NCT03203642

PROTOCOL: KD019-211

TITLE:	A Double-blind Randomized Parallel Group Study of the Efficacy and Safety of Tesevatinib in Subjects with Autosomal Dominant Polycystic Kidney Disease
DRUG:	Tesevatinib (KD019)
IND:	110588
SPONSOR:	Kadmon Corporation, LLC 450 East 29th Street New York, NY 10016
PROTOCOL VERSION AND DATE:	Version 2.0, 31 August 2018

PROTOCOL SIGNATURE PAGE

Sponsor's Approval

[redacted]

Investigator's Acknowledgement

I have read this protocol KD019-211.

Title: A Double-blind Randomized Parallel Group Study of the Efficacy and Safety of Tesevatinib in Subjects with Autosomal Dominant Polycystic Kidney Disease

I have fully discussed the objective(s) of this study and the contents of this protocol with the Sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the Sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Council for Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to my participation as an Investigator for this study to be terminated.

I understand that the Sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the Sponsor.

Investigator Name, Address, and Telephone Number: (please hand print or type)	

Signature: _____ Date: _____

EMERGENCY CONTACT INFORMATION

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 Pharmacovigilance vendor.

Table 1: Reporting of Serious Adverse Events

For SAE/Pregnancy reporting:	**For any other questions or to contact the Medical Monitor:**
APCER Life Sciences, Inc. Fax Number: 1-646-430-9549 In the event of an issue with the fax line, forward the serious adverse event information via email to: clinicalsaereporting@kadmon.com	[redacted]

PRODUCT QUALITY COMPLAINTS

Once a Product Quality Complaint is identified, investigators must report it to Kadmon. This includes any instances wherein the quality or performance of a Kadmon investigational product does not meet expectations (eg, inadequate or faulty closure, product contamination), the product does not meet the specifications defined in the application for the product (eg, wrong product such that the label and contents are different products), or the product does not meet appearance specifications (eg, broken or chipped tablets). For instructions on reporting adverse events (AEs) related to product complaints, see Section 8.

Please use the information below as applicable to report the Product Quality Complaint:

Phone: (724) 778-6155

Email Address: productcomplaints@kadmon.com

Please use the address below if investigational medicinal product needs to be returned:

Kadmon Corporation, LLC
Quality Assurance Department
119 Commonwealth Dr.
Warrendale, PA 15086

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ABBREVIATIONS

ADPKD	autosomal dominant polycystic kidney disease
AE	adverse event
ALT	alanine transaminase
ARPKD	autosomal recessive polycystic kidney disease
AST	aspartate transaminase
AUC	area under the plasma drug concentration time curve
CFR	Code of Federal Regulations
C_{max}	maximum plasma concentration
CPK	creatine phosphokinase
CRA	Clinical Research Associate
CYP	cytochrome P450
CV%	coefficient of variation
ECG	electrocardiogram
eCRF	electronic case report form
eGRF	estimated glomerular filtration rate
EGFR	epithelial growth factor receptor
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
htTKV	height-adjusted total kidney volume
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	institutional review board
IVRS	interactive voice response system
IWRS	interactive web response system
KDR	kinase insert domain receptor
LLN	lower limit of normal
mITT	modified intent to treat
MRI	magnetic resonance imaging

MTD	maximum tolerated dose
PK	Pharmacokinetic(s)
PKD	Polycystic kidney disease
PKD1/2	polycystin 1 or 2 gene
QD	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
SSRI	Selective serotonin reuptake inhibitor
T_{max}	observed time to reach peak plasma concentration
TK	tyrosine kinase
ULN	upper limit of normal
VEGFR2	vascular endothelial growth factor receptor 2

STUDY SYNOPSIS

Protocol number: KD019-211	**Study drug**: Tesevatinib (KD019)
Title of the study: A Double-blind Randomized Parallel Group Study of the Efficacy and Safety of Tesevatinib in Subjects with Autosomal Dominant Polycystic Kidney Disease	
Number of subjects (total and for each treatment arm): Approximately 160 subjects will be screened in order to enroll 100 subjects (50 subjects randomized to tesevatinib, 50 subjects randomized to placebo) of which at least 80 subjects (40 per group) are anticipated to complete all study procedures.	
Investigator(s): Multicenter study in the United States. Coordinating Principal Investigator – [redacted]	
Site(s): Approximately 25-30 sites in the United States	
Study period (planned): June 2017 to June 2020	**Clinical phase:** 2b
Objectives: **Primary**: To evaluate the change from baseline in height-adjusted total kidney volume (htTKV) as measured by magnetic resonance imaging (MRI) at Months 12, 18, 24, and 30 days post-dose in patients with autosomal dominant polycystic kidney disease (ADPKD) treated with tesevatinib or placebo. **Secondary**: To evaluate the safety and tolerability of tesevatinib 50 mg once daily (QD) in patients with ADPKD. To evaluate the change in eGFR using the MDRD-4 formula at the Month 12, 18, 24, and 30 days post-dose time points.	
Rationale: In nonclinical studies, tesevatinib selectively inhibited key kinases and validated targets in animal models of polycystic kidney disease (PKD). This Phase 2b, double-blind, placebo-controlled study in subjects with ADPKD will provide initial evidence of the treatment effect of tesevatinib in ADPKD subjects and allow for a better understanding of tesevatinib's safety profile in this patient population.	
Investigational product, dose, and mode of administration: Tesevatinib (KD019) 50 mg or matched placebo tablets will be administered orally QD.	

Methodology:

This is a multicenter, double-blind, randomized, parallel group study of tesevatinib tablet formulation administered to male and female subjects with ADPKD, 18 to 60 years of age and with an estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 and ≤ 80 mL/min/1.73 m^2.

Subjects will be screened up to 28 days before initiation of treatment with tesevatinib or placebo (certain screening assessments may be conducted up to 42 days prior to dosing). Screening assessments will include medical and PKD history, physical examination, vital signs, electrocardiograms (ECGs), clinical laboratory evaluation (including hematology, serum chemistry, coagulation, thyroid stimulating hormone, urinalysis, and pregnancy), ocular examination, echocardiogram, and MRI. Calculation of htTKV at screening for eligibility determination may be performed by a local radiologist.

Starting on Day 1, subjects will receive 50 mg QD of tesevatinib or placebo for up to 24 months. During the Early Treatment Period (Days 1 to 28), subjects will report to the study site on Days 1, 14, and 28; subjects will be followed every 28 days from Months 2 to 12 and every other month from Months 12 to 24. Safety assessments will be performed at regular intervals throughout the study and will include physical examinations, vital signs, ECGs, clinical laboratory evaluations, ocular examination and echocardiograms. Magnetic resonance imaging to determine the change from baseline in htTKV will be performed at Months 12, 18, and 24. Entry into the study will be based on local MRI readings, but central MRI readings and htTKV calculation will be performed at baseline and during the study.

All subjects will undergo an end-of-study evaluation approximately 30 days after the last dose of study drug.

Inclusion and exclusion criteria:

Inclusion criteria:

Subjects will be included in the study if they meet all of the following inclusion criteria:

1. 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. At least 18 years old and no more than 60 years old at the time of consent.
4. eGFR ≥ 25 mL/min/1.73 m^2 and ≤ 90mL/min/1.73 m^2, using the Modification of Diet in Renal Disease-4 variable formula.
5. htTKV must meet the following requirements (htTKV is calculated using total kidney volume obtained from MRI divided by height in meters):
    - ≥500 mL for subjects 18-35 year of age
    - ≥750 mL for subjects 36-49 years of age
    - ≥900 mL for subjects 50-60 years of age
6. Subject has the following laboratory values:
    - Platelets > lower limit of normal (LLN)

- Hemoglobin > 9 g/dL
- Total bilirubin ≤ 1.5 mg/dL
- Aspartate aminotransferase < 2.5 × upper limit of normal (ULN)
- Alanine aminotransferase < 2.5 × ULN
- Prothrombin time/partial thromboplastin time ≤ 1.5 × ULN
- International normalized ratio (INR) ≤ 1.5, except those subjects taking warfarin who must have INR ≤ 3
- Albumin ≥ LLN
- Amylase ≤ 1.5 x ULN
- Lipase ≤ 1.5 x ULN
- Serum potassium within normal limits
- Serum magnesium within normal limits

7. Female subjects of childbearing potential must have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy, bilateral tubal ligation, 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 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 2 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) intrauterine device **plus** 1 barrier method; (b) on stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, and transdermal) **plus** 1 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.
8. For male subjects who are sexually active and are partners of premenopausal women: agreement to use 2 forms of contraception as in criterion 7 above during the treatment period and for at least 6 months after the last dose of study drug, unless the male subject had a vasectomy.
9. Capable of understanding and complying with the protocol and has signed the informed consent form.

Exclusion criteria:

Subjects meeting any of the following criteria will be excluded from participation:

1. Previous partial or total nephrectomy or a kidney transplant.
2. Tuberous sclerosis, Hippel-Lindau disease, or acquired cystic disease.

3. Congenital absence of 1 kidney and/or need for dialysis or transplantation in the foreseeable future.
4. Moderate hematuria. Subjects with microhematuria may be enrolled, unless microhematuria is suspected to be due to infection or recent cyst rupture. If hematuria is due to cyst rupture, the subject may be rescreened after discussion with the Medical Monitor.
5. Uncontrolled hypertension (systolic blood pressure > 160 mmHg; diastolic blood pressure > 100 mmHg) while receiving antihypertensive therapy.
6. Uncontrolled diabetes mellitus (glycated hemoglobin > 8%).
7. Presence of renal or hepatic calculi (stones) causing symptoms.
8. Received any investigational therapy within 30 days prior to initiation of therapy (Day 1).
9. Received tolvaptan within 30 days prior to initiation of therapy (Day 1).
10. Received active treatment (within 4 weeks of initiation of therapy [Day 1]) for urinary tract infection.
11. History of pancreatitis or known risk factors for pancreatitis.
12. Subject meets any of the following cardiac criteria:
    - Mean QTc interval corrected for heart rate using Fridericia's formula (QTcF) of > 450 msec.
    - History of torsade de pointes, ventricular tachycardia or fibrillation, pathologic sinus bradycardia (< 50 beats per minute), 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. Inclusion of subjects with a history of atrial arrhythmias should be discussed with the Medical Monitor.
    - Family history of congenital long QT syndrome or unexplained cardiac death.
    - History of ventricular rhythm disturbances.
    - Symptomatic heart failure (per New York Heart Association guidelines), unstable angina, myocardial infarction, or cerebrovascular accident within 6 months prior to study entry.
    - Has a cardiac pacemaker.
    - History of pericardial effusion or presence of pericardial effusion on screening echocardiogram
13. Subject is taking any medication known to inhibit the cytochrome P450 (CYP)3A4 isozyme or any drugs that are CYP3A4 inducers, or any drugs associated with torsade de pointes or known to prolong the QTcF interval, including anti-arrhythmic medications within 2 weeks prior to screening. A stable regimen (≥ 4 weeks) of antidepressants of the selective serotonin reuptake inhibitor (SSRI) class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).
14. Uncontrolled intercurrent illness that would limit compliance with study requirements including, but not limited to ongoing or active infections or psychiatric illness.
15. Subject is pregnant, plans to become pregnant, or nursing.

16. Known to be positive for the human immunodeficiency virus or hepatitis B or C, as indicated by a positive test at screening.
17. Known to be immunocompromised.
18. Documented presence of renal vascular disease resulting in uncontrolled hypertension.
19. Has previously received an epithelial growth factor receptor (EGFR) inhibitor (including, but not limited to, erlotinib, gefitinib, osimertinib, afatinib, cetuximab, panitumumab, or an investigational agent).
20. Allergy or hypersensitivity to components of either tesevatinib, matched placebo, or their formulations.
21. Aphakic due to previous cataract surgery or congenital abnormality.

Note: The sponsor has the option to exclude a subject from enrollment, 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.

Maximum duration of subject involvement in the study:

The planned duration of the screening period is no more than 28 days prior to dosing (42 days for MRI and ocular assessments). The planned duration of treatment period is approximately 730 days (or 24 months). The follow-up period will be 30 days from the last dose of study drug.

Endpoints and statistical analysis:

Study data will be summarized for disposition, demographic and baseline characteristics, efficacy, and safety parameters. Unless otherwise noted, study data will be summarized by treatment group. Categorical data will be summarized by frequency distributions (number and percentages of subjects) and continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum). All data will be presented in subject listings.

Efficacy analyses will be based on the Efficacy Population, defined as all randomized subjects who have completed 12 months of tesevatinib or placebo treatment and have a centrally read MRI at baseline and after 12 months of treatment. The primary efficacy endpoint will be the change from baseline in htTKV at Month 12. An analysis of covariance model including treatment group as a factor and the baseline htTKV as a covariate will be used for efficacy analyses. The Type I error rate will be set at an alpha level of 0.05. Additional efficacy endpoints include change from baseline in htTKV at Months 18 and 24.

Safety analyses will be based on the modified Intent-To-Treat Population, defined as all randomized subjects who received at least 1 dose of study drug. Treatment-emergent adverse events (AEs) will be summarized using Medical Dictionary for Regulatory Activities (Version 19.0 or higher) system organ class and preferred term and presented by treatment group. Safety endpoints will include AEs and clinical laboratory evaluations (including serum creatinine, cystatin C, and calculated eGFR).

Based on the results presented in Caroli, et.al.[1] it is anticipated that the mean change from baseline in htTKV at 12 months will be 83.6 (± 90.0) mL in the placebo group. Assuming the mean change from baseline in htTKV at 12 months is 26.4 mL for the tesevatinib group, 40 subjects per group would yield approximately 80% power to detect a difference between

treatment groups based on a 2-sided t-test with a Type I error rate of 0.05. Ten additional subjects per group will be added (ie, for a total of 50 subjects per group) to adjust for drop-outs and differences in analysis methodologies (eg, the htTKV data will be log-transformed).

STUDY SCHEDULE

Table 2: Schedule of Assessments

Assessments	Screening[a] (-28 Days)	Early Treatment Period			Monthly Follow-up Treatment Period	End of Study[c]
		Day 1	Day 14 (± 1 Day)	Day 28 (± 1 Day)	Every 28 Days[b] Beginning at Month 2 (± 1 or ±3 Days)	30 Days from Last Dose (± 3 Days)
Informed consent	✔					
Medical and PKD history (include genotype, if available)	✔					
Physical examination[d] (including weight)	✔	✔	✔	✔	✔	✔
Vital signs[e]	✔	✔	✔	✔	✔	✔
Supine 12-lead ECG[f]	✔	✔	✔	✔	✔	✔
Clinical laboratory tests[g]	✔	✔	✔	✔	✔	✔
Ocular evaluation[h]	✔				✔	✔
Echocardiogram[i]	✔			✔	✔	✔
Pregnancy test[j]	✔	✔		✔	✔	✔
MRI[k]	✔				✔ (every 6 months beginning at Month 12)	✔
Randomization		✔				
Study drug/placebo dispensed		✔	✔	✔	✔	✔
Record adverse events	✔	✔	✔	✔	✔	✔
Record concomitant medication	✔	✔	✔	✔	✔	✔
Drug compliance/collection[l]		✔	✔	✔	✔	✔

Abbreviations: ECG, electrocardiogram; MRI, magnetic resonance imaging; PKD, polycystic kidney disease; QTc(F), QT interval corrected for heart rate using Fridericia's formula; TSH, thyroid stimulating hormone

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. Screening MRI and ocular assessments may be performed up to 6 weeks prior to Day 1.
b 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 between Months 12 and 24.
c. The End-of-study visit is to be performed 30 days (± 3 days) after last dose of study drug.
d. A complete physical examination is to be done at the Screening and End-of-study visits. Height will only be measured at Screening. Symptom-driven physical examinations will be performed on Days 1, 14, 28, every 28 days from Months 2 to 12, and every 2 months from Months 12 to 24. See Section 7.5.1 for a description of the body systems and evaluations to be performed at each visit (eg, cardiac tamponade, ocular toxicity and xerostomia assessments).
e. Vital sign measurements will include sitting blood pressure, heart rate, respiratory rate, and oral or tympanic temperature. On Day 1, measurements should be performed predose and 1 and 4 hours postdose. See Section 7.5.2 for details on vital signs measurement.
f. Supine 12-Lead ECGs will be performed at Screening, predose, 1, 4, and 8 hours postdose on Days 1 and 14; predose on Days 28 and Months 2 to 12, at each visit on Months 12 to 24; and at the End-of-study visit. Supine ECGs should be repeated 3 times consecutively within 30 minutes (with 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 based on local ECG read, refer to Section 6.7.1.2 for a description of the procedures to be followed.
g. Clinical laboratory tests will include hematology, serum chemistry, coagulation, TSH, and urinalysis (see Section 7.5.6 for a complete list of assessments). Thyroid stimulating hormone levels will be evaluated at Screening and then every 2 months. Serology testing will be done at Screening only.
h. Ocular evaluations are to be performed at Screening and at Months 3, 6, 9, 12, 18, and 24, and at the End-of-study visit (if applicable). The following assessments will 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, and optical coherence tomography of the optic nerve head and macula. Note: if a subject has had ocular evaluations within 3 months of the End-of-study visit, there is no need to repeat ocular evaluations at the End-of-study visit.
i. Echocardiograms are to be obtained at Screening, on Day 28, at Months 3, 6, 12, 18, and 24, and at the End-of-study visit (if applicable). Echocardiograms should include measurement of ejection fraction and assessment for pericardial effusion and valvular abnormalities. Note: If a subject has had an echocardiogram within 3 months of the End-of-study visit, there is no need to obtain an echocardiogram at the End-of-study visit. If pericardial effusion is diagnosed via echocardiogram, the subject should be rechecked within 1–3 months to monitor for progression.
j. Pregnancy testing in women of childbearing potential will be performed using urine samples. 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, every 3 months through Month 12, at every visit between Months 12 and 24, and at the End-of-study visit only. Positive urine samples will be confirmed via serum testing.
k. Screening MRI will be performed after informed consent form has been signed and prior to other screening assessments. Magnetic resonance imaging will be performed at Month 12, 18, and 24, and at the End-of-study visit
l. Subject diaries will be dispensed on Day 1 and reviewed/collected at each visit.

1. BACKGROUND INFORMATION

1.1. 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 [2]. 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 PKD 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 PKD, autosomal dominant (ADPKD) and autosomal recessive (ARPKD). In the more common form, ADPKD, the abnormal PKD gene (polycystin 1 or 2 [*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 ADPKD who do not have a family member with the disease. Autosomal recessive PKD 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.

In ADPKD, the mutation in either the *PKD1* or *PKD2* gene results in the abnormal, uncontrolled growth of renal tubular epithelial cells [3]. Epithelial growth factor receptor (EGFR) is overexpressed and mislocated from the basolateral to the luminal surface of renal tubular cells [4]. Epithelial growth factor receptor 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 [5]. Chronic proliferation results in renal cyst formation [6]. 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 [7]. 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 [8].

1.2. Tesevatinib

Tesevatinib (formerly named XL647 and KD019) is a new chemical entity that inhibits

multiple tyrosine kinases (TKs) (ErbB family members [EGFR and human epidermal growth factor receptor 2], vascular endothelial growth factor receptor 2/kinase insert domain receptor [VEGFR2/KDR]), and Src family kinases.

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.

Clinical Experience with Tesevatinib

Tesevatinib has been evaluated in over 350 subjects, including 232 subjects with solid tumor malignancies in 3 Phase 1 studies, 4 Phase 2 studies, and 1 Phase 3 study; 66 healthy subjects in 4 clinical pharmacology studies; and 73 subjects with PKD (Study KD019-101).

1.2.1.1. Tesevatinib in Oncology Indications

Details on completed and ongoing studies of tesevatinib in oncology indications, including advanced solid tumors, non-small cell lung carcinoma, breast cancer, and glioblastoma can be found in the Investigator's Brochure.

1.2.1.2. Tesevatinib in ADPKD

One Phase 1b/2a study, Study KD019-101, is currently ongoing in subjects with ADPKD. As of March 2017, 73 subjects were enrolled into 5 dosing cohorts in the study, including 9 subjects receiving 50 mg once daily (QD) (Cohort 1), 8 subjects receiving 100 mg QD (Cohort 2), 5 subjects receiving 150 mg QD (Cohort 3), 14 subjects receiving 150 mg Monday, Wednesday, and Friday (Cohort 4), and 10 subjects receiving 150 mg Monday and Thursday (Cohort 5); 15 additional subjects were enrolled in the Phase 2a portion of the study, and are receiving 50 mg QD (Table 3). In addition, 12 more subjects with baseline height-adjusted total kidney volume (htTKV) ≥ 1000 mL are currently enrolled and receiving tesevatinib 50 mg QD (SILK cohort).

Table 3: Summary of KD019-101 Dose / Schedule, Demographics and Median Total Kidney Volume (mL) at Baseline

Dose/Schedule	No. Subjects	Gender (M/F)	Median Age (Years)	Median TKV (mL)
50 mg/day[a]	24	9M/15F	39	1200[b]
100 mg/day	8	5M/3F	37	1197
150 mg/day	5	2M/3F	41	923
150 mg MWF	14	4M/10F	36	1158
150 mg MT	10	4M/6F	37	644
50 mg/day (SILK)	12	6M/6F	51	2371
Total	73	30M/43F	39 (19-74)	1225* (324-6930)

Abbreviations: F, female; M, male; MT, Monday, Thursday; MWF, Monday, Wednesday, Friday; TKV, total kidney volume

[a] Includes 9 subjects from Cohort 1 and 15 subjects who were enrolled in the Phase 2a portion of the study.

[b] One subject did not have a baseline TKV value.

To date, there have been a total of 3 subjects with treatment-emergent serious adverse events (SAEs) in Study KD019-101. One subject experienced a Grade 2 episode of gastroesophageal reflux disease leading to hospitalization that was determined to be unlikely related to study drug. The episode resolved with no sequelae. One subject experienced a Grade 2 episode of angioedema leading to admission to an urgent care center. This event was determined to be unlikely related to study drug and resolved with no sequelae. One subject experienced a Grade 4 episode of depression and suicidal ideation status post-suicide attempt leading to prolonged hospitalization. This subject had previously withdrawn consent and had received their last dose of study drug approximately 11 months prior to this ongoing event.

The most common AEs (≥15%) seen in Study KD019-101 were diarrhea (38%), nausea (30%), rash (29%), blood creatine phosphokinase (CPK) increased (25%), nasopharyngitis (21%), muscle spasms (19%), vomiting (18%), blood creatinine increased (15%), and headache (15%). In addition, amylase elevations were noted in 12% of subjects. Most of the AEs experienced were mild to moderate.

Adverse events of special interest as of the data cutoff of October 2016 are described below.

Diarrhea and Rash

Diarrhea and rash were both expected as they are a class effect of all EGFR inhibitors.

At 150 mg QD, 3 of 5 patients had moderate rash occurring during the first 28 days, the event led to study discontinuation in 2 of the patients. The tolerability of intermittent dosing schedules using 150 mg (Monday, Wednesday, and Friday or Monday and Thursday) was

improved over 150 mg QD, but 1 case of severe rash occurred in a patient receiving 150 mg on Monday and Thursday. While rash at the 150 mg dose level did not meet strict safety criteria for defining the maximum tolerated dose (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.

Creatine Phosphokinase Elevations

There were 41 subjects with elevations of CPK above the normal range in Study KD019-101. Ten subjects experienced moderate CPK elevation (> 2.5 × upper limit of normal [ULN] – 5.0 × ULN), and 7 subjects experienced severe CPK elevation (> 5.0 × ULN). Quantitative whole body radiography in rats indicates relatively low accumulation of tesevatinib in skeletal muscle. In Study KD019-101, muscle AEs correlated poorly with CPK levels. While elevations of CPK commonly occur with exercise, the lack of a control group in Study KD019-101 makes it difficult to fully evaluate the relationship between tesevatinib and CPK elevations.

Amylase Elevations

Mild, asymptomatic increases in amylase were also seen in Study KD019-101, including in subjects in the 50 mg QD cohort. Across dose levels, 22 cases of asymptomatic subjects with elevated amylase levels were reported. Eighteen of these elevations were mild (> ULN – 1.5 × ULN), 2 were moderate (> 1.5 × ULN – 2.0 × ULN), and 2 were severe (> 2.0 × ULN). Four subjects had elevated amylase levels at Screening and in 2 of these subjects' amylase levels rose to moderate or severe levels, leading to discontinuation from the study. 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, this subject was discontinued from the study. Both of these subjects with severe amylase elevations had elevations of both lipase and pancreatic amylase isozyme. Other subjects with amylase elevations have not had progressive increases in amylase levels during tesevatinib administration.

Previous studies of tesevatinib have been reviewed for cases of elevated amylase or pancreatitis. Amylase had not routinely been evaluated in previous studies. There was only 1 AE of 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 computed tomography 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 ^{14}C–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 in Study KD019-101, 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 × ULN, evaluation of lipase, amylase isoenzymes, and lipid levels are performed (see Section 7.5.6).

Serum Creatinine Elevations

The initial data 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 subjects receiving the 50 mg dose reveal that creatinine values were increased by 11.1% at Day 3, by 14.3% at Day 7, and increased by 10% at Day 28. Data after Day 28, including several subjects who have received tesevatinib for 24 months, do not indicate any significant ongoing change in creatinine. During the same time period, cystatin C levels did not change (median decreases were 0%, 1.9%, and 1.7% 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; 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.

QTc Prolongation

Four incidences of asymptomatic prolongation of QTc interval to > 480ms or > 60 ms over the baseline value were reported in Study KD019-101. One subject in the 100 mg QD cohort had a mean QT interval corrected for heart rate using Fridericia's formula (QTcF) of 510 msec at Month 5 of dosing. The subject had study drug interrupted and was dose reduced to 50 mg QD with resolution of QTcF prolongation. Another subject in that cohort presented on Day 7 with a mean QTcF of 487 msec. Study drug was held. On rechallenge at the same dose, QTcF was again prolonged at 485 msec. Study drug again was held and restarted at a reduced dose of 50 mg with resolution of QTcF prolongation. One subject receiving 150 mg every Monday, Wednesday and Friday on Day 12 presented with a mean QTcF of 485 msec. Study drug was held and restarted at 100 mg every Monday, Wednesday, and Friday with resolution of QTcF prolongation. One subject receiving 150 mg every Monday and Thursday presented on Month 12 with a mean QTcF of 484 msec. Study drug was held and restarted at 50 mg QD with resolution of QTcF prolongation.

An initial evaluation of QTc duration was performed with data from 37 subjects who received doses of 50 mg to 150 mg QD in Study KD019-101. The 50 mg QD dose of tesevatinib produced modest QTcF increases. The time-averaged increase in QTcF was 4-6 ms. The time point analyses demonstrated a peak increase in QTcF of 11-15 ms at 4 hours postdose on Day

14. At the mean maximum plasma concentration (C_{max}) of 72.5 mg/mL for the pooled 50 mg dose groups, the pharmacokinetic/pharmacodynamic model predicted a mean QTcF increase of 13.3 ms, with a 1-sided upper 95% confidence bound of 16.8 ms. The magnitude of the QTc effect of the tesevatinib 50 mg QD dose is similar to that produced by moxifloxacin 400 mg.

Pericardial Effusion

One subject in Study KD019-101 receiving 50 mg QD 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 as an 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.

Conclusions

Safety conclusions from Study KD019-101 are that tesevatinib 150 mg in various schedules was associated with skin rash that was not well tolerated. While the MTD dose of 100 mg QD 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 QD as the best tolerated daily dose. Tesevatinib 50 mg QD appeared to be a well-tolerated dose in patients with ADPKD, although some acneiform rash occurred.

Further details on Study KD019-101 can be found in the Investigator's Brochure.

1.2.1.3. 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 C_{max} generally increased approximately in proportion with dose over the full dose range (ie, 3.4 to 586 mg). Mean terminal half-life after 5 consecutive QD doses ranged from 50 to 92 hours, and appeared generally independent of dose. High inter-subject variability in exposure was observed with coefficient of variation (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 tesevatinib 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 QD for at least 29 consecutive days. Tesevatinib was rapidly absorbed following oral administration (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 accumulation ratio was 4.6 (accumulation ratio based on 300 mg QD dose). The median T_{max} at the MTD was 4 hours.

1.3. Study Rationale

Rationale for the ADPKD Indication

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 summary, both the nonclinical and clinical results to date suggest that tesevatinib may be a promising therapeutic for ADPKD.

Rationale for Dosage Selection

Safety reviews after the first 2 cohorts in Study KD019-101 (50 mg QD and 100 mg QD) deemed these cohorts to have adequate safety and to be tolerable. In the 150 mg QD cohort, 3 of 5 subjects enrolled withdrew 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 QD. While the MTD dose of 100 mg QD was based on criteria defined in the protocol, the occurrence of moderate QT prolongation in 2 subjects dosed at that level led to a decision later in the study to recommend 50 mg QD as the best tolerated daily dose.

Study KD019-101 is currently enrolling additional subjects at the dose of 50 mg QD (SILK cohort) in order to increase the robustness of the safety data in subjects with ADPKD treated with tesevatinib.

2. STUDY OBJECTIVES AND PURPOSE

2.1. Primary Objective

The primary objective of this study is to evaluate the change from baseline in htTKV as measured by magnetic resonance imaging (MRI) at Months 12, 18, 24, and 30 days post-dose in patients with ADPKD treated with tesevatinib or placebo.

2.2 Secondary Objective

The secondary objective of the study is to evaluate the safety and tolerability of tesevatinib 50 mg QD in patients with ADPKD, and to also evaluate the change in eGFR using the MDRD-4 formula at the Month 12, 18, 24, and 30 days post-dose time points.

3. STUDY DESIGN

This is a Phase 2b, multicenter, double-blind, randomized, parallel group study to evaluate the change from baseline in htTKV as measured by MRI in subjects with ADPKD treated with tesevatinib or placebo. Male and female subjects with ADPKD, 18 to 60 years of age and with an eGFR $\geq$ 30 mL/min/1.73 m^2 and $\leq$ 80 mL/min/1.73 m^2 will be enrolled. Up to 100 male and female subjects will be randomized 1:1 to receive 50 mg of tesevatinib QD or placebo. The study will be conducted at approximately 25-30 sites in the United States.

Subjects will be screened up to 28 days before initiation of treatment with tesevatinib or placebo (certain screening assessments may be conducted up to 42 days prior to dosing). Screening assessments will include medical and PKD history, physical examination, vital signs, electrocardiograms (ECGs), clinical laboratory evaluation (including hematology, serum chemistry, coagulation, thyroid stimulating hormone, urinalysis, and pregnancy), ocular examination, echocardiogram, and MRI. Calculation of htTKV at screening for eligibility determination may be performed by a local radiologist.

Starting on Day 1, subjects will receive 50 mg QD of tesevatinib or placebo for up to 24 months. During the Early Treatment Period (Days 1 to 28), subjects will report to the study site on Days 1, 14, and 28; subjects will be followed every 28 days from Months 2 to 12 and every other month from Months 12 to 24. Safety assessments will be performed at regular intervals throughout the study and will include physical examinations, vital signs, ECGs, clinical laboratory evaluations, ocular examination and echocardiograms. Magnetic resonance imaging to determine the change from baseline in htTKV will be performed at Months 12, 18, and 24. Entry into the study will be based on local MRI readings, but central MRI readings and htTKV calculation will be performed at baseline and during the study.

All subjects will undergo an end-of-study evaluation approximately 30 days after the last dose of study drug.

4. STUDY POPULATION

4.1. Inclusion Criteria

Subjects will be included in the study if they meet all of the following inclusion criteria:

1. 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. At least 18 years old and no more than 60 years old at the time of consent.
4. eGFR ≥ 25 mL/min/1.73 m^2 and ≤ 90 mL/min/1.73 m^2, using the Modification of Diet in Renal Disease-4 variable formula.
5. htTKV must meet the following criteria (htTKV is calculated using total kidney volume obtained from MRI divided by height in meters):
    - ≥ 500 mL for subjects 18-35 years of age
    - ≥ 750 mL for subjects 36-49 years of age
    - ≥ 900 mL for subjects 50-60 years of age
6. Subject has the following laboratory values:
    - Platelets > lower limit of normal (LLN)
    - Hemoglobin > 9 g/dL
    - Total bilirubin ≤ 1.5 mg/dL
    - Aspartate aminotransferase < 2.5 × ULN
    - Alanine aminotransferase < 2.5 × ULN
    - Prothrombin time/partial thromboplastin time ≤ 1.5 × ULN
    - International normalized ratio (INR) ≤ 1.5, except those subjects taking warfarin who must have INR ≤ 3
    - Albumin ≥ LLN
    - Amylase ≤ 1.5 x ULN
    - Lipase ≤ 1.5 x ULN
    - Serum potassium within normal limits
    - Serum magnesium within normal limits
7. Female subjects of childbearing potential must have a negative pregnancy test at screening. Females of childbearing potential are defined as sexually mature women without prior hysterectomy, bilateral tubal ligation, 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 child bearing potential if the amenorrhea is possibly due to prior chemotherapy, anti-estrogens, or ovarian suppression.

- Women of childbearing potential 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 2 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) intrauterine device **plus** 1 barrier method; (b) on stable doses of hormonal contraception for at least 3 months (eg, oral, injectable, implant, and transdermal) **plus** 1 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.

8. For male subjects who are sexually active and are partners of premenopausal women: agreement to use two forms of contraception as in criterion 7 above during the treatment period and for at least 6 months after the last dose of study drug, unless the male subject had a vasectomy.
9. Capable of understanding and complying with the protocol and has signed the informed consent form.

4.2. Exclusion Criteria

Subjects meeting any of the following criteria will be excluded from participation.

1. Previous partial or total nephrectomy or a kidney transplant.
2. Tuberous sclerosis, Hippel-Lindau disease, or acquired cystic disease.
3. Congenital absence of 1 kidney and/or need for dialysis or transplantation in the foreseeable future.
4. Moderate hematuria. Subjects with microhematuria may be enrolled, unless microhematuria is suspected to be due to infection or recent cyst rupture. If hematuria is due to cyst rupture, the subject may be rescreened after discussion with the Medical Monitor.
5. Uncontrolled hypertension (systolic blood pressure > 160 mmHg; diastolic blood pressure > 100 mmHg) while receiving antihypertensive therapy.
6. Uncontrolled diabetes mellitus (glycated hemoglobin > 8%).
7. Presence of renal or hepatic calculi (stones) causing symptoms.
8. Received any investigational therapy within 30 days prior to initiation of therapy (Day 1).
9. Received tolvaptan within 30 days prior to initiation of therapy (Day 1).

10. Received active treatment (within 4 weeks of initiation of therapy [Day 1]) for urinary tract infection.
11. History of pancreatitis or known risk factors for pancreatitis.
12. Subject meets any of the following cardiac criteria:
    - Mean QTc interval corrected for heart rate using Fridericia's formula (QTcF) 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. Inclusion of subjects with a history of atrial arrhythmias should be discussed with the Medical Monitor.
    - Family history of congenital long QT syndrome or unexplained cardiac death.
    - History of ventricular rhythm disturbances.
    - Symptomatic heart failure (per New York Heart Association guidelines), unstable angina, myocardial infarction, or cerebrovascular accident within 6 months prior to study entry.
    - Has a cardiac pacemaker.
    - History of pericardial effusion or presence of pericardial effusion on screening echocardiogram
13. Subject is taking any medication known to inhibit the CYP3A4 isozyme or any drugs that are CYP3A4 inducers, or any drugs associated with torsade de pointes or known to prolong the QTcF interval, including anti-arrhythmic medications within 2 weeks prior to screening. A stable regimen (≥ 4 weeks) of antidepressants of the selective serotonin reuptake inhibitor (SSRI) class is allowed (common SSRIs include escitalopram oxalate, citalopram, fluvoxamine, paroxetine, sertraline, and fluoxetine).
14. Uncontrolled intercurrent illness that would limit compliance with study requirements including, but not limited to ongoing or active infections or psychiatric illness.
15. Subject is pregnant, plans to become pregnant, or nursing.
16. Known to be positive for the human immunodeficiency virus or hepatitis B or C, as indicated by a positive test at screening.
17. Known to be immunocompromised.
18. Documented presence of renal vascular disease resulting in uncontrolled hypertension.
19. Has previously received an EGFR inhibitor (including, but not limited to, erlotinib, gefitinib, osimertinib, afatinib, cetuximab, panitumumab, or an investigational agent).
20. Allergy or hypersensitivity to components of either tesevatinib, matched placebo, or their formulations.
21. Aphakic due to previous cataract surgery or congenital abnormality.

Note: The sponsor has the option to exclude a subject from enrollment, 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.

4.3. Withdrawal of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The Investigator or Sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The withdrawal of a subject from investigational product by the Investigator should be discussed where possible with the Medical Monitor before the subject stops investigational product.

If 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 electronic case report form (eCRF). Study withdrawal should include the final assessments, as required by the protocol and every effort should be made to perform the End-of-study procedures (see Table 2).

A termination eCRF must be completed for all enrolled subjects.

Subjects who discontinue will not be replaced.

Subject Stopping Criteria

If an adverse event (AE) is a reason for discontinuation, then "Adverse event" must be recorded as the reason for discontinuation on the eCRF.

Reasons for discontinuation include but are not limited to:

- Adverse event (including, but not limited to, symptomatic pericardial effusion or cardiac tamponade)
- Intercurrent event preventing the administration of tesevatinib for more than 28 days
- Protocol violation
- Request by a regulatory agency (eg, institutional review board [IRB])
- Withdrawal by subject
- Lost to follow-up
- Lack of efficacy
- Pregnancy
- Other (must be specified).

Subjects 'Lost to Follow-up' Prior to Last Scheduled Visit

At least 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). One of these

documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return any unused investigational product and return to the site for final safety evaluations.

5. CONCOMITANT MEDICATION

5.1. Concomitant Medication and Potential Interactions

Subjects should not receive additional therapeutic treatment during the study period without the approval of the Sponsor's Medical Monitor.

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 and grapefruit juice with study drug or at any time during the study. 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 (see Appendix 1). Additionally, subjects should not take medications that are associated with a risk of QTcF interval prolongation and/or torsades de pointes (see Appendix 2).

Tesevatinib is 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.

Based on in vitro evaluation, tesevatinib may be a weak substrate for P-glycoprotein (P-gp). Since P-gp is extensively expressed in multiple tissues and is involved in the transport of a vast variety of biological molecules, drugs such as colchicine, verapamil, tamoxifen, cyclosporine, and digoxin should be monitored.

Anti-emetics and antidiarrheal medications should not be administered prophylactically before initial treatment with study drug. At the discretion of the Investigator, treatment of symptoms with anti-emetic and antidiarrheal medications may be undertaken per standard clinical practice.

Since tesevatinib is a potent inhibitor of multidrug and toxic compound extrusion (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.

5.2. 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 anti-arrhythmics (eg, quinidine, procainamide); Class III anti-arrhythmics (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. A list of concomitant medications associated with a risk of QTc interval prolongation and/or torsades de pointes can be found in Appendix 2.

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.

Beginning at Month 2, 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 on 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.

6. INVESTIGATIONAL PRODUCT

6.1. Identity of Investigational Product

Tesevatinib will be provided in 50 mg tablets; matched placebo will also be provided.

Tesevatinib tablets are white to off-white round tablets that contain 50% (w/w) active product ingredient in the current lactose-based immediate-release formulation.

6.2. Administration of Investigational Product(s)

Interactive Voice/Web Response System for Investigational Product Management

Study drug assignment and administration will use an interactive voice/web response system (IVRS/IWRS). Details are provided in Section 7.4.

Dosing

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.

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 orange, etc.) products should be avoided for the duration of study treatment. On days when subjects report to the study site for study procedures, study drug dosing will be done at the study site.

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. 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.

Blinding the Treatment Assignment

This is a double-blind, placebo-controlled study.

Allocation of Subjects to Treatment

This is a randomized, double-blind, placebo-controlled study. The actual treatment given to individual subjects is determined by a randomization schedule.

Subject screening numbers are assigned to all subjects as they consent to take part in the study. Within each site (numbered uniquely within a protocol), this number is assigned to subjects according to the sequence of presentation for study participation.

A randomization number/unique identifier is allocated once eligibility has been determined. Once a randomization number/unique identifier has been assigned, that number must not be used again if, for example, a subject is withdrawn from the study. If a randomization number/unique identifier is allocated incorrectly the Clinical Research Associate (CRA)/Study Monitor must be notified as soon as the error is discovered.

Individual subject treatment is automatically assigned by the IVRS/IWRS.

Unblinding the Treatment Assignment

Data that may potentially unblind the treatment assignment (ie, investigational product serum concentrations, treatment allocation, and investigational product preparation/accountability data) will be handled with special care during the data cleaning and review process. Any data that may unblind study team personnel will be presented as blinded information or otherwise will not be made available. If applicable, unblinded data may be made available to quality assurance representatives for the purposes of conducting independent drug audits.

The treatment assignment must not be broken during the study except in emergency situations where the identification of the investigational product is required for further treatment of the subject. In the event that the treatment assignment is broken, the date, the signature of the person who broke the code, and the reason for breaking the code are recorded on the IVRS/IWRS and the source documents. Upon breaking the blind, the subject is withdrawn from the study, but should be followed up for safety purposes. Any code-breaks that occur must be reported to the Sponsor. Code-break information is held by the pharmacist/designated person at the site and by Medical Monitor for the study or designee.

6.3. Labeling, Packaging, Storage, and Handling

Labeling

The following information will be printed on the label for clinical lots of study drug:

KD019 or Placebo 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

Packaging

Tesevatinib 50 mg tablets and matched placebo tablets are packaged in 30-cc high-density polyethylene bottles capped with 28-mm, childproof caps.

Changes to Sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the Sponsor.

Storage

The Investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

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). The Sponsor must be notified upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The Sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary.

Under no circumstances should product be dispensed to subjects until the impact is determined and product is deemed appropriate for use by Sponsor.

Study drug must be inventoried according to applicable regulations.

6.4. Investigational Product Quality Complaints

Once a Product Quality Complaint is identified, investigators must report it to Kadmon. This includes any instances wherein the quality or performance of a Kadmon investigational product does not meet expectations (eg, inadequate or faulty closure, product contamination), the product does not meet the specifications defined in the application for the product (eg,

wrong product such that the label and contents are different products), or the product does not meet appearance specifications (eg, broken or chipped tablets).

6.5. Drug Accountability

Investigators will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The Investigator or designee will acknowledge receipt of the investigational product documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The Investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (eg, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the Investigator. This delegation must be documented in the applicable study delegation of authority form.

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.

The Investigator or his/her designee (as documented by the Investigator in the applicable study delegation of authority form) will administer/dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensing will be documented on the eCRFs and/or other investigational product record. The Investigator is responsible for assuring the retrieval of all investigational product from subjects. No investigational product stock may be removed from the site where originally shipped without prior knowledge and consent by the Sponsor. If such transfer is authorized by the Sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

The Sponsor or its representatives must be permitted access to review the supplies storage and distribution procedures and records provided that the blind of the study is not compromised.

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 Sponsor's requirements.

With the written agreement of the Sponsor, at the end of the study all unused stock, subject returned investigational product, and empty/used investigational product packaging may be destroyed at the site or a local facility. In this case, destruction records identifying what was destroyed, when and how must be obtained with copies provided to the Sponsor. If the site cannot meet the Sponsor requirements for disposal, arrangements will be made between the site and the Sponsor or its representative for destruction or return of unused study drug supplies. Investigational products being returned to the Sponsor's-designated contractors must be counted and verified by clinical site personnel and the Sponsor (or designated contractor). For unused supplies where the original supplied tamper-evident feature is verified as intact,

the tamper evident feature must not be broken and the labeled amount is to be documented in lieu of counting. All certificates of delivery/drug receipts should be signed by the site representative to confirm contents of shipment. Shipment return forms, when used, must be signed prior to shipment from the site. Validated electronic return systems (ie, IVRS/IWRS) do not require a shipment form. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Authorization from the Sponsor should be sought prior to any shipment of investigational products. Shipment or destruction of investigational products must be in accordance with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the Sponsor's satisfaction.

6.6. Subject Compliance

Subjects must be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability must be assessed at the container/packaging level for unused investigational product that is contained within the original tamper evident sealed container (eg, bottles, trays, vials) or at the individual count level for opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

In addition, subject diaries will be used to evaluate compliance. Subject diaries will be dispensed on Day 1 and reviewed at each visit.

6.7. Warnings, Precautions, and Management

Adverse events that have been associated with tesevatinib include the following: diarrhea, skin rash, QTcF 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 dosing (Early Treatment Period).

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 28-day Early Treatment Period, 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.

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.

6.7.1.1. Suggestions for Rash Management

Papulopustular (acneiform) rash is the most common rash seen with EGFR inhibitors, and is typically seen in the first few weeks of treatment. It usually peaks at Weeks 4 to 6 and decreases in severity between Weeks 6 and 8. Post-inflammatory skin changes can last for months, so prevention and reactive treatment are important.

Suggestions for the management of skin rash are provided in Table 4.

Table 4: Suggestions for Skin Rash

Stage	Suggested Treatment for Skin Rash
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) • Use UVA ocular protection (ie, sunglasses with UVA filtering) when outside • Hypoallergenic makeup when possible
Once Rash Appears[a]	• Ongoing use of treatments from preventative treatments above • Mild (<10% BSA involved, without pruritus or tenderness) o Topical steroids (refer to Appendix 3 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) o 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** o Systemic Treatment ▪ Doxycycline 100 mg BID (less renal toxic than minocycline, but can cause photosensitivity) • Severe (> 30% BSA involved, limiting ADLs) o Refer to dermatology o 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** o Systemic treatment ▪ Doxycycline 100 mg BID ▪ Oral steroids: prednisolone 10 mg QD for 1 week or equivalent

Once Rash Reappears	• Over the course of treatment rash may come and go
	  ○ Hydrocortisone 1% cream with moisturizer and sunscreen BID, 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 discontinuation of tesevatinib should be discussed with the Medical Monitor.

Abbreviations: ADL, activity of daily living; BID, twice daily; BSA, body surface area; QD, once daily; SPF, sun protection factor; UVA, ultraviolet A
a See Appendix 3 for steroid potency chart.
Source: Lacouture, 2011[9], Kiyohara 2013[10], www.psoriasis.org

QT Interval Prolongation

Risk factors for occurrence of arrhythmia include hypokalemia, hypomagnesemia, bradycardia, and concurrent use of multiple medications that prolong the QTcF interval. In vivo observations of QTcF prolongation in association with use of tesevatinib have been observed, including severe QTcF prolongation. However, the lack of a clearly discernible pattern to such occurrence makes prediction of individual subject risk difficult. Therefore, the following are recommended:

- Study drug should be administered to subjects who have normal serum potassium and serum magnesium levels.
- Study drug should not be administered to subjects with pathologic bradycardia.
- Medications with potential for QTcF prolongation should not be used concurrently or started within 24 hours of study drug 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[11] and may require additional monitoring or adjustment if subjects develop diarrhea.

6.7.1.2. Response to QTcF Interval Prolongation

The following guidelines should be used in the management of QTcF prolongation. Subjects will have ECGs performed as outlined in Table 2. If the average QTcF interval (from 3 consecutive ECGs taken with an interval of at least 1-2 minutes within 30 minutes) 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.
- Manage as clinically indicated with cardiology consultation as needed.
- Contact the 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, appropriate management and ECG follow-up should be discussed with the Medical Monitor.

Elevated Amylase

If subjects develop an elevated serum amylase during the study that is > 2.0 × 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 back to the baseline value after the end of the drug holiday, study drug may be restarted, and amylase measured approximately 14 days later, and then at the start of each cycle of study drug administration. If results continue to be abnormal, the subject will be removed from study. If an elevated serum amylase that is > 2.0× ULN occurs a second time, the subject will be removed from the study.

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.

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 is diagnosed, study drug should be discontinued and treatment administered as necessary.

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 > 3 × ULN.

Management guidelines for liver function abnormalities are provided in Table 5.

Table 5: Management Guidelines for Liver Function Abnormalities

Liver Function Abnormality	Occurrence	Action
Hyperbilirubinemia		
2.5 – < 3 × ULN	1st	Hold dose; resume dosing when recovered or reduced to mild intensity.
	2nd	Off study.
> 3 × ULN	1st	Off study.
AST/ALT elevations		
2.5 – < 3 × ULN	1st	Hold dose; resume dosing when recovered or reduced to mild intensity.
	2nd	Hold dose and discuss management with Medical Monitor.
> 3 × ULN	1st	Hold dose and discuss management with Medical Monitor.
	2nd	Off study.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

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 guidelines outlined below 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. Results of the additional echocardiogram should be discussed 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.

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.

7. STUDY PROCEDURES

7.1. Study Schedule

The schedule of assessments for this study is provided in Table 2.

All screening assessments are to be performed within 28 days prior to the first dose of study drug, unless otherwise specified. Study eligibility will be based on satisfying all of the study inclusion and exclusion criteria. Day 1 is defined as the date the subject takes the first dose of study drug.

A screen failure is a subject who has given informed consent and failed to meet the inclusion and/or meet at least 1 of the exclusion criteria and has not been randomized or administered investigational product(s) as defined by the protocol.

7.2. Informed Consent Process

The subject will be given a verbal explanation of the study, including information about the study drug and the study procedures, and will have all questions adequately addressed. The subject must sign and date a consent form that has been approved by the IRB before the screening procedures are initiated. All subjects will be given a copy of the signed and dated informed consent form.

7.3. Demographics and Medical History

A complete medical history will be taken. Information to be documented includes demographic information, prior medical illnesses and conditions (including PKD genotype, if available), and surgical procedures.

7.4. Randomization

Each subject who completes the study screening assessments, meets all eligibility criteria will be assigned a unique identification number and will receive the corresponding treatment according to a randomization scheme generated by the IVRS/IWRS vendor. The randomization schedule will be prepared by the IVRS/IWRS vendor using a validated program. The IVRS/IWRS will assign a randomization number to subjects that will be used to link the subject to a treatment group and will specify a unique medication number for the study drug to be dispensed to the subject. Randomized subjects who terminate their study participation for any reason, regardless of whether study treatment was taken or not, will retain their randomization number. IVRS/IWRS personnel not involved with any of the protocol operations will prepare the randomization schedule.

7.5. Safety Measurements

Physical Examination, Height and Weight

A complete physical examination to include documentation of height (at Screening) and weight will be performed by a physician or staff member who is qualified to perform such examinations (eg, physician's assistant, nurse practitioner). Any abnormal or clinically significant findings from the physical examination must be recorded in the appropriate eCRF. Findings at screening and prior to dosing on Day 1 will be recorded as medical history.

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.)

Vital Signs

Vital sign measurements will be collected after the subject has been sitting for 5 minutes. Vital sign assessments will include measurements of sitting blood pressure (mm Hg), heart rate (beats per minute), respiration rate (breaths per minute), and temperature (Celsius). Predose vital signs should be collected within 4 hours prior to dosing, and postdose vital signs should be taken within ± 15 minutes of the scheduled time point.

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 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. The correct cuff and bladder size should be utilized and recorded. Two or more readings separated by 1–2 minutes should be averaged. If the first 2 readings differ by more than 5 mm Hg, 1 or 2 additional readings should be obtained and averaged.

Electrocardiogram

Electrocardiograms will be performed with the subject in a supine position having rested in this position for at least 5 minutes before each reading. Triplicates should be obtained, with an interval of 1-2 minutes between ECGs.

During the study, all ECGs will be digitally analyzed by a validated central ECG vendor. Additional details on collection of ECGs will be provided in a separate manual.

The QT interval will be corrected using Fridericia's formula, adapted from Fridericia, 1920 [12]:

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

All subjects must demonstrate an average screening QTcF value of ≤ 450 msec by central digital analysis in order to be enrolled in the study. During the study, immediate clinical management of subjects will 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 QTcF 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 removed from the trial (see guidelines in Section 6.7.1.2).

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 an SAE (see Section 8.2.3).

Echocardiogram

Echocardiograms for determination of ejection fraction and evaluation of pericardial effusion and cardiac valve function will be collected at the time points specified in Table 2.

Ocular Monitoring

Ocular monitoring will be performed at the time points specified in Table 2. Ocular monitoring will include an assessment of best corrected distance visual acuity, fundoscopic exam with non-dilated pupils, slit lamp photography of the iris, non-mydriatic photography of retina within the arcade, and optical coherence tomography of the optic nerve head and macula.

Clinical Laboratory Evaluations

A central laboratory will perform clinical laboratory evaluations.

The Investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. 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 eCRF page. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition may be, at the discretion of the Investigator or Sponsor, repeated until confirmed, explained, or resolved as soon as possible. If laboratory values constitute part of an event that meets criteria defining it as serious, the event (and associated laboratory values) must be reported as an SAE (see Section 8.2.3).

At the investigator's discretion, any subset of the laboratory panels in Table 6 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 6: Clinical Laboratory Tests

Serum Chemistry		
• albumin • amylase • alkaline phosphatase • ALT • AST • bicarbonate	• BUN • calcium • chloride • creatinine • CPK (plus CPK isoenzymes if CPK is elevated) • lactate dehydrogenase	• phosphorous • potassium • random glucose • sodium • total & direct bilirubin • total protein • magnesium
Hematology		
• RBC count • WBC with differential (including neutrophils, basophils, eosinophils, lymphocytes, monocytes)	• hemoglobin • hematocrit • platelet count	• MCV • MCH • MCHC
Coagulation		
• PT	• PTT	• INR
Urinalysis		
• 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)
Other		
• Creatinine clearance[a] • Pregnancy test[b]	• cystatin C • fasting triglycerides[c] • lipase[d] • amylase isoenzymes[e] • CPK isoenzymes[f]	• TSH • Hepatitis and HIV[f] • HbA1c[f]

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CPK, creatine phosphokinase; HbA1c, glycated hemoglobin; HIV, human immunodeficiency virus; INR, international normalized ratio; MCH, mean cell hemoglobin; MCHC, mean cell hemoglobin concentration; MCV, mean cell volume; PT, prothrombin time; PTT, partial thromboplastin time; RBC, red blood cell; TSH, thyroid stimulating hormone; ULN, upper limit of normal; WBC, white blood cell

a. To be calculated using serum creatinine (Modification of Diet in Renal Disease-4 variable formula).

b. Pregnancy tests will be done using urine samples. A positive test result (confirmed by serum testing) will require immediate discontinuation from the study.
c. To be collected in the event that serum amylase increases to > 1.5 × ULN
d. To be collected at Screening and in the event of that serum amylase increases to > 1.5 × ULN
e. To be collected in the event that CPK increases to > 2.0 × ULN.
f. To be collected only at Screening.

Concomitant Medications

Prior and concomitant medications will be recorded throughout the study (from Screening through 28 days following the last dose of study drug). Refer to Section 5 for details on concomitant medications that should be avoided or taken with caution during the study.

Adverse Events

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (eg, "Have you had any health problems since your last visit?"). Adverse events collection is detailed in Section 8.

7.6. Efficacy Measurements

Magnetic Resonance Imaging

Magnetic resonance imaging measurements will be used to explore the efficacy of tesevatinib. Kidney volume will be determined by MRI at the time points specified in Table 2.

The volume of each kidney should be measured in T1-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. Height-adjusted total kidney volume is calculated using total kidney volume obtained from MRI divided by height in meters.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1. Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An ***Adverse Event*** **(AE)** is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

All AEs should be captured on the AE eCRF.

Findings at screening and prior to dosing on Day 1 will be recorded as medical history. Where possible, a diagnosis, rather than a list of symptoms, should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), an outcome is reached, stabilization (the Investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained regardless of whether the subject is still participating in the study. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by the 5-point Clinical Symptom and Adverse Event Grading Scale provided in Table 7.

Table 7: 5-point 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

Relationship Categorization

A Physician/Investigator must make the assessment of relationship to investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as 'not related'. Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered 'related'. The causality assessment must be documented in the source document.

The additional guidance in Table 8 may be helpful.

Table 8: Relationship Assessment for Adverse Events

Term	Relationship	Definition
Definitely Related	Yes	The event is felt to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered related if: • It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues; • It could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors or other modes of therapy administered to the subject; and • It disappears or decreases* upon cessation of drug or reduction on dose and appears upon rechallenge; • It follows a known response pattern to the suspected drug. *There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. The first 3 criteria must be met for the event to be considered definitely related.
Probably Related	Yes	The event is felt with a high degree of certainty to be related to the administration of study drug. The relationship can be considered probably related if: • It follows a reasonable temporal sequence from the administration of study drug; • It could not be reasonably explained by the known characteristics of the subject's clinical state, environment or toxic factors or other modes of therapy administered to the subject; and • It disappears or decreases upon cessation of drug or reduction of dose;* • It follows a known response pattern to the suspected drug. *There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists. The first 3 criteria must be met for the event to be considered probably related.

Term	Relationship	Definition
Possibly Related	Yes	The event is felt to be unlikely due to the administration of study drug but the possibility cannot be ruled out with certainty. The relationship to study drug can be considered possibly related if: • It follows a reasonable temporal sequence from the administration of study drug; and • It could readily have been the result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subjects; • It follows a known response pattern to the suspected drug. The first 2 criteria must be met for the event to be considered possibly related.
Unlikely Related	No	The event is felt to be unlikely due to the administration of study drug after careful medical consideration. The relationship to study drug can be considered unlikely related if: • It does not follow a reasonable temporal sequence from administration of the drug; and • It could readily have been a result of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subjects; • It does not follow a known response pattern to the suspected drug; • It does not reappear or worsen when the drug is re-administered. The first 2 criteria must be met for the event to be considered unlikely related.
Not Related	No	The event is felt to be due to extraneous causes (disease, environment, etc.) that are not related to the administration of study drug.

Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the CRF. Outcomes are as follows:

- Resolved
- Resolved with Sequelae
- Ongoing
- Death
- Unknown

Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease. However, significant worsening of the symptoms should be recorded as an AE.

Clinical Laboratory Evaluations

A change in the value of a clinical laboratory investigation can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory values which were not present at baseline, further clinical or laboratory investigations should be performed until the values return to within the reference range or until a plausible explanation (eg, concomitant disease) is found for the abnormal clinical laboratory values.

The Investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory parameter is clinically significant and therefore represents an AE.

Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Table 2.

Any report of pregnancy for any female subject or the partner of a male subject must be reported within 1 business day to the Pharmacovigilance vendor (see Table 1). The female subject must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the Investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days post-partum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported within 24 hours using the Serious Adverse Event Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the Investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Serious Adverse Event Form as well as the Pregnancy Report Form. The test date of the first positive serum/urine pregnancy test or ultrasound result will determine the pregnancy onset date.

Overdose and Medication Error

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 study drug 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.

Cases of subjects missing doses of product are not considered reportable as medication errors.

Medication errors should be collected/reported for all products under investigation. The administration and/or use of the unassigned treatment is always reportable as a medication error. The administration and/or use of an expired product should be considered as a reportable medication error.

8.2. Serious Adverse Event Procedures

Reference Safety Information

The reference for safety information for this study is the Investigator's Brochure which the Sponsor has provided under separate cover to all Investigators.

Reporting Procedures

All initial and follow-up SAE reports must be reported by the Investigator to the Pharmacovigilance vendor (see Table 1) within 24 hours of the first awareness of the event. Note: The 24 hours reporting requirement for SAEs does not apply to reports of abuse, misuse, or overdose (see Section 8.1.7) unless they result in an SAE.

The Investigator must complete, sign, and date the Serious Adverse Event Form and verify the accuracy of the information recorded on the form with the corresponding source documents and fax or e-mail the form to the Pharmacovigilance vendor.

Serious Adverse Event Definition

A ***Serious Adverse Event*** **(SAE)** is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening

  NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe.

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect

- Is an important medical event. Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in inpatient hospitalization; or the development of drug dependency or drug abuse.

Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE.

However, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meets serious criteria must be reported as SAE(s).

8.3. Serious Adverse Event Collection Timeframe

All SAEs (regardless of relationship to study) are collected from the time the subject signs informed consent until the defined follow-up period stated in Table 2, and must be reported to the Pharmacovigilance vendor (see Table 1) within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the Investigator at any interval after the study has completed must be reported to the Pharmacovigilance vendor (see Table 1) within 24 hours of the first awareness of the event.

Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the SAE onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject prior to study entry or leading up to the onset date of the SAE or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product).

Regulatory Agency, Institutional Review Board, Independent Ethics Committee, and Site Reporting

Kadmon Regulatory Affairs (or designee) is responsible for notifying the relevant regulatory authorities of related, unexpected SAEs.

In addition, the Sponsor is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the tesevatinib program.

The Investigator is responsible for notifying the local IRB and the Sponsor of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1. Data Collection

The Investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A Study Monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's Meeting. It is expected that site personnel will complete the eCRF entry within 5 business days of the subject's visit.

9.2. Clinical Data Management

Data are to be entered into a clinical database as specified in the data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

9.3. Statistical Analysis Process

Details regarding the statistical methods and definitions will be provided in the Statistical Analysis Plan. The SAP will be finalized prior to unblinding to preserve the integrity of the statistical analysis and study conclusions.

Categorical data will be summarized by frequency distributions (number and percentages of subjects) and continuous data will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).

All data will be provided in by-subject listings.

All statistical analyses will be performed after the database is locked and unblinded. Statistical analyses will be performed using Version 9.1 or higher of SAS®.

9.4. Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

There is no planned interim analysis, adaptive design, or Data Monitoring Committee in this study.

9.5. Selection of Subjects to be Included in the Analyses

The following populations will be used in this study:

- The Modified Intent-To-Treat (mITT) population: as all randomized subjects who received at least 1 dose of study drug.

- The Efficacy Population: all subjects in the mITT population who complete at least 12 months of tesevatinib or placebo treatment and have a centrally read MRI at baseline and after 12 months of treatment.

9.6. Subject Disposition

Subjects in each analysis set, as well as subjects who complete the study, and subjects who prematurely discontinue from the study will be summarized by treatment group using descriptive statistics. In addition, for subjects who prematurely discontinue from the study, the reasons for discontinuation will be summarized by treatment group.

9.7. Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented by treatment group and overall for the mITT population.

Demographics and baseline characteristics will be examined to assess the comparability of the treatment groups at baseline. Continuous variables such as subject age, weight and height will be summarized using number of observations, mean, standard deviation, median, minimum, and maximum values. Categorical variables such as subject sex and race will be summarized using number of observations and percentages for each category.

Medical history will be summarized by treatment group using the number of observations and percentages of subjects reporting each category.

9.8. Investigational Product Exposure

Summary statistics for the duration of exposure to investigational product will be presented by treatment group. In addition, the number of dose interruptions will be provided in by-subject listings.

9.9. Prior and Concomitant Medication

Prior and concomitant medications will be coded using the World Health Organization drug dictionary. Prior and concomitant medications will be listed and summarized by preferred drug name and treatment group.

9.10. Efficacy Analyses

All efficacy analyses will be based on the Efficacy Population.

The primary efficacy endpoint will be the change from baseline in htTKV at Month 12. An analysis of covariance model including treatment group as a factor and the baseline htTKV as a covariate will be used for efficacy analyses. The Type I error rate will be set at an alpha level of 0.05. Additional efficacy endpoints include change from baseline in htTKV at Months 18, 24, and 30 days post-dose.

In addition, the change in eGFR at the Month 12, 18, 24, and 30-days post-treatment time points will be evaluated.

9.11. Safety Analyses

Safety analyses will be based on the mITT Population.

Treatment-emergent adverse events (TEAE) will be coded using the Medical Dictionary for Regulatory Activities (Version 19.0 or higher). The number of events, incidence, and percentage of TEAEs will be presented by system organ class and by preferred term for each treatment group. Treatment-emergent adverse events will be further summarized by severity and relationship to investigational product. Adverse events related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be summarized/listed.

Clinical laboratory tests (including serum creatinine, cystatin C, and eGFR), vital signs, and ECG findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

Physical examination, echocardiogram and ocular evaluation findings will be provided in listings.

9.12. Sample Size Calculation and Power Considerations

Based on the results presented in Caroli, et.al.[1] it is anticipated that the mean change from baseline in htTKV at 12 months will be 83.6 (± 90.0) mL in the placebo group. Assuming the mean change from baseline in htTKV at 12 months is 26.4 mL for the tesevatinib group, 40 subjects per group would yield approximately 80% power to detect a difference between treatment groups based on a 2-sided t-test with a Type I error rate of 0.05. Ten additional subjects per group will be added (ie, for a total of 50 subjects per group) to adjust for drop-outs and differences in analysis methodologies (eg, the htTKV data will be log-transformed).

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Council for Harmonisation (ICH), and local ethical and legal requirements.

10.1. Sponsor's Responsibilities

Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations and ICH Good Clinical Practice (GCP) Guideline E6 (1996).

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the Sponsor to inspect study data, subjects' medical records, and CRFs in accordance with current GCP and the respective local and inter/national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The Sponsor ensures that Local Regulatory Authority requirements are met before the start of the study. The Sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any Regulatory Authority approvals required prior to release of investigational product for shipment to the site.

Public Posting of Study Information

The Sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating Investigators' names and contact information.

Study Suspension, Termination, and Completion

The Sponsor may suspend or terminate the study or part of the study at any time for any reason. If the study is suspended or terminated, the Sponsor will ensure that applicable regulatory agencies and IRBs are notified as appropriate. Additionally, the discontinuation of a registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2. Investigator's Responsibilities

Good Clinical Practice Compliance

The Investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996) and applicable regulatory requirements and guidelines.

It is the Investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The

Investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The Investigator will maintain a list of appropriately qualified persons to whom the Investigator has delegated significant study-related tasks. *Curriculum vitae* for Investigators and sub-investigators are provided to the study Sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the Investigator should, with the subject's consent, inform them of the subject's participation in the study.

A Coordinating Principal Investigator is appointed to review the final Clinical Study Report for multi-site studies. Agreement with the final Clinical Study Report is documented by the signed and dated signature of the Coordinating Principal Investigator, in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

Protocol Adherence and Investigator Agreement

The Investigator and any co-investigators must adhere to the protocol as detailed in this document. The Investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an Investigator Agreement to confirm acceptance and willingness to comply with the study protocol.

If the Investigator suspends or terminates the study at their site, the Investigator will promptly inform the Sponsor and the IRB and provide them with a detailed written explanation. The Investigator will also return all investigational product, containers, and other study materials to the Sponsor. Upon study completion, the Investigator will provide the Sponsor, IRB, and regulatory agency with final reports and summaries as required by national regulations.

Communication with local IRBs, to ensure accurate and timely information is provided at all phases during the study, may be done by the Sponsor, applicable contract research organization, Investigator, or by the Coordinating Principle Investigator, according to national provisions and will be documented in the Investigator Agreement.

Documentation and Retention of Records

10.2.1.1. Case Report Forms

The Investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. Electronic case report forms must be completed by the Investigator or designee as stated in the site delegation log. Corrections to data will be made according to the Code of Federal Regulations (CFR) 21 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.

All data sent to the Sponsor must be endorsed by the Investigator.

The CRA/Study Monitor will verify the contents against the source data per the Monitoring Plan. If the data are unclear or contradictory, queries will be sent for corrections or verification of data.

10.2.1.2. Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but is not limited to: subject's medical file and original clinical laboratory reports.

All key data must be recorded in the subject's medical records.

The Investigator must permit authorized representatives of the Sponsor, the respective national, local, or foreign regulatory authorities, the IRB, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/Study Monitor (and auditors, IRB or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the Sponsor or its representatives, national or local regulatory authorities, or the IRB having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration [FDA] or an auditor).

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the Sponsor.

10.2.1.3. Audit/Inspection

To ensure compliance with relevant regulations, data generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), other regulatory authorities, the Sponsor or its representatives, and the IRB for each site.

10.2.1.4. Financial Disclosure

The Investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the value of the compensation for conducting the study could be influenced by the outcome of the study. The following information is collected: any significant payments from the Sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the Sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

In consideration of participation in the study, the Sponsor pays the Investigator or nominated payee the sums set out in the payment schedule attached to the Investigator agreement.

10.3. Ethical Considerations

Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from all study subjects prior to any study related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and GCP. Each subject or the subject's legally-authorized representative as applicable is requested to sign the Subject Informed Consent Form or a certified translation, if applicable after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative as applicable. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The Principal Investigator provides the Sponsor with a copy of the consent form which was reviewed by the IRB and which received their favorable opinion/approval. A copy of the IRB's written favorable opinion/approval of these documents must be provided to the Sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, Sponsor or Coordinating Principal Investigator) is responsible for this action. Additionally, if the IRB requires modification of the sample Subject Information and Consent document provided by the Sponsor, the documentation supporting this requirement must be provided to the Sponsor.

Institutional Review Board or Independent Ethics Committee

It is the responsibility of the Investigator to submit this protocol, the informed consent document (approved by the Sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs is defined in the Investigator Agreement.

Prior to implementing changes in the study, the Sponsor and the IRB must approve any revisions of any revised informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the Sponsor has received written IRB approval of and copies of revised documents.

The Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol, but in any case, at least once a year. The Investigator must also keep the local IRB informed of any serious and significant AEs.

10.4. Privacy and Confidentiality

All sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act of 1996 (HIPAA). A site that is not a Covered Entity as defined by HIPAA, must provide documentation of this fact to the Sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the Sponsor and/or its representatives will review their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the Sponsor; third parties with whom the Sponsor may develop, register, or market drug name; national or local regulatory authorities; and the IRB(s) that gave approval for the study to proceed. The Sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number. However, their initials and date of birth may also be collected and used to assist the Sponsor to verify the accuracy of the data, for example, to confirm that laboratory results have been assigned to the correct subject.

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5. Publication Policy

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the Sponsor in advance of submission. The review is aimed at protecting the Sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study 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.

11. REFERENCES

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12. APPENDICES

APPENDIX 1 CONCOMITANT DRUGS THAT INHIBIT CYP3A4 AND SHOULD NOT BE ADMINISTERED

Use of drugs that are moderate or strong inhibitors of the CYP3A4 family of enzymes is prohibited in patients who are receiving study drug.

This is not a comprehensive list, and all concomitant medications should be evaluated for possible interactions with study drug.

Moderate or Strong CYP3A4 Inhibitors	
Drug Type	**Drug Name**
Human immunodeficiency virus antivirals	indinavir
	nelfinavir
	ritonavir
	saquinavir
Antifungals	itraconazole
	fluconazole
	ketoconazole
Antibiotics	clarithromycin
	erythromycin
	telithromycin
Antidepressants	nefazodone
Calcium-channel blockers	diltiazem
	verapamil
Others	aprepitant
	grapefruit juice

Source: http://medicine.iupui.edu/clinpharm/ddis/main-table/

APPENDIX 2 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 study drug. Subjects who require treatment with these drugs should have study drug held for up to 21 days while receiving the treatment and should be closely monitored for QTcF prolongation and potential AEs. This list is not comprehensive and all concomitant medications should be evaluated for potential contribution to QTcF 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
Anticancer	arsenic trioxide
Anti-infective/pneumocystis pneumonia	pentamidine
Antimalarial	chloroquine, halofantrine
Antinausea	domperidone, droperidol
Antipsychotic	haloperidol, mesoridazine, thioridazine
Antipsychotic/anti-emetic	chlorpromazine
Antipsychotic/Tourette's tics	pimozide
Gastrointestinal stimulant/heartburn	cisapride
Opiate agonist/pain control/narcotic dependence	levomethadyl, methadone

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

APPENDIX 3 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
Cordran Tape, 0.05%	Flurandrenolide
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
Psorcon Ointment, 0.05%	Psorcon Ointment, 0.05%
Psorcon E Ointment, 0.05%	Psorcon E Ointment, 0.05%
Temovate Cream/Ointment/Solution, 0.05%	Clobetasol propionate
Ultravate Cream/Ointment, 0.05%	Halobetasol propionate
Ultravate Lotion, 0.05%	Halobetasol propionate
Vanos Cream, 0.1%	Fluocinonide
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

Brand Name	Generic Name
Class 4 – Mid-Strength	
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
Topicort LP Cream, 0.05%	Desoximetasone
Topicort LP Ointment, 0.05%	Desoximetasone
Westcort Ointment, 0.2%	Hydrocortisone Valerate
Class 5 - Lower Mid-Strength	
Capex Shampoo, 0.01%	Fluocinolone acetonide
Cordran Cream/Lotion	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
Pandel Cream, 0.1%	Hydrocortisone
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. https://www.psoriasis.org/about-psoriasis/treatments/topicals/steroids/potency-chart (accessed 15 February 2017)