NCT01559363

CLINICAL STUDY PROTOCOL

A Phase 1b/2a, Safety, Pharmacokinetic and Dose-Escalation Study of KD019 in Subjects with Autosomal Dominant Polycystic Kidney Disease

Protocol Number: KD019-101

Study Drug: Tesevatinib (formerly named KD019)

Sponsor: Kadmon Corporation, LLC
450 East 29th Street
New York, NY 10016

Medical Monitor: [redacted]

Date of Protocol: Original, 26 October 2011
Amendment 1: 02 December 2011
Amendment 2: 20 January 2012
Amendment 3: 05 March 2012
Amendment 4: 17 April 2012
Amendment 5: 25 October 2012
Amendment 6: 15 August 2013
Amendment 7: 06 February 2014
Amendment 8: 19 May 2014
Amendment 9: 30 May 2014
Amendment 10: 10 November 2014
Amendment 11: 17 June 2015
Amendment 12: 31 March 2016
Amendment 13: 06 October 2016

1 PROCEDURES IN CASE OF EMERGENCY

Serious Adverse Events

All serious adverse events (SAE)* occurring in subjects while on-study or within 30 days of receiving study drug regardless of relationship, must be promptly reported (within 24 hours) by telephone, email, or telefax to the sponsor (or designee).

Emergency Contact Information

For SAE/SUSAR reporting:	**For any other questions or to contact the medical monitor:**
INC Research Fax: 1 (877) 464-7787 In the event of an issue with the fax line, forward the SAESUSAR via email to: INCDrugSafety@INCResearch.com.	[redacted]

SAE AND SUSAR CRITERIA

* A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug (see Section 13.3.1 Serious Adverse Events for additional information):

- Death
- Life-threatening adverse drug event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/ incapacity
- A congenital anomaly/birth defect
- An important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

Some serious events will not be reported as SAEs, including:

- Disease progression
- Death due to disease progression occurring more than 30 days after the last dose of study drugs
- Medical or surgical procedures when the condition that leads to the procedure is an adverse event
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, that do not worsen
- Situations for which an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social and/or convenience admissions)

** A suspected unexpected serious adverse reaction (SUSAR) is any untoward and unintended response to an investigational product related to any dose administered, of which the nature or severity, is not consistent with the applicable product information (see also Section 11.3 of this document; Suspected Unexpected Serious Adverse Reactions). All suspected adverse reactions related to an investigational medicinal product that occur in the concerned trial and that are both unexpected and serious are subject to expedited reporting.

2 SPONSOR SIGNATURE

I have read and approve this protocol. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonization Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), and the ethical principles that have their origins in the Declaration of Helsinki.

[redacted]

3 INVESTIGATOR SIGNATURE

I have read this protocol, including all appendices, and I agree to conduct the study in compliance with all applicable regulations (including 21 CFR Part 312). I will also make a reasonable effort to complete the study within the time designated. I will provide all study personnel under my supervision copies of the protocol and access to all information provided by Kadmon Corporation, LLC. I will discuss this material with them to ensure that they are fully informed about the drug and the study.

I am aware that, prior to the commencement of this study, the Institutional Review Board must approve this protocol and the informed consent document associated with the clinical facility where the study will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol. I agree to provide all subjects with a signed and dated copy of their informed consent document, as required by FDA and ICH regulations. I further agree to report to Kadmon any adverse events in accordance with the terms of this protocol and FDA regulation 21 CFR 312.64.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Investigator Signature	Date of Signature (DD MMM YYYY)
Name of Investigator (please print)	

4 SYNOPSIS

Study Title	A Phase 1b/2a, Safety, Pharmacokinetic, Dose-Escalation Study of KD019 in Subjects With Autosomal Dominant Polycystic Kidney Disease
Number of Study Centers	Approximately 10–13 sites in the United States
Clinical Phase	Phase 1b/2a
Study Rationale	Tesevatinib (formerly named KD019) was originally developed for a solid tumor indication, and is currently being investigated for the treatment of cancer. In nonclinical studies, tesevatinib selectively inhibited key kinases and validated targets in animal models of polycystic kidney disease (PKD). In addition, it has shown either no or extremely weak inhibitory activity of other kinases that should reduce off-target effects. Tesevatinib has also been shown to be a potent inhibitor of receptor and cytoplasmic tyrosine kinases (TKs). The product was specifically optimized to simultaneously inhibit EGFR, human epidermal growth factor receptor 2 (HER2), Src, vascular endothelial growth factor receptor 2 (VEGFR2/ KDR), and ephrin receptor B4 (EphB4) tyrosine kinases with high potency, and demonstrated excellent activity in target-specific cellular functional assays. In nonclinical animal models, tesevatinib had acceptable oral bioavailability and has shown sustained inhibition of its targets in vivo following a single oral dose. In Phase 1 and 2 clinical studies conducted in healthy subjects and subjects with solid tumors, over 300 subjects have been treated to date; at least 185 of these have been treated at levels ≥ 300 mg daily. At least 53 subjects have received tesevatinib for ≥ 6 months, and safety and tolerability were acceptable. Tesevatinib is also in development for the treatment of breast cancer and non-small cell lung cancer (NSCLC). In summary, both the nonclinical results in PKD models and the clinical safety results in human oncology studies suggest that tesevatinib could be a promising therapeutic in autosomal dominant polycystic kidney disease (ADPKD).
Study Objectives	**Phase 1b:** Primary objective: • To determine the safety, plasma pharmacokinetics (PK), and maximum tolerated dose (MTD) of tesevatinib when administered to subjects with ADPKD. **Phase 2a:** Primary objective: • To evaluate the annualized change in glomerular filtration rate (GFR) in subjects with ADPKD when treated with tesevatinib.

	Secondary Objectives: • To evaluate subjects treated with tesevatinib with regard to: o Annualized percent change from baseline in total kidney volume (TKV) o Annualized change from baseline in the reciprocal of serum creatinine o Safety profile o Serum creatinine levels o PK and tolerability of 2 alternative dosing schedules (dosing on Monday, Wednesday, and Friday of each week, and dosing on Monday and Thursday of each week) Note: Exploratory measures of efficacy will also be performed throughout both phases of the study.
Study Design	This is an open-label, safety, PK, dose-escalation, multicenter study.
Study Methodology	In the Phase 1b portion of the study, approximately 24–30 subjects (8 subjects/cohort) have received 50 mg, 100 mg, or 150 mg of tesevatinib orally once daily for up to 24 months. At the end of each dosing cohort, a Data Safety Committee, which includes an independent safety monitor with clinical expertise in polycystic kidney disease, reviewed all safety data (PK, safety labs, ECGs, echocardiograms, and adverse events [AEs]) and decided whether dose escalation may occur. Dose escalation to the next higher dose was not started until the safety data from the preceding dose cohort was evaluated and deemed acceptable. Specifically, the decision to progress to the next higher dose was made after the safety data through a minimum of 28 days of follow-up was reviewed for at least 8 subjects in the preceding dose cohort and it was determined that it was safe to proceed to the next dose level. Dose escalation to the next planned tesevatinib dose cohort will be reviewed and dose adjustments may be made if any of the following safety criteria are met: • ≥ 25% of subjects in a cohort experience a severe (or higher) **related** AE in the same organ or body system • Any other **related** AE occurs in a subject that is deemed by the investigator to pose an unacceptable risk to other participants in the study such as symptoms of cardiac tamponade For Phase 1b subjects dosed with 50 mg/day: Following review of the 100-mg cohort it was initially determined that 100 mg/day was not the MTD. Study enrollment was opened at the 150-mg dose, and subjects initially treated in the Phase 1b 50-mg dose cohort had the option of increasing their dose of tesevatinib to 100 mg/day after they had received a minimum of 6 months of treatment at the 50 mg/day dose. After the MTD for daily dosing was established (100 mg QD),

	24 additional subjects were enrolled in the Phase 2a portion of the study using alternative schedules of tesevatinib administration. As the known toxicities of tesevatinib, including diarrhea and rash, may not be tolerable with daily dosing when used long-term in this subject population, alternative dosing schedules of 150 mg of tesevatinib on Monday, Wednesday, and Friday of each week and 150 mg on Monday and Thursday of each week were evaluated during this portion of the study. Several subjects are continuing on this dosing schedule to evaluate long term tolerability. Approximately 5 subjects treated on each alternative dosing schedule had PK samples obtained so that safety, tolerability, and exposure could be evaluated. In addition, subjects active in the Phase 1b portion had their dose increased or decreased to the established MTD of 100 mg QD. These subjects will continue on daily dosing in order to obtain data on longer term tolerability of daily dosing at the MTD. In both phases of the study, after the 28-day treatment period, subjects will, at the discretion of the investigator, continue to receive study treatment for 24 months from their first dose or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision. . Despite fulfilling the protocol criteria for determining the MTD for daily dosing, the 100 mg daily dose group exhibited a rate of QTc prolongation not acceptable for chronic use. Preliminary data from both the 50 mg daily cohort and the 150 mg Monday and Thursday cohort appear acceptable for chronic use and for further study in terms of safety. The 50 mg daily dose appears to be favorable due to dosing simplicity and to the occurrence of a Grade 3 rash in the 150 mg Monday and Thursday cohort. Additionally, the effect of missed dosing is reduced in the daily dosing cohort. Because of these factors, the 50 mg tesevatinib treatment appears to be the best tolerated dose, and will likely be taken forward in additional studies in ADPKD. In order to generate additional efficacy and safety information for this selected dosing regimen, 15 additional subjects were enrolled as an additional group in the Phase 2a portion of this protocol at a dose of 50 mg daily of tesevatinib. Each of the 15 subjects were required to complete either PK testing as described for other Phase 1b subjects in this protocol or iothalamate testing. Modeling of ADPKD subpopulations for a randomized Phase 3 clinical study has been performed. Enrollment criteria being considered for Phase 3 are ADPKD subjects with baseline eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2, and height-adjusted total kidney volume (htTKV) $\geq$ 1000 mL. In order to study the safety profile in this specific ADPKD subpopulation, up to 50 additional subjects with PKD and baseline eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2, and htTKV $\geq$ 1000 mL will be enrolled (Safety in Larger Kidneys [SILK Cohort]).

	In addition, all 50 subjects will undergo a mandatory 28-day drug holiday after completing the first month of treatment with tesevatinib. During this drug holiday, and for 4 weeks after, subjects will return to the clinic weekly for creatinine and tesevatinib plasma measurements. All subjects will resume tesevatinib treatment at the Month 2 study visit following completion of the 28-day drug holiday. Kidney volume will be determined by magnetic resonance imaging (MRI) at Screening (baseline measurement) and every 6 months thereafter. htTKV will be calculated using total kidney volume obtained from MRI divided by height in meters.
Study Population:	Approximately 120 male and female subjects with ADPKD will be enrolled. Approximately 30 subjects will be enrolled in the Phase 1b portion and approximately 90 subjects will be enrolled in the Phase 2a portion.
Diagnosis and Main Entry Criteria	Subjects will be eligible for enrollment as defined by the following inclusion and exclusion criteria. <u>Inclusion Criteria:</u> 1. The subject has a confirmed diagnosis of ADPKD based on Ravine's criteria. Subjects < 30 years of age must have at least 2 cysts (unilateral or bilateral) while subjects ≥ 30 years of age must have at least 2 cysts in each kidney (ie, total ≥ 4 cysts). 2. Cysts must be at least 1 cm in size to be considered. 3. Subject is ≥ 18 but ≤ 62 years of age at time of consent. 4. The subject has an eGFR ≥ 35 mL/min/1.73 m^2 and ≤ 80 mL/min/1.73 m^2, using the MDRD-4 variable formula (Appendix A). 5. The subject has an htTKV ≥ 1000 mL (htTKV is calculated using total kidney volume obtained from MRI divided by height in meters). 6. Subject has the following laboratory values: • Platelets >LLN • Hemoglobin > 9 g/dL • Total bilirubin ≤ 1.5 mg/dL • AST (SGOT) < 2.5 × upper limit of normal (ULN) • ALT (SGPT) < 2.5 × ULN • PT/PTT ≤ 1.5 × ULN • Albumin ≥ lower limit of normal • Amylase within normal limits • Lipase within normal limits 7. The subject has International Normalized Ratio (INR) ≤ 1.5, except those subjects taking warfarin who must have INR < 3.0.

	8. The subject has serum potassium levels and serum magnesium levels within the normal range. 9. The subject is capable of understanding and complying with the protocol and has signed the informed consent form. 10. Female subjects of childbearing potential have a negative pregnancy test at Screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression. • Women of childbearing potential (i.e., menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24 hour period prior to the first dose of study drug. • Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 6 months after their last dose of study drug. Effective birth control includes (a) IUD **plus** one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, transdermal) **plus** one barrier method; or (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner 11. For male subjects who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 10 above during the treatment period and for at least 6 months after the last dose of study drug. 12. The subject has no history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred.
	<u>Exclusion Criteria:</u> 1. The subject has had a previous partial or total nephrectomy or a kidney transplant. 2. The subject has tuberous sclerosis, Hippel-Lindau disease, or acquired cystic disease. 3. The subject has congenital absence of 1 kidney and/or need for dialysis. 4. Moderate hematuria. If due to cyst rupture, subject may be rescreened

	after discussion with medical monitor. 5. Uncontrolled hypertension (systolic blood pressure > 160 mmHg; diastolic blood pressure >100 mm Hg). 6. Uncontrolled diabetes mellitus (HbA1c > 8%). 7. Presence of renal or hepatic calculi (stones) causing symptoms. 8. The subject has received any investigational therapy within 30 days prior to study entry. 9. Active treatment (within 4 weeks of study entry) for urinary tract infection. 10. History of pancreatitis or has known risk factors for pancreatitis 11. The subject meets any of the following cardiac criteria: • Mean corrected Fridericia (Fridericia's formula, see Section 9.10) QTc interval (QTc[F]) of > 450 msec • History of torsade de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (<50 bpm), heart block (excluding first-degree block, being PR interval prolongation only), congenital long QT syndrome or new ST segment elevation or depression or new Q wave on ECG. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor. • Family history of congenital long QT syndrome or unexplained sudden cardiac death. • History of ventricular rhythm disturbances. • Symptomatic heart failure (per NYHA guidelines), unstable angina, myocardial infarction, or cerebrovascular accident (CVA) within 6 months prior to study entry. • Has a cardiac pacemaker. • History of pericardial effusion or presence of pericardial effusion on screening echocardiogram 12. The subject is taking any medication known to inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers, or any drugs associated with torsades de pointes or known to prolong the QTc(F) interval, including anti-arrhythmic medications within 2 weeks prior to Screening (refer to Appendix B for a sample listing of medications associated with QTc[F] prolongation). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine). 13. The subject has an uncontrolled intercurrent illness that would limit compliance with study requirements including, but not limited to ongoing or active infections or psychiatric illness. 14. The subject is pregnant or nursing.

	15. The subject is known to be positive for the human immunodeficiency virus (HIV), or hepatitis B or C, as indicated by a positive test at Screening. 16. Subject is known to be immunocompromised. 17. The subject has documented presence of renal vascular disease. 18. The subject has received erlotinib, gefitinib, cetuximab, panitumumab, or an investigational EGFR inhibitor at any time. 19. The subject has an allergy or hypersensitivity to components of either the tesevatinib or the formulation. 20. The subject is unable or unwilling to participate in PK sampling. 21. The subject is aphakic due to previous cataract surgery or congenital anomaly. **Note:** The sponsor has the option to exclude the enrollment of a subject if, based upon the subject's medical history or screening results, it is felt that a subject's safety may be at risk and/or if the safety data may confound the study results.
Study Drug	Tesevatinib is a new chemical entity that inhibits multiple tyrosine kinases (TKs) ErbB family members [EGFR and HER2/ErbB2], vascular endothelial growth factor receptor [VEGFR2/KDR]), and Src family kinases.
Dose and Administration	In the Phase 1b portion of the study, tesevatinib will be administered orally at doses of 50, 100, and 150 mg once daily. Study drug may be taken with or without food, and should be taken at approximately the same time every morning. Subjects should drink a full glass of water (approximately 8 ounces [240 mL]) immediately after study drug administration. In the Phase 2a portion of the study, tesevatinib will be administered on alternative dosing schedules of 150 mg of tesevatinib on Monday, Wednesday, and Friday of each week or 150 mg on Monday and Thursday of each week. Additionally, subjects active in the Phase 1b portion had their dose increased or decreased to the established MTD of 100 mg daily (continuing once-daily administration). If subjects are unable to be seen in clinic on the appropriate protocol specified study day, the schedule may also be Tuesday and Friday or Wednesday and Saturday. However, the same schedule must be adhered to throughout the study. Based on all information generated thus far, the 50 mg tesevatinib treatment is the best tolerated dose, and will likely be taken forward in additional studies in ADPKD. In order to generate additional efficacy and safety information on this selected dosing regimen, 15 additional subjects were enrolled as an additional group in the Phase 2a portion of this protocol at a dose of 50 mg of tesevatinib. Up to 50 additional subjects, with eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2 and htTKV $\geq$ 1000 mL will receive 50 mg of tesevatinib daily and will be added to the Phase 2a portion

	of the protocol. Other subjects already enrolled in the study will continue to receive the dose and schedule to which they were assigned or to which they were transferred. Subjects in all cohorts of the study, after the initial 28-day treatment period, will, at the discretion of the investigator, continue to receive study treatment for at least 24 months from their first dose or until the development of unacceptable toxicity, noncompliance, withdrawal of consent by the subject, or investigator decision. Subjects will be provided with an adequate supply of and instructions for taking the study drug. Study drug accounting will be performed at each visit.
Duration of Treatment	Subjects will receive study drug for 28 days after the initiation of treatment. After the initial 28-day safety and tolerability assessment period, subjects will, at the investigator's discretion, continue to receive study drug for a total of 24 months from the initiation of treatment. Subjects will be followed for a period of 30 days following the last dose of tesevatinib.
Concomitant Medications	Subjects should avoid ingesting grapefruit, pomelo, or Seville fruit (and juice) with tesevatinib or at any time during the study. Subjects should not take medications that are associated with a risk of QTc(F) interval prolongation and/or torsades de pointes. Additionally, subjects are not permitted to take concomitant medications that inhibit the CYP3A4 isozyme (eg, ketoconazole, itraconazole, erythromycin, clarithromycin) or inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampicin, or phenobarbital). Tesevatinib is also highly protein bound, and other drugs that are also highly protein bound with the exception of warfarin (eg, diazepam, furosemide, dicloxacillin, propranolol, and phenytoin) should be avoided. Antiemetics and antidiarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, treatment of symptoms with antiemetic and antidiarrheal medications may be undertaken per standard clinical practice. Since tesevatinib is a potent inhibitor of MATE transporter proteins, increased levels of concomitant medications that are secreted by the kidney proximal tubule cells into the renal tubule by MATE transporter proteins may occur. Thus, subjects taking cephalexin, cimetidine, dofetilide, fexofenadine, metformin, procainamide, and pyrimethamine should be monitored carefully.
Safety Assessments	Safety assessments will be performed at regular study intervals (refer to Study Assessment table) and include AEs, physical examinations, vital sign measurements, clinical laboratory evaluations (especially renal function), ECGs, echocardiograms, concomitant medication, and pregnancy testing. The AE reporting period for a subject enrolled in the study will begin after informed consent through 30 days after the last dose of tesevatinib. Clinical laboratory tests (hematology, chemistry, urinalysis, coagulation,

	and thyroid-stimulating hormone [TSH]) will include the following: • Hematology will include complete blood count (CBC) with differential, and platelet count. CBC includes red bloods cells (RBCs), hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC), and white blood cells (WBCs) with differential count to include neutrophils, eosinophils, basophils, lymphocytes, and monocytes. • Clinical chemistry will include albumin, amylase, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, creatinine phosphokinase, lactate dehydrogenase, potassium, random glucose, sodium, total & direct bilirubin, total protein, and magnesium. GFR will be estimated using the MDRD-4 formula, the CKD-EPI$_{2012cys}$ equation, and CKD-EPI$_{2012Scr\text{-}cys}$ equation. • Peripheral blood smears for analyses of any effect on bone marrow • Urinalysis will include assessment of protein, blood, leukocytes, glucose, ketones, bilirubin, urobilinogen, pH, color, appearance, and specific gravity. • Coagulation tests will include PT, PTT, and INR. • Creatinine clearance and cystatin C levels. • TSH levels will be evaluated at Screening and then every 3 months. Vital sign measurements will include sitting blood pressure, pulse rate, respiratory rate, and temperature (oral or tympanic). Cardiac safety will be determined by the use of 12-lead ECGs recorded at the site on validated digital recorders and analyzed by a core ECG laboratory. Additionally, echocardiograms will be obtained and will include measurement of ejection fraction and evaluation for pericardial effusion and valvular abnormalities. If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression. Ocular evaluations will be performed on each enrolled subject. Briefly, every 4 weeks, subjects will be asked if they have experienced any changes in vision, changes in color vision, or new loss of vision in any area. Additionally, at Screening, subjects newly enrolled into the study will have an evaluation of best corrected visual acuity and will be evaluated with fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, ,and optical coherence tomography (OCT) of the optic nerve head and macula. All ocular assessments should also be conducted at Months 3, 6, 9, 12, 18, and 24 of the study. Subjects enrolled into the study prior to the requirement for these ocular tests will have the same ocular assessments performed at their next regularly scheduled study visit, and then will have the same ocular

	assessments performed when they reach any assessment times that they have not already completed in the study (Months 3,6, 9, 12, 18, and 24). The initial data from the Phase 1b portion of this study (Protocol KD019-101) indicate that subjects with ADPKD may have elevations of creatinine without elevations in cystatin C. This appears to be due to inhibition of MATE transporter proteins by tesevatinib, which should be reversible. To demonstrate the reversible nature of the creatinine elevations, subjects on the Phase 1b portion of the study will have study drug held for a one-time drug holiday of at least 14 days and up to 28 days with creatinine and cystatin C measurements before and immediately after the drug holiday, as well as a predose PK sample prior to restarting study drug. All subjects in the SILK cohort will have weekly blood draws during the drug holiday period and during the 4 weeks immediately following the drug holiday period. These samples will be collected and analyzed for serum creatinine and cystatin C and plasma tesevatinib levels. In order to provide definitive data on renal function that is independent of creatinine or cystatin C measurements, iothalamate testing of renal clearance will be conducted at selected sites. In the Phase 2a 50 mg daily cohort of patients, only those subjects who can undergo iothalamate or PK testing will be enrolled. In addition, eGFR will be calculated using serum creatinine, serum cystatin-c, and using both serum creatinine and cystatin-c ($CKD\text{-}EPI_{2012Scr\text{-}cys}$; see Appendix A for equation).
Pharmacokinetics	During the Phase 1b and Phase 2a 50 mg daily portions of the study, blood samples will be collected for PK analyses on Study Day 1 (predose, 1, 2, 4, 8, and 24 hours postdose), Day 14 (predose, 1, 2, 4, and 24 hours postdose), and predose on Days 7, 21, and 28. Additional samples will be collected predose at every monthly visit thereafter up to and including the Month 6 visit for those subjects who continue dosing. In the Phase 2a portion of the study, approximately 70 subjects (5 in each alternative dosing schedule and 15 subjects in the 50 mg daily dosing schedule and 50 subjects in the SILK cohort) will have blood samples drawn for PK analyses. **For subjects receiving 150 mg of KD019 on Monday, Wednesday, and Friday:** Samples will be collected on Study Day 1 (predose, and 1, 2, 4, 8, and 24 hours postdose); predose on Days 3, 5, and 8; and on Day 12 (predose, and 1, 2, 4, and 24 hours postdose). **For subjects receiving 150 mg of KD019 on Monday and Thursday:** Samples will be collected on Study Day 1 (predose, and 1, 2, 4, 8, and 24 hours postdose); predose on Days 8, 11, and 18; and on Day 25 (predose, and 1, 2, 4, 8, and 24 hours postdose). **For subjects receiving 50 mg of KD019 daily:** Samples will be collected on Study Day 1 (predose, 1, 2, 4, 8, and 24 hours postdose), Day 14 (predose, 1, 2, 4, and 24 hours postdose), and predose on Days 7, 21, and 28. Additional samples will be

	collected predose at every monthly visit thereafter up to and including the Month 6 visit for those subjects who continue treatment (Follow-Up Treatment Period). **For subjects receiving 50 mg of tesevatinib daily (the SILK cohort):** Samples will be collected on Study Day 1 (predose, 1, 2, 4, and 8 hours postdose), Day 14 (predose, 1, 2, 4, and 8 hours postdose), and predose on Days 7, 21, and 28. Additional samples will be collected predose at every monthly visit thereafter up to and including the Month 6 visit. In addition, blood samples for PK analyses will be collected if the QTc(F) interval increases by > 60 msec above average predose value (average of Day 1 predose and screening values) or to the level of ≥ 480 msec.
Exploratory Efficacy	<u>In the Phase 2a Cohort:</u> • Evaluate the 6-month annualized change in GFR. • Evaluate the annualized change from baseline in the reciprocal of serum creatinine • Evaluate the annualized percent change from baseline in total kidney volume (TKV). TKV will be determined by MRI at Screening (baseline measurement), at the 6-month visit, and every 6 months thereafter.
Statistical Methods	Eight subjects per cohort are standard and a reasonable sample size for determination of safety and tolerability in this Phase 1b/2a study. In the Phase 2a cohort, 24 subjects were enrolled at the MTD using alternative dosing schedules of 150 mg of tesevatinib on Monday, Wednesday, and Friday of each week, or 150 mg of tesevatinib on Monday and Thursday of each week. There were 15 additional subjects in the Phase 2a cohort dosed at 50 mg of tesevatinib daily and up to 50 additional subjects are planned. These subjects who receive 50 mg daily of tesevatinib will provide 75% likelihood of having at least 1 AE if the true incidence of an AE is 5%. Demographic (eg, gender, age, race) and baseline characteristics (height, weight) will be summarized by dose level and cohort. Safety analyses will be performed on all subjects who receive any quantity of tesevatinib. Data generated from safety assessments will be presented in listings by subject and summarized by treatment cohort with the Phase 2a cohort being analyzed separately. Treatment-emergent AEs will be summarized using version 18.1 or higher of MedDRA System Organ Class (SOC) and preferred term, classified from verbatim terms. The incidence and percentage of subjects with at least 1 occurrence of a preferred term will be included, according to the most severe intensity. The number of events per preferred term will also be summarized. Causality (relationship to study treatment) will be summarized separately. ECG (QT/QTc[F]) and PK data will be provided in a prospective statistical plan that will detail the statistical method of analyzing the ECG data and morphological findings.

	Efficacy will be explored with regard to the effect of tesevatinib on eGFR. In the Phase 2a cohort, the 65 subjects in the 50 mg QD dose group will allow an 80% confidence interval of approximately ± 0.64 mL/min about an expected mean 6-month change from baseline of -2.5 mL/min when the standard deviation is 4.0 mL/min. Additional statistical details will be provided in a prospective statistical plan.

Table 4-1: Schedule of Events for Subjects Enrolled in the Safety in Larger Kidneys (SILK) 50 mg Daily Portion of the Study

Assessments	Screening [a] (-28 Days)	Early Treatment Period[b]					Drug Holiday Period	Month 2	Monthly Follow-Up Treatment Period[c]	End of Study[d]
		Day 1	Day 7 (±1 day)	Day 14 (±1 day)	Day 21 (±1 day)	Day 28 (±1 day)	4 Weekly Visits Beginning at Day 28 Visit (± 1 day)	4 Weekly Visits Beginning at Month 2 Visit (± 1 day)	Every 28 Days Beginning at Month 3 (± 3 days)	(30 Days from Last Dose) (± 3 days)
Informed consent	X									
Medical and PKD history (including genotype, if available)	X									
Physical examination (including weight)[e]	X	X	X	X	X	X		X[o]	X	X
Vital signs[f]	X	X	X	X	X	X		X[o]	X	X
Supine 12-Lead ECG[g]	X	X	X	X	X	X		X[o]	X	X
Clinical laboratory tests[h]	X	X	X	X	X	X	X	X[o]	X	X
Ocular evaluation[i]	X								X	
Echocardiogram[j]	X					X			X	X
Pregnancy test[k]	X	X				X				X
MRI[l]	X									X
Study drug administration		X X	X	X	X	X			X	
Concomitant medications [p]	X	X	X	X	X	X	X	X	X	X

Table 4-1: Schedule of Events for Subjects Enrolled in the Safety in Larger Kidneys (SILK) 50 mg Daily Portion of the Study

Assessments	Screening [a] (-28 Days)	Early Treatment Period[b]					Drug Holiday Period	Month 2	Monthly Follow-Up Treatment Period[c]	End of Study[d]
		Day 1	Day 7 (±1 day)	Day 14 (±1 day)	Day 21 (±1 day)	Day 28 (±1 day)	4 Weekly Visits Beginning at Day 28 Visit (± 1 day)	4 Weekly Visits Beginning at Month 2 Visit (± 1 day)	Every 28 Days Beginning at Month 3 (± 3 days)	(30 Days from Last Dose) (± 3 days)
Adverse events[p]	*To be collected from the time informed consent signed until 30 days after last dose of study drug.*									
PK sampling[m]		X	X	X	X	X		X[o]		
Plasma concentration							X	X		
Dispense/Collect study drug		X	X	X	X	X			X[o]	X

a. Screening evaluations may be combined with Day 1 pre-treatment laboratory evaluations if both are done within 4 days before first dose of study drug.
b. All protocol-specified clinic visits during the Treatment Period should occur within ± 1 day of the nominal visit day unless otherwise specified.
c. Follow-up Treatment Period visits to be performed monthly (every 28 ± 1 day). For those subjects continuing on study beyond 12 months, visits will occur every 2 months ± 3 days.
d. End-of-Study visit is to be performed 30 days (± 3 days) after last dose of study drug.
e. A complete physical examination is to be done at the Screening and End-of-Study visits. Height is only included in the Screening PE. Limited PEs will be performed on Days 1, 7, 14, 21, 28 and Day 1 of Months 2 and beyond (See Section 9, Study Assessments, for a description of the body systems, including evaluation for dry mouth, cardiac tamponade by history and examination, and changes in vision to be examined at each visit).
f. Vital sign measurements consist of sitting blood pressure, pulse rate, respiratory rate, and oral or tympanic temperature. On Day 1, measurements should be performed predose and 1 and 4 hours postdose. See Section 9 for appropriate blood pressure measuring technique.
g. Supine 12-Lead ECGs will be performed performed, immediately prior to blood sample collection, at Screening, predose, 1, 4, and 8 hours postdose on Days 1 and 14; predose on Days 7, 21, 28 and Day 1 of Months 2 and beyond; and at End-of-Study visit (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]). Time-matched tesevatinib plasma concentration will be determined at selected pre-dose and post-dose timepoints. If QTc(F) is prolonged to > 60 msec above baseline at any evaluation or to the level of ≥ 480 msec based on local ECG read, refer to Section 11.3.3.1 for procedure to be followed.
h. Clinical laboratory tests consist of hematology, serum chemistry panel, coagulation, TSH, and urinalysis (see Section 9.9 for a complete list of assessments). TSH levels will be evaluated at Screening and then every 3 months. **All subjects will return to the clinic weekly for 3 weeks after the Month 2 visit for collection of blood samples for serum creatinine, cystatin C, and tesevatinib concentration.**
    i. Ocular evaluations are to be performed at Screening and at Months 3, 6, 9, 12, 18, and 24. The following assessments should be performed: evaluation of best corrected visual acuity, fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and optical coherence tomography (OCT) of the optic nerve head and macula.
j. Echocardiograms are to be obtained at Screening, on Day 28, and at Months 3, 6 every 6 months thereafter, and End-of-Study visits and are to include measurement of ejection fraction and assessment for pericardial effusion and valvular abnormalities. Note: If subject has had echocardiogram within 2 months of End-of-Study visit, there is no need to obtain echocardiogram at End of Study visit. For those subjects who have already had their Month 12 visit, this may be performed at Month 13 and then subsequent echocardiograms may be performed on the same schedule as the MRIs. If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
k. Pregnancy tests will be done using urine samples in women of childbearing potential. Subjects must have a negative urine pregnancy test documented within the 24-hour period prior to the first dose of study drug. Pregnancy tests are to be performed at Screening, predose on Day 1, Day 28, Month 3 (and every 3 months thereafter), and End-of-Study visits only. Confirm with serum testing if urine sample is positive.
l. Screening MRI will be performed after informed consent form has been signed and prior to other screening assessments. MRI to be performed at Month 6 and then every 6 months thereafter. Note: If subject has had MRI within 3 months of End of Study visit, there is no need to obtain MRI at End-of-Study visit.
m. Blood samples will be collected for PK analyses on Study Day 1 (predose, 1, 2, 4, and 8 hours postdose), Day 14 (predose, 1, 2, 4, and 8 hours postdose), and predose on Days 7, 21, and 28. PK samples will also be drawn if the QTc(F) interval increases by > 60 msec above average baseline or to the level of

≥ 480 msec (see Section 11.3.3).

n. PK samples will be collected predose at every monthly visit up to and including Month 6 visit.

o. These assessments are to be performed ONLY at the Month 2 visit, not at the 3 weekly visits which follow during the Month 2 period.

p. Blood draws during the drug holiday or Month 2 visits may be performed by a visiting nurse at the subject's home; if the subject chooses this option, the study team should call the subject on the same day of the visit to inquire about concomitant medications and AEs.

Table 4-2: Schedule of Events for Subjects Enrolled in Phase 1b and Phase 2a 50 mg Daily Portions of the Study

Assessments	Screening[h] (-28 Days)	Early Treatment Period[i]						Monthly Follow-Up Treatment Period[q]	End of Study[k]
		Day 1	Day 3 (+1 day)	Day 7 (±1 day)	Day 14 (±1 day)	Day 21 (±1 day)	Day 28 (±1 day)	Every 28 Days (± 3 days)[j]	(30 Days from Last Dose) (± 3 days)
Informed consent	X								
Medical and PKD history (including genotype, if available)	X								
Physical examination (including weight)[a]	X	X[h]	X	X	X	X	X	X	X
Vital signs[b]	X	X	X	X	X	X	X	X	X
Supine 12-Lead ECG[c]	X	X		X	X	X	X	X	X
Clinical laboratory tests[d]	X[h]	X[h]	X	X	X	X	X	X	X
Ocular evaluation[e]	X							X	
Peripheral blood smear	X								X
Echocardiogram	X						X[l]	X[l]	X
Pregnancy test[f]	X	X					X	X *Every 3 Months*	X
MRI	X							X[m] *Every 6 Months*	X
Study drug administration		X	X	X	X	X	X	X[n]	
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	*To be collected from the time informed consent signed until 30 days after last dose of study drug.*								
PK sampling[g]		X		X	X	X	X	X[o]	
Iothalamate testing[p]		X			X				
Dispense/Collect study drug		X		X	X	X	X	X	X

a. A complete physical examination (PE) is to be done at the Screening and End-of-Study visits. Height is only recorded at the Screening PE. Thereafter, limited PEs will be performed on Days 1, 3, 7, 14, 21, 28 and Day 1 of Months 2 and beyond (See Section 9, Study Assessments, for a description of the body systems, including evaluation for dry mouth and cardiac tamponade by history and exam, and changes in vision to be examined at each visit).

b. Vital sign measurements consist of sitting blood pressure, pulse rate, respiratory rate, and oral or tympanic temperature. On Day 1, measurements should be performed predose and 1 and 4 hours postdose. See Section 9 for appropriate blood pressure measuring technique.

c. Supine 12-Lead ECGs will be performed at Screening, predose, and , 4 and 8 hours postdose on Days 1 and 14; predose on Days 7, 21, 28 and Day 1 of Months 2 and beyond; and at End-of-Study visit (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]). If QTc(F) is prolonged to > 60 msec above baseline at any evaluation or to the level of ≥ 480 msec, refer to Section 11.3.3.1 for procedure to be followed.

d. Clinical laboratory tests consist of hematology, serum chemistry panel, coagulation, TSH, and urinalysis (see Section 9.9 for a complete list of assessments). TSH levels will be evaluated at Screening and then every 3 months. (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)

   Ocular evaluations are to be performed at Screening and at Months 3, 6, 9, 12, 18, and 24. The following assessments should be performed: evaluation of best corrected visual acuity, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and optical coherence tomography (OCT) of the optic nerve head and macula.

f. Pregnancy tests will be done using urine samples in women of childbearing potential. To be performed at screening, predose on Day 1, Day 28, Month 3 (and every 3 months thereafter), and End-of-Study visits only. Confirm with serum testing if urine sample is positive.

g. In the Phase 1b and Phase 2a 50 mg daily portions of the study, blood samples will be collected for PK analyses on Study Day 1 (predose, 1, 2, 4, 8, and 24 hours postdose), Day 14 (predose, 1, 2, 4, and 24 hours postdose), and predose on Days 7, 21, and 28. PK samples will also be drawn if the QTc(F) interval increases by > 60 msec above average baseline or to the level of ≥ 480 msec (see Section 11.3.3).

h. Screening must occur within 28 days of first dose of study drug. Screening evaluations may be combined with Day 1 pre-treatment laboratory evaluations if both are done within 4 days before first dose of study drug.

i. All protocol-specified clinic visits during the Treatment Period should occur within ± 1 day of the nominal visit day unless otherwise specified.

j. Follow-up Treatment Period visits to be performed monthly (every 28 ± 3 days). These visits are only for those subjects who are continuing on study treatment beyond the initial 28-day Early Treatment Period. For those subjects continuing on study beyond 12 months, visits will occur every 2 months ± 3 days. Now that the MTD for daily dosing has been established, if it results in a dose increase for subjects not already receiving the MTD, the study assessments required for the monthly follow-up visits (ie, PK and postdose ECG and vital sign measurements not required) should be performed on Days 1 and 14 of the first month, then monthly for a total of 6 months, then every 2 months thereafter. The same schedule of evaluation will apply to any subjects increased from 50 mg/day to 100 mg/day after 6 months of treatment at 50 mg/day and after the 100 mg dose group is determined not to be a DLT dose cohort. Section 9.6 for study assessments to be performed and the timing of visits.

k. End-of-Study visit is to be performed 30 days (± 3 days) after last dose of study drug.

l. Echocardiograms are to be obtained at Screening, on Day 28, and at Months 3, 6 every 6 months thereafter, and End-of-Study visit and are to include measurement of ejection fraction and assessment for pericardial effusion. Note: If subject has had echocardiogram within 2 months of End-of-Study visit, no need to obtain echocardiogram at End of Study visit. For those subjects who have already had their Month 12 visit, this may be performed at Month 13 and then subsequent echocardiograms may be performed on the same schedule as the MRIs. If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.

m. Screening MRI should be performed following informed consent and prior to other Screening assessments. Results must be reviewed before the first dose of study drug is administered. MRI to be performed at Month 6 and then every 6 months thereafter. Note: If subject has had MRI within 3 months of End of Study visit, there is no need to obtain MRI at End-of-Study visit.

n. Subjects on the Phase 1b portion of the study will have study drug held for a one-time drug holiday of at least 14 and up to 28 days with creatinine and cystatin C measurements performed before and immediately after the drug holiday, as well as a predose PK sample prior to restarting study drug.

o. PK samples will be collected predose at every monthly visit up to and including Month 6 visit for those subjects in the Phase 1b and Phase 2a 50 mg daily portions of the

study who continue treatment (Follow-Up Treatment Period). NOTE: For subjects re-starting study drug after study drug holiday, collect a predose PK sample prior to restarting study drug.

p. Required for Phase 2a 50 mg subjects electing not to participate in PK testing. Based upon the results of testing, a third timepoint may be performed within the first two months of study drug dosing and after consultation with the medical monitor.

q. Follow-up Treatment Period visits to be performed monthly (every 28 ± 3 days). For those subjects continuing on study beyond 12 months, visits will occur every 2 months ± 3 days.

Table 4-3: Schedule of Events for Subjects in Phase 2a Portion of Study Dosed on Monday, Wednesday, and Friday

Assessments	Screening[j] (-28 Days)	Early Treatment Period[k]						Follow-Up Treatment Period	End of Study[m]
		Day 1	Day 3	Day 5	Day 8	Day 12 (±1 day)	Day 26 (±1 day)	Every 28 Days (± 3 days)[l]	30 Days from Last Dose (± 3 days)
Informed consent	X								
Medical and PKD history (including genotype, if available)	X								
Physical examination (including weight)[a]	X	X[l]				X	X	X	X
Vital signs[b]	X	X				X	X	X	X
Supine 12-Lead ECG[c]	X	X				X	X	X	X
Clinical laboratory tests[d]	X[i]	X[i]				X	X	X	X
Ocular evaluation[e]	X							X	
Peripheral blood smear	X								X
Iothalamate testing[f]	X					X			
Echocardiogram	X						X[n]	X[n]	X
Pregnancy test[g]	X	X					X	X *Every 3 Months*	X
MRI	X							X[o] *Every 6 Months*	X
Study drug administration[h]		X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X
Adverse events	*Collect from the time informed consent signed until 30 days after last dose of study drug.*								

PK sampling[i]			X	X	X	X			
Dispense/Collect study drug		X					X	X	X

a. Complete PE to be done at Screening and End-of-Study visits. Height is only included in the Screening PE. Thereafter, limited PEs will be performed on Days 1, 12, 26, and Day 1 of Months 2 and beyond (See Section 9, Study Assessments, for a description of the body systems, including evaluation for cardiac tamponade and dry mouth by history and exam, and changes in vision to be examined at each visit).
b. Vital sign measurements consist of sitting blood pressure, pulse rate, respiratory rate, and oral or tympanic temperature. On Day 1, measurements should be performed predose and 1 and 4 hours postdose. See Section 9 for appropriate blood pressure measuring technique. For subjects participating in PK, vital signs are also to be measured 8 hours postdose on Day 1.
c. Supine 12-Lead ECGs will be performed at Screening, predose, and 1 and 4 hours postdose on Days 1 and 12; predose on Day 26 and Day 1 of Months 2 and beyond; and at End-of-Study visit (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]). If QTc(F) is prolonged to > 60 msec above baseline at any evaluation or to the level of ≥ 480 msec, refer to Section 11.3.3.1 for procedure to be followed. For subjects participating in PK, ECGs are also to be performed 8 hours postdose on Day 1.
d. Clinical laboratory tests consist of hematology, serum chemistry panel, coagulation, and urinalysis (see Section 9.9 for a complete list of assessments).
e. Ocular evaluations are to be performed at Screening and at Months 3, 6, 9, 12, 18, and 24. The following assessments should be performed: evaluation of best corrected visual acuity, fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and optical coherence tomography (OCT) of the optic nerve head and macula.
f. Optional; to be conducted at selected sites in 3–7 subjects. Second time point should be done on Day 12, 13, 14 or 15, and all study related procedures required on Day 12 may be done at this visit. Based upon the results of testing, a third timepoint may be performed within the first 2 months of study drug dosing and after consultation with the medical monitor.
g. Urine pregnancy tests are to be done in women of childbearing potential at Screening, predose on Day 1, Day 26, at Month 3 (and every 3 months thereafter up through Month 12), and End-of-Study visits only. For subjects continuing on study past 12 months who have visits every 2 months, testing should be done every 2 months to coincide with their visit schedule. Confirm with serum testing if urine sample is positive.
h. Subjects will start Phase 2a with an alternative dosing schedule of 150 mg of KD019 on Monday, Wednesday, and Friday of each week.
i. In the Monday, Wednesday, and Friday dosing schedule of the Phase 2a portion of the study, approximately 5 subjects will have blood samples drawn for PK analyses. If accrual goals have nearly been met, only those who can undergo iothalamate or PK testing will be enrolled. Blood samples will be collected on Study Day 1 (predose, 1, 2, 4, 8, and 24 hours postdose), predose on Study Days 3, 5, and 8, and Study Day 12 (predose, and 1, 2, 4, and 24 hours postdose). (Subjects undergoing iothalamate testing will not undergo PK sampling.) Also, collect PK sample if QTc(F) interval increases by > 60 msec above average baseline or to the level of ≥ 480 msec (see Section 11.3.3.1).
j. Screening must occur within 28 days of first dose of study drug. Screening evaluations may be combined with Day 1 pre-treatment laboratory evaluations if both are done within 4 days before first dose of study drug. Results must be reviewed before the first dose of study drug is administered.
k. All protocol-specified clinic visits during the Treatment Period should occur within ± 1 day of the nominal visit day unless otherwise specified.
l. Follow-up Treatment Period visits to be performed monthly (± 3 days) for the first 12 months the subject is on study. Thereafter, Follow-up visits are to be performed bi-monthly (every 60 ± 3 days). For those subjects continuing on study beyond 12 months, visits will occur every 2 months. See Section 9.6 for study assessments to be performed and the timing of visits.
m. End-of-Study visit is to be performed 30 days (± 3 days) after last dose of study.
n. Echocardiograms are to be obtained at Screening, on Day 26, at Months 3, 6 and every 6 months thereafter, and at End-of-Study visit and are to include measurement of ejection fraction and assessment for pericardial effusion. Note: If subject has had echocardiogram within 2 months of End-of-Study visit, no need to obtain echocardiogram at End-of-Study visit. If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
o. MRI to be performed at Screening, Month 6 and then every 6 months thereafter. Note: If subject has had MRI within 3 months of End-of-Study visit, there is no need to

obtain MRI at End-of-Study visit.

Table 4-4: Schedule of Events for Subjects in Phase 2a Portion of Study Dosed on Monday and Thursday

Assessments	Screening[j] (-28 Days)	Early Treatment Period[k]					Follow-Up Treatment Period	End of Study[n]
		Day 1	Day 8[l] (PK Subjects)	Day 11 (±1 day)	Day 18[l] (PK Subjects)	Day 25 (±1 day)	Every 28 Days (±3 days)[m]	(30 Days from Last Dose) (±3 days)
Informed consent	X							
Medical and PKD history (including genotype, if available)	X							
Physical examination (including weight)[a]	X	X		X		X	X	X
Vital signs[b]	X	X		X		X	X	X
Supine 12-Lead ECG[c]	X	X		X		X	X	X
Clinical laboratory tests[d]	X[j]	X[i]		X		X	X	X
Ocular evaluation[e]	X						X	
Peripheral blood smear	X							X
Iothalamate testing[f]	X					X		
Echocardiogram	X					X[n]	X[o]	X
Pregnancy test[g]	X	X				X	X *Every 3 Months*	X
MRI	X						X[p] *Every 6 Months*	X
Study drug administration[h]		X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X
Adverse events	*Collect from the time informed consent signed until 30 days after last dose of study drug.*							
PK sampling[i]		X	X	X	X	X		

Dispense/Collect study drug		X				X	X	X

a. Complete PE to be done at Screening and End-of-Study visits. Height is only included in the Screening PE. Thereafter, limited PEs will be performed on Days 1, 11, 25, and Day 1 of Months 2 and beyond (See Section 9, Study Assessments, for a description of the body systems, including evaluation for cardiac tamponade and dry mouth by history and exam, and changes in vision to be examined at each visit).
b. Vital sign measurements consist of sitting blood pressure, pulse rate, respiratory rate, and oral or tympanic temperature. On Day 1 measurements should be performed predose and 1 and 4 hours postdose. For subjects participating in PK, vital signs also are also to be measured 8 hours postdose on Day 1. See Section 9 for appropriate blood pressure measuring technique.
c. Supine 12-Lead ECGs will be performed at Screening, predose, and 1 and 4 hours postdose on Days 1 and 25; predose on Day 11 and Day 1 of Months 2 and beyond; and at End-of-Study visit (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]). For subjects participating in PK, ECGs also are to be performed 8 hours postdose on Days 1 and 25. If QTc(F) is prolonged to > 60 msec above baseline at any evaluation or to the level of ≥ 480 msec, refer to Section 11.3.3.1 for procedure to be followed.
d. Clinical laboratory tests consist of hematology, serum chemistry panel, coagulation, and urinalysis (see Section 9.9 for a complete list of assessments). (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)
e. Ocular evaluations are to be performed at Screening and at Months 3, 6, 9, 12, 18, and 24. The following assessments should be performed: evaluation of best corrected visual acuity, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and optical coherence tomography (OCT) of the optic nerve head and macula.
f. Optional; to be conducted at selected sites in 3–7 subjects. Second time point should be done between Day 22 and 25 and all study related procedures required on Day 25 may be done at this visit. Based upon the results of testing, a third timepoint may be performed within the first 2 months of study drug dosing and after consultation with the medical monitor.
g. Urine pregnancy tests are to be done in women of childbearing potential at Screening, predose Day 1, Day 25, at Month 3 (and every 3 months through Month 12), and End-of-Study visits only. For subjects continuing on study past 12 months who have visits every 2 months, testing should be done every 2 months to coincide with their visit schedule. Confirm with serum testing if urine sample is positive.
h. Subjects will start Phase 2a with an alternative dosing schedule of 150 mg on Monday and Thursday of each week.
i. In the Monday/Thursday dosing schedule of the Phase 2a portion of the study, approximately 5 subjects will have blood samples drawn for PK analyses. If accrual goals have nearly been met, only those who can undergo iothalamate or PK testing will be enrolled. Blood will be collected on Study Day 1 (predose, and 1, 2, 4, 8, and 24 hours postdose); predose on Days 8, 11, and 18; and on Day 25 (predose, and 1, 2, 4, 8, and 24 hours postdose), and predose at every monthly visit thereafter (up to and including the Month 6 visit) (Subjects undergoing iothalamate testing will not undergo PK sampling.) Also, collect PK sample if QTc(F) interval increases by > 60 msec above average baseline or to the level of ≥ 480 msec (see Section 11.3.3.1).
j. Screening must occur within 28 days of first dose of study drug. Screening evaluations may be combined with Day 1 pre-treatment laboratory evaluations if both are done within 4 days before first dose of study drug. Results must be reviewed before the first dose of study drug is administered.
k. All protocol-specified clinic visits during the Treatment Period should occur within ± 1 day of the nominal visit day unless otherwise specified.
l. This visit is for subjects participating in PK sampling only.
m. Follow-up Treatment Period visits to be performed monthly (± 3 days) for the first 12 months the subject is on study. Thereafter, Follow-up visits are to be performed bi-monthly (every 60 ± 3 days). For those subjects continuing on study beyond 12 months, visits will occur **every 2 months**. See Section 9.6 for study assessments to be performed and the timing of visits.
n. End-of-Study visit is to be performed 30 days (± 3 days) after last dose of study drug.
o. Echocardiograms are to be obtained at Screening, on Day 25, at Months 3, 6 and every 6 months thereafter, and at End-of-Study visit and are to include measurement of ejection fraction and assessment of pericardial effusion. Note: If subject has had echocardiogram within 2 months of End-of-Study visit, no need to obtain echocardiogram at End-of-Study visit. If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.

p. MRI to be performed at Screening, Month 6, and then every 6 months thereafter. Note: If subject has had MRI within 3 months of End-of-Study visit, there is no need to obtain MRI at End-of-Study visit.

Table 4-5: Timing Window Allowances for PK Sampling, Vital Sign Measurements, and ECGs

Pharmacokinetic Sampling	
Timepoint	**Tolerance Window**
0 hour	-240 minutes to 0 hour
>0 hour – 2 hour	-2 minutes/+ 2 minutes
4 hour – 8 hour	-5 minutes/+ 5 minutes
24 hour	-30 minutes/+ 30 minutes

Vital Signs	
Timepoint	**Tolerance Window**
0 hour	-240 minutes to 0 hour
>0 hour – 4 hour	-10 minutes/+ 10 minutes
>4 hour – 8 hour	-30 minutes/+ 30 minutes

ECG	
Timepoint	**Tolerance Window**
0 hour	-240 minutes to 0 hour
>0 hour – 4 hour	-10 minutes/+ 10 minutes
>4 hour – 8 hour	-30 minutes/+ 30 minutes

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ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ARPKD	autosomal recessive polycystic kidney disease
AUC	area under the plasma drug concentration time curve
AUC_{0-x}	area under the plasma drug concentration time curve from 0 to X hours
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
$CKD\text{-}EPI_{2012cys}$	cystatin C-based CKD-EPI equation
$CKD\text{-}EPI_{2012Scr\text{-}cys}$	serum creatinine- and cystatin C-based CKD-EPI equation
C_{max}	maximum plasma concentration
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HER2	human epidermal growth factor receptor 2
HIV	human immunodeficiency virus
htTKV	height-adjusted total kidney volume
ICH	International Conference on Harmonization
ICF	informed consent form
ILD	Interstitial Lung Disease
INR	International Normalized Ratio
IRB	Institutional Review Board
KDR	kinase insert domain receptor
LDH	lactate dehydrogenase
LLN	lower limit of normal
MDRD-4	4-Variable Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No Observed Adverse Effect Level
NSCLC	non-small cell lung cancer
P-gp	P-glycoprotein
PK	pharmacokinetic
PKD	polycystic kidney disease
PT	prothrombin time
PTT	partial thromboplastin time
QTc(F)	QT interval, corrected
SAE	serious adverse event
SILK	safety in larger kidneys
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
T_{max}	observed time to reach peak plasma concentration
TK	tyrosine kinase
TKV	total kidney volume
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VEGFR2	vascular endothelial growth factor receptor 2

5 BACKGROUND AND RATIONALE

5.1 Polycystic Kidney Disease

Polycystic kidney disease (PKD) is the most common inherited kidney disease in the United States, occurring in approximately 1 in every 1,000 live births. It affects more than 600,000 people in the United States and 12 million worldwide (Wilson, 2004). It is the third most common single cause of kidney failure.

Polycystic kidney disease is characterized by the growth of numerous renal cysts, which cause abnormalities in both structure and function of the kidneys. Cysts also develop in other organs, particularly in the liver. Other manifestations of polycystic kidney disease include high blood pressure, urinary tract infections, kidney stones, hematuria, and aneurysms. Pain in the back, abdomen, and pelvis affects many PKD patients.

There are 2 types of polycystic kidney disease, autosomal dominant (ADPKD) and autosomal recessive (ARPKD). In the more common form, autosomal dominant PKD, the abnormal PKD gene (PKD1 or PKD2) is inherited from 1 parent who also has PKD. Affected individuals become aware of the disease at varying times from childhood to adulthood. If a family history exists, individuals are assessed regularly for manifestations of the disease. Others may have cysts detected during routine medical evaluations for hematuria or hypertension or an ultrasound examination for other medical symptoms and conditions. There is, however, a small percentage of people with autosomal dominant PKD who do not have a family member with the disease. ARPKD is associated with abnormal function of the kidneys and liver, and is usually diagnosed by ultrasound during fetal development or shortly after birth. Unlike ADPKD, a mutant PKHD1 gene must be contributed by each parent in order for ARPKD to occur in an offspring. Parents are usually unaware of being carriers of the mutant gene because they are asymptomatic.

ADPKD is caused by a mutation in either the polycystin 1 or 2 (PKD1 or PKD2) genes, resulting in the abnormal, uncontrolled growth of renal tubular epithelial cells (Chapman, 2008). In individuals with ADPKD, epithelial growth factor receptor (EGFR) is overexpressed and mislocated from the basolateral to the luminal surface of renal tubular cells (Torres et al, 2007). EGFR ligands are secreted by tubular cells and are found in human PKD cyst fluids. The combination of EGFR mislocation and ligand secretion establishes an autocrine loop resulting in persistent renal tubular cell proliferation (Torres, 2010). Chronic proliferation results in renal cyst formation (Belibi et al,

2004). The cysts then cause a structural distortion of the renal architecture, impeding normal nephron function. Cyst enlargement results in a massive increase in kidney volume and a progressive impairment of renal function (Grantham et al, 2006). Associated clinical symptoms include hypertension, recurrent flank pain, hematuria, and recurrent pyelonephritis. Currently, there are no disease-modifying therapies for ADPKD; all existing treatment strategies are palliative and aimed at controlling symptoms (Grantham, 2008).

5.2 Tesevatinib

Tesevatinib (formerly named XL647 and KD019) is a new chemical entity that inhibits multiple tyrosine kinases (TKs) (ErbB family members [EGFR and HER2], vascular endothelial growth factor receptor 2 [VEGFR2/KDR]), and Src family kinases.

5.2.1 Tesevatinib Nonclinical Toxicology

Tesevatinib nonclinical toxicology has been characterized in multiple species using a variety of dosing regimens. Details can be found in the Investigator's Brochure.

5.2.2 Clinical Experience with KD019

Tesevatinib has been evaluated in over 300 subjects, including 195 subjects with solid tumor malignancies in 3 Phase 1 studies, 3 Phase 2 studies, and 1 Phase 3 study; 66 healthy volunteer subjects in 4 clinical pharmacology studies; and 64 subjects with polycystic kidney disease (in this study, KD019-101). In these studies, at least 185 subjects have been treated at levels ≥ 300 mg daily and at least 53 subjects were treated with tesevatinib for ≥ 6 months. The MTD was determined to be 300 mg once daily.

5.2.2.1 Daily Administration

5.2.2.1.1 Phase 1

In the daily dosing Phase 1 study XL647-002, "A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of KD019 Administered Orally Daily to Subjects with Solid Tumors," 31 subjects were enrolled in successive cohorts to receive tesevatinib as a single oral dose daily. Subjects continued to receive tesevatinib on study in the absence of unacceptable tesevatinib - related toxicity or progressive disease (PD). The MTD was determined based on dose-limiting toxicities (DLTs) occurring in the first 28 days of treatment. Tumor imaging was conducted at baseline and approximately every 2 months thereafter while subjects received study drug.

A total of 31 subjects were treated across 5 dose levels: 75 mg (n = 3), 150 mg (n = 3), 200 mg (n = 3), 300 mg (n = 18), and 350 mg (n = 4). One DLT of Grade 3 drug-induced pneumonitis was observed at 300 mg, resulting in expansion of the 300 mg cohort to a total of 6 subjects. Two of 4 subjects enrolled at 350 mg experienced a DLT of Grade 3 QTc(F) prolongation (machine read), both clinically asymptomatic. These events were downgraded to Grade 2 following digital re-reads by a validated central ECG laboratory. The MTD was determined to be 300 mg and an additional 12 subjects were enrolled at this dose level.

The most common adverse events (AEs) considered either possibly or probably related to tesevatinib (frequency ≥ 10% of subjects) reported were Grade 1 and 2 diarrhea, dysgeusia, fatigue, rash, and clinically asymptomatic QTc(F) prolongation. One subject receiving a 300 mg daily dose of tesevatinib experienced 2 serious adverse events (SAEs) of Grade 3 drug-induced pneumonitis and Grade 4 myocardial infarction, which were both assessed by the investigator as related to study drug. Two additional subjects experienced SAEs assessed by the investigator as related to study drug: clinically asymptomatic Grade 3 QTc(F) prolongations (machine read), subsequently downgraded to Grade 2 following digital re-read by a validated central ECG laboratory (also DLTs, see above).

5.2.2.1.2 Phase 2

In the Phase 2 study, "A Phase 2 Study of KD019 in Subjects with Non-Small Cell Lung Cancer Who have Progressed after Responding to Treatment with Either Gefitinib or Erlotinib" (XL647-203), 41 subjects with relapsed or recurrent NSCLC (Stage IIIB or IV) with documented progressive disease after benefit from single agent erlotinib or gefitinib, including stable disease (SD), or with a known EGFR T790M mutation were enrolled to receive tesevatinib, 300 mg orally daily. Tumor imaging was conducted at baseline and approximately every 2 months thereafter while study drug was received. Subjects were allowed to stay on study in the absence of unacceptable tesevatinib -related toxicity or progressive disease.

A total of 41 subjects were treated and the most frequently reported AEs were diarrhea, nausea, cough, dry skin, and ECG QT prolonged. Adverse events that occurred in ≥ 10% of subjects and were considered related to tesevatinib consisted of diarrhea, rash, dry skin, fatigue, cough, and electrocardiogram QT prolonged. The majority of these events were Grades 1 and 2.

There were 22 SAEs reported for 12 of the 41 subjects enrolled in the study. Eight SAEs assessed by the investigator as related to tesevatinib were reported in 4 subjects. One subject experienced Grade 3 diarrhea (2 occurrences), Grade 3 abdominal pain, Grade 3 nausea, and Grade 3 vomiting. Each of the following SAEs were experienced by 1 subject: Grade 4 bilateral pulmonary emboli, Grade 3 ventricular ectopy (in a subject with a history of atrial fibrillation and MI), and Grade 3 QTc(F) prolongation (based on machine-read value). Two deaths were reported during the course of the study (within 30 days of the last dose of study drug), both of which were assessed as not related to study drug (tesevatinib). Both deaths were reported to be due to progressive disease.

5.2.2.2 Intermittent Administration

5.2.2.2.1 Phase 1

In the Phase 1 study, "A Phase 1 Dose-Escalation Study of the Safety and Pharmacokinetics of KD019 Administered Orally to Subjects with Solid Tumors" (XL647-001), subjects with advanced solid tumors were enrolled in successive cohorts to receive tesevatinib orally daily on Days 1-5, followed by a 9-day break, with cycles repeating every 14 days. This regimen is referred to as the "intermittent 5 & 9" schedule. Tumor imaging was conducted at baseline and approximately every 2 months thereafter while study drug was being received. Subjects were allowed to stay on study in the absence of unacceptable tesevatinib -related toxicity or progressive disease.

In this study, a total of 41 subjects were treated across 11 dose levels. Subjects received study drug as either a powder-in-bottle (PIB) formulation at 0.06, 0.12, 0.19, 0.28, 0.39, 0.78, 1.56, 3.12, 4.68, and 7.0 mg/kg, or a fixed-dose tablet formulation of 350 mg. One subject in the 3.12-mg/kg cohort had a DLT of asymptomatic QTc(F) prolongation, resulting in expansion of that cohort, with no further DLTs. The first 2 subjects who received 7.0 mg/kg experienced DLTs of Grade 3 diarrhea, despite treatment, requiring dose reduction to 4.68 mg/kg. The reduced dose was well tolerated in both of these subjects. Expansion of the 4.68-mg/kg cohort to 6 subjects occurred without further DLTs; therefore, 4.68 mg/kg was considered the MTD. All ongoing subjects had their tesevatinib dose converted to a fixed dose of 350 mg. One of these subjects developed Grade 3 diarrhea, requiring dose reduction. Five additional subjects were enrolled into the 350-mg cohort.

The most common AEs considered either possibly or probably related to tesevatinib (frequency > 10 % of subjects) consisted of Grade 1 or 2 diarrhea, rash, nausea, fatigue, dysgeusia, anorexia, vomiting, and dry skin. A total of 3 SAEs assessed by the investigator as related to tesevatinib were reported in 3 subjects: 1 subject at 0.28 mg/kg experienced a Grade 4 pulmonary

embolism, 1 subject at 7.0 mg/kg experienced Grade 3 diarrhea, and 1 subject receiving 350 mg and concomitant warfarin experienced a Grade 3 elevation in INR. The SAEs of diarrhea were assessed as probably related to tesevatinib, and the SAEs of pulmonary embolism and increased INR were assessed as possibly related to tesevatinib.

5.2.2.2.2 Phase 2

In this study "A Phase 2 Study of KD019 in Subjects with Non-Small Cell Lung Cancer," (XL647-201), selected subjects with NSCLC of adenocarcinoma histology, Stage IIIB, with malignant pleural effusion, or Stage IV were enrolled to receive 350 mg of oral tesevatinib daily on Days 1-5, followed by a 9-day break, with cycles repeating every 14 days. Subjects with clinical characteristics predictive of response to EGFR inhibitors (Asian, female, and/or minimal and remote smoking history) were enrolled. Tumor imaging was conducted at baseline and approximately every 2 months thereafter during study drug administration. Subjects were allowed to stay on study in the absence of unacceptable tesevatinib -related toxicity or progressive disease.

A total of 41 subjects were enrolled in the intermittent 5 & 9 dosing cohort. The majority of AEs reported were Grade 1 (71.0%) or Grade 2 (22.5%) and the most frequently reported AEs were diarrhea, fatigue, nausea, rash, and cough. The most frequently reported Grade 3 AEs were pleural effusion (experienced by 4/41 [9.8%] subjects), diarrhea, and electrocardiogram QT prolonged (each experienced by 3/41 [7.3%] subjects). Grade 4 pulmonary embolism was reported for 3/41 (7.3%) subjects. A total of 5 SAEs assessed by the investigator as possibly or probably related to tesevatinib were reported in 4 subjects. One subject experienced SAEs of Grade 3 gastrointestinal (GI) hemorrhage and duodenal ulcer, and the following SAEs were experienced by 1 subject each: Grade 3 pneumonia, Grade 2 hemoptysis, and clinically asymptomatic Grade 3 QTc(F) prolongation (machine-read, downgraded to Grade 2 following digital re-reads by a validated central ECG laboratory).

A second cohort in this study enrolled 14 subjects to receive KD019 orally daily at a dose of 300 mg. The majority of AEs reported in this cohort were Grade 1 (68.3%) or Grade 2 (22.2%). The most frequently reported AEs with daily dosing were diarrhea, fatigue, nausea, rash, and cough. The most frequently reported Grade 3 AEs were diarrhea, electrocardiogram QT prolonged, and pleural effusion (each reported by 2/14 subjects, 14.3%). Thirteen SAEs were reported in 6 of the 14 subjects. Three SAEs were assessed by the investigator as related to

tesevatinib: Grade 3 GI hemorrhage, Grade 3 hypercalcemia, and Grade 2 increased blood creatinine.

5.2.2.2.3 Initial Data from ADPKD Protocol KD019-101

Sixty-one subjects were enrolled into 5 dosing cohorts in the Phase 1b and Phase 2a portions of the study: 9 subjects into Cohort 1 at 50 mg daily, 8 subjects into Cohort 2 at 100 mg daily, 5 subjects into Cohort 3 at 150 mg daily, 14 subjects into Cohort 4 at 150 mg Monday, Wednesday, and Friday, 10 subjects into Cohort 5 at 150 mg Monday and Thursday, and an additional 15 Phase 2a subjects at 50 mg daily (Table 5-1).

Table 5-1: Summary of KD019-101 Dose / Schedule, Demographics and Median TKV (mL)

Dose/Schedule	No. Subjects	Gender (Male [M]/Female [F])	Median Age (Years)	Median TKV (mL)
50 mg/day	24	9M / 15F	39	1401*
100 mg/day	8	5M / 3 F	37	1525
150 mg/day	5	2M / 3 F	41	1094
150 mg MWF	14	4M / 10 F	36	1344
150 mg MT	10	4M / 6 F	37	795
Total	61	24M / 37F	38 (19-55)	1333.5* (411-4432)
*2 subjects did not yet have TKV values				

Safety reviews after the first 2 cohorts deemed these cohorts to have adequate safety and to be tolerable. In Cohort 3, 3 of 5 subjects enrolled have withdrawn consent primarily due to concerns with rash. It was noted that all 5 subjects in this cohort experienced rash within the first 28 days of treatment. In comparison, 4 out of 9 subjects in the 50-mg cohort and 1 out of 8 subjects in the 100-mg cohort experienced rash within the first 28 days. While rash at the 150 mg dose level did not meet strict safety criteria for defining the MTD, this dose level was considered intolerable for long-term administration in this population. Therefore, the MTD for daily dosing was determined to be 100 mg daily. While the MTD dose of 100 mg/day was based on criteria defined in the protocol, the occurrence of moderate QTc prolongation in 2 subjects dosed at that level led to a decision later in the study to recommend 50 mg/day as the best tolerated daily dose.

As the known toxicities of tesevatinib, including diarrhea and rash, have been seen in all 3 Phase 1b dosing cohorts, an alternative dosing schedule of dosing 150 mg of KD019 on Monday,

Wednesday, and Friday of each week was explored in the Phase 2a portion of the study to determine if it is more tolerable when used chronically in this subject population. The safety data of the 14 subjects who received 150 mg tesevatinib every Monday, Wednesday and Friday has been reviewed by the Data Safety Committee. There were 3 moderate events: 1 subject had moderate QTc(F) prolongation which resolved with dose modification as well as moderate diarrhea, and 1 subject with moderate rash which improved with topical corticosteroids and emollients. While the tolerability of this schedule appears to be superior to that of dosing tesevatinib 150 mg on a daily schedule, another dosing schedule of tesevatinib 150 mg administered on Monday and Thursday of each week was explored to determine if this dose and schedule would result in fewer moderate toxicities, particularly QTc(F) prolongation. To date, of the 10 subjects receiving 150 mg Monday and Thursday, there was no QTc(F) prolongation; however, 1 subject had a severe (Grade 3) maculopapular skin rash. Thus, while the 150 mg Monday and Thursday administration of tesevatinib generally appears to be a tolerable regimen, the occurrence of the Grade 3 maculopapular skin rash, together with the significant effect of missing any single dose in this regimen, has led to the decision to further evaluate the dose level of 50 mg daily prior to using this dose in a randomized study.

Following the enrollment of the additional 15 subjects in the Phase 2 50 mg dosing cohort, it was concluded that tesevatinib 150 mg in various schedules was associated with skin rash that was not well tolerated. Incidence of moderate QTc prolongation not acceptable for chronic use was associated with tesevatinib 100 mg daily. Tesevatinib 50 mg daily appeared to be a well-tolerated dose in patients with ADPKD, although some acneiform rash occurred. The study will enroll approximately 50 more subjects at the dose of 50 mg daily in order to increase the robustness of the safety data in subjects with ADPKD treated with tesevatinib.

The initial data from this study (Protocol KD019-101) indicate that subjects with ADPKD receiving tesevatinib have experienced elevations of creatinine without elevations in cystatin C. The median changes from screening values for creatinine and cystatin C from all 9 subjects in the 50-mg dose cohort reveal that creatinine values were increased by 7.5% at Day 3, by 22% at Day 7, and increased by 13% at Day 28. Data after Day 28, including 2 subjects who have received tesevatinib for 16 months, do not indicate any significant ongoing change in creatinine. Cystatin C levels, during the same time periods, did not change (median decreases of 4.5%, 1%, and 4% at Days 3, 7, and 28, respectively). Data from the 8 subjects enrolled into the 100-mg dose cohort, as well as subjects enrolled in subsequent cohorts, exhibited a similar pattern. This increase in

creatinine occurs early and after approximately 7 days, does not continue to increase, similar to the increase in serum creatinine seen with cimetidine. Increases in creatinine were seen in previous clinical studies of tesevatinib. For example, increases in serum creatinine in 10% of subjects were reported in Study XL647-201. However, most of the previous studies were in subjects with malignancies, and in previous studies, cystatin C levels were not evaluated, so increases in serum creatinine that may not represent renal dysfunction were not recognized.

In order to further investigate the effects of tesevatinib on serum creatinine levels, the effects of tesevatinib on a panel of transporter molecules (including OCT2 and MATE) were evaluated in vitro. Preliminary results indicate that tesevatinib potently inhibits MATE1 and MATE2-K transporter proteins. MATE transporter proteins carry creatinine out of kidney proximal tubule cells into the tubule lumen. Inhibition of MATE transporter proteins decreases secretion of creatinine into the proximal tubule lumen and leads to an increase in serum creatinine levels. To demonstrate the reversible nature of the creatinine elevations, subjects on the Phase 1b portion of the study will have study drug held for a one-time drug holiday of at least 14 and up to 28 days with creatinine and cystatin C measurements before and immediately after the drug holiday, as well as a predose PK sample prior to restarting study drug.

In addition, in order to have an independent method of evaluating renal function, 3–7 subjects in the Phase 2a portion of this study will be evaluated by iothalamate renal clearance testing before and after tesevatinib administration. If accrual goals have nearly been met and goals for subjects with PK or iothalamate testing have not been met, only those who can undergo iothalamate or PK testing will be enrolled. Iothalamate is a contrast agent widely utilized in renal clearance testing because, unlike creatinine, it is filtered at the glomerulus and not secreted in the proximal tubule. Testing is performed by injection of iothalamate with serum samples obtained for iothalamate evaluation over 3 hours post iothalamate injection. Thus, iothalamate renal clearance testing will provide an independent method for verification of renal function before and after tesevatinib administration.

In the current study, there have been 18 cases of asymptomatic subjects with elevated amylase levels. Fourteen of these elevations were mild (> ULN – 1.5 x ULN), 2 were moderate (> 1.5 X ULN – 2.0 x ULN), and 2 were severe (> 2.0 x ULN). Three subjects had elevated amylase levels at Screening and in 2 of these subjects' amylase levels rose to moderate levels, leading to discontinuation from the study. Other subjects with amylase elevations have not had progressive

increases in amylase levels during tesevatinib administration. One subject developed severe elevated amylase during infection with mononucleosis, and amylase levels returned to normal after recovery from that illness. A second subject with a baseline amylase level of 185 U/L had levels which continued to rise to a maximum of 365 U/L at Day 110. While this subject remained asymptomatic, with no clinical signs or symptoms of pancreatitis, subjects were discontinued from the study. Both of these subjects with severe amylase elevations had elevations of both lipase and pancreatic amylase isozyme.

Previous studies of tesevatinib have been reviewed for cases of elevated amylase or pancreatitis. Amylase was not routinely evaluated in any of these previous studies. There was only 1 AE of an increased amylase level or of possible pancreatitis. This was an elevation of amylase to 922 U/L in a subject with Stage IV non-small cell lung cancer who received tesevatinib at a dose of 300 mg/day. The subject was admitted to the hospital with diarrhea and abdominal pain, but lipase was normal and there were no CT findings consistent with pancreatitis. On serum amylase isoenzyme analysis, the subject had an elevation in salivary amylase. The investigator's conclusion was that the subject appeared to have an increase in amylase due to salivary amylase secretion by the tumor.

Quantitative Whole Body Autoradiography was performed in rats with C14–labeled tesevatinib. Among other findings, there was a high concentration (approximately 10 times that found in the blood) of tesevatinib in the salivary glands and pancreas. While tesevatinib could concentrate there for many reasons, it's at least possible that tesevatinib at high concentrations in the salivary gland and pancreas could lead to increased serum levels of amylase.

In summary, mild asymptomatic increases in amylase levels have been seen frequently during the study, including in subjects in the 50 mg daily cohort, and appear to be due to increases in pancreatic amylase. Subjects with baseline elevations in amylase are no longer eligible for tesevatinib ADPKD studies. If amylase levels rise to 1.5 x ULN, evaluation of lipase, amylase isoenzymes, and lipid levels are performed. Ongoing evaluations for the presence of pancreatic cysts will be performed using MRIs obtained to evaluate TKV. There were 28 subjects with elevations of CPK above the normal range. Twelve subjects experienced moderate CPK elevation (> 2.5 x ULN – 5.0 x ULN), and 3 subjects experienced severe CPK elevation (> 5.0 x ULN). In each case of severe CPK elevation, it appeared that the elevation was associated with exercise and did not recur after rechallenge or continued tesevatinib exposure. Quantitative whole body radiography in rats indicates relatively low accumulation of tesevatinib in skeletal muscle. In this

study, muscle AEs correlate poorly with CPK levels. While elevations of CPK commonly occur with exercise, the lack of a control group in this study makes it difficult to fully evaluate the relationship between tesevatinib and CPK elevations.

One subject on the current study in the 50 mg/day cohort developed a small pericardial effusion while on study. An echocardiogram performed per protocol on Day 28 revealed trace pericardial effusion, which was not seen on the screening echocardiogram. This result was reported an as AE and assessed by the investigator to be of moderate intensity and probably related to study drug. The subject was asymptomatic. Subsequent echocardiograms performed over the following 6 months while the subject continued to receive tesevatinib revealed no change in the pericardial effusion.

During this clinical trial there have been 4 incidences of asymptomatic prolongation of QTc interval to > 480ms or > 60 ms over the baseline value. One subject in cohort 2 (100 mg daily) at month 5 of dosing had a mean QTc(F) of 510 msec. The subject had study drug interrupted and was dose reduced to 50 mg daily with resolution of QTc(F) prolongation. Another subject on cohort 2 (100 mg daily) presented on Day 7 of study with a mean QTc(F) of 487 msec. Study drug was held. On rechallenge at the same dose, the QTc(F) was again prolonged at 485 msec. Study drug again was held and restarted at a reduced dose of 50 mg with resolution of QTc(F) prolongation. One subject receiving 150 mg every Monday, Wednesday and Friday on Day 12 presented with a mean QTc(F) of 485 msec. Study drug was held and restarted at 100 mg every Monday, Wednesday, and Friday with resolution of QTc(F) prolongation. One subject receiving 150 mg every Monday and Thursday presented on Month 12 with a mean QTc(F) of 484 msec. Study drug was held and restarted at 50 mg daily with resolution of QTc(F) prolongation.

5.2.2.3 Clinical Pharmacokinetics

A preliminary noncompartmental analysis of tesevatinib pharmacokinetics (PK) from Phase 1 studies of intermittent dosing indicated that tesevatinib was rapidly absorbed following oral administration, with a median observed time to reach peak plasma concentration (T_{max}) of 4-8 hours. Area under the plasma drug concentration time curve (AUC) and the maximum plasma concentration (C_{max}) generally increased approximately in proportion with dose over the full dose range (ie, 3.4 to 586 mg). Mean terminal half-lives after 5 consecutive daily doses ranged from 50 to 92 hours, and appeared generally independent of dose. High inter-subject variability in exposure was observed with CV % values of 46% and 43% for dose normalized C_{max} and AUC_{0-24},

respectively. Results from 5 subjects in the Phase 2 study who received 350 mg KD019 on the intermittent schedule showed that the concentration of tesevatinib appeared unchanged from cycle to cycle. These results suggest that tesevatinib does not accumulate significantly from one 14-day cycle to the next.

A preliminary noncompartmental PK analysis has been completed for 15 subjects given tesevatinib once daily for at least 29 consecutive days. Tesevatinib was rapidly absorbed following oral administration (cohort mean T_{max} ranged from 3.3 to 7.3 hours) and steady state appeared to have been reached by about Day 15. The estimated median value of accumulation was 4.6 at the MTD (ie, 300 mg/day). The median T_{max} at the MTD was 4 hours.

Average exposure was calculated at the MTD for both the once daily (ie, 300 mg/day) and intermittent 5 & 9 (ie, 350 mg/day) dosing regimens. At the MTD, the estimated average concentration over 28 days for once-daily dosing was 399 ng/mL, which was approximately 2-fold higher than the 28-day average concentration determined for intermittent dosing of 199 ng/mL, but was generally consistent with the 24-hour average concentration observed after the fifth dose of the Intermittent schedule (375 ng/mL).

5.3 Safety Profile of Tesevatinib

5.3.1 Tesevatinib

Adverse events of special interest noted in Study KD019-101 include asymptomatic increase in serum amylase, pericardial effusion, and asymptomatic QTc(F) prolongation, as described above in Section 5.2.2.2.3.

The most common AEs observed in subjects receiving 300 mg tesevatinib were diarrhea, rash, nausea, increased CPK, increased creatinine, vomiting, increased amylase, acne, back pain, and fatigue.

Interstitial Lung Disease: Non-fatal interstitial lung disease (ILD) has been reported in association with the use of tesevatinib in 1 subject with NSCLC of 152 subjects exposed to tesevatinib.

QTc(F) Prolongation: In clinical studies of tesevatinib, cases of QTc(F) prolongation have been observed. This section summarizes available data regarding cases of QTc(F) prolongation that were confirmed by a review by a central ECG laboratory.

Using non-standardized digital machines that provided an analysis of the data, including QTc(F) values, 12-lead ECG tracings were obtained. In most of the studies, multiple ECGs were scheduled to be taken at tesevatinib concentration nadir and T_{max}, but the timing was not exact in some protocols and the conditions were uncontrolled for the effects of diurnal variation, food, or concomitant medications. The preponderance of ECG testing was performed during the first 4-week cycle, but ECGs were obtained during subsequent cycles. The machine RECIST QTc(F) intervals were recorded directly onto the case report forms.

CTCAEv3 was used to assign the severity grade for QTc(F) AEs, and the criteria for each grade are presented below:

	Grade 1	**Grade 2**	**Grade 3**	**Grade 4**
Prolonged QTc(F) interval	QTc(F) >450–470 msec	QTc(F) > 470–500 msec or ≥ 60 msec above baseline	QTc(F) > 500 msec	QTc(F) > 500 msec with life threatening signs or symptoms; Torsades de pointes

In the 169 subjects with malignancies treated in 4 uncontrolled studies, the majority of whom had advanced, metastatic non-small cell lung cancer, 33 (20%) were found to have QT prolongation based on machine read ECGs at some time during treatment that met the CTCAE v3 definition of an AE: Grade 1 (7 [4%] subjects), Grade 2 (14 [8%] subjects), and Grade 3 (12 [7%] subjects). The majority of these subjects received ≥ 300 mg daily or 350 mg given for 5 days with 9 days off. There were no clinical findings associated with the ECG changes. There were no reports of QTc(F) prolongation in 32 healthy volunteer subjects who received a single 300 mg dose of KD019.

Clinical study data available for review encompassed Studies XL647-001, XL647-002, XL647-201, XL647-203, and XL647-004. Other studies (XL647-005) did not have data confirmed by central ECG laboratory. In terms of total exposure, 201 subjects received tesevatinib (169 subjects with cancer and 32 normal volunteers). Electrocardiograms for 178 of these subjects have been reviewed by the central ECG laboratory.

QTc(F) Summary

No SAEs of convulsion; sudden death; ventricular tachycardia, fibrillation, or flutter; or torsades de pointes have been received for the > 250 subjects exposed to tesevatinib, as per review of the Kadmon safety database. There was an SAE of ventricular extrasystole.

Digital ECG files from 178 subjects were supplied to a vendor (eRT) for analysis. ECGs from 60 subjects had further review by a cardiologist, including all 41 subjects in XL647-203, and an additional 19 subjects from XL647-001 (2), XL647-002 (12), and XL647-201 (5), because they were reported to have noteworthy QTc(F) prolongation on the ECG machine analysis. eRT then reclassified the findings using a different algorithm:

- Absolute QTc(F) value ≥ 500 msec
- QTc(F) increase > 60 msec above baseline with QTcF > 470 msec
- QTc(F) increase > 60 msec above baseline with QTcF ≤ 470 msec
- QTc(F) value > 470 msec with an increase ≤ 60 msec above baseline

Of these 60 subjects, eRT analyzed the digital files and identified 23 (38%) subjects who had no outlier findings, 5 (8%) subjects who had no QTc(F) prolongation on the digital analysis, and 2 (3%) subjects who eRT could not completely exclude as being product related, but whose prolonged QTc(F) value obtained on the machine read ECG was not felt to be measurable due to underlying RBBB or atrial fibrillation.

Of the 30 (50%) remaining subjects, eRT identified 25 with prolonged QTc(F) values of ≤ 60 msec, which eRT could not completely exclude as being product related. There were 3 subjects with QTc(F) > 60 msec that were felt to be possibly/probably related to drug treatment and 2 subjects who had QTc(F) values > 500 msec, which were felt to be probably related to drug treatment. The results of the central laboratory analysis are shown in Table 5-2.

Table 5-2: QT Prolongation: Cases Confirmed by Central Laboratory Review (By Study)

Study No.	Study Population	No. of Subjects Reviewed by eRT	Prolonged QTc(F) Marked Based on Machine	eRT Findings of Prolonged QTc(F)	Prolonged QTc(F) ≤ 60 msec	Prolonged QTc(F) > 60 msec	QTc(F) ≥ 500 msec
XL647-001	All comers	41	2	2	2	0	0
XL647-002	All comers	31	12	10	10	0	0
XL647-201 (5 days on/9 days off)	NSCLC	39	5	3	3	0	0
XL647-201 (Daily Dosing)	NSCLC	2					
XL647-203	NSCLC	41	41	15	10	3	2
XL647-004	Normal volunteers	24	0	0	0	0	0
Total		**178**	**60**	**30**	**25**	**3**	**2**

QTc(F)/Concentration Analysis

A preliminary analysis of delta QTc(F) (change from baseline value) versus plasma concentration was carried out using pooled data from studies with intermittent 5 days on and 9 days off dosing (Study XL647-001), single doses with crossover food effects (Study XL647-004), and once-daily dosing (Studies XL647-002 and XL647-203) regimens. Concentration-matched ECGs were available from 1104 records from 125 subjects. This analysis was done using QTc(F) values obtained from the central ECG laboratory. All ECGs digitized and read at a central laboratory and QTc(F) values were Fridericia corrected. The QTc(F) versus concentration relationship was described using linear, power, and E_{max} mixed effects models. Using bootstrap population parameter estimates pooled across all 3 models (ie, ~ 1000 bootstrap estimates per model).

Analyses showed that the concentration-QTc(F) relationship appears to be consistent across Studies XL647-001, XL647-002, XL647-004, and XL647-203 (ie, suitable for pooling, and argues against a marked time effect because XL647-004 is single dose). In these studies, QTc(F) prolongation increased with increasing plasma concentration. Based on these limited data, the concentration-QTc(F) relationship appears to be adequately described using a power model. In order to evaluate potential saturation of QTc(F) prolongation, additional data are needed at concentrations > 1000 ng/mL. At the projected C_{max} (552 ng/mL), the estimated 95% CI on

QTc(F) prolongation ranges from 34 to 43 msec. It should be noted that results extrapolated at concentrations > 600 ng/mL should be viewed with caution.

An initial evaluation of QTc duration was performed with data from 37 subjects in the KD019-101 ADPKD study who received daily doses of 50 mg to 150 mg. The 50 mg daily dose of tesevatinib, which is expected to be the clinical dose for further evaluation in autosomal dominant polycystic kidney disease, produced modest QTcF increases. The time-averaged increase in QTcF averaged 4-6 ms. The timepoint analyses demonstrated a peak increase in QTcF at 4 hours post-dosing on Day 14 of 11-15 ms. At the mean C_{max} of 72.5 mg/mL for the pooled 50 mg dose groups, the PK/PD model predicted a mean QTcF increase of 13.3 ms, with a one-sided upper 95% confidence bound of 16.8 ms. The magnitude of the QTc effect of the tesevatinib 50 mg dose is similar to that produced by moxifloxacin 400 mg.

5.4 Rationale

5.4.1 Rationale for the ADPKD Indication

This study is a Phase 1b/2a, multi-center, open-label, pharmacokinetic, dose-escalation study with safety and tolerability as the primary endpoint.

In nonclinical studies conducted under IND 69,215, tesevatinib has been shown to be a potent inhibitor of receptor and cytoplasmic tyrosine kinases (TKs). The product was specifically optimized to simultaneously inhibit the EGFR, human epidermal growth factor receptor 2 (HER2), Src, vascular endothelial growth factor receptor 2 (VEGFR2/KDR), and ephrin receptor B4 (EphB4) tyrosine kinases with high potency, and demonstrated excellent activity in target-specific cellular functional assays. In nonclinical animal models, tesevatinib had good oral bioavailability and has shown sustained inhibition of its targets in vivo following a single oral dose.

In clinical studies, over 250 subjects have been treated with tesevatinib in Phase 1 and Phase 2 clinical studies; 166 of these have been treated at levels ≥ 300 mg daily. Forty-four (44) subjects were treated with tesevatinib for ≥ 6 months. These clinical studies have shown minimal renal excretion, and established tesevatinib administration at 300 mg/day is safe for chronic dosing of an oncology patient population. The MTD was determined to be 300 mg once daily in patients with metastatic cancer.

In nonclinical studies, tesevatinib selectively inhibited key kinases and validated targets in animal models of PKD. Results from nonclinical efficacy studies demonstrated that tesevatinib possesses significant potential to prevent the formation of cysts due to an increased proliferation of renal ductal epithelial cells. Nonclinical studies using 2 rodent models (BPK mouse and PCK rat) of PKD have demonstrated that tesevatinib reaches its target, the kidneys, and inhibits the signaling pathway for MEK/ERK by inhibiting the phosphorylation of EGFR (and Src, Erb2, VEGFR2/KDR). The decreased phosphorylation of EGFR and Erb2 contributes towards decreased proliferation of epithelial cells in the kidneys and reduces renal enlargement in these 2 disease models.

In addition, tesevatinib has shown either no or extremely weak inhibitory activity against numerous other kinases, which should reduce off-target toxicity. In summary, both the nonclinical and clinical results to date suggest that tesevatinib may be a promising therapeutic for ADPKD.

5.4.2 Rationale for Dosage Selection

In the Phase 1b portion of the study, the planned starting dose in this study is 50 mg/person/day (approximately 0.83 mg/kg/day). This dose was selected based on the available nonclinical data, including no observed adverse effect levels (NOAEL), $C_{max,}$ and AUC_{0-24} data for rats, dogs and monkeys. In addition, clinical safety and pharmacokinetic data from Phase 1 studies in healthy subjects and patients with cancer also support the starting dose. Repeat-dose toxicokinetic studies in rats demonstrated a NOAEL of 10 mg/kg for tesevatinib, when administered by oral gavage for 14 or 90 days. The C_{max} and AUC_{0-24} measured after the final NOAEL dose in the 14- and 90-day studies was 138/183 ng/mL and 2013/3433 ng·hr/mL, respectively. In a third repeat-dose toxicity study, 10 mg/kg for 182 days (26 weeks) was considered above the NOAEL of 3 mg/kg, a dose associated with a C_{max} and AUC_{0-24} of 48-61 ng/mL (male-female) and 818-1090 ng·hr/mL (male-female, respectively). In the 14-day study, a C_{max} and AUC_{0-24} of 319 ng/mL and 5741 ng·hr/mL, (male and female, respectively), for the 30 mg/kg dose was above the NOEL due to generally reversible findings consistent with dehydration, inflammation, renal dysfunction, and stress. In the 180-day study, a C_{max} and AUC_{0-24} of 175–234 ng/mL (male-female) and 3470-4450 ng·hr/mL (male-female), respectively, for the 10 mg/kg dose was above the NOAEL due to toxicities that included death or moribund conditions not observed with 10 mg/kg dosing for 90 days in a separate toxicity study. Based on this data, the threshold C_{max} and AUC_{0-24} for adverse effects in rats is estimated to be approximately 175 ng/mL and 3470 ng·hr/mL, respectively.

In non-human primates, the NOAEL for tesevatinib was 2 and 6 mg/kg, when administered for 14 days by oral gavage and 26–39 weeks by nasogastric intubation, respectively. C_{max} and AUC_{0-24} for the oral gavage/nasogastric intubation NOAEL doses was (Male-Female) 28–38/77–70 ng/mL and 488–450/1080–995 ng·hr/mL, respectively. In the 14-day study a C_{max} and AUC_{0-24} of 106–116 ng/mL and 1855–1690 ng·hr/mL, respectively, for the 6 mg/kg dose was above the NOAEL due to findings of QTc(F) interval prolongation, heart rate decrease, and minimal increases in urea nitrogen and creatinine. It is noteworthy that in the toxicity study, in which the monkeys received tesevatinib for 26-39 weeks, 6 mg/kg was not associated with ECG findings or other findings considered adverse. Nevertheless, based on this data, the threshold C_{max} and AUC_{0-24} for adverse effects in non-human primates is estimated to be approximately 106 ng/mL and 1690 ng·hr/mL, respectively.

In a Phase 1 study of the safety and pharmacokinetics of tesevatinib administered to human subjects with solid tumors, a dose of 0.78 mg/kg was found to achieve a mean C_{max} (ng/ml) and AUC_{0-24} of 38.5 ng/mL and 763 ng·hr/mL, respectively, after a single oral dose on Day 1, and 125 ng/mL and 2680 after the final dose of a Day 1, 5, 6, 7, and 8 dosing regimen. In a separate Phase 1 study in subjects with solid tumors, a single dose of 75 mg tesevatinib was associated with a C_{max} and AUC_{0-24} of 37 ng/mL and 560 ng·hr/mL, respectively. Given this data, a starting dose of 50 mg/dose (approximately 0.83 mg/kg) in this proposed study is likely to result in a C_{max} and AUC_{0-24} below the thresholds for adverse effects predicted from rat and non-human primate toxicity studies discussed above. Moreover, the C_{max} achieved with a 50 mg/dose in subjects will be significantly below the C_{max} of 939–1612 ng/mL (male-female) observed in dogs to be the NOAEL for cardiovascular parameters. With continued daily dosing at 50 mg/dose in subjects, PK parameters will approach the thresholds estimated for rats and non-human primates, although adverse effects in humans at this dose are still not expected based on prior clinical work. In particular, a total of 16 healthy volunteers from two Phase 1 studies have received a single dose of tesevatinib at 6 times the planned starting dose (300 mg/dose) with unremarkable changes in clinical safety assessments, including 12-lead ECGs. C_{max} in these studies reached 158-226 ng/mL. Thus, a starting dose of 50 mg once daily should be considered a safe starting dose for the planned study in subjects with PKD.

Twenty-two subjects were enrolled into 3 dosing cohorts in the Phase 1b portion of the study: 9 subjects into Cohort 1 at 50 mg daily, 8 subjects into Cohort 2 at 100 mg daily, and 5 subjects into Cohort 3 at 150 mg daily. Safety reviews after the first 2 cohorts deemed these cohorts to have

adequate safety and to be tolerable. In Cohort 3 at 150 mg daily, 3 of 5 subjects enrolled have withdrawn consent primarily due to concerns with rash. It was noted that all 5 subjects in this cohort experienced rash within the first 28 days of treatment. In comparison, 4 out of 9 subjects in the 50-mg cohort and 1 out of 8 subjects in the 100-mg cohort experienced rash within the first 28 days. While rash in the 150-mg cohort did not meet strict safety criteria for defining the MTD, this dose level was considered intolerable for long term administration in this population. Therefore, the MTD for daily dosing was determined to be 100 mg daily.

PK modeling indicates that a Monday, Wednesday, Friday schedule for tesevatinib administration would decrease the C_{max} but retain most of the exposure to tesevatinib when compared to daily administration. This modeling takes into account the tesevatinib half-life of approximately 70 hours.

Thus, an alternative dosing schedule of 150 mg of tesevatinib administered on Monday, Wednesday, and Friday of each week was explored in the Phase 2a portion of the study to determine if it is more tolerable than daily administration when used chronically in this patient population. The safety data of the 14 subjects who received tesevatinib 150 mg every Monday, Wednesday, and Friday has been reviewed. There were 3 moderate events: 1 subject had moderate QTc(F) prolongation which resolved with dose modification and moderate diarrhea, and 1 subject with moderate rash which improved with topical corticosteroids and emollients. While the tolerability of this schedule appears to be superior to that of dosing tesevatinib 150 mg on a daily schedule, another dosing schedule of tesevatinib 150 mg administered on Monday and Thursday of each week was also explored to determine if this dose and schedule results in fewer moderate toxicities, particularly QTc(F) prolongation. One subject in the tesevatinib 150 mg Monday and Thursday cohort had a severe rash.

PK modeling suggests that reducing the tesevatinib schedule to 150 mg administered on a Monday, Thursday schedule would reduce the tesevatinib C_{max} slightly while reducing tesevatinib exposure more significantly. Thus, PK modeling predicts a C_{max} and AUC_{0-24} of 188 ng/mL and 4120 (ng•hr/mL**)** for the 150 mg Monday, Wednesday, Friday schedule for KD019 administration, and a C_{max} and AUC_{0-24} of 139 ng/mL and 2450 (ng•hr/mL**)** for the 150 mg Monday and Thursday schedule for tesevatinib administration. The effect of this change in schedule on the side effect profile, particularly the occurrence of QTc(F) prolongation, will be evaluated.

Approximately 5 subjects treated on each alternative schedules had PK samples obtained so that safety, tolerability, and exposure could be evaluated. If accrual goals have nearly been met and goals for subjects with PK or iothalamate testing have not been met, only those who can undergo iothalamate or PK testing will be enrolled.

Despite fulfilling the protocol criteria for determining the MTD for daily dosing, the 100 mg daily dose group exhibited a rate of QTc prolongation not acceptable for chronic use. Preliminary data from both the 50 mg daily cohort and the 150 mg Monday and Thursday cohort suggest that both dosing regimens appear acceptable for further study in terms of safety. However, the 50 mg daily schedule is less complex, and thereby less likely to have significant compliance issues, and a severe rash occurred in 1 subject in the 150 mg Monday and Thursday cohort. Because of the long half-life of tesevatinib, daily dosing reduces the effect of a missed dose when compared with twice weekly dosing. In preparation for randomized studies, 15 additional subjects were treated with 50 mg of tesevatinib daily to further evaluate efficacy and safety at this dose.

Modeling of ADPKD subpopulations for a randomized Phase 3 clinical study has been performed. Enrollment criteria being considered are ADPKD subjects with baseline eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2, and height-adjusted total kidney volume (htTKV) $\geq$ 1000 mL.

In order to study the safety profile in this specific ADPKD subpopulation, up to 50 additional subjects with PKD and baseline eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2, and htTKV $\geq$ 1000 mL will be enrolled (SILK Cohort). Up to 50 subjects will be enrolled and required to complete PK testing as described for other Phase 2a subjects in this protocol or iothalamate testing.

In addition, all 50 subjects will undergo a mandatory 28-day drug holiday after completing the first month of treatment with tesevatinib. During this drug holiday, and for 4 weeks after, subjects will return to the clinic weekly for creatinine and tesevatinib plasma measurements. All subjects will resume tesevatinib treatment at the Month 2 study visit following completion of the 28-day drug holiday.

5.5 Compliance Statement

This study will be conducted in compliance with Good Clinical Practice (GCP), including International Conference on Harmonization (ICH) Guidelines, and the Declaration of Helsinki. In

addition, the investigator agrees to adhere to the protocol and to all applicable local laws and regulatory requirements relevant to the use of new therapeutic agents in the countries involved.

The appropriate Institutional Review Boards (IRBs) must approve the protocol and any amendments and the subject informed consent form (ICF) prior to implementation.

Voluntary written informed consent must be obtained from every subject prior to participation in this clinical study. The rights, safety, and well-being of participating subjects are the most important considerations and should prevail over interests of science and society.

Study personnel involved in conducting this study will be qualified by education, training, and experience to perform their respective task(s). This study will not use the services of study personnel where sanctions have been invoked based upon scientific misconduct or fraud (eg, loss of medical licensure, debarment).

5.5.1 Good Clinical Practice

The principal investigator will ensure that the basic principles of Good Clinical Practice, as outlined in 21 CFR 312, subpart D, "Responsibilities of Sponsors and Investigators," 21 CFR, part 50 (1998) and 21 CFR, part 56, (1998) are followed.

Since this is a covered clinical study, the principal investigator is adhered to 21 CFR, part 54, (1998). A covered clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition subject to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that investigators and all sub-investigators must provide documentation of their financial interest or arrangements with Kadmon or proprietary interests in the drug being studied. This documentation must be provided prior to the participation of the principal investigator and any sub-investigator. The principal investigator and sub-investigator agree to notify Kadmon of any change in reportable interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last subject has completed the protocol-defined activities.

6 STUDY OBJECTIVES

6.1 Phase 1b Objective

The primary objective of the Phase 1b study is to determine the safety, plasma pharmacokinetics, and maximum tolerated dose (MTD) of tesevatinib when administered to subjects with ADPKD.

6.2 Phase 2a Objectives

The primary objective of the Phase 2a portion of the study is to evaluate the annualized change in glomerular filtration rate (GFR) in subjects with ADPKD when treated with tesevatinib.

The secondary objectives are to evaluate subjects treated with KD019 with regard to:

- Annualized percent change from baseline in total kidney volume (TKV)
- Annualized change from baseline in the reciprocal of serum creatinine
- Safety profile
- Serum creatinine levels
- PK and tolerability of 2 alternative dosing schedules (dosing on Monday, Wednesday, and Friday of each week and dosing on Monday and Thursday)

In addition, exploratory measures of efficacy will be performed throughout both phases of the study.

7 STUDY DESIGN

7.1 Study Sites

This study will be conducted at approximately 11 to 13 sites in the United States.

7.2 Overview of Study Design

This is a Phase 1b/2a, multicenter, open-label, dose-escalation, safety, MTD, and PK study in subjects with ADPKD. The Phase 1b portion of the study has been completed and the MTD for daily dosing was determined to be 100 mg daily. In this portion of the study, subjects received 50, 100, or 150 mg of tesevatinib orally once daily for 28 days or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision. After the initial 28-day safety and tolerability assessment period, subjects may have, at the discretion of the investigator, continued to receive study drug for a total of 24 months from the initiation of treatment.

For those subjects who had received a minimum of 6 months of treatment at the 50 mg/day dose, dose escalation to 100 mg/day was allowed after the 100 mg/day was evaluated for safety.

After the MTD for daily dosing had been established (100 mg QD), 24 additional subjects were enrolled in the Phase 2a portion of the study and treated using alternative dosing schedules of 150 mg/day of tesevatinib on Monday, Wednesday, and Friday of each week and 150 mg on Monday and Thursday of each week. These subjects consented to Amendment 10 were on the Monday and Thursday dosing schedule, with the exception of up to 3 subjects undergoing Iothalamate testing, where the goal was to have 1-2 subjects on each of the alternative dosing schedules undergo this testing. Also, subjects active in the Phase 1b portion had their dose increased or decreased to the established daily dose MTD of 100 mg (while continuing once-daily dosing to obtain long-term safety data).

Fifteen additional subjects, consented to Amendment 11, received 50 mg of tesevatinib daily. All subjects in this additional cohort were required to participate in either PK testing as described in the Phase 1b cohort summary or iothalamate testing as described for Phase 2a subjects.

Modeling of ADPKD subpopulations for a randomized Phase 3 clinical study has been performed. Enrollment criteria being considered are ADPKD subjects with baseline eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2, and htTKV $\geq$ 1000 mL.

In order to study the safety profile in this specific ADPKD subpopulation, up to 50 additional subjects with PKD and baseline eGFR ≥ 35 mL/min/1.73 m^2 and ≤ 80 mL/min/1.73 m^2, and htTKV ≥ 1000 mL will be enrolled (SILK Cohort). Each of the subjects to be enrolled will be required to complete PK testing as described for other Phase 2a subjects in this protocol. In addition, all 50 subjects will undergo a mandatory 28-day drug holiday after completing the first month of treatment with tesevatinib. During this drug holiday, and for 4 weeks after, subjects will return to the clinic weekly for creatinine and tesevatinib plasma measurements. Blood draws during the drug holiday may be performed by a visiting nurse at the subject's home; if the subject chooses this option, the study team should call the subject on the same day of the visit to inquire about concomitant medications and AEs. All subjects will resume tesevatinib treatment at the Month 2 study visit following completion of the 28-day drug holiday.

Subjects in all cohorts of the study, after the 28-day treatment period, will, if they desire and at the discretion of the investigator, continue to receive study treatment for 24 months from their first dose or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision.

7.2.1 Screening Period

Subjects will undergo screening evaluations to determine study eligibility, including medical history, physical examination, ECG, echocardiogram, ocular testing, hematology, serum chemistry and coagulation studies, and urinalysis. MRI will be performed to measure kidney volume.. Screening will be conducted within 28 days prior to the first dose of tesevatinib.

7.2.2 Treatment Period

After completion of the screening assessments and confirmation of study eligibility, subjects received tesevatinib in a dose-escalating manner. The Phase 1b portion of the study has been completed and the MTD for daily dosing was determined to be 100 mg daily. In this portion of the study, subjects received 50, 100, or 150 mg of tesevatinib for 28 days or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision. The first dose of study drug was administered in the clinic on Study Day 1. Subsequent doses were taken on an outpatient basis for the remainder of the 28-day Treatment Period. Subjects returned to the clinic for weekly safety and tolerability assessments.

At the end of each dosing cohort, a Data Safety Committee, including an independent safety monitor with significant clinical expertise in polycystic kidney disease, reviewed all safety data (PK, safety labs, ECGs, echocardiograms, and AEs) and decided whether dose escalation may occur. Dose escalation to the next higher dose was not started until the safety data from the preceding dose cohort was evaluated and deemed acceptable. Specifically, the decision to progress to the next higher dose was made after the safety data through a minimum of 28 days of follow-up was reviewed for at least 8 subjects in the preceding dose cohort and it was determined that it was safe to proceed to the next dose level.

For those subjects in the Phase 1b portion of the study who had received a minimum of 6 months of treatment at the 50 mg/day dose, dose escalation to 100 mg/day was allowed after the 100 mg/day was evaluated for safety.

After the MTD for daily dosing had been established (100 mg QD), 24 additional subjects were enrolled in the Phase 2a portion of the study and treated at the MTD using 2 alternative dosing schedules of 150 mg of tesevatinib on Monday, Wednesday, and Friday of each week and 150 mg on Monday and Thursday of each week. Also, subjects active in the Phase 1b portion had their dose increased or decreased to the established MTD of 100 mg (while continuing once-daily dosing to obtain long-term safety data).

Despite fulfilling the protocol criteria for determining the MTD for daily dosing, the 100 mg daily dose group exhibited a rate of QTc prolongation not acceptable for chronic use. Preliminary data from both the 50 mg daily cohort and the 150 mg Monday and Thursday cohort appear acceptable for further study in terms of safety. The 50 mg daily dose appears to be favorable due to dosing simplicity and the occurrence of a severe rash in the 150 mg Monday and Thursday cohort. Additionally, the effect of missed dosing is reduced in the daily dosing cohort. Because of these factors, the 50 mg tesevatinib treatment appears to be the best tolerated dose, and will likely be taken forward in additional studies. In order to generate additional efficacy and safety information on this selected dosing regimen, 15 additional subjects were enrolled as an additional group in the Phase 2a portion of this protocol at a dose of 50 mg of tesevatinib. Each of the 15 subjects were required to complete either PK testing as described for other Phase 1b subjects in this protocol or iothalamate testing. Fifteen subjects were enrolled in the Phase 2a portion of the protocol instead of the 20 subjects planned.

Modeling of ADPKD subpopulations for a randomized Phase 3 clinical study has been performed. Enrollment criteria for Phase 3 are ADPKD subjects with baseline eGFR ≥ 35 mL/min/1.73 m^2 and ≤ 80 mL/min/1.73 m^2, and htTKV ≥ 1000 mL. In order to study the safety profile in this specific ADPKD subpopulation, up to 50 additional subjects with PKD and baseline eGFR ≥ 35 mL/min/1.73 m^2 and htTKV ≥ 1000 mL will be enrolled.

Each of the 50 subjects to be enrolled will be required to complete PK testing as described for other Phase 2a subjects in this protocol.

In both phases of the study, after the 28-day treatment period, subjects will, at the discretion of the investigator, continue to receive study treatment for 24 months from their first dose or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision. .

Subjects will continue to undergo safety evaluations, including physical examination, ECG, AE collection, concomitant medication collection, echocardiogram, visual acuity testing, hematology, serum chemistry, coagulation studies, pregnancy testing, and urinalysis. MRI also will be performed.

Additionally, in order to evaluate reversibility of creatinine increases, subjects on the Phase 1b portion of the study will have study drug held for a one-time drug holiday of at least 14 and up to 28 days with creatinine and cystatin C measurements before and immediately after the drug holiday, as well as a predose PK sample prior to restarting study drug. This can be done 14 days after dose escalation to the MTD or any time after 6 months of KD019 administration.

7.3 Randomization and Blinding

This is an open-label, nonrandomized study.

8 STUDY POPULATION

8.1 Target Population

This study will be conducted in subjects with autosomal dominant polycystic kidney disease (ADPKD). Approximately 120 male and female subjects with ADPKD will be enrolled. Approximately 30 subjects will be enrolled in the Phase 1b portion and approximately 90 subjects will be enrolled in the Phase 2a portion.

8.2 Inclusion Criteria

A subject must meet the following criteria to be eligible for the study:

1. The subject has a confirmed diagnosis of ADPKD based on Ravine's criteria. Subjects < 30 years of age must have at least 2 cysts (unilateral or bilateral) while subjects ≥ 30 years of age must have at least 2 cysts in each kidney (ie, total ≥ 4 cysts).
2. Cysts must be at least 1 cm in size to be considered.
3. Subject is ≥ 18 but ≤ 62 years of age at time of consent.
4. The subject has an eGFR ≥ 35 mL/min/1.73 m^2 and ≤ 80 mL/min/1.73 m^2 using the MDRD-4 variable formula (Appendix A).
5. The subject has an htTKV ≥ 1000 mL (htTKV is calculated using total kidney volume obtained from MRI divided by height in meters).
6. Subject has the following laboratory values:
    - Platelets >LLN
    - Hemoglobin > 9 g/dL
    - Total bilirubin ≤ 1.5 mg/dL
    - AST (SGOT) < 2.5 × upper limit of normal (ULN)
    - ALT (SGPT) < 2.5 × ULN
    - PT/PTT ≤ 1.5 ULN
    - Albumin ≥ lower limit of normal
    - Amylase within normal limits

- Lipase within normal limits

7. The subject has International Normalized Ratio (INR) ≤ 1.5, except those subjects taking warfarin who must have INR < 3.0.
8. The subject has serum potassium levels and serum magnesium levels within the normal range.
9. The subject is capable of understanding and complying with the protocol and has signed the informed consent form.
10. Female subjects of childbearing potential have a negative pregnancy test at Screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy or who have had any evidence of menses in the past 12 months. However, women who have been amenorrheic for 12 or more months are still considered to be of childbearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.
    - Women of childbearing potential (ie, menstruating women) must have a negative urine pregnancy test (positive urine tests are to be confirmed by serum test) documented within the 24-hour period prior to the first dose of study drug.
    - Sexually active women of childbearing potential enrolled in the study must agree to use two forms of accepted methods of contraception during the course of the study and for 6 months after their last dose of study drug. Effective birth control includes (a) IUD **plus** one barrier method; (b) on stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, transdermal) **plus** one barrier method; or (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm); or (d) a vasectomized partner
11. For male subjects who are sexually active and who are partners of premenopausal women: agreement to use two forms of contraception as in criterion 10 above during the treatment period and for at least 6 months after the last dose of study drug.

12. The subject has no history of another malignancy in the 5 years prior to study entry, except treated non-melanoma skin cancer or superficial bladder cancer or carcinoma in-situ of the cervix or Stage 1 or 2 cancers of other sites that have been treated surgically and have not recurred.

8.3 Exclusion Criteria

A subject who meets any of the following criteria is ineligible for the study:

1. The subject has had a previous partial or total nephrectomy or a kidney transplant.
2. The subject has tuberous sclerosis, Hippel-Lindau disease, or acquired cystic disease.
3. The subject has congenital absence of 1 kidney and/or need for dialysis.
4. Moderate hematuria (≥ moderate). If due to cyst rupture, subject may be rescreened after discussion with medical monitor.
5. Uncontrolled hypertension (systolic blood pressure > 160 mmHg; diastolic blood pressure > 100 mm Hg).
6. Uncontrolled diabetes mellitus (HbA1c > 8%).
7. Presence of renal or hepatic calculi (stones) causing symptoms.
8. The subject has received any investigational therapy within 30 days prior to study entry.
9. Active treatment (within 4 weeks of study entry) for urinary tract infection.
10. History of pancreatitis or has known risk factors for pancreatitis.
11. The subject meets any of the following cardiac criteria:
    - Mean corrected Fridericia (Fridericia's formula, see Section 9.10) QTc interval (QTc[F]) of > 450 msec
    - History of torsade de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (<50 bpm), heart block (excluding first-degree block, being PR interval prolongation only), congenital long QT syndrome or new ST segment elevation or depression or new Q wave on ECG. Subjects with a history of atrial arrhythmias should be discussed with the medical monitor.

- Family history of congenital long QT syndrome or unexplained sudden cardiac death.
- History of ventricular rhythm disturbances.
- Symptomatic heart failure (per NYHA guidelines), unstable angina, myocardial infarction, or cerebrovascular accident (CVA) within 6 months prior to study entry.
- Has a cardiac pacemaker.
- History of pericardial effusion or presence of pericardial effusion on screening echocardiogram

12. The subject is taking any medication known to inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers, or any drugs associated with torsades de pointes or known to prolong the QTc(F) interval, including anti-arrhythmic medications within 2 weeks prior to Screening (refer to Appendix B for a sample listing of medications associated with QTc[F] prolongation). A stable regimen (≥ 4 weeks) of antidepressants of the SSRI class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).
13. The subject has an uncontrolled intercurrent illness that would limit compliance with study requirements including, but not limited to ongoing or active infections or psychiatric illness.
14. The subject is pregnant or nursing.
15. The subject is known to be positive for the human immunodeficiency virus (HIV), or hepatitis B or C, as indicated by a positive test at Screening.
16. Subject is known to be immunocompromised.
17. The subject has documented presence of renal vascular disease.
18. The subject has received erlotinib, gefitinib, cetuximab, panitumumab, or an investigational EGFR inhibitor at any time.
19. The subject has an allergy or hypersensitivity to components of either the tesevatinib or the formulation.
20. The subject is unable or unwilling to participate in PK sampling.

21. The subject is aphakic due to previous cataract surgery or congenital anomaly.

    Note: The sponsor has the option to exclude the enrollment of a subject if, based upon the subject's medical history or screening results, it is felt that a subject's safety may be at risk and/or if the safety data may confound the study results.

9 STUDY ASSESSMENTS AND PROCEDURES

9.1 Screening Period

Informed consent must be obtained before any study-specific samples are taken or study-specific tests or evaluations are conducted. The following screening assessments should be performed within 28 days before the first dose of study drug is administered on Day 1. Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria. Laboratory panels for serum chemistry, coagulation, hematology, urinalysis, and pregnancy testing as necessary, are defined in Section 9.9.

Please note that blood pressure measurements are to be performed using appropriate technique (per guidelines of the American Heart Association). Specifically, subjects should be seated quietly for at least 5 minutes in a chair with their backs supported, their feet flat on floor (legs uncrossed), and their arms bared on a hard surface, with the arm slightly abducted and bent, with palm up and the midpoint of upper arm at heart level. Correct cuff and bladder size should be utilized. Two or more readings separated by 1–2 minutes should be averaged. If the first two readings differ by more than 5 mm Hg, additional (1 to 2) readings should be obtained and averaged. Record cuff size, arm used, and subject's position (if not seated).

At study visits in which a complete physical examination is required, the investigator should perform a thorough examination of all body systems (exception: genitourinary and reproductive should be symptom-directed). At study visits in which a limited physical examination is required, the investigator should inquire about signs/symptoms, general appearance, eyes (pupillary reaction, ophthalmoscopy, eye movements), oral mucosa, heart and pulses, lungs, abdomen (liver/spleen), kidneys, and neurological (symptom-directed and may include mental state, speech, gait/posture, arm swinging, facial movements, tongue, muscle wasting (power and tone), coordination, reflexes, and sensation.)

In addition, at each visit, subjects should be assessed for toxicities that may be associated with tesevatinib. This includes assessing for the following:

- Pericardial effusions and complications such as cardiac tamponade by assessing for tachycardia, dyspnea, edema, and neck vain distention
- Ocular toxicity due to photo absorbance at wavelengths between 290 and 370 nm, positive phototoxic potential, and distribution into the skin and eye
- Xerostomia due to absorption of tesevatinib in the salivary gland.

9.2 Subjects Enrolled in SILK Cohort

9.2.1 Screening Visit

At the screening visit (-28 days), information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and PKD history (including genotype if known)
- Complete physical examination, including height and weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, oral/tympanic temperature)
- Supine 12-Lead ECG (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]; perform ECG immediately prior to blood sample collection)
- Clinical laboratory tests by central laboratory (hematology, coagulation, serum chemistry panel, and urinalysis)
- Ocular evaluation including evaluation of best corrected visual acuity, fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and optical coherence tomography (OCT) of the optic nerve head and macula
- Echocardiogram
- Urine pregnancy test, if applicable. Subject must have a negative urine pregnancy test documented within the 24-hour period prior to the first dose of study drug. Positive results are to be confirmed with serum testing.
- MRI (As htTKV ≥ 1000 mL is an inclusion criterion, screening MRI will be performed after informed consent form has been signed and prior to other screening assessments.) htTKV is calculated using total kidney volume obtained from MRI divided by height in meters.
- Concomitant medications

9.2.2 Early Treatment Period

9.2.2.1 Day 1

Results of clinical and laboratory evaluations, including ECGs, must be reviewed prior to dosing to confirm that the subject continues to meet eligibility criteria. At the Day 1 (± 1 day) visit, the following procedures and evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)

- Vital sign measurements (predose and 1 and 4 hours postdose)
- Supine 12-Lead ECG (to be performed predose, and 1, 4, and 8 hours postdose prior to any time-matched blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Clinical laboratory tests by central laboratory. (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Blood samples for PK analysis (to be collected at predose and 1, 2, 4, and 8 hours postdose)
- Dispense up to a 1-month supply of study drug

9.2.2.2 Days 7, 21, and 28

At Days 7, 21, and 28 (± 1 day) visit, the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose); perform ECG before any time-matched blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.

- Clinical laboratory tests by central laboratory
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Blood samples for PK analysis (to be collected at predose and 1, 2, 4, and 8 hours postdose)
- Echocardiogram (Day 28 only)

- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test) (Day 28 only)
- Dispense/collect study drug

9.2.2.3 Day 14

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements (predose and 1 and 4 hours postdose)
- Supine 12-Lead ECG (to be performed predose, and 1, 4, and 8 hours postdose prior to any time-matched blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Clinical laboratory tests by central laboratory.
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Blood samples for PK analysis (to be collected at predose and 1, 2, 4, and 8 hours postdose)

9.2.3 Drug Holiday

All subjects will undergo a 28-day drug holiday after 28 days of treatment with tesevatinib. During this drug holiday and for 4 weeks after the holiday, subjects will have the following procedures performed:

- Serum creatinine and serum cystatin C tests by central laboratory
- Tesevatinib plasma concentration
- Concomitant medications
- Adverse events

The blood samples for serum creatinine, serum cystatin C, and tesevatinib plasma concentration can be drawn in the clinic or at the subject's home, by the study's remote nursing vendor.

If the subject has the blood samples drawn at home, the study team should call the subject on that same day to collect the concomitant medication and adverse event information

The first day of the drug holiday will be the day after the Day 28 Study Visit. At the completion of the 28-day drug holiday, subjects will return for the month 2 study visit.

9.2.4 Month 2

Following the 28-day drug holiday subjects will return to the clinic for the month 2 visit (± 1 day) and the following procedures will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose prior to collection of any time-matched blood samples (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
  - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Blood samples for PK analysis (to be collected predose at the Month 2, 3, 4, 5 and 6 visits only)
- Dispense/collect study drug

All subjects will have a collection of blood samples for serum creatinine, cystatin C, and tesevatinib concentration weekly for an additional 3 weeks after the Month 2 visit, to be collected pre-dose. These blood samples can be drawn in the clinic or at the subject's home, by the study's remote nursing vendor.
Adverse event and concomitant medication information will also be collected at these weekly visits. If the subject has the blood samples drawn at home, the study team should call the subject on the same day to collect this information

9.2.5 Monthly Follow-Up Treatment Period

9.2.5.1 Months 3–12

Subjects will return to the clinic monthly (every 28 ± 3 days) and the following procedures will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements

- Supine 12-Lead ECG (to be performed predose prior to collection of any blood samples) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.

- Clinical laboratory tests by central laboratory
- Ocular evaluation including evaluation of best corrected visual acuity, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and OCT of the optic nerve head and macula (to be performed at Months 3 and 6 and every 6 months thereafter).
- Echocardiogram (to be obtained at Months 3 and 6 and every 6 months thereafter). Note that if pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
- Pregnancy test (urine) for women of childbearing potential (to be performed at the Month 3 visit and every 3 months thereafter); if positive perform serum pregnancy test
- MRI (to be obtained at Month 6 and every 6 months thereafter)
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Blood samples for PK analysis (to be collected predose at the Month 2, 3, 4, 5 and 6 visits only)
- Dispense/collect study drug

9.3 Subjects Enrolled in Phase 1b and Phase 2a 50 mg Daily Portions of the Study (does not apply to SILK cohort)

9.3.1 Screening Visit

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and PKD history (including genotype if known)
- Complete physical examination, including height and weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, oral/tympanic temperature)

- Supine 12-Lead ECG (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]; perform ECG immediately prior to blood sample collection)
- Echocardiogram
- MRI
- Clinical laboratory tests by central laboratory (hematology, coagulation, serum chemistry panel, and urinalysis)
- Ocular evaluation evaluation of best corrected visual acuity, fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and OCT of the optic nerve head and macula
- Peripheral blood smear
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Concomitant medications
- Adverse event assessment

9.3.2 Early Treatment Period

9.3.2.1 Day 1

Results of clinical and laboratory evaluations, including ECGs, must be reviewed prior to dosing to confirm that the subject continues to meet eligibility criteria. At the Day 1 Visit, the following procedures and evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements (predose and 1 and 4 hours postdose)
- Supine 12-Lead ECG (to be performed predose, and 1 and 4 hours postdose prior to any blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Clinical laboratory tests by central laboratory. (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Study drug administration
- Concomitant medications
- Blood samples for PK analysis (to be collected at predose and 1, 2, 4, 8, and 24 hours postdose)
- Iothalamate testing (if the subject elects not to participate in PK sampling)

- Adverse event assessment
- Dispense up to a 1-month supply of study drug/collect study drug

9.3.2.2 Day 3

At the Day 3 visit (+ 1 day), the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Clinical laboratory tests by central laboratory
- Study drug administration
- Concomitant medications
- Adverse event assessment

9.3.2.3 Days 7, 14, and 21

At the Days 7, 14, and 21 visits (± 1 day), the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose); perform ECG before any blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
  - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Perform drug accountability and dispense adequate supply of study drug (if subject was not dispensed a 1-month supply on Day 1)
- Study drug administration
- Concomitant medications
- Predose blood samples for PK analysis
- Iothalamate test (only on Day 14)
- Adverse event assessment

9.3.2.4 Day 28

At the Day 28 visit (± 1 day), the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)

- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose); perform ECG before any blood sample collection (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
  - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Echocardiogram
  - Note that if pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Clinical laboratory tests by central laboratory
- Study drug administration
- Concomitant medications
- Predose blood samples for PK analysis
- Adverse event assessment
- Perform drug accountability and dispense adequate supply of study drug (for those subjects continuing on study)

9.3.3 Monthly Follow-Up Treatment Period for Those Subjects Continuing Study Drug

9.3.3.1 Months 2–12

Subjects will return to the clinic monthly (every 28 ± 3 days) and the following procedures will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose prior to collection of any blood samples) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
  - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Echocardiogram (to be obtained at Months 3 and 6 and every 6 months thereafter). Note that if pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.

- MRI (to be obtained at Month 6 and every 6 months thereafter)
- Pregnancy test (urine) for women of childbearing potential (to be performed at the Month 3 visit and every 3 months thereafter); if positive perform serum pregnancy test
- Clinical laboratory tests by central laboratory
- Perform drug accountability and dispense adequate supply of study drug
- Study drug administration
- Concomitant medications
- Blood samples for PK analysis (to be collected predose at the Month 2, 3, 4, 5 and 6 visits only)
- Adverse event assessment

9.3.4 Study Drug Holiday Visits

Study drug holidays will be at least 14 and up to 21 days in length. On the first day of the study drug holiday (during which time study drug will not be administered), subjects will come to the clinic and the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Blood sample collection for creatinine and cystatin C measurements
- Concomitant medications
- Adverse event assessment

Immediately after the study drug holiday (on the first day that study drug will be restarted), subjects will come to the clinic and the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Blood sample collection for creatinine and cystatin C measurements (to be collected predose)
- Blood sample for PK analysis (to be collected predose)
- Study drug administration
- Concomitant medications
- Adverse event assessment

NOTE: This visit can be done 14 days after dose escalation to the MTD or any time after 6 months of tesevatinib administration.

9.4 For Subjects Enrolled in Phase 2a Portion of Study and Dosed on Mondays, Wednesday, and Fridays

9.4.1 Screening Visit

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and PKD history (including genotype if known)
- Complete physical examination, including height and weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, oral/tympanic temperature)
- Supine 12-Lead ECG (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]; perform ECG immediately prior to blood sample collection)
- Clinical laboratory tests by central laboratory (hematology, coagulation, serum chemistry panel, and urinalysis)
- Ocular evaluation including evaluation of best corrected visual acuity, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and OCT of the optic nerve head and macula
- HIV and Hepatitis B & C tests by central laboratory
- Peripheral blood smear
- Iothalamate testing
    - In a subset of 3–7 subjects at selected sites, optional iothalamate testing may be performed by injection of iothalamate with serum samples obtained for iothalamate evaluation over 3 hours post iothalamate injection. Sites may use their site-specific protocol for testing.
- Echocardiogram
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- MRI
- Concomitant medications
- Adverse event assessment

9.4.2 Early Treatment Period

9.4.2.1 Day 1

Results of clinical and laboratory evaluations, including ECGs, must be reviewed prior to dosing to confirm that the subject continues to meet eligibility criteria.

At the Day 1 Visit, the following procedures and evaluations will be performed:

- Limited physical examination, including weight (see Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements (predose and 1 and 4 hours postdose). For subjects participating in PK analysis, vital sign measurements also to be performed 8 hours postdose.
- Supine 12-Lead ECG (to be performed predose, and 1 and 4 hours post-dose prior to any blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]). For subjects participating in PK analysis, an ECG is also to be performed 8 hours postdose.

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory. (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Study drug administration (using an alternate dosing schedule of 150 mg of KD019 on Monday, Wednesday, and Friday of each week)
- Collect blood samples from approximately 5 subjects for PK analyses (predose, 1, 2, 4, 8, and 24 hours postdose). (Subjects undergoing iothalamate testing will not undergo PK sampling.)
- Concomitant medications
- Adverse event assessment
- Dispense an adequate supply of study drug

9.4.2.2 Days 3, 5, and 8 (PK Subjects Only)

On Days 3, 5, and 8, the following procedures and evaluations will be performed for only those subjects undergoing PK sampling:

- Study drug administration
- Collect predose blood samples for PK analyses Concomitant medications

- Adverse event assessment

9.4.2.3 Day 12

At the Day 12 visit (± 1 day), the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose, and 1 and 4 hours postdose); perform ECG before any blood sample collection (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Iothalamate testing
  - In a subset of 3–7 subjects at selected sites, optional iothalamate testing may be performed by injection of iothalamate with serum samples obtained for iothalamate evaluation over 3 hours post iothalamate injection. Sites may use their site-specific protocol for testing.
  - Note: The second time point should be done on Day 12, 13, 14, or 15 and all study-related procedures required on Day 12 may be done at this visit.
- Collect blood samples from subjects undergoing PK analyses (predose, and 1, 2, 4, and 24 hours postdose). (Subjects undergoing iothalamate testing will not undergo PK sampling.) Also, collect PK sample if QTc(F) interval increases by > 60 msec above average baseline or to the level of ≥ 480 msec (see Section 11.3.3).
- Perform drug accountability and dispense adequate supply of study drug (if subject was not dispensed an adequate supply on Day 1)
- Study drug administration
- Concomitant medications
- Adverse event assessment

9.4.2.4 Day 26

At the Day 26 visit (± 1 day), the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements

- Supine 12-Lead ECG (to be performed predose); perform ECG before any blood sample collection (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Echocardiogram. Note that if pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Perform drug accountability and dispense adequate supply of study drug

9.5 For Subjects Enrolled in Phase 2a Portion of Study and Dosed on Mondays, and Thursdays

9.5.1 Screening Visit

At the screening visit, information will be collected and subjects will have clinical evaluations as follows:

- Informed consent
- Medical history and PKD history (including genotype if known)
- Complete physical examination, including height and weight
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, oral/tympanic temperature)
- Supine 12-Lead ECG (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]; perform ECG immediately prior to blood sample collection)

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory (hematology, coagulation, serum chemistry panel, and urinalysis)

- Ocular evaluation including evaluation of best corrected visual acuity, fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and OCT of the optic nerve head and macula
- HIV and Hepatitis B & C tests by central laboratory
- Peripheral blood smear
- Iothalamate testing
    - In a subset of 3–7 subjects at selected sites, optional iothalamate testing may be performed by injection of iothalamate with serum samples obtained for iothalamate evaluation over 3 hours post iothalamate injection. Sites may use their site-specific protocol for testing.
- Echocardiogram
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- MRI
- Concomitant medications
- Adverse event assessment

9.5.2 Early Treatment Period

9.5.2.1 Day 1

Results of clinical and laboratory evaluations, including ECGs, must be reviewed prior to dosing to confirm that the subject continues to meet eligibility criteria.

At the Day 1 Visit, the following procedures and evaluations will be performed:

- Limited physical examination, including weight (see Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements (predose and 1 and 4 hours postdose). For subjects participating in PK analysis, vital sign measurements also are to be performed 8 hours post-dose.
- Supine 12-Lead ECG (to be performed predose, and 1 and 4 hours postdose prior to any blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs]). For subjects participating in PK analysis, ECGs are also to be performed 8 hours post dose.

    Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory. (Need not be repeated if screening visit occurred within 4 days prior to Day 1 visit.)

- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Study drug administration
- Collect blood samples from approximately 5 subjects for PK analyses (predose, 1, 2, 4, 8, and 24 hours postdose). (Subjects undergoing iothalamate testing will not undergo PK sampling.)
- Concomitant medications
- Adverse event assessment
- Dispense up to a 3-month supply of study drug

9.5.2.2 Days 8 and 18 (PK Subjects Only)

On Days 8 and 18, the following procedures and evaluations will be performed only for those subjects undergoing PK sampling:

- Collect predose blood samples for PK analyses
- Study drug administration
- Concomitant medications
- Adverse event assessment

9.5.2.3 Day 11

At the Day 11 visit (± 1 day), the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12 Lead ECG (to be performed predose, prior to any blood sample collection) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]).

  Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Collect blood samples from subjects undergoing PK analyses (predose). Also collect PK sample if QTc(F) interval increases by > 60 msec above average baseline or to the level of ≥ 480 msec (see Section 11.3.3).
- Study drug administration
- Concomitant medications
- Adverse event assessment

9.5.2.4 Day 25

On Day 25, subjects are to return to the clinic and the following evaluations will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements (to be performed predose, and 1 and 4 hours postdose); for subjects participating in PK analysis, vital sign measurements also are to be performed 8 hours postdose.
- Supine 12-Lead ECG (to be performed predose, and 1 and 4 hours postdose); for subjects participating in PK analysis, an ECG is also to be performed 8 hours postdose. Perform ECG before any blood sample collection whenever possible (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
    - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Echocardiogram
    - Note: If pericardial effusion is noted on the echocardiogram, a follow-up echocardiogram should be performed within 1–3 months to monitor for progression
- Iothalamate testing
    - In a subset of 3–7 subjects at selected sites, optional iothalamate testing may be performed by injection of iothalamate with serum samples obtained for iothalamate evaluation over 3 hours post iothalamate injection. Sites may use their site-specific protocol for testing.
        - For those subjects undergoing iothalamate testing, Day 25 visit may be done on Days 22, 23, 24, or 25
- Collect blood samples from subjects undergoing PK analyses (predose, and 1, 2, 4, 8, and 24 hours postdose). (Subjects undergoing iothalamate testing will not undergo PK sampling.) Also, collect PK sample if QTc(F) interval increases by > 60 msec above average baseline or to the level of ≥ 480 msec (see Section 11.3.3).
- Study drug administration
- Concomitant medications
- Adverse event assessment
- Perform drug accountability and dispense adequate supply of study drug if appropriate

9.5.3 Monthly Follow-Up Treatment Period for Those Subjects Continuing on Study Drug – Both Phase 2a Dosing Schedules

9.5.3.1 Months 2–12

Subjects will return to the clinic monthly (every 28 ± 3 days) and the following procedures will be performed:

- Limited physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose prior to collection of any blood samples) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
  - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- Clinical laboratory tests by central laboratory
- Echocardiogram (to be obtained at Months 3 and 6, and every 6 months thereafter)
  - Note: If pericardial effusion is noted on the echocardiogram, a follow-up echocardiogram should be performed within 1–3 months to monitor for progression
- Pregnancy test (urine) for women of childbearing potential (to be performed at the Month 3 visit and every 3 months thereafter); if positive perform serum pregnancy test
- MRI (to be obtained at Month 6 and every 6 months thereafter)
- Perform drug accountability and dispense adequate supply of study drug
- Study drug administration
- Concomitant medications
- Adverse event assessment

9.6 Phase 1b and 2a Subjects Continuing KD019 beyond 12 Months

For subjects continuing to receive study drug beyond 12 months, the following safety assessments should be performed every 2 months (± 3 days):

- Limited physical examination, including weight (See Section 9 of protocol for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (to be performed predose prior to collection of any blood samples) (repeat 3 times consecutively within 30 minutes [must have an interval of at least 2 minutes between ECGs])

Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.

- Clinical laboratory tests by central laboratory
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Perform drug accountability and dispense adequate supply of study drug
- Study drug administration
- Concomitant medications
- Adverse event assessment

The following safety assessments should be performed <u>every 6 months</u>:

- Echocardiogram (for those subjects who have already had their Month 12 visit, this may be performed at Month 13 and then subsequent echocardiograms may be performed on the same schedule as the MRIs)

  Note: If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
- MRI

For Phase 1b subjects experiencing a <u>dose increase from 50 mg to 100 mg, now that the MTD for daily dosing has been established</u>: The study assessments in Section 9.6 (above) should be performed as follows:

- Days 1 and 14 of the first month, then monthly for a total of 6 months
- Every 2 months thereafter
  An echocardiogram and MRI should still be performed every 6 months

9.7 End-of-Treatment Visit (End-of-Study) – All Subjects

Thirty days (± 3 days) after the last dose of study drug, subjects are to return to the study site to complete all end-of-treatment assessments as follows:

- Complete physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements
- Supine 12-Lead ECG (prior to any blood sample collection; repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs])
- Clinical laboratory tests by central laboratory (hematology, coagulation, serum chemistry panel, and urinalysis)

- Ocular evaluation including evaluation of best corrected visual acuity, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, pils, and OCT of the optic nerve head and macula (to be performed at Months 3 and 6 and every 6 months thereafter).
- Echocardiogram (if not performed within 2 months of this visit). Note that if pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.
- MRI (if not performed within 3 months of this visit)
- Peripheral blood smear
- Pregnancy test (urine) for women of childbearing potential (if positive, perform serum pregnancy test)
- Concomitant medications
- Adverse event assessment
- Final return and accounting of study drug

9.8 Unscheduled/AE Resolution Visits: To Occur as Needed

If additional visits are needed (eg, for resolution of an AE), the following procedures and evaluations may be performed as needed:

- Complete physical examination, including weight (See Section 9 for a listing of systems to be examined/reviewed)
- Vital sign measurements (sitting blood pressure, pulse, respiratory rate, oral/tympanic temperature)
- Supine 12-Lead ECG (repeat 3 times consecutively within 30 minutes [must have an interval of at least 1-2 minutes between ECGs].
  - Note: If QTc(F) is > 60 msec above highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec, refer to Section 11.3.3. This should be done based upon the local site analysis.
- PK sampling (if appropriate; see Section 0 for additional information)
- Clinical laboratory tests (hematology, coagulation, serum chemistry panel, and urinalysis)
- Pregnancy test (urine) for women of childbearing potential (if positive perform serum pregnancy test)
- Adverse event assessment
- Concomitant medications
- Echocardiogram

9.9 Laboratory Assessments

A central laboratory will perform hematology, serum chemistry, coagulation, and urinalysis tests and results will be provided to the investigator. The peripheral blood smears will be analyzed to monitor for effect of study drug on bone marrow. Blood and urine samples for hematology, coagulation, serum chemistry, and urinalysis will be prepared using standard procedures. Laboratory panels are defined as listed in Table 9-1. At the investigator's discretion, any subset of the laboratory panels in Table 9-1 may be duplicated in local laboratories for an immediate medical assessment. However, inclusion and exclusion criteria as well as the final statistical analysis will be based on results from the central laboratory.

Table 9-1: Clinical Laboratory Panels

Hematology	Serum Chemistry	Urinalysis
• Red blood cell count • WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes) • hemoglobin • hematocrit • platelet count • mean corpuscular volume (MCV) • Mean corpuscular hemoglobin (MCH) • Mean corpuscular hemoglobin concentration (MCHC) • Peripheral blood smear[a]	• albumin • amylase • alkaline phosphatase • ALT • AST • bicarbonate • BUN • calcium • chloride • creatinine • CPK • lactate dehydrogenase • phosphorous • potassium • random glucose • sodium • total & direct bilirubin • total protein • magnesium • TSH[b]	• appearance • color • pH • specific gravity • ketones • leukocytes • protein • glucose • bilirubin • urobilinogen • occult blood (microscopic examination of sediment will be performed only if the results of the urinalysis dipstick evaluation are positive)

Coagulation	Other	
• PT • PTT • INR	• Creatinine clearance[c] • Cystatin C • Fasting triglycerides[d] • Lipase[e] • Amylase isoenzymes[f] • CPK isoenzymes[f]	• HIV and Hepatitis testing[g]

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; INR = international normalized ratio; MCHC = mean cell hemoglobin concentration; MCV = mean cell volume; PT = prothrombin time; PTT = partial thromboplastin time

a. To be collected prior to dosing at Screening and at the End-of-Study visit.
b. To be collected at Screening and every 3 months thereafter.
c. To be calculated using serum creatinine, serum cystatin-c (CKD-EPI$_{2012cys}$), and using both serum creatinine and cystatin-c (CKD-EPI$_{2012Scr-cys}$).
d. To be collected in the event that serum amylase increases to > 1.5 × ULN
e. To be collected at Screening and in the event of that serum amylase increases to > 1.5 × ULN
f. To be collected in the event that CPK increases to > 2.0 x ULN.
g. To be collected only at screening visit.

Abnormalities in clinical laboratory tests that lead to a change in subject management (eg, dose delay, requirement for additional medication or monitoring) are considered clinically significant for the purposes of this study, and will be recorded on the AE electronic case report form (eCRF) page. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated lab values) must be reported as an SAE (see Section 13.3.1).

9.10 Electrocardiogram Assessments

For subjects enrolled in the SILK cohort, ECGs are to be performed at Screening; predose, 1, 4 and 8 hours postdose on Days 1 and 14; predose on Days 7, 21, and 28; on Day 1 of Months 2 and beyond; and at the End-of-Study visit. Time-matched tesevatinib plasma concentrations will be collected at predose, 1, 4, and 8 hours postdose on Days 1 and 14; and predose on Days 7, 21, and 28.

For subjects enrolled into the Phase 1b and Phase 2a 50 mg daily portions of the study, ECGs are to be performed at Screening; predose and 1 and 4 hour postdose on Days 1 and 14; predose on Days 7, 21, and 28; on Day 1 of Months 2 and beyond; and at the End-of-Study visit.

For subjects enrolled into the Monday, Wednesday, Friday dosing schedule of the Phase 2a portion of the study, supine 12-Lead ECGs will be performed at Screening; predose, and 1 and 4 hours postdose on Days 1 and 12; predose on Day 26; and on Day 1 of Months 2 and beyond; and at End-of-Study visit

For subjects enrolled into the Monday, Thursday dosing schedule of the Phase 2a portion of the study, supine 12-Lead ECGs will be performed at Screening; predose, and 1 and 4 hours postdose on Days 1 and 25; predose on Day 11; and on Day 1 of Months 2 and beyond; and at End-of-Study visit.

- Note: An 8-hour postdose ECG should also be performed for those subjects in either dosing schedule of the Phase 2a undergoing PK sampling

When possible, ECGs are to be performed before any blood sample collection.

ECGs are to be repeated 3 times consecutively within 30 minutes (must have an interval of at least 1–2 minutes between ECGs).

During the study, all ECGs will be digitally analyzed by a validated ECG laboratory. This central vendor will place ECG machines at sites under contract with Kadmon. ECGs will be transmitted electronically to the central vendor for analysis. Reports, including clinical alerts resulting from the analysis of the ECGs, will be provided back to sites. Sites will be trained on the use of the ECG machines, and instructions for performing ECG assessments will be provided in the ECG manual.

The QT interval will be corrected using Fridericia's formula[1]:

$$QT_F = \frac{QT}{RR^{1/3}}$$

Refer to Appendix D for sample calculation.

Prior to enrollment, all subjects must demonstrate an average screening QTc(F) value of < 450 msec by central digital analysis. Immediate clinical management of subjects will initially be based on results of machine-read ECGs at the sites. However, the central digital analysis will prevail as it becomes available. In addition, the central digital analysis will be used for any AE and SAE documentation.

An increase in QTc(F) interval (by central digital analysis) to a value > 60 msec above baseline or to the level of ≥ 480 msec requires further monitoring and, after collection of a PK blood sample and discussion with the medical monitor on appropriate management, the subject may be dose reduced or removed from the study (see guidelines in Section 11.3.3).

Abnormalities in the ECG that lead to a change in subject management (eg, requirement for additional medication or monitoring) or result in clinical signs and symptoms are considered clinically significant for the purposes of this study and will be recorded on the AE eCRF. If ECG abnormalities meet criteria defining them as serious, they must be reported as SAE (see Section 13.3.1).

9.11 Echocardiogram Assessments

An echocardiogram will be performed at Screening, on Day 28 (Day 25 or 26 for Phase 2a subjects), at the Month 3 and 6 visits, and every 6 months thereafter and at the End-of-Study visit.

[1] Adapted from: Fridericia LS (1920). "The duration of systole in the electrocardiogram of normal subjects and of patients with heart disease." *Acta Medica Scandinavica* (53): 469–486.

The echocardiogram is to include measurement of ejection fraction and evaluation for pericardial effusion and cardiac valve function. If pericardial effusion is diagnosed via echocardiogram, subject should be rechecked within 1–3 months to monitor for progression.

9.12 Ocular Evaluations

Ocular evaluations will be performed on each enrolled subject. Briefly, every 4 weeks, subjects will be asked if they have experienced any changes in vision, changes in color vision, or new loss of vision in any area. Additionally, at Screening, subjects newly enrolled into the study will have an evaluation of best corrected visual acuity and will be evaluated with fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, and optical coherence tomography (OCT) of the optic nerve head and macula. All ocular assessments should also be conducted at Months 3, 6, 9, 12, 18 and 24 of the study. Subjects enrolled into the study prior to the requirement for these ocular tests will have the same ocular assessments performed at their next regularly scheduled study visit, and then will have the same ocular assessments performed when they reach any assessment times that they have not already past in the study (Months 3,6, 9, 12, 18, and 24).

9.13 Pharmacokinetic Assessments

During the Phase 1b and Phase 2a 50 mg daily portions of the study, a blood sample will be collected predose and 1, 2, 4, 8, and 24 hours postdose for PK analyses on Day 1; predose and 1, 2, 4, and 24 hours postdose on Day 14; and predose on Days 7, 21, and 28. PK samples will be drawn predose at every monthly visit thereafter (up to and including the Month 6 visit) for subjects who continue dosing.

In the Phase 2a portion of the study, 70 subjects (5 in each alternative dosing schedule and 15 subjects in the 50 mg daily dosing schedule, and 50 subjects in the SILK cohort) will have blood samples drawn for PK analyses.

For subjects receiving 150 mg of KD019 on Monday, Wednesday, and Friday: Samples will be collected on Study Day 1 (predose, 1, 2, 4, 8, and 24 hours postdose), predose on Days 3, 5, and 8, and on Day 12 (predose, 1, 2, 4, and 24 hours postdose).

For subjects receiving 150 mg of KD019 on Monday and Thursday: Samples will be collected on Study Day 1 (predose, and 1, 2, 4, 8, and 24 hours postdose); predose on Days

8, 11, and 18; and on Day 25 (predose, and 1, 2, 4, 8, and 24 hours postdose), predose at every monthly visit thereafter (up to and including the Month 6 visit)

For subjects receiving 50 mg of KD019 daily: Samples will be collected on Study Day 1 (predose, 1, 2, 4, 8, and 24 hours postdose), Day 14 (predose, 1, 2, 4, and 24 hours postdose), and predose on Days 7, 21, and 28. Additional samples will be collected predose at every monthly visit thereafter up to and including the Month 6 visit for those subjects who continue treatment (Follow-Up Treatment Period).

For subjects receiving 50 mg of tesevatinib daily (the SILK cohort): Samples will be collected on Study Day 1 (predose, 1, 2, 4, and 8 hours postdose), Day 14 (predose, 1, 2, 4, and 8 hours postdose), and predose on Days 7, 21, and 28. Additional samples will be collected predose at every monthly visit thereafter up to and including the Month 6 visit.

All subjects in the SILK cohort will have weekly blood draws during the Drug Holiday period and during the 4 weeks immediately following the Drug Holiday period. These samples will be collected and analyzed for serum creatinine and cystatin C and plasma tesevatinib levels.

In addition, a PK sample should be drawn any time the QTc(F) increases to > 60 msec above the highest average predose reading (average of baseline and screening) or to the level of ≥ 480 msec (based on the local ECG read).

Tesevatinib concentration measurements will be conducted in all plasma samples collected under this protocol. Efforts will be made to identify the specific structure of major tesevatinib metabolites present in all plasma samples collected from 1–24 hours after dosing on Days 1 and 14 of the Phase 1b and Phase 2a 50 mg daily portions and on Days 1, 12, and 25 of the Phase 2a portion of the study.

Plasma samples will be managed and stored by a central vendor. Detailed instructions for sample collection and preparation will be provided in a separate laboratory manual.

9.14 Magnetic Resonance Imaging for Exploratory Efficacy Assessments

Magnetic resonance imaging (MRI) measurements will be used to explore the efficacy of tesevatinib. Kidney volume will be determined by MRI at Screening (baseline measurement), at the Month 6 visit, and every 6 months thereafter.

The volumes of individual kidneys should be measured in T_1-weighted images with use of a stereologic method and calculated from the set of contiguous images by summing the products of the area measurements and slice thickness. htTKV is calculated using total kidney volume obtained from MRI divided by height in meters.

9.15 Iothalamate Testing

In the Phase 2a portion of the study, optional iothalamate testing of renal clearance will be conducted at selected sites in 3–7 subjects at Screening. A second test is to be performed as noted in Table 4-2 (Monday, Wednesday, Friday dosing) and Table 4-4 (Monday and Thursday dosing). Based upon the results of testing, a third timepoint may be performed within the first 2 months of study drug dosing and after consultation with the medical monitor. Sites may use their site-specific protocol for testing.

Plasma clearance of iothalamate will be measured after IV or SC injection of iothalamate. Iothalamate is a contrast agent widely utilized in renal clearance testing because, unlike creatinine, it is filtered at the glomerulus and not secreted in the proximal tubule. Testing is performed by injection of iothalamate with serum samples obtained for iothalamate evaluation over 3 hours post iothalamate injection. Thus, iothalamate renal clearance testing will provide an independent method for verification of renal function before and after tesevatinib administration.

10 REMOVING SUBJECTS FROM STUDY

Every reasonable effort will be made to keep the subject in the study; however, in the event that a subject is withdrawn from the study, every effort will be made by the investigator to complete and report the reasons for withdrawal as thoroughly as possible. The reason for termination must be clearly documented on the appropriate page of the eCRF. Study withdrawal should include the final assessments, as required by the protocol and every effort should be made to perform the study follow-up procedures (eg, laboratory tests, physical examination including an evaluation of toxicity/adverse events). Refer to Table 4-1 through Table 4-4, Study Assessments.

A termination eCRF must be completed for all enrolled subjects.

10.1 Subject Withdrawal (Stopping Rules)

A subject's participation in the study may be prematurely discontinued for any of the following reasons:

1. Subject self-withdrawal.
2. Request by a regulatory agency (eg, Institutional Review Board).
3. Safety reasons, eg, adverse event including, but is not limited to, symptomatic pericardial effusion or cardiac tamponade.
4. Subject experiences generalized impairment or mental incompetence that would result in the subject's inability to continue in the study.
5. If, in the investigator's medical judgment, further participation would be injurious to the health and wellbeing of the subject, or is not in the best interest of the subject.
6. Administrative reasons, such as subject non-compliance or protocol violation.
7. Pregnancy
8. An intercurrent event preventing the administration of tesevatinib for more than 28 days for those continuing on study after the initial 28-day treatment period (unless otherwise specified in the protocol).

Subjects who are withdrawn from the study due to toxicity are to be followed until there is either:

- Resolution or stabilization to baseline
- The subject is lost to follow-up
- The event is otherwise explained

If there is an ongoing toxicity associated with tesevatinib, subjects must be followed with appropriate medical management until resolution or stabilization.

A reasonable effort should be made to contact any subject who is lost to follow-up during the course of the study in order to complete assessments and retrieve any outstanding data. If a subject is unreachable by telephone after 3 attempts, the minimum of a registered letter should be sent requesting that the subject make contact with the investigator.

Once a subject discontinues from the study for any reason, every effort will be made to collect all clinical and laboratory data as scheduled for the End-of-Treatment visit (see Section 9.7).

10.2 Study Discontinuation

Kadmon Corporation has the right to terminate or to stop the study at any time. Reasons for study discontinuation may include, but are not limited to the following:

- The incidence or severity of AEs in this or other studies evaluating the drug indicates a potential health hazard to subjects.
- Subject enrollment is unsatisfactory.
- Drug supply issues.
- Data recording is inaccurate or incomplete.
- Excessive subject self-withdrawal.
- Significant protocol deviations (eg, violation of eligibility criteria, dosing errors, missing data for study endpoint analysis).

10.3 Replacements

During the Phase 1b portion of the study, if any subject does not complete 28 days of treatment (excluding discontinuation or decrease in dose due to an AE), they will be replaced. A replacement subject will be obtained using the original eligibility criteria in the same dose cohort. Subjects discontinued from the Phase 2a portion of the study will not be replaced.

The maximum number of replacement subjects will be 6 subjects.

11 STUDY DRUG

Tesevatinib will be provided in 50, 100, and 150 mg tablets. Kadmon will provide each investigator with adequate supplies of tesevatinib. Study drug must be stored at a controlled room temperature of 20°-25°C (66°-77°F). Brief excursions are permitted between 15°C and 30°C (59°F and 86°F). Drug must be inventoried according to applicable regulations.

Subjects will be provided with an adequate supply of study drug and instructions for taking the study drug at home. Unused drug must be returned to the study site at each visit for accounting and reconciliation. Tesevatinib tablets are white to off-white round tablets that contain 50% (w/w) API in the current lactose-based immediate release (IR) formulation. Tesevatinib 50-, 100-, and 150-mg tablets are packaged in 30-cc high-density polyethylene (HDPE) bottles capped with 28-mm, childproof caps. The following information will be printed on the label for clinical lots of KD019:

KD019 50-mg Tablets – 32 count
Lot: xxxxx.xxx
Direction: Take as directed by physician.
Store at controlled room temperature of 20°-25°C (66°-77°F). Brief excursions permitted between 15°C and 30°C (59°F and 86°F).
Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
Caution: New Drug – Limited by Federal Law to Investigational Use 21CFR312.6 (a).
Keep out of the reach of children and pets.
Kadmon Corporation, LLC New York, NY 10016 USA

KD019 Tablets 100-mg – 32 count
Lot: xxxxx.xxx
Direction: Take as directed by physician.
Store at controlled room temperature of 20°-25°C (66°-77°F). Brief excursions permitted between 15°C and 30°C (59°F and 86°F).
Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
Caution: New Drug – Limited by Federal Law to Investigational Use 21CFR312.6 (a).
Keep out of the reach of children and pets.
Kadmon Corporation, LLC New York, NY 10016 USA

KD019 Tablets 150-mg – 32 count
Lot: xxxxx.xxx
Direction: Take as directed by physician.
Store at controlled room temperature of 20°-25°C (66°-77°F). Brief excursions permitted between 15°C and 30°C (59°F and 86°F).
Caution: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed.
Caution: New Drug – Limited by Federal Law to Investigational Use 21CFR312.6 (a).
Keep out of the reach of children and pets.
Kadmon Corporation, LLC New York, NY 10016 USA

11.1 Tesevatinib Administration

In the Phase 1b portion of the study, tesevatinib will be administered orally at doses of 50, 100, and/or 150 mg once daily. In the Phase 2a portion of the study, tesevatinib will be administered on alternative schedules of 150 mg on Monday, Wednesday, and Friday of each week, 150 mg on Monday and Thursday of each week, or 50 mg once daily. If subjects are able to be seen in clinic on the appropriate protocol specified study day, the schedule could also be Tuesday and Friday or Wednesday and Saturday. However, the same schedule must be adhered to throughout the study.

Study drug may be taken with or without food at approximately the same time every morning. Subjects should drink a full glass of water (approximately 8 ounces [240 mL]) immediately after study drug administration. Grapefruit and similar (pomelo fruit, Seville, etc.) products should be avoided for the duration of study treatment.

Subjects must be instructed not to make up missed doses unless the missed dose can be taken within 12 hours of the normal dosing time. Subjects should not re-take study drug doses in the event of vomiting.

Subjects will receive study drug for 28 days after the initiation of treatment (this will be 25 or 26 days for subjects on the Monday/Thursday and Monday/Wednesday/Friday cohorts of the Phase 2a portion of the study). After the initial 28-day safety and tolerability assessment period, subjects will, at the investigator's discretion, continue to receive study drug for a total of 24 months from the initiation of treatment or until the development of unacceptable toxicity, noncompliance, or withdrawal of consent by the subject, or investigator decision.

In order to evaluate reversibility of creatinine increases, subjects on the Phase 1b portion of the study will have study drug held for a one-time drug holiday of at least 14 and up to 28 days with

creatinine and cystatin C measurements before and immediately after the drug holiday, as well as a predose PK sample prior to restarting study drug. This can be done 14 days after dose escalation to the MTD or any time after 6 months of KD019 administration. A drug holiday has also been added to the SILK cohort.

All subjects also will be followed for a period of 30 days following their last dose of tesevatinib.

11.2 Dose Escalation and Entry of Subjects into the Next Cohort

In the Phase 1b portion of the study, cohorts will be filled sequentially. Once assigned to a cohort, each subject will continue to be treated at the same dose level and schedule throughout the course of the study. For subjects dosed with 50 mg/day: If the 100-mg cohort has been evaluated and the determination made that 100 mg/day is not the MTD, and study enrollment is opened at the 150 mg dose, then subjects initially treated in the 50 mg dose cohort will have the option of increasing their dose of tesevatinib to 100 mg/day after they have received a minimum of 6 months of treatment at the 50 mg/day dose. The participating study centers will be notified (eg, phone, e-mail, telefax) and confirmed in writing when accrual to a cohort has been closed.

Accrual to the next cohort will not occur until the 28-day data from a previous cohort have been received and all safety data have been reviewed.

At the end of each dosing cohort, a Data Safety Committee including an independent safety monitor with significant clinical expertise in polycystic kidney disease will review all safety data (PK, safety labs, ECGs, echocardiogram, and AEs). An independent cardiologist will review all ECGs and echocardiograms. Once all data has been reviewed it will be determined whether dose escalation may occur. Dose escalation to the next higher dose will not begin until the safety data from the preceding dose cohort has been evaluated and deemed acceptable. Specifically, the decision to progress to the next higher dose will be made after the safety data through a minimum of 28 days of follow-up are reviewed for at least 8 subjects in the preceding dose cohort and it is determined that it is safe to proceed to the next dose level.

Dose escalation to the next planned tesevatinib dose will be reviewed and dose adjustments may be made if any of the following safety criteria are met:

- ≥ 25% of subjects in a cohort experience a severe (or higher) **related** adverse event in the same organ or body system

- Any other **related** adverse event occurs in a subject that is deemed by the investigator to pose an unacceptable risk to other participants in the study such as symptoms of cardiac tamponade

After the MTD for daily dosing was established, 24 additional subjects were enrolled in the Phase 2a portion of the study and treated at 150 mg/day using alternate schedules of tesevatinib administration. As the known toxicities of tesevatinib, including diarrhea and rash, may not be tolerable with daily dosing when used long-term in this subject population, alternative dosing schedules of either Monday, Wednesday, and Friday of each week or Monday and Thursday of each week were evaluated during this portion of the study. Additionally, as the MTD for daily dosing has been determined to be 100 mg/day, subjects active in the Phase 1b portion had their dose either increased or decreased to this dose. These subjects have continued on daily dosing in order to evaluate long-term tolerability of the daily dosing regimen.

Drug holiday may start 14 days after dose escalation to the MTD or any time after 6 months of tesevatinib administration.

11.3 Warnings, Precautions, and Management

Adverse events that have been associated with tesevatinib include the following: diarrhea, skin rash, QTc(F) prolongation, hepatotoxicity, and pulmonary toxicity. Study drug may be held for up to 28 days at the discretion of the investigator (unless otherwise specified below), except during the first 28 days of treatment in the Phase 1b portion of the study.

11.3.1 Diarrhea

Diarrhea should be managed according to accepted practice (eg, with loperamide). Subjects with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require interruption of study drug until resolution to ≤ mild in intensity. If subjects are in the monthly treatment period, drug may be held for up to 28 days. If severe diarrhea occurs during the initial 28-day treatment period on the Phase 1b portion of the study, subjects must be discontinued from the study. In the event of severe or persistent diarrhea, nausea, anorexia, or vomiting associated with dehydration, study drug should be discontinued, and appropriate measures should be taken to rehydrate the subject intensively via intravenous administrations. Subjects should be advised to contact the investigator immediately if they develop significant diarrhea; should this occur, an electrolyte panel, including magnesium and potassium, and ECG should be performed.

If unacceptable diarrhea recurs on reintroduction of tesevatinib at the same dose, then dose reduction of tesevatinib should be discussed with the medical monitor.

11.3.2 Skin Rash

Skin rash should be managed according to locally accepted clinical recommendations. Study drug may be held up to 28 days at the discretion of the investigator and after discussion with the medical monitor. The following guidelines may be considered.

11.3.2.1 Suggestions for Rash Management

[Lacouture 2011, Kiyohara 2013, http://www.psoriasis.org]

Papulopustular (acneiform) rash:

- Most common rash seen with EGFR inhibitors
- Typically seen in the first few weeks of treatment
- Usually peaks at Weeks 4–6
- Then will decrease in severity at Weeks 6–8
- Post-inflammatory skin changes can last for months, so prevention and reactive treatment are important

Suggestions for preventative treatment:

- Subject education prior to starting treatment on what to expect
- Gentle cleansing of skin using mild soap products
- Use of moisturizer twice daily making sure to include hands, feet and nails
- Avoid sun when possible and use of sunscreen SPF 30 or higher (preferably titanium dioxide or zinc oxide)
- Subjects should be advised to use UVA ocular protection (ie, sunglasses with UVA filtering) when outside
- Hypoallergenic makeup when possible

Suggestions for treatment once a rash appears (see Appendix E for steroid potency chart):

- Ongoing use of treatments from preventative treatments above
- Mild (<10 % BSA involved, without pruritus or tenderness)
  - Topical steroids (refer to Appendix E for a steroid potency chart that categorizes brand-name topical steroid medications)
    - For face use medium potency
    - For body use strong potency
    - **Note: As soon as rash improves the lowest strength steroid that controls rash should be used, especially on the face**
- Moderate (10%–30% BSA involved, ± pruritus/tenderness; limiting instrumental ADLs and causing psychosocial impact)
  - Topical steroids
    - For face use strong potency
    - For body use very strong potency
    - **Note: As soon as rash improves the lowest strength steroid that controls rash should be used, especially on the face**
  - Systemic treatment
    - Doxycycline 100 mg BID (less renal toxic than minocycline, but can cause photosensitivity)
- Severe (> 30% BSA involved, limiting ADLs)
  - Refer to dermatology
  - Topical steroids
    - All areas very strong potency
    - **Note: As soon as rash improves the lowest strength steroid that controls rash should be used, especially on the face**
  - Systemic treatment
    - Doxycycline 100 mg BID
    - Oral steroids: prednisolone 10 mg QD for 1 week or equivalent

Suggestions for once a rash reappears:

- Over the course of treatment rash may come and go
  - Hydrocortisone 1% cream with moisturizer and sunscreen twice daily, in combination with doxycycline 100 mg BID
  - May need to follow guidelines above if rash worsens

If unacceptable rash recurs on reintroduction of tesevatinib at the same dose, then dose reduction of tesevatinib should be discussed with the medical monitor.

11.3.3 QT Interval Prolongation

Acquired long QT syndrome can lead to life-threatening ventricular arrhythmias, particularly torsades de pointes. Risk factors for occurrence of arrhythmia include hypokalemia, hypomagnesemia, bradycardia, and concurrent use of multiple medications that prolong the QTc(F) interval. In vivo observations of QTc(F) prolongation in association with use of tesevatinib have been observed, including severe QTc(F) prolongation. However, the lack of a clearly discernible pattern to such occurrence makes prediction of individual subject risk difficult. Therefore, the following are recommended:

- Tesevatinib should be administered to subjects who have normal serum potassium and serum magnesium levels.
- Tesevatinib should not be administered to subjects with pathologic bradycardia.
- Medications with potential for QTc(F) prolongation should not be used concurrently or started within 24 hours of tesevatinib administration.

Subjects should be carefully monitored for symptoms of arrhythmia (ie, dyspnea, chest pain or tightness, palpitations, dizziness) and for episodes of syncope. An ECG should be obtained if these symptoms occur. In addition, serum potassium and magnesium must be maintained within the normal range (Strevel et al, 2007) and may require additional monitoring or adjustment if subjects develop diarrhea.

11.3.3.1 Response to QTc(F) Interval Prolongation

The following guidelines should be used in the management of QTc(F) prolongation. Subjects will have ECGs performed at times designated by the protocol (ECGs will be repeated 3 times consecutively within 30 minutes [must have an interval of at least 1–2 minutes between ECGs]). If the average QTc(F) interval increases to > 60 msec above the highest average predose value (average of Day 1 predose and screening values) or to the level of ≥ 480 msec according to local site analysis:

- Hold study drug until central read is confirmed.

- Check electrolytes, especially magnesium and potassium; correct abnormalities as clinically indicated.
- Obtain blood sample for PK analysis.
- Manage as clinically indicated with cardiology consultation as needed.
- Contact medical monitor to discuss additional monitoring.

If results are confirmed by the central reader, the subject may be removed from the study after discussion with the medical monitor. If the subject continues in the study, discuss with the medical monitor appropriate management (including possibility of dose reduction) and ECG follow-up.

11.3.4 Elevated Amylase

If subjects develop an elevated serum amylase during the study that is >1.5 ×ULN, then additional evaluations should be performed. These should include evaluating serum lipase, amylase isoenzymes, and fasting triglycerides as well as obtaining history regarding symptoms of pancreatitis, symptoms of dry mouth, and use of alcohol. The subject should have a drug holiday for 28 days, with amylase measured at the end of the drug holiday. If the amylase is within normal range after the end of the drug holiday, tesevatinib may be restarted at a reduced dose, and amylase measured approximately 14 days later, and then at the start of each cycle of tesevatinib administration. If results continue to be abnormal, the subject will be removed from study. If an elevated serum amylase that is >1.5 ×ULN occurs a second time, the subject will be removed from the study.

11.3.5 Elevated Creatinine Phosphokinase

If subjects develop an elevated serum CPK during the study that is >2.0 ×ULN, additional evaluations should be performed. These should include evaluating serum CPK isoenzymes as well as obtaining history regarding muscle-related symptoms or strenuous or prolonged exercise.

11.3.6 Pulmonary Toxicity

If subjects experience an acute onset of new and/or progressive, unexplained pulmonary symptoms such as dyspnea, cough, and fever, study drug should be held while subjects are

evaluated. If interstitial lung disease (ILD) is diagnosed, study drug should be discontinued and treatment administered as necessary.

11.3.7 Hepatotoxicity

Rare cases of hepatic failure have been reported. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Liver function test abnormalities (including elevated ALT, AST, and bilirubin) have been observed in clinical studies with tesevatinib. Interruption of study drug should be considered in subjects developing liver function abnormality ≥ 3x ULN

Dose Modifications for Hyperbilirubinemia

	> ULN 2.5 × ULN	**2.5– <3 × ULN**	**>3 × ULN**	
KD019	Treat at same dose level	1st Occurrence: Hold dose; reduce 1 dose level when recovered to mild intensity.	1st Occurrence: Off Study	
		2nd Occurrence: Off study		

Dose Modifications for Transaminitis (AST/ALT)

	> ULN – 2.5 × ULN	**2.5– <3 × ULN**	**>3 × ULN**	
KD019	Treat at same dose level	1st Occurrence: Hold dose; reduce 1 dose level when recovered or reduced to mild intensity.	1st Occurrence: Hold dose and discuss management with Medical Monitor	
		2nd Occurrence: Hold dose and discuss management with Medical Monitor	2nd Occurrence: Off study	

11.3.8 Pericardial Effusion

Pericardial effusions have been seen in oncology studies with tesevatinib. In addition, 1 subject with ADPKD receiving 50 mg tesevatinib daily developed a trace pericardial effusion. The

following guidelines should be followed in the event that a subject develops a pericardial effusion while receiving tesevatinib:

For an asymptomatic pericardial effusion that is at least moderate in size, a follow-up echocardiogram should be performed within 1–3 months to monitor for progression. Discuss results of the additional echocardiogram with the medical monitor to determine subject management.

Subjects should be monitored for signs and symptoms of cardiac tamponade. In addition to the monthly to bimonthly physical exam of blood pressure, pulse, respiration, weight, heart, and lung, physical exam should also asses for tachycardia, dyspnea, neck vein distension, and edema.

11.3.9 Adrenal Insufficiency

One case of adrenal insufficiency has been reported in an oncology subject receiving tesevatinib. Subjects should be monitored for signs or symptoms of adrenal insufficiency and the medical monitor immediately notified if symptoms are observed.

11.4 Study Drug Accountability and Subject Treatment Compliance

Drug accountability and subject treatment compliance will be assessed using drug dispensing and return records. The principal investigator is responsible for ensuring adequate accountability of all used and unused study drug. While the principal investigator may delegate components of drug accountability tasks to documented designee(s) (eg, pharmacist), the ultimate responsibility for drug control and accountability resides with the investigator. This includes acknowledgment of receipt of each shipment of study drug (quantity and condition) and the maintenance of subject dispensing records and returned study product documentation. Dispensing records will document quantities received from Kadmon and quantities dispensed to subjects, including lot number, date dispensed, subject identification number, subject initials, and the initials of the person dispensing study drug. Reasons for deviation from the expected dispensing regimen also must be recorded.

At study initiation, the study monitor will evaluate and obtain a copy of each site's written standard operating procedure for study drug disposal/destruction in order to ensure that it complies with the requirements of Kadmon.

At the end of the study, following final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy any remaining unused study drug supplies, including empty containers, according to institutional procedures for destruction, reviewed and approved by Kadmon prior to material destruction. If the site cannot meet the requirements of Kadmon for disposal, arrangements will be made between the site and Kadmon or its representative, for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

12 CONCOMITANT MEDICATION AND TREATMENT

If the subject must use a concomitant medication during the study, it is the responsibility of the principal investigator to ensure that details regarding the medication are recorded on the eCRF.

Subjects should avoid ingesting grapefruit, pomelo or Seville fruit (and juice) with tesevatinib or at any time during the study. Subjects should not take medications that are associated with a risk of QTc(F) interval prolongation and/or torsades de pointes. Additionally, subjects are not permitted to take concomitant medications that inhibit (eg, ketoconazole, itraconazole, erythromycin, clarithromycin) or induce (eg, dexamethasone, phenytoin, carbamazepine, rifampicin, or phenobarbital) the CYP3A4 isozyme. Tesevatinib is also highly protein bound, and other drugs that are also highly protein bound with the exception of warfarin (eg, diazepam, furosemide, dicloxacillin, propranolol, and phenytoin) should be avoided.

Antiemetics and antidiarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the investigator, treatment of symptoms with antiemetic and antidiarrheal medications may be undertaken per standard clinical practice.

Since tesevatinib is a potent inhibitor of MATE transporter proteins, increased levels of concomitant medications that are secreted by the kidney proximal tubule cells into the renal tubule by MATE transporter proteins may occur. Thus, subjects taking cephalexin, cimetidine, dofetilide, fexofenadine, metformin, procainamide, and pyrimethamine should be monitored carefully.

12.1 Additional Therapy

A subject should not receive additional therapeutic treatment during the study period without the approval of the sponsor's medical monitor.

12.2 Interaction of Tesevatinib with Other Medications

12.2.1 Tesevatinib

Microsomal oxidation of tesevatinib involves CYP3A4; the percentage conversion of tesevatinib in human microsomes was low. This suggests a low potential for other drugs to significantly affect the biotransformation of tesevatinib in humans through interaction with CYP-mediated metabolic pathways.

P-glycoprotein (P-gp) is extensively expressed in multiple tissues and is involved in the transport of a vast variety of biological molecules. It is not possible to screen for all drugs possibly influenced by p-glycoprotein but will monitor the main drugs such as colchicine, verapamil, tamoxifen, cyclosporine, and digoxin.

12.2.2 Management of Subjects Requiring Concomitant Medications Associated with QT Interval Prolongation

Tesevatinib has been associated with prolongation of the QT interval. Subjects requiring treatment with drugs known to be associated with torsades de pointes or significant QT interval prolongation may not be enrolled into this study. This includes Class IA antiarrhythmics (eg, quinidine, procainamide); Class III antiarrhythmics (eg, amiodarone, sotalol, dofetilide); phenothiazine anti-psychotics: (eg, chlorpromazine, mesoridazine, pimozide, thioridazine); quinolone antibiotics: (eg, gatifloxacin, moxifloxacin, sparfloxacin); macrolide antibiotics (eg, erythromycin, clarithromycin, and troleandomycin) and other drugs that have a contraindication or boxed warning regarding QT prolongation in the prescribing information.

Appendix B, Concomitant Medications Associated with a Risk of QTc(F) Interval Prolongation and/or Torsades de Pointes, contains a partial list of drugs associated with a risk of QT interval prolongation and/or torsades de pointes.

Drugs associated with QT interval prolongation should be avoided in subjects receiving study drug. Should a subject develop a condition for which a medication known to affect QT interval is indicated, consideration should be given to the additive risk of QT interval prolongation versus the potential benefit of treatment with the required medication and/or study drug. Contact the medical monitor prior to the administration of the concomitant medication.

During the follow-up period, subjects who require short-term (2 to 3 weeks, not to exceed 21 days) treatment with a concomitant medication associated with QT interval prolongation should have the study drug held until the concomitant treatment course is complete. The decision about whether the subject can continue on study following this interruption will be determined by the medical monitor. If the subject restarts study drug after discussion with the medical monitor, an ECG will be performed prior to restarting study drug.

13 SAFETY

13.1 Safety Parameters

The 5-point Clinical Symptom and Adverse Event Grading Scale will be used for grading toxicities (see Appendix C). Subjects will be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital sign measurements, and laboratory data. Safety parameters to be measured/assessed include eligibility assessment, medical history, vital sign measurements, physical examinations, concomitant medications, hematology, serum chemistries, coagulation profiles, peripheral blood smears, renal function (creatinine clearance and cystatin C), urinalysis, pregnancy testing, ECGs, and echocardiograms.

13.2 Adverse Event Definition

An adverse event (AE) is defined as any unintended or undesirable, noxious, or pathological change, compared to pre-existing conditions, experienced by a subject during a clinical study or the follow-up period, regardless of relationship to study drug. Adverse events include:

- Suspected adverse drug reactions
- Reactions from drug overdose, abuse, withdrawal, sensitivity, or toxicity
- Significant changes or abnormalities, when compared to baseline, in structure (sign), function (symptom), clinical laboratory results, ECG results, or physiological testing. This includes any worsening of a pre-existing condition temporally associated with the use of study drug
- Pre- or post-treatment complications that occur as a result of protocol-mandated procedures
- Pre-existing events, that increase in intensity/severity or change in nature
- Other medical events, regardless of their relationship to the study drug, such as injury, surgery, accidents, extensions of symptoms, or apparently unrelated illnesses

For the purpose of data collection, all untoward events that occur after informed consent through 30 days after the last dose of tesevatinib must be recorded on eCRFs by the investigational site. This requirement includes AEs from unscheduled as well as scheduled visits.

An AE does not include:

- Medical or surgical procedures (eg, surgery, endoscopy, tooth extraction, transfusion); when the condition that leads to the procedure is an adverse event.
- Pre-existing diseases, or conditions or laboratory abnormalities present or detected prior to the screening visit, those do not worsen.
- Situations where an untoward medical occurrence has not occurred (eg, hospitalization for elective surgery, social, and/or convenience admissions).
- Overdose of either KD019 or a concomitant medication without any signs or symptoms, unless the subject is hospitalized for observation.

13.3 Evaluating Adverse Events

The investigator will determine the seriousness, intensity (severity), and causality (relationship) of an AE associated with the use of the study drug (ie, events where there is a reasonable possibility that the event may have been caused by the study drug) based on the following definitions:

13.3.1 Serious Adverse Events

(Notify sponsor or designee within 24 hours of first awareness; document on eCRF)

The SAE definition and reporting requirements are in accordance with the ICH Guideline for Clinical Safety Data Management, Definitions, and Standards for Expedited Reporting, Topic E2A.

An SAE is any untoward medical occurrence that at any dose results in any of the following outcomes, regardless of relationship to study drug:

- **Death:** Any death that occurs while the subject is "on study" as well as any death that occurs within 30 days after the last dose of study drug.

  Note: Death is an outcome of an AE, and not an AE in itself. The event(s) that caused death (eg, illness, accident) constitutes the SAE.

- **Life threatening:** Any adverse drug event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred (ie, this does not include a reaction that had it occurred in a more severe form, might have caused death).

- **Inpatient hospitalization or prolongation of existing hospitalization:** any AE requiring in-patient hospitalization. A visit to the emergency room or hospital clinic would not be considered in-patient hospitalization; however, it could be considered serious if medical intervention was necessary in order to prevent a serious outcome.

  "In-patient hospitalization" means the subject has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation to and care within an emergency department.

  In the absence of an AE, the investigator should not report hospitalization or prolongation of hospitalization. Examples are the following:

  - Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol.
  - Hospitalization or prolongation of hospitalization is part of routine procedure followed by study center.
  - Hospitalization for survey visits or annual physicals.

  In addition, a hospitalization planned before the start of the study for a pre-existing condition which has not worsened would not be considered an SAE. Complications that occur during hospitalizations are AEs. If a complication prolongs hospitalization, it is an SAE.

- **Persistent or significant disability/ incapacity:** Any substantial disruption of a person's ability to conduct normal life functions.
- **Congenital anomaly/birth defect**
- **Important medical event:** Any adverse event that may not result in death, that may not be immediately life threatening, or require hospitalization may be considered a SAE when, based upon appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent an SAE outcome.

13.3.2 Unexpected Adverse Events

(Notify sponsor or designee by the next business day; document on eCRF)

An unexpected AE is any adverse drug event that is not identified in nature, severity, or frequency in the current protocol, IB or in other reports or information provided to the investigator. This refers to any AE that has not been previously observed, (eg, included in the IB), rather than from the perspective of such an event not being anticipated from the pharmacological properties of the product. For example: hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator brochure only referred to elevated hepatic enzymes or hepatitis. Unexpected adverse events may or may not be serious.

13.3.3 Non-Serious Adverse Events

(Document on eCRF)

All other AEs, not fulfilling the previous definitions, are classified as non-serious.

13.3.4 Protocol-Related Adverse Events

AEs that are not related to KD019 may be considered by the investigator or the medical monitor to be related to the conduct of the clinical study. That is, the event may be related to the fact that a subject is participating in the study. For example, a protocol-related AE may be an event that occurs during a washout period or that is related to a procedure required by the protocol.

13.3.5 Relationship/Causality to Study Drug

The investigator will assess the relationship of the event to study drug as (1) not related; (2) unlikely related; (3) possibly related; (4) probably related; or (5) definitely related.

In assigning the causal relationship, the following should also be considered:

- Temporal relationship – Did the effect occur in a reasonable temporal association with administration of KD019?
- Pattern consistent with known drug effect – Is the effect an expected consequence of KD019 administration based upon the known biologic effects, toxicologic data, and prior experience with KD019 or closely related drugs?
- Other potential etiologies – Is there another more likely cause of the adverse effect?

- Challenge – Did the adverse event recur or worsen upon re-exposure to KD019 or upon an increase in the dose? (Note: Intentional re-challenge for the purpose of assessing causal relationship of an adverse event to the study drug should NOT be performed.)
- De-challenge – Did the adverse event resolve or diminish upon cessation of KD019 treatment or reduction in dose?

13.3.6 Recording Adverse Events

All AEs (including SAEs) are to be accurately recorded on the Adverse Event page of the subject's eCRF and not as remarks elsewhere on the eCRF. The following aspects of the AE must be recorded:

- The onset date and time (when applicable) of the AE
- Intensity/severity (per the Clinical Symptom and Adverse Event Grading Scale, Appendix C)
- The resolution date and time of the AE, when applicable
- A description of the AE
- Any factors considered as possibly promoting the occurrence of the AE
- Concomitant medication/therapy including name, dose, dose frequency, indication, and dates of use
- An assessment of the relationship/causality by the investigator; a decisive factor in the documentation is the temporal relationship between the AE and study drug.

13.3.7 Adverse Event Monitoring and Follow-Up

The investigator will follow all subjects who experience adverse events until the event has resolved or has stabilized (ie, the subject has returned to the baseline state or the investigator does not expect any further improvement or worsening of the subject's condition). The appropriate follow-up visits must be scheduled and the specific tests repeated or performed as necessary. Where a diagnosis is possible, it is preferable to report this diagnosis rather than a series of terms (signs/symptoms) relating to the diagnosis.

13.3.8 Laboratory and ECG Abnormalities

Note: For the purposes of this study, ECG abnormalities will be handled in the same manner as laboratory abnormalities.

Non-Clinically Significant (NCS) Laboratory Abnormalities

All laboratory results must be filed in the subject's medical record and be monitored. The investigator must review laboratory results in a timely manner demonstrated by signature/date and assignment of clinical significance assessment. Non-clinically-significant laboratory abnormalities, ie, minor deviations from the normal range, are expected and it is likely that no medical intervention will be required. Such results will not be considered to be adverse events.

Clinically Significant (CS) Laboratory Abnormalities

CS laboratory abnormalities will be graded using the CTCAE.
All severe and life-threatening laboratory result abnormalities and any laboratory abnormality that is considered to be clinically significant by the investigator will be recorded on the AE eCRF. An abnormal test result will be considered an AE if:

- It is not associated with an already reported AE, diagnosis or pre-existing condition
- There is a change in concomitant medication or intervention as needed, in direct response to the laboratory result
- The investigator exercises his/her discretion to make significance determinations for any subject laboratory result or result that requires intervention

All such lab abnormalities will be repeated and assessed by the investigator, or licensed (MD), as soon as possible for "seriousness" and if they meet the regulatory definition of "serious", they will be reported as SAEs following regulatory and protocol requirements. Repeat laboratory tests may be run in order to monitor the result.

Serious Laboratory Abnormalities

Any lab abnormality meeting the regulatory definition of "serious" must be recorded on both the adverse event eCRF/record and the Serious Adverse Event Form. If a subject experiences a serious toxicity or dies, the FDA will be notified within 24 hours, as required.

13.3.9 Pregnancy

If any subject or the partner of a subject becomes pregnant following the first dose of tesevatinib, the subject will be taken off study. If any subject or a partner of a subject becomes pregnant, the subject and/or their partner will be followed regularly until birth or termination of the pregnancy. The pregnancy must be immediately reported to the sponsor. Forms for reporting pregnancies will be provided to the study sites upon request. The anticipated date of birth or termination of the pregnancy should be provided at the time of the initial report. The outcome of a pregnancy (for a subject or for the partner of a subject) must be reported to the medical monitor as soon as it is known. If the pregnancy ends for any reason before the anticipated date initially reported, the investigator must notify the Kadmon medical monitor as soon as possible.

If the outcome of the pregnancy meets any criterion for classification as a SAE (including stillbirth, neonatal death, spontaneous abortion, or congenital anomaly – including that in an aborted fetus) the investigator must follow the procedures for reporting SAEs. Any neonatal death occurring ≤ 30 days after birth will be reported as a SAE.

13.3.10 Serious Adverse Event Reporting

Governing Regulatory Requirements

Compliance with this request for prompt reporting is essential in that the sponsor is responsible for informing the US Food and Drug Administration (FDA) and other regulatory authorities as well as all other participating investigators of the event.

Under FDA ruling (US Code of Federal Regulations, Title 21 CFR Part 312.32) and the ICH Guidelines for Clinical Safety Data Management Definitions and Standards for Expedited Reporting, the sponsor is required to submit written documentation, in the form of a safety report, detailing:

- Any event associated with the use of the drug, that is both serious and unexpected, or
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity

Written submission must be made by the sponsor to the FDA and the IRBs as soon as possible and in no event later than 15 calendar days after the sponsor's initial notification of the event. The sponsor shall also inform all investigators.

In addition, the sponsor is further required to report, by either telephone or facsimile transmission or in writing to the FDA the occurrence of any unexpected fatal or life-threatening event associated with the use of the drug and no later than 7 calendar days after notification of the event.

Time-Frame for Reporting

Any death, pregnancy, or SAE experienced by a patient from the time of informed consent until 30 days after receiving the last dose of study drug, regardless of relationship to study drug, or any death that occurs more than 30 days after receiving study drug, and is believed to be study drug-related, must be promptly reported (within 24 hours of the investigator becoming aware of the event) by fax to the sponsor (or designee). [redacted]

In the event of an issue with the fax line, forward the SAE form via email to INCDrugSafety@INCResearch.com.

The investigator will be able to contact the safety Medical Monitor at all times:

Information to be Provided by the Investigator

SAEs must be recorded on the SAE eCRF page. This requirement includes all SAEs that occur after informed consent and through 30 days after last dose of study treatment, and in addition, any SAE that are assessed as possibly related to study treatment by the investigator, even if the SAE occurs more than 30 days after the last dose of study treatment.

The minimum information required for SAE reporting includes identity of investigator, site number, subject number, an event description, SAE term(s), onset date, the reason why the event is considered to be serious (ie, the seriousness criteria) and the investigator's assessment of the

relationship of the event to study treatment (not related, unlikely related, possibly related, probably related, or definitely related). Additional SAE information including medications or other therapeutic measures used to treat the event, action taken with the study treatment due to the event, and the outcome/resolution of the event will be recorded on the SAE form. Forms for reporting SAEs will be provided to the study sites.

In all cases, the investigator should continue to monitor the clinical situation and report all material facts relating to the progression or outcome of the SAE. Furthermore, the investigator may be required to provide supplementary information as requested by the Kadmon Drug Safety personnel or designee.

When reporting SAEs, the following additional points should be noted:

- When the diagnosis of an SAE is known or suspected, the investigator should report the diagnosis or syndrome as the primary SAE term, rather than as signs or symptoms. Signs and symptoms may then be described in the event description. For example, dyspnea should not be used as an SAE term if the diagnosis which caused the dyspnea is known to be malignant pleural effusion.
- Death should not be reported as an SAE, but as an outcome of a specific SAE. The cause of death is the SAE. In the exceptional case where the events leading to death are unknown, then death may be used as an event term. If an autopsy was performed, the autopsy report should be provided.
- While most hospitalizations necessitate reporting of an SAE, some hospitalizations do not require SAE reporting, as follows:
    - Elective or previously scheduled surgery, (eg, a previously scheduled ventral hernia repair)
    - Procedures for pre-existing conditions that have not worsened after initiation of treatment
    - Pre-specified study hospitalizations for observation
    - Events that result in hospital stays of less than 24 hours and that do not require admission, (eg, an emergency room visit for hematuria that results in a diagnosis of cystitis and discharge to home on oral antibiotics)
- SAEs must, however, be reported for any surgical or procedural complication resulting in prolongation of the hospitalization.

13.3.11 Regulatory Reporting

Kadmon Drug Safety (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Kadmon will make a determination as to whether the criteria for expedited reporting have been met.

Kadmon (or designee) will submit SAEs that meet the criteria for expedited reporting to the Regulatory Authorities in accordance with local regulations governing safety reporting. Reporting of SAEs by the investigator to his or her IRB will be done in accordance with the standard operating procedures and policies of the IRB. Adequate documentation must be maintained showing that the IRB was properly notified.

13.3.12 Follow-up Information on a Serious Adverse Event

Appropriate diagnostic tests should be performed and therapeutic measures, if indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has returned to baseline or is otherwise explained by the investigator.

Follow-up data concerning the SAE (eg, diagnostic test reports, physician's summaries, etc.) also must be submitted to Kadmon, as they become available, by telefax or email transmission, until resolution of the SAE.

13.4 Other Safety Considerations

13.4.1 Medication Errors

Any medication error that results in an AE, even if it does not meet the definition of serious, requires reporting within 24 hours to the medical monitor. An overdose of tesevatinib without any associated signs or symptoms, unless the subject is hospitalized for observation, will not constitute an AE but will be recorded as a protocol deviation.

13.4.2 Follow-Up of Serious Adverse Events

Any SAE that led to treatment discontinuation (including clinically significant abnormal laboratory values that meet these criteria) and is ongoing 30 days after last dose of study treatment must be followed until the event has resolved or has stabilized (ie, the subject has returned to the baseline state, or the investigator does not expect any further improvement or worsening of the subject's condition). This follow-up guidance also applies to SAEs that occur *more than 30 days after last dose* of study treatment.

13.5 Safety Monitoring

To minimize the possibility of exposing study subjects to unusual risk, at the end of each dosing cohort, the safety information from this study will be reviewed by an independent Data Safety Committee, including an independent safety monitor with clinical expertise in PKD and an independent cardiologist. Safety data will be reviewed, and a recommendation will be made to the study sponsor as to whether it is safe to proceed to the next dosing cohort.

14 STATISTICAL CONSIDERATIONS

All descriptive and inferential statistical analyses will be performed using the most recently released and available SAS statistical software, unless otherwise noted. For categorical variables, the number and percent of each category within a parameter will be calculated for non-missing data. For continuous variables, the mean, median, and standard deviation, as well as the minimum and maximum values, will be presented.

Statistical significance will be declared when the two-tailed p-value is found to be less than or equal to 0.05, unless otherwise noted. Missing data will not be imputed unless otherwise stated. All clinical data captured will be provided in data listings.

14.1 General Design

In the Phase 1b portion of the study, subjects received 50, 100, or 150 mg of tesevatinib for 28 days or until the development of unacceptable toxicity, noncompliance, withdrawal of consent by the subject, or investigator decision. After the MTD for daily dosing had been established according to criteria in the protocol (100 mg QD), 24 additional subjects were enrolled in the Phase 2a portion of the study and treated using two alternative dosing schedules of 150 mg of tesevatinib on Monday, Wednesday, and Friday of each week and 150 mg on Monday and Thursday of each week. While the MTD dose of 100 mg/day was based on criteria defined in the protocol, the occurrence of moderate QTc prolongation in 2 subjects dosed at that level led to a decision to further evaluate the dose of 50 mg/day.

Modeling of ADPKD subpopulations for a randomized Phase 3 clinical study has been performed. Enrollment criteria being considered for Phase 3 are ADPKD subjects with baseline eGFR $\geq$ 35 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2, and htTKV $\geq$ 1000 mL. In order to study the safety profile in this specific ADPKD subpopulation, up to 50 additional subjects with PKD and baseline eGFR $\geq$ 35 mL/min/1.73 m2, and $\leq$ 80 mL/min/1.73 m2, and htTKV $\geq$ 1000 mL will be enrolled (SILK Cohort). Each of the up to 50 subjects to be enrolled will be required to complete either PK testing as described for other Phase 2a subjects in this protocol or iothalamate testing. In addition, all 50 subjects will undergo a mandatory 28-day drug holiday after completing the first month of treatment with tesevatinib. During this drug holiday, and 4 weeks after, subjects will return to the clinic weekly for creatinine and tesevatinib plasma

measurements. All subjects will resume tesevatinib treatment at the Month 2 study visit following completion of the 28-day drug holiday.

14.2 Sample Size Justification

Eight subjects per cohort is a standard and reasonable sample size for determination of safety in this Phase 1b portion of the study. Given the frequency and timing of the most common AEs in prior clinical studies of tesevatinib, 8 treated subjects per dose is sufficient to describe the safety profile of tesevatinib in this subject population. These subjects who receive 50 mg daily of tesevatinib will provide 75% likelihood of having at least 1 AE if the true incidence of an AE is 5%.

In the Phase 2a cohort, the 65 subjects in the 50 mg QD dose group will allow an 80% confidence interval of approximately ± 0.64 mL/min about an expected mean 6-month change from baseline of -2.5 mL/min when the standard deviation is 4.0 mL/min.

14.3 Statistical Considerations

14.3.1 Study Populations

Adult subjects with ADPKD will be enrolled. The safety population will consist of all subjects who receive at least 1 dose of tesevatinib. An evaluable subject will be defined as one who has completed 28 days (for subjects in the Phase 2a portion of the study this will be 25 or 26 days in the Monday/Thursday and Monday/Wednesday/Friday cohorts, and 28 days in the 50 mg daily dosing cohort). Phase 1b unevaluable subjects (subjects who are not evaluable for toxicity) will be replaced. Subjects who do not complete the study, for whatever reason, will have all available data up until the time of termination related to the reason they were terminated included in the analysis. Completion of the study for subjects enrolled in the Phase 1b portion will be defined as uninterrupted completion of the first 28 days of study drug administration, and completion of the study for subjects entered in the Phase 2a portion of the study will be defined as completion of the Month 6 MRI.

For the Phase 2a cohort, all subjects treated will be included in the analyses based on their available data.

14.3.2 Subject Accountability, Demographics, and Baseline Characteristics

Subject disposition will be tabulated by dose cohort. Similarly, subject demographic information and baseline characteristics including PKD traits will be displayed by treatment. Any discrepancy between treatment assigned and treatment received will be accounted for in these displays. Data for screen failures, pertaining to why they failed to qualify to enroll will also be collected.

Similar analyses will be presented for the Phase 2a cohort.

14.3.3 Tesevatinib Exposure

The amount of tesevatinib administered by visit and overall (total dose) will be tabulated and presented by subject in data listings for all cohorts. In addition, delays and all other alterations in tesevatinib administration will be presented.

14.3.4 Concomitant Medications

Concomitant medications will be coded using WHO Drug Dictionary (WHO-DD March 2013, Type B2 or later) and the data will be summarized by dose cohort and presented in tables and listings.

14.3.4.1 Interim Analyses

On Study Day 1, subjects will receive their first daily dose of tesevatinib. During the Phase 1b portion of the study, all subjects within a dosing cohort must complete 28 days of follow-up and the safety data reviewed before subjects from a subsequent dose cohort receive tesevatinib at the next higher dose. Subjects in Cohort 1 will receive the starting dose 50 mg tesevatinib (Dose Level 1). After all subjects in Cohort 1 complete a minimum of 28 days of follow-up and the safety data have been reviewed, dose escalation involving new subjects can begin with Cohort 2 subjects receiving 100 mg tesevatinib daily (Dose Level 2). Similarly, after all subjects in Cohort 2 complete a minimum of 28 days of follow-up and safety data review, dose escalation involving new subjects can precede with Cohort 3 receiving 150 mg tesevatinib daily (Dose Level 3).

14.3.5 Pharmacokinetics

Plasma concentrations of tesevatinib from subjects will be analyzed using validated assays at a central laboratory, and PK parameters will be estimated using standard PK methodology. Plasma

tesevatinib concentrations and PK parameters will be summarized using descriptive statistics. Efforts will be made to identify the specific structure of major tesevatinib metabolites present in all plasma samples collected from 1–24 hours after dosing on Days 1 and 14 in Phase 1b and on Days 1 and 12 (Monday, Wednesday, and Friday dosing) and Days 1 and 25 (Monday and Thursday dosing) in Phase 2a.

14.3.6 Efficacy/Activity

Descriptive statistics, including confidence intervals for GFR, will be presented over time for the Phase 2a cohort. In addition, identical statistics for the change and percent change from baseline GFR over time will be presented with the 6-month change from baseline being of particular interest.

Similar descriptive statistics will be presented for the reciprocal of serum creatinine endpoints.

14.3.7 MRI

Exploratory efficacy analysis will include MRI measurements of kidney volume. htTKV will be calculated using total kidney volume obtained from MRI divided by height in meters. Kidney volume will be determined by MRI at Screening (baseline measurement), and every 6 months thereafter. These results, including change and percent change from baseline, will be summarized descriptively, including confidence intervals. Log transformation may be needed if these data are found not to be normally distributed. A separate set of analyses will be presented for the Phase 2a cohort.

14.3.8 Safety Data

Safety analyses will be performed on all subjects who receive any quantity of study drug. AEs that are unrelated to treatment and that occur more than 30 days after the administration of the last dose of treatment will not be reported or analyzed. Safety evaluation will be performed based on the actual study treatment a subject has received. A separate set of safety analyses will be presented for the Phase 2a cohort.

Safety observations and measurements include AEs, safety laboratory tests, vital sign measurements, physical examinations, pregnancy status, echocardiograms, ECG assessments, and pharmacokinetic data.

Adverse events will be summarized both overall and by dose cohort and tabulated by severity and relationship to tesevatinib (causality). The original terms used by investigators to identify adverse events in the eCRFs will be mapped into preferred terms using MedDRA® (Version 18.1 or higher). Adverse events will then be grouped by MedDRA® preferred terms into frequency tables according to body system. The number and percentage of subjects experiencing adverse events will be tabulated by body system and preferred term both overall and by dose cohort. When an adverse event occurs more than once, the maximum severity and causality will be counted. Additionally, serious adverse events, adverse events that are related to tesevatinib, and adverse events that are unrelated to tesevatinib will be summarized separately. Concurrent illnesses will be listed and examined as possible confounders in the treatment relationship. Finally, any other potentially related adverse events will be analyzed and discussed, as necessary. Concurrent medications/therapies will also be listed.

A listing of all AEs and SAEs by subject will also be provided. The duration of AEs will be determined and included in listings, along with action taken and outcome. Incidence of laboratory abnormalities will be summarized. The worst on-study grade after the first dose of study drug will be summarized. The incidence of NCI-CTCAE Grade ≥ 3 (Version 4.03) laboratory abnormalities under treatment and shifts in toxicity grading from baseline to highest grade post-baseline will be displayed. Results for variables that are not part of the NCI CTCAE (Version 4.03) will be presented in the listings as below, within, and above the normal limits of the local laboratory. Pregnancy test results will be summarized by time point and dose cohort.

Iothalamate testing will be evaluated as data are received to ensure that testing is consistent with no effect on renal function.

Vital sign measurements will be summarized at each scheduled time point using descriptive statistics. Physical examination results will be summarized by scheduled time point. Physical examination results will also be presented in the subject data listings. Physical findings including height and weight will be presented for each subject by visit and dose cohort.

Digital ECG results and wave intervals measurements will be summarized and reported by subject visit and dose cohort and/or as appropriate. QTc(F) prolongation results will be

summarized separately. Covariate analyses will be employed as necessary (eg, QTc[F] interval vs. plasma drug concentration).

Echocardiogram results will be summarized and reported by subject visit and dose cohort and/or as appropriate.

15 DATA QUALITY ASSURANCE

All data will be entered in a validated electronic data capture system using single data entry. Standard procedures (including following data review guidelines, manual clinical review based on subject profiles, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to ensure accurate data. Clinical personnel will review all data listings for outliers, data inconsistencies, and spelling errors.

During the course of the study, a study monitor (CRA) will make site visits to review protocol compliance, compare eCRFs against individual subject's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements.

Electronic CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that subject confidentiality is maintained. Checking the eCRFs for completeness, clarity and cross checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits, and will be carried out giving due consideration to data protection and medical confidentiality. Each investigator will have assured Kadmon of full access to complete source data for study participants and associated necessary support at all times.

In addition to routine monitoring procedures, audits of clinical research activities in accordance with SOPs may be performed to evaluate compliance with the principles of GCP. A regulatory authority may also wish to conduct an inspection (during the study or even after its completion). If a regulatory authority requests an inspection, the investigator must immediately inform Kadmon that this request has been made.

Study conduct may be assessed during the course of the study by a Clinical Quality Assurance representative(s) to ensure that the study is conducted in compliance with the protocol. This designee, as well as the CRA, will be permitted to inspect the study documents (study protocol, eCRFs, investigational product accountability, original study-relevant medical records). All subject data will be treated confidentially. In the course of the clinical study, access will be available to Kadmon or designee (eg, CRO) to view the eCRFs after completion of the individual

sections of the study. Furthermore, the study protocol, each step of the data-recording procedure and the handling of the data as well as the study report may be subject to independent review by a Quality Assurance representative. Clinical site and study audits will be conducted as necessary to assure the validity of the study data.

16 ETHICAL ASPECTS

16.1 Local Regulations

The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH E6 Tripartite Guideline and in a manner consistent with the most recent version of the Declaration of Helsinki. The investigator will ensure that the conduct of the study complies with the basic principles of GCP as outlined in the current version of 21 CFR, subpart D, Part 312, "Responsibilities of Sponsors and Investigators", Part 50, "Protection of Human Subjects", and Part 56, "Institutional Review Boards".

16.2 Informed Consent

A properly executed, written informed consent document, in compliance with 21 CFR, Part 50 and the International Conference on Harmonization (ICH) guidelines, will be obtained from each subject before the subject is entered into the study and before any study screening procedure is performed that involves risk. Attention will be directed to the basic elements required for incorporation into the informed consent under US Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a]) and (21 CFR 50.25[b]), as necessary. Sample ICFs will be supplied to each site. Kadmon or its designee must review any proposed deviations from the sample ICF. The final IRB-approved document must be provided to Kadmon for regulatory purposes.

It is the responsibility of the investigator, or a person designated by the investigator, to obtain written informed consent from each subject (or the subject's legally authorized representative) participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. In the case where the subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject has orally consented to participation in the study, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood. A copy of the ICF must be provided to the subject or to the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language. The site will retain the original signed/dated consent form and any associated HIPAA authorization for all consented subject candidates.

The eCRF for this study contains a section for documenting informed subject consent, and this must be completed appropriately. Signed ICFs must remain in each subject's study file and must be available for verification by study monitors at any time. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated as necessary. All subjects (including those already being treated) should be informed of the new information, should be given a copy of the revised form, and should give their written consent to continue in the study.

16.3 Institutional Review Board

This study is being conducted in compliance with the protocol, the ICH GCP Guidelines, and the applicable regulatory requirements under a United States IND application. This protocol (and any modifications) and appropriate consent procedures must be reviewed and approved by an IRB. This board must operate in accordance with the current federal or local regulations. The investigator will send a letter or certificate of IRB approval to Kadmon (or designee) before subject enrollment and whenever subsequent modifications to the protocol are made.

16.4 Future Use of Subject Samples

Not all of the tissue and blood components obtained during this study may be required for the tests that are part of the clinical study. Following the conclusion of the study, the samples may be used for additional research. These samples will be held for a maximum of 5 years. This may include pharmacogenomics profiling analyzing CYP enzyme polymorphisms. This will be of particular interest given the use of tesevatinib in a new patient population who may experience toxicity not previously seen in earlier studies, and may help identify those at risk for toxicity at various doses. This research will help to understand disease subtypes, drug response and toxicity, and possibly identify new drug targets or biomarkers that predict subject response to treatment. The use of the samples for internal research will be done according to the guidelines defined by the FDA guidance for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individual Identifiable (issued 25 April 25 2006) and the EMEA Reflection Paper on Pharmacogenetic Samples, Testing and Data Handling (EMEA/CHMP/PGxWP/201914/2006). If a subject requests destruction of their tissue and blood samples and the samples have not yet been de-identified, Kadmon will destroy the samples as described in this FDA guidance. Kadmon will notify the investigator in writing that the samples have been destroyed.

17 CONDITIONS FOR MODIFYING THE PROTOCOL

Protocol modifications to ongoing studies must be made only after consultation between a Kadmon representative and the investigator. Protocol modifications will be prepared, reviewed, and approved by Kadmon representatives.

All protocol modifications must be submitted to the IRB for information and approval in accordance with local requirements, and to regulatory agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to study subjects, or when the change involves only logistical or administrative aspects of the study (eg, change in monitor, change of telephone number) or to eliminate an immediate hazard to study subjects. In these circumstances, immediate approval of the chairman of the IRB must be sought, and the investigator should inform Kadmon, and the full IRB within 5 business days after the emergency occurs.

18 CONDITIONS FOR TERMINATING THE STUDY

Kadmon has the right to terminate the study at any time. In terminating the study, Kadmon and the investigator will ensure that adequate consideration is given to the protection of the subjects' interests.

The following data and materials are required by Kadmon before a study can be considered to be complete or terminated:

- Laboratory findings, clinical data, and all special test results from Screening through the end of the study, including the follow-up period for all enrolled subjects.
- Case Report Forms/Records. Electronic case report forms (eCRFs) will be used in this study. Records (including correction forms) for all enrolled subjects will be properly completed by appropriate study personnel, and signed and dated by the principal investigator, as required.
- Principal investigator sign-off of all required eCRF forms.
- Completed Drug Accountability Records, Drug Inventory Log, and Inventory of Returned Drug forms or documentation of destruction, as appropriate.
- Return of all unused study drug to Kadmon unless an alternate disposition method is agreed upon at study initiation by Kadmon and investigational site(s).
- Copies of protocol amendments and other documents, and IRB approval/notification, as applicable.
- A summary of the study prepared by the principal investigator (IRB summary closure letter is an acceptable equivalent).

19 STUDY DOCUMENTATION, CRFS, AND RECORD KEEPING

19.1 Investigator's Files and Retention of Documents

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two separate categories as follows: (1) investigator's study file and (2) subject clinical source documents.

The investigator's study file will contain the protocol and protocol amendments, eCRFs, query forms, IRB and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually predefined by the project to record key efficacy and safety parameters independent of the eCRFs) may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, X-ray, pathology and special assessment reports, signed ICFs, consultant letters, email communication and subject screening and enrollment logs. The investigator must keep these two categories of documents on file for at least 2 years following the marketing application approval date for the study treatment and for the indication being investigated or for 2 years after the investigation is discontinued and the FDA is notified. After that period of time, the documents may be destroyed subject to local regulations with prior written permission from Kadmon. If the investigator wants to assign the study records to another party or move them to another location, Kadmon must be notified in advance.

If the investigator cannot guarantee the archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and Kadmon to store these in a sealed container outside of the study site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the study site.

19.2 Source Documents and Background Data

Investigators must maintain adequate and accurate source documents on which the eCRFs for each subject are based. They are separate and distinct from the eCRFs.

These records include detailed notes on:

- Medical history
- Date and time of informed consent with HIPAA authorization either contained in the ICF or presented to the subject candidate as a standalone document
- Description of the complete consenting process
- The basic identifying information that linked the subject's medical record with the eCRFs
- The results of all diagnostic tests performed, diagnoses made, therapy provided, and any other data on the condition of the subject
- The medical condition of the subject during their involvement in the study
- All adverse events
- The subject's exposure to the study medication
- The subject's exposure to any concomitant therapy
- All relevant observations and data on the condition of the subject throughout the study
- Justification for all entries in the subject's eCRF
- Radiology images (hard copy and digital), and reports if required
- Death information and any available autopsy data

A subject log of all potentially eligible subjects considered, but not consented, for obvious deviations from the entry criteria, will be kept at each site. The log will contain subjects' initials, diagnosis, eligibility, or, if not eligible, reason for not consenting. All consented subjects will be logged, regardless of whether they ultimately enroll.

Upon request, the investigator will supply Kadmon with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

19.3 Audits and Inspections

The investigator should understand that source documents for this study should be made available to appropriately qualified personnel from the Kadmon Quality Assurance Unit (or designee), or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

19.4 Electronic Case Report Forms

Clinical study data for this study will be captured on electronic case report forms (eCRF) designed for computer processing and analysis. This computerized system will be validated and compliant with 21 CFR Part 11. Corrections to data will be made according to 21 CFR Part 11, Electronic Records; Electronic Signatures. If corrections are made after review and sign-off by the investigator, he/she must be aware of the changes and provide written acknowledgement. There will also be an electronic audit trail. The investigator agrees to provide all information requested on the eCRF in an accurate manner according to instructions provided. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to Kadmon in the eCRF and in all required reports.

An eCRF is required to be submitted for every subject who receives any amount of study drug. This includes submission of retrievable data on subjects who withdraw before completion of the study. Prior to submission, eCRFs must be reviewed for completeness and accuracy, and signed and dated where indicated by the principal investigator or authorized delegate from the study staff. If a subject stops treatment or terminates from the study, the dates and reasons must be noted on the eCRF.

20 MONITORING THE STUDY

All aspects of the study will be carefully monitored by Kadmon or authorized representatives according to GCP and standard operating procedures (SOPs) for compliance with applicable government regulations.

It is understood that the responsible Kadmon study monitor (or designee) will contact and visit the investigator regularly and will be allowed on request to inspect the various records of the study (eCRFs and other pertinent data) provided that subject confidentiality is maintained in accordance with local requirements. The principal investigator (or a designee) and key study personnel must be available to assist the monitor during these visits. The investigator (or designee) must agree to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

It will be the monitor's responsibility to inspect the eCRFs in comparison to source documents at regular intervals throughout the study according to the monitoring plan, to verify the adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them and clarifying any data queries. The monitor should have access to laboratory test reports and other subject records needed to verify the entries on the eCRF. The completed and corrected eCRFs/CRFs for completed visits will either be collected by the monitor at the end of the study or obtained electronically for data processing. The investigator is responsible for the timely completion of eCRFs by assigned study staff. The eCRFs are expected to be completed within seven (7) days of the subject's visit. A copy of the eCRFs will be retained by the investigator who must ensure that it is stored in a secure place with other study documents, such as the protocol, the Investigator's Brochure, and any protocol amendments.

Upon completion of the study, the monitor will make a final assessment of the conduct of the study and inventory all clinical supplies to be returned to Kadmon.

21 CONFIDENTIALITY OF STUDY DOCUMENTS AND SUBJECT RECORDS

The investigator must ensure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to Kadmon and the IRB, subjects should be identified by an identification code and/or initials and not by their names. The investigator should keep a subject enrollment log. The investigator should maintain documents not for submission to Kadmon (eg, subjects' written consent forms) in strict confidence.

Authorized regulatory officials and Kadmon personnel (or their representatives) will be allowed full access to inspect and copy the records. All study drug, subject bodily fluids and tissue, and/or other materials collected shall be used solely in accordance with this protocol, unless otherwise agreed to in writing by Kadmon.

The principal investigator also agrees that all information received from Kadmon, including but not limited to the Investigator's Brochure, this protocol, eCRFs, the investigational new drug, and any other study information remain the sole and exclusive property of Kadmon during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The principal investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

22 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

The results of this study may be published or presented at scientific meetings. The investigator agrees to submit all manuscripts or abstracts to Kadmon for review at least 30 days before submission. This allows Kadmon to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator.

In the event that Kadmon coordinates a publication or presentation of study results from all study sites, the participation of investigator or other representatives of study site as a named author shall be determined in accordance with Kadmon policy and generally accepted standards for authorship.

23 REFERENCES

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Appendix A: Equations to Predict Glomerular Filtration Rate (MDRD-4, CKD-EPI$_{2012cys}$, and CKD-EPI$_{2012Scr-cys}$)

4-Variable Modification of Diet in Renal Disease (MDRD-4) Equation

High Level Formula for Black or African-American Males:

$$\text{Estimated GFR} = 175 \times (\text{Creatinine}^{-1.154}) \times (\text{Age}^{-0.203}) \times 1.212$$

High Level Formula for Males NOT Black or African-American (any other option):

$$\text{Estimated GFR} = 175 \times (\text{Creatinine}^{-1.154}) \times (\text{Age}^{-0.203})$$

High Level Formula for Black or African-American Females:

$$\text{Estimated GFR} = 175 \times (\text{Creatinine}^{-1.154}) \times (\text{Age}^{-0.203}) \times 1.212 \times 0.742$$

High Level Formula for Females NOT Black or African-American (any other option):

$$\text{Estimated GFR} = 175 \times (\text{Creatinine}^{-1.154}) \times (\text{Age}^{-0.203}) \times 0.742$$

CKD-EPI$_{2012cys}$ Equation to Predict Glomerular Filtration Rate (GFR)

Gender	Scys (mg/L)	Equation
female	≤ 0.8	$133 \times (\text{Scys}/0.8)^{-0.499} \times 0.996^{\text{age}}$ (× 0.932)
	> 0.8	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{age}}$ (× 0.932)
male	≤ 0.8	$133 \times (\text{Scys}/0.8)^{-0.499} \times 0.996^{\text{age}}$
	> 0.8	$133 \times (\text{Scys}/0.8)^{-1.328} \times 0.996^{\text{age}}$

Note: Age is shown as years.
Scr = serum creatinine; Scys = serum cystatin C; CKD-EPI$_{2012cys}$ = cystatin C-based CKD-EPI equation developed in 2012

CKD-EPI$_{2012Scr-cys}$ Equation to Predict Glomerular Filtration Rate (GFR)

Gender	Scr (mg/dL)	Scys (mg/L)	Equation
female	≤ 0.7	≤ 0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$130 \times (Scr/0.7)^{-0.248} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ (× 1.08, if black)
	> 0.7	≤ 0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$130 \times (Scr/0.7)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ (× 1.08, if black)
male	≤ 0.9	≤ 0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$135 \times (Scr/0.9)^{-0.207} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ (× 1.08, if black)
	> 0.9	≤ 0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.375} \times 0.995^{age}$ (× 1.08, if black)
		> 0.8	$135 \times (Scr/0.9)^{-0.601} \times (Scys/0.8)^{-0.711} \times 0.995^{age}$ (× 1.08, if black)

Note: Age is shown as years.
Scr = serum creatinine; Scys = serum cystatin C; CKD-EPI$_{2012Scr-cys}$ = serum creatinine- and cystatin C-based CKD-EPI equation

CKD-EPI$_{2012cys}$ and CKD-EPI$_{2012Scr-cys}$ Equations abstracted from: Zhu Y, Ye X, Zhu B, Pei X, Wei L, et al. Comparisons between the 2012 New CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) Equations and Other Four Approved Equations. *PLoS ONE.* 2014. 9(1): e84688. doi:10.1371/journal.pone.0084688

Appendix B: Concomitant Medications Associated With a Risk of QTc(F) Interval Prolongation and/or Torsades de Pointes

Use of these drugs should be avoided in subjects who are receiving KD019. Subjects who require treatment with these drugs should have KD019 held for up to 21 days while receiving the treatment and should be closely monitored for QTc(F) prolongation and potential AEs. **This list is not comprehensive and all concomitant medications should be evaluated for potential contribution to QTc(F) prolongation. Refer to the following web site whenever a potential concomitant medication is needed for additional listings and information:**

https://crediblemeds.org/index.php?rf=US

Drug Type	Drug Name
Anti-anginal	bepridil
Anti-arrhythmic	amiodarone, disopyramide, dofetilide, ibutilide, procainamide, quinidine, sotalol
Antibiotic	clarithromycin, erythromycin, azithromycin, sparfloxacin, gatifloxacin, moxifloxacin, troleandomycin
Anti-cancer	arsenic trioxide
Anti-infective/pneumocystis pneumonia	pentamidine
Anti-malarial	chloroquine, halofantrine
Anti-nausea	domperidone, droperidol
Anti-psychotic	haloperidol, mesoridazine, thioridazine
Anti-psychotic/anti-emetic	chlorpromazine
Anti-psychotic/Tourette's tics	pimozide
GI stimulant/heartburn	cisapride
Opiate agonist/pain control/narcotic dependence	levomethadyl, methadone

Reference: http://www.arizonacert.org/medical-pros/drug-lists/drug-lists.htm

Appendix C: Clinical Symptom and Adverse Event Grading Scale

CLINICAL ADVERSE EVENT GRADING SCALE		
Severity	**Grade**	**Definition**
Mild	1	Awareness of symptom, but easily tolerated. Usually transient requiring no special treatment; does not interfere with usual status or activities
Moderate	2	May be ameliorated by simple therapeutic measures; may interfere with usual activities
Severe	3	Incapacitating; unable to perform usual activities
Life-threatening	4	Requires immediate intervention; need for emergency treatment
Death	5	Resulting in the subsequent death of the subject

Appendix D: QTc(F) Calculation

The formula is: $QTc(F) = QT/(RR^{1/3})$

- Manually and carefully measure the QT msec (use the longest)
- The "RR interval in seconds" = dividing 60/heart rate
- Power of 1/3 = 0.34
- Take the RR and elevate it to the power of 0.34
- Divide the QT by that number

Example:

For a QT of 400 msec and a heart rate of 80 bpm

RR interval = 60/heart rate = 60/80 = 0.75

$0.75^{0.34} = 0.9$

400/0.9 = QTc(F) = 444 msec

The QTc(F) for a QT of 400 msec and a heart rate of 80 bpm is 444.

Appendix E: Topical Steroid Potency Chart

The following potency chart categorizes brand- name topical steroid medications along with the name of the corresponding generic drug. The medications are listed in order of their potency. Please note that the percentage of ingredient in the medication does not necessarily correlate with the strength of the steroid. The list may not be comprehensive.

Brand Name	Generic Name
Class 1 – Superpotent	
Clobex Lotion/Spray/Shampoo, 0.05%	Clobetasol propionate
Cormax Cream/Solution, 0.05%	Clobetasol propionate
Diprolene Ointment, 0.05%	Augmented betamethasone
Olux E Foam, 0.05%	Clobetasol propionate
Olux Foam, 0.05%	Clobetasol propionate
Temovate Cream/Ointment/Solution, 0.05%	Clobetasol propionate
Ultravate Cream/Ointment, 0.05%	Halobetasol propionate
Vanos Cream, 0.1%	Fluocinonide
Cordran Tape, 0.05%	Flurandrenolide
Class 2 - Potent	
Diprolene Cream AF, 0.05%	Augmented betamethasone
Elocon Ointment, 0.1%	Mometasone furoate
Florone Ointment, 0.05%	Diflorasone diacetate
Halog Ointment/Cream, 0.1%	Halcinonide
Lidex Cream/Gel/Ointment, 0.05%	Fluocinonide
Psorcon E Cream, 0.05%	Diflorasone diacetate
Topicort Cream/Ointment, 0.25%	Desoximetasone
Topicort Gel, 0.05%	Desoximetasone
Class 3 – Upper Mid-Strength	
Cutivate Ointment, 0.005%	Fluticasone propionate
Lidex-E Cream, 0.05%	Fluocinonide
Luxiq Foam, 0.12%	Betamethasone valerate
Topicort LP Cream, 0.05%	Desoximetasone
Class 4 – Mid-Strength	

Brand Name	Generic Name
Cordran Ointment, 0.05%	Flurandrenolide
Elocon Cream/Lotion, 0.1%	Mometasone furoate
Kenalog Cream/Spray, 0.1%	Triamcinolone acetonide
Synalar Ointment, 0.025%	Fluocinolone acetonide
Westcort Ointment, 0.2%	Hydrocortisone Valerate
Class 5 - Lower Mid-Strength	
Capex Shampoo, 0.01%	Fluocinolone acetonide
Cordran Cream/Lotion, 0.05%	Flurandrenolide
Cutivate Cream/Lotion, 0.05%	Fluticasone propionate
Dermatop Cream, 0.1%	Prednicarbate
DesOwen Lotion, 0.05%	Desonide
Locoid Cream/Lotion/Ointment/ Solution, 0.1%	Hydrocortisone butyrate
Pandel Cream, 0.1%	Hydrocortisone probutate
Synalar Cream, 0.025/	Fluocinolone acetonide
Westcort Cream, 0.2%	Hydrocortisone valerate
Class 6 – Mild	
Aclovate Cream/Ointment, 0.05%	Alclometasone dipropionate
Derma-Smoothe/FS Oil, 0.01%	Fluocinolone acetonide
Desonate Gel, 0.05%	Desonide
Synalar Solution, 0.01%	Fluocinolone acetonide
Verdeso Foam, 0.05%	Desonide
Class 7 - Least Potent	
Cetacort Lotion, 0.5%/1%	Hydrocortisone
Cortaid Cream/Spray/Ointment, 1%	Hydrocortisone
Hytone Cream/Lotion, 1%/2.5%	Hydrocortisone
Micort-HC Cream, 2%/2.5%	Hydrocortisone
Nutracort Lotion, 1%/2.5%	Hydrocortisone
Synacort Cream, 1%/2.5%	Hydrocortisone

Abstracted from: National Psoriasis Foundation. Topical treatments for Psoriasis. 2013. http://www.psoriasis.org/document.doc?id=164 (accessed 24 February 2014).