PART 1: Administrative Details	
Full Study Title	A Phase 2/3 Adaptive, Double-blind, placebo-controlled Study to Evaluate the Efficacy and Safety of VX-147 in Adult and Pediatric Subjects with APOL1-mediated Proteinuric Kidney Disease.
Protocol/ Document Number	VX21-147-301 Protocol Version 5.0 dated 10th August 2023
Date of Receipt of the Application	22nd November 2023
Phase of Study	2/3
Study Registration Details	PACTR number: PACTR202301768862135 Clinical trial certificate – No. FDA/CT/243
Name and Address of Applicant(s)	Pharmaceutical Product Development South Africa (Pty) Limited, part of Thermo Fisher Scientific PO Box 37 Woodlands 2080 Johannesburg South Africa
Name and Address of Sponsor(s)	Vertex Pharmaceuticals Incorporated 50 Northern Avenue, Boston, MA 02210-1862 USA
Name and Address of Principal Investigator(s)	Dr. Charlotte Osafo The Bank Hospital Block F6 Shippi Road, Cantonments Accra, Ghana
Study Sites	The Bank Hospital
Study Duration	96 weeks
FAPAR Number	FDA/CT/PAR/246

PART 2: Investigational Product(s)	
Name of Investigational Product(s) including Comparator(s).	Inaxaplin (VX-147) Matching placebo
Justification of Investigational Product(s) including comparators	As APOL1 mutations increase the likelihood of developing proteinuria, inhibition of APOL1 is expected to mitigate progression of kidney function decline. 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. The therapeutic hypothesis is that VX-147 will bind APOL1 and block APOL1-mediated toxic effects in the podocyte, which will lead to decreased proteinuria and

	improved clinical outcomes. VX-147 has been safe and well tolerated in studies of healthy volunteers and subjects with APOL1-mediated focal segmental glomerulosclerosis (FSGS).

PART 3: Study Summary

Study Objectives

Primary Objectives

- To evaluate the efficacy of VX-147 to reduce proteinuria
- To evaluate the efficacy of VX-147 on renal function as measured by eGFR slope

Secondary Objectives

- To evaluate the efficacy of VX-147 to decrease the risk of the composite clinical outcome
- To evaluate the safety and tolerability of VX-147
- To identify the optimal dose from Phase 2 to carry forward to Phase 3
- To characterize the plasma pharmacokinetics (PK) of VX-147
- To evaluate the acceptability of VX-147 in pediatric subjects

Exploratory Objectives

- To evaluate changes in patient-reported health-related quality of life measures
- To evaluate changes in biomarkers in blood and urine

Study Design

This is an adaptive Phase 2/3 study of VX-147 in subjects with APOL1-mediated proteinuric kidney disease that is designed to select a dose of VX-147 and establish the efficacy and safety of the selected dose. Subjects, investigators, and the sponsor will be blinded to treatment assignment in Phase 2 and Phase 3. In Phase 2, approximately 66 subjects will be randomized 1:1:1 to receive VX-147 15 mg qd, VX-147 45 mg qd, or placebo on a background of standard of care.

Doses for Phase 2 were selected based on the efficacy, safety, and PK results from prior and ongoing clinical studies with VX-147. After the last subject in Phase 2 completes the Week 12 Visit, the independent data monitoring committee (IDMC) will review UPCR, safety, and PK data in Phase 2 and recommend a Phase 3 dose. Approximately 400 subjects are planned to be enrolled in Phase 3. Subjects enrolled before the Phase 3 dose is selected and who received the selected dose or placebo will continue their original treatment assignment in a blinded manner until study completion.

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Subjects enrolled before the Phase 3 dose selection who received the non-selected dose will switch to the selected dose in a blinded manner, after the Phase 3 dose is determined. After dose selection, there will be an interim analysis (IA) when subjects at the VX-147 selected dose or placebo complete 48 weeks of follow-up, and there will be a final analysis at study completion (i.e., when enrolled subjects have at least 2 years of eGFR data and approximately 187 composite clinical outcome events have occurred). To preserve study integrity, the IA will be done by an independent, unblinded statistician from the IDMC. At the IA, the primary endpoint of UPCR at Week 48 is sequentially tested in the overall population and then, if positive, in the FSGS subgroup; if both are positive, eGFR slope will be tested in the overall population. When the study completes, a final analysis will be done for the primary endpoint of eGFR slope and if positive, the secondary endpoint of time to composite clinical outcome will be tested. Subjects in Phase 2 and Phase 3 will be stratified based on screening UPCR (≥1.5 g/g or <1.5 g/g) and screening eGFR (<45 mL/min or ≥45 mL/min). Additionally, subjects in Phase 3 will be stratified based on region, the use of sodium glucose cotransporter2 (SGLT2) inhibitors at baseline, and FSGS diagnosis (FSGS and non-FSGS).

All subjects will complete a safety-follow up visit (SFUV) 28 (±7) days after the last dose of study drug. Subjects who reach ESKD will discontinue dosing of study drug but remain in the study until the study completes.

Eligibility Criteria

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

Inclusion Criteria:

1. Subject (or their legally appointed representative) will sign and date informed consent form (ICF) and, when appropriate, an assent form.
2. Willing and able to comply with scheduled visits, treatment plan, study restrictions (Section 9.5) laboratory tests, contraceptive guidelines, and other study procedures.
3. Subject has an APOL1 genotype of G1/G1, G2/G2, or G1/G2 obtained with a Vertex-designated investigational clinical study assay.
4. For Phase 2, subjects must be between the ages of 18 and 65 years at time of signing ICF, inclusive. For Phase 3, subjects must be between the ages of 12 and 65 years at time of signing ICF, inclusive. Pediatric subjects may be enrolled only after IDMC review of Phase 2 data is completed, the Phase 3 dose is selected, and a recommendation by the IDMC on the inclusion of pediatric subjects is made. Up to approximately 15% of the total number of subjects planned for enrollment may be >61 to ≤65 years of age.
5. A BMI of 18 to 45 kg/m^2, inclusive, and a total body weight ≥40 kg.

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6. A UPCR of ≥0.7 g/g and <10 g/g in the first morning void based on the average of 3 measurements collected on 3 separate days within a 7-day period, during the Screening Period.
7. Estimated glomerular filtration rate (eGFR) ≥25 to <75 mL/min/1.73 m^2 based on the Modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation without the race adjustment for subjects ≥18 years on Day 1 and CKD-EPI40 equation for subjects <18 years on Day 1.
8. On a stable, maximum tolerated labeled dose (at least 4 weeks before screening) of an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), unless documented to be intolerant to ACE-inhibitor/ARB.
9. Subjects taking sodium glucose co-transporter-2 (SGLT2) inhibitors, mineralocorticoid receptor antagonists (MRAs) or permitted immunosuppression (prednisone ≤ 10 mg or steroid equivalent, mycophenolate, tacrolimus or cyclosporine) must have been on a stable dose for 4 weeks before screening

Exclusion Criteria

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
   - Clinically significant liver disease
   - Ongoing alcohol abuse or illicit drug use
   - Any condition possibly affecting drug absorption (e.g., gastrectomy, gastrointestinal tract surgery except appendectomy and cholecystectomy)
   - Stroke or myocardial infarction within 6 months before screening
2. Evidence of FSGS with a known cause other than due to APOL1 mutations. 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.
   - FSGS occurring in a subject with known sickle cell disease.

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- 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. History of diabetes mellitus.
4. Known underlying cause of kidney disease in the opinion of the investigator including but not limited to biopsy-confirmed or suspected cases of the following: lupus nephritis, myeloma kidney, glomerular basement membrane disease, membranoproliferative glomerulitis, polycystic kidney disease, sickle cell disease, diabetic nephropathy, HIV nephropathy, autoimmune-induced nephropathy, amyloidosis, anti-phospholipase A2 receptor-mediated nephropathy, monoclonal gammopathy related kidney disease, complement related glomerulonephritis, thrombotic microangiopathy or hemolytic uremic syndrome, Alport syndrome, immunoglobulin A (IgA) nephropathy, post-streptococcal glomerulonephritis, or acute kidney injury within the past 3 months if eGFR is not at pre-injury baseline
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:
   - Serum albumin <1 g/dL
   - Total bilirubin ≥1.5 × upper limit of normal (ULN)
   - Aspartate transaminase (AST) or alanine transaminase (ALT) ≥2 × ULN
   - Hemoglobin < 9 mg/dL
6. 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.
7. Any clinically significant ECG abnormality (as determined by the investigator) or median QTcF of triplicate standard 12-lead ECGs >450 msec at screening.
8. Positive for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) RNA, or positive HIV test during screening.
9. Screening blood pressure ≥180 mm Hg (systolic) or ≥100 mm Hg (diastolic), based on the average of 3 measurements.
10. Pregnant or nursing female subjects. Females of childbearing potential must have a negative pregnancy test at screening (serum test) and Day 1 (urine test).
11. Participation in another interventional clinical study within 28 days or 5 half-lives, whichever is longer, before the first dose of study drug.

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12. Inability to adhere to the study restrictions defined in Section 9.5, including restrictions before the first dose of study drug for strong CYP3A4 inhibitors or moderate and strong inducers, cyclophosphamide, rituximab, or high dose systemic corticosteroids (>10 mg/day of prednisone or prednisone equivalent).
13. Subject, or close relative of the subject, is the investigator or a sub-investigator, research assistant, pharmacist, study coordinator, or other staff directly involved with the conduct of the study at that site. An adult (aged 18 years or older) who is a relative of a study staff member may be enrolled in the study provided the following:

- The adult lives independently of and does not reside with the study staff member; and
- The adult participates in the study at a site other than the site at which the family member is employed.

14. Known hypersensitivity to investigational medicinal product or to any of its excipients.

The target population for the study are male and female subjects aged 18 to 60 years

Date of Commencement (Expected)

15th April 2024

Status of Study

The study is yet to commence

PART 4: Scientific Discussion

Summary of Review Comments

Quality

The applicant submitted the following documents which were reviewed and found satisfactory to fulfill the quality requirement of the trial:

- Investigational Medicinal Product Dossier (IMPD) Quality Section: Drug Substance version 4.0 dated 31st July 2023
- Investigational Medicinal Product Dossier (IMPD) Quality Section: Drug Product (Coated tablet) version 4.0 dated 10th October 2023
- Investigational Medicinal Product Dossier (IMPD) Quality Section: Drug Product (Coated placebo tablet) version 4.0 dated 10th October 2023

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Safety

A first-in-human safety study, VX18-147-001 was conducted in healthy subjects. In Study 001, VX-147 was found to be safe and generally well tolerated at single doses up to 50 mg and multiple doses up to 45 mg qd for 14 days. In Parts A and B, all adverse events (AEs) were mild or moderate in severity, and there were no serious AEs. Overall, 1 subject discontinued study drug due to an AE of rash papular (Part B), which was considered unlikely related to study drug.

VX-147 has been investigated in 5 completed Phase 1 studies in healthy subjects: a first-in human single ascending dose (SAD)/multiple ascending dose (MAD) study (Study VX18-147- 001), an ADME study (Study VX19-147-002), an oral contraceptive DDI study (Study VX19- 147-004), CYP3A4 DDI study (Study VX19-147-005), and an additional SAD/MAD study (Study VX20-147-008). There is 1 ongoing Phase 1 relative bioavailability study in healthy subjects (Study VX21-147-009) and 1 ongoing Phase 2 study (VX19-147-101) in patients with APOL1-mediated FSGS (Part A [treatment period] complete, Part B [off-treatment follow up period ongoing]).

In healthy volunteer studies, VX-147 has been safe and well tolerated at all doses tested (range 7.5 to 165 mg single dose and 15 to 120 mg multiple doses for up to 14 days); no clinically significant trends have been noted in adverse events, laboratory measurements, vital signs, and ECGs.

For this study, 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

Efficacy

A proof of concept study, Study VX19-147-101 was conducted to evaluate the efficacy, safety, and pharmacokinetics (PKs) of VX-147 in adults with APOL1-mediated focal segmental glomerulosclerosis (FSGS). This was a Phase 2a, open-label, single-arm, 2-part study that enrolled patients with biopsy-proven FSGS, 2 APOL1 mutations, UPCR ≥3 g/g to <10g/g, and eGFR ≥30 mL/min/1.73m^2.

The primary endpoint was the percent change in urine protein-to-creatinine ratio (UPCR) at Week 13, with safety and pharmacokinetics as secondary endpoints.

The study met its primary endpoint of the percent change from baseline in UPCR at Week 13. A rapid, statistically significant, and clinically meaningful reduction in UPCR of 47.6% compared to baseline was observed at Week 13. The mean magnitude of effect was

PART 4: Scientific Discussion

consistent in both cohorts, regardless of baseline level of proteinuria, and consistent regardless of background standard of care (data on file). The treatment response was observed early (within 2 weeks of treatment) and continued throughout the treatment period.

For this study, the primary efficacy endpoint is eGFR slope. There will be interim and final analysis.

Overall comments

After initial review, the application was deferred with queries to be addressed by the applicant. Following the satisfactory response to all queries on the submission, the study was approved and issued a clinical trial certificate.

The applicant is committed to ensuring that the study is conducted in compliance with Good Clinical Practice (GCP) and applicable regulatory requirements.

PART 5: Application Review Process

The application was reviewed through the reliance pathway. The application was thus reviewed within 29 working days.

PART 6: Status after Review

The study was approved on 27th March 2024 and is yet to commence

References

1. Investigational Medicinal Product Dossier (IMPD) Quality Section: Drug Substance version 4.0 dated 31st July 2023
2. Investigational Medicinal Product Dossier (IMPD) Quality Section: Drug Product (Coated tablet) version 4.0 dated 10th October 2023
3. Investigational Medicinal Product Dossier (IMPD) Quality Section: Drug Product (Coated placebo tablet) version 4.0 dated 10th October 2023
4. Protocol Revised Version 5.0 dated 10th August 2023
5. Adult Participant Information sheet and Informed Consent Form (initial doses) version 1.0 dated 6th November 2023
6. Adult Participant Information sheet and Informed Consent Form (decided doses) version 1.0 dated 6th November 2023
7. Adult Participant Information Sheet and Informed Consent Form (Asante Twi) version 1.0 dated 18th May 2023
8. Pregnancy Information Collection Informed Consent Form version 1.1 dated 16th May 2023
9. Main Parent Information sheet and Informed Consent Form (decided doses) version 1.0 dated 6th November 2023
10. Adolescent Participant Information sheet and Assent Form (12-17years) version 1.0 dated 10th October 2023
11. Pregnancy Information Collection Informed Consent Form dated 10th October 2023
12. Investigator's Brochure Version 5 dated 11th February 2022
13. Clinical Assessment of Clinical Trial Application version 01 dated 2nd September 2019.
14. Quality Assessment of Clinical Trial Application version 01 dated 2nd September 2019.
15. The Concept of Benefit / Risk. Presentation to the APEC Preliminary Workshop on Review of Drug Development in Clinical Trials by Celia Lourenco.
16. ICH E6(R2) guideline for good clinical practice dated 9 November 2016.
17. ICH E2A guideline for clinical safety data management: definitions and standards for expedited reporting dated 27 October 1994.
18. ICH E8 general considerations for clinical trials dated 17 July 1997
19. ICH E9 statistical principles for clinical trials dated 05 February 1998
20. ICH E10 choice of control and related issues in clinical trials dated 20 July 2000
21. ICH E17 general principles for planning and design of multi-regional clinical trials