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Inaxaplin for Proteinuric Kidney Disease in Persons with Two *APOL1* Variants

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ABSTRACT

BACKGROUND

Persons with toxic gain-of-function variants in the gene encoding apolipoprotein L1 (*APOL1*) are at greater risk for the development of rapidly progressive, proteinuric nephropathy. Despite the known genetic cause, therapies targeting proteinuric kidney disease in persons with two *APOL1* variants (G1 or G2) are lacking.

METHODS

We used tetracycline-inducible APOL1 human embryonic kidney (HEK293) cells to assess the ability of a small-molecule compound, inaxaplin, to inhibit APOL1 channel function. An *APOL1* G2–homologous transgenic mouse model of proteinuric kidney disease was used to assess inaxaplin treatment for proteinuria. We then conducted a single-group, open-label, phase 2a clinical study in which inaxaplin was administered to participants who had two *APOL1* variants, biopsy-proven focal segmental glomerulosclerosis, and proteinuria (urinary protein-to-creatinine ratio of ≥0.7 to <10 [with protein and creatinine both measured in grams] and an estimated glomerular filtration rate of ≥27 ml per minute per 1.73 m^2 of body-surface area). Participants received inaxaplin daily for 13 weeks (15 mg for 2 weeks and 45 mg for 11 weeks) along with standard care. The primary outcome was the percent change from the baseline urinary protein-to-creatinine ratio at week 13 in participants who had at least 80% adherence to inaxaplin therapy. Safety was also assessed.

RESULTS

In preclinical studies, inaxaplin selectively inhibited APOL1 channel function in vitro and reduced proteinuria in the mouse model. Sixteen participants were enrolled in the phase 2a study. Among the 13 participants who were treated with inaxaplin and met the adherence threshold, the mean change from the baseline urinary protein-to-creatinine ratio at week 13 was −47.6% (95% confidence interval, −60.0 to −31.3). In an analysis that included all the participants regardless of adherence to inaxaplin therapy, reductions similar to those in the primary analysis were observed in all but 1 participant. Adverse events were mild or moderate in severity; none led to study discontinuation.

CONCLUSIONS

Targeted inhibition of APOL1 channel function with inaxaplin reduced proteinuria in participants with two *APOL1* variants and focal segmental glomerulosclerosis. (Funded by Vertex Pharmaceuticals; VX19-147-101 ClinicalTrials.gov number, NCT04340362.)

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A Quick Take is available at NEJM.org

Persons with two apolipoprotein L1 (*APOL1*) variants (G1 or G2) are at higher risk for proteinuric chronic kidney disease (CKD), and those with CKD have an accelerated time to end-stage kidney disease as compared with persons without two *APOL1* variants.[1-7] These toxic gain-of-function variants are thought to enhance APOL1 channel function that directly damages podocytes.[8-11] The resultant cellular injury leads to progressive glomerular dysfunction and proteinuria, which result in a variety of histologic and clinical manifestations, including focal segmental glomerulosclerosis and hypertensive kidney disease.[2,12-22]

Patients with focal segmental glomerulosclerosis and two *APOL1* variants are typically treated with diuretics and inhibitors of the renin–angiotensin–aldosterone system, along with glucocorticoids or other agents that are intended to correct a presumed immunologic disorder, as is the case in patients with other forms of focal segmental glomerulosclerosis. Unfortunately, such therapies have limited efficacy and substantial side effects.[23-25] Given the lack of effective disease-specific treatment options, there is a need for therapies that directly target the underlying genetic cause of proteinuric CKD in persons with two *APOL1* variants.

Among patients with CKD, including those with two *APOL1* variants, the degree of proteinuria is directly associated with the likelihood of progression to end-stage kidney disease, and several agents that reduce proteinuria have been shown to attenuate CKD progression and reduce the risk of cardiovascular events.[26-30] On the basis of the pathogenic mechanism of glomerular injury caused by toxic gain-of-function *APOL1* variants, we hypothesized that inhibition of APOL1 channel function would substantially reduce podocyte damage, reduce proteinuria, and ultimately attenuate loss of kidney function in patients with proteinuric CKD and two *APOL1* variants. We report here the characterization of inaxaplin (also known as VX-147), a selective, oral, small-molecule inhibitor of APOL1 channel function, and its effects on proteinuria in a phase 2a clinical study involving participants with two *APOL1* variants and biopsy-proven focal segmental glomerulosclerosis, a severe, rapidly progressive form of CKD.

Methods

Preclinical Development

To quantify the effect of inaxaplin on APOL1 ion flux, we constructed inducible, cultured, human embryonic kidney (HEK293) cell lines expressing the *APOL1* reference sequence (G0) and two disease-associated variants (G1 and G2) under the control of a tetracycline promoter. Inaxaplin was assessed for its effect on thallium ion flux, a surrogate for potassium ion flux.[31] The flow of thallium ions into the cells was quantified with the use of a thallium-sensitive dye.

To assess the direct target engagement of APOL1 by inaxaplin, we developed a microscale thermophoresis binding assay using fluorescently labeled recombinant APOL1 protein. The binding of inaxaplin to APOL1 was quantified by changes to fluorescently labeled APOL1.

We created a transgenic *APOL1* mouse model homozygous for the *APOL1* G2 variant and induced kidney dysfunction by injecting G2-homozygous mice with interferon gamma; saline (vehicle) injections were used as a negative control. To evaluate the potential to reduce proteinuria, we prophylactically administered inaxaplin (at a dose of 3 mg per kilogram of body weight three times daily) or vehicle to G2-homozygous mice for 3 days before the interferon gamma injection (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We obtained a spot urinary albumin-to-creatinine ratio every 24 hours for 72 hours.

Study Procedures

We then conducted a two-part, single-group, open-label, phase 2a clinical study (VX19-147-101) at 12 sites in France, the United Kingdom, and the United States. We enrolled adult participants 18 to 65 years of age who had a body weight of more than 50 kg, a body-mass index (the weight in kilograms divided by the square of the height in meters) of 18.0 to 40.0, biopsy-proven focal segmental glomerulosclerosis, two *APOL1* variants (G1 and G1, G2 and G2, or G1 and G2), and nephrotic- or subnephrotic-range proteinuria. *APOL1* genotyping was performed with the use of in vitro diagnostic assay developed by Vertex Pharmaceuticals (the sponsor) and LabCorp. This assay consists of two real-time polymerase-chain-

reaction assays that use Taqman to detect the G1 and G2 variants in whole-blood samples. Nephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio (with protein and creatinine both measured in grams) of at least 2.7 and less than 10, and subnephrotic-range proteinuria as a urinary protein-to-creatinine ratio of at least 0.7 and less than 2.7. All the participants had an estimated glomerular filtration rate (GFR) of at least 27 ml per minute per 1.73 m^2 of body-surface area (on the basis of the 2009 Chronic Kidney Disease Epidemiology Collaboration estimating equation for estimated GFR, which includes a coefficient for race).

Participants were required to continue taking stable doses of standard-care medications from at least 28 days before commencing inaxaplin through follow-up. Such medications could include, but were not limited to, systemic glucocorticoids (prednisone at a dose of ≤10 mg per day or equivalent), immunosuppressants (tacrolimus, cyclosporine, or mycophenolate mofetil), and renin–angiotensin–aldosterone inhibitors. As a condition of participation in the study, we prohibited travel during the study to countries where African sleeping sickness (African trypanosomiasis) is endemic. Additional details are provided in the Supplementary Appendix.

STUDY DESIGN AND OVERSIGHT

Part A of the phase 2a study was designed to evaluate the ability of inaxaplin to reduce proteinuria. Participants were enrolled into one of two groups on the basis of the degree of proteinuria (nephrotic or subnephrotic range) at screening and received inaxaplin treatment for 13 weeks (15 mg once daily for 2 weeks, followed by 45 mg once daily for 11 weeks) (Fig. S2). A safety follow-up visit was required 28 days (within a window of ±7 days) after the receipt of the last dose of inaxaplin. After the completion of inaxaplin treatment in part A, participants had the option to enroll in part B, which was designed to explore the percent change in proteinuria for up to 12 weeks after the completion of treatment in part A.

The study was designed by the sponsor in collaboration with the steering committee. All the participants provided written informed consent before the study began. Data collection was performed by the sponsor and the VX19-147-101 Study Group; data analysis was performed by the sponsor in collaboration with the steering committee. The first author wrote the first draft of the manuscript with the assistance of medical writers employed by the sponsor. All the authors had access to the data, critically reviewed the manuscript, and approved the manuscript for submission for publication. The investigators vouch for the accuracy and completeness of the data generated at their respective sites, and the investigators and the sponsor vouch for the fidelity of the study to the protocol (available at NEJM.org). Confidentiality agreements were in place between the sponsor and the investigative sites.

OUTCOMES

The primary efficacy outcome was the percent change from the baseline urinary protein-to-creatinine ratio at week 13. Secondary outcomes included safety and pharmacokinetics. The safety analysis was based on adverse events, clinical laboratory values, standard 12-lead electrocardiograms, and vital signs.

STATISTICAL ANALYSIS

The sample size was selected on the basis of the precision of the expected estimator. Assuming a standard deviation of 0.672 (in log scale), we calculated that a sample size of 10 would provide the study with a precision of 0.294 (in log scale) for the estimation of the geometric mean percent change from baseline in the urinary protein-to-creatinine ratio. The precision of the estimate corresponds to the half-width of its 80% confidence interval (in log scale). As prespecified in the statistical analysis plan (which is available with the protocol), the primary efficacy analysis included all the participants who had at least 80% adherence to inaxaplin treatment. We also report the results of efficacy analyses that included all the participants regardless of treatment adherence.

We calculated the urinary protein-to-creatinine ratio as the mean of the three values from first-morning void urine samples obtained within a 7-day window. To reduce skewness, we analyzed the percent change from the baseline urinary protein-to-creatinine ratio at week 13 by first log-transforming the data for the ratio be-

fore the analyses and then calculating the change from baseline in log-transformed values.[32] We calculated the geometric mean percent change from the baseline urinary protein-to-creatinine ratio at week 13 and the corresponding two-sided confidence interval by back-transforming the estimated simple mean of the change from baseline in log-transformed data. Safety analyses included all the participants who received at least one dose of inaxaplin; safety data were summarized with the use of descriptive statistics.

RESULTS

EFFICACY IN PRECLINICAL MODELS

Our in vitro and in vivo studies showed that inaxaplin bound directly to the APOL1 protein, inhibited APOL1 channel function, and reduced proteinuria in a transgenic mouse model of *APOL1*-mediated kidney disease. Specifically, in cellular assays, inaxaplin blocked the channel function of APOL1 in a concentration-dependent manner, as shown by the reduced APOL1-induced thallium ion flux in tetracycline-inducible APOL1 HEK293 cells (Fig. 1A). In this cell model, thallium flux was minimal in the absence of APOL1 expression, and APOL1-mediated thallium flux was nearly eliminated by the administration of inaxaplin (Fig. 1B). Inaxaplin bound directly to APOL1 protein, as shown by a microscale thermophoresis binding assay (Fig. 1C).

In an *APOL1* G2-homozygous transgenic mouse model, the injection of interferon gamma resulted in heavy proteinuria; in contrast, no proteinuria was seen when control Friend leukemia virus B (FVB) mice were exposed to interferon gamma. The prophylactic administration of inaxaplin (3 mg per kilogram three times daily) or vehicle for 3 days, with the first dose given on day 1 approximately 1.5 hours before the interferon gamma injection, significantly reduced the area under the curve for the mean urinary albumin-to-creatinine ratio in interferon gamma–injected G2-homozygous mice by an average of 74.1% (Fig. 1D and Fig. S3).

POPULATION

Data from part A of the phase 2a study are summarized here, and exploratory data from part B are summarized in the Supplementary Appendix. A flow diagram of the enrollment, treatment, and follow-up of the participants is shown in Figure S4. Study enrollment began in September 2020 and was completed in August 2021. The demographic and clinical characteristics of the participants are shown in Table 1 and Tables S1 and S2. The demographic characteristics were generally representative of the expected participant population (Table S3). The mean (±SD) age of the 16 enrolled participants was 38.8±14.5 years, and the mean baseline urinary protein-to-creatinine ratio was 2.08±0.90 among all the participants who had received at least one dose of inaxaplin and 2.21±0.95 among the 13 participants who were evaluable in the efficacy analysis (Table 2). Among the 16 participants, 3 did not have at least 80% adherence to treatment and were therefore not included in the primary efficacy analyses, as prespecified in the statistical analysis plan (see the Supplementary Appendix). The baseline characteristics of the participants, including the estimated GFR at baseline and the distribution of standard-care medications, were generally similar among the 3 participants with nephrotic-range proteinuria and the 13 with subnephrotic-range proteinuria and among the 13 participants who were included in the primary analysis and the 3 who were not.

PRIMARY OUTCOME

A mean change in the urinary protein-to-creatinine ratio of −47.6% (95% confidence interval [CI], −60.0 to −31.3) was observed at week 13 (Table 2); the percent change from baseline at week 13 for each participant is shown in Figure 2A. The treatment response from baseline was rapid and approximately linear, with a decrease seen by day 15; proteinuria continued to decrease through week 13 (Fig. 2B). Reduction in proteinuria was seen in both the nephrotic- and subnephrotic-range groups (mean change in the urinary protein-to-creatinine ratio, −47.7% and −47.5%, respectively) (Table 2) and was unrelated to background standard-care medications. In an analysis that included all 16 participants, regardless of adherence to inaxaplin treatment, the mean change in the urinary protein-to-creatinine ratio at week 13 was −44.0% (95% CI, −56.3 to −28.3); one participant did not have a reduction (Fig. S5). Although this participant had 100% adherence to treatment, there were no clinical characteristics that appeared to have influenced the lack of treatment response.

As compared with the baseline reduction in

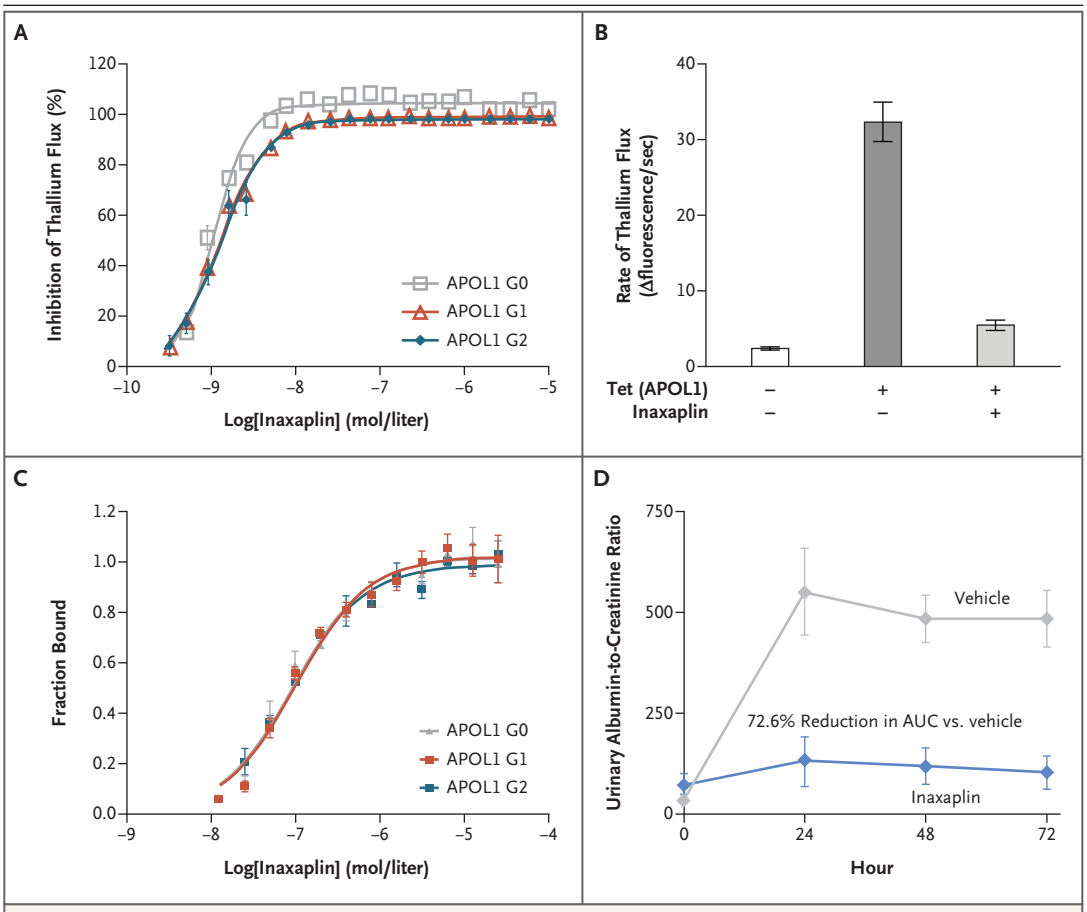

Figure 1. Preclinical Data.

Panel A shows the percent inhibition of thallium ion flux in cell lines expressed by the apolipoprotein L1 (*APOL1*) reference sequence (G0) and disease-associated variants *APOL1* G1 and *APOL1* G2 as a function of inaxaplin concentration. Representative traces from four independent experiments that were run in duplicate are shown; the total number of replicates were 4 for APOL1 G0, 32 for APOL1 G1, and 4 for APOL1 G2. The shapes represent the percent inhibition at that concentration of inaxaplin, whereas the line is a nonlinear regression best fit to all the points. Panel B shows representative data from 32 independent experiments in APOL1 G1–expressing cells, showing the dependency of thallium flux on the expression and activity of APOL1. Plus signs indicate treatment with the indicated agent, and minus signs indicate its absence; tetracycline (tet) is used to include APOL1 expression. The Δ denotes change. Panel C shows the fraction bound of fluorescently labeled APOL1 G0, APOL1 G1, and APOL1 G2 as a function of inaxaplin concentration. The analysis involved two measurements for APOL1 G0 and APOL1 G2 and four measurements for APOL1 G1. Panel D shows the ability of inaxaplin to reduce interferon gamma–induced proteinuria in *APOL1* G2–homozygous mice. Two independent experiments were performed with individual replicate data: among 9 mice that received inaxaplin at a dose of 3 mg per kilogram of body weight three times daily, the reduction in the area under the curve (AUC) for the urinary albumin-to-creatinine ratio was 72.6% (as compared with results in 10 mice that received vehicle); among 6 mice that received inaxaplin, this reduction was 75.5% (as compared with 10 mice that received vehicle; data not shown), for an average reduction of 74.1%. In all panels, I bars indicate the standard error.

proteinuria that was observed at the end of part A of the study, in the exploratory part B of the study (in which data from nine participants were assessed), the mean urinary protein-to-creatinine ratio increased from −47.6% to −30.1% at week 4. The urinary protein-to-creatinine ratio remained stable for an additional 8 weeks (Fig. S6).

ADVERSE EVENTS AND SAFETY

Among the 16 participants who received at least one dose of inaxaplin, 15 (94%) had at least one

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline.*

Characteristic	Total (N=16)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=13)
Age — yr	38.8±14.5	45.0±10.5	37.3±15.2
Sex — no. (%)			
Male	7 (44)	1 (33)	6 (46)
Female	9 (56)	2 (67)	7 (54)
APOL1 genotype — no. (%)			
G1/G1	9 (56)	3 (100)	6 (46)
G2/G2	1 (6)	0	1 (8)
G1/G2	6 (38)	0	6 (46)
Body-mass index	29.6±6.4	32.7±6.4	28.9±6.4
Urinary protein-to-creatinine ratio†	2.08±0.90	3.47±1.07	1.77±0.49
Estimated GFR — ml/min/1.73 m^2	51.2±14.0	51.4±22.2	51.2±12.8
Standard-care medication			
ACE inhibitor			
≥28 days before day 1 — no. (%)	8 (50)	1 (33)	7 (54)
On day 1 — no./total no. (%)	8/8 (100)	1/1 (100)	7/7 (100)
Angiotensin-receptor blocker			
≥28 days before day 1 — no. (%)	7 (44)	3 (100)	4 (31)
On day 1 — no./ total no. (%)	6/7 (86)	2/3 (67)‡	4/4 (100)
Immunosuppressants§			
≥28 days before day 1 — no. (%)	4 (25)	1 (33)	3 (23)
On day 1 — no./ total no. (%)	4/4 (100)	1/1 (100)	3/3 (100)

* Plus–minus values are means ±SD. Data are shown for all the participants who received at least one dose of inaxaplin and who had at least one postbaseline efficacy assessment. Nephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio (with protein and creatinine both measured in grams) of at least 2.7 to less than 10 and an estimated glomerular filtration rate (GFR) of at least 27 ml per minute per 1.73 m^2 of body-surface area. Subnephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio of at least 0.7 to less than 2.7 and an estimated GFR of at least 27 ml per minute per 1.73 m^2. ACE denotes angiotensin-converting enzyme.

† For the urinary protein-to-creatinine ratio, the baseline value was the mean of the urinary protein-to-creatinine ratios from three urine samples obtained during screening.

‡ One participant had a reduction in the dose during the screening period, which was documented as a postenrollment eligibility deviation.

§ Immunosuppressants included systemic glucocorticoids. The following medications were taken by participants: prednisone (one participant), mycophenolate mofetil (one), and tacrolimus (two).

adverse event. All the adverse events were mild or moderate in severity; there were no treatment discontinuations due to adverse events. Adverse events that occurred in more than 2 participants were headache, back pain, and nausea (Table 3). Three participants had adverse events that were considered by the investigator to be possibly related to inaxaplin (2 participants with headache and 1 participant with headache, abdominal distension, dyspepsia, and back pain). Two serious adverse events occurred in 1 participant: deep-vein thrombosis and uterine leiomyoma; neither event was considered by the investigator to be related to inaxaplin. There were no clinically significant safety findings in other clinical or laboratory assessments, including the hemoglobin level, liver-enzyme levels, total bilirubin level, lipid concentrations, electrocardiograms, or vital signs. Participants had a stable estimated GFR and blood pressure throughout the study (Fig. S7 and Table S4).

Table 2. Mean Percent Change from the Baseline Urinary Protein-to-Creatinine Ratio at Week 13.*

Variable	Total (N=13)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=10)
Mean urinary protein-to-creatinine ratio			
At baseline	2.21±0.95	3.47±1.07	1.84±0.52
At wk 13	1.27±0.73	1.83±0.58	1.10±0.71
Geometric percent change from baseline at wk 13 (95% CI)	−47.6 (−60.0 to −31.3)	−47.7 (−70.1 to −8.5)	−47.5 (−63.4 to −24.6)

* Plus–minus values are means ±SD. Baseline and week 13 assessments of the urinary protein-to-creatinine ratio for each of the participants were calculated as the mean of three first-morning void measurements obtained within a 7-day window. The efficacy analysis set included all the participants who completed inaxaplin treatment and had at least 80% adherence to treatment. CI denotes confidence interval.

DISCUSSION

Inaxaplin is an oral, small-molecule inhibitor of APOL1 channel function that showed activity in an *APOL1* transgenic mouse model of proteinuric kidney disease. In our open-label, phase 2a clinical study involving participants with two *APOL1* variants and biopsy-proven focal segmental glomerulosclerosis, 15 of 16 participants who were treated with inaxaplin had a clinically meaningful mean reduction in the urinary protein-to-creatinine ratio at week 13. For the 13 evaluable participants, the mean change in the urinary protein-to-creatinine ratio of −47.6% (95% confidence CI, −60.0 to −31.3) was observed at week 13. Reduction in proteinuria was observed early and continued throughout the 13-week treatment period.

All the adverse events appeared to be mild or moderate in severity; no serious adverse events were considered by the investigators to be related to inaxaplin treatment. There were no treatment discontinuations due to adverse events. The reduction in proteinuria that we observed was more pronounced in the study participants than what has been typically observed with standard-care medications; all the participants had a stable estimated GFR, without an early decrease in the estimated GFR, as has been observed with some standard-care medications for CKD.[33-35] A reduction in proteinuria or albuminuria of more than 40% is considered to be clinically meaningful on the basis of data from nearly 30,000 patients, in whom a 30% reduction in albuminuria translated to a 27% reduction in the risk of a composite clinical end point of end-stage kidney disease, an estimated GFR below 15 ml per minute per 1.73 m^2, or a doubling of the serum creatinine level (57% reduction in the estimated GFR).[36] Collectively, these data provide a rationale to test the hypothesis that with a longer treatment period, inaxaplin therapy may prevent or slow progression to end-stage kidney disease.

Our preclinical studies showed that inaxaplin bound directly to the APOL1 protein, specifically blocking APOL1 ion flux, and reduced proteinuria in an *APOL1* transgenic mouse model of proteinuric kidney disease. The treatment effect that was predicted from these preclinical studies was evident in our phase 2a study with regard to a reduction in proteinuria of more than 40% in participants with two *APOL1* variants and focal segmental glomerulosclerosis.

Studies of the genetics of *APOL1* in humans have shown a key role for the G1 and G2 alleles in proteinuric kidney disease,[1-6] but the specific function or role of APOL1 in producing a kidney phenotype has not been clear. We hypothesized that the ion-channel function of APOL1 responsible for trypanosome lysis is also the function that is relevant to kidney disease. The results of this phase 2a study, in which a specific inhibitor of APOL1 channel function was administered, are consistent with the putative role of APOL1 ion flux in patients with two *APOL1* variants and biopsy-proven focal segmental glomerulosclerosis. The effects of inaxaplin therapy in this short-term clinical study involving participants with

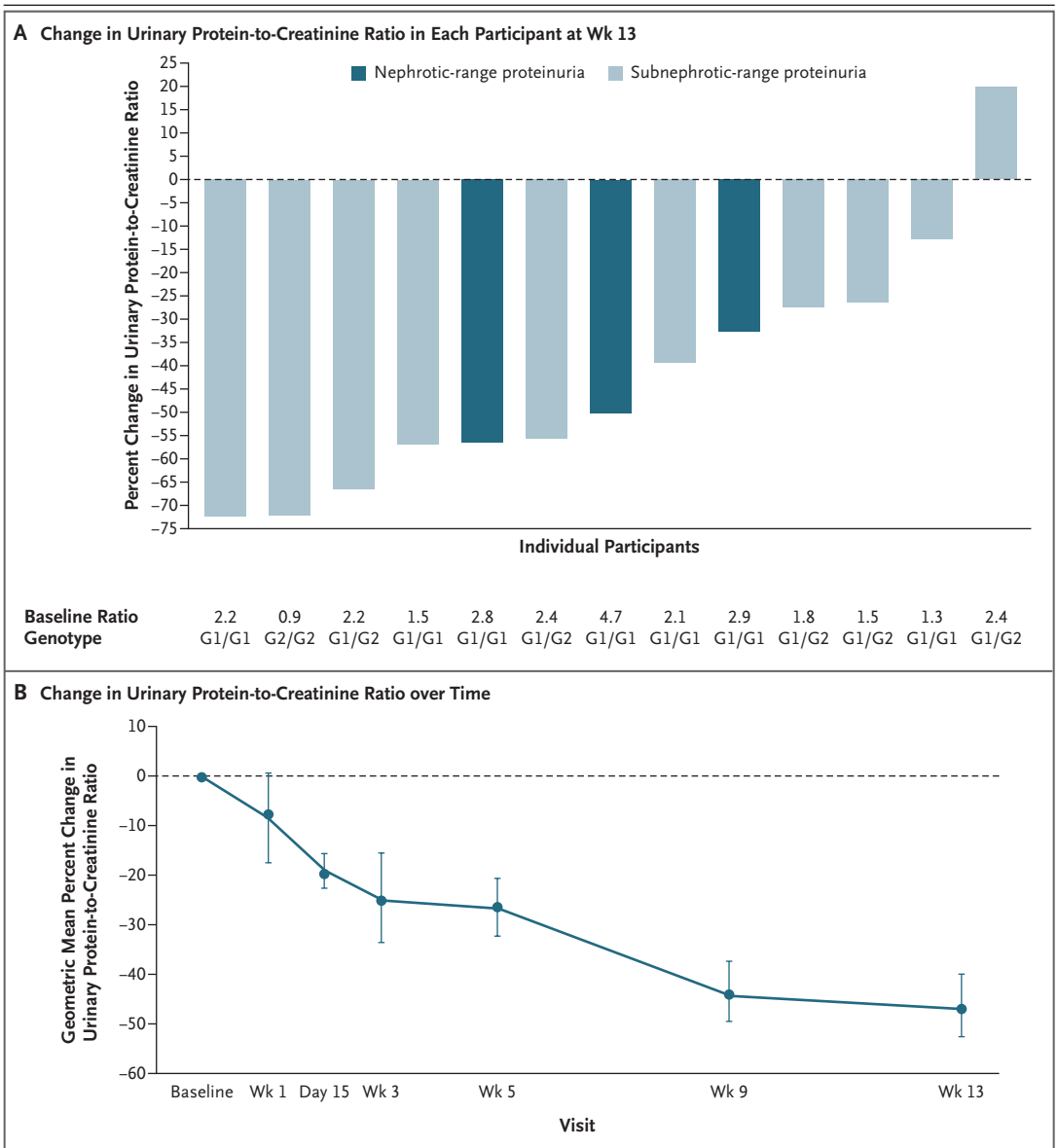

Figure 2. Efficacy Outcomes.

Data for 13 evaluable participants are shown. Panel A shows a waterfall plot of the percent change from baseline (dashed line) in the urinary protein-to-creatinine ratio at week 13. The baseline urinary protein-to-creatinine ratio and *APOL1* genotype in each participant are shown under the graph. Nephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio (with protein and creatinine both measured in grams) of at least 2.7 to less than 10 and an estimated glomerular filtration rate (GFR) of at least 27 ml per minute per 1.73 m^2 of body-surface area. Subnephrotic-range proteinuria was defined as a urinary protein-to-creatinine ratio of at least 0.7 to less than 2.7 and an estimated GFR of at least 27 ml per minute per 1.73 m^2. Panel B shows the geometric mean percent change from baseline (dashed line) in the urinary protein-to-creatinine ratio over time during the 13-week treatment period and combines data from the participants regardless of nephrotic- or subnephrotic-range status. I bars indicate the geometric standard error.

two *APOL1* variants and biopsy-proven focal segmental glomerulosclerosis (a severe, rapidly progressive form of proteinuric CKD) remain to be studied in persons with two *APOL1* variants and other types of proteinuric CKD, such as hypertensive kidney disease. If such additional studies

Table 3. Adverse Events.*

Event	Total (N=16)	Participants with Nephrotic-Range Proteinuria (N=3)	Participants with Subnephrotic-Range Proteinuria (N=13)
Any adverse event†	15 (94)	3 (100)	12 (92)
Adverse events according to severity			
Mild	7 (44)	1 (33)	6 (46)
Moderate	8 (50)	2 (67)	6 (46)
Severe	0	0	0
Life-threatening	0	0	0
Serious adverse event‡	1 (6)	0	1 (8)
Adverse event leading to treatment discontinuation	0	0	0
Adverse event occurring in ≥2 participants			
Headache	4 (25)	1 (33)	3 (23)
Back pain	3 (19)	0	3 (23)
Nausea	3 (19)	1 (33)	2 (15)
Decrease in blood bicarbonate level	2 (12)	0	2 (15)
Diarrhea	2 (12)	1 (33)	1 (8)
Dizziness	2 (12)	0	2 (15)
Dyspepsia	2 (12)	0	2 (15)
Fatigue	2 (12)	0	2 (15)

* The safety analysis included all the participants who received at least one dose of inaxaplin.
† Adverse events that were considered by the investigator as being possibly related to inaxaplin occurred in three participants: headache in one participant in the nephrotic-range group and in one in the subnephrotic-range group and headache, abdominal distension, dyspepsia, and back pain in one participant in the subnephrotic-range group.
‡ Two serious adverse events occurred in one participant: deep-vein thrombosis and uterine leiomyoma. Neither event was considered by the investigator to be related to inaxaplin.

indicate that APOL1 inhibition is effective, the use of inaxaplin may have potential as a precision medicine approach to a group of kidney diseases currently defined according to histologic or clinical manifestations but which instead could be defined according to genetic cause (i.e., two *APOL1* variants); this hypothesis is being tested in an ongoing phase 2–3 placebo-controlled trial of inaxaplin (ClinicalTrials.gov number, NCT05312879).

The present phase 2a clinical study was designed as a partially decentralized study in order to minimize the burden to participants. With our study design, participants had the option to complete assessments on-site or at home with a visiting nurse, a factor that enabled successful completion of the study, especially during the coronavirus disease 2019 pandemic. Our study has certain limitations. It was small, short in duration, and not placebo-controlled. Focal segmental glomerulosclerosis in patients who are homozygous (or compound heterozygous) for two *APOL1* variants is a rare, rapidly progressive disease with a very low likelihood of spontaneous remission of proteinuria. Although we did not determine a sample size on the basis of power calculations, we anticipated a relatively large reduction in proteinuria and believed that the selected sample size on the basis of precision estimation would be sufficient to determine the range of proteinuria reduction that could inform the design of subsequent, longer-term, placebo-controlled trials. In participants who received placebo in placebo-controlled trials involving patients with proteinuric CKD, reductions of up to 15% in the urinary protein-to-creatinine ratio have been observed,[37,38] a treatment effect that is much smaller than what we observed in this study.

One participant with subnephrotic-range pro-

teinuria did not have a decrease in proteinuria with inaxaplin therapy in our study. The adherence to treatment in this participant was 100%; neither the lead country investigator nor the treating nephrologist could identify any clinical characteristics that might have influenced the lack of treatment response. Patients with nephrotic-range proteinuria often have the most severe manifestations of focal segmental glomerulosclerosis. Although only three participants with nephrotic-range proteinuria were enrolled in this study, the results in these participants appeared to be consistent with those observed in participants who had less-severe proteinuria. Finally, although just nine participants entered the optional extension of the study (part B), we were encouraged that the reduction in proteinuria was sustained after the completion of treatment in some participants.

In this phase 2a study, the primary-outcome results provided initial evidence that the targeted inhibition of APOL1 function reduced proteinuria, a marker of glomerular injury that has been associated with progressive kidney disease, driven by toxic gain-of-function APOL1 protein variants.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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