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Safety and Tolerability of the APOL1 Inhibitor, Inaxaplin, following Single- and Multiple-Ascending Doses in Healthy Adults

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Abstract
Introduction: Toxic gain-of-function *Apolipoprotein L1* (*APOL1*) variants contribute to the development of proteinuric nephropathies collectively referred to as APOL1-mediated kidney disease (AMKD). Despite standard-of-care treatments, patients with AMKD experience accelerated progression to end-stage kidney disease. The identification of two *APOL1* variants as the genetic cause of AMKD inspired development of inaxaplin, an inhibitor of APOL1 channel activity that reduces proteinuria in patients with AMKD. ***Methods:*** We conducted two phase 1 studies evaluating the safety, tolerability, and pharmacokinetics of single-ascending doses (SAD) and multiple-ascending doses (MAD) of inaxaplin in healthy participants. In the SAD cohorts, participants were randomized to receive inaxaplin as a single dose (range, 7.5 mg to 165 mg) or placebo. In the MAD cohorts, participants were randomized to receive multiple doses of inaxaplin (range, 15 to 120 mg daily) or placebo for 14 days. We assessed safety and tolerability based on adverse events (AEs), clinical laboratory values, electrocardiograms (ECGs), and vital signs. ***Results:*** A total of 178 participants were randomized in the SAD/MAD cohorts of both studies (mean age: 36.7 years; 94.9% male). The proportion of participants with any AEs was similar in the inaxaplin (24.6%) and placebo (22.7%) groups. All AEs were mild or moderate in severity; there were no serious AEs. Headache was the most common AE: 10.4% and 2.3% in the inaxaplin and placebo groups, respectively. There were no drug-related treatment discontinuations and no clinically relevant trends in laboratory values, ECGs, or vital signs. ***Discussion/Conclusion:*** Inaxaplin is safe and well tolerated at single doses up to 165 mg and multiple doses up to 120 mg daily for 14 days. These results are consistent with the favorable safety profile of inaxaplin in a completed phase 2a proof-of-concept study. Together, these findings support continued evaluation of inaxaplin in an ongoing phase 2/3 pivotal trial as a potential precision medicine for patients with AMKD.

Introduction

Apolipoprotein L1 (APOL1)-mediated kidney disease (AMKD) is a rapidly progressive, proteinuric chronic kidney disease (CKD) driven by the presence of two toxic

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gain-of-function variants in the *APOL1* gene [1–7]. There are currently no specific treatments for AMKD; current standard-of-care aims to reduce proteinuria, slow the decline in kidney function, and/or prevent associated complications, typically including usual renoprotective measures (i.e., renin-angiotensin-aldosterone system [RAAS] inhibitors), and in some cases, other antihypertensive medications, immunosuppressive/anti-inflammatory agents, and diuretics [8–10]. More recently, sodium-glucose cotransporter 2 (SGLT2) inhibitors are included in standard-of-care as they have been shown to reduce proteinuria and preserve kidney function in patients with proteinuric kidney disease without diabetes [11, 12]. In patients with diabetes and kidney disease, some glucagon-like-peptide receptor agonists have also demonstrated reductions in proteinuria and improved kidney outcomes [13]. While these treatments – usually in combination – often provide meaningful clinical benefits and may slow disease progression, they are non-targeted, carry a risk of adverse effects, and do not address the underlying pathophysiology of AMKD; as a result, we continue to see an inexorable decline toward kidney failure in a sizeable fraction of patients [8–10].

The underlying genetic cause of AMKD is a toxic gain-of-function in the *APOL1* gene (*G1 or G2*) thought to enhance APOL1 channel function and damage glomerular cells (e.g., podocytes and endothelial cells) in response to an inflammatory trigger; the resulting cellular damage disrupts the glomerular filtration barrier, resulting in proteinuria, and often leads to accelerated loss of kidney function (Fig. 1) [14–19]. This toxic gain-of-function activity of APOL1 is thought to be the common mechanism that ultimately leads to kidney failure, regardless of the clinical or histological presentation [4, 14]. However, genetic testing is not routinely performed for patients with CKD and patients with subnephrotic proteinuria and two *APOL1* variants may be misdiagnosed as having unspecified or hypertensive CKD [20, 21].

The identification of two *APOL1* variants as the genetic cause of AMKD inspired the development of targeted therapies to address the underlying cause of disease. Based on the mechanism of disease, targeted inhibition of APOL1 should inhibit glomerular damage, reduce proteinuria, and ultimately slow the progression of kidney disease. Inaxaplin (previously known as VX-147) is an oral, small molecule inhibitor of APOL1 channel function that has been shown to reduce proteinuria in patients with AMKD in a phase 2a proof-of-concept study [14] and has the potential to prevent further structural damage and slow the progression of renal dysfunction in persons who have two *APOL1* variants. Herein we report the safety, tolerability, and pharmacokinetics of inaxaplin from two phase 1 single-ascending dose (SAD)/multiple-ascending dose (MAD) studies in healthy participants.

Methods

Overview of Study Procedures

We conducted two phase 1, randomized, double-blind, placebo-controlled SAD/MAD studies of inaxaplin in healthy participants. The first-in-human study of inaxaplin (Study VX18-147-001 or Study 1) evaluated single ascending doses of 7.5 mg up to 50 mg and multiple ascending doses of 15 mg once daily, 15 mg twice daily, or 45 mg once daily in healthy participants. To provide additional clinical information on the safety of higher doses of inaxaplin, a second phase 1 study of inaxaplin (Study VX20-147-008 or Study 2) evaluated single ascending doses of 90 mg up to 165 mg and multiple ascending doses of 60 mg up to 120 mg once daily in healthy participants. Study 1 was conducted at two sites in the United States (Madison, WI and Dallas, TX) between June 2019 and January 2020. Study 2 was conducted at one site in the United States (Salt Lake City, UT) between August 2020 and March 2021.

Study Participants

In both studies, we enrolled healthy men and women of non-childbearing potential who were at least 18 years of age with body weight of >50 kg and body mass index (BMI) 18.0 to 32.0 kg/m^2. Demographics were collected during the screening visit; race was self-reported by participants and recorded by site personnel. "Healthy" was defined by no clinically relevant abnormalities identified by a detailed medical history, full physical examination, including blood pressure and pulse rate measurement, standard 12-lead electrocardiogram (ECG), and clinical laboratory tests.

Study Design

Part A of both phase 1 studies was designed to evaluate the safety and tolerability of single oral ascending doses of inaxaplin administered to healthy participants. In Study 1, participants were randomized 3:1 to receive a single dose of inaxaplin (7.5 mg, 15 mg, 30 mg, 50 mg) or placebo. In Study 2, participants were randomized 3:1 to receive a single dose of inaxaplin (90 mg, 135 mg, 165 mg) or placebo.

Part B of both phase 1 studies was designed to evaluate the safety and tolerability of multiple oral ascending doses of inaxaplin administered to healthy participants. In Study 1, participants were randomized 3:1 to receive multiple doses of inaxaplin (15 mg once daily, 15 mg twice daily, 45 mg once daily) or placebo for 14 days. In Study 2, participants were randomized 3:1 to receive multiple doses of inaxaplin (60 mg once daily, 90 mg once daily, 120 mg once daily) or placebo for 14 days.

All SAD and MAD cohorts included unique participants. There was no cross-over of participants within or across study cohorts. All participants had a Safety Follow-up Visit 7–10 days after the last dose of study drug.

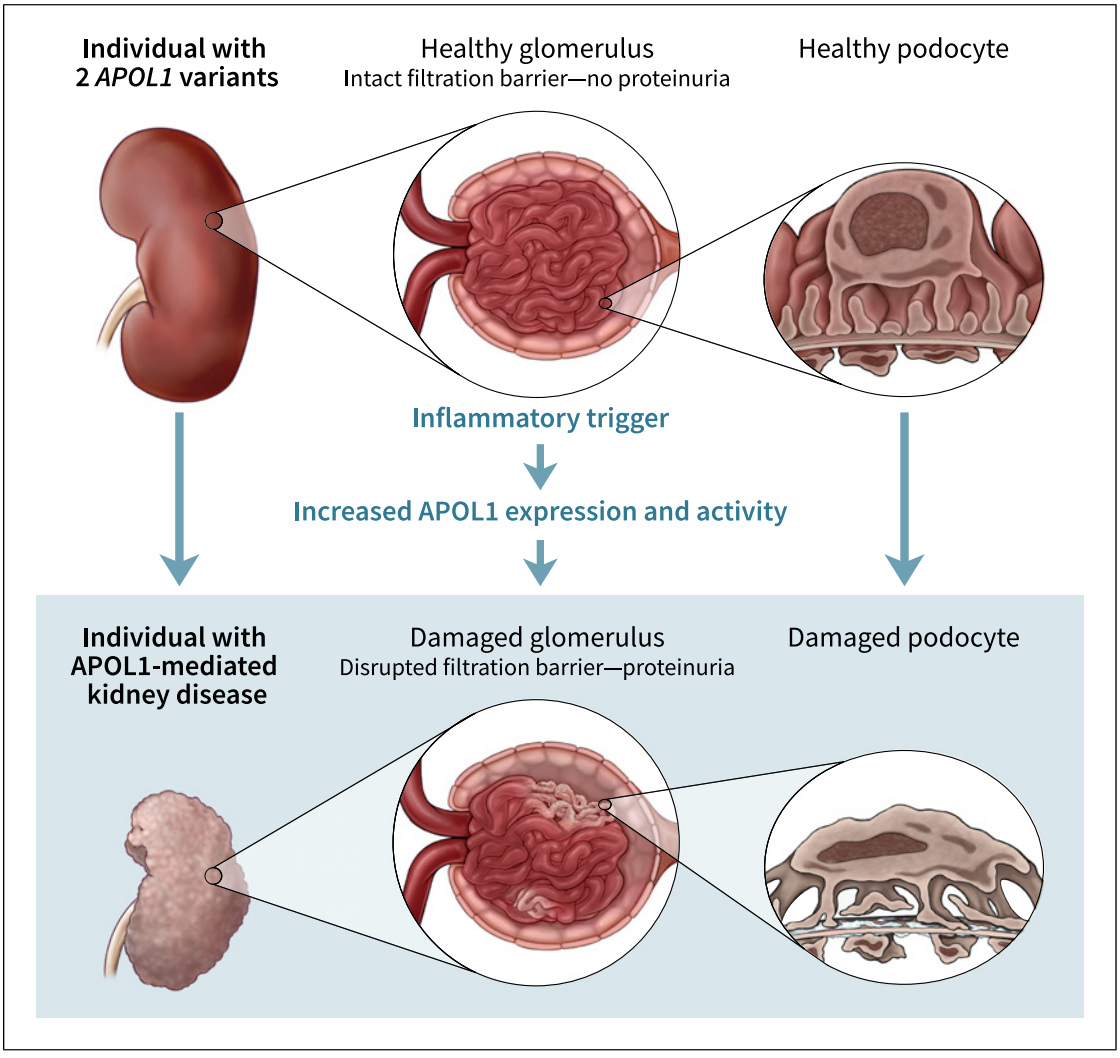

Fig. 1. Toxic gain-of-function *APOL1* variants lead to progressive glomerular dysfunction and proteinuria across multiple clinically and histologically defined kidney diseases. In response to an inflammatory trigger, enhanced APOL1 channel function directly damages podocytes, which disrupts the glomerular filtration barrier, causes proteinuria, and leads to the subsequent severe and rapid deterioration in kidney function.

Safety Assessments

The primary objective for Parts A and B of both phase 1 studies was to determine safety and tolerability based on assessment of adverse events (AEs), clinical laboratory assessments (serum chemistry, hematology, coagulation, and urinalysis), standard 12-lead ECG measures (performed in triplicate), and vital signs.

Pharmacokinetic Assessments

In both studies, we assessed plasma pharmacokinetic (PK) parameter estimates of inaxaplin (i.e., time of maximum concentration [t_{max}], maximum observed concentration [C_{max}], area under the concentration vs. time curve from the time of dosing to 24 h [AUC_{0-24h}], terminal phase half-life [$t_{½}$], apparent volume of distribution [V/F], and apparent clearance at steady-state [CLss/F]) after multiple oral ascending doses of inaxaplin derived from plasma concentration-time data. We also assessed urine PK parameter estimates. We assessed the potential of inaxaplin to either induce or inhibit CYP3A4 enzymes in Study 1 by measuring the effect of inaxaplin administration on serum concentrations of midazolam, a sensitive CYP3A4 substrate.

See online Supplementary Materials (for all online suppl. material, see https://doi.org/10.1159/000538255) for additional details regarding PK assessments and analyses.

Statistical Analyses

In both phase 1 studies, we used descriptive analyses on safety data including AEs, clinical laboratory assessments, vital signs, and ECGs. Since ECGs were performed in triplicate, the mean of each individual ECG parameter measurement (i.e., PR, RR, QRS, QT, QTcF, heart rate) at each specific visit and time point was used as the ECG for that

Table 1. Demographics and Baseline Characteristics

	Placebo[a] (*N* = 44)	Inaxaplin Total[b] (*N* = 134)
Sex, *n* (%)		
Male	41 (93.2)	128 (95.5)
Female	3 (6.8)	6 (4.5)
Age (years), mean (±SD)	36.7 (11.3)	36.6 (11.6)
BMI (kg/m^2), mean (±SD)	27.07 (3.14)	26.22 (3.30)
Race, *n* (%)		
White	30 (68.2)	94 (70.1)
Black or African American	12 (27.3)	32 (23.9)
Asian	0	1 (0.7)
American Indian or Alaska Native	0	3 (2.2)
Multiracial	1 (2.3)	4 (3.0)
Other	1 (2.3)	0
Ethnicity, *n* (%)		
Hispanic or Latino	10 (22.7)	21 (15.7)
Not Hispanic or Latino	34 (77.3)	113 (84.3)

BMI, body mass index; MAD, multiple ascending doses; *N*, Safety Set sample size; *n*, number of participants; SAD, single ascending doses; SD, standard deviation. This table includes all participants in the SAD and MAD cohorts of both phase 1 studies who received any dose of study drug. [a]Placebo is pooled from all SAD and MAD cohorts in both phase 1 studies. There were 21 participants who received placebo in the SAD cohort and 23 participants who received placebo in the MAD cohort. [b]Inaxaplin Total is pooled from all SAD and MAD cohorts in both phase 1 studies, based on participants treated with any dose of inaxaplin. There were 63 participants who received inaxaplin in the SAD cohort and 71 participants who received inaxaplin in the MAD cohort.

specific visit and time point for summary purposes. In addition to analyses performed in the SAD and MAD cohorts separately for the two studies, we conducted a pooled analysis across cohorts.

Results

Study Population

One hundred and seventy eight participants were randomized and received at least one dose of study drug in the SAD and MAD cohorts of the two phase 1 studies. Participant demographics and baseline characteristics are shown in Table 1. The mean (± standard deviation) age of all participants was 36.7 (±11.5) years. Demographics and baseline characteristics were similar across the inaxaplin and placebo groups.

Study Disposition

The disposition of the participants in the SAD and MAD cohorts of both studies is presented in Table 2 (SAD and MAD cohorts) and online Figure S1 (MAD cohorts). There were no study drug discontinuations in the SAD cohorts in both studies as participants only received a single dose of study drug. Among participants in the MAD cohorts who received at least one dose of study drug, 50 (70.4%) participants in the inaxaplin group and 18 (78.3%) participants in the placebo group completed study drug.

The majority of treatment discontinuations occurred in two MAD cohorts of Study 2 and were due to sponsor decision (21 participants). Dosing in one cohort (inaxaplin 60 mg once daily MAD group: *N* = 9; placebo MAD group: *N* = 3) was paused to investigate an ECG finding in a single participant that was ultimately found to be due to ECG equipment malfunction (dosing was stopped prior to day 2 dose for the incident participant and prior to day 3 dose in all other participants). As dosing was interrupted, the cohort was discontinued per sponsor decision. Dosing in a second MAD cohort in Study 2 (inaxaplin 90 mg once daily MAD group: *N* = 8; placebo *N* = 2) was halted due to one participant who discontinued treatment due to the AE of COVID-19 (inaxaplin 90 mg once daily MAD group). Due to possible exposure to infection, the sponsor decided to discontinue the remainder of the cohort (inaxaplin 90 mg once daily MAD group: *N* = 7; placebo MAD group: *N* = 2)

Table 2. Disposition

	Placebo	Inaxaplin Total
Completed study drug (SAD only), *n/N* (%)	21/21 (100.0)	63/63 (100.0)
Completed study drug (MAD only), *n/N* (%)	18/23 (78.3)	50/71 (70.4)
Discontinued study drug (MAD only), *n/N* (%)[a]	5/23 (21.7)	21/71 (29.6)
Reason for discontinuation from study drug (MAD only), *n/N* (%)		
Adverse event[b]	0	3/71 (4.2)
Participant refused further dosing (not due to AE)	0	1/71 (1.4)
Other non-adherence[c]	0	1/71 (1.4)
Sponsor decision[a]	5/23 (21.7)	16/71 (22.5)

AE, adverse event; MAD, multiple ascending doses; *N*, number of participants in SAD or MAD cohorts; *n*, number of participants; SAD, single ascending dose. This table includes all participants in the SAD and MAD cohorts of both Study 1 and Study 2 who received any dose of study drug. [a]In the Study 2, 21 participants in two MAD cohorts discontinued treatment due to sponsor decision; this includes 12 participants (inaxaplin 60 mg once daily group: *N* = 9; placebo group: *N* = 3) who discontinued study drug due to ECG equipment malfunction and 9 participants (inaxaplin 90 mg once daily group: *N* = 7; placebo group: *N* = 2) who discontinued study drug due to the impact of the COVID-19 pandemic. [b]Three participants in the MAD cohorts discontinued inaxaplin due to AEs of tachycardia, papular rash, and COVID-19 infection; AEs were mild or moderate in severity and considered by the investigator as not related to study drug. [c]Non-adherence with the study schedule.

on day 2. The inaxaplin 60 mg once daily and 90 mg once daily MAD cohorts in Study 2 were repeated with a distinct set of participants. In addition to the participant who discontinued treatment due to the AE of COVID-19, there were two additional participants who discontinued treatment due to an AE.

Adverse Events and Safety

A summary of AEs for the SAD and MAD cohorts of both phase 1 studies is presented in Table 3; this table includes the two MAD cohorts in Study 2 that were prematurely discontinued by the sponsor due to ECG equipment malfunction and COVID-19 infection. A summary of AEs for the MAD cohorts in Study 1 is presented in Table 4. A summary of AEs for the MAD cohorts in Study 2 is presented in Table 5; this table does not include the two MAD cohorts that were prematurely discontinued by the sponsor due to ECG equipment malfunction and COVID-19 infection.

Across the SAD and MAD cohorts of both phase 1 studies, 43 (24.2%) participants had at least one AE (Table 3). The percent of participants who had at least one AE was similar in the inaxaplin treatment group (24.6%) compared to the placebo group (22.7%). All AEs were mild or moderate in severity. None of the AEs were considered by the investigator as related to inaxaplin. There were no serious adverse events (SAEs) (Table 3).

AEs occurring in more than two participants in the SAD and MAD cohorts of both phase 1 studies were headache, fatigue, diarrhea, COVID-19, cough, rhinorrhea, dyspepsia, abdominal pain, constipation, nausea, oropharyngeal pain, and throat irritation (Table 3). Most of these AEs had similar or lower incidences in the inaxaplin group compared to placebo, except for headache (10.4% in the inaxaplin group compared to 2.3% in the placebo group) (Table 3).

Three participants in the inaxaplin group discontinued study drug due to AEs (Table 3). One participant in the inaxaplin 45 mg once daily MAD group in Study 1 discontinued treatment due to an AE of papular rash, which was mild in severity, resolved without treatment, and was considered unlikely related to the study drug by the investigator (Table 4). One participant in the inaxaplin 60 mg once daily MAD group in Study 2 discontinued treatment due to an AE of tachycardia (Table 5); this participant reported anxiety as an AE (of mild intensity) and reported similar instances of test anxiety in the past. The AE of tachycardia was considered mild in severity, resolved without treatment, and was considered by the investigator as not related to study drug. In Study 2, one participant in the inaxaplin 90 mg once daily MAD group discontinued treatment due to the AE of COVID-19 (as described above), which was moderate in severity, resolved without treatment, and was considered by the investigator as not related to inaxaplin (Table 3).

Table 3. Summary of Adverse Events: All Participants

	Placebo[a] (*N* = 44)	Inaxaplin Total[b] (*N* = 134)
Participants with any AEs, *n* (%)	10 (22.7)	33 (24.6)
Participants with AEs by severity, *n* (%)		
Mild	9 (20.5)	29 (21.6)
Moderate	1 (2.3)	4 (3.0)
Severe	0	0
Life-threatening	0	0
Participants with SAEs, *n* (%)	0	0
Participants with AEs leading to treatment discontinuation, *n* (%)[c]	0	3 (2.2)
AEs occurring in at least two participants, *n* (%)[d]		
Headache	1 (2.3)	14 (10.4)
Fatigue	2 (4.5)	2 (1.5)
Diarrhea	0	4 (3.0)
COVID-19	0	3 (2.2)
Cough	0	3 (2.2)
Rhinorrhea	1 (2.3)	2 (1.5)
Dyspepsia	0	3 (2.2)
Abdominal pain	1 (2.3)	2 (1.5)
Constipation	0	2 (1.5)
Nausea	0	2 (1.5)
Oropharyngeal pain	0	2 (1.5)
Throat irritation	0	2 (1.5)

AE, adverse event; MAD, multiple ascending doses; *N*, Safety Set sample size; *n*, number of participants; SAD, single ascending doses; SAE, serious adverse event. This table includes all participants in the SAD and MAD cohorts of both phase 1 studies who received any dose of study drug (including the two MAD cohorts in Study 2 that were prematurely discontinued due to sponsor decision). [a]Placebo is pooled from all SAD and MAD cohorts in both Study 1 and Study 2. There were 21 participants who received placebo in the SAD cohort and 23 participants who received placebo in the MAD cohort. [b]Inaxaplin Total is pooled from all SAD and MAD cohorts in both Study 1 and Study 2, based on participants treated with any dose of inaxaplin. There were 63 participants who received inaxaplin in the SAD cohort and 71 participants who received inaxaplin in the MAD cohort. [c]Three participants in the MAD cohort discontinued study drug due to AEs of papular rash (Study 1; inaxaplin 45 mg once daily), tachycardia (Study 2; inaxaplin 60 mg once daily), and COVID-19 infection (Study 2; inaxaplin 90 mg once daily); the participant who discontinued study drug due to the AE of COVID-19 was in a cohort in Study 2 that was prematurely discontinued due to sponsor decision. AEs were mild or moderate in severity and considered by the investigator as not related or unlikely related to study drug. [d]In the two MAD cohorts from Study 2 that were prematurely discontinued due to sponsor decision, there were eight AEs including four AEs of headache (one in the placebo group; three in the inaxaplin group), two AEs of COVID-19 (both in the inaxaplin group), one AE of fatigue (placebo group) and one AE of dyspnea (inaxaplin group).

During the course of the SAD and MAD cohorts of both phase 1 studies, no clinically relevant trends were noted in any of the clinical laboratory results. Specifically, mean serum creatinine concentrations, serum lipid profile (i.e., total cholesterol, HDL cholesterol, LDL cholesterol, and triglyceride concentrations), and leukocyte counts were similar between the inaxaplin and placebo groups for all timepoints. There were no clinically relevant between-groups differences in vital signs and no unexpected findings on physical examination during the SAD and MAD cohorts of both phase 1 studies.

There was no evidence of effects of inaxaplin on ECG parameters. There were no participants with a maximum QT interval corrected by Fridericia's formula (QTcF; calculated from ECG assessments) interval >480 msec. No participants in the SAD or MAD cohorts had a QTcF interval increase >60 msec.

Table 4. Summary of Adverse Events: MAD Cohorts of Study 1

	Placebo[a] (*N* = 9)	Inaxaplin 15 mg once daily (*N* = 9)	Inaxaplin 15 mg twice daily (*N* = 9)	Inaxaplin 45 mg once daily (*N* = 9)	Inaxaplin Total[b] (*N* = 27)
Participants with any AEs, *n* (%)	2 (22.2)	4 (44.4)	5 (55.6)	1 (11.1)	10 (37.0)
Participants with AEs by severity, *n* (%)					
Mild	2 (22.2)	4 (44.4)	5 (55.6)	1 (11.1)	10 (37.0)
Moderate	0	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Participants with SAEs, *n* (%)	0	0	0	0	0
Participants with AEs leading to treatment discontinuation, *n* (%)[c]	0	0	0	1 (11.1)	1 (3.7)
AEs occurring in at least two participants, *n* (%)					
Headache	0	1 (11.1)	2 (22.2)	0	3 (11.1)
Fatigue	1 (11.1)	2 (22.2)	0	0	2 (7.4)
Cough	0	3 (33.3)	0	0	3 (11.1)
Dyspepsia	0	0	3 (33.3)	0	3 (11.1)
Constipation	0	0	2 (22.2)	0	2 (7.4)
Oropharyngeal pain	0	1 (11.1)	1 (11.1)	0	2 (7.4)
Throat irritation	0	1 (11.1)	1 (11.1)	0	2 (7.4)
Rhinorrhea	1 (11.1)	1 (11.1)	0	0	1 (3.7)
Sneezing	1 (11.1)	1 (11.1)	0	0	1 (3.7)

AE, adverse event; MAD, multiple ascending doses; *N*, Safety Set sample size; *n*, number of participants; SAE, serious adverse event. This table includes all participants in the MAD cohorts of Study 1 who received at least one dose of study drug. [a]Placebo is pooled from all MAD cohorts in Study 1. [b]Inaxaplin Total is pooled from all MAD cohorts in Study 1, based on participants treated with any dose of inaxaplin. [c]Participant in the inaxaplin 45 mg once daily MAD group discontinued study drug due to AE of papular rash; AE was mild in severity and considered by the investigator as unlikely related to study drug.

Pharmacokinetics

The PK of inaxaplin was generally dose proportional, and the variability in PK parameters was generally low and did not appear to change across the dose range (online Table S1). Half-life was consistent across both studies ranging from approximately 13.3 to 22.9 h, which supports once daily dosing (online Table S1). Renal clearance was a minor excretion pathway for inaxaplin; dose adjustments are therefore not anticipated for the intended patient population which will include patients with renal function impairment (online Table S2). There were no clinically significant PK drug-drug interactions between inaxaplin and midazolam (online Table S3). Additional PK details are provided in the Online Supplementary Materials.

Discussion

There is a critical need for safe and efficacious therapies addressing the underlying cause of AMKD. Inaxaplin is an oral, small molecule that selectively inhibits APOL1 channel function in vitro, reduces proteinuria in a transgenic mouse model of AMKD, and has been shown to reduce proteinuria by a mean of 47.6% compared to baseline in patients with AMKD [14].

In these two phase 1 randomized, double-blind, placebo-controlled studies, we evaluated the safety, tolerability, and PK of single- and multiple-ascending doses of inaxaplin in 178 healthy participants. Inaxaplin was generally well tolerated at single doses up to 165 mg and at multiple doses up to 120 mg once daily for 14 days. All AEs were mild or moderate in severity and there were no SAEs. Only three participants discontinued inaxaplin due to an AE (COVID-19, tachycardia, papular rash), all of which were mild or moderate in severity and considered by the investigator as not related or unlikely related to inaxaplin. Headache was the only AE that was more frequent in the inaxaplin group than in the placebo group. Most headaches were mild in severity and resolved without treatment. The incidence of headache was lower in participants treated with doses of inaxaplin ≤45 mg once daily (11.1%) than

Table 5. Summary of Adverse Events: MAD Cohorts of Study 2

	Placebo[a] (*N* = 9)	Inaxaplin 60 mg once daily (*N* = 9)	Inaxaplin 90 mg once daily (*N* = 9)	Inaxaplin 120 mg once daily (*N* = 9)	Inaxaplin Total[b] (*N* = 27)
Participants with any AEs, *n* (%)	5 (55.6)	6 (66.7)	3 (33.3)	3 (33.3)	12 (44.4)
Participants with AEs by severity, *n* (%)					
Mild	4 (44.4)	6 (66.7)	3 (33.3)	3 (33.3)	12 (44.4)
Moderate	1 (11.1)	0	0	0	0
Severe	0	0	0	0	0
Life-threatening	0	0	0	0	0
Participants with SAEs, *n* (%)	0	0	0	0	0
Participants with AEs leading to treatment discontinuation, *n* (%)[c]	0	1 (11.1)	0	0	1 (3.7)
AEs occurring in at least two participants, *n* (%)					
Headache	0	2 (22.2)	1 (11.1)	2 (22.2)	5 (18.5)
Palpitations	1 (11.1)	0	1 (11.1)	0	1 (3.7)
Abdominal pain	1 (11.1)	0	0	1 (11.1)	1 (3.7)
Diarrhea	0	0	1 (11.1)	1 (11.1)	2 (7.4)

AE, adverse event; MAD, multiple ascending doses; *N*, Safety Set sample size; *n,* number of participants; SAE, serious adverse event. This table includes all participants in the MAD cohorts of Study 2 who were not prematurely discontinued and who received at least one dose of study drug. [a]Placebo is pooled from MAD cohorts in Study 2 (except for the two MAD cohorts that were prematurely discontinued based on sponsor decision). [b]Inaxaplin Total is pooled from MAD cohorts in Study 2, based on participants treated with any dose of inaxaplin, (except for the two MAD cohorts that were prematurely discontinued based on sponsor decision). [c]Participant in the inaxaplin 60 mg once daily treatment group discontinued study drug due to an AE of tachycardia; AE was mild in severity and considered by the investigator as not related to study drug.

in those treated with doses of inaxaplin ≥60 mg once daily (18.5%). Serum creatinine, plasma lipids, leukocyte counts, and ECG parameters were similar between the inaxaplin and placebo groups with minimal changes from baseline over time. A limitation of these studies, like most phase 1 studies, is that participants were predominantly men (owing to exclusion of women of childbearing age).

Overall, these findings are consistent with the safety results from a phase 2a proof-of-concept study, in which 16 participants with two *APOL1* variants and focal segmental glomerulosclerosis (FSGS) received inaxaplin daily for 13 weeks (15 mg for 2 weeks, 45 mg for 11 weeks) on top of standard-of-care treatment [14]. APOL1-mediated FSGS is a particularly severe form of AMKD. Inaxaplin was generally well tolerated in all 16 participants who received at least one dose of inaxaplin; all AEs were mild or moderate, none led to treatment discontinuation, and there were no SAEs related to inaxaplin. Similar to the phase 1 studies in healthy participants, the most common AE observed in the phase 2a proof-of-concept study in patients with AMKD was headache [14]. Moreover, in 13 evaluable participants, treatment with inaxaplin resulted in a substantial and clinically meaningful 47.6% reduction in proteinuria at Week 13 [14]. Proteinuria is a direct indicator of podocyte damage and is strongly correlated with progression to kidney failure [22–25]. The safety and efficacy of inaxaplin at 15 mg once daily and 45 mg once daily (which is in the lower range of doses explored in these phase 1 studies) is currently being evaluated in a randomized, double-blind, placebo-controlled, phase 2/3 adaptive trial in adults with AMKD (ClinicalTrials.gov number, NCT05312879).

The clinical pharmacology properties of inaxaplin are favorable and supports once daily dosing in the target population. It exhibits dose proportional PK with low variability across doses up to 120 mg once daily for 14 days with a half-life ranging from 13.3 to 22.9 h. Inaxaplin is not a clinically significant inhibitor or inducer of CYP3A4. Renal clearance is a minor elimination pathway; thus, no dose adjustment is anticipated for the intended patient population that is expected to include patients with renal function impairment.

In conclusion, these two phase 1 studies provide evidence that among healthy participants, inaxaplin is well tolerated at single doses up to 165 mg and at

multiple doses up to 120 mg once daily for 14 days. These findings are consistent with the safety results in the phase 2a proof-of-concept study in 16 participants with two *APOL1* variants and FSGS [14]. Collectively, these findings support subsequent clinical trial development in a pivotal study evaluating the safety and efficacy of inaxaplin in reducing proteinuria and preserving kidney function in a broad population of patients with AMKD.

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Statement of Ethics

These studies are in compliance with the guidelines for human subjects and were conducted ethically in accordance with the World Medical Association Declaration of Helsinki, local applicable laws and regulations, and current Good Clinical Practice guidelines as described by the International Council for Harmonization. The study protocols were approved by the Advarra Institutional Review Board in the United States (Advarra IRB Identifiers: Pro00035356, Pro00034297, and Pro00044276). All participants provided written informed consent before the start of the studies.

Conflict of Interest Statement

Drs. Ogo Egbuna, George Manos, Simon Tian, and Fanuel Hagos are employees of Vertex Pharmaceuticals and own stock or stock options in the company. Dr. Vincent Audard has received honoraria from Travere, support for attending meetings from Sanofi, and participates on Data Safety Monitoring Boards (DSMBs) or Advisory Boards for Alnylam, Addmedica, Travere, AstraZeneca, Vifor, and Bayer. Dr. Glenn Chertow has served on the Board of Directors of Satellite Healthcare, a non-profit dialysis provider. He has served as Chair or Co-Chair of Trial Steering Committees with Akebia, AstraZeneca, CSL Behring, Sanifit, and Vertex. He has served as an Advisor to Applaud, Ardelyx, Calico, CloudCath, Durect, Eliaz Therapeutics, Miromatrix, Outset, Physiowave, Renibus, and Unicycive. He has served on DSMBs with Bayer, Mineralys, and ReCor.

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Author Contributions

These trials were designed by Vertex Pharmaceuticals. Drs. Ogo Egbuna and George Manos contributed to the study design and analysis and interpretation of the data. Drs. Simon Tian and Fanuel Hagos contributed to analysis and interpretation of the data. Drs. Vincent Audard and Glenn Chertow contributed to the interpretation of the data. Drs. Ogo Egbuna and Glenn Chertow wrote the first draft of the manuscript with the assistance of medical writers employed by Vertex Pharmaceuticals. All authors critically reviewed the manuscript, agreed to be accountable for all aspects of the work, and approved the manuscript for submission.

Data Availability Statement

Data generated or analyzed from the SAD and MAD cohorts of two phase 1 studies (VX18-147-001 and VX20-147-008) are included in this manuscript. Further inquiries can be directed to the corresponding author.

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