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

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• 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

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Renal disorders (excl nephropathies)
Study type	Interventional

Summary

ID

NL-OMON56156

Source
ToetsingOnline

Brief title
VX21-147-301

Condition

- Renal disorders (excl nephropathies)

Synonym
APOL1-mediated proteinuric kidney disease

Research involving
Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Vertex Pharmaceuticals Incorporated

Intervention

Keyword: Phase 2/3, VX-147

Outcome measures

Primary outcome

• Percent change in UPCR from baseline at Week 48 (assessed at the IA)

• eGFR slope (with >=48 weeks of eGFR data assessed at the IA and at least 2 years of eGFR data assessed at the final analysis)

Secondary outcome

• Time to composite clinical outcome of a sustained decline of >=30% from baseline in estimated glomerular filtration rate (eGFR), the onset of end-stage kidney disease (ESKD; i.e., maintenance dialysis for >=28 days, kidney transplantation, or a sustained eGFR of <15 mL/min/1.73 m2) or death. (Sustained is defined as confirmation by a second measurement after >=28 days) (assessed at the final analysis)

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

• Plasma PK parameters of VX-147

• To evaluate the acceptability of VX-147 in pediatric subjects

• Acceptability of tablet formulation of VX-147 in pediatric subjects using the convenience domain of the Treatment Satisfaction Questionnaire for

Study description

Background summary

The apolipoprotein L1 (APOL1) gene is expressed in multiple organs in humans, including the liver and kidney.1,2 The biologic function of APOL1 is to protect against parasitic infection (Trypanosoma brucei brucei [T. b. brucei]).3 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.4 APOL1 has been shown to drive progression of chronic kidney disease (CKD), including interferon-induced nephropathy, human immunodeficiency virus nephropathy, lupus nephritis, focal segmental glomerulosclerosis, and other forms of nondiabetic kidney disease.2, 5-8 There are 2 mutations of APOL1 termed G1 and G2. 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.8 These APOL1 mutations occur exclusively in patients of African ancestry.
CKD occurring in patients with 2 APOL1 mutations is termed APOL1-mediated kidney disease (AMKD). The mechanism by which APOL1 mutations contribute to the development and progression of kidney disease is thought to be due to the pore-forming abilities.2, 5-7, 9 In the kidney, APOL1 is expressed in podocytes, endothelial cells (including glomerular endothelial cells), and some tubular cells.2, 9 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.10
Individuals of African ancestry have a higher risk of developing kidney disease, and the kidney disease has a more aggressive course with a decline to end-stage kidney disease (ESKD)

faster than in individuals of non-African ancestry.2, 5-8 Although this was first
believed to be due to disparities in healthcare, genome-wide association studies demonstrated
that the presence of 2 APOL1 mutations explain up to 70% of the cause for non-diabetic kidney
disease.11 The presence of G1/G1, G2/2 or G1/G2 leads to 3 times to 17 times greater risk of
kidney disease development;12, 13 and, if kidney disease occurs, then there is 2 to 3 times 8, 14
greater risk of ESKD compared to people without 2 APOL1 mutations. The effect of the APOL1
mutations can begin in childhood, often presenting as treatment-resistant proteinuria.15, 16

Study objective

• 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

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 (Figure 2 1). 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. 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 approximately 290 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 for the IDMC. At the IA, the primary endpoint of percent change in UPCR from baseline 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.

Intervention

Active substance: VX*147
Activity: APOL1 inhibitor
Strength and route of administration: VX-147 15 mg tablets or matching placebo tablets for oral administration

Study burden and risks

Risks Associated with VX147
The safety of this investigational product has not been fully established. As of December 2021, VX*147, the Study Drug, has been investigated in several studies. 229 participants have received the study drug VX-147 (including 213 healthy participants and 16 participants with APOL1-mediated FSGS), and VX-147 was generally well tolerated. FSGS (focal segmental glomerulosclerosis) is a disease in which scar tissue develops on the small parts of the kidneys that filter waste from the blood.
The most common side effects occurring in 2 or more healthy participants out of 100 in the studies include:
· Headache: Occurring in 9 out of 100 participants
· Diarrhea (loose, watery stools): Occurring in 4 out of 100 participants
· Nausea (feeling like vomiting): Occurring in 2 out of 100 participants

The most common side effects occurring in 2 or more participants with APOL1-mediated FSGS out of 16 in the studies include:
• Headache: Occurring in 4 out of 16 participants
• Backpain: Occurring in 3 out of 16 participants
• Nausea (feeling like vomiting): Occurring in 3 out of 16 participants
• Blood Bicarbonate decrease (a substance that helps maintain acid levels in the blood): Occurring in 2 out of 16 participants

• Diarrhea (loose, watery stools): Occurring in 2 out of 16 participants
• Dizziness: Occurring in 2 out of 16 participants
• Heartburn: Occurring in 2 out of 16 participants
• Fatigue (tiredness): Occurring in 2 out of 16 participants

Drug Interaction Risks (medicines working with or against each other):
The combination of the Study Drug and any other medications, dietary supplements, natural remedies, and vitamins could be harmful to you. It is very important that you tell your study doctor about every medicine, dietary supplement, natural remedy, and vitamin you are taking, or changes to what you are taking, while you are in the study. There may be certain things that you cannot consume during the study.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)

Elderly (65 years and older)

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 years at time of signing ICF and 65 years at Screening, inclusive. For Phase 3, subjects must be between the ages of 12 years at time of signing ICF and 65 years at Screening, inclusive. 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 18.0 to 40.0 kg/m2, inclusive, and a total body weight >=40 kg.
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 m2 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 convertingenzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), but not both concomitantly, unless documented tobe intolerant to ACE inhibitor/ARB.
9. Screening blood pressure, based on the average of 3 measurements, of >=180 mm Hg (systolic) or >=100 mm Hg (diastolic).

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.
• 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 < 10 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, based on the average of 3 measurements, of >=150 mm Hg (systolic) or >=90 mm Hg (diastolic), for subjects >=18 years old and >=140 mm Hg systolic and >=90 mm Hg diastolic for subjects

<18 years old.
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.
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 or a caregiver 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. 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.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	08-02-2023
Enrollment:	20

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	VX-147
Generic name:	N/A

Ethics review

Approved WMO Date:	07-06-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-10-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl
Approved WMO Date:	20-12-2022
Application type:	Amendment
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Application type:	Amendment
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Approved WMO Date:	06-10-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
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Approved WMO Date:	21-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
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Approved WMO Date:	11-01-2024
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660 1100 DD Amsterdam 020 566 7389 mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2021-004762-35-NL
CCMO	NL81273.018.22