1 TITLE PAGE

VERTEX PHARMACEUTICALS INCORPORATED

Statistical Analysis Plan (Methods)

Protocol Number VX19-147-101, Version 5.0 (Interim and Final Analysis)

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

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3 MODIFICATIONS

3.1 Modifications to the Approved Clinical Study Protocol

Not applicable.

3.2 Modifications to the Approved Statistical Analysis Plan

Not applicable.

3.3 Modifications to the Approved IDMC Charter

Not applicable.

4 INTRODUCTION

This statistical analysis plan (SAP) describes the efficacy and safety analyses and is based on the most recent approved clinical study protocol (CSP), the most recent approved electronic case report form (eCRF), and the most recent approved eCRF completion guidelines. It also documents analyses not specified in the protocol, which will provide supportive information for the scientific understanding of the drug entity.

The Vertex Biometrics Department will perform the statistical analysis of the efficacy and safety data; SAS® Version 9.4 Software (SAS Institute, Cary, North Carolina, USA) or higher will be used to generate all statistical outputs (tables, figures, listings and datasets).

The SAP (Methods) will be finalized and approved before the interim analysis datacut (if applicable) or clinical database lock, whichever occurs earlier. Any revisions to the approved SAP will be documented and approved in an amendment to the SAP prior to the clinical database lock. Any revisions made to the SAP after the clinical database lock will be documented in the clinical study report for this study.

The analysis addressing the pharmacokinetic (PK) objective of the study will be described in the Clinical Pharmacology Analysis Plan (CPAP) which will be developed separately by the Clinical Pharmacology department at Vertex Pharmaceuticals Incorporated (Vertex).

5 STUDY OBJECTIVES

5.1 Part A (Treatment Period)

5.1.1 Primary Objective

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

5.1.2 Secondary Objectives

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

5.2 Part B

5.2.1 Exploratory Objective

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

6 STUDY ENDPOINTS

6.1 Part A

6.1.1 Primary Endpoints

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

6.1.2 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

6.1.3 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])

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

6.2.1 Exploratory Endpoints

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

7 STUDY DESIGN

7.1 Overall 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 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 < 2.7g/g and eGFR approximately ≥30 mL/min/1.73 m^2.

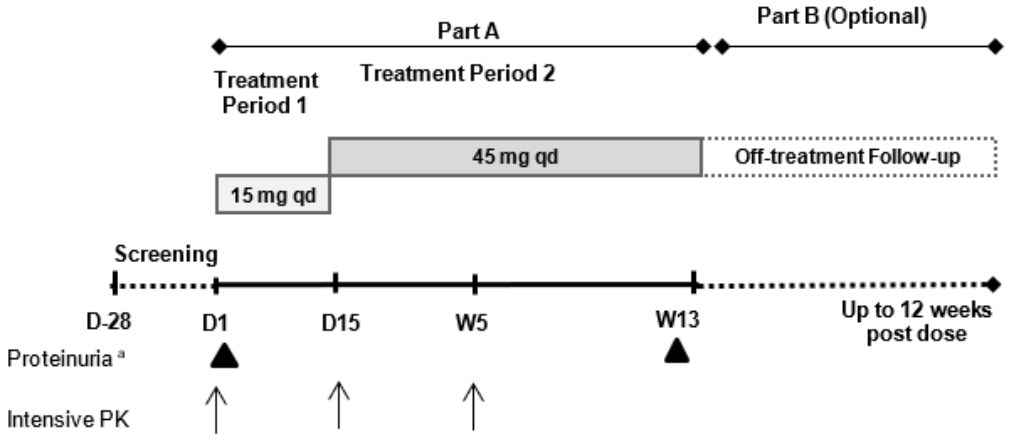
Subjects in Cohort 1 and Cohort 2 are permitted to take a stable low dose of systemic corticosteroid (prednisone ≤10 mg per day or prednisone equivalent) and/or an allowed immunosuppressant (i.e., tacrolimus, mycophenolate, or cyclosporine).

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 of the CSP).

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

Figure 7-1 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.

7.2 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), 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% confidence interval (CI), in log scale.

Table 7-1 displays the expected size of the 80% CIs for the GMPC at various values of the observed GMPC. Approximately 10 subjects will be enrolled in each cohort.

Table 7-1 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%)

7.3 Randomization

This is an open-label study. Randomization is not required because all subjects will receive VX-147.

7.4 Blinding and Unblinding

This is an open-label study. Refer to Section 10.7 of CSP for details.

8 ANALYSIS SETS

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

8.1 All Subjects 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.

8.2 Full Analysis Set

The **Full Analysis Set** (FAS) will include all subjects who received at least 1 dose of study drug in the Treatment Period and with 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.

8.3 Follow-up Set

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 Off-treatment Follow-up Period, unless otherwise specified.

8.4 Safety Set

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

9 STATISTICAL ANALYSIS

9.1 General Considerations

The Schedule of Assessments is provided in Section 3 of the CSP. The precision standards for reporting variables are provided in an internal Biometrics document that specifies the programming rules including the precision for derived variables.

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).

Categorical variables will be summarized using counts and percentages.

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. 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. For systolic and diastolic blood pressure, 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. 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 Safety Follow-up Visit, (2) ETT Visit if it replaces the Safety Follow-up Visit, or (3) the date of the last dose + 28 days for subjects who do not have a Safety Follow-up Visit. The TE Period will be used for safety analyses unless specified otherwise.

Unscheduled visits: Data obtained from unscheduled visits will be included in the analysis as follows:

- In scheduled visit windows per specified visit windowing rules
- In the derivation of baseline
- In the derivation of maximum and minimum values during TE period, and maximum and minimum change from baseline values during TE period for safety analyses
- In individual subject data listings as appropriate

Visit Window: The analysis visit windows for the protocol-defined visits are provided in Appendix A.

Incomplete or missing data will not be imputed, unless specified otherwise.

Outliers: No formal statistical analyses will be performed to detect and/or remedy the presence of statistical outliers, unless specified otherwise.

Multiplicity: No multiplicity adjustment will be performed.

9.2 Background Characteristics

9.2.1 Subject Disposition

Disposition summary will be provided by cohort and overall.

The number of subjects, based on the All Subject Set, in the following disposition categories, will be summarized:

- All Subjects Set
- Full Analysis Set
- Safety Set
- Follow-up Set

Treatment Period (Part A): The number and percentage of subjects, based on the FAS, in each of the following disposition categories, will be summarized:

- Completed treatment
- Prematurely discontinued treatment and the reason for discontinuation from treatment
- Completed Safety Follow-up Visit
- Completed study
- Prematurely discontinued the study and the reason for discontinuation from study

Off-treatment Follow-up Period (Part B): The number and percentage of subjects, based on the FAS, in the following disposition categories, will be summarized:

- Completed study
- Prematurely discontinued the study and the reason for discontinuation from study

A listing will be provided for subjects who discontinued treatment or who discontinued study with reasons for discontinuation.

9.2.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized based on the FAS by cohort and overall.

Demographic data will include the following:

- Age (in years)
- Sex (female and male)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, and not collected per local regulations)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not collected per local regulations, Other, and Multiracial [if more than 2 races reported from a subject])

Baseline and disease characteristics will include the following:

- Weight (kg)
- Height (cm)
- BMI (kg/m^2)
- *APOL1* genotype (*G1/G1, G2/G2, or G1/G2*)
- UPCR (g/g)
- UACR (g/g)
- eGFR ($mL/min/1.73\ m^2$)
- eGFR ($mL/min/1.73\ m^2$) category (<40, ≥ 40 to <60, ≥ 60)
- Systolic blood pressure (mmHg)
- Diastolic blood pressure (mmHg)
- Prior medication of any systemic corticosteroid (Yes, No)
- Prior medication of any immunosuppressants (Yes, No)

- Prior medication of any angiotensin converting enzyme (ACE) inhibitor (Yes, No)
- Prior medication of any angiotensin II receptor blocker (ARB) (Yes, No)
- Prior medication of any neprilysin inhibitor (Yes, No)
- Prior medication of any sodium-glucose cotransporter-2 (SGLT2) inhibitor (Yes, No)
- Prior medication of any diuretic (Yes, No)
- Prior medication of any renin inhibitor (Yes, No)
- Prior medication of any statin (Yes, No)
- Medical history of diabetes (Yes, No)

In addition, data listings will also be provided for:

- Informed consent
- Inclusion/Exclusion criteria violation for subjects with any such violations

9.2.3 Medical History

Medical history will be coded by using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be summarized descriptively based on the FAS by MedDRA system organ class (SOC) and preferred term (PT). This summary will be provided by cohort and overall. The corresponding data listing will also be provided.

9.2.4 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary and categorized as the following for the purpose of analysis:

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

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

Post-treatment medication: Medication continued or newly received after the TE Period

A given medication may be classified as a prior medication, a concomitant medication or a post-treatment medication; both a prior and a concomitant; both concomitant and post-treatment; or prior, concomitant, and post-treatment medication.

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, concomitantly during the TE Period, or after the TE Period, it will be considered in all 3 categories of prior, concomitant medication, and post-treatment medication.

Missing or partial dates will be imputed for medication. Details for imputing missing or partial start and/or stop dates of medication are described in Appendix B.

Prior medications and Concomitant medications will be summarized based on the FAS by Preferred Name. This summary will be provided by cohort and overall. Post-treatment medications will only be listed.

9.2.5 Study Drug Exposure and Compliance

Study drug exposure (in days) will be calculated as (last date of dosing – first date of dosing) + 1, regardless of study drug interruption, and will be summarized descriptively based on the Safety Set by cohort and overall. Study drug exposure (in weeks) will be summarized in categories for Treatment Period: ≤1 week, >1 to ≤2 weeks, >2 to ≤3 weeks, >3 to ≤5 weeks, >5 to ≤9 weeks, >9 to ≤12 weeks, and >12 weeks using counts and percentages.

Study drug compliance will be calculated as 100 × [1 - (total number of days of study drug interruption) / (duration of study drug exposure in days)]. A study drug interruption on a given day is defined as any interruption of the study drug on that day. A study drug interruption that continues through the end of the study participation (i.e., subject does not resume study drug before the end of the study participation) will not be included in the compliance calculation. Study drug compliance will be summarized descriptively based on the FAS by cohort and overall. It will also be summarized in categories: <80% and ≥80%, using counts and percentages.

9.2.6 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. IPD rules will be developed and finalized before database lock. IPDs will be identified by the PD review team according to the protocol deviation plan.

IPDs will be summarized descriptively by cohort and overall.

9.3 Efficacy Analysis

Efficacy analyses for Treatment Period (Part A) will be based on FAS and efficacy analyses for Off-treatment Follow-up Period (Part B) will be based on Follow-up Set, unless specified

otherwise. All efficacy analyses will be conducted separately for Cohort 1 and Cohort 2, as well as combined.

9.3.1 Analysis of the Primary Efficacy Variable

9.3.1.1 Definition of the Primary Efficacy Variable

The primary efficacy endpoint is percent change from baseline in UPCR at Week 13. The Week 13 UPCR value will be calculated by averaging a maximum of 3 nonmissing UPCR values measured within a 7-day period as described in Appendix A.

9.3.1.2 Analysis of the Primary Efficacy Variable

The primary efficacy endpoint will be analyzed based on combined Cohort 1 and Cohort 2. Subjects non-compliant with study drug will not be included in the analysis.

The primary analysis of the primary efficacy endpoint will be based on the following steps: (1) Log-transform the UPCR values to reduce skewness; (2) Calculate the mean of the change from baseline in log-transformed UPCR, corresponding standard error (SE) and 2-sided 80% CI; (3) The geometric mean and geometric standard error (GSE) will be calculated by back-transforming (exponential-transform) the corresponding estimates obtained in step (2). GMPC from baseline will be obtained as [geometric mean – 1]*100%. The corresponding 2-sided 80% CI will be calculated by [back-transforming (exponential-transform) the CI obtained in step (2) – 1]*100%.

The GMPC from baseline in UPCR at Week 13, GSE (%), along with the corresponding 2-sided 80% CI will be provided. In addition, the corresponding 2-sided 95% CI will be provided for descriptive purposes.

In addition, the primary efficacy endpoint will also be summarized in a similar way separately for Cohort 1 and Cohort 2.

9.3.1.3 Supportive Analyses

There will be no supportive analysis for the primary efficacy endpoint.

9.3.1.4 Sensitivity Analysis

No sensitivity analysis for the primary efficacy variable is planned.

9.3.1.5 Subgroup Analysis

No subgroup analysis for the primary efficacy variable is planned.

9.3.2 Analysis of Exploratory Efficacy Variables

9.3.2.1 Definition of Exploratory Efficacy Variable

UPCR (and UACR) values at Week 5, Week 9 and Week 13 will be calculated as the average of the available UPCR (and UACR) measurements (maximum 3) taken during Week 5, Week 9 or Week 13 within a 7-day period as described in Appendix A.

9.3.2.2 Analyses of Exploratory Efficacy Variable

Percent change from baseline in UPCR over time during the Treatment Period: Analysis of this variable will be based on steps as described for primary analyses in Section 9.3.1.2. Subjects non-compliant with study drug will not be included in the analysis. The GMPC from baseline in UPCR, GSE (%) along with the corresponding 2-sided 80% CI and 95% CI at each post-baseline visit (Week 1, Day 15, Week 3, Week 5, Week 9, and Week 13) will be provided. The GMPC from baseline in UPCR at each post-baseline visit during the Treatment Period will also be presented in a figure.

Percent change from baseline in urine albumin-to-creatinine ratio (UACR) at Week 13: Analysis of this variable will be conducted in the same way as described for primary analyses Section 9.3.1.2. Subjects non-compliant with study drug will not be included in the analysis. The GMPC from baseline in UACR at Week 13, GSE (%) along with the corresponding 2-sided 80% CI will be provided.

Percent change from baseline in UACR over time during the Treatment Period: Analysis of this variable will be based on steps as described for primary analyses in Section 9.3.1.2. Subjects non-compliant with study drug will not be included in the analysis. The GMPC from baseline in UACR, GSE (%) along with the corresponding 2-sided 80% CI at each post-baseline visit (Week 1, Day 15, Week 3, Week 5, Week 9, and Week 13) will be provided. The GMPC from baseline in UACR at each post-baseline visit during the Treatment Period will also be presented in a figure.

Percent change from baseline in UPCR at the end of the Off-treatment Follow-up Period: Analysis of this variable will be based on steps as described for primary analyses in Section 9.3.1.2. Subjects non-compliant with study drug will not be included in the analysis. The GMPC from baseline in UPCR, GSE (%) along with the corresponding 2-sided 80% CI and 95% CI at each visit in Off-treatment Follow-up Period (Part B Week 4, Week 8, and Week 12) will be provided. The GMPC from baseline in UPCR at each post-baseline visit during the Off-treatment Period will also be presented in a figure.

9.4 Safety Analysis

All safety analyses will be performed based on the Safety Set by cohort and overall.

The overall safety profile of VX-147 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 descriptive analyses of safety will be performed, and no statistical hypothesis testing will be performed.

9.4.1 Adverse Events

AEs will be coded according to MedDRA. For analysis purposes, AEs will be classified as pretreatment AEs and TEAEs as follows:

Pretreatment AEs: AEs that occurred before the first dose of study drug

Treatment-emergent AEs: AEs that worsened or started on or after the first dose date of study drug through the end of the TE Period

For AEs with completely missing or partial start dates, if there is no clear evidence that the AEs started before or after the first dose of study drug, the AEs will be classified as TEAEs.

Imputation rules for missing or partial AE start date are defined as Appendix C.

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

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

- Related serious TEAEs
- TEAEs leading to death

Summaries will be presented by MedDRA SOC and 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, and only the maximum severity level will be presented in the severity summaries, and the strongest relationship level in the relationship summaries.

All AEs, including pretreatment AEs and TEAEs will be presented in an individual subject data listing based on the All Subjects Set. In addition, a listing containing individual subject adverse event data for TEAEs leading to treatment discontinuation, TEAEs leading to treatment interruption, SAEs and all deaths will be provided separately.

9.4.2 Clinical Laboratory

All statistical analyses of laboratory values will be performed using SI units. For treatment-emergent laboratory measurements, the observed values and change from baseline values of the continuous hematology, chemistry, and coagulation results will be summarized at each visit.

The number and percentage of subjects with selected test values meeting at least 1 threshold analysis criterion event during the TE period will be summarized. The threshold analysis criterion shift from baseline will also be summarized for selected laboratory test values. The threshold analysis criteria are provided in Appendix D.

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.

9.4.3 Electrocardiogram

For the treatment-emergent ECG measurements, a summary of observed values and change from baseline values will be provided at each visit and time point, as applicable, for the following ECG measurements: heart rate (HR; beats per minute [bpm]), PR (msec), RR (msec), QRS duration (msec), QT (msec), and QT corrected for HR intervals (QTcF [msec]). In addition, the number and percentage of subjects by maximum treatment-emergent value of QT/QTcF intervals, categorized as ≤450 msec, >450 msec and ≤480 msec, >480 msec and ≤500 msec, and >500 msec, as well as maximum treatment-emergent change from baseline value of QT/QTcF

intervals, categorized ≤0 msec, >0 to ≤30 msec, >30 and ≤60 msec, and >60 msec will be provided.

The number and percentage of subjects meeting at least 1 threshold analysis criterion during the TE period will be summarized. The threshold analysis criteria are provided in Appendix D.

In addition, a listing containing individual subject ECG values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.4 Vital Signs

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

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

In addition, a listing containing individual subject vital signs values will be provided. This listing will include data from both scheduled and unscheduled visits.

9.4.5 Physical Examination

Physical examination (PE) results will be presented in individual subject data listings only.

9.4.6 Other Safety Analysis

Change from baseline in weight (kg) will be summarized at each visit.

9.4.7 COVID-19 Impacted Visits

A listing containing subjects' visits impacted due to COVID-19 will be provided.

9.5 Other Analyses

9.5.1 Analysis of SF-36

SF-36 is a patient-reported generic measure of health status. The questionnaire provides information about functional health and wellbeing, as well as 2 psychometrically based physical and mental health summary measures. Physical and mental component summary scores will be provided by commercially available software, i.e., QualityMetric Health Outcomes™ Scoring Software. Analysis of SF-36 will be conducted separately for Cohort 1 and Cohort 2, as well as combined.

Change from baseline in patient-reported outcome (PRO) Short Form Health Survey 36 (SF-36) over time during the Treatment Period: The change from baseline in the SF-36 physical component summary scores and the change from baseline in the SF-36 mental component summary scores will be summarized descriptively at Week 5 and Week 13.

Change from baseline in SF-36 at 4 weeks after the last dose (SFUV): The change from baseline in the SF-36 physical component summary scores and the change from baseline in the SF-36 mental component summary scores will be summarized descriptively at 4 weeks after the last dose of VX-147.

10 INTERIM AND IDMC ANALYSES

10.1 Interim Analysis

Interim analyses may be done at the discretion of the sponsor to allow for regulatory interactions and clinical development planning. Interim analyses will be performed and reviewed by an independent Vertex team not involved in the conduct of the study.
Interim analyses will be based on all data included in the IA data cuts.

10.1.1 General Consideration

General considerations, reporting conventions, and analysis methods specified for the final analysis apply to the IA, unless otherwise specified.

For the IA, the **TE period** will include the time period starting from the date of the first dose of study drug to either (1) the Safety Follow-up Visit, (2) ETT Visit if it replaces the Safety Follow-up Visit, (3) the date of the last dose + 28 days for subjects who do not have a Safety Follow-up Visit, or (4) the IA data cut date if subjects haven't completed the Treatment Period or haven't discontinued the study at the time of the IA data cut.

10.1.2 Background Characteristics

Refer to Section 9.2 for summary of background characteristics for IA. In addition, treatment ongoing will be summarized as disposition categories for IA.

10.1.3 Efficacy Analysis

Refer to Section 9.3 for efficacy analysis for IA.

10.1.4 Safety Analysis

Refer to Section 9.4 for safety analysis for IA.

10.1.5 Other Analysis

Refer to Section 9.59.4 for other analysis for IA.

10.2 Independent Data Monitoring Committee Analysis

Not applicable.

11 REFERENCES

Not applicable.

12 APPENDICES

Appendix A: Analysis Visit Windows for Efficacy, Safety, and Exploratory Assessments

Table 12-1 Analysis Visit Windows for Efficacy, Safety, and Exploratory Assessments

Assessment	Visit[1]	Target Study Day	Analysis Visit Window (in study days)[2, 3, 4, 5]
Efficacy Assessments			
• UPCR	Baseline	Not applicable	<1
	Week 1	8	(1, 11]
	Day 15	15	(11, 18]
	Week 3	22	(18, 29]
	Week 5	36	(29, 50]
	Week 9	64	(50, 78]
	Week 13	92	(78, 106]
	Part B Week 4	120	(106, 134]
	Part B Week 8	148	(134, 162]
	Part B Week 12	176	(162, 190]
• UACR	Baseline	Not applicable	<1
	Week 1	8	(1, 11]
	Day 15	15	(11, 18]
	Week 3	22	(18, 29]
	Week 5	36	(29, 50]
	Week 9	64	(50, 78]
	Week 13	92	(78, 106]
Safety Assessments			
• Serum Chemistry • Hematology • Coagulation	Baseline	1	≤1 Pre-dose
	Week 1	8	[1 Post-dose, 11]
	Day 15	15	(11, 18]
	Week 3	22	(18, 29]
	Week 5	36	(29, 50]
	Week 9	64	(50, 78]
	Week 13	92	(78, 106]
	Safety Follow-up	Not applicable	Use nominal visit
• Standard 12-lead ECG	Baseline	1	≤1 Pre-dose
	Day 1 (2 hours post dose)	1	Nominal visit for all visits
	Week 1	8	
	Day 15 predose	15	
	Day 15 (2 hours post dose)	15	
	Week 3	22	
	Week 5	36	
	Week 9	64	
	Week 13	92	
	Safety Follow-up	Not applicable	

• Vital Signs • Weight	Baseline Week 1 Day 15 Week 3 Week 5 Week 9 Week 13 Safety Follow-up	1 8 15 22 36 64 92 Not applicable	≤1 [1 Post-dose, 11] (11, 18] (18, 29] (29, 50] (50, 78] (78, 106] Use nominal visit
Exploratory Assessments			
• SF-36	Baseline Week 5 Week 13 Safety Follow-up	1 36 92 Not applicable	≤1 [1 Post-dose, 64] (64, 106] Use nominal visit

Notes:

[1]Visit name for analysis purpose is used to report data in tables and figures.

[2]The analysis visit windows will be applied using the following rules for both scheduled and unscheduled visits:

a. If no numerical measurement is available within a visit window, the measurement will be considered missing for the visit.
b. If there is more than 1 numerical measurement available within a visit window, use the following rules:
    i. The measurement closest to the target day will be used; or
    ii. If there are multiple measurements with the same distance from the target day, the latest measurement will be used. If the latest measurement cannot be determined, then unscheduled visit will be selected.
    iii. If there are multiple measurements from the central laboratory and local laboratory with the same distance from the target day, the measurement from the central laboratory will be used.

[3]For measurements collected on the date of first dose of study drug in Treatment Period, if it cannot be determined whether the measurement is before or after the first dose:

a. Scheduled measurement will be treated as pre-dose observation;
b. Unscheduled measurement will be treated as post-dose observation.

[4]For safety assessment, the Safety Follow-up analysis visit will be based on nominal Safety Follow-up visit. If a subject doesn't have a nominal Safety Follow-up visit but has an ETT visit occurs 3 weeks (21 days) or later following the last dose of study drug, then the ETT visit will be mapped into Safety Follow-up analysis visit.

[5]UPCR and UACR at Week 5, Week 9 and Week 13 will be calculated by averaging maximum 3 nonmissing UPCR and UACR values measured within a 7-day period within the visit window.

a. If there is only 1 assessment within the visit window, use the single value
b. If there are more than 1 assessment within the visit window:
    i. find the earliest assessment within the visit window, and then find the number of assessments within 7 days after the earliest assessment;
    ii. find the second assessment within the visit window, and then find the number of assessments within 7 days after the second assessment;
    iii. find the third assessment within the visit window, and then find the number of assessments within 7 days after the third assessment, if applicable;
    iv. Compare the number of assessments from step i to iii, use the assessments from the step that has the maximum number. If number of assessments are the same from multiple steps, then use the step with the first assessment closest to target study day.

Derived Variable:

1. Missing first dose date or last dose date
    - If the first dose date is missing, use Day 1 visit date to impute.
    - If the last dose date is missing or partial date is reported, the last dose date will be imputed based on, in descending order priority, the Early Treatment Termination (ETT) visit date, last visit date before the Safety Follow-up, or the last study drug administration date from EC SDTM domain, as appropriate. The imputation algorithm will ensure the imputed last dose date does not exceed the study participation end date.
2. Electrocardiogram:
   If ECGs are performed in triplicate at any visit and timepoint:
    - For summary purpose, the average of these ECGs at a specific visit and time point will be used as the ECG for that specific visit and time point.
    - For threshold analysis purpose, all reported ECG values will be used.
3. Systolic and diastolic blood pressures:
   If systolic and diastolic blood pressures are performed in triplicate at any visit:
    - For summary purpose, the average of these systolic and diastolic blood pressures at a specific visit will be used as the systolic and diastolic blood pressures for that specific visit.
    - For threshold analysis purpose, all reported systolic and diastolic blood pressures will be used.

Appendix B: Imputation Rules for Missing Prior/Concomitant Medication Dates

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date and time:
    a. If DAY is missing, use the first day of the month.
    b. If DAY and Month are both missing, use the first day of the year.
    c. If DAY, Month and Year are all missing, use a date before the first dose date (to impute in practical, use the informed consent date).
2. Missing or partial medication stop date:
    a. If only DAY is missing, use the last day of the month.
    b. If DAY and Month are both missing, use the last day of the year.
    c. If DAY, Month and Year are all missing, assign 'continuing' status to stop date (to impute in practical, use the End of Study Date to impute).

In summary, the prior, concomitant, or post categorization of a medication is described below.

Table 12-2 Prior, Concomitant, and Post Categorization of a Medication

	Medication Stop Date		
Medication Start Date	**< First Dose Date of Study Drug**	**≥ First Dose Date and ≤ End Date of TE Period**	**> End Date of TE Period**
< First dose date of study drug	P	PC	PCA
≥ First dose date and ≤ End date of TE period	-	C	CA
> End date of TE period	-	-	A

P: Prior; C: Concomitant; A: Post

Appendix C: Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start date are defined below. If the imputed AE start date is before the study informed consent date, the AE start date will be imputed using the study informed consent date.

- **If only Day of AE start date is missing:**
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then
        - if AE start year and month are equal to the month and year of first dose date, then impute the AE start day as the day of first dose date;
        - else impute the AE start day as 1.
    - else impute the AE start day as 1.

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE or TEAE.

- **If Day and Month of AE start date are missing:**
    - If the full (or partial) AE end date is NOT before the first dose date or AE end date is missing, then
        - if AE start year is equal to the year of first dose date, then impute the AE start month and day as the month and day of first dose date;
        - else impute the AE start month as January and day as 1.
    - else impute the AE start month as January and day as 1.

  Compare the imputed AE start date with TE period to determine whether the AE is pretreatment AE or TEAE.

- **If Year of AE start date is missing:**

  If the year of AE start is missing or AE start date is completely missing then query site.
    - If the full (or partial) AE end date is NOT before the first dose date of the Treatment Period or AE end date is missing, then impute the AE start date as the first dose date.
    - else impute the AE start date as the informed consent date.

Missing or partially missing AE end date will not be imputed.

Appendix D: Criteria for Threshold Analysis

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Clinical Chemistry		
ALT	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
AST	>ULN - ≤3xULN >3x - ≤5xULN >5x - ≤8xULN >8x - ≤20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
ALT or AST	(ALT>ULN - ≤ 3xULN) or (AST>ULN - ≤3xULN) (ALT>3x - ≤5xULN) or (AST>3x - ≤5xULN) (ALT>5x - ≤8xULN) or (AST>5x - ≤8xULN) (ALT>8x - ≤20xULN) or (AST>8x - ≤20xULN) ALT>20xULN or AST>20xULN	FDA DILI Guidance Jul 2009.
Alkaline Phosphatase	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	FDA DILI Guidance Jul 2009.
Total Bilirubin	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤3xULN >3 - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
Direct Bilirubin	>ULN - ≤1.5xULN >1.5 - ≤2xULN >2 - ≤3xULN >3 - ≤10xULN >10xULN	FDA DILI Guidance Jul 2009.
ALT and Total Bilirubin	ALT>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
AST and Total Bilirubin	AST>3xULN and TBILI>2xULN	FDA DILI Guidance Jul 2009.
(ALT or AST) and Total Bilirubin	(ALT>3xULN or AST>3xULN) and TBILI>2×ULN	FDA DILI Guidance Jul 2009.

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
GGT	>ULN - ≤2.5xULN >2.5 - ≤5.0xULN >5.0 - ≤20.0xULN >20.0xULN	CTCAE grade 1-4
Albumin	<LLN - ≥30 g/L <30 - ≥20 g/L <20 g/L	CTCAE grade 1-3
Amylase	>1x - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Creatinine	>ULN - ≤1.5xULN >1.5 - ≤3.0xULN >3.0 - ≤6.0xULN >6.0xULN	CTCAE grades 1-4
Lipase	>ULN - ≤1.5xULN >1.5x - ≤2xULN >2x - ≤5xULN >5xULN	Criteria based upon CTCAE
Total protein	<LLN >ULN	No CTCAE
Creatine kinase	>ULN - ≤2.5xULN >2.5 - ≤5xULN >5 - ≤10xULN >10xULN	CTCAE grades 1-4
Cholesterol	<5.18 mmol/L ≥5.18 - <6.22 mmol/L ≥6.22 mmol/L	ATP III guideline
Triglycerides	<1.70 mmol/L ≥1.70 - <2.26 mmol/L ≥2.26 - <5.65 mmol/L ≥5.65 mmol/L	ATP III guideline
HDL Cholesterol	<1.04 mmol/L ≥1.04 - <1.55 mmol/L ≥1.55 mmol/L	ATP III guideline
LDL Cholesterol	<2.59 mmol/L ≥2.59 - <3.37 mmol/L ≥3.37 - <4.14 mmol/L ≥4.14 - <4.92 mmol/L ≥4.92 mmol/L	ATP III guideline
Hematology		

Table 12-3 Threshold Analysis Criteria for Laboratory Tests (as applicable)

Parameter	Threshold Analysis	Comments
Hemoglobin	Hgb decreased (anemia) <LLN - ≥100 g/L <100 - ≥80 g/L <80 g/L	CTCAE grade 1-3
	Hgb increased >ULN - ≤20 g/L above ULN >20 g/L above ULN - ≤40 g/L above ULN >40 g/L above ULN	CTCAE grade 1-3
Platelets	Platelet decreased <LLN - ≥75.0 x 10e9 /L <75.0 - ≥50.0 x 10e9 /L <50.0 - ≥25.0 x 10e9 /L <25.0 x 10e9 /L	CTCAE grade 1-4
	Platelet increased >ULN	No CTCAE available
Reticulocytes/Erythrocytes (%)	<LLN >ULN	No CTCAE
Coagulation		
Activated partial thromboplastin time (PTT)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5xULN	CTCAE grade 1-3
Prothrombin time (PT) International Normalized Ratio (INR)	>ULN - ≤1.5xULN >1.5 - ≤2.5xULN >2.5 x ULN*	CTCAE grade 1-3

* ULN for patient taking oral anticoagulant will be used.

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
HR	Bradycardia	Per HV grade 2, 3, plus shift change
	<50 bpm <45 bpm Decrease from baseline ≥10 bpm Decrease from baseline ≥20 bpm <50 bpm and decrease from baseline ≥10 bpm <50 bpm and decrease from baseline ≥20 bpm	

Table 12-4 Threshold Analysis Criteria for ECGs

Parameter	Threshold Analysis	Comments
	Tachycardia	Per HV grade 1, 2, 3, plus shift change
	>100 bpm	
	>115 bpm	
	>130 bpm	
	Increase from baseline ≥10 bpm	
	Increase from baseline ≥20 bpm	
	>100 bpm and increase from baseline ≥10 bpm	
	>100 bpm and increase from baseline ≥20 bpm	
PR	≥240 ms	
	≥300 ms	
	≥200 ms and increase from baseline ≥40 ms	
	≥200 ms and increase from baseline ≥100 ms	
QRS	>110 ms	
	>160 ms	
	Increase from baseline ≥20 ms	
	Increase from baseline ≥40 ms	
QTc	>450 to <500ms (Male) or >470 to <500ms (Female)	To be applied to any kind of QT correction formula.
	≥500 ms	
	Increase from baseline	
	Increase from baseline >10 ms	
	Increase from baseline >20 ms	
	Increase from baseline >40 ms	
	Increase from baseline >60 ms	

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
Pulse Rate	Same as above in ECG category	
SBP increased	>140 mmHg	809/770 analyses
	>160 mmHg	
	>10 mmHg increase from baseline	
	>20 mmHg increase from baseline	
	>140 mmHg & >10 mmHg increase from baseline	
	>140 mmHg & >20 mmHg increase from baseline	
	>160 mmHg & >10 mmHg increase from baseline	
	>160 mmHg & >20 mmHg increase from baseline	

Table 12-5 Threshold Analysis Criteria for Vital Signs

Parameter	Threshold Analysis	Comments
SBP decrease	<90 mmHg <80 mmHg >10 mmHg decrease from baseline >20 mmHg decrease from baseline <90 mmHg and >10 mmHg decrease from baseline <90 mmHg and >20 mmHg decrease from baseline <80 mmHg and >10 mmHg decrease from baseline <80 mmHg and >20 mmHg decrease from baseline	Per HV grade 1, 3, plus shift change
DBP increased	>90 mmHg >100 mmHg >5 mmHg increase from baseline >10 mmHg increase from baseline >90 mmHg and >5 mmHg increase from baseline >90 mmHg and >10 mmHg increase from baseline >100 mmHg and >5 mmHg increase from baseline >100 mmHg and >10 mmHg increase from baseline	
DBP decreased	<60 mmHg <45 mmHg >5 mmHg decrease from baseline >10 mmHg decrease from baseline <60 mmHg and >5 mmHg decrease from baseline <60 mmHg and >10 mmHg decrease from baseline <45 mmHg and >5 mmHg decrease from baseline <45 mmHg and >10 mmHg decrease from baseline	
Weight	Weight gain ≥5 % increase from baseline ≥10 % increase from baseline ≥ 20% increase from baseline	CTCAE grade 1-3
	Weight loss ≥5 % decrease from baseline ≥10 % decrease from baseline ≥ 20% decrease from baseline	CTCAE grade 1-3