A Multicenter, Open-label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination With Everolimus to Treat Subjects With Advanced Renal Cell Carcinoma

Rexahn Protocol Number RX-0201-P2-A-09
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Key Sponsor Contacts:

Callie Heaton, MS, CCRA
Rexahn Pharmaceuticals
15245 Shady Grove Rd Suite 455
Rockville, MD 20850
Telephone: 1-240-268-5300 X312
Fax: 1-240-268-5310

Christine Peterson, Ph.D.
Rexahn Pharmaceuticals
15245 Shady Grove Rd Suite 455
Rockville, MD 20850
Telephone: 1-240-268-5300 X320

Key CRO Contact

Julie Pickett, RN, BSN, MSM
Project Manager, CRO
Vector Oncology, LLC
6555 Quince, Suite 400
Memphis, TN 38119
Telephone: 901-297-3385

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Amendment 3 Date:	05 February 2016
Amendment 4 Date:	08 March 2017

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled "A Multicenter, Open-label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination With Everolimus to Treat Subjects With Advanced Renal Cell Carcinoma", Amendment 04 dated 08 March 2017, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH E6) and applicable local regulatory requirements.

I agree to ensure that Financial Disclosure Statements will be completed by:

- Me (including, if applicable, my spouse [or legal partner] and dependent children)
- My sub-investigators (including if applicable, their spouse [or legal partner] and dependent children)

before study initiation, during the study if there are changes that affect my financial disclosure status and after the study is completed.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Rexahn Pharmaceuticals, Inc.

_____
Signature

_____ _____
Name of Principal Investigator Date (DD Month YYYY)

As a representative of Rexahn, I agree to the provisions described in this protocol.

_____
Signature

_____ _____
Name of Rexahn Representative Date (DD Month YYYY)

Title: A Multicenter, Open-label, Phase 1b/2 Study to Evaluate the Safety and Efficacy of RX-0201 in Combination With Everolimus to Treat Subjects With Advanced Renal Cell Carcinoma

Study Phase: Phase 1b/2

Indication: Advanced Renal Cell Carcinoma

Primary Objectives:

To determine the maximum tolerated dose (MTD) of RX-0201, up to a target dose of 250 mg/m^2/day, when given in combination with everolimus (Stage 1)

To determine progression free survival in subjects with advanced renal cell carcinoma treated with the combination of RX-0201 and everolimus versus everolimus alone (Stage 2)

Secondary Objectives:

To assess the pharmacokinetics of RX-0201 in combination with everolimus (Stage 1)

To evaluate parameters of clinical benefit as measured by duration of response, time to response, and response rate (Stage 2)

To evaluate the safety and tolerability of RX-0201 in combination with everolimus versus everolimus alone (Stage 1 and Stage 2)

Exploratory Objective:

To investigate blood or tumor response/ resistance to RX-0201 and everolimus as assessed by AKT pathway biomarkers, tumor apoptosis biomarkers and other biomarkers (Stage 1 and Stage 2)

To further evaluate the peak plasma concentration of RX-0201 at the target dose (Stage 2)

Endpoints:

Primary Endpoints:

Incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities (Stage 1)

Progression free survival at 4.5 months (Stage 2)

Secondary Endpoints:

Pharmacokinetic profile of RX-0201 (Stage 1)

Incidence of adverse events, changes in clinical laboratory tests and vital signs over time (Stage 1 and Stage 2)

Tumor response, duration of response, time to response, and response rates (Stage 2)

Exploratory endpoints:

Blood levels of AKT pathway biomarkers, tumor apoptosis biomarkers or other biomarkers (Stage 1 and Stage 2)

Plasma concentration of RX-0201 at the end of infusion (Stage 2)

Study Design:

This study will be a 2-stage multi-center, open-label study to assess the safety and tolerability of

RX-0201 in combination with everolimus versus everolimus alone to treat subjects with advanced renal cell carcinoma

- Stage 1 will be an open-label, dose-escalation study of RX-0201 to identify a safe and tolerable dose of RX-0201 up to a target dose of 250 mg/m^2/day when given in combination with everolimus.
- Stage 2 will be an open-label, 2-arm study of RX-0201 in combination with everolimus versus everolimus alone. Subjects will receive RX-0201, at the dose identified in Stage 1, in combination with everolimus for up to 8 cycles to determine safety and efficacy of the combination.

Sample Size:

Stage 1; n = approximately 9 subjects will be enrolled in Stage 1 to receive the combination of everolimus (10 mg) and RX-0201 at increasing doses of RX-0201 to the MTD or up to a target dose of 250 mg/m^2/day.

Stage 2; n = approximately 23 subjects will be treated with everolimus and RX-0201.

Study Centers: Up to 20 sites in the United States

Summary of Subject Eligibility Criteria:

Inclusion Criteria

Disease Related

- Documented histological or cytological diagnosis of renal cell cancer with a clear-cell component
- Measurable or evaluable disease defined by Response Evaluation Criteria for Solid Tumors (RECIST) ver. 1.1
- Must have received at least one course of therapy with a VEGFR-targeting tyrosine kinase inhibitor (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib) and progressed within 6 months of planned first dose of study treatment
- Prior therapy with cytokines (i.e., IL-2, Interferon) and/or VEGF-ligand inhibitors (i.e., bevacizumab) are permitted
- Prior vaccine therapy in the adjuvant setting is permitted
- Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within approximately 4 weeks after initiation of study treatment; exceptions (eg, histology determined by fine needle aspirate or tissue is no longer available) require written documentation of why a sample is not available and prior approval by the sponsor before enrollment/ randomization
- ECOG performance status of 0,1 or 2
- Life expectancy > 3 months

Demographic

- Males and females ≥ 18 years of age at screening

Ethical

- Before any study-specific procedures are performed, the appropriate written informed consent must be obtained

Exclusion Criteria

Disease Related

- Disease-associated symptoms requiring immediate therapy or other interventions
- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before planned first dose of study drug

Laboratory Values

- Absolute neutrophil count < 1.5 x 10^9/L
- Platelet count < 100 x 10^9/L
- Hemoglobin < 9 g/dL
- Bilirubin > 1.5 X upper limit of normal (ULN)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 X ULN (OR > 5 X ULN in the presence of known liver metastases)
- Serum creatinine > 1.5 X ULN OR estimated creatinine clearance ≤ 60 ml/min (Cockcroft-Gault)
- Partial thromboplasin time (PTT) > 1.25 X ULN
- Prothrombin time (PT) > 1.25 X ULN AND/OR international normalization ratio (INR) > 1.4

Medications:

- Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before planned first dose of study drug. Systemic treatment with radionuclides within 6 weeks before planned first dose of study drug. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible
- Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (e.g., temsirolimus)
- Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before planned first dose of study drug
- Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before planned first dose of study drug
- Taking strong inducers or inhibitors of CYP450s for subjects receiving everolimus
- Chronic treatment with corticosteroids or other immunosuppressive agents
- Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet inhibitors
- Subjects with a known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients
- Not recovered from toxicities related to any prior treatments, unless adverse events are clinically non-significant and/or stable on supportive therapy

General

- History of any medical, psychiatric, or social (e.g., addictive disorder) conditions, or laboratory abnormality that in the opinion of the investigator, may increase the risks associated with study participation or treatments that may interfere with the conduct of the study or the interpretation of study results
- Major surgery within 2 months before planned first dose of study drug. Complete wound healing from major surgery must have occurred within 1 month before planned first dose of study drug and from minor surgery at least 10 days before planned first dose of study drug

- Myocardial infarction within the previous 6 months before planned first dose of study drug
- Active infection requiring parenteral antibiotics within 2 weeks before planned first dose of study drug
- Diagnosis of another malignancy within 2 years before planned first dose of study drug, except for superficial skin cancers, or localized, low grade tumors
- Currently enrolled in and has not yet completed at least 30 days since ending other investigational device or drug study before planned first dose of study drug, or subject is currently receiving other investigational agent(s)
- Prior or current history of hepatitis B, hepatitis C or human immunodeficiency virus
- Pregnant, planning a pregnancy or breastfeeding during the study
- Sexually active fertile subjects (male and female) must agree to use medically accepted methods of contraception during the course of the study and for 30 days after the last dose of study treatment
- Unwilling or unable to comply with study requirements or not available for follow-up assessments
- Any other major illnesses that in the investigator's judgment substantially increases the risk associated with the subject's participation in the study

Investigational Product Dosage and Administration:

Everolimus will be administered daily at 10 mg orally at approximately the same time each day consistently with or without food per the approved label instructions in Stage 1 and Stage 2.

In Stage 1, RX-0201 will be administered at a starting dose of 125 mg/m^2/day, by a 24 hour continuous intravenous infusion for 14 days followed by 7 days of rest in each 21 day cycle. RX-0201 doses will be escalated until a maximum tolerated dose (MTD) or a target dose of 250 mg/m^2/day is reached. The MTD or the target dose will be tested further in Stage 2.

Subjects in Stage 1 and Stage 2 may receive up to 8 cycles of combined therapy until withdrawal of consent, pregnancy, substantial noncompliance with study procedures, intolerable adverse event, documented radiological disease progression or death, principal investigator judgment that it is in the best interest of the subject to stop treatment, or study discontinuation. Subjects, who the principal investigator feels are receiving benefit, may continue to receive additional cycles of therapy following discussions with the Sponsor.

Study Duration:

Each subject should complete all study procedures in approximately 8 months (i.e., screening period up to 14 days; treatment period up to eight 21-day cycles, safety follow-up approximately 30 days after the last dose of study medication). However, for subjects approved to receive additional treatment cycles, the duration may be longer than 8 months. The study duration is estimated at approximately 30 months.

Key Screening Procedures: (key procedures, see Section 7.2 for a complete list):

- Review of inclusion and exclusion criteria
- Medication, cancer history, cancer treatments and medical history
- Vital signs: resting pulse, resting respiration, temperature and resting blood pressure
- Physical examination including height and weight
- ECOG performance status assessment
- Laboratory tests

- Collection of archival paraffin embedded tumor tissue, if available.
- Radiological imaging for disease assessments should be according to RECIST ver. 1.1 as described in Appendix E (within 21 days before enrollment/randomization) and must include an imaging scan (i.e., computerized tomography or magnetic resonance imaging) of the abdomen and pelvis and other site of disease. The imaging modality selected must remain the same throughout the study.

Key Treatment Procedures (key procedures, for a complete list see Sections 7.3, 7.4, and 7.5):

- Record adverse events and concomitant medications
- Resting vital signs and weight
- ECOG performance status assessment
- Laboratory tests
- Blood collection for biomarker assessments (within ±1 day of the imaging assessment)
- Radiological imaging for a disease assessment every 6 weeks (i.e., at the end of every 2 cycles of combined or single agent therapy)
- Pharmacokinetic sampling (Cycle 1 in Stage 1 only)

Statistical Considerations:

The primary objective of Stage 1 will be to determine the dose of RX-0201 to be administered in combination with 10 mg of everolimus. Approximately 9 subjects will be enrolled in Stage 1 to be treated with everolimus and increasing doses of RX-0201 up to a target dose or the MTD.

After the dose of RX-0201 is determined in Stage 1, Stage 2 will begin accrual.

Stage 2 will now be an open label study enrolling approximately 20 subjects with the dose of RX-0201 selected in Stage 1 in combination with everolimus. The primary objective of Stage 2 will be to assess progression free survival as determined by imaging assessments after every 2 cycles of treatment (i.e., approximately every 6 weeks).

Other than the safety evaluation required to determine whether to proceed to Stage 2, no planned formal interim analysis will be performed.

All reported adverse events will be assigned a body system, and preferred term within a body system, according to the current version of MedDRA the adverse event preferred term dictionary. The number and percent of subjects reporting adverse events (all, serious, and related) will be tabulated by treatment.

Study Glossary

Term	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AKT	Protein Kinase B
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMP	Data Management Plan
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
INR	International Normalization Ratio
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
TKI	Tyrosine Kinase Inhibitor
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
WHO	World Health Organization

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1. OBJECTIVES

1.1 Primary

- To determine the maximum tolerated dose (MTD) of RX-0201, up to a target dose of 250 mg/m^2/day, when given in combination with everolimus (Stage 1)
- To determine progression free survival in subjects with advanced renal cell carcinoma treated with the combination of RX-0201 and everolimus versus everolimus alone (Stage 2)

1.2 Secondary

- To assess the pharmacokinetics of RX-0201 in combination with everolimus (Stage 1)
- To evaluate parameters of clinical benefit as measured by duration of response, time to response, and response rate (Stage 2)
- To evaluate the safety and tolerability of RX-0201 in combination with everolimus versus everolimus alone (Stage 1 and Stage 2)

1.3 Exploratory

- To investigate blood or tumor response/ resistance to RX-0201 and everolimus as assessed by AKT pathway markers, tumor apoptosis markers and other biomarkers (Stage 1 and Stage 2)
- To further evaluate the peak plasma concentration of RX-0201 at the target dose (Stage 2)

2. BACKGROUND AND RATIONALE

2.1 Disease and Treatments

Renal cell carcinoma (RCC) is responsible for about 2-3% of all malignant diseases in adults and is the most lethal of all genitourinary malignancies (Mihaly et al., 2012). Traditionally, more than 40% of patients with RCC have died of their cancer, in contrast with the 20% mortality rates associated with prostate and bladder carcinomas (Shahani et al., 2010). Overall, 8.9 new cases are diagnosed per 100,000 population per year. Clinical signs do not develop early due to the location of the tumor, and consequently the overall five-year survival is as low as 20-25%. The most important feature in the selection of the appropriate therapy is the presence of metastases (Mihaly et al., 2012).

The primary treatment is surgery ranging from partial nephrectomy for localized RCCs to cytoreductive nephrectomy in extended tumors with multiple metastases. Then, for advanced,

metastatic or recurrent disease a systemic therapy can be administered. As RCCs are generally resistant to chemo- and radiotherapy, this systemic management consists of the administration of targeted therapy agents (Mihaly et al., 2012).

Agents representing the current standards operate on members of the RAS signal transduction pathway. First line systemic treatment includes the oral, small-molecule, multi-targeted receptor tyrosine kinase inhibitors (TKI) sunitinib (targeting vascular endothelial growth factor), sorafenib (dual-specificity tyrosine kinase inhibitor), and pazopanib (a multi-targeted receptor tyrosine kinase inhibitor), the intravenous mTOR inhibitor, temsirolimus, and the oral mTOR inhibitor, everolimus (an inhibitor of the mammalian target of rapamycin), (Mihaly et al., 2012).

Everolimus, another derivative of sirolimus, is an immunosuppressant mTOR inhibitor approved by the Food and Drug Administration in 2009 for patients with advanced RCC after progression following treatment with sunitinib or sorafenib. An advantage of everolimus over temsirolimus is its oral administration leading to higher compliance (Mihaly et al., 2012).

Based on data showing statistically significant improvement in progression free survival as compared with placebo, everolimus established clinical benefit as a second-line therapy in patients who progress on first-line targeted therapy, including sunitinib and sorafenib (Shahani et al. 2010). Everolimus can be proposed as the new standard of care in the second-line setting for patients progressing on targeted therapy with VEGF inhibitor (George et al., 2009).

The recent trend in the RCC clinical trials is the initial introduction of new agents in second line treatment which then advance into first line (Mihaly et al., 2012). While evidence is growing about the role of everolimus as a second-line monotherapy for advanced RCC, the combination of everolimus with another agent is a viable option if the second agent targets the signaling in a different cancer pathway (Shahani et al., 2010).

2.2 AKT and Cancer

Strong evidence exists that AKT-1 protein product plays a very important role in cancer progression by stimulating cell proliferation and inhibiting apoptosis. In cancer cells, over-expression of constitutively activated AKT-1 in many cell types promotes cellular transformation by two distinct mechanisms. AKT-1 appears to promote proliferation under conditions in which cells should normally be growth arrested. AKT-1 inhibits apoptosis by virtually all cell-death-inducing molecules. These mechanisms enable AKT-1 to promote the survival of tumor cells under conditions in which those cells should die. Therefore, AKT-1 may be an attractive drug target for the treatment of cancer.

Overexpression of p-Akt may contribute to the development and progression of malignancies (e.g. prostate (van de ST et al., 2005), breast (Stal et al, 2003), ovarian (Kurose et al., 2001), endometrial (Uegaki et al., 2005), pancreatic ductal (Yamamoto et al., 2004), thyroid (Ringel et al., 2001), squamous cell carcinomas (Massarelli et al., 2005), multiple myeloma (Hsu et al, 2001) and renal cancer (Rathmell et al., 2005) have a negative impact on prognosis. High antiphospho-specific AKT immunostaining was significantly associated with poor cancer specific survival rate and metastases in renal cell carcinoma (Horiguchi et al., 2003). Increases in both cytoplasmic and nuclear p-Akt levels were independent prognostic factors for reduced renal cancer patient survival (Hager et al, 2009). Molecular correlates of patient survival further implicate AKT as having a role in tumor progression, involving specific DNA methylation events in kidney cancer (Cancer Genome Atlas Research Network, 2013). Neither tumour grade nor stage influenced p-Akt expression, whereas the clear cell and papillary subtypes showed increased p-Akt more often than chromophobe or sarcomatoid types of renal cancer (Hager et al, 2009).

2.3 RX-0201 Background

RX-0201 is a 20-mer oligonucleotide that is complementary to AKT-1 messenger ribonucleic acid (mRNA). Antisense oligonucleotides are being studied for potential use as therapeutic agents for cancer. Antisense oligonucleotides are short deoxyribonucleic acid (DNA) molecules that can interfere with gene expression by forming duplexes with complimentary sequences of target mRNA. The antisense oligonucleotides can inhibit protein expression by causing AKT-1 mRNA inactivation. The AKT-1 (also called protein kinase B or PKB) gene family consists of 3 widely expressed, closely related proto-oncogenes known as AKT-1, AKT-2, and AKT-3, respectively. Once activated, AKT protein products can phosphorylate a range of proteins and thereby control several cellular processes (Staal, 1987).

2.3.1 Nonclinical Studies

The specificity of RX-0201-mediated effect on AKT-1 mRNA levels was examined in human renal cell carcinoma (von Hippel-Lindau protein-deficient renal cell carcinoma cell line) UMRC2 cells. The treatment of UMRC2 cells with RX-0201 at concentrations of 0.1 - 0.3 µM resulted in almost complete reduction of AKT-1 mRNA levels. *In vitro* pharmacology studies have demonstrated that RX-0201 suppressed cell proliferation of human cancer cells of various origins, including pancreatic cells. RX-0201 was evaluated for antitumor activity in athymic nude mice implanted with fragments of human tumors, which included PANC-1 pancreatic carcinoma cell line. While no significant antitumor effects were observed in PANC-1, treatment with RX-0201 did appear to result in increased survival benefits at the dose levels tested.

When treated with RX-0201 no significant effects were seen in acute toxicity studies in Cynomolgus monkeys and Sprague-Dawley rats. Possible RX-0201 related effects in 14-day toxicity studies in Cynomolgus monkeys included decreased red blood cells and histological findings in the liver, kidneys, and lymphatic tissues. Possible RX-0201 related effects in 14-day toxicity studies with Sprague-Dawley rats include: lower red blood cell parameters seen in all treated groups that persisted through the recovery period, as well as changes in kidney and liver histology and other hematologic and blood chemistry parameters.

The effect of RX-0201 when given in combination with everolimus on renal cancer cell proliferation was studied in Caki-1 and UMRC2 cells. An additive effect on growth inhibition was observed when either Caki-1 or UMRC2 cells were treated with a combination of RX-0201 and everolimus. These results suggest that when RX-0201, when combined with everolimus, may increase inhibition of cell proliferation.

2.3.2 Prior Clinical Experience

In a phase 1 single agent dose escalation study of RX-0201, doses ranging from 6.0 to 315 mg/m^2/day were administered to 17 subjects with solid tumors. The maximum tolerated dose of single agent administration was 250 mg/m^2/day. Fatigue was the most commonly reported adverse event in 82% of subjects (14/17). Arthralgia (joint pain) and nausea were the second most commonly reported adverse events with 47% (8/17) and 35% (6/17) of subjects reporting these events, respectively. Fatigue was also the most frequently reported adverse event determined by the investigator to be related to RX-0201, with 70.6% (12/17) of subjects reporting the event, 29.4% (5/17) of the subjects reported a mild fatigue, 23.5% (4/17) of subjects reported a moderate fatigue, and 17.6% (3/17) subjects reported a severe fatigue.

A Phase 2 study of RX-0201 and gemcitabine in metastatic pancreatic cancer has been completed. In Stage 1 of this study, 11 subjects were enrolled and received gemcitabine at 1000 mg/m^2 for 30 minutes followed by a continuous infusion of RX-0201 at a dose of 200 mg/m^2/day for 14 days. In Stage 2 of this study, 20 additional subjects were treated with gemcitabine at 1000 mg/m^2 for 30 minutes followed by 200 mg/m^2/day of RX-0201. The most commonly reported treatment emergent adverse events related to RX-0201 were thrombocytopenia (8.7%), decreased platelet count (7.7%), neutropenia (6.7%), fatigue (5.8%), and decreased hemoglobin (5.8%).

The Phase 1b portion of this study has been completed. Seven males and 3 females, (median age 61 years) were treated with 125 mg/m^2/day (n=3), 200 mg/m^2/day (n=4), and 250 mg/m^2/day (n=3) RX-0201 in combination with 10 mg everolimus. The most common toxicities attributed to the combination were rash, mouth ulceration, weight loss, thrombocytopenia, facial edema,

fatigue, and pruritus. No significant events were attributed to RX-0201 alone. Most events (81%) were mild or moderate in severity. Based on the tolerability, 250 mg/m^2/day RX-0201 dose was declared the recommended Phase 2 dose.

As of 06 March 2017, nine subjects have been randomized and treated in the Phase 2 portion of the study. The treatment of metastatic renal cell carcinoma and recruitment for this study have been significantly impacted by the approval of 3 new therapies (nivolumab, cabozantinib, and lenvatinib + everolimus). Treatment with everolimus alone in the clinical study setting is no longer a preferred option for clinicians and patients. Therefore, the everolimus alone treatment arm and randomization component is being removed in this protocol amendment.

3. EXPERIMENTAL PLAN

3.1 Study Design

The current study will be a phase 1b/2, multicenter, open label study conducted in 2 stages. Stage 1 will be an open-label, dose-escalation phase 1b study of RX-0201 administered in combination with everolimus. It is expected that 250 mg/m^2/day or a lower dose of RX-0201 will be identified as safe and well-tolerated when administered in combination with everolimus. The initial dose of RX-0201 will be 125 mg/m^2/day. RX-0201 will be administered by continuous intravenous infusion for 14 days followed by 1 week of rest. The dose of RX-0201 identified in Stage 1 will be studied further in the dose expansion portion (Stage 2). In Stage 1 and Stage 2, everolimus (10 mg) will be administered daily according to the approved label instructions.

Stage 2 will be an open-label, 2-arm phase 2 study of RX-0201 in combination with everolimus versus everolimus alone. Subjects will receive either RX-0201, at the dose identified in Stage 1, in combination with everolimus for up to 8 cycles until withdrawal of consent, pregnancy, substantial noncompliance with study procedures, intolerable adverse event, documented radiological disease progression (per RECIST ver. 1.1 see Appendix E), death, principal investigator judgment that it is in the best interest of the subject to stop treatment, or study discontinuation. For subjects receiving RX-0201 and everolimus therapy and, in the opinion of the investigator, is receiving benefit after 8 cycles, additional cycles of RX-0201 plus everolimus may be administered following discussions with the Sponsor. Prior to this amendment, subjects were randomized to receive everolimus alone. Subjects randomized to the everolimus only treatment arm will complete the study after 8 cycles but may continue to receive everolimus off-study.

The study endpoints are defined in Section 9.2.

3.2 Number of Centers

Up to 20 sites in the US will participate in this study. Sites that do not enroll subjects within 3 months of site initiation may be terminated.

3.3 Number of Subjects

In Stage 1 approximately 9 subjects will be enrolled to receive escalating doses of RX-0201 in combination with everolimus. The number of subjects enrolled into Stage 1 will vary depending upon the number of dose levels needed to determine the MTD up to a target dose of 250 mg/m^2/day of RX-0201.

In Stage 2 approximately 23 subjects will be treated (i.e., 3 subjects in the everolimus arm and up to 20 subjects in the everolimus/RX-0201 arm).

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

Each subject should complete all study procedures in approximately 8 months (i.e., screening period up to 14 days; treatment period up to eight 21-day cycles, safety follow up approximately 30 days after the last dose of study medication).

Subjects in Stage 1 and Stage 2 may receive up to 8 cycles of RX-0201 until the earliest of disease progression (per RECIST ver. 1.1 see Appendix E), an intolerable RX-0201-related toxicity, withdrawal of consent, pregnancy, substantial noncompliance with study procedures, principal investigator judgment that it is in the best interest of the subject to stop treatment, or study discontinuation.

Subjects assigned to the RX-0201 and everolimus treatment arm, who the principal investigator feels are receiving benefit, may continue to receive treatment beyond 8 cycles following discussions with the Sponsor. The duration for these subjects will be >8 months with each additional cycle of treatment lasting 21 days.

The study duration is estimated at approximately 30 months.

3.4.2 End of Study

The end of the study is estimated to be approximately 30 days after the last subject completes the protocol specified treatment.

4. SUBJECT ELIGIBILITY

The following eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility

criteria may not be waived by the investigator, and conformance to the eligibility criteria is subject to review in the case of a Good Clinical Practice (GCP) or a regulatory authority audit. Any questions regarding a subject's eligibility should be discussed with the study sponsor and medical monitor prior to enrollment/randomization.

Before **any** study-specific procedures are performed, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Screening Log

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (i.e., age, sex, race), date, and outcome of the screening process (e.g., enrolled into study, reason for ineligibility, or declined to participate).

4.2 Inclusion Criteria

Disease related

- Documented histological or cytological diagnosis of renal cell cancer with a clear-cell component
- Measurable or evaluable disease defined by Response Evaluation Criteria for Solid Tumors (RECIST) ver. 1.1
- Must have received at least one course of therapy with a VEGFR-targeting tyrosine kinase inhibitor (eg, sorafenib, sunitinib, axitinib, pazopanib or tivozanib) and progressed within 6 months of planned first dose of study treatment.
- Prior therapy with cytokines (i.e., IL-2, Interferon) and/or VEGF-ligand inhibitors (i.e., bevacizumab) are permitted
- Prior vaccine therapy in the adjuvant setting is permitted
- Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within approximately 4 weeks after inititation of study treatment; exceptions (e.g., histology determined by fine needle aspirate or tissue is no longer available) require written documentation of why a sample is not available and prior approval by the sponsor before enrollment/ randomization
- ECOG performance status of 0, 1 or 2
- Life expectancy > 3 months

Demographic

- Males and females ≥ 18 years of age at screening

Ethical

- Before any study-specific procedures are performed written informed consent must be obtained (see Section 11.1)

4.3 Exclusion Criteria

Disease Related

- Disease-associated symptoms requiring immediate therapy or other interventions
- Known brain metastases or cranial epidural disease unless adequately treated with radiotherapy and/or surgery and stable for at least 3 months before planned first dose of study drug

Laboratory

- Absolute neutrophil count < 1.5 x 10^9/L
- Platelet count < 100 x 10^9/L
- Hemoglobin < 9 g/dL
- Bilirubin > 1.5 X upper limit of normal (ULN)
- Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 X ULN (OR > 5 X ULN in the presence of known liver metastases)
- Serum creatinine > 1.5 X ULN OR estimated creatinine clearance ≤ 60 ml/min (Cockroft-Gault)
- Partial thromboplastin time (PTT) > 1.25 X ULN
- Prothrombin time (PT) > 1.25 X ULN OR international normalization ratio (INR) > 1.4

Medications

- Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before planned first dose of study drug. Systemic treatment with radionuclides within 6 weeks before planned first dose of study drug. Subjects with clinically relevant ongoing complications from prior radiation therapy are not eligible
- Prior treatment with everolimus, or any other specific or selective TORC1/PI3K/AKT inhibitor (e.g., temsirolimus)
- Receipt of any type of small molecule kinase inhibitor (including investigational kinase inhibitor) within 2 weeks before planned first dose of study drug
- Receipt of any type of anticancer antibody (including investigational antibody) within 4 weeks before planned first dose of study drug
- Taking strong inducers or inhibitors of CYP450s for subjects receiving everolimus
- Chronic treatment with corticosteroids or other immunosuppressive agents
- Concomitant anticoagulation at therapeutic doses with oral anticoagulants or platelet inhibitors
- Subjects with a known hypersensitivity to everolimus or other rapamycins (sirolimus, temsirolimus) or to its excipients
- Not recovered from toxicities related to any prior treatments, unless adverse events are clinically non-significant and/or stable on supportive therapy

General

- History of any medical, psychiatric, or social (e.g., addictive disorder) conditions, or laboratory abnormality that in the opinion of the investigator, may increase the risks associated with study participation or treatments that may interfere with the conduct of the study or the interpretation of study results

- Major surgery within 2 months before planned first dose of study drug. Complete wound healing from major surgery must have occurred within 1 month before planned first dose of study drug and from minor surgery at least 10 days before planned first dose of study drug
- Myocardial infarction within the previous 6 months before planned first dose of study drug
- Active infection requiring parenteral antibiotics within 2 weeks before planned first dose of study drug
- Diagnosis of another malignancy within 2 years before planned first dose of study drug, except for superficial skin cancers, or localized, low grade tumors;
- Currently enrolled in and has not yet completed at least 30 days since ending other investigational device or drug study before planned first dose of study drug, or subject is currently receiving other investigational agent(s).
- Prior or current history of hepatitis B, hepatitis C or human immunodeficiency virus
- Pregnant, planning a pregnancy or breastfeeding during the study
- Sexually active fertile subjects (male and female), must agree to use medically accepted methods of contraception during the course of the study and for 30 days after the last dose of study treatment. Female subjects must meet at least one of the following criteria:
    - be surgically sterile (i.e., have had bilateral tubal ligation, hysterectomy, or bilateral oophorectomy at least 6 months before enrollment; appropriate documentation will be required),
    - be post-menopausal for at least 12 months OR
    - if sexually active, be willing to use double-barrier contraception (e.g., condom with spermicide), intrauterine device, steroidal contraceptive (oral, transdermal, implanted, or injected) or other method, approved by the sponsor.
- Unwilling or unable to comply with study requirements or not available for follow-up assessments
- Any other major illnesses that in the investigator's judgment substantially increases the risk associated with the subject's participation in the study

5. SUBJECT ENROLLMENT

5.1 Subject Recruitment

Subjects will be enrolled from the cancer populations being followed at the investigational sites. The site personnel will discuss the possibility of participation directly with subjects being seen in the center who may be appropriate candidates for the study. A description of the protocol will be posted on the www.clinicaltrials.gov website.

5.2 Subject Registration

Before subjects may be entered into the study, Rexahn requires a copy of the site's written institutional review board (IRB) approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 11.3). A subject must

personally sign and date the consent form before any study specific screening assessments are done. Procedures that are performed as standard of care may be used for screening provided they are still within the 14 day screening period unless otherwise indicated.

After a subject has completed the necessary screening assessments, any questions regarding the eligibility of a subject should be discussed with the study sponsor before enrollment/randomization of the subject into the study. A subject will be considered enrolled or randomized when they are determined eligible and receive their treatment assignment.

The study sponsor or its designee will assign each subject a unique subject identification number (a 2-digit site number followed by a 3-digit subject number). The subject number must be used for subject identification on all study-related documents (e.g., electronic case report forms (eCRFs), clinic notes, laboratory samples, CT scans, MRIs, etc.). In order to obtain a subject number, the site must provide completed eligibility documents to the sponsor or designee who will provide confirmation of eligibility by either fax or e-mail to the site. Of note, subjects may be rescreened for laboratory values not meeting the criteria only once for study eligibility. A subject will be considered enrolled or randomized when the treatment has been assigned.

5.3 Subject Enrollment/ Randomization and Treatment Assignment

Subjects in Stage 1 will be enrolled to receive the combination everolimus with escalating doses of RX-0201. Subjects in Stage 2 will no longer be randomized to 1 of 2 treatment arms (i.e., everolimus versus everolimus/RX-0201). All subjects in Stage 2 will now be assigned to the everolimus/ RX-0201 treatment arm.

The site will provide documentation showing that the subject meets the eligibility requirements. Following a review of supporting documentation, by the sponsor or its designee, the site will receive the treatment assignment and a confirmation of enrollment/randomization. Subjects should be dosed within 5 days of enrollment/randomization.

5.4 Subject Replacement

Subjects in Stage 1 who are enrolled but not treated and subjects who discontinue treatment before completion of Cycle 1 for reasons other than the occurrence of a DLT may be replaced. Any replacement subject will be enrolled into the same dosing group as that for the subject who withdrew.

Subjects in Stage 2 who are enrolled but not treated will be replaced.

6. TREATMENT PROCEDURES

The only investigational product in this study will be RX-0201. RX-0201 will be administered in combination with everolimus. Everolimus will not be provided by the sponsor.

6.1 Study Drug Administration

6.1.1 Everolimus Dose Administration

Subjects will take 10 mg of everolimus orally, once daily at approximately the same time every day, consistently either with or without food. Everolimus should be swallowed whole with approximately 8-10 ounces of water.

If a subject misses a dose of everolimus, they may still take it up to 6 hours after the time they would normally have taken it. If more than 6 hours have elapsed, they should be instructed to skip the dose for that day. The next day, they should take everolimus at the usual time. Subjects should not take 2 doses to make up for the one dose that they missed.

Drug compliance should be recorded in the subject's medical record and in the eCRF. This information will include amount of everolimus that should have been taken over a given time interval and the amount actually taken by the subject. (Section 10.3)

6.1.2 RX-0201 Dosing Schedule

RX-0201 will be administered on a cyclical basis. For subjects assigned to receive RX-0201 and everolimus, a cycle will be defined as the period elapsing from the first day of RX-0201 administration through Day 21 of the cycle or to the recovery from any adverse events sufficient that a new cycle of therapy can be administered (e.g., on Day 29 or Day 36), whichever occurs later. Once a new cycle starts, the prior cycle is considered to be completed. For subjects assigned to the everolimus only arm, a cycle will be defined as the period elapsing from the first day of everolimus administration through Day 21 of the cycle or to the recovery from any adverse events sufficient that a new cycle of therapy can be administered, whichever occurs later.

6.1.3 RX-0201 Dose Administration

The dose of RX-0201 will be based upon the subject's actual weight measured on the morning of the planned dosing. The body surface area will be calculated using the Dubois or Mosteller formulas; the same formula must be used for the subject throughout the study. All body surface area and dosing calculations will be documented in the subject's medical record and eCRF, if applicable. The starting dose of RX-0201 will be 125 mg/m^2/day. This dose will be administered to eligible subjects in a 24 hour continuous intravenous infusion for 2 weeks followed by 1 week of rest in each 21 day cycle.

For each RX-0201 treatment cycle, a total of two 1000 ml infusion bags containing RX-0201 will be used. Each infusion bag will be prepared immediately before use and will contain enough RX-0201 for 7 days plus 10% overage (or overage acceptable by institutional practices) of infusion (see Appendix D for details). The first bag will be prepared on Day 1 of each 21 day cycle. The second bag will be prepared on Day 8 of each 21 day cycle. Day 15 will be the start of the 1 week rest period.

RX-0201 will be administered via continuous infusion using an ambulatory infusion pump through a vein in the arm or a indwelling catheter (i.e. Port-a-Cath® or PICC line).

RX-0201 should not be mixed with or administered as an infusion simultaneously with other medicinal products. The indwelling infusion line should be flushed with saline before and after the investigational product administration to avoid mixing with other drug products or intravenous solutions. Pharmacokinetic samples should be obtained in the opposite arm.

The date, time (i.e., start and stop) and volume infused (i.e., either initial and remaining volumes or volume infused off the pump) will be recorded in the subject's medical record and eCRF, if applicable.

6.2 Rationale for the RX-0201 Dose and Dosing Interval

The RX-0201 dosing schedule was selected on the basis of results from a first in human Phase 1 single agent study (RX-0201-P1-A-03) and a Phase 2 RX-0201 combination with gemcitabine study in pancreatic cancer (RX-0201-P2-A-07). Because there is no clinical data available using RX-0201 in combination with everolimus, Stage 1 of the study will assess the safety of RX-0201 in combination with everolimus.

6.3 RX-0201 Dose Limiting Toxicity

Initially 3 subjects will be enrolled to receive everolimus plus 125 mg/m^2/day of RX-0201. If there are any dose limiting toxicities (DLTs) attributed to RX-0201 the following dose-escalation decisions will be followed:

Table 1: Phase 1 RX-0201 Dose Escalation

Dose Group	Theoretical dose(mg/m^2/day)	Escalation
1	125	-
2	200	1.60
3	250	1.25

The following dose-escalation rules will be employed:

- If 0 of the first 3 subjects experience DLT during the first 3 weeks of treatment, then the dose will be escalated to the next higher level in 3 subsequent subjects.
- If 1 of the first 3 subjects experiences DLT at the current dose during the first 3 weeks of treatment, then 3 more subjects will be accrued at the same dose level.
- If 0 of the 3 additional subjects experience DLT during the first 3 weeks of treatment, then the dose will be escalated to the next higher level in 3 subsequent subjects.
- If ≥ 1 of the 3 additional subjects in a cohort experiences DLT in the first 3 weeks of treatment, the MTD has been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level).
- If ≥ 2 of 3 or ≥ 2 of 6 subjects experience DLT during the first 3 weeks of treatment, then the MTD has been exceeded and 3 more subjects will be treated at the next lower dose level (if only 3 subjects were previously treated at that prior dose level).
- Each group of 3 subjects within a cohort must be observed for a minimum period of 3 weeks without DLT before subsequent subjects are enrolled at the next higher dose level.
- Escalation to the next dose level of the study can occur upon review of the safety data from all ongoing and previous subjects and with the concurrence of the study sponsor and the principal investigators.

In the event that attribution of causality of potential DLTs to study drug may be equivocal, discussions with the investigators, medical monitor and sponsor will occur and additional subjects may be enrolled at that dose level. Reviews will be conducted by the investigators, medical monitor and sponsor of all available safety data on an ongoing basis throughout the study. The study sponsor or its designee will notify the sites when enrollment into a dose level is complete and when the next dose level is open to enrollment during Stage 1.

6.4 Determination of MTD or the RX-0201 Recommended Stage 2 Starting Dose

The establishment of the MTD or the safety of the target RX-0201 dose of 250 mg/m^2/day will be based on a review of the overall safety data by the investigators, medical monitor and sponsor. The MTD is the highest starting dose level associated with first-cycle DLTs in < 33.3% of subjects. Once the safety of the MTD of the target RX-0201 dose of 250 mg/m^2/day is initially established, additional subjects (up to 20 subjects total) will be enrolled to receive the target RX-0201 dose of 250 mg/m^2/day in Stage 2. Selection of a recommended Stage 2 starting dose

from within the tested dose range will be based on evaluation of available safety information with findings regarding compliance, and achievement of targeted pharmacokinetic values.

6.5 Definitions of Dose Limiting Toxicity

Reference should be made to the CTCAE, Version 4.03 for grading of the severity of adverse events and laboratory abnormalities. A DLT will be defined as any of the following adverse events that is considered by the investigator as related to RX-0201:

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L) with fever or lasting 3 days or longer
- Any Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with ≥ Grade 1 hemorrhage
- Any ≥ Grade 3 coagulation abnormality (defined by PT and/or INR and PTT values) associated with clinical hemorrhage ≥ Grade 1.
- Nausea/vomiting ≥ Grade 3 despite maximal antiemetic therapy; diarrhea ≥ Grade 3 despite maximal anti-diarrheal therapy.
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
- Any other non-hematological toxicity ≥ Grade 3 with the exception of alopecia

6.6 RX-0201 Dosage Modifications

Whenever possible, dose modifications of study drug should be discussed between the investigator, medical monitor, and the sponsor prior to implementation. The appropriate clinic staff should administer the new dose level and inform the subject about the change in dose level.

6.6.1 RX-0201 Dose Modifications During a Cycle

If a subject experiences a RX-0201-related DLT (as defined in Section 6.5), SAE, or other intolerable adverse event and requires a dose reduction, RX-0201 administration should be interrupted, as necessary, until the adverse event resolves or stabilizes to an acceptable degree (generally to the pretreatment severity grade). If appropriate, more frequent laboratory monitoring may be instituted until abnormalities have recovered to the pretreatment severities. Thereafter, RX-0201 may be reinstituted, but the dose of RX-0201 for the remainder of that cycle should be reduced by 1 dose level. Successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate RX-0201 at Dose Level 1 (125 mg/m^2/day) then the subject should be discontinued from RX-0201 therapy.

6.6.2 RX-0201 Dose Modifications at the Beginning of the Next Cycle

A new cycle of RX-0201 treatment may begin no earlier than Day 1 of the new cycle but should be delayed, as necessary, until adverse events or laboratory abnormalities have returned to baseline levels. If adverse events or laboratory abnormalities are not resolved to baseline, week-by-week delays in initiating the new cycle of treatment should be instituted. Once all toxicities have returned to baseline, the next cycle of therapy can be initiated.

Subjects experiencing any of the DLTs described in Section 6.5 in the current cycle of therapy should have the dose in the next cycle of therapy reduced by 1 dose level. Subjects who required an intra-cycle dose reduction, during the current cycle of therapy, should have the dose in the next cycle of therapy administered at no higher than the highest dose tolerated in the current cycle. Successive inter-cycle adjustments to progressively lower dose levels can be made. If the subject cannot tolerate RX-0201 at Dose Level 1 (125 mg/m^2/day) then the subject should be discontinued from RX-0201 therapy.

Subjects in Stage 1 will receive additional cycles at the same dose to which they were assigned in Cycle 1.

6.6.3 RX-0201 Dose Re-Escalation

After a dose is reduced, the dose need not be re-escalated, even if there is minimal or no toxicity with the reduced dose. However, if the subject tolerates a reduced dose of RX-0201 for ≥ 3 weeks then the RX-0201 dose may be increased to the next higher dose level, at the discretion of the investigator. Such re-escalation may be particularly warranted if further evaluation reveals that the adverse event that led to the dose reduction was not RX-0201-related. Successive adjustments to progressively higher dose levels can be made at 3-week intervals.

6.6.4 RX-0201 Dose Escalation (Stage 1 only)

Subjects receiving a dose of RX-0201 in Stage 1 that is less than the MTD or target dose and for whom the principal investigator feels are receiving benefit, may receive an increased dose following discussions with the Sponsor.

6.6.5 Everolimus Adjustments, and Modifications

Dose adjustments for everolimus will be allowed for adverse events according to the approved package insert or best clinical practices. See everolimus package insert for full details regarding dose adjustment.

6.7 Everolimus Dose Delays

Dose delays for everolimus will be allowed according to the approved package insert or best clinical practices. If the start of a cycle (i.e., day 1 of a cycle) is delayed due to everolimus related toxicity, then RX-0201 dosing may continue on schedule.

If an adverse event occurs that is related to RX-0201, everolimus may continue on schedule.

If an adverse event occurs that is related to the combination of RX-0201 and everolimus, dosing of both drugs may be delayed until the event is resolved.

6.8 RX-0201 Dose Delays

If the start of a cycle (i.e., day 1 of a cycle) is delayed due to RX-0201 related toxicity, then everolimus dosing may continue on schedule.

If an adverse event occurs that is related to the combination of RX-0201 and everolimus, dosing of both drugs may be delayed until the event is resolved.

6.9 Discontinuation of Study Treatment

All study participants may receive study treatment for up to 8 cycles. Therapy beyond 8 cycles may be considered following discussions among the sponsor and investigator.

However:

- Any subject has the right to withdraw from study treatment or study follow-up at any time.
- Any subject who has objective evidence of cancer progression should be withdrawn from study treatment.
- Any subject whose medical condition substantially changes after entering the study should be carefully evaluated by the investigator in consultation with the sponsor; such subjects should be withdrawn from study treatment if continuing would place them at risk.
- Any subject who becomes pregnant or begins breastfeeding should be withdrawn from study treatment.
- Any subject who becomes significantly noncompliant with study drug administration, study procedures, or study requirements should be withdrawn from study treatment in circumstances that increase risk or substantially compromise the interpretation of study results.
- The investigator, in consultation with the sponsor, may withdraw any subject from the study treatment, if, in the investigator's opinion, it is not in the subject's best interest to continue.

- The sponsor, relevant regulatory agencies, or the IRB may request discontinuation of the study at any time.

The date the subject is withdrawn from study treatment or from the study and the reason for discontinuation will be recorded in the subject's medical record and on the appropriate eCRF.

When a subject is withdrawn from study treatment or is permanently removed from study treatment (regardless of the reason), all of the evaluations required at the end-of-treatment visit should be performed and any additional evaluations should be completed that may be necessary to ensure that the subject is free of untoward effects. The subject should be encouraged to seek appropriate follow up for any continuing health problems.

Subjects who discontinue study treatment may still continue on study follow-up. Thus, all subjects receiving study drug will be followed during the post treatment follow-up assessments unless the subject withdraws consent for such follow-up.

6.10 Concomitant Therapy

To the extent possible, administration of any prescription or over-the-counter drug products other than protocol specified medication(s) should be minimized during the study period. Subjects should be discouraged from use of street drugs, herbal remedies, self-prescribed drugs, tobacco products, or excessive alcohol at any time during the clinical study.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and the reason for use should be recorded on the eCRFs.

For subjects receiving everolimus unless otherwise specified the approved label should be consulted.

6.10.1 Analgesics

Investigators may give analgesics, as necessary, for pain control.

6.10.2 Antibiotics, Antifungals, and Antivirals

For subjects who develop an infection, appropriate medical therapy (e.g., with antibiotics, antifungals, or antivirals) or other interventions should be instituted. Investigators should use appropriate medical judgment in determining whether a subject continues with study treatment(s) during treatment for the infection.

6.10.3 Anticancer or Experimental Systemic Therapies Other than Investigational Treatments

No other systemic anticancer therapies (including chemotherapy, antibody therapy, immunotherapy, or other experimental therapies) of any kind are permitted while the subject is receiving study treatment. Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

6.10.4 Antidiarrheals

For subjects who develop diarrhea, the causal relationship to existing medical conditions, concomitant medications, or gastrointestinal infection should be considered and eliminated. Depending upon the clinical circumstances, endoscopy and biopsy may be warranted.

Antidiarrheals are not allowed prior to the administration of study treatment(s) on Cycle 1 Day 1 in Stage 1 and antidiarrheals should not be taken prophylactically in subsequent cycles. However, antidiarrheals can be administered on subsequent treatment days and in subsequent cycles, based on the judgment of the treating physician and local institutional practices.

6.10.5 Antiemetics

Antiemetics are not allowed prior to the administration of study treatment(s) on Cycle 1 Day 1 in Stage 1. However, antiemetics can be administered on subsequent treatment days and in subsequent cycles, based on the judgment of the treating physician and local institutional practices.

6.10.6 Contraception

Sexually active females of childbearing potential must accept continuous heterosexual abstinence as a lifestyle choice or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days following discontinuation of study treatment(s). A female subject is considered to be of childbearing potential unless she has had a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy; has medically documented ovarian failure (with serum estradiol and follicle-stimulating hormone [FSH] levels within the institutional postmenopausal range and a negative serum or urine β-human chorionic gonadotropin [β-HCG]), or is menopausal (age ≥ 55 years with amenorrhea for ≥ 12 months). Protocol-recommended methods of contraception include

barrier method with spermicide, intrauterine device (IUD), or steroidal contraceptive (oral, transdermal, implanted, or injected).

Sexually active male subjects who can father a child (i.e., are fertile) must accept continuous heterosexual abstinence as a lifestyle choice; limit intercourse to female partners who are surgically sterile, post-menopausal, or using effective contraception or agree to use a protocol-recommended method of contraception during heterosexual intercourse throughout the study treatment period and for 30 days following discontinuation of RX-0201. A male subject is considered fertile unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy. The investigator should counsel subjects on the most effective methods for avoiding pregnancy during the trial. Protocol-recommended contraceptive methods are double-barrier methods (e.g., diaphragm with spermicide or male condom with spermicide) use of an intrauterine device, or steroidal contraceptive (oral, transdermal, implanted, or injected).

The sponsor should be consulted regarding any questions relating to childbearing status or contraception.

6.10.7 Corticosteroids

Systemic or enteric corticosteroids are not allowed prior the administration of study treatment(s) on Cycle 1 Day 1 of Stage 1. Subjects may receive topical or inhaled corticosteroids while on study. In addition, subjects who develop conditions that may be alleviated by systemic or enteric corticosteroid therapy are permitted to receive such drugs and are not required to discontinue study participation

6.10.8 Diet

There are no specific dietary restrictions in the study other than that subjects avoid grapefruit and grapefruit juice or using herbal remedies or dietary supplements (in particular, St. John's wort) while taking everolimus.

6.10.9 Drugs with Potential for Interactions with Everolimus

In order for subjects to be maintained on the 10 mg dose of everolimus according to the approved label strong inducers and inhibitors of the P450 class should be avoided while on study.

For subjects that are treated with everolimus the following should be avoided:

- Strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole)
- Moderate CYP3A4 and/or PgP inhibitors (e.g., amprenavir, fosamprenavir, aprepitant, erythromycin, fluconazole, verapamil, diltiazem)

- Strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital).

6.10.10 Erythropoietin and Granulocyte Colony-Stimulating Factors

Use of erythropoietic agents (e.g., erythropoietin or darbepoetin alfa) is not permitted during Cycle 1 in Stage 1. Thereafter, such agents may be administered for Grade ≥ 3 anemia, but their use in this study is discouraged.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered given the potential for GM-CSF-related inflammatory symptoms.

Use of granulocyte colony-stimulating factor (G-CSF) (e.g., filgrastim, PEG-filgrastim, lenograstim) is not allow during Cycle 1 in Stage 1. Prophylactic administration of G-CSF and concomitant administration of the study treatment(s) and G-CSF is not permitted in support of protocol therapy. However, administration of G-CSF may be considered in a subject who, despite dose modification, is experiencing recurrent difficulties with recovering from neutropenia in a timely fashion. In addition, therapeutic use of G-CSF in subjects with serious neutropenic complications such as tissue infection, sepsis syndrome, fungal infection, etc., may be considered at the investigator's discretion.

Reference may be made to the American Society of Clinical Oncology guidelines (Rizzo et al., 2008; Smith et al., 2006).

6.10.11 Immunization

Due to its potential effects on lymphoid cells, RX-0201 might theoretically impair primary or secondary responses to immunization. Everolimus also has known immunosuppressant properties. For subjects who are at substantial risk of an infection (e.g., influenza) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

If a vaccine is administered after the initiation of study therapy, vaccination should not be performed during Cycle 1 of Stage 1 or during any other cycle in a period when the patient is experiencing Grade ≥ 2 leukopenia. Vaccination with live virus vaccines during study treatment and close contact with those who have received live vaccines should be avoided.

6.10.12 Radiation Therapy

Radiation therapy is not permitted during Cycle 1 in Stage 1. Thereafter, short-term, palliative radiation therapy can be used for the management of known, non-progressing bony metastatic lesions if refractory to standard pain management algorithms.

The radiosensitizing properties of RX-0201 and everolimus have not yet been established. Before treatment occurs, the investigator should discuss the method/frequency of radiation administration with the sponsor and medical monitor.

6.10.13 Surgery or Other Invasive Procedures

The effects of RX-0201 on coagulation or wound healing are unknown. Potential RX-0201 myelosuppressive or immunosuppressive effects could enhance the risk of peri-procedural bleeding or infection.

Elective surgical procedures (other than placement of IV access devices) should be avoided during study drug administration. However, subjects may undergo necessary surgical or invasive procedures for serious intercurrent medical problems; in these circumstances, study drug should be interrupted. Investigators should use appropriate medical judgment in determining whether to resume study drug in the post-procedure period. For subjects resuming study drug, any myelosuppressive effects of the drug should have returned to baseline levels and the subject should be clinically stable before reinitiating therapy.

6.10.14 Transfusions

Red blood cell or platelet transfusions may be administered, as clinically indicated.

7. STUDY PROCEDURES

Refer to the Schedule of Assessments (for details see Appendix A and Appendix B) for an outline of procedures required at each visit. All safety blood and urine samples should be submitted to the local laboratory on the day of collection. Blood for evaluation of RX-0201 pharmacokinetics, any archived tumor tissue, any tumor biopsy samples and biomarker samples should be prepared and shipped to the central lab for analysis.

Source documents, including but not limited to, radiological imaging including baseline scans must be stored and available for subsequent review by the sponsor or their designee.

7.1 General Study Procedures

A signed and dated IRB-approved informed consent must be obtained before any study specific screening procedures are performed. Assessments that are performed as standard of care procedures may be used for screening if performed before the informed consent is signed, provided they are still within the screening period time frame.

7.2 Screening Procedures – Stage 1 and Stage 2

The following screening assessments must be performed and results available within 14 days (unless otherwise noted) before enrollment/randomization:

- Written informed consent
- Review of inclusion and exclusion criteria
- Medical and medication history review, documentation of diagnosis and previous treatments including details of tumor diagnosis (e.g., date of diagnosis, histology, stage at diagnosis and current stage) and most recent disease assessment
- Complete physical examination including weight and height
- Performance status (ECOG)
- Resting vital signs: resting pulse, resting respiration rate, resting blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements
- Laboratory tests (for details see Appendix C)
    - Urinalysis
    - Hematology panel
    - Chemistry panel
    - Coagulation
    - Serum pregnancy test for female subjects of childbearing potential
- Radiological imaging to assess disease extent. Radiological assessment must include CT scan or MRI of the abdomen and pelvis and the modality selected should be the same throughout the study. Imaging assessment to be done within 21 days of enrollment/ randomization. Some imaging assessments may be collected for central review.
- Assessment of archived tumor sample availability from initial diagnosis or at diagnosis of advanced metastatic disease; written documentation to be provided to Sponsor before enrollment/randomization if samples are not available
- Review and confirm subject eligibility
- Subject receives treatment assignment from the Sponsr or assigned designee.

7.3 Treatment Period – Stage 1

For Stage 1 Study Day 1 will be defined as the day that the protocol specified treatment(s) are administered. On days when pharmacokinetic sampling is planned everolimus will be taken at the clinic.

7.3.1 Pre-dosing Assessments Cycle 1 Day 1 - Stage 1

The following procedures will be performed within 3 days **before** the administration of any study treatment unless otherwise described:

- Record concomitant medication(s).
- ECOG performance status.
- Weight Measurement and BSA Calculation - The body surface area will be calculated using either the Dubois or Mosteller formulas and the calculations documented in the subject's medical record and electronic case report form. The same formula must be used for a subject throughout the study.

- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Laboratory tests (for analyte description see Appendix C). If screening laboratory tests were performed within 72 hours of Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.
    - Hematology panel
    - Chemistry panel
    - Coagulation tests
    - Urinalysis
    - Urine pregnancy test (if applicable, Cycle 1 only). If a serum pregnancy test was done and determined negative within 72 hours of dosing a urine pregnancy test is not needed.
    - Blood collection for biomarker analysis
    - Pre-treatment pharmacokinetic sample (must be collected immediately prior to Cycle 1 dosing).
- Collection of archived tumor tissue within 4 weeks after initiation of treatment

7.3.2 Everolimus Dosing – Cycle 1 Day 1 - Stage 1

Everolimus (10 mg) will be administered orally (for details see Section 6.1.1) at the clinic. The time of the dosing will be recorded.

7.3.3 RX-0201 Dosing – Cycle 1 Day 1 - Stage 1

RX-0201 will be prepared based upon body surface area and the assigned dose. All dosing calculations will be documented in the subject's medical records (see Appendix D for details). The infusion bag will be connected and the RX-0201 infusion pump turned on and the start time recorded.

7.3.4 Post-dosing Assessments Cycle 1 Day 1 - Stage 1

The following assessment will be done after the start of the RX-0201 infusion:

- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements whenever a pharmacokinetic sample is collected.
- Pharmacokinetic samples will be collected at the following time points:
    - 1 hour ± 5 minutes, 2 hours ± 5 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, and 6 hours ± 10 minutes after start of infusion.
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Record concomitant medication(s)

7.3.5 Cycle 1 Day 2 - Stage 1

- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Record concomitant medication(s).
- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Blood sample for RX-0201 pharmacokinetics will be collected:
  - At 24 hours ± 1 hour (Cycle 1 Day 2) after the start of the RX-0201 infusion on Cycle 1 Day 1
- Everolimus (10 mg) will be taken orally at the clinic. The time of the dosing will be recorded.

7.3.6 Everolimus Dosing – Cycle 1 Days 3 to 14 - Stage 1

Everolimus (10 mg) will be administered orally at home (for details see Section 6.1.1) each day.

7.3.7 Cycle 1 Day 8 - Stage 1

- Recording of concomitant medication(s).
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Everolimus compliance – Record the number of tablets taken at home since the last visit.
- Turn off the RX-0201 infusion pump, disconnect the infusion bag and record the volume infused during the past 7 days in the subject's medical record and eCRF.
- Weight and BSA Calculation – Calculate the body surface area using the Dubois or Mosteller formulas and document the calculation in the subject's medical record and eCRF.
- Prepare RX-0201 as described in the pharmacy manual (see details in Appendix D). Document dosing calculations in the subject's medical record and eCRF.
- Connect the infusion bag and turn on the RX-0201 infusion pump.

7.3.8 Cycle 1 Day 15 - Stage 1

- Recording of concomitant medication(s).
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Everolimus compliance – Record the number of tablets taken at home since the last visit.
- Everolimus (10 mg) will be taken orally (for details see Section 6.1.1) at the clinic. The time of the dosing will be recorded.

- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Blood sample for RX-0201 pharmacokinetics will be collected:
  - Immediately prior to the end of RX-0201 infusion
- Turn off the RX-0201 infusion pump, disconnect the infusion bag and record the volume infused during the past 7 days in the subject's medical record and eCRF.
- Blood sample for RX-0201 pharmacokinetics will be collected:
  - 1 hour ± 5 minutes, 2 hours ± 5 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, and 6 hours ± 10 minutes after the infusion pump has been turned off.

7.3.9 Cycle 1 Day 16 - Stage 1

- Recording of concomitant medication(s)
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug will be followed to resolution or return to baseline.
- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Blood sample for RX-0201 pharmacokinetics will be collected:
  - 24 hours ± 1 hour after the infusion pump has been turned off on Cycle 1 Day 15.
- Everolimus (10 mg) will be taken orally (for details see Section 6.1.1) at the clinic. The time of the dosing will be recorded.

7.3.10 Everolimus Dosing – Cycle 1 Days 17 to 21 - Stage 1

Everolimus (10 mg) will be administered orally at home (for details see Section 6.1.1) each day.

7.4 Treatment Period - Cycles 2 to n – Stage 1

Subjects who complete Cycle 1 in Stage 1, and for whom the principal investigator feels may benefit from additional treatment cycles, may continue to receive additional cycles of RX-0201 plus everolimus therapy and will follow the treatment procedures and assessments outlined in Sections 7.5 and 7.6 starting at Cycle 2 Day 1. Otherwise, an End of Treatment visit should be completed.

7.5 Treatment Period - Cycles 1 to n – Stage 2

7.5.1 Pre-dosing Assessments - Cycles 1 to n, Day 1 - Stage 2

The following procedures will be performed within 5 days **before** the administration of any study treatment unless otherwise described:

- Record concomitant medication(s) (Cycles 1 – 16 only)
- ECOG performance status
- Weight measurement

- BSA Calculation - The body surface area will be calculated using either the Dubois or Mosteller formulas (Appendix D) if the subject is assigned to receive RX-0201, and the calculations will be documented in the subject's medical record and eCRF. The formula used must be the same for the subject throughout the study.
- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Laboratory tests (for analyte description see Appendix C)
  - Hematology panel
  - Chemistry panel
  - Coagulation tests (Cycles 1 – 16 only)
  - Urinalysis (Cycles 1 – 16 only)
  - Urine pregnancy test (if applicable, Cycle 1 only)
  - Blood collection for biomarker analysis (Cycle 1 only)
- Tumor biopsy (optional- Stage 2 subjects)
- Collection of archived tumor tissue within 4 weeks after initiation of treatment (Stage 2 subjects)

7.5.2 Everolimus Dosing Cycles 1 to n, Days 1 - 21 - Stage 2

Everolimus (10 mg) will be taken orally on Cycle 1 Day 1 at the clinic. Doses after Cycle 1 Day 1 will be taken by the subject at home at approximately the same time every day and consistently with or without food.

7.5.3 RX-0201 Dosing – Cycles 1 to n, Day 1 - Stage 2

Subjects in Stage 2 that were randomized to the everolimus only arm will not receive RX-0201.

RX-0201 will be prepared based upon body surface area and the assigned dose for subjects in Stage 1 or Stage 2 assigned to the everolimus/ RX-0201 treatment arm. All dosing calculations will be documented in the subject's medical record and eCRF (see Appendix D for details). The bag containing RX-0201 will be connected to the infusion pump and the start time recorded when the pump is turned on.

7.5.4 Cycles 1 to n, Day 8 - Stage 2

- Recording of concomitant medication(s). The assessment may be completed by phone for subjects previously randomized to the everolimus alone arm.
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug(s) will be followed to resolution or return to baseline. The assessment may be completed by phone for subjects previously randomized to the everolimus alone arm.
- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements. (Cycles 1 – 16 only). The

assessment may be completed by local physician's office for subjects previously randomized to the everolimus alone arm.

- Weight measurement. The assessment may be completed by local physician's office for subjects previously randomized to the everolimus alone arm.
- Everolimus compliance – Record the number of tablets taken at home since the last visit. The assessment may be completed by phone for subjects previously randomized to the everolimus alone arm. Confirm via drug diary or pill count at the next in site visit.

Subjects also receiving RX-0201

- Turn off the RX-0201 infusion pump, disconnect the infusion bag and record the volume infused during the past 7 days in the subject's medical record and eCRF, if applicable.
- BSA Calculation – Calculate the body surface area using either the Dubois or Mosteller formulas and document the calculation in the subject's medical record and eCRF.
- Prepare RX-0201 as described in the pharmacy manual (Appendix D). Document dosing calculations in the subject's medical record and eCRF.
- Connect the infusion bag and turn on the RX-0201 infusion pump.

7.5.5 Cycles 1 to n, Day 15 - Stage 2

- For subjects receiving RX-0201, a blood sample for RX-0201 plasma concentration will be collected immediately prior to the end of RX-0201 infusion in Cycle 1 only. If the sample is inadvertently not drawn, the sample will be collected on Day 15 in a subsequent cycle.
- Recording of concomitant medication(s). The assessment may be completed by phone for subjects previously randomized to the everolimus alone arm.
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug(s) will be followed to resolution or return to baseline. The assessment may be completed by phone for subjects previously randomized to the everolimus alone arm.
- Resting vital signs: pulse, respiration rate, blood pressure (i.e., after the subject has been seated for at least 5 minutes), and temperature measurements. (Cycles 1 – 16 only). The assessment may be completed by local physician's office for subjects previously randomized to the everolimus alone arm.
- Everolimus compliance – Record the number of tablets taken at home since the last visit. The assessment may be completed by phone for subjects previously randomized to the everolimus alone arm. Confirm via drug diary or pill count at the next in site visit.

Subjects also receiving RX-0201

- Turn off the RX-0201 infusion pump, disconnect the infusion bag and record the volume infused during the past 7 days in the subject's medical record and eCRF, if applicable.

7.6 Cycles 1 to n, Days 18-21 – Imaging Assessment – Stage 2

- Disease assessment will occur at the end of Cycles 2, 4, 6, 8, … n (i.e., after every 6 weeks of therapy).
- Radiological imaging to assess disease extent. Radiological assessment must include CT scan or MRI of the abdomen and pelvis and the modality selected should be the same throughout the study. The results of the imaging assessment must be available

and reviewed before the start of the next cycle. Some imaging assessments may be collected for a second review by a central imaging vendor.

- Disease assessment should be conducted according to the RECIST ver. 1.1 guidelines modified as described in Appendix E.
- Blood collection for biomarker sample analysis within 1 day of tumor assessment

7.7 Unscheduled Visit(s) – Stage 1 and Stage 2

An unscheduled visit may be performed at any time during the study at the request of the subject or as deemed necessary by the investigator. The date and reason for the unscheduled visit will be documented in the subject's medical record and eCRF, as well as any other data obtained (e.g., adverse events, concomitant medications and treatments, and results from procedures or tests).

7.8 End of Treatment or Early Termination Visit - Stage 1 and Stage 2

The following procedures will be performed:

- Record concomitant medication(s)
- Record adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug(s) will be followed to resolution or return to baseline.
- ECOG performance status
- Vital signs: resting pulse, resting respiration rate, resting blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Everolimus compliance – Record the number of tablets taken at home since the last visit.
- Laboratory tests
  - Urinalysis
  - Hematology panel
  - Chemistry panel
  - Coagulation
  - Pregnancy test (if applicable, urine or serum)
  - Tumor assessment, including CT/MRI as applicable. Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a follow-up tumor assessment at the End of Trial or Early Termination visit providing it is ≥ 3 weeks from the last prior tumor assessment in order to confirm the response based on RECIST ver. 1.1 criteria.

    Blood sample for biomarker analysis will be taken within 1 day of the tumor assessment.

Subjects also receiving RX-0201

- Turn off the RX-0201 infusion pump, disconnect the infusion bag and record the volume infused in the subject's medical record and eCRF if applicable.

7.9 Safety Follow-Up Visit – Stage 1 and Stage 2

Subjects will undergo the safety follow-up visit 30 days (+ 7 days) after the subject receives the last dose of everolimus or RX-0201, whichever is administered last.

The following procedures will be performed:

- Recording of concomitant medication(s), including any anticancer therapies administered subsequent to the administration of either protocol specified medication.
- Recording of adverse event(s). Serious adverse events will be reported immediately. Any adverse event that is considered related to study drug(s) will be followed to resolution or return to baseline.
- ECOG performance status
- Vital signs resting pulse, resting respiration rate, resting blood pressure (i.e., after the subject has been seated for at least 5 minutes) and temperature measurements.
- Other Assessment(s)

7.10 Predictive and Pharmacodynamic Biomarkers

Biomarkers are objectively measured and evaluated indicators of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In oncology, there is particular interest in the molecular changes underlying the oncogenic processes that may identify cancer subtypes, stage disease, assess the amount of tumor growth, or predict disease progression, metastasis, responses, or resistance to therapeutic agents. These investigations may be useful in developing markers to identify disease subtypes, guide therapy, and/or predict disease progression.

A blood sample will be collected prior to study treatment and around the time of tumor assessments to measure biomarkers (e.g., including but not limited AKT-1 and phosphorylated AKT).

In addition, any paraffin-embedded tumor samples collected independent from this study (whether before or during for the assessment of cancer) and the corresponding pathology report will be gathered by investigational sites. If paraffin blocks cannot be shipped, unstained slides and a core punch biopsy will be prepared from paraffin embedded tumor samples collected independent of the study before and during the study from each subject for analysis. These investigational studies may be useful in developing markers to identify disease subtypes, guide therapy and/or predict disease response or progression.

A tumor biopsy will be collected pre-treatment (optional Stage 2).

Refer to the laboratory manual for detailed collection and handling procedures for all predictive biomarker samples.

7.11 Sample Storage and Destruction

These blood and tumor samples and any other components from the cells may be stored for up to 20 years to research scientific questions related to cancer and/or RX-0201. The subject retains the right to have the sample material destroyed at any time by contacting the principal investigator.

The sponsor will be the exclusive owner of any data, discoveries, or derivative materials from the sample materials and is responsible for the destruction of the sample(s) at the request of the research subject through the principal investigator or at the end of the storage period. The principal investigator will provide the sponsor with the required study and subject numbers so that any remaining blood and tumor samples and any other components from the cells can be located and destroyed. If a commercial product is developed from this research project, the sponsor will own the commercial product. The subject will have no commercial rights to such product and will have no commercial rights to the data, information, discoveries, or derivative materials gained or produced from the sample. See Section 11.4 for subject confidentiality.

8. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

8.1 Definitions

8.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a trial subject who is administered a drug or biologic (medicinal product) or who is using a medical device; the event does not necessarily have a causal relationship with study drug administration or usage.

For this protocol, untoward medical occurrences that should be reported as adverse events include the following:

- Any unfavorable and unintended symptom, sign (including an abnormal laboratory finding), or disease temporally associated with the use of study drug, whether or not related to the study drug.
- Any pre-existing condition that increases in severity or changes in nature during or as a consequence of study drug administration.
- Any complication that occurs as a result of a protocol-mandated procedure (e.g., venipuncture, ECG, telemetry) in the study drug administration or follow-up periods.
- Any injury or accident occurring during the study drug administration, or follow-up periods. If a medical condition is known to have caused the injury or accident (e.g., a fall secondary to

dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.

- Any abnormality in physiological testing or a physical examination finding that requires clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Any laboratory (e.g., clinical chemistry, hematology, urinalysis) or investigational abnormality (e.g., ECG, X-ray) independent of the underlying medical condition that requires clinical intervention, results in further investigation (beyond ordering a repeat [confirmatory] test), or leads to investigational medicinal product interruption or discontinuation unless it is associated with an already reported clinical event. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin) should be recorded.
- A complication related to pregnancy or termination of a pregnancy (see Section 8.7.2 for additional information).

None of the following events is considered an adverse event:

- Laboratory abnormalities not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of overall laboratory monitoring.
- A diagnostic, medical or surgical procedure (e.g., surgery, endoscopy, tooth extraction, transfusion). However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event and the resulting appendectomy should be recorded in the subject's medical records and eCRF.
- A pre-existing disease or condition or laboratory abnormality present or detected before the initial screening visit and that does not worsen.
- An intervention not associated with an untoward medical occurrence (e.g., hospitalization for elective surgery or for social and/or convenience reasons).
- An overdose without clinical sequelae.

8.1.2 Serious Adverse Events

A serious adverse event is defined as an untoward medical occurrence that results in any of the following outcomes:

- Death (i.e., all deaths occurring between signing of the consent form to within 30 days after last study drug administration), including deaths due to disease progression. Deaths that occur as a result of an adverse event that started during the study period should be reported. The reported adverse event should be the event that caused the death. Death is the outcome of this serious adverse event.
- Life-threatening situation (i.e., with an immediate risk of death from the event as it occurred but not including an event that, had it occurred in a more serious form, might have caused death).
- In-patient hospitalization or prolongation of existing hospitalization. Of note, an untoward medical occurrence that occurs during hospitalization is an adverse event but a complication that prolongs hospitalization is a serious adverse event. In-patient hospitalization comprises formal admission to a hospital for medical reasons, for any length of time, whether or not hospitalization extends overnight. However, hospital admissions for administration of the study drug, procedures required by the study protocol, or tumor-related diagnostic procedures are not considered serious.
- Persistent or significant disability/incapacity.
- Congenital anomaly/birth defect in the offspring of a subject who received the study drug.
- Other medically significant event. Such events may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events might include:
    - Allergic bronchospasm requiring intensive treatment in an emergency room or at home
    - New cancers or blood dyscrasias
    - Convulsions that do not result in hospitalization
    - Development of drug dependency or drug abuse

8.2 Unexpected Adverse Event

An unexpected adverse event is defined as an event that has a nature or severity, or specificity that is not consistent with the applicable investigator brochure or that is symptomatically and pathophysiologically related to a known toxicity but differs because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.

"Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed and reported rather than an experience that has not been anticipated based on the pharmacological properties of the study drug.

8.2.1 Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, each study subject will be questioned about adverse events at each scheduled clinic visit or during each telephone contact with the subject following initiation of study drug administration. The type of question asked should be open-ended, e.g., *"Have you had any new health problems?"* or a similar type of query.

8.3 Reporting Procedures for All Adverse Events

All adverse events will be assessed by the investigator or qualified designee and recorded in the eCRFs. The investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the adverse event and/or serious adverse event and not described as the individual signs or symptoms. The following information should be recorded:

- Description of the adverse event using concise medical terminology
- Description as to whether or not the adverse event is serious (see Section 8.1.2)
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity of the adverse event (see Section 8.4)
- A description of the potential relatedness of the adverse event to study drug or a study procedure (see Section 8.5)
- The action taken due to the adverse event
- The outcome of the adverse event

8.4 Grading of the Severity of an Adverse Event

The severity of adverse events will be graded using the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (available at *http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 1.

Table 2. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affect clinical status, and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

The distinction between the seriousness and the severity of an adverse event should be noted. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 8.1.2 above.

8.5 Describing Adverse Event Relationship to Study Drug and Study Procedures

The relationship of an adverse event to study drug should be assessed using clinical judgment, describing the event as either unrelated (no) or related (yes) consistent with the following definitions:

- No: Evidence exists that the adverse event had an etiology other than the study drug. For serious adverse events, an alternative causality must be provided (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
- Yes: A temporal relationship exists between the adverse event onset and administration of the investigational medicinal product that cannot be readily explained by the subject's clinical state or concomitant therapies. Furthermore, the adverse event appears with some degree of certainty to be related to the study drug based on the known therapeutic and pharmacologic actions or adverse event profile of the investigational medicinal product. In case of cessation or reduction of the dose, the adverse event abates or resolves. In case of interruption and rechallenge, the event reappears upon rechallenge.

Of note, even in circumstances when the study drug is given intermittently or is interrupted temporarily before the onset of the adverse event, consideration should be given as to whether the study drug may have contributed to the event.

The relationship to protocol-mandated study procedures (e.g., procedures such as venipuncture or performance of an electrocardiogram) should be assessed using the following considerations:

- No: Evidence exists that the adverse event has an etiology other than the study procedure.
- Yes: The adverse event occurred as a result of a protocol-mandated procedure.

8.6 Adverse Event Reporting Requirements

8.6.1 Site Reporting Requirements

Classification of an event as serious or nonserious (see Section 8.1.2) determines the reporting procedures to be followed by the site.

Site reporting requirements for adverse events are summarized in Table 3 below.

Table 3. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Submit the designated serious adverse event report form to sponsor or designee, and to the site IRB, as per local IRB requirements; include copies of relevant source documents (e.g., progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries)
	Within 24 hours	Telephone call or e-mail to the study sponsor medical monitor[a]
	Per eCRF submission procedure	Record and submit information on appropriate CRFs
Nonserious	Per eCRF submission procedure	Record and submit information on appropriate CRFs

a See Safety Management Plan and Site Study Binder for study contact information
Abbreviations: eCRF=electronic case report form, IRB=institutional review board

For serious adverse events, the Serious Adverse Event Report Form must be completed in addition to completing the adverse event portion of the CRF. The information in the adverse event portion of the Serious Adverse Event Report Form(s) and CRF must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms.

Particularly for fatal or life-threatening events, copies of progress notes, autopsy reports, laboratory and diagnostic test results, discharge summaries, and other relevant documents should be e-mailed or faxed when requested and applicable. Follow-up information to the serious adverse event should be clearly documented as “follow up” in the serious adverse event report form and must be faxed or emailed to these same parties. The study sponsor may request additional information from the investigator to ensure the timely completion of accurate safety reports.

The subject's name, address, and other personal identity information should be obscured on any source documents (e.g., progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) but without losing the traceability of a document to the study subject identifiers. Only the subject's study number, initials, or date of birth are to be provided.

In the rare event that the investigator does not become aware of the occurrence of a serious adverse event immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the adverse event.

Contact details for the study sponsor medical monitor will be provided in the Safety Management Plan and Site Study Binder.

8.6.2 Study Sponsor Reporting Requirements

Each serious adverse event report received from the investigator must be evaluated by the investigator as well as the study sponsor medical monitor. Each is required to review all unanticipated problems involving risk to subjects or others, serious adverse events, and all subject deaths associated with the protocol and provide an unbiased written report of the event. At a minimum, the study sponsor medical monitor should comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The designated study sponsor medical monitor should also indicate whether they concur with the details of the report provided by the study investigator.

For regulatory reporting purposes, the event is classified as related if any of the investigator or study sponsor medical monitor determines that the event is related to the study drug (see Section 8.5). For reporting purposes, an adverse event will be considered expected if the study sponsor determines that the event is expected (see Section 8.2).

The study sponsor awareness date will be used in determining adverse event regulatory reporting timelines. The study sponsor awareness date is defined as the earliest date the study sponsor or an agent (e.g., a site monitor) becomes aware of an adverse event. This is the date the regulatory reporting clock begins and the date is considered Day 0.

The study sponsor serious adverse event regulatory reporting requirements are described in Table 4.

Table 4. Study Sponsor Reporting Requirements for Adverse Events

Type of Event			Type of Report	Timeframe for Reporting To Health Authorities
Fatal or Life-Threatening	Unexpected	Related		
Yes	Yes	Yes	Letter notification (may also include CIOMS I/MedWatch form)	Within 7 calendar days of study sponsor awareness date or according to local regulations
			CIOMS I/MedWatch form	Within 15 calendar days of study sponsor awareness date or according to local regulations
No	Yes	Yes	CIOMS I/MedWatch form	Within 15 calendar days of study sponsor awareness date or according to local regulations
Yes	No	Yes	Annual report	Annually
No	No	Yes		
Yes	Yes	No		
No	Yes	No		
Yes	No	No		
No	No	No		

Abbreviations: CIOMS= Council for International Organizations of Medical Sciences

If notification of an adverse event requiring expedited reporting is received, the study sponsor (or designees) will contact each clinical investigator prescribing RX-0201 by e-mail, fax, or overnight mail such that the investigator can promptly notify the site IRB (within 7 calendar days for deaths or life-threatening events or within for 15 calendar days for other reportable events from the study sponsor awareness date). All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study, and subject deaths related to participation in the study will also be promptly reported via telephone, facsimile, or e-mail by the study sponsor (or designees) to appropriate health regulatory authorities.

8.7 Special Situation Reporting Requirements

8.7.1 Definitions of Special Situations

Special situation include pregnancy; medication error, abuse, misuse, or overdose.

- Information regarding pregnancy is provided in Section 8.7.2.
- A medication error is any preventable event that can cause or lead to inappropriate medication use or subject harm while the medication is in the control of a healthcare professional or subject.
- Abuse is defined as persistent, sporadic or intentionally excessive use of a drug by a subject when such use is accompanied by harmful physical and/or psychological effects.

- Misuse is defined as any use of a drug in a way that is not in accordance with the protocol instructions and may be accompanied by harmful physical and/or psychological effects.
- An overdose is defined as a dose taken (accidentally or intentionally) that meets the criteria for overdose prescribed by the protocol (see Section 6.1.3). In cases of a discrepancy in drug accountability, overdose will be established only when it is clear that the subject has taken excessive amounts of drug or the investigator has reason to suspect that the subject has taken excessive amounts of drug.

8.7.2 Pregnancy

The following safety reporting instructions related to pregnancy are included as a precaution.

Each female subject should be instructed to discontinue further study therapy and inform the investigator immediately if she becomes pregnant at any time between the first dose of study drug until 30 days after the last ingestion of study drug.

Each male subject should be instructed to inform the investigator immediately if he impregnates a woman at any time between the 1st dose of study drug until 30 days after the last ingestion of study drug

The investigator should counsel the subject regarding the possible effects of investigational medicinal product exposure on the fetus and the need to inform the study site of the outcome of the pregnancy.

Neither a pregnancy itself nor an induced elective abortion to terminate the pregnancy without medical reasons is considered an adverse event; such occurrences should be reported on the appropriate pregnancy reporting forms. However, if the outcome of the pregnancy meets the criteria for classification as a serious adverse event (i.e., spontaneous abortion, induced abortion due to complications, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting serious adverse events, i.e., report the event to the sponsor or designee by telephone and follow up by submission of the appropriate adverse event CRFs (see Section 8.6.1).

Additional information regarding reporting pregnancy outcomes may be required:

- Any spontaneous abortion, including miscarriage and missed abortion will be reported as a serious adverse event.
- An induced therapeutic abortion to terminate any pregnancy due to complications or other medical reasons will be recorded as a serious adverse event. The underlying medical reason for this procedure should be recorded as the adverse event term.

- All neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious adverse events. In addition, any infant death after 1 month that the investigator assesses as related to the in-utero exposure to the study drug should also be reported.
- In the case of a live birth, the "normality" of the newborn can be assessed at time of birth (i.e., there is no required minimum follow-up of a presumably normal infant before the Pregnancy Outcome Report CRF can be completed).
- The "normality" of an aborted fetus can be assessed by gross visual inspection unless there are pre-abortion laboratory findings suggestive of a congenital anomaly, in which case pathologic examination should be requested.

Information regarding any pregnancy in a study subject or the female partner of a male subject must be documented on a Pregnancy Reporting Form and forwarded to the sponsor or designee within 24 hours of learning of the pregnancy. Monitoring of the pregnancy in both female study subjects and female partners of male study subjects should continue until the conclusion of the pregnancy. The outcome of the pregnancy should be reported on the Pregnancy Outcome Report Form within 5 days of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported directly to the study sponsor.

8.7.3 Instructions for Reporting Special Situations

Along with information regarding the circumstances of the special situation, any clinical sequelae occurring in association sequelae with that situation should be reported as adverse events or serious adverse events according to the reporting requirements for those events (see Section 8.6). Details of signs or symptoms, clinical management and outcome should be reported, if available.

8.8 Other Events Requiring Rapid Reporting

DLTs are events [toxicities] specifically identified in this protocol that must be reported to the Sponsor or designee in an expedited manner in Stage 1. Information regarding DLTs should be recorded on a protocol-designated DLT report form and sent to the study sponsor or designee within 24 hours of site personnel becoming aware of the event. DLTs may or may not be serious adverse events as defined in this protocol but may be serious adverse events if they meet one or more of the criteria for a serious adverse event (see Section 8.1.2). If a DLT is also a serious adverse event, it should be reported both on the DLT report form and per the

instructions for reporting serious adverse events (see Section 8.6.1). Recording of a DLT in the relevant CRFs will also be required.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design

9.1.1 Stage 1

Stage 1 is a dose escalation study to determine the MTD up to a target dose of 250 mg/m^2/day of RX-0201 in combination with everolimus. The starting dose of RX-0201 will be 125 mg/m^2/day. The secondary objectives of Stage 1 of the study are described in Section 1.2.

9.1.2 Stage 2

Prior to starting Stage 2, the principal investigators, medical monitor and sponsor will review the safety, laboratory and dosing information to make decisions regarding the start of Stage 2. Approximately 20 additional subjects will be treated with the combination of everolimus and RX-0201. The primary objective of Stage 2 is to determine progression free survival. The primary analysis will be conducted approximately 6 months after the last enrolled subject is treated. The secondary objectives of Stage 2 of the study are described in Section 1.2.

9.2 Study Endpoints, Subsets, and Covariates

9.2.1 Study Endpoints

9.2.1.1 Primary Endpoints

- Incidence of adverse events and clinical laboratory abnormalities defined as dose-limiting toxicities (Stage 1)
- Progression free survival at 4.5 months (Stage 2)

9.2.1.2 Secondary Endpoints

- Pharmacokinetics profile of RX-0201 (Stage 1)
- Incidence of adverse events, changes in clinical laboratory tests and vital signs over time (Stage 1 and Stage 2)
- Tumor response, duration of response, time to response, and response rates (Stage 2)

9.2.1.3 Exploratory endpoints

- Blood levels of AKT pathway biomarkers, tumor apoptosis biomarkers or other biomarkers (Stage 1 and Stage 2)
- Plasma concentration of RX-0201 at the end of infusion (Stage 2)

9.2.2 Analysis Populations

Data from stages 1 and 2 of this study will be combined for both safety and efficacy analyses when appropriate. The following definitions of the various analysis sets to be used will therefore be applied to subjects in Stage 1 and Stage 2 of the study.

Safety Analysis Set:

The safety analysis set includes all subjects who receive at least one dose of study drug(s) with subjects analyzed according to the treatment received. All safety data will be analyzed in accordance with this analysis set.

Full Analysis Set:
The Full Analysis set includes all enrolled or randomized subjects with subjects analyzed according to the treatment assigned at enrollment/randomization. All efficacy endpoints will be analyzed using the Full Analysis set.

Per Protocol Analysis Set:

The Per-Protocol Analysis set will include all subjects without pre-specified major protocol deviations. Sensitivity analyses of some efficacy endpoints may be performed using the per-protocol analysis set.

Evaluable for Tumor Response Analysis Set (Stage 2 only):

The tumor response analysis set will includes all subjects in the Full Analysis Set (and Per-Protocol Set if applicable) with a uni-dimensional measurable lesion at baseline (as per RECIST ver. 1.1).

9.2.3 Covariates

If appropriate based on sample size, the following covariates may be used to examine selected safety and efficacy endpoints in subgroups or in multivariate analyses.

- Sex: Male and Female
- Age: < 65, ≥ 65 to ≤ 75, > 75
- ECOG: 0 or 1 or 2

9.3 Sample Size Considerations

Approximately 9 subjects will be enrolled in Stage 1 of the study. Stage 1 is designed to determine the MTD up to a target dose of 250 mg/m^2/day of RX-0201, thus the sample size for the study is not based on a formal statistical hypothesis but will be determined based on observed number of first-cycle DLTs at each dose level. The sequential 3+3 dose-escalation is

consistent with usual oncologic paradigms for dose ranging as the intent is to limit the number of subjects who are exposed to toxic doses of the treatment combination. The trial will use the standard National Cancer Institute (NCI) definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the first cycle of therapy).

The planned sample size for Stage 2 is approximately 10 subjects in the everolimus arm and 20 subjects in the everolimus/ RX-0201 arm. The primary goal is to provide preliminary estimates of safety and efficacy endpoints when combining everolimus and RX-0201. Safety endpoints will be reported as described in Section 8. The primary efficacy endpoint is progression free survival estimated using the Kaplan-Meier method and associated 90% confidence intervals. Median PFS is expected to be 4.5 months in the everolimus only arm and 9 months in the combination arm. With 10 evaluable subjects in the everolimus only arm the width of the two-sided 90% confidence interval for 9-month PFS will be no more than ± 0.28. With 20 evaluable subjects in the combination arm the width of the two-sided 90% confidence interval for 9-month PFS will be no more than ± 0.20.

9.4 Access to Individual Subject Treatment Assignments

Stage 1 and Stage 2 will be open-label. Treatment assignments will be known to all personnel involved in the study.

9.5 Interim Safety Analysis and Early Stopping Guidelines

The principal investigators, medical monitor and sponsor will be responsible for reviewing the ongoing safety and laboratory data, and making decisions regarding dose de-escalation and dose stopping in accordance with the rules set out in Section 6.3 for Stage 1. Other than the safety evaluation required to determine whether to proceed to Stage 2 of accrual, no planned formal interim analysis will be performed.

If concerns arise during any data reviews, the sponsor may request additional specific safety data be collected and recommend modifying study conduct.

The sponsor may also terminate the study at any time for reasons which may or may not be related to safety or study conduct.

9.5.1 General Approach/Considerations

A Statistical Analysis Plan (SAP) will be finalized prior to database lock and will include more details of analysis populations and summary strategies. Any changes from the statistical analyses described in this document will be described in the SAP, and any deviation from the final SAP will be described in the final clinical study report.

Safety, Efficacy, and PK assessments will be summarized separately for Stage 1 and Stage 2. Additional summaries and analyses of pooled Phase 1 and 2 data may also be generated based on applicability of dosing regimens.

Descriptive statistics will be provided for selected demographic, safety, and efficacy, and exploratory endpoints by treatment group and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of selected endpoints may also be presented. For any variable, unless specified otherwise, baseline is defined as the last assessment prior to the first dose of study specified treatment.

9.5.2 Analysis of Key Study Endpoints

9.5.2.1 Adverse Events

Each reported adverse event will be assigned a System Organ Class (SOC), a higher level group term, a high level term and a preferred term according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA). The severity of adverse events will be assigned in accordance with the NCI CTCAE version 4.03 guidelines.

All adverse events will be listed by subject. The subject incidence rate of adverse events occurring between informed consent and first dose of study drug will be summarized by system organ class and preferred term for the Safety Analysis Set.

The incidence rate of treatment emergent adverse events, defined as all adverse events reported as new or worsened after the start of study drug, will be summarized by treatment group, system organ class, preferred term and maximum severity (where appropriate) for all adverse events, serious adverse events, adverse events leading to discontinuation of study specified treatment, adverse events leading to discontinuation from the study and fatal adverse events using subjects in the safety population. In addition, summaries of exposure adjusted adverse event rates may also be presented. These summary tables will also be repeated for treatment related adverse events. The number and percent of subjects reporting adverse events (all, serious, and related) will be tabulated by dose levels. Narratives of all serious and fatal adverse events will also be provided.

A listing and summary of the incidence of dose limiting toxicities present will be reviewed to make dose escalation decisions in Stage 1 review (dose limiting toxicity assessment set) will also be produced by treatment group and by subject.

9.5.2.2 Laboratory Safety Data

All hematology, chemistry, coagulation and urinalysis will be listed by treatment group and subject. Where normal ranges are available, values outside of the range will be flagged. The data will be summarized by treatment group using standard descriptive statistics at each of the scheduled time point in the study. For continuous parameters, a summary of the changes from baseline to each post dose laboratory assessment will also be produced for each treatment group.

Shift analysis for selected laboratory parameters between baseline and both the final visit worst-case on-study value will be summarized according to NCI CTCAE version 4.03 toxicity grades.

9.5.2.3 Time to Event Analyses

The detailed statistical analysis methods for each endpoint will be described in the statistical Analysis Plan (SAP). The Kaplan-Meier method will be applied to the following time to event endpoints:

- Progression-Free Survival: The time from first study dose to the first observation of disease progression (as classified by RECIST ver. 1.1) or death due to any cause.
- Time to response: The time from first study dose to the first observation of a complete or partial tumor response that is subsequently confirmed.
- Duration of response: The time from the first observation of a complete response or partial tumor response (whichever comes first) to the subsequent time of disease progression or death (whichever comes first) will be calculated as the duration of response for each subject.

Kaplan-Meier estimates and 2-sided 95% confidence interval for landmark times by 6-week intervals will be produced for the endpoint of progression-free survival time. Descriptive statistics for the duration and time to response for the responding subjects will be calculated.

9.5.2.4 Tumor Response by RECIST ver. 1.1

Tumor response data will be reported descriptively in the form of listings for all subjects in Stage 2. For each treatment group, the objective response rate will be determined and estimated using RECIST ver. 1.1 (see Appendix E for details).

The overall tumor response at any scheduled time points post the first dose of study specified treatment with missing data will be assumed to be a non-responder (i.e., not a confirmed complete or partial response). Subjects without at least one uni-dimensional measurable lesion per the modified RECIST ver. 1.1 criteria will be excluded from the analyses. For each

treatment group in Stage 1 and Stage 2 of the study, the proportion of subjects with an objective response (a confirmed complete or partial response) will be presented.

9.5.3 Background Information and Other Analyses

9.5.3.1 Subject Accountability

Demographic and Baseline characteristics:

Demographic and baseline characteristics for subjects in the Safety Analysis set will be summarized by treatment group.

Subject Disposition:

The number of subjects screened, number and percentage of subjects enrolled or randomized, received at least one dose of study drug, received no study drug, completed or discontinued any of their assigned treatments, completed or discontinued the study will be summarized combining data over all treatment groups, and with the exception of the number of subjects screened, separately for each dose. In addition, number and percentage of subjects in each of the 5 analysis data sets (safety analysis set, full analysis set, per-protocol analysis set, and evaluable for tumor response analysis set,) will be summarized by treatment group.

Study Discontinuation:
The number of subjects enrolled or randomized, number and percentage of subjects completing and the number discontinuing the study early (including the reasons) will be summarized by treatment group and in total over all treatments. Summaries of the reasons for early termination broken down by the cycle of treatment will also be produced.

Treatment Discontinuation:

The number of subjects enrolled or randomized and the number and percentage of subjects who discontinued any of their assigned treatments will be summarized by treatment group. This will also be split by the number and percentage of subjects discontinuing everolimus versus everolimus and RX-0201 (including the discontinuation reasons). An additional summary splitting the treatment discontinuations by cycle of treatment will also be provided.

Protocol Deviations:
The number and percentage of subjects with important protocol deviations will be presented by deviation type for all enrolled or randomized subjects. A summary will also be produced by treatment group and in total over all treatments.

9.5.3.2 Medical History

Medical history will be coded using MedDRA dictionary. A by-subject listing will be presented for the medical history.

9.5.3.3 Concomitant Medications

All concomitant medications will be grouped by medication class and by active ingredient within medication class according to the WHO Drug medication dictionary. The number and percentage of subjects receiving each medication will be summarized by active ingredient and medication class for each treatment group.

9.5.3.4 Vital Signs

Resting vital signs including pulse, blood pressure, respiration rate, temperature and weight, will be collected at screening, days 1, 8 and 15 of each cycle, end of treatment (or early termination), and safety follow-up visits. They will be summarized descriptively as well as change from baseline results by treatment group and assessment time point.

10. INVESTIGATIONAL PRODUCT

10.1 RX-0201

RX-0201 is a fully phosphorothioated 20-mer oligonucleotide synthesized by Avecia Biotechnology Inc, Milford, MA. The study drug was manufactured by Formatech, Andover, MA. Labeling and clinical distribution will be done by Catalent, Mt. Laurel, NJ. RX-0201 will be supplied as a sterile lyophilized powder that will be reconstituted with sterile water for injection immediately prior to its administration by continuous infusion.

RX-0201 will be provided as a lyophilized powder in 10 ml glass vials with rubber stoppers for intravenous administration. Each vial will contain 438 mg of RX-0201. The formulated RX-0201 is a lyophilized powder and is to be stored at -30º to -15ºC away from light. The powder will be reconstituted using sterile water for injection prior to administration by continuous intravenous infusion. The reconstituted product should be stored at 2º to 8ºC for no more than 4 hours if administration is delayed. Appropriate temperature monitoring should be maintained and recorded by the site during the study. The reconstituted drug product, diluted in 0.9% saline, is stable at 25°C to 40°C for up to 8 days.

10.2 RX-0201 Labeling

All labels for study drug vials will meet all applicable requirements of the Food and Drug Administration, Annex 13 of Current Good Manufacturing Practice (cGMP) (Manufacture of Investigational Medicinal Products, July 2003), and/or other local regulations, as applicable.

10.3 Everolimus

Subjects will take everolimus tablets at a dose of 10 mg per day. The 10 mg tablets appears white to slightly yellow, elongated tablets with a beveled edge and no score, engraved with "UHE" on one side and "NVR" on the other. Everolimus is packaged in blister packs.

Everolimus will not be provided by the sponsor, nor will it be relabeled.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial generic informed consent form will be provided to the investigator for preparing the site specific informed consent document. Updates to the templates will be communicated in writing by the clinical study manager to the investigator. The written informed consent document should be prepared in the language(s) of the potential patient population and must be agreed to by the Sponsor and institutional review board.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational product is administered.

The consent form may need to be revised during the study should important new information become available that may be relevant to the safety of the subject. In this instance approval should always be given by the institutional review board and existing subjects informed of the changes and re-consented. This is documented in the same way as previously described.

The Investigator should, with the consent of the subject, inform the subject's primary physician about participation in the clinical study.

The acquisition of informed consent should be documented in the subject's medical records, and the informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion (not necessarily an investigator). Two original signed informed consents will be obtained; one form should be retained in accordance with institutional policy, and the other signed consent form should be provided to the subject.

11.2 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Rexahn or its designee before recruitment of subjects into the study and shipment of investigational product.

The investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Rexahn, in accordance with local procedures.

The investigator will be responsible for obtaining annual IRB approval and renewal throughout the duration of the study. Copies of the investigator's reports and the IRB continuance of approval must be sent to Rexahn or its designee.

11.3 Pre-Study Documentation Requirements

The investigator is responsible for forwarding the following documents to Rexahn for review before study initiation from Rexahn or its designee can occur:

- Signed and dated protocol signature page (Investigator's Agreement)
- Copy of approved informed consent form and subject information sheet, if applicable
- Copy of the IRB approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator and all co/sub-investigators
- IRB composition and/or written statement that institutional review board is in compliance with regulations
- Laboratory normal ranges and documentation of laboratory certification (or equivalent)
- Signed study contract
- Completed FDA form 1572
- Completed Financial Disclosure statements for the principal investigator, all sub-investigators, and their spouses (legal partners) and dependent children

11.4 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained. On the eCRFs or other documents submitted to Rexahn, subjects should be identified by their initials and a subject study number only. Documents that are not for submission to Rexahn (e.g., signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with government regulatory/ICH GCP guidelines it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the subject's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The

investigator is obligated to inform and obtain the consent of the subject to permit named representatives to have access to his/her study-related records without violating the confidentiality of the subject.

11.5 Investigator Signatory Obligations

Each clinical study report should be signed by the investigator or, in the case of multicenter studies, the coordinating investigator.

The coordinating investigator, identified by Rexahn or its designee, will either be:

- a recognized expert in the therapeutic area
- an investigator who provided significant contributions to either the design or interpretation of the study
- an investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

In accordance with ICH Topic E 6 (R1) Guideline for GCP the Investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and documented approval from the IRB of a protocol amendment, except where necessary to eliminate an immediate hazard(s) to study subjects, or when the change(s) involves only logistical or administrative aspects of the study (e.g., change in monitor(s), change of telephone number(s)).

Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The IRB must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IRB to Rexahn or its designee.

All amendments to the protocol must be approved in writing by both the appropriate regulatory authorities and the IRB, except for administrative amendments, which require notification but not written approval. Once approved, the protocol amendment will be distributed to all recipients of the original protocol, with instructions to append the amendment to the protocol.

If, in the judgment of the local IRB, the Investigator and/or sponsor, the protocol amendment alters the study design, procedures and/or increases the potential risk to the subject, the currently approved written informed consent form will require modification. The modified informed consent form must also be reviewed and approved by the sponsor, appropriate

regulatory authorities, and the IRB. In such cases, repeat informed consent must be obtained from subjects enrolled or randomized in the study before participation continues.

Both Rexahn and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Rexahn.

12.2 Protocol Adherence and Deviations

The protocol must be read thoroughly and the instructions must be followed. However, exceptions will be made in emergency situations when the protection, safety, and well-being of the subject requires immediate intervention based on the judgment of the Investigator or a responsible, appropriately trained, and credentialed professional(s) designated by the Investigator as a sub-investigator.

In the event of a significant protocol deviation due to an emergency, accident, or error, the Investigator or designee must contact the Medical Monitor at the earliest possible time by telephone. This allows for an early joint decision to be made as to whether or not the subject should continue in the study. The Investigator, the Sponsor, and the Medical Monitor will document this decision.

12.3 Study Documentation and Archive

The investigator should maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Rexahn and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed eCRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of pre-study documentation, and all correspondence to and from the IRB and Rexahn

- If kept, proof of receipt, Investigational Product Accountability Record, Return of Investigational Product for Destruction, Final Investigational Product Reconciliation Statement, and all drug-related correspondence
- In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between Rexahn and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify Rexahn in writing of the new responsible person and/or the new location.

12.4 Study Monitoring and Data Collection

The Rexahn representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (e.g., eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Rexahn monitor is responsible for verifying the eCRFs at regular intervals approximately every 4-8 weeks or more frequently if needed as described in the monitoring plan throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to subject medical records and other study-related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

12.5 Inspections and Auditing Procedures

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Rexahn's or its designee's Clinical Quality Assurance Department (or designees). Inspection of site facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Government regulatory authorities may also inspect the Investigator during or after the study. The Investigator or designee should contact the Sponsor/CRO immediately if this occurs.

He/she must cooperate fully with regulatory authorities or other audits conducted at a convenient time in a reasonable manner.

The purpose of an audit is to assess whether ethics, regulatory and quality requirements are fulfilled.

12.6 Case Report Forms

Electronic case report forms (eCRFs) will be used to store and transmit subject information. The file structure and format for the eCRFs will be provided by the Sponsor or their representative and should be handled in accordance with the instructions provided.

The eCRFs must be reviewed, signed and dated by the Investigator.

Data should be entered into the eCRFs completely by the appropriate site personnel. The eCRFs must be completed as soon as possible after any subject evaluation or communication. The eCRFs must be accessible to study monitors and other regulatory auditors.

12.7 Data Collection

All data will be captured at the site using paper or electronic source documents. A source document identifier list will be created and signed during the study initiation visit

Data management will be performed by Rexahn or its designee. Details for data management will be described in a data management plan (DMP) which will be finalized before start of the clinical conduct.

Concomitant medications entered into the database will be coded using the WHODrug dictionary. AEs will be coded using the MedDRA terminology.

After the above actions have been completed and the database has been declared to be complete and accurate, it will be locked for data analysis. Any changes to the database after that time can only be made with the approval of the Sponsor.

12.8 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors, 2005), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Rexahn for corporate review. The Clinical Study Agreement among the institution, principal investigator, and Rexahn will detail the procedures for, and timing of, Rexahn's review of publications.

12.9 Compensation

Subject will be treated and/or compensated for any study-related illness/injury pursuant to the information provided in the Compensation for Injury section of the Informed Consent which will describe any compensation that will be provided during the study.

13. REFERENCES

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14. APPENDICES

Appendix A. Stage 1 Schedule of Assessments

	SCR[1]	Cycle 1					Cycle n[2]				EOT or ET	SFU[3]
		Day					Day				Visit	Visit
Procedures and Treatments	-14	1	2	8	15	16	1	8	15	18 - 21		
Informed consent	X											
Medical and medication history	X											
Complete physical examination including weight and height	X											
ECOG performance status	X	X[4]					X[4]				X	X
Pregnancy test	X[5]	X[4, 6]									X	
Weight and BSA calculation		X[4]		X			X[4]	X				
Resting vital signs	X	X[7]	X	X	X	X	X[4]	X	X		X	X
Hematology[8], chemistry[8], and coagulation[8]	X	X[4]					X[4]				X	
Urinalysis[8]	X	X[4]					X[4]				X	
Eligibility confirmation, enrollment	X											
Everolimus administration[9]		X →	→	→	→	→	→	→	→	→		
Everolimus compliance[10]				X	X		X	X	X		X	
RX-0201 infusion		X →	→	→			X →	→	→			
RX-0201 compliance				X	X			X	X		X[11]	
Adverse events[12] and concomitant medication assessment		X	X	X	X	X	X	X	X		X	X
Pharmacokinetic sampling[13]		X	X		X	X						
Disease assessment(s)	X[1]									X[14]	X[15]	
Biomarker blood sample		X[4]								X[16]	X[16]	
Archival Tumor Tissue		X[17]										

Abbreviations: SCR = screening, ECOG = Eastern Cooperative Oncology Group, SFU = safety follow up visit; EOT = end of treatment visit; ET = early termination

1 Screening procedures will be performed within 14 days of enrollment/ randomization, except baseline tumor assessment, which can be evaluated within 21 days of enrollment/ randomization
2 Cycles 2 – 8 will follow the same assessment schedule
3 Safety follow-up visit will occur approximately 30 (+ 7) days after the last administration of RX-0201 or everolimus, whichever occurs later
4 Assessment can be performed within 3 days before Day 1 of each cycle
5 A serum pregnancy test must be negative for all females of childbearing potential
6 A urine pregnancy test must be negative for all females of childbearing potential before treatment begins. If a serum pregnancy test was done and determined negative within 72 hours of planned first dose a urine pregnancy test is not needed
7 Vital signs can be assessed up to 3 days before Day 1 and will be assessed whenever a PK sample is collected in Cycle 1
8 See Appendix C for analytes to be collected. If screening laboratory tests were performed within 72 hours of Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. Samples to be taken before any RX-0201 or everolimus is administered
9 Everolimus will be taken at the clinic on Days 1, 2, 15, and 16 of Cycle 1, and Day 1 of all other cycles
10 Subjects will bring all everolimus packaging (empty and full) to the clinic to determine drug compliance
11 RX-0201 compliance will be checked at the Early Termination if the subject was receiving RX-0201 at the time of early termination.
12 All adverse events attributed to study drug(s) will be assessed until resolution or return to baseline
13 Blood will be collected for subjects enrolled in only Stage 1 at the following time points:
    - Immediately prior to Cycle 1 infusion, then at 1 hour ± 5 minutes, 2 hours ± 5 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 hours (± 1 hour) (ie, Day 2) after start of RX-0201 infusion .
    - Immediately prior to the end of Cycle 1 infusion (ie, Day 15), then at 1 hour ± 5 minutes, 2 hours ± 5 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes, and 24 hours (± 1 hour) (ie, Day 16) after the RX-0201 infusion pump has been turned off
14 Disease assessment will occur at the end of every 2 cycles
15 Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a follow-up tumor assessment at the End of treatment or Early Termination visit providing it is ≥ 3 weeks from the previous tumor assessment in order to confirm the response based on RECIST ver. 1.1 criteria
16 Biomarker blood samples will be collected within 1 day of the disease assessment (approximately at the end of every 2 cycles and at EOT/ET if applicable)
17 Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within approximately 4 weeks after initiation of study treatment; exceptions require written documentation of why a sample is not available and prior approval by the sponsor before enrollment

Appendix B. Stage 2 Schedule of Assessments

	SCR[1]	Cycle 1			Cycle n[2]				EOT or ET	SFU[3]
		Day			Day				Visit	Visit
Procedures and Treatments	-14	1	8	15	1	8	15	18-21		
Informed consent	X									
Medical and medication history	X									
Complete physical examination including weight and height	X									
ECOG performance status	X	X[4]			X[4]				X	X
Pregnancy test	X[5]	X[4, 6]							X	
Weight and BSA calculation (everolimus/RX-0201 arm only)		X[4]	X[18]		X[4]	X[18]				
Resting vital signs	X	X[4]	X[18]	X[18]	X[4, 16]	X[16, 18]	X[16, 18]		X	X
Hematology[7], chemistry[7], and coagulation[7, 16]	X	X[4]			X[4]				X	
Urinalysis[7]	X	X[4]			X[4, 16]				X	
Eligibility confirmation, randomization	X									
Everolimus administration[8]		X →						→		
Everolimus compliance[9]			X[18]	X[18]	X	X[18]	X[18]		X	
RX-0201 infusion (everolimus/RX-0201 arm only)		X →			X →					
RX-0201 compliance (everolimus/RX-0201 arm only)			X	X		X	X		X[10]	
Adverse events[11] and concomitant medication[16] assessment		X	X[18]	X[18]	X	X[18]	X[18]		X	X
Pharmacokinetic sampling				X[17]						
Disease assessment(s)	X[1]							X[12]	X[13]	
Biomarker blood sample		X[4]						X[14]	X[14]	
Archival Tumor Tissue		X[15]								
Tumor biopsy (optional)		X[4]								

Abbreviations: SCR = screening, ECOG = Eastern Cooperative Oncology Group, SFU = safety follow up visit; EOT = end of treatment visit; ET = early termination

1 Screening procedures will be performed within 14 days of enrollment/ randomization, except baseline tumor assessment, which can be evaluated within 21 days of enrollment/ randomization
2 Cycles 2 – n will follow the same assessment schedule
3 Safety follow-up visit will occur approximately 30 (+ 7) days after the last administration of RX-0201 or everolimus, whichever occurs later
4 Assessment can be performed within 5 days before Day 1 of each cycle
5 A serum pregnancy test must be negative for all females of childbearing potential
6 A urine pregnancy test must be negative for all females of childbearing potential before treatment begins. If a serum pregnancy test was done and determined negative within 72 hours of planned first dose a urine pregnancy test is not needed
7 See Appendix C for analytes to be collected. If screening laboratory tests were performed within 72 hours of Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1. Samples to be taken before any RX-0201 or everolimus is administered
8 Everolimus (10 mg) will be taken at the clinic on Cycle 1 Day 1, and then at home every day thereafter
9 Subjects will bring all everolimus packaging (empty and full) to the clinic to determine drug compliance. For subjects receiving everolimus alone, compliance will be verified at least once per cycle when the subject returns to the site.
10 RX-0201 compliance will be checked at the Early Termination if the subject was receiving RX-0201 at the time of early termination.
11 All adverse events attributed to study drug(s) will be assessed until resolution or return to baseline
12 Disease assessment will occur at the end of every 2 cycles
13 Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a follow-up tumor assessment at the End of treatment or Early Termination visit providing it is ≥ 3 weeks from the previous tumor assessment in order to confirm the response based on RECIST ver. 1.1 criteria
14 Biomarker blood samples will be collected within 1 day of the disease assessment (approximately at the end of every 2 cycles and at EOT/ET if applicable)
15 Tissue blocks or tissue sections from initial diagnosis or upon diagnosis of advanced metastatic disease will be available for submission to the central laboratory within approximately 4 weeks after initiation of study treatment; exceptions require written documentation of why a sample is not available and prior approval by the sponsor before randomization
16 Cycles 1-16 only
17 For subjects receiving RX-0201, one blood sample will be drawn prior to the end of infusion. If the sample draw is inadvertently missed, it can be drawn on Day 15 in a subsequent cycle.
18 For subjects receiving everolimus alone, the assessment may be completed by phone.

Appendix C. Laboratory Analytes

Chemistry
Sodium
Potassium
Chloride
Total protein
Albumin
Calcium
Phosphorus
Glucose
BUN
Serum Creatinine
Uric acid
Total bilirubin
Amylase
Lipase
Alkaline phosphatase

AST (SGOT)
ALT (SGPT)
GGT
Creatine Kinase

Urinalysis
Specific gravity
pH
Hemoglobin
Protein
Glucose
Bilirubin
Ketones
WBC
RBC
Epithelial cells
Bacteria

Hematology
RBC
Hemoglobin
Hematocrit
MCV
MCHC
Platelets
WBC
Differential
- Eosinophils
- Basophils
- Lymphocytes
- Neutrophils

Coagulation
PT or INR
PTT

Other Labs
Urine HCG
Serum HCG
HBV*
HCV*
HIV*

ALT = alanine amino transferase; AST aspartate amino transferase; BUN = blood, urea, nitrogen; GGT = gamma-glutamyl transferase; HBV = hepatitis B virus; HCV = Hepatitis C virus; HCG = human chorionic gonadotropin; HIV = Human Immunodeficiency Virus; INR = international normalized ratio; MCV = mean corpuscular volume; MCHC = mean corpuscular hemoglobin concentration; PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; WBC = white blood cells
*If a subject's HIV, HBV, or HCV status can be confirmed via medical record to be negative, new tests do not need to be performed.

Appendix D. Pharmacy Guide

RX-0201

Packaging and Formulation

RX-0201 was manufactured by Avecia Biotechnology in Milford, MA and packaged by Formatech in Andover, MA and distributed using Calent's distribution processes (Mt. Laurel, NJ) clinical study drug distribution procedures. RX-0201 will be supplied as a sterile lyophilized powder that will be reconstituted with sterile water for injection immediately prior to its administration by continuous infusion. Each 10 ml glass vial will contain 438 mg of RX-0201.

Labeling

Each vial will be labeled with the product name, study number, Sponsor name, lot number, manufacturing date, storage conditions and Investigational use statement.

Storage

The study drug, RX-0201 must be stored between --30 to -15°C. If the storage temperature is outside the range please contact Rexahn or its designee for instructions.

Records of the actual storage conditions during the period of the study must be maintained (e.g., records of the date and time and initials of person checking, and the "working day" temperatures of the room used for storage of clinical study supplies, continuous temperature recordings, or regularly maintained temperature alarm systems used in conjunction with temperature recording).

Preparation for Intravenous Administration

For each cycle of RX-0201, a total of 2 infusion bags will be used, one 1000 ml infusion bag for each of the two 7-day treatment weeks. Each infusion bag lasts approximately 7 days and will be prepared at the time of use, with a 7-day dose plus overage. In order to conserve the drug product, it is recommended that only a 10% overage be prepared. However, recognizing that individual site pharmacy policy may only allow full day doses to be administered, other overages (e.g. 1 day or ~14%) may be prepared when required. In each RX-0201 treatment cycle, the first bag will be prepared at the beginning of the infusion, Day 1, and the second bag will be prepared on Day 8. The site staff will calculate the total weekly dose for each subject based upon their BSA calculation, using either the DuBois or Mosteller formulas. The same formula for calculating BSA for a subject should be used throughout the study. The calculation will be documented in the subject's source records. If a subject's prior 2 weight measurements have varied ≤ 10%, the site staff may use the previous BSA calculation to expedite the drug ordering and preparation process.

RX-0201 will be administered via continuous infusion with an ambulatory infusion pump. If the pump fails, the subject will notify the site. The pump will be replaced.

The dose of infused RX-0201 in 1000 ml infusion bags will be prepared as follows on the day when administration is to begin:

1. On Days 1 and 8 of each RX-0201 cycle, calculate the body surface area (BSA) for the subject using the DuBois or Mosteller formulas. The body weight will be taken on the day of planned dosing. This BSA will be recalculated for each drug administration.

   DuBois: BSA (m^2) = 0.20247 x Height (m) $^{0.725}$ x Weight (kg) $^{0.425}$

   Mosteller: BSA (m^2) = (Height (cm) x Weight (kg) / 3600)^{½}

- Calculate the total weekly dose for each subject based upon the subject's BSA using the following formula which includes a 10% overage:

  Total Weekly RX-0201 Dose plus 10% (0.7 day) overage (mg) = BSA (m^2) x 125 (or 200 or 250) mg/m^2/day x 7 days x <u>1.10</u>

- Determine the number of RX-0201 vials needed for the dosing.
- Allow RX-0201 vials to equilibrate to room temperature prior to use. Vials may be thawed at 2 to 8°C for up 24 hours and/or at room temperature for up to 2 hours prior to reconstitution.
- Reconstitute each RX-0201 vial containing 438 mg by adding 6.6 ml of sterile water for injection to prepare a concentration of 66.4 mg/ml of RX-0201. Reconstituted vials should be stored at 2 to 8°C for no longer than 4 hours.
- Calculate the volume (in ml) of drug to be added to the 1000 ml infusion bag containing normal saline for 7 days of dosing plus 10% overage using the following formula:

Total volume of RX-0201 (ml) = Total Weekly RX-0201 Dose + overage (mg) calculated in Step 2 divided by 100 mg/ml

RX-0201 in normal saline will be infused into the subject via an intravenous access device (such as a Port-a-Cath® or PICC line) using a volumetric infusion pump with an in-line 0.2-0.22 micron sterile (disposable) filter at a rate of 5.0 ml/hour. The total volume administered over a 7-day period (168 hours) will be 840 ml. If a 10% overage is prepared, the bag will contain 924 ml.

Each bag will be prepared as follows on the day when administration is to begin:

- Commercially supplied saline bags:
    - Create a bag with a volume of 924 ml (10% overage) of normal saline. Using a commercially supplied 1000 ml bag of normal saline remove the manufacturer's overfill plus 76 ml to reduce the volume of the bag to 924 ml.
    - From the 924 ml bag, remove a volume of normal saline to equal the amount of RX-0201 diluted above in Step 5 above (Total Volume of RX-0201 + overage).
- Saline bags produced using automated on-site pharmacy systems:
    - Create a bag with a volume equal to 924 ml (10% overage) less the amount of RX-0201 diluted above in Step 5 above (Total Volume of RX-0201 + overage).
- Add the calculated volume of the reconstituted RX-0201 (100 mg/ml) to the infusion bag and mix completely (turn the bag upside down several times but do not shake vigorously).
- Remove all air from the bag before use.

When the subject returns to the site at the end of the infusion the volume and amount of RX-0201 infused will be recorded into the subject's medical record.

Supply and Return of Drug

At study initiation and as needed thereafter, RX-0201 will be shipped to a responsible person (e.g., a pharmacist) at the investigator's institution, who will check the amount and condition of the drug and enter these data into the Proof of Receipt Form and Investigational Product Accountability Record. The Proof of Receipt Form should then be sent to Rexahn or its designee and the original retained at the site. At the end of the study, or as directed, all RX-0201 supplies will be destroyed at the site or returned to Rexahn or its designee.

Investigational Product Accountability

An Investigational Product Accountability Record for the investigational products as mandated by the protocol must be kept current and should contain:

- the dates and quantities of investigational product received from Rexahn
- lot number for product received
- subject's identification (subject number and initials)
- date and quantity of investigational product dispensed (and remaining, if from individual subject drug units)

- the initials of the dispenser
- dose preparation records
- date and quantity of drug returned to the investigator/pharmacy, if appropriate

Where applicable, describe whether the returned investigational product will need to be weighed or counted.

The Return of Investigational Product for Destruction Form must be completed and included in the shipment of used and unused investigational product to Rexahn or its designee. At the end of the study, the Final Investigational Product Reconciliation Statement must be completed and provided to Rexahn.

These inventories must be made available for inspection by an authorized Rexahn representative and regulatory agency inspectors. The investigator is responsible for the accountability of all used and unused clinical study supplies.

Appendix E. RECIST ver. 1.1

(Eisenhauer, E. A., et al., 2009)

Definitions

- **Measurable Disease** - the presence of at least one measurable lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.
- **Measurable Lesions** - lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm); 10mm caliper measurement by clinical exam (when superficial); or 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).
- **Non-measurable Lesions** - all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with spiral CT scan), ie, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of the skin or lung, and also abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques. Lytic bone lesions, with an identifiable soft tissue component, evaluated by CT or MRI, can be considered as measurable lesions if the soft tissue component otherwise meets the definition of measurability previously described. Blastic bone lesions are non-measurable.

- All measurements should be taken and recorded in metric notation, using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 21 days before study day 1.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion throughout the trial.
- Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Methods of Measurement

- CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (e.g. for body scans but not for lung). CT and MRI should be performed with cuts of 5 mm or less in slice thickness contiguously. When CT scans have a slice thickness >5 mm, the minimum size should be twice the slice thickness. Spiral CT should be performed using a 5 to 8 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- Ultrasound should not be used to measure tumor lesions.
- Cytology and histology can be used to differentiate between partial response and complete response in rare cases (eg, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Baseline Documentation of "Target" and "Non-Target" Lesions

- All measurable lesions up to a maximum of two lesions per organ and five lesions in total, representative of all involved organs should be identified as **target lesions** and recorded and measured during screening.
- It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
- A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. The baseline sum diameters will be used as reference by which to characterize any objective tumor regression in the measurable dimension of the disease. If lymph nodes are to be included in the sum, only the short axis will contribute.All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded during screening. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout the study. It is possible to record multiple nontarget lesions involving the same organ as a single item on the eCRF (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Subsequent Documentation of "Target" and "Non-Target" Lesions

- All target lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, if target lesions or lymph nodes become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure', a default value of 5mm should be assigned
- When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'
- Finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor. This is particularly important when patient's baseline lesions show PR or CR. When in doubt, subsequent timepoint should be evaluated. Lesion seen in anatomical region which was not imaged at baseline = new lesion

<u>Response Criteria</u>

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
* Partial Response (PR):	At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum of diameters.

* Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum recorded since the treatment started (nadir). The sum must also demonstrate an absolute increase of at least 5 mm over nadir.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease.

Evaluation of Non-Target Lesions

* Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker levels. Alll lymph nodes must be non-pahological in size (<10 mm short axis).
* Non-CR/ Non-PD:	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker levels above normal limits.
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.Unequivocal progression of existing non-target lesions is defined as: (1) overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy; or (2) in the absence of measurable disease, change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from ‘trace’ to ‘large’, an increase in lymphangitic disease from localized to widespread
Not evaluable (NE)	When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Non-CR/ non-PD	No	PR

CR	NE	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; NE = Not Evaluable

- Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.
- In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmation

- To be assigned a status of partial response or complete response, changes in tumor measurements must be confirmed by repeat assessments during the study.
- In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6 – 8 weeks) that is defined in the study protocol.

Overall Response First Timepoint	Overall Response Subsequent Timepoint	BEST overall response
CR	CR	CR
CR	PR	SD, PD, OR PR
CR	SD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
CR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD

PR	PD	SD provided minimum criteria for SD duration are met. Otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met. Otherwise NE
NE	NE	NE

Duration of Overall Response

- The duration of overall response is measured from the time measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrence or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started.

Duration of Stable Disease

- SD is measured from the start of the treatment until the criteria for disease progression are met, taking as reference the smallest measurements recorded since the treatment started.