Official Protocol Title:	An Open-Label Phase 2 Study To Evaluate PT2385 for the Treatment of von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma
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PROTOCOL PT2385-202

AN OPEN-LABEL PHASE 2 STUDY TO EVALUATE PT2385 FOR THE TREATMENT OF VON HIPPEL-LINDAU DISEASE-ASSOCIATED CLEAR CELL RENAL CELL CARCINOMA

Protocol Number:	PT2385-202/MK-3795-003
Sponsor:	Peloton Therapeutics, Inc., a wholly owned subsidiary of Merck & Co., Inc. (hereafter referred to as Peloton Therapeutics) 126 East Lincoln Avenue PO Box 2000 Rahway, New Jersey, 07065, USA
Medical Monitor:	PPD
Version:	5.0
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Version 3.0	02 December 2016
Version 4.0	05 January 2017

INVESTIGATOR'S AGREEMENT

I have received and read the Investigator's Brochure for PT2385. I have read the PT2385-202 protocol and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

SPONSOR APPROVAL AND SIGNATURE PAGE

SPONSOR'S APPROVAL OF PROTOCOL PT2385-202:

PPD

Medical Monitor

Date

PROCEDURES IN CASE OF EMERGENCY

Emergency Contact Information

Role in Study	Name	Address and Telephone Number
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1. SYNOPSIS

Name of Sponsor/Company: Peloton Therapeutics, Inc.	
Name of Investigational Product: PT2385	
Name of Active Ingredient: PT2385	
Title of Study: An Open-Label Phase 2 Study To Evaluate PT2385 for the Treatment of von Hippel-Lindau Disease-Associated Clear Cell Renal Cell Carcinoma	
Study Center(s): Up to 3	
Principal Investigator: PPD	
Estimated Date First Patient Enrolled: January 2017	**Phase of Development:** 2

Objectives:

Primary:

To assess overall response rate (ORR) of von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC) tumors in VHL patients treated with PT2385 as determined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1). ORR is defined as the proportion of patients with a best confirmed response of complete response (CR) or partial response (PR).

Secondary:

- To evaluate progression-free survival (PFS) in patients with VHL disease-associated ccRCC tumors treated with PT2385
- To evaluate duration of response (DOR) and time to response (TTR) in patients with VHL disease-associated ccRCC tumors treated with PT2385 who achieve a PR or better as determined by RECIST 1.1
- To study the effect of treatment with PT2385 on VHL disease-associated non-ccRCC tumors by modifying RECIST 1.1 criteria to assess tumors in individual organ systems independently rather than collectively
- To study the safety and tolerability of PT2385
- To study the pharmacokinetics (PK) of PT2385

Exploratory:

- To evaluate changes in pharmacodynamic (PD) markers (e.g., serum erythropoietin [EPO]) in patients treated with PT2385

Methodology:

This open-label Phase 2 study will evaluate the efficacy, safety, PK, and PD of PT2385 in patients with VHL disease who have at least 1 measurable VHL disease-associated ccRCC tumor (as defined by RECIST 1.1). PT2385 will be administered orally at a dosage of 800 mg twice daily; treatment will be continuous. Patients will be entered in the study after meeting all inclusion criteria and no exclusion criteria. This study will be conducted with a 2-stage design, which allows for an early assessment of futility. A response will be defined as either a PR or CR occurring at any time after initiation of treatment, based on assessment of ccRCC tumors. All responses must be confirmed after the initial response is documented. Changes in VHL disease-associated non-ccRCC tumors will also be evaluated independently by modifying RECIST 1.1 criteria to assess tumors in individual organ systems independently rather than collectively.

Twenty-five patients will be enrolled during the first stage. A Data Monitoring Committee (DMC) will perform the safety review for the first 6 patients and the futility analysis for Stage 1 of the study. The DMC will review safety and any treatment-limiting toxicities to confirm whether the study should continue to enroll or if modifications to the protocol are needed. The DMC will review the response data from the first 25 patients to determine if at least 3 patients have a confirmed PR or better and that the threshold for opening Stage 2 has been met. Treatment-limiting toxicities will be assessed according to pre-defined criteria.

In the second stage of the study, 25 additional patients will be enrolled, to a maximum accrual of 50 patients.

Patients will undergo clinical and laboratory evaluations every 2 weeks for the first 4 weeks and then every 4 weeks (i.e., 28 days) according to the Schedule of Events. Patients will be evaluated radiologically for evidence of response or progression approximately 12 weeks after initiation of treatment and every 12 weeks thereafter while continuing in the study. Patients with evidence of stable disease or disease response, i.e., CR or PR, will continue to receive treatment in the absence of serious toxicity. Patients who demonstrate disease progression of renal lesions at any time will be withdrawn from study treatment. Patients who discontinue study treatment for any reason will be followed either by telephone or office visit to for their medical history, surgical history, disease status, and survival status. These patients will be followed every 6 months for up to 3 years following completion of enrollment in the study or until the patient either withdraws consent or dies.

Number of patients (planned):

50 patients

Diagnosis and main criteria for inclusion: Patients must meet all of the following criteria to be enrolled in this study.

1. Has the ability to understand and willingness to sign a written informed consent form before the performance of any study procedures
2. Is of age ≥ 18 years
3. Has at least 1 measurable ccRCC tumor and no solid ccRCC tumor greater than 3.0 cm, based on radiologic diagnosis (histologic diagnosis not required); may have VHL disease-associated lesions in other organ systems
4. Has a diagnosis of von Hippel-Lindau disease, based on a germline VHL alteration
5. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2

6. Has normal organ and marrow function as defined below:
   - White blood cell count ≥ 3,000/μL, absolute neutrophil count ≥ 1,500/μL, hemoglobin level ≥ 9 g/dL without transfusion support within 2 weeks prior to enrollment; platelet count ≥ 100,000/μL;
   - Serum creatinine level ≤ 2.0 × upper limit of normal (ULN) or measured 24-hour creatinine clearance ≥ 30 mL/min; and
   - Levels of AST and ALT < 2.5 × ULN, total bilirubin < 1.5 × ULN (< 3 × ULN in patients with Gilbert's disease), and alkaline phosphatase ≤ 2.5 × ULN
7. If a female patient of child bearing potential, or a male patient with a female partner of child-bearing potential (defined as all women physiologically capable of becoming pregnant), must agree to use highly effective methods of contraception during screening, during the period of drug administration and for 30 days after stopping study drug administration. Highly effective contraception methods include the following:
   - Total abstinence,
   - Male or female sterilization, or
   - Combination of any 2 of the following (a + b or a + c or b + c):
     a. Use of oral, injected or implanted hormonal methods of contraception
     b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
     c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
8. Female patients of child-bearing potential must have a negative serum pregnancy test result within 7 days before first administration of study drug.

Main Criteria for Exclusion: Patients will be excluded from this study if they meet any of the following criteria.

1. Has participated or plans to participate in another clinical trial of an investigational drug (or a medical device) within 30 days of study enrollment
2. Has had prior treatment with or known allergy or hypersensitivity to a HIFα inhibitor
3. Has had prior radiotherapy or systemic anti-cancer therapy for ccRCC (includes anti-VEGF therapy or any systemic investigational anti-cancer agent)
4. Has a prior or concomitant non-VHL disease-associated invasive malignancy with the exception of adequately treated basal or squamous cell carcinoma of the skin, cervical carcinoma in situ or any other malignancy from which the patient has remained disease free for more than 2 years
5. Has any history of metastatic disease
6. Has any condition possibly affecting absorption, distribution, metabolism, or excretion of drugs that may confound the analyses conducted in this study (e.g., previous surgery on the gastrointestinal tract that includes removal of parts of stomach, bowel, liver, gallbladder, or pancreas)
7. Has known hypersensitivity to any component in the formulation of PT2385

8. Has had radiotherapy to any non-ccRCC site within 4 weeks prior to entering the study or has not recovered from adverse events (AE) (to ≤ Grade 1 National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 [NCI CTCAE 4.03]) related to agents administered more than 4 weeks earlier
9. Has had any surgical procedure for VHL disease or any major surgical procedure completed within 4 weeks prior to entering the study or has any surgical lesions from recent major surgical procedures that are not well healed
10. Has an immediate need for surgical intervention for tumor treatment
11. Has known history of positive test results for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
12. Has an active infection requiring systemic treatment
13. Has a bleeding diathesis or coagulopathy
14. Has had any major cardiovascular event within 6 months prior to study drug administration including but not limited to myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic event, pulmonary embolism, or New York Heart Association Class III or IV heart failure
15. Has any other clinically significant cardiac, respiratory, or other medical or psychiatric condition that might interfere with participation in the trial or interfere with the interpretation of trial results
16. If a female patient, intends to breast feed a child during study or within 30 days after administration of the last dose of study drug

Investigational product, dosage and mode of administration:

PT2385 tablets, 800 mg (four 200 mg tablets) administered orally, twice daily

Duration of treatment:

Patients may continue to receive PT2385 in the absence of unacceptable treatment-related toxicity or unequivocal disease progression.

Reference therapy, dosage and mode of administration:

None

Criteria for evaluation:

Efficacy

Primary Endpoint: Overall response rate (ORR) in VHL disease-associated ccRCC tumors, defined as the proportion of the best confirmed response of CR or PR (as assessed by the Independent Review Committee (IRC)) as determined by RECIST 1.1, modified to follow ccRCC tumors only

Secondary Endpoints:

- Progression-free survival (PFS) in VHL disease-associated ccRCC tumors, defined as the interval from the start of study treatment until the earlier of the first documentation of disease progression determined by RECIST 1.1 or death from any cause, and calculated for patients with a best confirmed response of CR or PR
- Duration of response (DOR) in VHL disease-associated ccRCC tumors, defined as the interval from the first documentation of response, as determined by RECIST 1.1, to the earlier of the first documentation of disease progression or death from any cause

- Time to response (TTR) in VHL disease-associated ccRCC tumors, defined as the interval from the start of study treatment to the first documentation of a response, as determined by RECIST 1.1, and calculated for patients with a best confirmed response of CR or PR
- Best confirmed response, PFS, DOR, and TTR for non-ccRCC tumors associated with VHL disease in different organ systems, by modifying RECIST 1.1 criteria to assess tumors in individual organ systems

Exploratory endpoints:

- Changes in PD markers (e.g., serum EPO)

Safety**:**

Safety and tolerability will be determined by symptoms, signs, and abnormal laboratory test results

Safety assessments include the following:

- Physical examinations
- Vital sign measurements (including pulse oximetry)
- 12-lead electrocardiograms (ECG) with QTc interval determination
- Clinical laboratory measurements
- Concomitant medications
- Incidence, intensity, and relationship of AEs and serious adverse events (SAEs)
- Effects on fertility in males (orchidometry, semen analysis, and measurement of testosterone, follicle-stimulating hormone, luteinizing hormone, and inhibin B levels)

Pharmacokinetics will be evaluated.

Statistical methods:

Sample size determination

This study will be conducted with a 2-stage design (Green and Dahlberg, 1992), which allows for an early assessment of futility. If after the first 25 patients have been accrued to the study, 2 or fewer patients have had a confirmed response, further accrual will be temporarily suspended for up to a year or until at least 3 responses are seen; if at least 3 responses are not seen within 1 year after enrollment of the 25th patient, no further patients will be enrolled and the study will be discontinued. In addition, if more than 2 of the first 6 patients enrolled experience treatment-limiting toxicity during the first 4 weeks of their treatment, the protocol will be modified or the study will be stopped. If 3 or more of the 25 patients respond, enrollment will proceed to the second stage of the study.

A total of 25 patients will be enrolled into the second stage of the study for a total required enrollment of 50 patients. If at least 13 of the 50 patients (25 + 25) respond (CR or PR), then the hypothesis that PT2385 is ineffective will be rejected.

The required sample size for this 2-stage design is based on the following design parameters: The null hypothesis is that PT2385 is ineffective, defined as an ORR (best confirmed response of PR or CR) of 15% ($P_0 = 0.15$). The alternative hypothesis is that PT2385 is effective, defined as an ORR of 30% ($P_1 = 0.3$). The probability of falsely concluding that the agent is effective when it is truly ineffective is 0.05 (alpha) and the probability of falsely concluding that the agent is ineffective when it is truly effective is 0.2 (beta).

Efficacy Assessments

Efficacy analyses will be conducted on the Efficacy Analysis Set, i.e., for patients enrolled in the study who have received at least 1 dose of PT2385. Clear cell renal cell tumor response will be assessed according to RECIST 1.1, modified to follow ccRCC tumors only. The ccRCC ORR will

be summarized. Estimates of the ccRCC ORR along with the associated 90% and 95% exact binomial confidence intervals (Clopper-Pearson method) will be provided. The binomial probability that the observed ccRCC ORR is > 0.15 will be calculated. Best confirmed response will be summarized. The ccRCC TTR will be calculated for patients who achieve a ccRCC CR or PR. The maximum percent decrease in ccRCC tumor burden will be displayed using waterfall plots. The ccRCC PFS and ccRCC DOR will be summarized descriptively using the Kaplan-Meier method. The median and quartiles of ccRCC PFS and ccRCC DOR will be calculated along with 90% and 95% confidence intervals.

Summaries of the response endpoints will also be provided for subgroups of the Efficacy Analysis Set as follows: Subgroups will be defined based on site of primary tumors other than ccRCC at screening, blood level of PT2385 based on the PK assessments, and duration of PT2385 treatment. The analyses of ORR, PFS, best confirmed response, and DOR will be performed in each of these subgroups.

The ORR, PFS, DOR, and TTR will be summarized for the individual types of non-ccRCC tumors using modified RECIST 1.1 criteria. The modification to RECIST 1.1 is to evaluate different organ system tumors independently (e.g., VHL disease-associated solid tumors in the pancreas, adrenal gland, or hemangioblastomas or retinal angiomas).

The determination of response and progression will be made by the local investigators. The investigator assessments will be used for decisions regarding treatment for individual patients and by the DMC for approval to open Stage 2 of the study. The response outcomes will also be reviewed and determined by an Independent Review Committee (IRC). For the primary analysis of ORR, the determination of response will be based on independent radiologic assessment conducted by the IRC. Both the investigators' and the IRC's assessments will be used for the summaries and analyses of efficacy.

Safety Assessments

Safety data analysis will be conducted for all patients receiving at least 1 dose of PT2385 (Safety Analysis Set). Adverse Events will be coded using Medical Dictionary for Regulatory Activities (MedDRA) terminology. Analyses will consist of data summaries for AEs, SAEs, clinical laboratory parameters, vital sign measurements, and ECG data. The QTc intervals will be summarized according to the method recorded on the electronic Case Report Form. The number and percentage of patients experiencing 1 or more AEs will be summarized by the relationship to study drug and severity. Laboratory parameters will be summarized using descriptive statistics, by post-treatment shifts relative to baseline, and data listings of clinically significant abnormal laboratory test results. Vital sign measurements and ECG data will be summarized by changes from baseline values using descriptive statistics.

Pharmacokinetic Assessments

The plasma concentrations of PT2385 and PT2639 at each collection time will be summarized.

Pharmacodynamic Assessments

Pharmacodynamic assessments will be conducted on the Efficacy Analysis Set. Summary statistics will be computed for baseline biomarkers. The change and percent change from baseline will be calculated for each subsequent measurement. Summary statistics will be computed for each collection time point. To investigate the effect of biomarkers on efficacy, the association of baseline biomarkers with ORR and PFS will be investigated using multivariate techniques, subgroup analyses, and regression modeling.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Abbreviation or Specialist Term	Explanation
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
aPTT	activated partial thromboplastin time
ARNT	aryl hydrocarbon receptor nuclear translocator
ASCO	American Society of Clinical Oncology
BUN	blood urea nitrogen
Ca	calcium
CCND1	cyclin d1
ccRCC	clear cell renal cell carcinoma
Cl	chloride
CO2	bicarbonate
CR	complete response
CRF	case report form
CT	computerized tomography
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	duration of response
ECG	electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EPO	erythropoietin
Fe	iron
Flt-1/VEGFR1	fms-like tyrosine kinase-1/vascular endothelial growth factor receptor 1
G CSF	granulocyte colony-stimulating factor
GCP	good clinical practice
GLUT1	glucose transporter 1

Abbreviation or Specialist Term	Explanation
HCT	hematocrit
Hgb	hemoglobin
HIF	hypoxia inducible factor
HIF-1α	hypoxia inducible factor 1 alpha
HIF-2 α	hypoxia inducible factor 2 alpha
HIV	human immunodeficiency virus
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IRB	institutional review board
IRC	Independent Review Committee
IUD	intrauterine device
IUS	intrauterine system
K	Potassium
KDR	kinase insert domain containing receptor
KM	Kaplan-Meier
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MPV	mean platelet volume
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
Na	Sodium
NCI CTCAE 4.03	National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03
ORR	overall response rate
PBPK	physiologically-based pharmacokinetic
PD	Pharmacodynamics
PDGF	platelet-derived growth factor
PFS	progression-free survival
PK	Pharmacokinetic
Plt	Platelets

Abbreviation or Specialist Term	Explanation
PO4	phosphate
PR	partial response
PT	prothrombin time
RDW	red blood cell distribution width
RECIST 1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
Retic	reticulocyte count
RP2D	recommended phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TBILI	total bilirubin
TEAE	treatment-emergent adverse event
TGF-α	transforming growth factor alpha
TK	toxicokinetic
t_{max}	time at which maximum concentrations occurred
TTR	time to response
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFA	vascular endothelial growth factor A
VEGFR2	vascular endothelial growth factor receptor 2
VHL	von Hippel-Lindau disease
WBC	white blood cells

4. INTRODUCTION

4.1. Background

4.1.1. Von Hippel-Lindau Disease and Renal Cell Carcinoma

Von Hippel-Lindau (VHL) disease is a hereditary cancer disease transmitted in an autosomal dominant fashion, in which affected individuals are at risk for the development of tumors in a number of organs. Affected individuals have a germline mutation and/or deletion of the VHL gene, and are at risk for developing tumors and fluid-filled sacs (cysts) in a number of organs (Linehan et al, 2001; Linehan et al, 2002; Linehan et al, 1995; Clifford and Maher, 2001; Maher and Kaelin, 1997; Kaelin, 2002). Tumors can initially appear during young adulthood; however, the signs and symptoms of von Hippel-Lindau disease can present throughout life (Genetics Home Reference, downloaded February 23, 2016).

Patients with VHL disease are at risk for developing renal cysts and clear cell renal cell carcinomas (ccRCC), pheochromocytomas, pancreatic cysts, neuroendocrine tumors, hemangioblastomas of the brain and spinal cord, retinal angiomas, inner ear endolymphatic sac tumors, and epididymal and broad ligament cystadenomas. Renal cell carcinoma occurs in 30% to 70% of individuals with VHL disease and is the leading cause of mortality (Chittiboina and Lonser, 2015).

Von Hippel-Lindau disease-associated renal tumors, which are uniformly ccRCC histological subtype, are malignant tumors that can metastasize and are generally incurable once metastatic (Hwang et al, 2003; Poston et al, 1995). The clinical management of VHL disease-associated renal tumors involves active surveillance until the largest renal tumor reaches approximately 3 cm, at which time nephron-sparing surgical intervention is recommended. This threshold was determined by an analysis of patient data collected over a 30-year time period; no patient with maximum renal tumor diameter less than 3 cm developed metastases (Walther, Choyke et al, 1999; Pavlovich et al, 2002). Surgical management may involve partial or complete nephrectomy; partial nephrectomy is recommended whenever possible. Patients affected with VHL disease are at risk for the development of up to 600 renal tumors and 1300 renal cysts. Von Hippel-Lindau renal cancer surgery is often very extensive; as many as 90 tumors may be removed from a kidney during a single surgery. Complications from such extensive surgery are not uncommon and can include significant blood loss, infection, loss of the kidney, pulmonary emboli, and death. A retrospective review of 30 patients who underwent a total of 34 partial nephrectomies, with removal of at least 20 tumors in each kidney revealed perioperative complications in > 50% of the cases. Other complications included blood loss, significant renal function decline, and 1 death (Fadahunsi, 2011).

Surgery does not cure VHL disease patients with ccRCC; surgery is intended to prevent the development of metastasis. In the great majority of patients, the tumors continue to recur and repeated surgeries are required to prevent death from metastatic kidney cancer. These surgeries carry significant morbidity and, sometimes, mortality. Many patients have undergone 4 or 5 sequential surgeries on a single kidney, sometimes on both kidneys. The extensive renal surgeries required inevitably leads to progressive decrease in renal function in these patients. Many patients will develop renal insufficiency, which may lead to shortened

life span, and some patients require dialysis and/or renal transplantation. Despite the most aggressive lifelong surveillance with the most experienced clinical/surgical team, a number of these patients will still go on to develop metastatic ccRCC, which is almost always fatal (Walther, Choyke et al 1995; Walther, Lubensky et al, 1995; Herring et al, 2001; Hwang et al, 2003; Drachenberg et al, 2004; Grubb et al, 2005; Bratslavsky, Liu et al, 2008; Boris et al, 2009; Bratslavsky, Linehan et al, 2010; Liu et al, 2010; Fadahunsi et al, 2011; Gupta et al, 2013). The life expectancy of VHL disease patients with ccRCC is only 40 to 52 years (Chittiboina and Lonser, 2015).

Once the renal tumors have metastasized the treatment algorithm follows that of advanced sporadic ccRCC with anti-VEGF/VEGFR therapy, immune-modulators and mTOR inhibitors (inhibitors of the mammalian target of rapamycin). These agents have had a limited role in the treatment of VHL disease or VHL disease-associated ccRCC prior to metastases. Both sunitinib (a multi-kinase inhibitor) and vandetanib (a dual VEGFR/EGFR inhibitor) have been evaluated in Phase 2 studies in VHL disease patients (Jonasch et al, 2011; Stamatakis et al, 2013). While both agents demonstrated activity, their tolerability was a major issue, resulting in discontinuation of treatment in a significant proportion of patients and discontinuation of development of the products for this disease. Consequently, the treatment approach for VHL disease-associated renal tumors remains surgical resection of tumors greater than 3 cm in diameter.

4.1.1.1. The von Hippel-Lindau Tumor Suppressor Gene

A study of VHL kindreds at the National Cancer Institute (NCI) led to identification of the *VHL* gene (Latif et al, 1993). The *VHL* gene is a classical tumor suppressor gene and tumorigenesis due to VHL inactivation conforms to Knudson's 'two-hit' hypothesis (Knudson, 1986). The gene has 3 exons that encode the VHL protein (Latif et al, 1993).

While *VHL* mutations were initially identified in the germline of patients with VHL disease, inactivation of the gene by somatic mutation or promoter hypermethylation has also been described in a high proportion of sporadic ccRCC. The function of VHL proteins and the biochemical consequences of *VHL* gene inactivation have been studied extensively. Von Hippel-Lindau protein forms a complex with other cellular proteins including elongins B and C, and Cullin 2 (Pause et al, 1997). This complex plays an important role in the degradation of cellular proteins via the ubiquitin pathway. Inactivation of the *VHL* gene consequently leads to accumulation of proteins targeted for degradation through this pathway. These proteins include the alpha subunits of a group of transcriptionally active proteins called the hypoxia inducible factors (HIFs) (Maxwell et al, 1999). Accumulation of HIFs results in overexpression of several genes including those encoding vascular endothelial growth factor A (VEGFA), glucose transporter 1 (GLUT1), transforming growth factor alpha (TGF-α), platelet-derived growth factor (PDGF), cyclin D1 (CCND1) and erythropoietin (EPO) (Linehan et al, 2001; Linehan et al, 2002; Linehan et al, 1995; Clifford and Maher, 2001). VEGFA is an important regulator of tumor angiogenesis that supports tumor growth and progression. VEGFA exerts its activity through several receptor tyrosine kinases expressed on endothelial cells, chief among them being the fms-like tyrosine kinase-1/vascular endothelial growth factor receptor 1 (Flt-1/VEGFR1) and the kinase insert domain containing receptor/vascular endothelial growth factor receptor 2 (KDR/VEGFR2) (Ferrara, 2001). In addition to promoting angiogenesis in the tumor microenvironment, *VHL*

inactivation can also directly promote tumor growth via the autocrine and paracrine effects of transforming growth factor alpha (TGF-α), and PDGF, which act through receptor tyrosine kinases such as the epidermal growth factor receptor (EGFR, a receptor for TGF-α) expressed on tumor cell surface. Thus, VHL deficiency initiates a series of downstream events that promote tumor progression.

4.1.1.2. HIF-2α

A strong connection has been established among the histologic features of ccRCC, mutations in the VHL tumor suppressor gene and the subsequent activation of HIF-2α transcriptional activity (Shen and Kaelin, 2013). More than 90% of sporadic ccRCC tumors have defective or deficient VHL function through deletion, mutation, or hypermethylation of the *VHL* gene (Sato et al, 2013). Although both HIF-1α and HIF-2α are stabilized upon VHL loss, a greater role has been ascribed to HIF-2α in the pathobiology of ccRCC. As much as 40% of sporadic ccRCC have reduced copy number and expression of HIF-1α, and HIF-2α alone is sufficient to support the growth of ccRCC mouse xenografts (Sato et al, 2013, Kondo et al, 2002). In this setting, HIF-2α will accumulate, even under normoxic conditions, and drive the expression of genes associated with tumor growth. Preclinical studies showed that HIF-2α depletion or pharmacologic antagonism is sufficient to inhibit ccRCC tumor growth (Kondo et al, 2002; Wallace et al, 2016; Chen et al, 2016; Cho et al, 2016). HIF-2α has therefore been established as an oncogenic driver in ccRCC, where VHL deficiency is the underlying genomic alteration. In VHL disease, renal tumors are of clear cell histology (Lund et al, 1994; Poston et al, 1995). Further, expression of HIF-2α has been found to correlate with disease development in renal cancer, as well as in paraganglioma and pheochromocytoma associated with VHL disease (Mandriota et al, 2002; Pollard et al, 2006). Thus, HIF-2α stabilization and activation appears to be common to the spectrum of neoplasms associated with VHL deficiency, suggesting that HIF-2α may be a major driver of the disease pathology. Inhibition of this transcription factor is a novel approach that could lead to a significant new treatment option for patients with VHL disease.

4.1.2. PT2385

PT2385 is a first-in-class small molecule inhibitor of HIF-2α, which impairs hypoxic signaling in cancer cells.

4.1.2.1. Pharmacologic Activity

PT2385 is a potent and selective inhibitor both in vitro and in vivo and has been shown to inhibit signaling by disrupting the formation of the HIF-2α: aryl hydrocarbon receptor nuclear translocator (ARNT) heterodimer in cells. Thus, in tumors where HIF-2α is activated, PT2385 blocks the transcription of several genes involved in oncogenesis, CCI [redacted]

Additionally, PT2385 has demonstrated anti-tumor activity in CCI [redacted] mouse xenograft models of *VHL* mutant ccRCC, resulting in tumor stasis after oral administration at 3 mg/kg twice daily, and nearly complete regression after oral administration at 10 mg/kg twice daily and 20 mg/kg once daily. In efficacy studies comparing once and twice daily dosing, the response was greater (3 mg/kg twice daily versus 6 mg/kg once daily) and more

rapid (10 mg/kg twice daily versus 20 mg/kg once daily) with twice daily dosing. PT2385 has shown no activity (up to 10 μM) against other Per-ARNT-Sim-B (PAS-B) domain-containing proteins or against a large panel of receptors, ion channels, and kinases. Studies to date have not revealed any cardiovascular, central nervous system or respiratory safety pharmacology issues with PT2385 treatment in vitro or in vivo. Refer to the Investigator's Brochure for additional information.

Preclinical studies demonstrate that PT2385 is a potent and selective inhibitor of HIF-2α. Additionally, they demonstrate that inhibition of HIF-2α with PT2385 is efficacious in the treatment of sporadic ccRCC tumors with VHL mutations in mouse models. Although there are no mouse models for evaluating PT2385 in VHL disease pathologies, the preclinical and clinical data for PT2385 in sporadic ccRCC support its testing in ccRCC associated with VHL disease, given the identical histologic and molecular characteristics of these 2 types of renal cancer.

4.1.2.2. Pharmacokinetic Data

Absorption of PT2385 following administration of an oral dose was rapid in all species, with the time at which maximum concentrations occurred (t_{max}) between 0.5 and 2 hours in most preclinical studies. Oral bioavailability was high in mice and dogs (95% and 89%, respectively), moderate in rats (41%), and low in monkeys (16%) following a single oral dose.

Overall, exposure to PT2385 in rats and dogs was somewhat dose proportional up to doses of 300 mg/kg, was less than dose proportional up to 450 or 600 mg/kg, and showed little to no increase with doses of 1000 mg/kg. There was no consistent evidence of a sex difference in PT2385 exposure in rats and dogs.

PT2385 showed time-dependent pharmacokinetics following 28-day twice-daily dosing in rat and dog toxicokinetic (TK) studies. The ratio of Day 28/Day 1 PT2385 $AUC_{0\text{-}tau}$ (area under the plasma concentration curve from time over 1 dose interval) decreased as dose increased, which was more severe in dogs than in rats.

Tissue distribution after administration of a single oral dose of PT2385 was evaluated in rats. The highest concentration of PT2385 was observed in the liver followed by the heart, kidney lung, plasma and brain. Permeability across the blood-brain barrier was also demonstrated after administration of repeat doses in mice and in rats, where concentrations of PT2385 were similar in plasma and brain tissue. The in vitro plasma protein binding of PT2385 was moderate and ranged from 64% to 82% across species (82% for human plasma protein).

In vitro, the primary biotransformation route of PT2385 was direct conjugation to form a glucuronide conjugate (PT2639), oxidative metabolism to M+16, oxidative defluorination and subsequent conjugation to glucuronides. No human specific metabolite was found. Enzyme phenotyping results suggested PT2385 was primarily metabolized via UGT2B17, UGT2B7, UGT2B15, CYP2C19 and CYP3A4 in human.

PT2385 is not a potent inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (IC50 > 8.8 μg/mL). It is unlikely to significantly inhibit these CYPs at the clinically relevant PT2385 concentrations (maximum peak concentration [C_{max}] ~ 3.14 μg/mL).

PT2385 induced concentration-dependent increases in CYP2B6 and CYP3A4 mRNA in cultured human hepatocytes. Simcyp physiologically-based pharmacokinetic (PBPK) model simulations indicate a weak-to-moderate CYP3A4 substrate midazolam drug-drug interaction (DDI) (~50% reduction in midazolam AUC) at the clinical relevant PT2385 doses. A qualitative assessment of the DDI liability of sunitinib, cabozantinib, and axitinib when co-administered with PT2385 was performed using literature data; the expected DDI effects with these kinase inhibitors are smaller than the effect predicted for midazolam. Simulations also indicate that PT2385 is a weak CYP2B6 inducer (< 11% AUC reduction for CYP2B6 substrate bupropion at the clinical relevant PT2385 doses).

4.1.2.3. Toxicity

The nonclinical toxicology studies were designed to assess the toxicity potential of PT2385, with appropriate TK monitoring. Exploratory studies assessed the tolerability of PT2385 in mice, rats and dogs. Based on the findings that the putative metabolites predicted in humans were also observed in rat and dog hepatocytes, and oral administration of PT2385 to these species achieved good bioavailability, the rat and dog were selected for definitive toxicity studies. The tolerability studies demonstrated a reversible dose-responsive effect on the red blood cell compartment. This effect encompassed the total red blood cell count, hemoglobin concentration and hematocrit with reductions in all indices. The immature red cell fraction, as noted by the reticulocyte count, was also impacted in a reversible manner.

The definitive toxicity studies were designed to assess the safety and reversibility of effects from PT2385 administration. Twice-daily PT2385 was administered orally for 28 days to rats and dogs in GLP studies. Overall results demonstrated PT2385 to be clinically well tolerated for up to 28 days with twice-daily administration. There were no deaths in either toxicity study. A recoverable mild anemia was identified in both studies, similar to the pilot experiments. In both the rat and dog studies, a hepatocellular hypertrophy was observed histologically, indicative of an adaptive response. This effect was completely reversible following removal of the test item. Based on metabolism studies examining CYP3A4 and CYP2B6 mRNA induction in human hepatocytes, this effect may relate to induction of hepatic enzymes. This histological finding corresponded with a dose-dependent increase in liver weights and a reduction in plasma concentrations from Day 1 to Day 28 in both the rat and dog.

From the 28-day studies, the only identified target organs for toxicity were the testes and epididymis in male rats. The effect was dose responsive on the seminiferous tubule epithelium and ranged from mild to marked in severity. Following the recovery period, the testes did not demonstrate recovery of effect, while the epididymis demonstrated a partial recovery of effect. Possibly, a longer recovery period that captured the entire cycle of spermatogenesis (63 days) could have afforded complete recovery. No target organs were identified in female rats.

PT2385 did not have a consistent effect on the testes of male dogs, however sporadic effects were noted. These changes were considered related to the young age of the animals. No target organs were identified in female dogs.

Assessment of genotoxicity included in vitro bacterial mutagenicity and chromosomal aberration assays. Both assays were conducted with and without metabolic activation and both yielded negative results with PT2385.

PT2385 will be administered orally at a dosage of 800 mg twice daily. This dose was identified in the initial study of PT2385 in humans, a Phase 1 study in patients with advanced clear cell renal cell carcinoma, as the recommended Phase 2 dose (RP2D) (Courtney et al, 2016). The starting dose in that study was 100 mg twice daily based on the identification of the mid dose, 200 mg/kg/day, as the highest non-severely toxic dose because of associated minimal to moderate changes in the testes and epididymis that were not completely reversible.

4.1.2.4. Clinical Studies

PT2385 has not previously been studied in patients with VHL disease. Clinical studies of PT2385 in ccRCC are ongoing. Under Protocol PT2385-101, patients with advanced ccRCC who had been treated with at least 1 prior treatment with a VEGF inhibitor were treated with PT2385 twice daily in a 3+3 Phase 1 design to determine the maximum tolerated dose (MTD)/RP2D and to evaluate safety, PK, and pharmacodynamics (PD). The 26 patients enrolled in the dose-escalation portion received PT2385 at oral dosages of 100 to 1800 mg twice daily. No dose limiting toxicities (DLTs) were observed at any dose level. Exposure generally increased with dose up to the 800 mg dose, without a further increase from 800 to 1800 mg. At 800 mg, PT2385 was rapidly absorbed with a C_{max} of 3.14 µg/mL and a $t_{1/2}$ of 17 hours. The targeted C_{min} of 280 ng/mL was exceeded in the majority of patients receiving a twice daily dose of ≥ 800 mg. Circulating plasma levels of EPO rapidly decreased within 24 hours in most patients receiving ≥ 800 mg and remained suppressed during the 16-week sampling period. Based on safety, PK, and EPO PD data, the RP2D has been defined as oral 800 mg twice daily. An additional 25 patients were enrolled in an expansion cohort at the RP2D. As of August 15, 2016, the most common adverse events (AEs) of any severity have been anemia, peripheral edema, and fatigue. One patient had a complete response (CR), 4 patients had a partial response (PR), and 16 patients had stable disease (SD) for more than 16 weeks. PT2385 administration was safe and well tolerated, and has demonstrated early evidence of clinical activity in these heavily pre-treated patients with advanced ccRCC (Courtney et al, 2016).

A Phase 1 food effect study of PT2385 was conducted in healthy female volunteers. The most common AEs were headache, injection site bruising, and nausea. The presence of food had a mild effect (19% to 37% increase) on the exposure to PT2385 in this study; little to no effect was observed in exposure to PT2639, the major metabolite, in the presence of food.

4.2. Study Rationale

This study is part of the clinical program to investigate PT2385 as a treatment for VHL disease-associated ccRCC.

Patients affected with VHL, a rare hereditary cancer syndrome, are at risk to develop ccRCC as well as pheochromocytomas; pancreatic cysts; neuroendocrine tumors; hemangioblastomas of the brain and spinal cord; retinal angiomas; inner ear endolymphatic sac tumors; and epididymal and broad ligament cystadenomas. The current treatment

paradigm is based upon frequent monitoring and surgery, as no therapies are approved for treatment of VHL disease. Although effective in limiting metastatic disease spread, surgery is associated with significant morbidity, particularly in patients undergoing multiple surgical interventions. Development of systemic options that can delay or obviate the need for surgery is, therefore, desirable.

Patients enrolled in this present study will be treated with oral PT2385, 800 mg twice daily. Overall response rates in this patient population will provide insight into the efficacy of PT2385 as reduction in tumor size relates to preclusion or delay of surgery-associated morbidity and mortality.

5. TRIAL OBJECTIVES AND PURPOSE

This open-label Phase 2 study will evaluate the efficacy, safety, tolerability, PK, and PD of PT2385 for the treatment of VHL disease-associated ccRCC.

5.1. Primary Objective

To assess overall response rate (ORR) of von Hippel-Lindau (VHL) disease-associated ccRCC tumors in VHL patients treated with PT2385 as determined by Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1, Appendix 3); ORR is defined as the proportion of patients with a best confirmed response of complete response (CR) or partial response (PR).

5.2. Secondary Objectives

- To evaluate progression-free survival (PFS) in patients with VHL disease-associated ccRCC tumors treated with PT2385
- To evaluate duration of response (DOR) and time to response (TTR) in patients with VHL disease-associated ccRCC tumors treated with PT2385 who achieve a PR or better as determined by RECIST 1.1
- To study the effect of treatment with PT2385 on VHL disease-associated non-ccRCC tumors by modifying RECIST 1.1 criteria to assess tumors in individual organ systems independently rather than collectively
- To study the safety and tolerability of PT2385
- To study the pharmacokinetics (PK) of PT2385

5.3. Exploratory Objectives

- To evaluate changes in pharmacodynamic (PD) markers (e.g., serum EPO) in patients treated with PT2385

6. INVESTIGATIONAL PLAN

6.1. Overall Study Design

This open-label Phase 2 study will evaluate the efficacy, safety, PK, and PD of PT2385 in patients with VHL disease who have at least 1 measurable VHL disease-associated ccRCC tumor (as defined by RECIST 1.1). PT2385 will be administered orally at a dosage of 800 mg twice daily. Treatment will be continuous; the drug will be administered twice daily every day. Patients will be entered in the study after meeting all inclusion criteria and no exclusion criteria. This study will be conducted with a 2-stage design, which allows for an early assessment of futility. A response will be defined as either a PR or CR occurring at any time after initiation of treatment, based on assessment of ccRCC tumors. All responses must be confirmed after the initial response is documented. Changes in VHL disease-associated non-ccRCC tumors will also be evaluated independently by modifying RECIST 1.1 criteria to assess tumors in individual organ systems independently rather than collectively.

Twenty-five patients will be enrolled during the first stage. A Data Monitoring Committee (DMC) will perform the safety review for the first 6 patients and the futility analysis for Stage 1 of the study. The DMC will review safety and any treatment-limiting toxicities to confirm whether the study should continue to enroll or if modifications to the protocol are needed. The DMC will review the response data from the first 25 patients to determine if at least 3 patients have a confirmed PR or better in ccRCC tumors and that the threshold for opening Stage 2 has been met. Treatment-limiting toxicities will be assessed according to Section 6.4. Study termination criteria are presented in Section 6.5.

In the second stage of the study, 25 additional patients will be enrolled, to a maximum accrual of 50 patients.

Patients will undergo clinical and laboratory evaluations every 2 weeks for the first 4 weeks and then every 4 weeks (i.e., 28 days) according to the Schedule of Events. Patients will be evaluated radiologically for evidence of response or progression approximately 12 weeks after initiation of treatment and every 12 weeks thereafter while continuing in the study. Patients with evidence of stable disease or disease response, i.e., CR or PR, will continue to receive treatment in the absence of serious toxicity. Patients who demonstrate disease progression of their ccRCC tumors at any time will be withdrawn from study treatment.

Patients who need surgical intervention for VHL-disease associated non-ccRCC tumors, and who do not meet the RECIST 1.1 criteria for progression of the ccRCC tumors, while participating in the study, may be allowed to resume study drug administration, as long as study drug has been withheld no more than 8 weeks, and there is no progression of ccRCC tumors. Patients with non-ccRCC tumors that meet the RECIST 1.1 criteria for progression will be withdrawn from study treatment.

Patients who undergo resection of non-renal VHL disease-associated lesions, and who do not meet the RECIST 1.1 criteria for progression of those lesions, may resume treatment with PT2385 once the surgical incisions have adequately healed, and if in the opinion of the Principal Investigator, the patient is likely to experience clinical benefit.

Patients who discontinue from study treatment for any reason will be followed every 6 months either by telephone or office visit to determine their medical history, surgical history,

disease status, and survival status. These patients will be followed for up to 3 years following the completion of enrollment in the study or until the patient either withdraws consent or dies.

6.2. Number of Patients

A total of 50 patients will be enrolled in the study: 25 patients will be enrolled in the first stage; 25 patients will be enrolled in the second stage.

6.3. Treatment Assignment

After meeting all inclusion and no exclusion criteria, enrolled patients will be assigned to treatment with open-label PT2385. The treatment will be administered orally at a dosage of 800 mg twice daily (four 200 mg PT2385 tablets twice daily).

6.4. Dose Adjustment Criteria

For patients who experience a treatment-limiting toxicity and require dose modification, the guidelines in Table 1 will be used to determine the dose modification required. If the Investigator believes that the guidelines should not apply, he/she will contact the Sponsor's medical monitor to discuss the circumstances and the appropriate dose modification.

Patients requiring surgical intervention for non-renal lesions during the course of the study should have study drug treatment interrupted. Study drug may be restarted when the surgical incision has adequately healed, provided there is no evidence of progression of ccRCC, and study drug interruption has been for no more than 8 weeks. Patients with non-renal lesions that meet the RECIST 1.1 criteria for progression will be withdrawn from study treatment.

Patients requiring study drug interruption for more than 3 weeks will be withdrawn from study treatment, except in the instance of interruption for surgery as noted above.

Treatment-limiting toxicity in the first 6 patients will be defined as any of the following events occurring in the first 28 days of treatment, graded using the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI CTCAE 4.03):

- Hematologic
  - Febrile neutropenia (absolute neutrophil count < 1,000/μL plus body temperature ≥ 38.5°C)
  - Grade 4 neutropenia lasting for > 5 days (in the absence of growth factor support)
  - Grade 3 thrombocytopenia with bleeding
  - Grade 4 thrombocytopenia
  - Grade 4 anemia unexplained by underlying disease
- Gastrointestinal
  - Grade 3 or 4 nausea, vomiting, or diarrhea that persists for > 48 hours despite optimal antiemetic or antidiarrheal treatment

- Hepatic
  - Grade 3 or greater increase in transaminase levels, if confirmed upon repeat testing within 48 hours
  - Grade 3 or 4 increase in transaminase levels if accompanied by a Grade 2 increase in bilirubin level and an alkaline phosphatase level > 2 × upper limit of normal (ULN)
- Other
  - Any other study drug-related Grade 3 or 4 non-hematologic toxicity, except for Grade 3 asymptomatic hypoxia unless considered clinically significant by the Investigator
  - Any study drug-related Grade 3 or 4 laboratory toxicity that does not resolve within 48 hours and is considered clinically significant by the Investigator.

Table 1 Guidelines for Dose Modification

Toxicity	Occurrence	Action
Hematologic • ANC < 1,000/μL + body temperature ≥ 38.5°C, or • Gr 4 neutropenia for > 5 days, or • Gr 3 thrombocytopenia with bleeding, or • Gr 4 thrombocytopenia, or • Gr 4 anemia unexplained by underlying disease	1st	Hold study drug. Once toxicity has resolved to < Gr 2 or baseline, restart PT2385 at a 25% reduction of the assigned dose.
	2nd	Hold study drug. Once toxicity has resolved to < Gr 2 or baseline, restart PT2385 at a 50% reduction of the assigned dose
	3rd	Discontinue PT2385.
Gastrointestinal • Gr 3 or 4 nausea, vomiting, or diarrhea if persistent for > 48 hours despite optimal antiemetic or antidiarrheal therapy	1st	Hold study drug. Once toxicity has resolved to < Gr 2 or baseline, restart PT2385 at a 25% reduction of the assigned dose.
	2nd	Hold study drug. Once toxicity has resolved to < Gr 2 or baseline, restart PT2385 at a 50% reduction of the assigned dose
	3rd	Discontinue PT2385
Hepatic • ≥ Gr 3 increase in transaminase levels, if confirmed upon repeat testing within 48 hours, or • Gr 3 or 4 increase in transaminase levels if accompanied by a Gr 2 increase in bilirubin level and an alkaline phosphatase level < 2 × ULN	1st	Discontinue PT2385

Toxicity	Occurrence	Action
Other • Any other Gr 3 toxicity, with the exception of Gr 3 cardiovascular, vascular or thrombotic events and Gr 3 asymptomatic hypoxia unless considered clinically significant by the Investigator	1st	Hold study drug. Once toxicity has resolved to < Gr 2 or baseline, restart PT2385 at a 25% reduction of the assigned dose.
	2nd	Hold study drug. Once toxicity has resolved to < Gr 2 or baseline, restart PT2385 at a 50% reduction of the assigned dose
	3rd	Discontinue PT2385
Other • Any study drug-related Gr 3 cardiovascular, vascular or thrombotic events • Any other study drug-related Gr 4 non-hematologic toxicity • Any study drug-related Gr 3 or 4 laboratory toxicity that does not resolve within 48 hours and is considered clinically significant by the Investigator	1st	Discontinue PT2385

ANC = absolute neutrophil count; Gr = Grade; ULN = upper limit of normal.

6.5. Criteria for Study Termination

If more than 2 of the first 6 patients enrolled in the first stage of the study experience treatment-limiting toxicity within the first 4 weeks of their treatment, the protocol will be modified or the study will be stopped. If after the first 25 patients have been enrolled in the study, 2 or fewer patients have had a confirmed ccRCC tumor response of PR or better, further enrollment will be temporarily suspended for up to a year or until at least 3 confirmed responses are seen. If 3 confirmed responses have not been observed within1 year after enrollment of the 25th patient, no further patients will be enrolled and the study will be stopped.

A Data Monitoring Committee (DMC) will perform the safety review for the first 6 patients and the futility analysis for Stage 1 of the study. The DMC will consist of the Principal Investigator(s) participating in this study, the Medical Monitor, and representatives from Peloton. The DMC will meet shortly after the sixth patient has been observed for 28 days after the administration of their initial PT2385 dose. The DMC will review safety and any treatment-limiting toxicities to confirm whether the study should continue to enroll or if modifications to the protocol are needed. The DMC will review the response data from the first 25 patients to determine if at least 3 patients have a confirmed PR or better in ccRCC tumors and that the threshold for opening Stage 2 has been met. Treatment-limiting toxicities will be assessed according to Section 6.4.

7. SELECTION AND WITHDRAWAL OF PATIENTS

7.1. Informed Consent

Written informed consent (see Section 16.3) must be obtained from the patient before any study related procedures are performed and whenever the study procedures change or new safety information becomes available that may affect the patient's willingness to participate.

Male patients must be provided with information about the option for sperm banking before providing written informed consent.

7.2. Patient Eligibility

Inclusion and exclusion criteria should be reviewed during the time period indicated for Screening in Appendix 1, Schedule of Events. Patients must meet all of the inclusion and none of the exclusion criteria for study entry.

7.2.1. Patient Inclusion Criteria

Patients must meet all of the following criteria to be enrolled in this study.

1. Has the ability to understand and willingness to sign a written informed consent form before the performance of any study procedures
2. Is of age ≥ 18 years
3. Has at least 1 measurable ccRCC tumor and no solid ccRCC tumor > 3.0 cm, based on radiologic diagnosis (histologic diagnosis not required); may have VHL disease-associated lesions in other organ systems
4. Has a diagnosis of von Hippel-Lindau disease, based on a germline VHL alteration
5. Has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (see Appendix 2)
6. Has normal organ and marrow function as defined below:
   - White blood cell count ≥ 3,000/µL, absolute neutrophil count ≥ 1,500/µL, hemoglobin level ≥ 9 g/dL without transfusion support within 2 weeks prior to enrollment; platelet count ≥ 100,000/µL;
   - Serum creatinine level ≤ 2.0 × ULN or measured 24-hour creatinine clearance ≥ 30 mL/min; and
   - Levels of AST and ALT < 2.5 × ULN, total bilirubin < 1.5 × ULN (< 3 × ULN in patients with Gilbert's disease), and alkaline phosphatase ≤ 2.5 × ULN

7. If a female patient of child-bearing potential, or a male patient with a female partner of child-bearing potential (defined as all women physiologically capable of becoming pregnant), must agree to use highly effective methods of contraception during screening, during the period of drug administration and for 30 days after stopping study drug administration. Highly effective contraception methods include the following:
   - Total abstinence,
   - Male or female sterilization, or
   - Combination of any 2 of the following (a + b or a + c or b + c):
     a. Use of oral, injected or implanted hormonal methods of contraception
     b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
     c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository
8. If a female patient of child-bearing potential, must have a negative serum pregnancy test result within 7 days before first administration of study drug.

7.2.2. Patient Exclusion Criteria

Patients will be excluded from this study if they meet any of the following criteria.

1. Has participated or plans to participate in another clinical trial of an investigational drug (or a medical device) within 30 days of study enrollment
2. Has had prior treatment with or known allergy or sensitivity to a HIFα inhibitor
3. Has had prior radiotherapy or systemic anti-cancer therapy for ccRCC (includes anti-VEGF therapy or any systemic investigational anti-cancer agent)
4. Has a prior or concomitant non-VHL disease-associated invasive malignancy with the exception of adequately treated basal or squamous cell carcinoma of the skin, cervical carcinoma in situ or any other malignancy from which the patient has remained disease free for more than 2 years
5. Has any history of metastatic disease
6. Has any condition possibly affecting absorption, distribution, metabolism or excretion of drugs that may confound the analyses conducted in this study (e.g., previous surgery on the gastrointestinal tract that includes removal of parts of stomach, bowel, liver, gallbladder, or pancreas)
7. Has known hypersensitivity to any component in the formulation of PT2385
8. Has had radiotherapy to any non-ccRCC site within 4 weeks prior to entering the study or has not recovered from adverse events (AE) (to ≤ Grade 1 NCI CTCAE 4.03) related to agents administered more than 4 weeks earlier

9. Has had any surgical procedure for VHL disease or any major surgical procedure completed within 4 weeks prior to entering the study or has any surgical lesions from recent major surgical procedures that are not well healed
10. Has an immediate need for surgical intervention for tumor treatment.
11. Has known history of positive test results for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)
12. Has an active infection requiring systemic treatment
13. Has a bleeding diathesis or coagulopathy
14. Has had any major cardiovascular event within 6 months prior to study drug administration including but not limited to myocardial infarction, unstable angina, cerebrovascular accident, transient ischemic event, pulmonary embolism, or New York Heart Association Class III or IV heart failure (see Appendix 5)
15. Has any other clinically significant cardiac, respiratory, or other medical or psychiatric condition that might interfere with participation in the trial or interfere with the interpretation of trial results
16. If a female patient, intends to breast feed a child during study or within 30 days after administration of the last dose of study drug.

7.2.3. Patient Withdrawal Criteria

Patients have the right to withdraw from the study or study treatment at any time for any reason. The Investigator may discontinue a patient from the study or study treatment for any of the following reasons:

- Disease progression per RECIST 1.1
- Occurrence of an AE, development of an intercurrent illness/condition, or change in patient's condition that leads the Investigator to be concerned about the patient's welfare
- Treatment-limiting toxicity or intolerable toxicity
- Noncompliance with study procedures
- Failure to comply with study drug administration instructions, to return for follow up, or to meet other requirements of the study
- Pregnancy in a female patient during the study
- Death
- Withdrawal of consent

The reason for a patient's withdrawal from the study or study treatment will be recorded in the case report form (CRF). Patients who withdraw from study participation for any reason may not re-enter the study at any time.

Patients who discontinue from study treatment will be asked to complete the early termination and safety follow-up procedures according to the Schedule of Events, Appendix 1. During the safety follow-up the patient should be evaluated for continuation or resolution of any treatment-related AEs/SAEs

Long-term follow-up will begin at the time a patient discontinues study treatment for any reason and will continue for up to 3 years following completion of enrollment in the study or until the patient withdraws consent or dies.

8. TREATMENT OF PATIENTS

8.1. Description of Study Drug

Table 2 Investigational Product

	Investigational Product
Product Name	PT2385
Dosage Form	Tablet
Unit Dose	200 mg
Route of Administration	Oral
Physical Description	White capsule-shaped tablet
Manufacturer	Peloton Therapeutics, Inc., Dallas, TX

8.2. Concomitant Medications

Patients may not receive chemotherapy, anti-neoplastic hormonal therapy, or any investigational anti-neoplastic agent during the course of this study. Immunosuppressive agents are prohibited during the course of study participation. Systemic steroids may not be used in the study at doses greater than the equivalent of 20 mg prednisone daily with the exception of intermittent use for the treatment of emesis.

Patients may receive limited fraction palliative radiotherapy after 12 weeks to control local tumor-related symptoms if irradiation is unlikely to induce major organ toxicity and only if in the opinion of the Investigator, the patient does not have progressive disease. The radiation field cannot encompass a target lesion. Radiation to a target lesion is considered progressive disease and the patient should be removed from study treatment.

Antiemetic agents may be used for the treatment of nausea and vomiting but may not be administered prophylactically. Granulocyte colony-stimulating factor (G-CSF) should be administered only for severe or prolonged neutropenia or for neutropenic sepsis. There will be no constraint on the use of growth factors during subsequent treatment; however, prophylactic use is discouraged and adherence to the American Society of Clinical Oncology (ASCO) guidelines is recommended. Erythropoietin should not be administered during the first 28 days of study drug treatment.

Patients should receive all necessary supportive care, including blood products, transfusions, antibiotics, pain medications, bisphosphonates, and replacement hormonal therapies (insulin, thyroid hormones, estrogen/progesterone) as needed, but levels should be closely monitored.

PT2385 is primarily metabolized by UGT2B17, UGT2B7, UGT2B15, CYP2C19 and CYP3A4. Strong inhibitors of CYP2C19 and CYP3A4 should be avoided in patients receiving PT2385 (Appendix 6).

PT2385 has been shown to induce the enzymes CYP3A4 and CYP2B6 in cultured human hepatocytes. Simcyp PBPK model simulations indicate weak-to-moderate CYP3A4 substrate midazolam DDIs (~50% reduction in midazolam AUC) at the clinically relevant PT2385 doses. Simulations also indicate that PT2385 is a weak CYP2B6 inducer (< 11%

AUC reduction for CYP2B6 substrate bupropion at the clinically relevant PT2385 doses). PT2385 is not a potent inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4 (IC_{50} > 8.8 µg/mL). It is unlikely to significantly inhibit these CYPs at the clinically relevant PT2385 concentrations (C_{max} ~ 3.14 µg/mL). A partial list of CYP3A4, CYP2B6, CYP2C9, and CYP2C19 substrates is provided in Appendix 7.

Patients taking medications metabolized by CYP3A4 and CYP2B6 should be monitored carefully for decreases in drug effect. Patients taking medications metabolized by CYP2C9 and CYP2C19 should be monitored for potential increases in drug effect.

All concomitant medication(s) used during the study and within 28 days before the start of study drug administration will be reported on the appropriate CRF page.

8.3. Treatment Compliance

The Investigator or his/her designated and qualified representatives will dispense study drug only to patients enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

The number of tablets returned at a visit will be used to assess compliance; any discrepancy from the expected number of returned tablets will be discussed with the patient.

Patients who fail to comply with the requirements of the study may be withdrawn from the study.

8.4. Randomization and Blinding

There will be no randomization or blinding in this open-label study.

9. STUDY DRUG MATERIALS AND MANAGEMENT

9.1. Study Drug

PT2385 tablets are supplied by Peloton Therapeutics, Inc. as immediate-release 200 mg tablets for oral administration. Each PT2385 tablet contains PT2385, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, polysorbate 80, and magnesium stearate.

9.2. Study Drug Packaging and Labeling

The 200 mg strength of PT2385 will be supplied in 100-cc high-density polyethylene bottles with induction-seal liners and a child-resistant closure. Each bottle of study drug will contain 60 tablets of a single strength (200 mg) of PT2385.

Bottles provided to the site will be labeled with the following information:

1. PT2385, 200 mg
2. Protocol PT2385-202
3. Lot number
4. Contains 60 200 mg PT2385 tablets
5. Instructions: Take orally as directed
6. CAUTION: New Drug – limited by federal law to investigational use
7. FOR ORAL USE ONLY
8. Store at controlled room temperature 15°C to 30°C (59°F to 86°F)
9. Peloton Therapeutics, Inc., Dallas, TX

9.3. Study Drug Storage

PT2385 must be stored in a secure location at controlled room temperature, 15°C to 30°C (59°F to 86°F).

9.4. Study Drug Preparation

PT2385 will be provided to each site pharmacy and the Investigator or designee will provide tablets to each patient with clear instructions on the number of tablets to be taken each day until the next study visit.

9.5. Administration

Following confirmation of eligibility, enrolled patients will be assigned to open-label PT2385. Four PT2385 200 mg tablets will be taken orally twice daily (for a total of 8 tablets or 1600 mg daily), with doses approximately 12 hours apart. Study drug may be administered without regard to food.

Missed doses may be made up if taken within 4 hours after the scheduled administration time. Study drug may not be taken within 8 hours before the scheduled time for administration of the next dose. Patients who vomit after study drug administration should not retake that study drug dose but should resume taking study drug with the next scheduled dose.

9.6. Study Drug Accountability

The dispensing pharmacist or designated qualified individual will write the date dispensed and the patient's identification number or initials on the Drug Accountability Source Documents. All medication supplied will be accounted for on the Drug Accountability Record.

9.7. Study Drug Handling and Disposal

All partially used or unused study drug supplies will be destroyed at the site in accordance with approved written site procedures, or returned to Peloton Therapeutics or its designee as described in the pharmacy manual. The Investigator will maintain a record of the amount and dates when unused supplies were either destroyed or returned to Peloton Therapeutics or a designated vendor for destruction. All records will be retained as noted in Section 17.2.

10. ASSESSMENT OF EFFICACY

10.1. Efficacy Parameters

Primary endpoint: Best confirmed response in VHL disease-associated ccRCC tumors, defined as the proportion of the best confirmed response of CR or PR (as assessed by the Independent Review Committee (IRC)) as determined by RECIST 1.1, modified to follow ccRCC tumors only. ORR is defined as the proportion of patients with a best confirmed response of CR or PR.

Secondary endpoints:

- Progression-free survival (PFS) in VHL disease-associated ccRCC tumors, defined as the interval from the start of study treatment until the earlier of the first documentation of disease progression determined by RECIST 1.1 or death from any cause, and calculated for patients with a best confirmed response of CR or PR
- Duration of response (DOR) in VHL disease-associated ccRCC tumors, defined as the interval from the first documentation of response, as determined by RECIST 1.1, to the earlier of the first documentation of disease progression or death from any cause, and calculated for the patients with a best confirmed response of CR or PR
- Time to response (TTR) in VHL disease-associated ccRCC tumors, defined as the interval from the start of study treatment to the first documentation of a response, as determined by RECIST 1.1, and calculated for patients with a best confirmed response of CR or PR
- Best confirmed response, PFS, DOR, and TTR for non-ccRCC tumors associated with VHL disease in different organ systems, by modifying RECIST 1.1 criteria to assess tumors in individual organ systems (Appendix 4)

Exploratory endpoint:

- Changes in PD markers (e.g., serum EPO)

10.1.1. Response in VHL Disease-Associated ccRCC Tumors

Anti-tumor activity will be assessed by non contrast or contrast computerized tomography (CT) or magnetic resonance imaging (MRI) at baseline, within 7 days before the Week 13 visit and every 12 weeks thereafter. Patients will be imaged using the same technique at baseline and each follow up assessment.

Response assessments will be made using RECIST 1.1 (Appendix 3), modified to follow ccRCC tumors only. Best confirmed response and PFS will be determined for all patients. DOR and TTR will be determined for all patients with a best confirmed response of PR or CR. The ORR for VHL disease-associated ccRCC tumors will be determined.

10.1.1.1. Response in VHL Disease-Associated Tumors

Best confirmed response rate, PFS, DOR, and TTR for tumors associated with VHL disease in other (non-renal) organ systems (pancreas or adrenal gland, or hemangioblastomas or retinal angiomas) will be evaluated by modifying RECIST 1.1 criteria. Tumors will be

assessed in individual organ systems independently (Appendix 4). The ORR for each of the other VHL disease-associated non-ccRCC tumors will be determined.

10.1.2. Pharmacodynamics and Biomarker Assessments

Blood samples for analysis of PD effects (biomarkers) will be obtained at the Week 1, Day 1 visit before and 6 hours after study drug administration. Pharmacodynamic biomarkers to be assessed may include, but are not limited to, levels of EPO and VEGFA. Whole blood samples will be collected for single nucleotide polymorphism analyses of genes (231) encoding proteins that may be involved in the transport or metabolism of PT2385.

Details for the collection, processing, storage, and shipment of samples for the determination of PD effects can be found in the study laboratory manual.

10.1.2.1. Tissue Sample Collection

Archival tumor tissue samples will be obtained whenever possible from all patients. Additionally, fresh tissue samples will be obtained from consenting patients in whom tumor tissue is accessible (patients who undergo tumor excision during the study). Tumor tissue samples will be analyzed for HIF-2α and HIF-1α expression by immunohistochemistry..

Tumor tissue samples may be subjected to mRNA analyses for the expression of HIF-1α, HIF-2α and target genes that have been found in preclinical studies to be associated with the sensitivity of ccRCC tumors to HIF-2a antagonism (Chen et al, 2016). Genomic DNA from tumor tissues may also be analyzed to confirm the loss of heterozygozity of *VHL*, and to assess the status of genes, such as *PBRM1*, *BAP1*, *TP53*, *SETD2*, and *TCEB1*, that have been found to be altered in ccRCC (Sato et al, 2013). Data from these analyses will be used retrospectively to evaluate their utility as predictors of clinical benefit from treatment with PT2385.

Details for the collection, processing, storage and shipment of tissue samples can be found in the study laboratory manual.

11. PHARMACOKINETIC ASSESSMENTS

Blood samples for the determination of plasma concentrations of PT2385 and its primary metabolite PT2639 will be collected at the Week 1, Day 1 visit before and 6 hours after study drug administration and at the Week 3, Week 5 and every 4 weeks through the Week 17 visits before study drug administration (Schedule of Events, Appendix 1). The date and time of collection of all PK blood samples should be recorded.

Validated liquid chromatography/mass spectrometry methods will be used to assay the samples for plasma concentrations of PT2385 and PT2639. Additional metabolites, if detected, may be assessed using non-validated methods. Details for the collection, processing, storage, and shipment of samples can be found in the study laboratory manual.

12. ASSESSMENT OF SAFETY

12.1. Safety Assessments

Safety assessments include the following:

- Physical examinations
- Vital sign measurements (including pulse oximetry)
- 12-lead electrocardiograms (ECG) with QTc interval determination
- Clinical laboratory measurements
- Concomitant medications
- Incidence, intensity, and relationship of AEs and serious adverse events (SAEs)
- Effects on fertility in males (orchidometry, semen analysis, and measurement of testosterone, follicle-stimulating hormone, luteinizing hormone, and inhibin B levels)

Safety and tolerability will be determined by symptoms, signs, and abnormal laboratory test results. The Investigator will monitor the laboratory test findings. Abnormalities of laboratory test results may or may not, in the opinion of the Investigator, be considered clinically significant. All clinically significant abnormal laboratory test results will be reported on the Adverse Event CRF and will be followed until a return to normal or baseline levels. Abnormal laboratory values that require intervention must be reported on the Adverse Event CRF. Any laboratory test result that is abnormal during the course of the study but not considered clinically significant will be followed at the discretion of the Investigator.

12.1.1. Demographic/Medical History

Demographic data include gender, age, race, and ethnicity, and will be collected during the time period indicated for Screening in Appendix 1. Medical and surgical history will be recorded during Screening and will include documentation of the date/year of VHL diagnosis, documentation of prior therapies for VHL and documentation of all currently active and relevant medical and surgical conditions.

12.1.2. Eastern Cooperative Oncology Group Status

Eastern Cooperative Oncology Group (ECOG) Status performance status will be assessed using the grading system shown in Appendix 2, at the time points indicated in Appendix 1.

12.1.3. Vital Signs

Vital signs (blood pressure, pulse, respirations, pulse oximetry and temperature) will be assessed as noted in Appendix 1. All blood pressure measurements should be taken after the patient has rested in a seated position for at least 3 minutes.

Monitoring of oxygen saturation

Oxygen saturation should be measured by pulse oximetry at each visit and at any time a patient presents with any new or worsening respiratory symptoms. Readings at rest and on exertion should be obtained at each time point. The extent of the exertion should be based on the judgment of the Investigator, but should remain consistent for each individual patient throughout the study. If the patient's status changes, the Investigator can alter the extent of exertion based on their medical judgment. If a patient shows changes on pulse oximetry (oxygen saturation < 92%) or other pulmonary disease related signs (e.g., hypoxia, fever) or symptoms (e.g., dyspnea, cough, fever) consistent, the patient should be immediately evaluated to rule out pulmonary toxicity. Evaluation may include chest x-ray, arterial blood gas analysis, pulmonary function testing including diffusion capacity, and co-oximetry as well as evaluations for specific causes of hypoxia/dyspnea, such as CT scan, CT angiogram or ventilation-perfusion scan.

12.1.4. Weight and Height

Weight will be measured and recorded at each study visit according to the Schedule of Events (Appendix 1). Height will be assessed during Screening only.

12.1.5. Physical Examination

The physical examination will include evaluation of the head, eyes, ears, nose, and throat (HEENT), cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems. Physical examinations should be performed according to the Schedule of Events (Appendix 1). Funduscopic exams must be performed at Screening, Baseline, and every 12 weeks during the treatment period. Before administration of the first dose of study drug, any new or worsened abnormalities (other than those due to protocol required procedures) should be recorded as medical history. After the initiation of study drug administration, any clinically significant new or worsened abnormalities noted on the physical examination will be recorded as AEs. No rectal or pelvic examination is required.

12.1.6. Electrocardiogram

A 12-lead ECG will be obtained after 5 to 15 minutes of rest in the supine position using equipment at the site and according to the schedule in Appendix 1. The Investigator or designee will evaluate the ECG for abnormalities.

12.1.7. Laboratory Assessments

Clinically significant abnormal laboratory findings identified during the screening period should be recorded as medical history in the CRF.

Laboratory samples will be collected according to the schedules in Appendix 1.

Clinically significant abnormal laboratory test results should be followed until a return to normal or baseline values.

Details for the collection, processing, storage, and shipment of samples can be found in the study laboratory manual.

12.1.7.1. Hematology

Hematology tests will include RBC count, white blood cell (WBC) count, hemoglobin (Hgb), hematocrit (HCT), WBC differential count (neutrophils, lymphocytes, eosinophils, monocytes, and basophils), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean platelet volume (MPV), red blood cell distribution width (RDW), platelet count (Plt), and reticulocyte count (retic).

12.1.7.2. Blood Chemistry

Blood chemistry tests will include sodium (Na), potassium (K), magnesium (Mg), chloride (Cl), bicarbonate (CO2), calcium (Ca), phosphate (PO4), blood urea nitrogen (BUN), creatinine, total protein, glucose, lactate dehydrogenase (LDH) (Week 1 only), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBILI), and albumin.

12.1.7.3. Iron Panel

Blood samples will be collected for an iron panel to include: iron (Fe), ferritin, transferrin saturation, and total iron binding capacity.

12.1.7.4. Prothrombin Time, Activated Partial Thromboplastin Time, and International Normalized Ratio

Blood samples collected during screening will be used to determine prothrombin time (PT), activated partial thromboplastin time (aPTT), and international normalized ratio (INR) to assess coagulation.

12.1.7.5. Urinalysis

Urinalysis will include appearance, glucose, ketones, blood, protein, nitrite, bilirubin, specific gravity, pH, urobilinogen, and leukocytes. If the results are positive for blood or protein, a microscopic examination should be included.

12.1.7.6. Pregnancy Screen

A serum pregnancy test must be performed within 7 days before the first study drug administration. A urine pregnancy test will be performed according to the schedule in Appendix 1.

12.1.7.7. Male Fertility Analysis

Fertility tests for male patients will include orchidometry, semen analysis, and measurement of testosterone, follicle-stimulating hormone, luteinizing hormone, and inhibin B levels, according to the Schedule of Events, Appendix 1. Male patients must be provided with information about the option for sperm banking before providing written informed consent.

12.2. Adverse and Serious Adverse Events

12.2.1. Definition of Adverse Events

12.2.1.1. Adverse Events

An AE is defined as any untoward medical occurrence in a patient regardless of its causal relationship to study treatment. An AE can be any unfavorable and unintended sign (including any clinically significant abnormal laboratory test result), symptom, or disease temporally associated with the use of the study drug, whether or not it is considered to be study drug related. Included in this definition are any newly occurring events and any previous condition that has increased in severity or frequency since the administration of study drug. Disease progression is a study endpoint and consequently, should not be reported as an AE. However, if a patient dies from disease progression with no other immediate causes, "disease progression" should be reported as an SAE (Section 12.7).

All AEs that are observed or reported by the patient during the study (from the time of administration of the first dose of study drug until the final visit indicated in Appendix 1) must be reported, regardless of their relationship to study drug or their clinical significance.

12.2.1.2. Serious Adverse Events

An SAE is any AE occurring at any dose and regardless of causality that meets any of the following criteria.

- Results in death
- Is life-threatening
- Requires inpatient hospitalization > 24 hours or prolongation of existing hospitalization
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital anomaly or birth defect in an offspring of a patient taking study drug
- Is an important medical event

The term "life-threatening" refers to an event in which the patient is at immediate risk of death at the time of the event. The term does not refer to an event that hypothetically might cause death if it were more severe.

Important medical events are those that may not meet any of the criteria defined above; however, they may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the SAE definition.

Pregnancy is not considered an AE; however, information will be collected for any pregnancies that occur during the study (from the time the first dose of study drug is administered until the final visit indicated in Appendix 1). Certain pregnancy outcomes will require submission as an SAE.

The Investigator is responsible for reporting to Peloton Therapeutics or designee all AEs and SAEs that are observed or reported by the patient during the study (from the time the first dose of study drug is administered until the final visit indicated in Appendix 1), regardless of their relationship to study drug or their clinical significance. All SAEs reported or observed during the study must be followed to resolution or until the Investigator deems the event to be chronic or the patient to be stable. Peloton Therapeutics or designee may contact the Investigator to obtain additional information on any SAE that has not resolved at the time the patient completes the study.

12.3. Eliciting Adverse Event Information

At every study visit, patients must be asked a standard, non-directed question, such as, "How do you feel?" or "How have you been feeling since your last visit?" to elicit any medically related changes in their well-being. They may also be asked if they have been hospitalized, had any accidents, used any new medications, or changed concomitant medication regimens (including prescription drugs, over-the-counter medications, vitamins, herbal products, and minerals). Responses should be recorded in the source documents.

In addition to patient observations, AEs must be documented for any clinically significant diagnosis resulting from abnormal laboratory test values, physical examination findings, or ECG abnormalities, or from other documents that are relevant to patient safety.

12.4. Assessment of Causality

The Investigator must use the following classifications and criteria to characterize the relationship or association of PT2385 in causing or contributing to the AE:

Unrelated: This relationship suggests that there is no association between the study drug and the reported event.

Unlikely: This relationship suggests that the temporal sequence of the event with study drug administration makes a causal relationship improbable and/or other factors also provide plausible explanations.

Possible: This relationship suggests that treatment with the study drug caused or contributed to the AE. That is, the event follows a reasonable temporal sequence from the time of study drug administration, and/or, follows a known response pattern to the study drug, but could have been produced by other factors.

Probable: This relationship suggests that a reasonable temporal sequence of the event with study drug administration exists and, based upon the known pharmacological action of the drug, known or previously reported adverse reactions to the drug or class of drugs, or judgment based on the Investigator's clinical experience, the association of the event with study drug administration seems likely.

12.5. Assessment of Severity

The Investigator will grade the severity of the AEs as Grades 1, 2, 3, 4, or 5 based on NCI CTCAE 4.03 or subsequent versions released during the study. If the CTCAE do not apply, severity should be defined as shown in Table 3.

Table 3 Adverse Event Severity Grades

Grade	Description
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living.
3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
4	Life-threatening consequences; urgent intervention indicated.
5	Death related to AE.

The NCI CTCAE 4.03 will be provided to the Investigator.

12.6. Recording Adverse Events

All conditions present before administration of the first dose of study drug should be documented as medical history. All drug-related (possible or probable, see Section 12.4) AEs and abnormal laboratory test results reported or observed during the study must be followed to resolution (either return to baseline or within normal limits). All other AEs will be followed through the final visit indicated in Appendix 1. Information to be collected includes type of event, date of onset, date of resolution, Investigator-specified assessment of severity and relationship to study drug, seriousness, as well as any action taken.

While an AE is ongoing, changes in the severity (e.g., worsening and improving) should be noted in the source documents but, when documenting the AE, only the total duration and greatest severity should be recorded in the CRF. AEs characterized as intermittent require documentation of onset and duration.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. Preexisting conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the patient experiences a worsening or complication of such a concurrent condition, the worsening or complication (except disease progression) should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., “worsening of…”).

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory test values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory test values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiologic fluctuation). If abnormal laboratory test values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine levels in renal failure), only the diagnosis should be reported as an AE.

Elective procedures (surgeries or therapies) that were scheduled before the start of AE collection are not considered AEs. These elective procedures should not be recorded as AEs, but should be documented in the patient's source documents as elective (e.g., elective periodontal surgery). However, if a pre-planned procedure is performed early (e.g., as an emergency) because of a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

12.7. Reporting Serious Adverse Events

Any AE that meets the previously described criteria for "serious" must be reported to the Sponsor's designee within 24 hours from the time when site personnel first learn about the event. To report the SAE, fax or email the completed SAE form to SCRI Development Innovations Pharmacovigilance Department (contact information listed in Table 4) within 24 hours of awareness. For questions regarding SAE reporting, SCRI Development Innovations Safety personnel can be contacted by phone, fax or email, see Table 4.

Table 4 Serious Adverse Event Reporting Contact Information

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. Within 24 hours of receipt of new information, the updated follow-up SAE form, along with any supporting documentation (e.g., patient discharge summary or autopsy reports), should be faxed to SCRI Development Innovations Pharmacovigilance Department (Table 4).

Peloton Therapeutics or designee will notify regulatory agencies of any fatal or life-threatening unexpected events associated with the use of the study drug as soon as possible but no later than 7 calendar days after the initial receipt of the information. Initial notification will be followed by a written report within the timeframe established by the appropriate regulatory agency. For other SAEs that do not meet the fatal or life-threatening unexpected criteria, but are deemed by the Investigator to be associated with the use of the study drug (that is, "possible" or "probable" in causality assessment), Peloton Therapeutics or designee will notify the appropriate regulatory agencies in writing within the timeframe established by those regulatory agencies. Peloton Therapeutics or designee will provide copies of any reports to regulatory agencies regarding serious and unexpected SAEs to the Investigators for their information and submission to their institutional review board (IRB), as appropriate.

Principal Investigators are responsible for informing their IRB of any SAEs at their site, as appropriate. Serious AE correspondence with regulatory authorities or IRBs must be submitted to Peloton Therapeutics or designee for recording in the study file.

12.8. Pregnancy

Female patients of child-bearing potential are defined as patients who are not surgically sterile (no history of bilateral tubal ligation, hysterectomy, or bilateral salpingo-oophorectomy), do not have fallopian inserts with confirmed blockage, have not had reproductive potential terminated by radiation, and have not been postmenopausal for at least 1 year.

12.8.1. Methods of Birth Control

During screening, while taking study drug, and until 30 days after taking the final dose of study drug, female patients of child-bearing potential and male patients who have female partners of child-bearing potential (defined as all women physiologically capable of becoming pregnant) must practice one of the following methods of birth control:

- Total abstinence,
- Male or female sterilization, or
- Combination of any 2 of the following (a + b or a + c or b + c):
    a. Use of oral, injected or implanted hormonal methods of contraception
    b. Placement of an intrauterine device (IUD) or intrauterine system (IUS)
    c. Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/vaginal suppository

12.8.2. Suspected Pregnancy

During the study, all females of child-bearing potential must be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., late or missed menstrual period). Male patients must be instructed to contact the Investigator if a sexual partner suspects she may be pregnant.

If a patient or Investigator suspects that the patient may be pregnant, study drug administration must be held until the results of a serum pregnancy test are available. If pregnancy is confirmed, the patient must discontinue taking study drug. The Investigator must immediately report a pregnancy associated with study drug exposure and record the event. The protocol-required early termination procedures noted in Appendix 1 must be performed. Other appropriate follow-up procedures should be considered if indicated.

Pregnancy is not considered an AE; however, the Investigator must follow a pregnant patient, or the pregnant female partner of a male patient (if consenting), and report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants resulting from such pregnancies should be followed for a minimum of 8 weeks. Peloton Therapeutics or designee may contact the Investigator to request additional information throughout the course of the pregnancy.

The following post-pregnancy outcomes must be considered SAEs and will require additional reporting in the CRF and on an SAE form.

- Congenital anomaly/birth defect
- Stillbirth
- Spontaneous miscarriage

13. STATISTICS

This section describes the statistical methodology to be used in the analysis of protocol endpoints. These methods will be documented in a formal statistical analysis plan (SAP) detailing the analyses to be performed, which will be developed before the final database lock. The SAP will serve as the final arbiter of all statistical analyses. The SAP will describe the analysis of all safety, efficacy, PK, and PD response variables. Any changes to the methodology described in the final approved SAP will be presented and discussed in the clinical study report.

13.1. Determination of Sample Size

This study will be conducted with a 2-stage design (Green and Dahlberg, 1992) which allows for an early assessment of futility. If after the first 25 patients have been enrolled to the study, 2 or fewer patients have had a confirmed response, further enrollment will be temporarily suspended for up to a year or until at least 3 responses are seen; if 3 responses are not seen within 1 year after enrollment of the 25th patient, no further patients will be enrolled and the study will be discontinued. In addition, if more than 2 of the first 6 patients enrolled experience treatment-limiting toxicity during the first 4 weeks of their treatment, the protocol will be modified or the study will be stopped. If 3 or more of the 25 patients respond, enrollment will proceed to the second stage of the design.

A total of 25 patients will be enrolled into the second stage of the study for a total required enrollment of 50 patients. If at least 13 of the 50 patients (25 + 25) respond (CR or PR), then the hypothesis that PT2385 is ineffective will be rejected.

The required sample size for this 2-stage design is based on the following design parameters: The null hypothesis is that PT2385 is ineffective, defined as an ORR (best confirmed response of PR or CR) of 15% (P_0=0.15). The alternative hypothesis is that PT2385 is effective, defined as an ORR of 30% (P_1=0.3). The probability of falsely concluding that the agent is effective when it is truly ineffective is 0.05 (alpha) and the probability of falsely concluding that the agent is ineffective when it is truly effective is 0.2 (beta).

13.2. Analysis Populations

The analysis populations include the following:

Enrolled Population: The Enrolled Population is defined as all patients who have been screened and have provided written informed consent. This population will be used for the summary of patient disposition and data listings.

Efficacy Analysis Set: The Efficacy Analysis Set is defined as all patients who have been enrolled and received at least 1 dose of PT2385. This population is the primary population for analysis of efficacy.

Safety Analysis Set: The Safety Analysis Set is defined as all patients who have been enrolled and received at least 1 dose of PT2385. This population is the primary population for the summaries of demographics, baseline data, safety data, and exposure.

13.3. Statistical Analyses

All statistical summaries and analyses will be performed in SAS® Version 9.1 or higher (SAS Institute Inc., Cary, NC, USA) on a PC platform.

Results will be reported using summary tables, figures, and data listings. No inferential statistical analyses will be performed. For continuous variables, the number of patients with non missing data (n), mean, standard deviation, median, minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented. Unless otherwise indicated, percentages will be calculated based upon the number of patients in the Safety Analysis Set as the denominator. Graphical methods will be used, as appropriate, to illustrate study endpoints.

Summaries will be provided for the total number of patients in the population of interest and for selected variables, and subsets of patients in the population of interest.

Data recorded on the electronic case report forms and any derived data will be presented by patient in data listings.

13.3.1. Handling of Missing, Unused, or Spurious Data

The handling of dropouts and missing disease status assessments for the efficacy variables is described in their definitions. Missing data will not be estimated or carried forward for any of the other summaries.

If only a partial date is available and is required for a calculation of whether a medication is concomitant or an AE is treatment emergent, the start and stop dates will be imputed according to a predefined standard. Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009). No other imputation of missing data will be performed.

13.3.2. Patient Characteristics and Patient Disposition

Demographics (including gender, age, race, and ethnicity), disease characteristics, and other baseline data (e.g., medical history, concomitant medications) will be summarized using descriptive statistics. The number of patients who enter, who complete treatment, who complete long-term follow-up, who withdraw from treatment prematurely (along with the reason), and who withdraw from the long-term follow-up prematurely (along with the reason) will be tabulated.

13.3.3. Exposure

All study drug administration data will be summarized for the Safety Analysis Set. The duration of PT2385 exposure in weeks, defined as (date of administration of last dose minus date of administration of first dose of PT2385 plus 1) divided by 7 and the total amount of PT2385 administered will be summarized.

13.3.4. Efficacy Analyses

The primary summaries of all response data will be based on the Efficacy Analysis Set.

Response of ccRCC tumors will be measured by contrast enhanced computerized tomography (CT) or magnetic resonance image (MRI) scan and assessed according to RECIST 1.1, modified to follow ccRCC tumors only.

Response assessments of ccRCC CR and PR should be confirmed by a second assessment. Where confirmed responses are required, the date of the first assessment will be used in all analyses. In the case that the confirmation assessment is not available, the assessment at the next scheduled time point will be used for confirmation. If there are no assessments, the response will be taken to be unconfirmed and a non response.

The ccRCC ORR is defined as the proportion of patients for whom the best confirmed ccRCC response is CR or PR, determined by RECIST 1.1. Estimates of the ccRCC ORR along with the associated 90% and 95% exact binomial confidence intervals (Clopper Pearson) will be provided. The binomial probability that the observed ccRCC ORR is > 0.15 will be calculated. Best confirmed ccRCC response will be summarized.

The ccRCC PFS is defined the interval from the start of study treatment until the earlier of the first documentation of ccRCC disease progression determined by RECIST 1.1 or death from any cause, whichever occurs first. Renal cell carcinoma PFS will be right censored for patients who meet one of the following conditions: 1) no post baseline disease assessments, 2) non protocol systemic anticancer treatment started before documentation of disease progression or death, 3) surgery that is considered to affect response before documentation of disease progression or death, 4) death or disease progression after more than 1 missed disease assessment visit, 5) alive and does not have documentation of disease progression before a data analysis cutoff date. The Kaplan-Meier (KM) method will be used to estimate the distribution of ccRCC PFS. Quartiles including the median will be estimated by KM method along with their 95% confidence intervals. A figure showing the estimated ccRCC PFS distribution will be provided. KM cumulative estimators along with the associated 95% CIs will be provided for ccRCC PFS rates at 26, 39 and 52 weeks. Duration of follow up for ccRCC PFS will be summarized according to the KM estimate of potential follow up also termed “reverse Kaplan-Meier.”

The ccRCC DOR will be calculated for patients who achieve a ccRCC CR or PR. For such patients, the ccRCC DOR is defined as the interval from first documentation of response, as determined by RECIST 1.1, to the earlier of the first documentation of disease progression or death from any cause. Dates of progression and censoring will be determined as described for the analysis of ccRCC PFS. Kaplan-Meier methods will be used to estimate the distribution of ccRCC DOR. Quartiles including the median will be estimated by KM method along with their 95% confidence intervals. KM cumulative estimators along with the associated 95% CIs will be provided for ccRCC DOR rates at 26, 39 and 52 weeks. These estimates will be used as estimates of durable response.

The ccRCC TTR will be calculated for patients who achieve a ccRCC CR or PR. Renal cell carcinoma TTR is defined as the interval from the start of study treatment to the first documentation of a ccRCC response of PR or better, as determined by RECIST 1.1.

The maximum percent decrease in ccRCC total tumor burden will be displayed using waterfall plots.

Summaries of the response endpoints will also be provided for subgroups of the Efficacy Analysis Set as follows: Subgroups will be defined according to blood level of PT2385 based on the PK assessments and duration of PT2385 treatment. The analyses of ccRCC ORR, ccRCC PFS, ccRCC best confirmed response, ccRCC DOR, and ccRCC TTR will be performed in each of these subgroups.

The ORR, PFS, best confirmed response, DOR, and TTR will be summarized for the non-ccRCC tumors associated with VHL disease based on the subgroups of patients in the Efficacy Analysis Set who have the particular type of tumor. The determination of best response and date of progression will be determined by modifying RECIST 1.1 criteria to assess tumors in individual organ systems independently (e.g., VHL disease-associated solid tumors in the pancreas or adrenal gland, or hemangioblastomas or retinal angiomas).

The determination of response and progression will be made by the local investigators. The investigator assessments will be used for decisions regarding treatment for individual patients and by the DMC for approval to open Stage 2 of the study. The response outcomes will also be reviewed and determined by an Independent Review Committee (IRC). For the primary analysis of ORR, the determination of response will be based on independent radiologic assessment conducted by the IRC. Both the investigators' and the IRC's assessments will be used for the summaries and analyses of efficacy.

13.3.5. Pharmacodynamic Analyses

Blood samples for assessment of pharmacodynamic parameters such as EPO will be obtained in conjunction with PK samples, before (pre-dose) and 6 hours after study drug administration at the Week 1 visit and only before study drug administration at the Week 3 and 5 visits.

The value, change from baseline, and percent change from baseline will be listed and summarized for each scheduled time-point during the study for each of the pharmacodynamic parameters.

To investigate the effect of these potential biomarkers on efficacy, the association of baseline pharmacodynamic parameters with ORR and PFS will be investigated using exploratory multivariate techniques, subgroup analyses, and regression modeling.

The summaries will be based on the Safety Analysis Set. The exploratory analyses will be performed for the Efficacy Analysis Set.

13.3.6. Safety Analyses

Safety data analysis will be conducted for all patients in the Safety Analysis Set. Analyses will consist of data summaries for AEs/SAEs, clinical laboratory parameters, vital signs, and ECGs.

13.3.6.1. Adverse Events

Adverse events occurring from the time the patient gives consent but prior to study drug administration will be captured on the Medical History CRF. All AEs occurring on or after the first day of treatment and within 30 days after administration of the last dose of study drug will be considered to be a treatment-emergent adverse event (TEAE).

Adverse events will be coded according to the latest Version of the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be coded according to NCI CTCAE 4.03. Treatment-related AEs are AEs that are not stated as unrelated to PT2385.

An overall summary of TEAEs will summarize the number (%) of patients with at least 1 of the following.

- TEAE
- PT2385 related TEAE
- Grade 3 or higher TEAE
- Grade 3 or higher PT2385 related TEAE
- Grade 5 TEAE
- SAE
- Leading to discontinuation of PT2385

Summaries of the following TEAEs will be provided by system organ class and preferred term.

- All TEAEs
- TEAEs by maximum severity
- TEAEs grade 3 or higher
- PT2385 related TEAEs
- Grade 3 or higher PT2385 related TEAE
- Serious TEAEs
- TEAEs that led to permanent discontinuation of study of PT2385

A summary of the number of deaths within 30 days of administration of the last dose of study drug and deaths more than 30 days after administration of the last dose of study drug will be provided.

Listings will be provided of AEs identified as treatment-limiting toxicity, deaths, SAEs, and AEs leading to discontinuation of PT2385 tablet treatment.

13.3.6.2. Clinical Laboratory Data

Summary statistics (n, arithmetic mean, standard deviation, median, minimum, and maximum) for the observed data and change from baseline will be presented for clinical laboratory data and abnormal clinically significant lab. Selected laboratory values will also be categorized according to their NCI CTCAE 4.03 toxicity grade. Shift tables will be presented for the baseline toxicity grade by the worst toxicity grade during the study and the toxicity grade at the end of treatment for the biochemistry and hematology parameters with NCI CTCAE toxicity grading.

13.3.6.3. Other Safety Data

Summary statistics (n, arithmetic mean, standard deviation, median, minimum, and maximum) for the observed data and change from baseline will be presented for vital sign parameters.

Summaries of ECG findings and shifts from baseline will be tabulated.

13.3.7. Pharmacokinetic Analyses

Blood samples for calculation of concentration of PT2385 and PT2639 will be obtained before (pre-dose) and 6 hours after study drug administration at the Week 1 visit and only before study drug administration at the Week 3, Week 5, and every 4 weeks through the Week 17 visits. The blood concentrations of PT2385 and PT2639 at each collection time will be summarized. Figures displaying individual and mean blood concentrations will be provided.

13.4. Analysis Time Points

13.4.1. Final Analysis

The final analysis for the study will be conducted once all patients have completed the study and the database is clean and locked.

13.4.2. Interim Analysis

There is one formal interim analysis for futility planned for this study. The response data for the first 25 patients in Stage 1 of the study will be reviewed by a DMC. The DMC will consist of the principal Investigator(s) participating in this study, the Medical Monitor, and representatives from Peloton. The DMC will determine if the threshold for opening Stage 2 has been met.

In addition, the data for the first 6 patients will be reviewed by the DMC. The DMC will meet shortly after the sixth patient has been observed for 28 days after the administration of their initial PT2385 Tablet dose. The DMC will review safety and any treatment-limiting toxicities to confirm whether the study should continue to enroll or if modifications to the protocol are needed.

14. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

14.1. Study Monitoring

Before an investigational site can enter a patient into the study, a representative of Peloton will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the Investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of Peloton or its representatives. This will be documented in a Clinical Study Agreement between the Sponsor and the Investigator.

During the study, a monitor from Peloton or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the case report forms, and that investigational product accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the case report forms with the patient's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each patient (e.g. clinic charts).
- Record and report any protocol deviations not previously sent to Peloton.
- Confirm AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded the Sponsor and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

14.2. Audits and Inspections

Authorized representatives of Peloton, a regulatory authority, an Independent Ethics Committee or an Institutional Review Board may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), and any applicable regulatory requirements. The Investigator should contact Peloton immediately if contacted by a regulatory agency about an inspection.

14.3. Institutional Review Board (IRB)

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

14.4. Confidentiality

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain patient confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the patient (or the patient's guardian), except as necessary for monitoring and auditing by the Sponsor, its designee, the FDA or applicable regulatory authorities, or the IRB.

The Principal Investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished confidential information disclosed to them for the purpose of the study. Prior written agreement from the Sponsor or designee must be obtained for the disclosure of any said confidential information to other parties.

14.5. Modification of the Protocol

Any changes that arise after the approval of the protocol must be documented as protocol amendments. The FDA must be notified of protocol amendments. The changes will become effective only after approval of the Sponsor, the Principal Investigator, and the IRB. In cases when the protocol is modified to enhance patient safety, changes may be implemented and the amendment must be immediately submitted to the IRB.

The Principal Investigator is responsible for informing the IRB of all problems involving risks to patients according to national legislation. In case of urgent safety measures, the Sponsor will immediately notify the FDA in accordance with 21 CFR 312.32.

14.6. Protocol Deviations

The Principal Investigator or designee must document any protocol deviation. The IRB must be notified of all protocol deviations in a timely manner by the Investigator as appropriate. Protocol deviations will be documented by the responsible monitor during monitoring visits, and those observations will be communicated to the Investigator.

If there is an immediate hazard to a patient, the Principal Investigator may deviate from the protocol without prior Sponsor and IRB approval. The Sponsor and IRB must be notified of the deviation immediately.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Quality Assurance

To ensure compliance with Good Clinical Practices (GCP) and all applicable regulatory requirements, Peloton Therapeutics may conduct a quality assurance audit.

15.2. Financial Disclosure

Principal Investigators and sub Investigators are required to provide financial disclosure information before starting the study. In addition, the Principal Investigator and sub Investigators must provide the Sponsor or designee with updated information, if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study.

Any potential Investigator who has a vested financial interest in the success of this study may not participate in this study.

15.3. Sponsor Obligations

The Sponsor or designee is not financially responsible for further testing/treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor or designee is not financially responsible for treatment of non-study-related fatalities, physical injuries, or damage to health that may occur during the clinical study, as well as the patient's underlying disease.

15.4. Investigator Documentation

Before beginning the study, the Principal Investigator will be asked to comply with ICH E6(R1) 8.2 and Title 21 of the Code of Federal Regulations (CFR) by providing the essential documents to the Sponsor or designee, which include but are not limited to the following.

- An original Investigator signed Investigator agreement page of the protocol
- The IRB approval of the protocol
- The IRB approved informed consent, samples of site advertisements for recruitment for this study, and any other written information regarding this study that is to be provided to the patient or legal guardians
- A Form FDA 1572, fully executed, and all updates on a new fully executed Form FDA 1572
- Curriculum vitae for the Principal Investigator and each sub Investigator listed on Form FDA 1572. A curricula vitae and current licensure, as applicable, must be provided. The curricula vitae must have been signed and dated by the Principal Investigators and sub Investigators within 2 years before study start up to indicate the documents are accurate and current
- Completed financial disclosure forms to allow the Sponsor or designee to submit complete and accurate certification or disclosure statements required under US Title 21 CFR 54. In addition, the Investigators must provide to the Sponsor or designee a

commitment to update this information promptly if any relevant changes occur during the course of the investigation and for 1 year after the completion of the study

- Laboratory certifications and normal ranges for any laboratories used by the site for the conduct of this study

15.5. Clinical Study Insurance

In accordance with the respective national drug laws, the Sponsor has taken out patient liability insurance for all patients who give their consent and enroll in this study. This insurance covers potential study related fatalities, physical injuries, or damage to health that may occur during the clinical study.

15.6. Use of Information

All information regarding PT2385 supplied by the Sponsor to the Investigator is privileged and confidential. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. Furthermore, the Investigator is obligated to provide the Sponsor with complete data obtained during the study. The information obtained from the clinical study will be used towards the development of PT2385 and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

16. ETHICS

16.1. Ethics Review

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board (IRB) before study start. Each Investigator must provide the Sponsor or its designee a signed and dated statement that the protocol and informed consent have been approved by the IRB before consenting patients. Before study initiation, the Investigator is required to sign a protocol signature page confirming agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to the Sponsor, its designee, and regulatory authorities as required.

The IRB chairperson or designee must sign all IRB approvals and must identify the IRB by name and address, the clinical protocol, and the date approval and/or favorable opinion was granted.

The Principal Investigator is responsible for obtaining reviews of the clinical research at intervals specified by the IRB, but not exceeding 1 year. The Principal Investigator must supply the Sponsor or designee with written documentation of reviews of the clinical research.

16.2. Ethical Conduct of the Study

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (e.g., US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

The Principal Investigator agrees to conduct the study in accordance with the ICH Guidance for Industry on GCP ICH E6(R1) and the principles of the Declaration of Helsinki. The Principal Investigator must conduct all aspects of this study in accordance with all national, state, and local laws or regulations.

16.3. Written Informed Consent

Because the study will be conducted under a United States Investigational New Drug Application, a signed informed consent form, in compliance with Title 21 of the United States CFR Part 50, will be obtained from each patient before the patient enters the study. An informed consent template may be provided by the Sponsor or designee to the Investigators. The consent must be reviewed by the Sponsor or designee before IRB submission. Once reviewed, the consent will be submitted by the Principal Investigator to his or her IRB for review and approval before the start of the study. If the informed consent form is revised during the course of the study, all participants affected by the revision must sign the revised IRB approved consent form.

Before enrollment, each prospective patient will be given a full explanation of the study and be allowed to read the approved informed consent form. Once the Principal Investigator or designee is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing the informed consent form.

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB approved informed consent. Informed consent must be obtained before conducting any study specific procedures (i.e., all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the patient source documents.

Any changes to the proposed consent form suggested by the Investigator must be agreed to by the Sponsor before submission to the IRB, and a copy of the approved Version and the notice of approval must be provided to the Sponsor's designated monitor after IRB approval.

The Principal Investigator or designee will provide a copy of the informed consent form (signed copy to be provided per applicable law) to the patient and/or legal guardian. The original form will be maintained in the patient's medical records at the site.

17. DATA HANDLING AND RECORDKEEPING

17.1. Inspection of Records

Peloton will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, patient charts and study source documents, and other records relative to study conduct.

17.2. Retention of Records

The Investigator will maintain all study records according to ICH GCP and applicable regulatory requirement(s). Records will be retained for at least 2 years after the last marketing application is approved or 2 years after formal discontinuation of the clinical development of the investigational product. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. The Sponsor must be notified in writing if a custodial change occurs.

17.3. Case Report Forms

All CRF data will be entered in paper or electronic forms at the investigational site. If an Electronic Data Capture (EDC) system is used to capture data electronically for all enrolled patients, it will be 21 CFR Part 11 compliant.

18. PUBLICATION POLICY

Peloton Therapeutics reserves the right to review all planned communications and manuscripts based on the results of this study. This reservation of the right is not intended to restrict or hinder publication or any other dissemination of study results, but to allow the Sponsor to confirm the accuracy of the data, to protect proprietary information, and to provide comments based on information that may not yet be available to the study Investigators. Peloton Therapeutics supports communication and publication of study results whatever the findings of the study. Peloton Therapeutics also encourages disclosure of any conflict of interest from all authors or Investigators when manuscripts are submitted for publication.

Those individuals who have contributed greatly to this study, as determined by Peloton Therapeutics, will serve on any publication committee for the study.

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20. APPENDICES

Appendix 1 Schedule of Events

Assessment	Pre-Treatment Period	Treatment Period				Post-Treatment Period/ Early Termination	
	Screening (Day -28 to Day -1)	Week 1[1] (Day 1)	Weeks 3 and 5[1] (± 1 Day)	Weeks 9, 13, 17, and Every 4 Weeks[1] (± 2 Days)	Extended Treatment[2] Every 12 Weeks (± 1 Week)	Safety Follow-Up 28 Days After Last Dose of Study Drug Taken (± 7 Days)	Long Term Follow-up (every 6 months)[16]
Informed Consent	X						
Assess Inclusion/Exclusion	X						
Demographics and Medical	X						
Physical Examination[3]	X	X	X	X	X	X	
Vital Signs[4]	X	X[4]	X	X	X	X	
Weight	X	X	X	X	X	X	
Height	X						
ECOG	X	X	X	X	X	X	
Dispense/Collect Study Drug		X	X	X	X		
Hematology[5]	X	X	X	X	X	X	
Serum Chemistry[6]	X	X	X	X	X	X	
PT, aPTT, INR	X						
Iron Panel[7]	X	X	X	X		X	
Urinalysis[8]	X	X	X	X	X	X	
Pregnancy Test[9]	X	X	X	X	X	X	
ECG[10]	X	X[10]	X[10]	X[10]			
Tumor Assessment[11]	X			X[11]	X		
Pharmacokinetic Sample[12]		X	X	X			
Pharmacodynamic Sample[13]		X	X	X			
Assessment of Male Fertility[14]	X			X[14]		X[14]	
Tissue Sample Collection[15]	X						
Adverse Events		X	X	X	X	X	
Concomitant Medications	X	X	X	X	X		
Study Drug Administration		----------X----------					
Patient Status[16]							X

ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; PT/aPTT = prothrombin time/activated partial thromboplastin time.

1. Assessments are to be done on Day 1 of each visit week. For the Weeks 3 and 5 visits, assessments may be ± 1 day; for the Week 9, 13, and 17 visits and for visits every 4 weeks thereafter, assessments may be ± 2 days.
2. For patients deriving clinical benefit at 1 year and continuing to take study drug after 1 year, visits will be conducted at 12-week intervals.
3. Funduscopic exams must be performed at Screening, Baseline, and every 12 weeks during the treatment period.
4. At the Week 1 visit, patients will take their morning dose of PT2385 in the clinic. Vital signs (pulse, blood pressure, respirations, temperature, and pulse oximetry) will be measured at least 30 minutes before and at 1, 2, 4, and 6 hours after study drug administration. For all remaining clinic visits, vital signs should be measured during each clinic visit and the time the measurements are taken should be recorded. Oxygen saturation (measured by pulse oximetry) should be measured at both rest and on exertion each time vital signs are measured; at the Week 1 visit, oxygen saturation should be measured before study drug administration and at 6 hours after study drug administration only. Those patients with dyspnea or asymptomatic desaturation (oxygen saturation < 92%) will be further evaluated as clinically indicated; evaluation may include chest x-ray, arterial blood gas analysis, pulmonary function testing including diffusion capacity, co-oximetry as well as evaluation for specific causes of hypoxia/dyspnea, such as CT scan, CT angiogram or ventilation-perfusion scan..
5. Hematology assessments include complete blood count, differential, platelet count and reticulocyte count.
6. Serum chemistry assessments include glucose, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, albumin, electrolytes (sodium, potassium, chloride, bicarbonate), calcium, magnesium, phosphate, blood urea nitrogen, creatinine, and total protein levels; lactate dehydrogenase level at Week 1 only.
7. Iron panel assessments including iron, ferritin, transferrin saturation and total iron binding capacity should be captured at Screening, and every 4 weeks for the first year thereafter.
8. Samples for urinalysis (including microscopic if abnormalities on macroscopic examination) will be obtained at Screening and the Week 1, 3, 5, 9, 13, and 17 visits, and every 4 weeks thereafter.
9. Female patients of child-bearing potential will have a serum pregnancy test within 7 days before the first study drug administration; a urine pregnancy test will be performed at the Week 1, 3, 5, 9, 13, and 17 visits, and every 4 weeks thereafter.
10. A 12-lead ECG will be obtained, in triplicate, before and at 1.5 hours after study drug administration at the Week 1, 3, and 17 visits.
11. Tumor assessment including non-contrast or contrast computed tomography (CT), or magnetic resonance imaging (MRI) will be obtained at screening and within 7 days before the Week 13 visit, and every 12 weeks thereafter (e.g., before the visits for Weeks 25, 37, etc.).
12. At the Week 1 visit, patients will take their morning dose of PT2385 in the clinic and will have 4 mL of blood drawn for pharmacokinetic (PK) assessment before (pre-dose) and 6 hours after study drug administration. At the Week 3, 5, 9, 13, and 17 week visits, patients will take their morning dose of PT2385 in the clinic. The blood sample for PK assessment is to be obtained before study drug administration on these days.
13. Blood samples for analysis of pharmacodynamic effects of PT2385 (e.g., erythropoietin) will be obtained in conjunction with PK samples, before (pre-dose) and 6 hours after study drug administration at the Week 1 visit and only before study drug administration at the Weeks 3, 5, 9, 13 and 17 visits; patients should not take their dose of PT2385 until after this blood collection has occurred at these visits. Two whole blood samples will be collected at the Week 1 visit only for sequencing of genes encoding proteins that may be involved in regulating PT2385 metabolism.
14. Tests (orchidometry, semen analysis, and measurement of testosterone, follicle stimulating hormone, luteinizing hormone, and inhibin B levels) are to be conducted at Screening, the Week 17 visit, and 13 weeks after last study drug administration for those male patients for whom a clinically significant effect on fertility was seen at Week 17.
15. Archival tumor tissue samples will be obtained whenever possible from all patients. Additionally, fresh tissue sample will be obtained from consenting patients in whom tumor tissue is accessible (patients who undergo tumor excision during the study).
16. Long-term follow-up may be accomplished via an in person visit or telephone. The patient will be questioned about the following since their last study visit or telephone contact: medical history, surgical history, disease status, and survival status.

Appendix 2 ECOG Performance Status

(Oken, 1982)

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Appendix 3 RECIST 1.1 Summary

Abstracted from Eisenhauer EA, et al. 2009

Time Point Response: Patients with Target (± Non-Target) Disease

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable

Time Point Response: Patients with Non-Target Disease Only

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease and NE = not evaluable

A ‘Non-CR/non-PD is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Appendix 4 Evaluation of Non-Renal VHL Related Disease

Wherever possible, non-renal lesions will be assessed using RECIST 1.1, modified to assess that type of lesion only. Assessments of specific lesion types will be made as described below.

- Pancreatic Lesions

  CT/MRI of the pancreas will be obtained at baseline and follow-up and evaluated using RECIST 1.1.

- Pheochromocytomas

  Serum and urine catecholamine levels will be evaluated at baseline and follow-up visits.

- Adrenal Lesions

  CT/MRI of the adrenal glands will be obtained at baseline and follow-up and evaluated using RECIST 1.1

- CNS Hemangioblastomas

  MRI of the brain and spine will be obtained at baseline and follow-up and evaluated using RECIST 1.1

- Retinal Angiomas

  Evaluation of these lesions at baseline and follow-up will include the following:

  - Fundoscopic examination with notation of the size and location of angiomas
  - Visual acuity and visual fields in patients with lesions close to the macula or affecting vision.

- Inner Ear Endolymphatic Sac Tumors

  CT/MRI of the head will be obtained at baseline and follow-up and evaluated using RECIST 1.1.

- Epididymal Cystadenomas

  The epidydimis will be assessed at baseline and follow-up using ultrasound.

Appendix 5 New York Heart Association Functional Classification

New York Heart Association Criteria Committee, March 1994.

Class	Functional Capacity: How a patient with cardiac disease feels during physical activity
I	Patients with cardiac disease but resulting in no limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort increases.

Appendix 6 Partial List of Strong CYP2C19 and CYP3A4 Inhibitors

CYP2C19 Inhibitors	CYP3A4 Inhibitors
esomeprazole	indinavir
lansoprazole	nelfinavir
omeprazole	ritonavir
pantoprazole	clarithromycin
cimetidine	itraconazole
fluoxetine	ketoconazole
	nefazodone
	saquinavir
	suboxone
	telithromycin

For a comprehensive list see: http://medicine.iupui.edu/clinpharm/ddis/main-table/

Appendix 7 Partial List of Substrates of CYP3A4, CYP2B6, CYP2C9, and CYP2C19

CYP3A4 Substrates	CYP2B6 Substrates	CYP2C9 Substrates	CYP2C19 Substrates
clarithromycin	artemisinin	ibuprofen	esomeprazole
erythromycin	bupropion	naproxen	Lansoprazole
quinidine	efavirenz	tolbutamide	Omeprazole
alprazolam	ketamine	glipizide	Pantoprazole
diazepam	meperidine	losartan	Phenytoin
midazolam	methadone	irbesartan	Amitriptyline
cyclosporine	nevirapine	glyburide	Carisoprodol
indinavir	propofol	glipizide	Citalopram
nelfinavir	selegiline	celecoxib	Clopidogrel
ritonavir	sorafenib	fluoxetine	cyclophosphamide
cisapride		rosiglitazone	Imipramine
chlorpheniramine		tamoxifen	Labetalol
terfenadine		valproic acid	Nilutamide
amlodipine		zafirlukast	Progesterone
diltiazem			Propranolol
nifedipine			Teniposide
atorvastatin			Voriconazole
lovastatin			
simvastatin			
estradiol			
testosterone			
carbamazepine			
codeine			
fentanyl			
haloperidol			
ondansetron			

For a comprehensive list see: http://medicine.iupui.edu/clinpharm/ddis/main-table/