigational product is stored in a secured area, under recommended storage conditions, and in accordance with applicable regulatory requirements. To ensure adequate records, all study drugs will be accounted for in the drug accountability forms as instructed by Vertex.

Detailed instructions regarding the storage, handling, and dispensation of the study drug will be provided in the Pharmacy Manual.

Table 10-1 Study Drug

Drug Name	Dosing Form/ Route	Dosage	How Supplied
VX-147	Tablet/ oral	15-mg	Supplied as 15-mg tablets
VX-147	Tablet/ oral	45-mg	Supplied as 3 × 15-mg tablets

10.4 Drug Accountability

The pharmacist or designated study site staff will maintain information about the dates and amounts of (1) study drug received; (2) study drug dispensed to the subjects; and (3) study drug returned by the subjects. A central pharmacy will be used. Subjects will be instructed to return all used and unused materials associated with the study drug to the home health nurse or site. These materials will be retained at the site or central pharmacy according to instructions provided by Vertex or its designee. The study monitor will review study drug records and inventory throughout the study. If a site or central pharmacy uses a site-specific drug accountability system and/or process, including processes associated with the destruction of returned materials, the process must be documented and approved by Vertex. The study monitor must review the drug accountability documentation on a regular basis. The study monitor will promptly communicate to Vertex any discrepancies he/she is unable to resolve with the site.

10.5 Disposal, Return, or Retention of Unused Drug

The study site staff or pharmacy personnel will retain all materials returned by the subjects until the study monitor has performed drug accountability. The investigator will ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Vertex. Destruction will be adequately documented.

10.6 Compliance

To ensure treatment compliance, the investigator or designee will supervise all study drug dosing that occurs at the site or in the subject's home at required study visits. At each visit, site personnel/home health care nurses will review that the subject is compliant with study drug dosing and remind the subject of study drug dosing requirements. Compliance will also be assessed by ongoing study drug count.

If a subject demonstrates continued noncompliance of study drug dosing despite educational efforts, the investigator should consider discontinuing the subject from the study

10.7 Blinding and Unblinding

This is an open-label study.

11 ASSESSMENTS

The schedule of assessments is shown in Table 3-1 through Table 3-3.

11.1 Subject and Disease Characteristics

Subject and disease characteristics include the following: demographics, medical history, height, and weight.

Medical history will be elicited from each subject and extracted from medical records during screening. Based on the medical history, the subject will be assessed for any disqualifying medical conditions as specified in the inclusion and exclusion criteria. The medical history will include a complete review of systems, past medical and surgical histories, and any allergies.

Height and weight will be measured with shoes off with light weight clothing (no outerwear). BMI will be calculated from weight and height.

11.2 Pharmacokinetics

11.2.1 Blood Sampling

Blood samples will be collected to determine plasma concentrations of VX-147. Metabolites of VX-147 may be analyzed, if necessary. These samples may also be used for further evaluation of the bioanalytical method, evaluation of unbound concentration of VX-147, and for exploratory analyses that provide information on the metabolic pathways used by or affected by VX-147; these results may not be included in the clinical study report.

All efforts will be made to obtain the PK samples at the exact nominal time relative to dosing. Acceptable windows for sampling times are shown in Table 11-1. Samples collected outside of these acceptable windows will be considered protocol deviations.

Table 11-1 Acceptable Pharmacokinetic Sampling Windows

Sampling Time	Time From Scheduled Sampling Allowed
Predose	Up to 60 minutes before dose
From 0.25 up to ≤4 hours after study drug dosing	± 15 minutes
> 4 hours after study drug dosing	± 120 minutes
48 hours after study drug dosing	± 180 minutes

For each visit with a PK blood draw, a record of study drug administration will be collected. The collection date and exact time that each PK blood sample is drawn will also be recorded.

Samples from the PK sampling will be kept frozen by Vertex or its designee until all analyses have been completed and then disposed of according to Vertex or designee standard operating procedures.

11.2.2 Processing and Handling of Pharmacokinetic Samples

Detailed procedures for the collection of samples and further procedures for processing and handling of samples for PK analysis will be in a separate document.

11.2.3 Bioanalysis

Samples will be analyzed using a validated analytical method in compliance with Vertex or designee standard operating procedures. A description of the assay and validation data will be provided in separate reports.

11.3 Urine Sampling for UPCR, UACR, and Safety Laboratory Panel

Urine will be collected from the first morning void (predose) for use in efficacy and safety analyses. Efficacy analyses will include UPCR (primary endpoint) and UACR (exploratory endpoint), as calculated from protein, albumin, and creatinine measured in the urine. Safety assessments will include the urine laboratory parameters in Section 11.6.2. During the Screening, Week 5, Week 9, and Week 13 Visits, when 3 samples are collected on 3 separate days within a 7-day period, the third sample collected will be used for the safety laboratory and biomarker assessments; all 3 samples will be used for UPCR and UACR.

If the subject does not remember to collect their first morning void on the scheduled visit day, the subject may provide the sample on another day within the visit window.

Details about the collection and processing of urine samples will be provided in the Laboratory Manual.

11.4 APOL1 Genotyping

A blood sample will be collected for determining APOL1 genotype during screening. This sample is not required if a genotype result is available from a previous Vertex study using a Vertex-approved clinical study assay.

The results of the genotyping test will be provided to the investigator. The investigator will inform the subject of the *APOL1* genotype. Vertex will ensure that subjects can obtain the services of a genetic counselor, if desired. The site will be responsible for managing the corresponding logistics.

11.5 Exploratory Assessments

These data will be used for internal exploratory purposes. Detailed procedures for the collection of blood and urine, as well as additional procedures for processing and handling samples, will be provided in a separate document.

11.5.1 Blood Biomarker Samples

Blood samples will be collected for potential exploratory evaluation of correlations between blood markers (e.g., post-translational APOL1 protein modification, peptides, lipids, endogenous metabolites, etc.) with PK and AEs observed in the study. The samples may also be used for the evaluation of safety biomarkers.

11.5.2 Urine Biomarker Samples

Urine samples will be collected from the first morning void for potential exploratory evaluation of correlations between urine biomarkers (e.g., exosomes) with PK treatment response, and AEs observed in the study. At visits where triplicate urine samples are collected, only the third urine sample will be used for urine biomarker analysis. Additional details will be provided in the Laboratory Manual.

11.5.3 SF-36

Subjects will complete the SF-36 in their native language (if validated translations are available) before all other study assessments at each scheduled time point. If there is no validated translation available in the subject's native language, the subject will not complete the questionnaire. The questionnaire provides information about functional health and wellbeing, as well as 2 psychometrically based physical and mental health summary measures.

11.6 Safety

Safety evaluations will include AEs, clinical laboratory assessments, clinical evaluation of vital signs, ECGs, and physical examinations (PEs).

11.6.1 Adverse Events

All AEs will be assessed, documented, and reported in accordance with ICH GCP Guidelines. Section 13.1 outlines the definitions, collection periods, criteria, and procedures for documenting, grading, and reporting AEs. A separate document that details AE CRF completion guidelines for investigators as well as training will be provided.

11.6.2 Clinical Laboratory Assessments

The safety laboratory test panels are shown in Table 11-2. For purposes of study conduct, blood and urine samples will be analyzed at a central laboratory, with the exception of urine pregnancy tests and if there are extenuating circumstances due to COVID-19, as described below.

Urine samples for safety laboratory assessments may be collected at the same time as the urine samples for efficacy and biomarker assessments (See Section 11.3). Refer to sample handling guidelines to ensure that each sample collected is submitted appropriately to the lab for analysis at each visit. At the Screening, Week 5, Week 9, and Week 13 Visits, only the third urine sample will be used for safety urinalysis and biomarker assessments; urine protein, creatinine, and albumin will be assessed for all 3 samples collected during this visit.

On days when overnight fasts are required (see Table 3-2 and Table 3-3), subjects will abstain from food and beverages for 8 hours before the start of the visit. During this period, water may be consumed up to 1 hour before study drug administration.

Local laboratories may be used at the discretion of the local investigator for management of urgent medical issues. If a local laboratory test value is found to be abnormal and clinically significant, it will be verified by the central laboratory as soon as possible after the investigator becomes aware of the abnormal result. If it is not possible to send a timely specimen to the central laboratory (e.g., the subject was hospitalized elsewhere), the investigator may base the assessment of an AE on the local laboratory value. Laboratory test results that are abnormal and considered clinically significant will be reported as AEs (see Section 13.1).

The central laboratory should be used for all assessments when possible, and Vertex should be notified if a local laboratory is to be used. If the subject is unable to have a clinic or home health visit due to extenuating circumstance of the COVID-19 global pandemic, local laboratories may be used after Day 1 for blood safety samples. When local labs are used for blood safety sample collection, the site will obtain the results from the local lab and ensure data are captured in the electronic data capture (EDC) per Section 13.5. Local labs may not be used for screening assessments.

Table 11-2 Safety Laboratory Test Panels

Serum Chemistry	Hematology	Urinalysis[a]
Glucose	Hemoglobin	Leukocyte esterase
Blood urea nitrogen[b]	Hematocrit	Nitrite
Creatinine	Erythrocytes	Urine protein[c]
Creatine kinase	Mean corpuscular volume	Urine creatinine[c]
Sodium	Platelets	Urine albumin[c]
Potassium	Reticulocytes	Urine blood
Calcium	Leukocytes	
Chloride	Differential (absolute and percent):	
Magnesium	Eosinophils	Urine ketones
Bicarbonate	Basophils	Urine glucose
Phosphate	Neutrophils	Urobilinogen
Total bilirubin, direct bilirubin	Lymphocytes	Urine pH
Alkaline phosphatase	Monocytes	Specific gravity
Aspartate transaminase	Blood smear[e]	
Alanine transaminase	**Coagulation**	
Amylase	Activated partial thromboplastin time	
Lipase	Prothrombin time	
Gamma-glutamyl transferase	Prothrombin time International Normalized Ratio	
Protein		
Albumin		
Cholesterol[d]		
Triglycerides[d]		
Low-density lipoprotein-direct[d]		
High-density lipoprotein[d]		

[a] For the Day 1 predose sample, microscopic examination of urine will be done, and results will be provided for leukocytes, erythrocytes, crystals, bacteria, and casts.
[b] If blood urea nitrogen cannot be measured, urea may be substituted.
[c] eGFR will be calculated using the CKD-EPI equation, and AKI will be determined using KDIGO criteria.[24] Urine protein, creatinine, and albumin measurements will be used for efficacy and safety.
[d] Lipid profile will only be measured at the visits with fasting: Day 1, Week 3, Week 13, ETT, and SFUV.
[e] A blood smear will be collected on Day 1, Week 13, and the ETT Visit.

Additional Tests at Screening: The following additional tests will be performed during screening to assess eligibility:

- *Serum beta-human chorionic gonadotropin (β-hCG) for all subjects*: Serum samples will be analyzed for β-hCG at the central laboratory.
- *Follicle-stimulating Hormone (Screening Period only):* Blood sample for FSH will be measured for any suspected postmenopausal female with at least 12 months of continuous spontaneous amenorrhea. Serum FSH levels must be within the postmenopausal reference range of the performing laboratory to be considered postmenopausal.
- *APOL1*: A blood sample will be collected to determine *APOL1* genotype, if required per Table 3-1.
- *HIV-1 and HIV-2 antibodies:* A blood sample will be collected for serology.
- *Hepatitis B surface antigen:* A blood sample will be collected for serology.

- *Hepatitis C Virus (HCV):* A blood sample will be collected for serology and nucleic acid testing. If the antibody test is positive, a nucleic acid test will be done.

Algorithm for assessing out of range laboratory values at Screening:

If one or more lab values NOT specified in the eligibility criteria (Section 8) are outside the normal range, the following choices are available:

- The subject may be excluded.
- The subject may be included if the lab value(s) are not clinically significant, as determined by the principal investigator (PI).
- The subject may be included if the lab abnormality is consistent with a pre-existing medical condition that is NOT excluded per protocol.
- Repeat the test for the individual lab assessment per the guidance in Section 9.1.1.1.

Pregnancy Testing for Female Subjects of Childbearing Potential (Section 11.6.5):

- Urine pregnancy tests will either be performed and analyzed at the site or, when there is a home health visit, at home using a home kit provided by the site/home health nurse. The urine pregnancy test on Day 1 must be negative before the first dose of study drug. Additional pregnancy tests may be required according to local regulations and/or requirements.

If a urine pregnancy test is positive, all study drug dosing will stop, and the pregnancy will be confirmed with a serum β-hCG test. If pregnancy is confirmed, the procedures outlined in Section 11.6.5.2 will be followed.

Additional Evaluations: Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate.

11.6.3 Physical Examinations and Vital Signs

A PE of all body systems and vital signs assessment will be performed at screening visits in the clinic. Screening visits done with a home health nurse will have an abbreviated PE. At other visits, an abbreviated PE will be done. Symptom-directed PEs and symptom-directed vital signs assessments can be performed by the investigator or healthcare provider at any time if deemed necessary by the investigator.

A complete PE includes a review of the following systems: head, neck, and thyroid; eyes, ears, nose, and throat (EENT); respiratory; cardiovascular; lymph nodes; abdomen; skin; musculoskeletal; and neurological. Breast, anorectal, and genital examinations will be performed when medically indicated. After screening, any clinically significant abnormal findings in PEs will be reported as AEs.

The abbreviated PE will include an assessment of the following body systems: cardiovascular system; respiratory system; skin; and abdomen.

Vital signs include blood pressure (systolic and diastolic), oral temperature, pulse rate, and respiration rate. The subject will be instructed to rest for at least 5 minutes before vital signs are assessed. At each scheduled timepoint, blood pressure will be recorded in triplicate.

11.6.4 Electrocardiograms

Standard 12-lead ECGs will be performed using a machine with printout. Additional standard 12-lead ECGs will be performed at any other time if clinically indicated. The performance of all ECGs will adhere to the following guidelines:

- The ECG will be done before any other procedures that may affect heart rate, such as blood draws.
- The subject will be instructed to rest for at least 5 minutes before having an ECG.
- The test should be performed in the supine position

A printout of the ECG traces will be made for safety review by the investigator and maintained with source documentation. Clinically significant ECG abnormalities occurring during the study through the SFUV will be recorded as AEs.

If study sites cannot use QTcF they should discuss alternatives with the medical monitor.

To ensure safety of the subjects, a qualified individual at the study site will make comparisons to baseline measurements. If the QTcF is increased by >60 msec from the baseline or an absolute QTcF value is ≥500 msec for any scheduled ECG, 2 additional ECGs will be performed approximately 2 to 4 minutes apart to confirm the original measurement. If either of the QTcF values from these repeated ECGs remains above the threshold value (>60 msec from baseline or ≥500 msec), a single ECG will be repeated at least hourly until QTcF values from 2 successive ECGs fall below the threshold value that triggered the repeat measurement. A subject with a confirmed QTcF value above the threshold value will discontinue dosing.

11.6.5 Contraception and Pregnancy

The effects of VX-147 on conception, pregnancy, and lactation in humans are not known. Refer to the VX-147 Investigator's Brochure for additional details.

11.6.5.1 Contraception

Study participation requires compliance with the contraception guidelines outlined below:

Contraception for the couple is waived for the following:

- True abstinence for the subject, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, and post-ovulation methods) and withdrawal are not acceptable methods of contraception. True abstinence must be practiced from the Screening Visit through 90 days after the last dose of study drug.
- If the male is infertile (e.g., bilateral orchiectomy).
- If the female is of non-childbearing potential. To be considered of non-childbearing potential, the female must meet at least 1 of the following criteria:
    - Postmenopausal: Amenorrheic for at least 12 consecutive months and a serum FSH level within the laboratory's reference range for postmenopausal females
    - Documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy
      Note: All other females (including females with tubal ligations and females who do not have a documented hysterectomy or bilateral oophorectomy/salpingo-oophorectomy) will be considered to be of childbearing potential.

- Same sex relationships.

For subjects for whom the contraception requirement is not waived:

For male subjects with female partners of childbearing potential, in addition to wearing a condom, study participation requires a commitment from the subject that at least 1 allowed method of contraception (in addition to a condom) will be used as a couple. Refer to Table 11-3 for allowed methods of contraception.

For female subjects with childbearing potential, study participation requires a commitment from the subject that at least 1 allowed method of contraception is used as a couple. Allowed methods of contraception are listed in Table 11-3.

Methods of contraception must be in successful use from signing of consent, approximately 28 days before the first dose of study drug (unless otherwise noted), and until 90 days following the last dose of study drug.

Table 11-3 Allowed Methods of Contraception

Method	Male Subjects and Their Female (Non-study) Partners	Female Subjects and Their Male (Non-study) Partners
Vasectomy 6 months or more previously, with a documented negative postvasectomy semen analysis for sperm	Yes	Yes
Documented tubal ligation 4 weeks or more previously	Yes	Yes
Continuous use of an intrauterine device for at least 90 days before the first dose of study drug	Yes	Yes
Oral, patch, implanted, injected, or vaginal hormonal contraceptives, if used consistently and correctly for at least 60 days before the first dose of study drug	Yes	Yes

Additional notes:

- Male subjects must use a condom to avoid exposing a potential fetus to study drug via the seminal fluid. The female condom is not an acceptable method due to the increased risk of tearing when the female and male condoms are used at the same time.
- Male and female subjects who are not sexually active at the time of screening must agree to follow the contraceptive requirements of this study if they become sexually active with a partner of the opposite sex.
- Male subjects must not donate sperm from the first study drug dose until 90 days after the last dose of study drug.
- Female subjects of childbearing potential should not plan to become pregnant during the study or within 90 days after the last dose of study drug.
- For male subjects with a female partner of childbearing potential, the couple should not plan to become pregnant during the study or within 90 days after the last dose of study drug.

- If applicable, additional contraception requirements may need to be followed according to local regulations and/or requirements.
- Unique situations that may not fall within the above specifications may be discussed with the Vertex medical monitor or designee on an individual basis.

11.6.5.2 Pregnancy

Subjects will be counseled to inform the investigator of any pregnancy that occurs during study treatment and for 90 days after the last dose of study drug.

If a female subject, or the female partner of a male subject, becomes pregnant while participating in the study, the study drug will be permanently discontinued immediately. The investigator will notify the medical monitor and Vertex Global Patient Safety (GPS) within 24 hours of the site's knowledge of the subject's (or partner's) pregnancy, and send the Pregnancy Information Collection Form to Vertex GPS.

A subject (or their partner, if relevant) who becomes pregnant while on study will be followed until the end of the pregnancy. The infant will be followed for 1 year after birth, provided informed consent is obtained. A separate ICF, which may be obtained in person or remotely, will be provided to explain these follow-up activities. Pregnancy itself is not an AE.

12 STATISTICAL AND ANALYTICAL PLANS

This section presents a summary of the planned final analyses for efficacy, safety, and clinical pharmacology. Efficacy and safety statistical analysis details will be provided in the statistical analysis plan (SAP) for this study, and clinical pharmacology analysis details will be provided in the clinical pharmacology analysis plan (CPAP), both of which will be finalized before last subject last visit for the treatment period (Part A).

12.1 Sample Size and Power

The sample size was not calculated based on power assumptions, because this is an estimation study. The primary endpoint is percent change from baseline in UPCR at Week 13. Assuming an SD of 0.672 (in log scale),[25] a sample size of 10 subjects will provide a precision of 0.294 (in log scale) for the estimation of the Geometric Mean Percent Change (GMPC) from baseline in UPCR. The precision of the estimate corresponds to the half width of its 80% CI, in log scale. Table 12-1 displays the expected size of the 80% CIs for the GMPC at various values of the observed GMPC. Up to 10 subjects will be enrolled in Cohort 1, and approximately 10 subjects will be enrolled in Cohort 2.

Table 12-1 Two-sided 80% Confidence Interval for GMPC from Baseline in UPCR

Number of Subjects Completing	Assumption for SD in Log Scale	Observed Geometric Mean (corresponding percent reduction from baseline)			
		0.5 (-50%)	0.6 (-40%)	0.7 (-30%)	0.8 (-20%)
10	0.672	0.37, 0.67 (-63%, -33%)	0.45, 0.81 (-55%, -19%)	0.52, 0.94 (-48%, -6%)	0.60, 1.07 (-40%, 7%)

12.2 Analysis Sets

The following analysis sets are defined: All Subjects Set, Full Analysis Set (FAS), Safety Set, and Follow-up Set.

The **All Subjects Set** will include all subjects who were enrolled in the study. This analysis set will be used for all individual subject data listings and disposition summary tables, unless otherwise specified.

The **FAS** will include all subjects who received at least 1 dose of study drug in the Treatment Period and have at least 1 post-baseline efficacy assessment. The FAS will be used to summarize subject demographics and baseline characteristics, and for all efficacy analyses in the Treatment Period, unless otherwise specified.

The **Follow-up Set** will include all subjects who entered the Off-treatment Follow-up Period (Part B) and have at least 1 efficacy assessment in that period. The Follow-up Set will be used for all efficacy analyses in the Follow-up Period, unless otherwise specified.

The **Safety Set** will include all subjects who received at least 1 dose of study drug. The Safety Set will be used for all safety analyses, unless otherwise specified.

12.3 Statistical Analysis

This section presents a summary of the planned statistical analyses of efficacy, safety and PK endpoints of the study. Statistical analysis details will be provided in the SAP.

12.3.1 General Considerations

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, SD, median, minimum value (min), and maximum value (max). The precision of the measurement for each continuous variable will be specified in the SAP. Unless otherwise specified, minimum and maximum values will be reported with the same precision as the units of the raw data. The mean, median, and SD will be reported to 1 additional decimal place. Any values that require a transformation to standard units (metric or International System [SI]) will be converted with the appropriate precision.

Categorical variables will be summarized using counts and percentages. Percentages will be presented to 1 decimal place.

Baseline value, unless specified otherwise, will be defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of study drug in the Treatment Period (i.e., the Day 1 Visit). For ECGs, baseline will be defined as the most recent pretreatment measurement (or the average of triplicate measurements, if the most recent pretreatment measurement is obtained in triplicate) before the first dose of study drug in the Treatment Period (i.e., the Day 1 visit). For UPCR (and UACR) data baseline value will be the average of UPCR (UACR) values from the 3 urine samples collected during screening for the purpose of assessing eligibility.

Change (absolute change) from baseline will be calculated as Post-baseline value − Baseline value.

Treatment emergent (TE) Period will include the time from the first dose of study drug in the Treatment Period to either (1) the SFUV, (2) ETT Visit if it replaces the SFUV, or (3) the date of the last dose + 28 days for subjects who do not have a SFUV. The TE Period will be used for safety analyses unless specified otherwise.

The analysis visit windows for protocol-defined visits will be described in the SAP.

The rules for handling missing data due to treatment or study discontinuation will be described in the SAP.

Data will be analyzed separately for the Treatment Period (Part A) and the Off-treatment Follow-up Period (Part B), unless specified otherwise.

12.3.2 Background Characteristics

12.3.2.1 Subject Disposition

The number and percentage of subjects in each disposition category in the Treatment Period (e.g., included in the All Subjects Set, included in the Safety Set, completed Treatment Period, completed SFUV, and discontinued treatment or study with a breakdown of the reasons for discontinuation) will be summarized.

The number and percentage of subjects in each disposition category in the Off-treatment Follow-up Period (e.g., included in the Follow-up Set, completed Follow-up Period, and discontinued study/Follow-up Period with a breakdown of the reasons for discontinuation) will be summarized.

12.3.2.2 Demographics and Baseline Characteristics

Demographics, background (e.g. medical history), and baseline characteristics will be summarized using descriptive summary statistics.

The following demographics and baseline characteristics will be summarized and will include (but not limited to): sex, race, age, weight, height, BMI, UPCR, UACR, and eGFR.

12.3.2.3 Prior and Concomitant Medications

Medications used will be coded using the World Health Organization Drug Dictionary (WHO-DD) and categorized as the following:

Prior medication: any medication that started before the date of the first dose of study drug, regardless of when the medication ended

Concomitant medication: medication continued or newly received on or after the date of the first dose of study drug through the end of the TE Period

A given medication may be classified as prior, concomitant, or both prior and concomitant.

If a medication start date is on or after the first dose date of study drug, then the medication will be categorized as concomitant medication regardless of whether the medication end date is missing or not. If a medication end date is before the first dose date of study drug, then the medication will be categorized as prior medication regardless of whether the medication start date is missing or not. Note that medication that started before the first dose of study drug and continued after the first dose will be categorized as prior medication and separately as concomitant medication.

If a medication has a missing or partially missing start/end date or time and if it cannot be determined whether it was taken before the first dose of study drug, or concomitantly, it will be considered in both categories of prior and concomitant medication.

Prior medications and concomitant medications will be summarized descriptively using frequency tables by Preferred Name.

Details for imputing missing or partial start and/or stop dates of medication will be in the SAP.

12.3.2.4 Study Drug Exposure and Compliance

Exposure to study drug will be summarized in terms of duration of treatment a subject received (in days), defined as: last dose date – first dose date + 1 day, regardless of study drug interruption.

Study drug compliance based on study drug exposure, will be summarized, and will be calculated as: $100 \times [1 – (\text{total number of days of any study drug interruption})/(\text{duration of study drug exposure in days})]$.

12.3.2.5 Important Protocol Deviations

An important protocol deviation (IPD) is a deviation that may significantly affect the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. The rules for identifying an IPD will be described in the SAP.

IPDs will be provided in an individual subject data listing.

12.3.3 Efficacy Analysis

Analyses will be done separately for Cohort 1 and Cohort 2, as well as combined.

12.3.3.1 Analysis of Primary Variables

The primary efficacy endpoint is percent change from baseline in UPCR at Week 13. The Week 13 UPCR value will be calculated as the average of the available UPCR measurements (maximum 3) taken during Week 13. The baseline value will be the average of the 3 UPCR values from the urine samples collected during screening.

The percent change from baseline in UPCR at Week 13 will be analyzed by first log transforming the UPCR data before analyses to reduce skewness and calculating the change from baseline in log-transformed values. The GMPC from baseline in UPCR will be estimated along with the corresponding 2-sided 80% CI. The GMPC from baseline and associated confidence limits will be calculated by back-transforming the estimated simple mean of change from baseline in log-transformed data.

Sensitivity analyses for handling missing data due to treatment or study discontinuation will be described in the SAP.

12.3.3.2 Analysis of Other Variables

In all exploratory analyses of UPCR and UACR related data, the Week 5, Week 9, and Week 13 UPCR/UACR value will be calculated as the average of the available UPCR/UACR measurements (maximum 3) taken during these weeks, and the baseline value will be the average of the 3 UPCR/UACR values from the urine samples collected for this purpose during screening.

The percent change from baseline in UPCR over time during the Treatment period is an exploratory efficacy endpoint. Similar to the primary endpoint analysis, UPCR data will be log-transformed and change from baseline at each planned visit, up to Week 13, will be analyzed using the log-transformed UPCR values. The GMPC from baseline and associated 2-sided 80% CI at each planned visit will be calculated by back-transforming the corresponding estimated simple mean and CI from the log-transformed data.

Other exploratory efficacy endpoints include percent change from baseline in urinary albumin to-creatinine ratio (UACR) at Week 13, and percent change from baseline in UACR over time during the Treatment period. Analysis of these 2 endpoints will be similar to that performed for the corresponding UPCR endpoints.

Off-treatment Follow-up Period (Part B): The exploratory endpoint of percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period will be analyzed similarly to the primary efficacy endpoint.

Additional details of these analyses will be provided in the SAP.

12.3.4 Safety Analysis

All safety analyses will be based on data from the TE Period for all subjects in the Safety Set. The overall safety profile of study drug will be assessed in terms of the following safety and tolerability endpoints:

- Incidence of treatment-emergent adverse events (TEAEs)
- Clinical laboratory values (hematology, serum chemistry, coagulation studies, and urinalysis)
- Standard 12-lead ECG outcomes
- Vital signs

Only a descriptive analysis of safety will be performed.

All safety data will be presented in individual subject data listings.

12.3.4.1 Adverse Events

For analysis purposes, AEs will be classified as pretreatment AEs or TEAEs, defined as follows:

Pretreatment AE: any AE that started before the first dose date of study drug

TEAE: any AE that worsened (either in severity or seriousness) or that was newly developed on or after the first dose date of study drug through the end of the TE Period

For AEs with completely missing or partially missing start dates, if there is no clear evidence that the AEs started before or after study treatment, the AEs will be classified as TEAEs.

AE summary tables will be presented for TEAEs only and will include the following:

- All TEAEs
- TEAEs by strongest relationship
- TEAEs by maximum severity
- TEAEs leading to treatment discontinuation

- Serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA System Organ Class (SOC) and Preferred Term (PT) using frequency counts and percentages (i.e., number and percentage of subjects with an event). When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Only the maximum severity level will be presented in the severity summaries, and the strongest relationship level will be presented in the relationship summaries.

In addition, a listing of individual subject level AE data for TEAEs leading to treatment discontinuation, SAEs, and deaths will be provided separately. All AEs, including pretreatment AEs, will be in individual subject data listings.

12.3.4.2 Clinical Laboratory Assessments

For treatment emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized in SI units by visit.

The number and percentage of subjects with at least 1 laboratory event outside threshold criteria for the event during the TE Period will be summarized, including a shift of the event from baseline to post-baseline. The threshold criteria will be in the SAP.

Results of urinalysis and the urine/serum pregnancy test will be in individual subject data listings only.

In addition, a listing of individual subject hematology, chemistry, and coagulation values outside the normal reference ranges will be provided. This listing will include data from both scheduled and unscheduled visits.

12.3.4.3 Electrocardiogram

For treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided by visit and time point, as applicable, for the following ECG measurements: RR (msec), heart rate (HR; beats per minute [bpm]), PR (msec), QRS duration (msec), QT (msec), and QT corrected for HR intervals (QTcF [msec]).

The number and percentage of subjects meeting a threshold analysis criterion during the TE Period will be summarized. The threshold analysis criteria will be provided in the SAP.

Clinically significant abnormal findings will be reported as AEs.

Additional ECG analyses may be described in the SAP.

12.3.4.4 Vital Signs

For treatment-emergent vital signs measurements, the observed values and change from baseline values will be summarized by visit: systolic and diastolic blood pressure (mm Hg), body temperature (°C), pulse rate (bpm), and respiratory rate (breaths per minute).

The number and percentage of subjects with at least 1 event outside the threshold criteria for a vital sign during the TE Period will be summarized. The threshold analysis criteria will be provided in the SAP.

Clinically significant abnormal findings in vital signs will be reported as AEs.

Additional vital signs analyses may be described in the SAP.

12.3.4.5 Physical Examination

PE findings will be presented in individual subject data listings only.

12.3.4.6 Other Safety Analysis

Change from baseline in weight will be summarized by visit.

12.3.5 Other Analyses

Analysis of the exploratory endpoints for SF-36 will be provided in the SAP.

12.3.6 Interim and Independent Data Monitoring Committee Analyses

Interim analyses may be done at the discretion of the sponsor to allow for regulatory interactions and clinical development planning. There is no independent Data Monitoring Committee for this study.

12.4 Clinical Pharmacology Analysis

The following systemic exposure parameters will be estimated using noncompartmental and population PK analysis: AUCτ during a dosing interval, C_{max} and C_{trough} will be estimated for all subjects who provide adequate number of PK samples:

- on Day 1 after single administration of the lower dose;
- at Week 2 after the first administration of the higher dose;
- at Week 5 after multiple administrations of the higher dose.

In addition, observed C_{trough} will be reported at Weeks 1, 3, 9, and 13. Based on availability of data after the last administration of the higher dose, half-life will be reported after multiple administrations of the higher dose.

12.4.1 Pharmacokinetic Analysis

Mean and/or median plasma concentrations versus time will be plotted on log and linear scales. The PK parameters (C_{max}, C_{trough}, AUC_{τ}, and other parameters as needed) of VX-147 estimated by noncompartmental analysis will be listed and summarized using summary statistics. Ongoing analyses of plasma concentrations of VX-147 may be conducted before database lock.

Details of the analyses will be in the CPAP.

12.4.2 Pharmacokinetic/Pharmacodynamic Analyses

A population PK analysis of plasma concentration versus time data of VX-147 will be performed using the nonlinear mixed-effects modeling approach. Population and individual PK parameters: clearance after oral administration (CL/F) and apparent volume of distribution at steady state (Vss/F) will be estimated and the influence of various covariates (such as age, gender, and body weight) on these parameters will be investigated in an exploratory way. If deemed necessary, data may be pooled with data from other studies with VX-147 in order to improve the parameter estimates from the model.

Plasma concentration response relationship (PD markers and AEs, if any) will be explored. A more detailed description of the methodology to be followed will be in either the CPAP or the population PK/PD analysis plan. Listings of VX-147 plasma concentration data will be in the bioanalytical report. The population PK analysis will be in a stand-alone report.

13 PROCEDURAL, ETHICAL, REGULATORY, AND ADMINISTRATIVE CONSIDERATIONS

13.1 Adverse Event and Serious Adverse Event Documentation, Severity Grading, and Reporting

13.1.1 Adverse Events

13.1.1.1 Definition of an Adverse Event

An AE is defined as any untoward medical occurrence in a subject during the study; the event does not necessarily have a causal relationship with the treatment. This includes any newly occurring event or worsening of a pre-existing condition (e.g., increase in its severity or frequency) after the ICF is signed.

An AE is considered serious if it meets the definition in Section 13.1.2.1.

13.1.1.2 Clinically Significant Assessments

Study assessments including laboratory tests, ECGs, PEs, and vital signs will be assessed and those deemed to have clinically significant worsening from baseline will be documented as an AE. When possible, a clinical diagnosis for the study assessment will be provided, rather than the abnormal test result alone (e.g., urinary tract infection, anemia). In the absence of a diagnosis, the abnormal study assessment itself will be listed as the AE (e.g., bacteria in urine or decreased hemoglobin).

An abnormal study assessment is considered clinically significant if the subject has 1 or more of the following:

- Concomitant signs or symptoms related to the abnormal study assessment
- Further diagnostic testing or medical/surgical intervention
- A change in the dose of study drug or discontinuation from the study

Repeat testing to determine whether the result is abnormal, in the absence of any of the above criteria, does not necessarily meet clinically significant criteria. The determination of whether the study assessment results are clinically significant will be made by the investigator.

A laboratory value that is Grade 4 will not automatically be an SAE. A Grade 4 laboratory value will be an SAE if the subject's clinical status indicates a life-threatening AE.

13.1.1.3 Documentation of Adverse Events

All AEs will be collected from the time the ICF is signed until the following times:

- For subjects who do not enroll: until time of screen failure (e.g., screen failure, withdrawal of consent)
- For enrolled subjects who have a SFUV: through the SFUV

- For enrolled subjects who do not have a SFUV, the earliest of
    - 28 days after the last dose of study drug, or
    - the ETT Visit, if that visit is 3 weeks or later following the last dose of study drug (see Section 9.1.2.3)

As noted in Table 3-1, for subjects undergoing a 2-step screening process, AEs related to phlebotomy will be collected for up to 24 hours after the blood collection; AEs will not be collected during the time between a subject undergoing genotype screening and the start of the Screening Visit.

All subjects will be queried, using nonleading questions, about the occurrence of AEs at each study visit. When possible, a constellation of signs and/or symptoms will be identified as 1 overall event or diagnosis. All AEs for enrolled subjects will be recorded in the CRF and source document. AEs for subjects who are screened but not subsequently enrolled will be recorded only in the subject's source documents. The following data will be documented for each AE:

- Description of the event
- Classification of "serious" or "nonserious"
- Date of first occurrence and date of resolution (if applicable)
- Severity
- Causal relationship to study drug(s)
- Action taken
- Outcome
- Concomitant medication or other treatment given

13.1.1.4 Adverse Event Severity

The investigator will determine and record the severity of all serious and nonserious AEs. The guidance available at the following website will be consulted: Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0, Cancer Therapy Evaluation Program, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm (Accessed February 2020). The severity of an AE described by a term that does not appear in the CTCAE will be determined according to the definitions in Table 13-1.

Table 13-1 Grading of AE Severity

Classification	Description
Mild (Grade 1)	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Moderate (Grade 2)	Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[a]
Severe (Grade 3)	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[b]
Life-threatening (Grade 4)	Life-threatening consequences, urgent intervention indicated

Table 13-1 Grading of AE Severity

Classification	Description
Death (Grade 5)	Death related to AE

Source: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
ADL: activities of daily living; AE: adverse event
Note: A semi-colon indicates 'or' within the description of the grade.
[a] Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

13.1.1.5 Adverse Event Causality

Every effort will be made by the investigator to assess the relationship of the AE, if any, to the study drug(s). Causality will be classified using the categories in Table 13-2.

Table 13-2 Classifications for AE Causality

Classification	Definition
Related	There is an association between the event and the administration of investigational study drug, a plausible mechanism for the event to be related to the investigational study drug and causes other than the investigational study drug have been ruled out, and/or the event reappeared on re-exposure to the investigational study drug.
Possibly related	There is an association between the event and the administration of the investigational study drug and there is a plausible mechanism for the event to be related to investigational study drug, but there may also be alternative etiology, such as characteristics of the subject's clinical status or underlying disease.
Unlikely related	The event is unlikely to be related to the investigational study drug and likely to be related to factors other than investigational study drug.
Not related	The event is related to an etiology other than the investigational study drug (the alternative etiology will be documented in the subject's medical record).

13.1.1.6 Study Drug Action Taken

The investigator will classify the study drug action taken with regard to the AE. The action taken will be classified according to the categories in Table 13-3.

Table 13-3 Classifications for Study Drug Action Taken With Regard to an AE

Classification	Definition
Dose not changed	Study drug dose not changed in response to an AE
Dose reduced	Study drug dose reduced in response to an AE
Drug interrupted	Study drug administration interrupted in response to an AE
Drug withdrawn	Study drug administration permanently discontinued in response to an AE
Not applicable	Action taken regarding study drug administration does not apply. "Not applicable" will be used in circumstances such as when the investigational treatment had been completed before the AE began and no opportunity to decide whether to continue, interrupt, or withdraw treatment is possible.

13.1.1.7 Adverse Event Outcome

An AE will be followed until the investigator has determined and provided the final outcome. The outcome will be classified according to the categories in Table 13-4.

Table 13-4 Classifications for Outcome of an AE

Classification	Definition
Recovered/resolved	Resolution of an AE with no residual signs or symptoms
Recovered/resolved with sequelae	Resolution of an AE with residual signs or symptoms
Not recovered/not resolved (continuing)	Either incomplete improvement or no improvement of an AE, such that it remains ongoing
Fatal	Outcome of an AE is death. "Fatal" will be used when death is at least possibly related to the AE.
Unknown	Outcome of an AE is not known (e.g., a subject lost to follow-up)

13.1.1.8 Treatment Given

The investigator ensures adequate medical care is provided to subjects for any AEs, including clinically significant laboratory values related to study drug. In addition, the investigator will describe whether any treatment was given for the AE. "Yes" is used if any treatment was given in response to an AE, and may include treatments such as other medications, surgery, or physical therapy. "No" indicates the absence of any kind of treatment for an AE.

13.1.2 Serious Adverse Events

13.1.2.1 Definition of a Serious Adverse Event

An SAE is any AE that meets any of the following outcomes:

- Fatal (death, regardless of cause, that occurs during participation in the study or occurs after participation and is suspected of being a delayed toxicity due to administration of the study drug)
- Life-threatening, such that the subject was at immediate risk of death from the reaction as it occurred
- Inpatient hospitalization or prolongation of hospitalization
- Persistent or significant disability/incapacity (disability is defined as a substantial disruption of a person's ability to conduct normal life functions)
- Congenital anomaly or birth defect
- Important medical event that, based upon appropriate medical judgment, may jeopardize the subject or may require medical or surgical intervention to prevent 1 of the outcomes listed above (e.g., an allergic bronchospasm requiring intensive treatment in an emergency room or at home)

If a subject has a hospitalization or procedure (e.g., surgery) for an event or condition that occurred before the subject signed the ICF, and the hospitalization or procedure was planned before the subject signed the ICF, the hospitalization or procedure will not be considered to

indicate an SAE, unless an AE caused the hospitalization or procedure to be rescheduled sooner or to be prolonged relative to what was planned. In addition, hospitalizations clearly not associated with an AE (e.g., social hospitalization for purposes of respite care) will not be considered to indicate an SAE.

Clarification will be made between the terms "serious" and "severe" because they are not synonymous. The term "severe" is often used to describe the intensity (severity) of a specific event, as in mild, moderate, or severe myocardial infarction. The event itself, however, may be of relatively minor medical significance, such as a severe headache. This is not the same as "serious", which is based on subject/event outcome or action described above, and is usually associated with events that pose a threat to a subject's life or functioning. Seriousness, not severity, serves as a guide for defining expedited regulatory reporting obligations.

13.1.2.2 Reporting and Documentation of Serious Adverse Events

All SAEs that occur after obtaining informed consent through the SFUV, regardless of causality, will be reported by the investigator to Vertex GPS **within 24 hours of identification**. In addition, all SAEs that occur after the SFUV and are considered related to study drug(s) will be reported to Vertex GPS **within 24 hours of identification**.

For SAEs that occur after obtaining informed consent through the SFUV, the SAE Form will be completed for new/initial events as well as to report follow-up information on previously reported events. Investigators are asked to report follow-up information as soon as it becomes available to ensure timely reporting to health authorities.

Please send completed SAE Forms to Vertex GPS via:

[redacted]

For technical issues related to submitting the form, contact telephone: [redacted]

SAEs that occur after the SFUV and are considered related to study drug(s) will be recorded on the Vertex Clinical Trial Safety Information Collection Form (hereafter referred to as the "SAE Form") using a recognized medical term or diagnosis that accurately reflects the event. SAEs will be assessed by the investigator for relationship to the investigational study drug(s) and possible etiologies. On the SAE Form, relationship to study drug(s) will be assessed only as related (includes possibly related) or not related (includes unlikely related), and severity assessment will not be required. For the purposes of study analysis, if the event has not resolved at the end of the study reporting period, it will be documented as ongoing. For purposes of regulatory safety monitoring, the investigator is required to follow the event to resolution and report the outcome to Vertex using the SAE Form.

13.1.2.3 Expedited Reporting and Investigator Safety Letters

Vertex, as study sponsor, is responsible for reporting suspected, unexpected, serious adverse reactions (SUSARs) involving the study drug(s) to all regulatory authorities, IECs, and participating investigators in accordance with ICH Guidelines and/or local regulatory requirements, as applicable. In addition, Vertex, or authorized designee, will be responsible for the submission of safety letters to central IECs.

It is the responsibility of the investigator or designee to promptly notify the local IRB/IEC of all unexpected serious adverse drug reactions involving risk to human subjects.

13.2 Administrative Requirements

13.2.1 Ethical Considerations

The study will be conducted in accordance with the current ICH GCP Guidelines, which are consistent with the ethical principles founded in the Declaration of Helsinki, and in accordance with local applicable laws and regulations. The IRB/IEC will review all appropriate study documentation to safeguard the rights, safety, and well-being of the subjects. The study will be conducted only at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, sample ICF, advertisements (if applicable), written information given to the subjects (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator or Vertex, as allowable by local applicable laws and regulations.

13.2.2 Subject Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from the subject, before study participation and before performing any study-related procedures. Remote consent may be used. Remote consent would include a phone call or telemedicine visit between the site and subject for the consent discussion. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH GCP and all applicable laws and regulations and will be subject to approval by Vertex or its designee.

13.2.3 Investigator Compliance

No modifications to the protocol will be made without the approval of both the investigator and Vertex. Changes that significantly affect the safety of the subjects, the scope of the investigation, or the scientific quality of the study (i.e., efficacy assessments) will require IRB/IEC notification before implementation, except where the modification is necessary to eliminate an apparent immediate hazard to human subjects. Vertex will submit all protocol modifications to the required regulatory authorities.

When circumstances require an immediate departure from procedures set forth in the protocol, the investigator will contact Vertex to discuss the planned course of action. If possible, contact will be made before the implementation of any changes. Any departures from the protocol will be fully documented in the source documentation and in a protocol deviation log.

13.2.4 Access to Records

The investigator will make the office and/or hospital records of subjects enrolled in this study available for inspection by Vertex or its representative at the time of each monitoring visit and for audits. The records will also be available for direct inspection, verification, and copying, as required by applicable laws and regulations, by officials of the regulatory health authorities (FDA and others). The investigator will comply with applicable privacy and security laws for use and disclosure of information related to the research set forth in this protocol.

13.2.5 Subject Privacy

To maintain subject confidentiality and to comply with applicable data protection and privacy laws and regulations, all CRFs, study reports, and communications relating to the study will identify subjects by assigned subject numbers, and access to subject names linked to such numbers will be limited to the site and the study physician and will not be disclosed to Vertex. As required by applicable laws and regulations in the countries in which the study is being conducted, the investigator will allow Vertex and/or its representatives access to all pertinent medical records to allow for the verification of data gathered in the CRFs/SAE Forms and the review of the data collection process. The FDA and regulatory authorities in other jurisdictions, including the IRB/IEC, may also request access to all study records, including source documentation, for inspection.

For sites participating in the US, and in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated regulations, an executed HIPAA authorization will be obtained by the site from each subject (or the legal representative of the subject) before research activities may begin. Each HIPAA authorization will comply with all HIPAA requirements including authorization allowing the site access to and use of the subject's personally identifiable health information, authorization for the site to disclose such information to Vertex, the FDA, and other parties requiring access under the protocol, and statements as to the purpose for which such information may be used and for how long.

13.2.6 Record Retention

The investigator will maintain all study records according to ICH GCP Guidelines and/or applicable local regulatory requirement(s), whichever is longest, as described in the Clinical Trial Agreement. If the investigator withdraws from the responsibility of keeping the study records, custody will be transferred to a person willing to accept the responsibility and Vertex will be notified.

13.2.7 Study Termination

At any time, Vertex may terminate this study in its entirety or may terminate this study at any particular site. In addition, for reasonable cause, either the investigators or their IRBs/IECs may terminate the study at their center.

Conditions that may lead to reasonable cause and warrant termination include, but are not limited to:

- Subject or investigator noncompliance
- Unsatisfactory subject enrollment
- Lack of adherence to protocol procedures
- Lack of evaluable and/or complete data
- Potentially unacceptable risk to study subjects
- Decision to modify drug development plan
- Decision by the FDA or other regulatory authority

Written notification that includes the reason for the clinical study termination is required.

13.2.8 End of Study

The end of study is defined as the last scheduled visit (or scheduled contact) of the last subject.

13.3 Data Quality Assurance

Vertex or its designated representative will conduct a study site visit to verify the qualifications of each investigator, inspect clinical study site facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each subject. Study data for each enrolled subject will be entered into a CRF by study site personnel using a secure, validated, web-based EDC application. Vertex will have read-only access to site-entered clinical data in the EDC application.

Instances of missing, discrepant, or uninterpretable data will be queried with the investigator for resolution. Any changes to study data will be made to the CRF and documented in an audit trail, which will be maintained within the clinical database.

13.4 Monitoring

Monitoring and auditing procedures developed or approved by Vertex will be followed to comply with GCP Guidelines. On-site or remote (as applicable by local regulation) checking of the CRFs/SAE Forms for completeness and clarity, cross-checking with source documents, and clarification of administrative matters will be performed.

The study will be monitored by Vertex or its designee. Monitoring will be done by personal visits from a representative of Vertex or designee (study site monitor), who will review the CRFs/SAE Forms and source documents. The study site monitor will ensure that the investigation is conducted according to the protocol design and regulatory requirements.

13.5 Electronic Data Capture

Vertex will provide the study sites with secure access to and training on the EDC application is sufficient to permit study site personnel to enter or correct information in the CRFs on the subjects for which they are responsible.

A CRF will be completed for each enrolled study subject. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data will indicate the subject's participation in the study and will document the dates and details of study procedures, AEs, other observations, and subject status.

The investigator, or designated representative, will complete the CRF as soon as possible after information is collected.

The audit trail entry will show the user's identification information and the date and time of any correction. The investigator will provide formal approval of all the information in the CRFs, including any changes made to them, to endorse the final submitted data for the subjects for whom the investigator is responsible.

Vertex will retain the CRF data and corresponding audit trails. A copy of the final archival CRF in the form of a compact disc (CD) or other electronic media will be placed in the investigator's study file.

13.6 Confidentiality and Disclosure

Any and all scientific, commercial, and technical information disclosed by Vertex in this protocol or elsewhere will be considered the confidential and proprietary property of Vertex. The investigator shall hold such information in confidence and shall not disclose the information to any third party except to such of the investigator's employees and staff as have been made aware that the information is confidential and who are bound to treat it as such and to whom disclosure is necessary to evaluate that information. The investigator shall not use such information for any purpose other than determining mutual interest in performing the study and, if the parties decide to proceed with the study, for the purpose of conducting the study.

The investigator understands that the information developed from this clinical study will be used by Vertex in connection with the development of the study drug and other drugs and diagnostics, and therefore may be disclosed as required to other clinical investigators, business partners and associates, the FDA, and other government agencies. The investigator also understands that, to allow for the use of the information derived from the clinical study, the investigator has the obligation to provide Vertex with complete test results and all data developed in the study.

13.7 Publications and Clinical Study Report

13.7.1 Publication of Study Results

Vertex is committed to reporting the design and results of all clinical studies in a complete, accurate, balanced, transparent, and timely manner, consistent with Good Publication Practices (GPP3).[26]

Publication Planning: Vertex staff along with the lead PIs, the steering committee (SC), and/or the publication committee (PC) will work together to develop a publication plan.

Authorship: Authorship of publications will be determined based on the Recommendations for Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, which states that authorship should be based on the following 4 criteria[27]:

1. Substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data;
2. Drafting of the article or revising it critically for important intellectual content;
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 conditions 1, 2, 3, and 4. All persons designated as authors should qualify for authorship, and all those who qualify should be listed. Contributions such as medical writing, enrollment of subjects, acquisition of funding, collection of data, or general supervision of the research group, alone, do not justify authorship.

Contributors: Contributors who meet fewer than all 4 of International Committee of Medical Journal Editors (ICMJE) criteria for authorship will not be listed as authors, but their contribution will be acknowledged and specified either as a group (e.g., "study investigators") or individually (e.g., "served as scientific advisor").

Publication Review: As required by a separate clinical study agreement, Vertex must have the opportunity to review all publications, including any manuscripts, abstracts, oral/slide presentations, and book chapters regarding this study before submission to congresses or journals for consideration.

13.7.2 Clinical Study Report

A clinical study report (CSR), written in accordance with the ICH E3 Guideline, will be submitted in accordance with local regulations.

14 REFERENCES

1 McGrogan A, Franssen C, de Vries C. The incidence of primary glomerulonephritis worldwide: a systematic review of the literature. Nephrology Dialysis Transplantation. 2011;26(2):414-30.

2 D'Agati VD, Kaskel FJ, Falk RJ. Focal segmental glomerulosclerosis. N Engl J Med. 2011;365(25):2398-411.

3 Kopp JB, Nelson GW, Sampath K, Johnson RC, Genovese G, An P, et al. APOL1 genetic variants in focal segmental glomerulosclerosis and HIV-associated nephropathy. J Am Soc Nephrol. 2011;22(11):2129-37.

4 Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, et al. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. Science. 2010;329(5993):841-5.

5 Shukha K, Mueller JL, Chung RT, Curry MP, Friedman DJ, Pollak MR, et al. Most ApoL1 is secreted by the liver. J Am Soc Nephrol. 2017;28(4):1079-83.

6 Madhavan SM, O'Toole JF, Konieczkowski M, Ganesan S, Bruggeman LA, Sedor JR. APOL1 localization in normal kidney and nondiabetic kidney disease. J Am Soc Nephrol. 2011;22(11):2119-28.

7 Vanhamme L, Paturiaux-Hanocq F, Poelvoorde P, Nolan DP, Lins L, Van Den Abbeele J, et al. Apolipoprotein L-I is the trypanosome lytic factor of human serum. Nature. 2003;422(6927):83-7.

8 Perez-Morga D. Apolipoprotein L-I promotes trypanosome lysis by forming pores in lysosomal membranes. Science. 2005;309(5733):469-72.

9 Cooper A, Ilboudo H, Alibu VP, Ravel S, Enyaru J, Weir W, et al. APOL1 renal risk variants have contrasting resistance and susceptibility associations with African trypanosomiasis. Elife. 2017;6:e25461.

10 Ma L, Chou JW, Snipes JA, Bharadwaj MS, Craddock AL, Cheng D, et al. APOL1 renal-risk variants induce mitochondrial dysfunction. J Am Soc Nephrol. 2017;28(4):1093-105.

11 Beckerman P, Bi-Karchin J, Park ASD, Qiu C, Dummer PD, Soomro I, et al. Transgenic expression of human APOL1 risk variants in podocytes induces kidney disease in mice. Nat Med. 2017;23(4):429-38.

12 Tzur S, Rosset S, Shemer R, Yudkovsky G, Selig S, Tarekegn A, et al. Missense mutations in the APOL1 gene are highly associated with end stage kidney disease risk previously attributed to the MYH9 gene. Hum Genet. 2010;128(3):345-50.

13 Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Annals of internal medicine. 2009;150(9):604-12.

14 Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, et al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. New England Journal of Medicine. 2012;367(1):20-29.

15 Chun MJ, Korbet SM, Schwartz MM, Lewis EJ. Focal segmental glomerulosclerosis in nephrotic adults: presentation, prognosis, and response to therapy of the histologic variants. J Am Soc Nephrol. 2004;15(8):2169-77.

16 Stirling CM, Mathieson P, Boulton-Jones JM, Feehally J, Jayne D, Murray HM, et al. Treatment and outcome of adult patients with primary focal segmental glomerulosclerosis in five UK renal units. QJM. 2005;98(6):443-9.

17 Cattran DC, Rao P. Long-term outcome in children and adults with classic focal segmental glomerulosclerosis. Am J Kidney Dis. 1998;32(1):72-9.
18 (KDIGO) KDIGO. 2012 Clinical Practice Guideline for the Evaluation and Management of Glomerulonephritis. Kidney Int. 2012;2(2):15-16.
19 Korbet SM, Schwartz MM, Lewis EJ. Primary focal segmental glomerulosclerosis: clinical course and response to therapy. Am J Kidney Dis. 1994;23(6):773-83.
20 Troyanov S, Wall CA, Miller JA, Scholey JW, Cattran DC, Toronto Glomerulonephritis Registry G. Focal and segmental glomerulosclerosis: definition and relevance of a partial remission. J Am Soc Nephrol. 2005;16(4):1061-8.
21 Rydel JJ, Korbet SM, Borok RZ, Schwartz MM. Focal segmental glomerular sclerosis in adults: presentation, course, and response to treatment. Am J Kidney Dis. 1995;25(4):534-42.
22 Gipson DS, Trachtman H, Kaskel FJ, Radeva MK, Gassman J, Greene TH, et al. Clinical trials treating focal segmental glomerulosclerosis should measure patient quality of life. Kidney International. 2011;79(6):678-85.
23 Komers R, Gipson DS, Nelson P, Adler S, Srivastava T, Derebail VK, et al. Efficacy and Safety of Sparsentan Compared With Irbesartan in Patients With Primary Focal Segmental Glomerulosclerosis: Randomized, Controlled Trial Design (DUET). Kidney International Reports. 2017;2(4):654-64.
24 Kidney Disease: Improving Global Outcomes (KDIGO) Working Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. Kidney International Supplement. 2012;2(1)
25 Trachtman H, Nelson P, Adler S, Campbell KN, Chaudhuri A, Derebail VK, et al. DUET: A Phase 2 Study Evaluating the Efficacy and Safety of Sparsentan in Patients with FSGS. Journal of the American Society of Nephrology. 2018;29(11):2745-54.
26 Battisti WP, Wager E, Baltzer L, Bridges D, Cairns A, Carswell CI, et al. Good Publication Practice for Communicating Company-Sponsored Medical Research: GPP3. Ann Intern Med. 2015;163(6):461-4.
27 (ICMJE) ICoMJE. International Committee of Medical Journal Editors (ICMJE). Recommendations for conduct, reporting, editing, and publication of scholarly work in medical journals. [Internet]. Available from: http://www.icmje.org/recommendations. Accessed 06 September.

15 PROTOCOL SIGNATURE PAGES

15.1 Sponsor Signature Page

Protocol #: VX19-147-101	Version #: 6.0	Version Date: 26 July 2021
Study Title: A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis		

This clinical study protocol has been reviewed and approved by the sponsor.

15.2 Investigator Signature Page

Protocol #: VX19-147-101	Version #: 6.0	Version Date: 26 July 2021
Study Title: A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX-147 in Adults With APOL1-mediated Focal Segmental Glomerulosclerosis		

I have read Protocol VX19-147-101, Version 6.0, and agree to conduct the study according to its terms. I understand that all information concerning VX-147 and this protocol supplied to me by Vertex Pharmaceuticals Incorporated (Vertex) is confidential.

Printed Name

Signature Date