Poster 372

APOL1 Inhibition by VX-147 as a Targeted Therapy for APOL1-Mediated Kidney Disease

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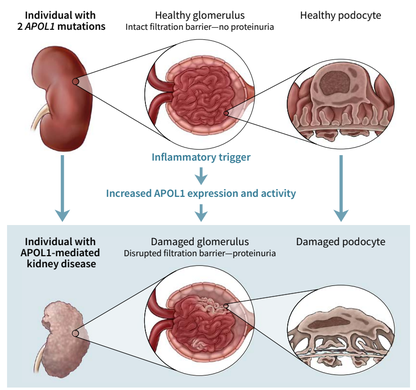
INTRODUCTION

- APOL1-mediated kidney disease (AMKD) is a proteinuric nephropathy caused by toxic gain-of-function mutations in *APOL1*[1]
- APOL1 pore function disrupts the glomerular filtration barrier, causes proteinuria, and leads to rapid deterioration in kidney function in response to an inflammatory trigger[2]
- There are currently no approved treatments targeting the underlying genetic cause of AMKD
- VX-147, a selective, oral, small molecule inhibitor of APOL1 pore function, is the first investigational treatment targeting APOL1 activity
- We present the characterization of VX-147 and the results of a Phase 2a clinical trial evaluating the efficacy and safety of VX-147 in reducing proteinuria

Figure 1. Mechanism of APOL1-Mediated Kidney Disease



APOL1 pore function directly damages podocytes in response to an inflammatory trigger. This cellular damage disrupts the glomerular filtration barrier, causes proteinuria, and leads to severe and rapid deterioration in kidney function.
APOL1: apolipoprotein L1 (italics = gene; no italics = protein).

OBJECTIVE

This trial focused on APOL1-mediated focal segmental glomerulosclerosis (FSGS) as a model of AMKD to evaluate the hypothesis that inhibition of APOL1 activity will reduce proteinuria in patients with AMKD

METHODS

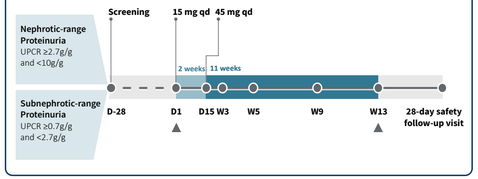
Preclinical

- A human embryonic kidney 293 (HEK293) cell line expressing *APOL1 G1* under control of a tetracycline promoter was used to quantify the effect of VX-147 on APOL1-mediated thallium ion flux
- Kidney dysfunction was induced in a transgenic *APOL1* mouse model homozygous for the *APOL1 G2* mutation ($G2_{Hom}$) by injecting interferon γ (IFN-γ). Changes in proteinuria were assessed after VX-147 administration

Clinical

- VX19-147-101 is a Phase 2a, single-arm, open-label trial in participants with biopsy-proven FSGS, 2 *APOL1* mutations, urine protein to creatinine ratio (UPCR) of ≥0.7 g/g and <10 g/g, and estimated glomerular filtration rate (eGFR) of ≥27 mL/min/1.73 m² (NCT04340362)
- Participants were administered VX-147 orally once daily for 13 weeks (2 weeks of 15 mg then 11 weeks of 45 mg) on top of standard of care followed by a 28-day safety follow-up visit
- The primary endpoint assessed the percent change from baseline in UPCR at Week 13. Secondary endpoints included safety, tolerability, and plasma pharmacokinetics

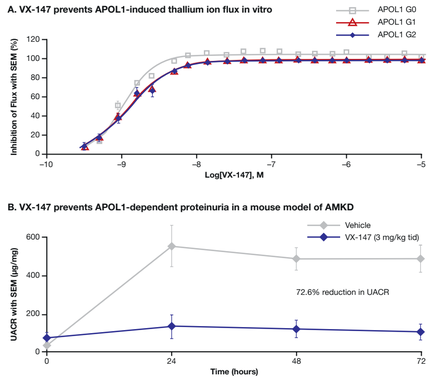
Figure 2. VX-147-101 Clinical Trial Design



The figure is not drawn to scale. Part A, shown here, evaluated the ability of VX-147 to reduce proteinuria. Proteinuria was assessed at multiple timepoints (gray circles). Eligible participants who completed Part A could enter the optional Part B, which was designed to explore the percent change in proteinuria off-treatment. All participants were required to complete a 28-day safety follow-up visit. Gray triangles represent timepoints for the primary efficacy analysis.
D: Day; qd: once daily; UPCR: urine protein to creatinine ratio; W: Week.

RESULTS

Figure 3. Preclinical Results



Panel A shows the percent inhibition of thallium ion flux in *APOL1 G0*, *APOL1 G1*, and *APOL1 G2* expressing cell lines as a function of compound concentration. Representative traces from 4 independent experiments run in duplicate are displayed (total number of replicates are: n=32 for APOL1 G1; n=4 for APOL1 G0; and n=4 for APOL1 G2).
Panel B shows the ability of VX-147 in reducing IFNγ-induced proteinuria in *APOL1* $G2_{Hom}$ mice. Two independent experiments were performed with individual replicate data: reduction in UACR of 72.6% (shown) and 75.5% (not shown), for an average of 74.1%.
AMKD: APOL1-mediated kidney disease; APOL1: apolipoprotein L1 (italics = gene; no italics = protein); SEM: standard error of the mean; tid: three times a day; UACR: urine albumin to creatinine ratio.

Table 1. Baseline Demographics and Clinical Characteristics

Parameter	Nephrotic-range[a] n=3	Subnephrotic-range[b] n=13	Total N=16
Mean age, years (SD)	45.0 (10.5)	37.3 (15.2)	38.8 (14.5)
APOL1 genotype, n (%)			
G1/G1	3 (100.0)	6 (46.2)	9 (56.3)
G2/G2	0	1 (7.7)	1 (6.3)
G1/G2	0	6 (46.2)	6 (37.5)
Mean UPCR, g/g (SD)[c]	3.47 (1.07)	1.77 (0.49)	2.08 (0.90)
Mean eGFR, mL/min/1.73 m² (SD)	51.4 (22.2)	51.2 (12.8)	51.2 (14.0)
Standard of care, n (%)			
ACE inhibitor	1 (33.3)	7 (53.8)	8 (50.0)
ARB	3 (100)	4 (30.8)	7 (43.8)
Immunosuppressant[d]	1 (33.3)	2 (15.4)	3 (18.8)
Systemic corticosteroid	0	1 (7.7)	1 (6.3)

This table includes all participants who received at least 1 dose of VX-147 and who had at least 1 post-baseline efficacy assessment.
[a]UPCR of ≥2.7 g/g and <10 g/g, and eGFR of ≥27 mL/min/1.73 m².
[b]UPCR of ≥0.7 g/g and <2.7 g/g, and eGFR of ≥27 mL/min/1.73 m².
[c]For UPCR, baseline is defined as the average of UPCR values from 3 urine samples collected during screening.
[d]The following medications were taken by participants: mycophenolate mofetil (n=1) and tacrolimus (n=2).
ACE: angiotensin converting enzyme; APOL1: apolipoprotein L1 gene; ARB: angiotensin receptor blocker; eGFR: estimated glomerular filtration rate; SD: standard deviation; UPCR: urine protein to creatinine ratio.

Table 2. Primary Endpoint Results: Mean Percent Change from Baseline in UPCR at Week 13

	Nephrotic-range[a] n=3	Subnephrotic-range[b] n=10	Total N=13[c]
Mean UPCR at baseline, g/g (SD)	3.47 (1.07)	1.84 (0.52)	2.21 (0.95)
Mean UPCR at Week 13, g/g (SD)	1.83 (0.58)	1.10 (0.71)	1.27 (0.73)
Geometric mean percent change from baseline at Week 13 (95% CI)	−47.7 (−70.1, −8.5)	−47.5 (−63.4, −24.6)	−47.6 (−60.0, −31.3)

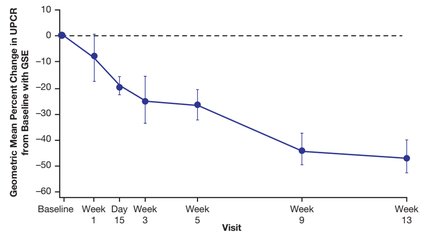
Baseline and Week 13 assessments for each of the participants were calculated as the mean of 3 first morning void measurements collected within a 7-day window.
[a]UPCR of ≥2.7 g/g and <10 g/g, and eGFR of ≥27 mL/min/1.73 m².
[b]UPCR of ≥0.7 g/g and <2.7 g/g, and eGFR of ≥27 mL/min/1.73 m².
[c]16 participants were enrolled; as pre-specified in the statistical analysis plan, 3 participants were not included in the primary efficacy analysis due to not meeting ≥80% treatment compliance.
CI: confidence interval; eGFR: estimated glomerular filtration rate; SD: standard deviation; UPCR: urine protein to creatinine ratio.

Table 3. Summary of Adverse Events

Parameter	Nephrotic-range[a] n=3 n (%)	Subnephrotic-range[b] n=13 n (%)	Total N=16 n (%)
Participants with any AE	3 (100)	12 (92.3)	15 (93.8)
AE by maximum severity			
Mild	1 (33.3)	6 (46.2)	7 (43.8)
Moderate	2 (66.7)	6 (46.2)	8 (50.0)
Severe	0	0	0
Life-threatening	0	0	0
Participants with SAEs[c]	0	1 (7.7)	1 (6.3)
AEs leading to death	0	0	0
AEs leading to treatment discontinuation	0	0	0
AEs occurring in at least 2 participants			
Headache	1 (33.3)	3 (23.1)	4 (25.0)
Back pain	0	3 (23.1)	3 (18.8)
Nausea	1 (33.3)	2 (15.4)	3 (18.8)
Blood bicarbonate decreased	0	2 (15.4)	2 (12.5)
Diarrhea	1 (33.3)	1 (7.7)	2 (12.5)
Dizziness	0	2 (15.4)	2 (12.5)
Dyspepsia	0	2 (15.4)	2 (12.5)
Fatigue	0	2 (15.4)	2 (12.5)

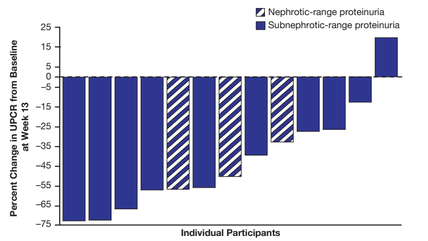
Table includes all participants who received at least 1 dose of VX-147.
[a]UPCR of ≥2.7 g/g and <10 g/g, and eGFR of ≥27 mL/min/1.73 m².
[b]UPCR of ≥0.7 g/g and <2.7 g/g, and eGFR of ≥27 mL/min/1.73 m².
[c]Two SAEs occurred in 1 participant: deep vein thrombosis and uterine leiomyoma; neither were related to VX-147.
AE: adverse event; eGFR: estimated glomerular filtration rate; SAE: serious adverse event; UPCR: urine protein to creatinine ratio.

Figure 4. Reduction in Proteinuria Occurred Early and Continued Over 13 Weeks



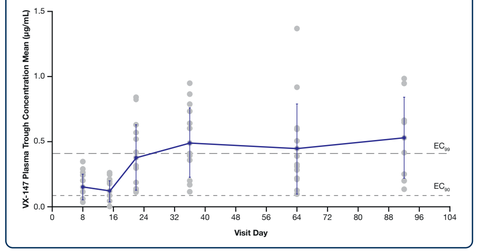
Data shown are for evaluable participants.
GSE: geometric standard error; UPCR: urine protein to creatinine ratio.

Figure 5. VX-147 Reduced Proteinuria in Participants with Nephrotic- and Subnephrotic-Range Proteinuria



Data shown are for evaluable participants.
UPCR: urine protein to creatinine ratio.

Figure 6. Plasma Exposures Were Consistent with >90% Inhibition of APOL1 Function in Preclinical Assays



The gray dashed lines represent the EC_{50} and EC_{90} from the in vitro assay in which VX-147 blocked *APOL1*-mediated thallium ion flux. Gray circles represent individual participant C_{trough} levels in trial VX19-147-101. Error bars indicate standard deviation.
APOL1: apolipoprotein L1 (italics = gene; no italics = protein); EC_{50}: effective concentration to achieve 90% inhibition; EC_{90}: effective concentration to achieve 99% inhibition.

CONCLUSIONS

- **VX-147 is an oral, small molecule inhibitor of APOL1 pore function that showed efficacy in a mouse model of AMKD[3]**
- **Treatment with VX-147 resulted in a rapid, statistically significant, and clinically meaningful reduction of 47.6% in UPCR, on top of standard of care, in participants with *2 APOL1* mutations and FSGS**
- **Efficacy results were consistent in participants with nephrotic- and subnephrotic-range proteinuria**
- **All adverse events were mild or moderate; none led to treatment discontinuation. There were no serious adverse events related to VX-147**
- **These results provide the first clinical evidence that inhibition of APOL1 function substantially reduces proteinuria in AMKD, and mark a milestone in the understanding of APOL1 as a therapeutic mechanism in kidney disease**
- **APOL1 inhibition with VX-147 represents a novel precision medicine approach for the treatment of genetically mediated kidney disease and supports further investigation in a broader population of patients with AMKD**

References

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2. Friedman DJ, Pollak MR. *Annu Rev Physiol*. 2020;82:323-42.
3. Zimmerman B, et al. *J Am Soc Nephrol*. 2021;32:abstract PO1305.

Disclosures

The study was sponsored by Vertex Pharmaceuticals Incorporated. **MP** and **DF** are inventors of patents related to APOL1 kidney disease, equity holders in Apolo1Bio, and have received research funding and consulting fees from Vertex Pharmaceuticals. **MC**, **CX**, **OE**, and **MB** are employees of Vertex Pharmaceuticals and may own stock/stock options at the company. **AF** was an employee of Vertex Pharmaceuticals at the time the study was conducted and may own stock/stock options at the company. **MP**, **DF**, **LB**, **RF**, **DG**, **ML**, **AO**, and **GC** are members of the VX-147-101 steering committee. **LB** is a consultant for Protalix, Sangamo, and Vertex Pharmaceuticals. **GC** is a consultant for Akebia, Ardelyx, AstraZeneca, Gilead, Reata, Sanifit, and Vertex Pharmaceuticals, holds stock/stock options at Ardelyx, CloudCath, Cricket, Durect, Outset, and Physiowave, and has received research funding from Amgen and Janssen.

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