Note: There is no separate Statistical Analysis Plan (SAP) document to include with this protocol. The previous sponsor and responsible party that conducted this study, Rexahn Pharmaceuticals, did not provide a SAP for this study to the current sponsor and responsible party, Processa Pharmaceuticals. An abbreviated clinical study report, not a full clinical study report, was generated at study completion. Section 10 of this protocol (pages 75-88) includes the statistical analysis details for this study.

A Phase1, Open-Label, Dose-Ranging, Safety and Pharmacokinetic Study to Determine the Maximum Tolerated Dose of RX-3117 Administered Orally as a Single-Agent to Subjects with Advanced Malignancies

Rexahn Protocol Number RX-3117-P1-01

NCT02030067

Clinical Study Sponsor:
Rexahn Pharmaceuticals, Inc
15245 Shady Grove Road, Suite 455
Rockville, MD 20850 USA
Telephone (240) 268-5300
Fax (240) 268-5310

Key Sponsor Contacts:
Christine Peterson, Ph.D.
Rexahn Pharmaceuticals, Inc
15245 Shady Grove Road, Suite 455
Rockville, MD 20850 USA
Telephone (240) 268-5300 x 320
Fax (240) 268-5310

Kathy Tran
Rexahn Pharmaceuticals, Inc
15245 Shady Grove Road, Suite 455
Rockville, MD 20850 USA
Telephone (240) 268-5300 x 365
Fax (240) 268-5310

Date: Original 07 November 2013
Amendment 01 27 December 2013
Amendment 02 17 October 2014
Amendment 03 06 August 2015
Amendment 04 19 February 2016

Confidentiality Notice

Investigator's Agreement

I have read the attached protocol entitled A Phase1, Open-Label, Dose-Ranging, Safety and Pharmacokinetic Study to Determine the Maximum Tolerated Dose of RX-3117 Administered Orally as a Single-Agent to Subjects with Advanced Malignancies, dated 19 February 2016, 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 and applicable regulations/guidelines.

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 subinvestigators (including, if applicable, their spouses [or legal partners] 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)

I, Christine Peterson, as representative of Rexahn, agree to the provisions described in this protocol.

_____
Signature

_____ _____
Christine Peterson Date (DD Month YYYY)
Rexahn Pharmaceuticals Inc.

Protocol Synopsis

Title: A Phase1, Open-Label, Dose-Ranging, Safety and Pharmacokinetic Study to Determine the Maximum Tolerated Dose of RX-3117 Administered Orally as a Single-Agent to Subjects with Advanced Malignancies

Study Phase: Phase 1/2

Indication: Advanced Malignancies

Phase 1 Objectives:	
Primary Objectives:	To evaluate the safety and tolerability of escalating RX-3117doses and multiple schedules in subjects with advanced or metastatic solid tumors
	To determine the maximum tolerated dose of RX-3117 when administered orally to subjects with advanced solid tumors
Secondary Objectives:	To determine the pharmacokinetic profile of RX-3117
	To evaluate the antitumor activity of RX-3117
	To evaluate the potential for QT interval prolongation due to RX-3117
Exploratory Objective:	To investigate predictive and pharmacodynamic blood or tumor biomarkers suggested from nonclinical studies/literatures which may be predictive of a response or resistance to RX-3117 treatment
Phase 2 Objectives:	
Primary Objective:	To estimate the antitumor activity of RX-3117 in subjects with advanced malignancies (relapsed or refractory pancreatic or advanced bladder cancer)
Secondary Objective	To assess additional measures of antitumor activity
	To characterize the safety profile associated with RX-3117
	To evaluate population pharmacokinetics using a limited sampling
Exploratory Objectives:	To investigate the effect of RX-3117 on potential biomarkers in blood or tumor samples
	To evaluate the change in tumor burden response
Phase 1 Endpoints:	
Primary Endpoints:	Overall safety profile characterized by the type, frequency, severity, timing of onset, duration and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or electrocardiograms (ECGs)
	Enumeration and description of any dose limiting toxicities (DLTs) that occur during Cycle 1, serious adverse events, or adverse events leading to discontinuation of study treatment.
Secondary Endpoints	Pharmacokinetic parameters (e.g., time to maximum observed

	concentration [T_{max}], maximum observed plasma concentration [C_{max}], trough concentration [C_{trough}], area under the concentration-time curve [AUC])
	Indices of anti-tumor activity (e.g., overall response rate [ORR], time to response [TTR], duration of response [DOR], and progression-free survival [PFS]) during treatment.
Exploratory Endpoints	Baseline biomarker expression/concentration, including (but not limited to) concentrative nucleoside transporter (CNT) 2; equilibrative nucleoside transporter (ENT) 1; uridine-cytidine kinase (UCK) 1 and 2; DNA methyltransferase (DNMT) 1, 3a and 3b; and ribonucleotide reductases (RRM) 1 and 2 and RX-3117 incorporation into DNA/RNA.
Phase 2 Endpoints:	
Primary Endpoint	Progression free survival rate and/or objective clinical response rate
Secondary Endpoints	Time to progression, overall response rate and duration of response
	Adverse events, serious adverse events, assessments of clinical laboratory values, and vital sign measurements
	Pharmacokinetic profile
Exploratory Endpoints	Biochemical levels of drug targets in tumor and blood samples
	Changes in tumor burden
Study Design:	This will be a Phase 1 multicenter, dose- and schedule-finding, open-label, single-agent study of RX-3117 administered orally to subjects with advanced or metastatic solid tumors followed by a 2-stage Phase 2 study design. Subjects will be treated for up to 8 cycles of therapy. In the Phase 1 portion of the study subjects with any advanced solid tumor malignancies will be enrolled. During the Phase 1 portion of the study, the maximum tolerated dose (MTD) or a recommended phase 2 dose (RP2D) and schedule will be determined and the pharmacokinetics of RX-3117 characterized in eligible subjects. In the Dose Expansion, subjects will be enrolled in 1 of 3 diagnosis groups: relapsed or refractory pancreatic, colorectal or advanced bladder cancers. In the Phase 2 portion, subjects will be enrolled in 1 of 2 diagnosis groups: relapsed or refractory pancreatic or advanced bladder cancers. The Dose Expansion and Phase 2 portion will use the dose and schedule identified in the Phase 1. The Phase 2 portion will follows a 2-stage design. An interim analysis will be conducted when 10 response evaluable subjects in each tumor indication are enrolled and have had the opportunity to complete a minimum of 4 cycles of therapy or have discontinued therapy due to progressive disease. In the second stage of the Phase 2, enrollment for a disease group will proceed if responses are observed within the first 10 response-evaluable subjects enrolled in that disease group. Approximately 40 additional subjects will be enrolled in each of the disease indications. Subjects will be treated for up to 8 cycles of therapy.

Sample Size: Number of planned subjects is approximately 152 subjects (40 subjects in the Phase 1, depending upon the number of dose levels needed to identify the maximum tolerated

dose (MTD), 12 subjects in the Dose Expansion, 20 subjects in Stage 1 of the Phase 2 and 80 subjects in Stage 2 of the Phase 2).

Duration: The study will consist of a screening period (up to 14 days; [up to 21 days for tumor imaging]), up to eight 28-day treatment cycles, an end-of-treatment visit, and a follow up visit approximately 30 days after the last dose of RX-3117. Subject participation is anticipated to be approximately 10 months. Additional cycles of therapy may be provided following discussions with the investigator, sponsor and medical monitor. Subjects may remain on study treatment until the earliest of disease progression, an intolerable RX-3117-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.

Summary of Subject Eligibility Criteria:

Inclusion Criteria

Disease Related

- Confirmed histologic or cytologic evidence of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens (Phase 1).
- Confirmed histologic or cytologic evidence of metastatic pancreatic, colorectal or advanced bladder cancers that failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens (Phase 1 Dose Expansion)
- Confirmed histologic or cytologic evidence of metastatic pancreatic or advanced bladder cancers that failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens (Phase 2)
- Measurable or evaluable disease using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1.
- Life expectancy of at least 3 months
- ECOG performance status 0, 1 or 2 (Phase 1)
- ECOG performance status 0 or 1 (Phase 2)
- Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, systemic corticosteroids, or investigational therapy) for the treatment of cancer within 2 weeks before planned start of study therapy.
- All acute toxic effects of any prior antitumor therapy resolved to Grade $\leq$ 1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], or neurotoxicity [Grade 1 or 2 permitted], or anemia [Grade 2 permitted])

Demographic

- Males or females who are 18 years or older
- Able to swallow capsules

Laboratory

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Serum creatinine ≤ 1.5 times the upper limit of normal OR 24-hour measured urine creatinine clearance ≥ 50 mL/min for subjects with serum creatinine levels > 1.5 times the upper limit of normal
- Serum bilirubin ≤ 1.5 times the upper limit of normal OR ≤ 3 times the upper limit of normal in the presence of known liver metastases

- Aspartate aminotransferase (AST; SGOT) and alanine amino transferase (ALT; SGPT) ≤ 2.5 times the upper limit of normal OR ≤ 5 times the upper limit of normal in the presence of known liver metastases
- Alkaline phosphatase ≤ 2.5 times the upper limit of normal OR ≤ 5 times the upper limit of normal in the presence of known liver or bone metastases
- Prothrombin time (PT) < 1.2 times the upper limit of normal unless receiving therapeutic anticoagulation, International normalized ratio (INR) up to 3-4 times the upper limit of normal if on therapeutic anticoagulation and partial thromboplastin time (PTT) < 1.2 times the upper limit of normal unless receiving therapeutic anticoagulation.
- For women of childbearing potential: Negative serum pregnancy test during screening and negative serum or urine pregnancy test at start of study therapy (Cycle1 Day 1).

Reproductive

- For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of study drug.
- For fertile male subjects having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study therapy throughout the study treatment period and for 30 days following the last dose of study drug and to refrain from sperm donation from the start of study treatment throughout the study treatment period and for 30 days following the last dose of study drug.

Ethical

- In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's cancer.
- Before any study-specific procedure, the appropriate written informed consent must be obtained

Exclusion Criteria

Disease Related

- Primary brain tumors or clinical evidence of active brain metastasis

Medications

- Systemic corticosteroid use within 7 days before planned start of study therapy

General

- Active infection requiring parenteral or oral antibiotics within 2 weeks before planned start of study therapy
- Uncontrolled diabetes as assessed by the investigator
- Second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers treated with curative intent and no known active disease within 3 years before planned start of study therapy
- QTcF interval greater than 470 msec, with a known history of QTcF prolongation, is taking medications known to prolong QTcF, or has history of torsade de pointes.
- Documented history of hepatitis B, hepatitis C or human immunodeficiency virus
- History of any other concurrent conditions that could preclude the subject's participation in the study, pose an undue medical hazard, or interfere with the interpretation of the study results, including, but not limited to, subjects with congestive heart failure (New York Heart Association [NYHA] Class III or IV), cardiac arrhythmia, or acute coronary syndromes within 6 months before planned start of study therapy
- History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.

- Any other medical, psychiatric, or social condition, which in the opinion of the investigator, would preclude participation in the study, pose an undue medical hazard, interfere with the conduct of the study, or interfere with interpretation of the study results
- Pregnant, planning a pregnancy or breast feeding during the study
- Concurrent participation in another therapeutic clinical trial
- Has any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery, bariatric surgery)
- Has known hypersensitivity to prior gemcitabine, azacytidine or cytosine arabinoside exposure
- Unwilling or unable to comply with study requirements or planned unavailability for follow-up assessments.

Investigational Product Dosage and Administration:

RX-3117 will be provided as 30-mg, 100-mg, 200-mg and 500-mg capsules. The capsules will consist of hydroxypropylmethyl cellulose and be packaged in a high-density polyethylene (HDPE) bottle with a child-resistant closure and an induction seal. Subjects will take RX-3117 3 times per week (i.e., preferably on a Monday, Wednesday and Friday), 5 times per week (i.e., for 5 consecutive days followed by 2 days off), or daily for 7 days for 3 weeks followed by 1 week of rest, in each 28-day cycle.

Subjects will be fasting for 8 hours, the dose will be taken with 4-8 ounces of water, and a light meal will be permitted approximately 1 hour later. During Cycle 1 subjects will be dispensed doses of RX-3117 each week and during cycles 2 to 8 doses will be dispensed at the start of each cycle.

The starting dose will be 30 mg/day. The dose escalation will begin with an accelerated design (Simon et al., 1997) in single subjects. After the occurrence of a single ≥ Grade 2 adverse event that is considered related to RX-3117, the study will transition to a standard 3 + 3 design using a modified Fibonacci sequence. Doses will be rounded to accommodate available dose strengths. Additional doses and schedules may be recommended by the review committee which includes investigators, medical monitor and sponsor.

Control Group: There will be no control group.

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

- Review of inclusion and exclusion criteria
- Medical history including histology report confirming diagnosis of solid tumor malignancies, concomitant medications/treatment(s) including cancer therapies
- Resting vital signs: pulse, respiration, temperature, blood pressure and pulse oximetry
- Physical examination including height and weight
- Performance status assessment (i.e., ECOG)
- Laboratory tests
- 12-lead electrocardiogram
- Tumor imaging assessment

Key Treatment Procedures (key procedures, see Section 7.3 for a complete list):

- Collection of archival tumor tissue if available

- Collection of tumor biopsy for biomarker (optional)
- Collection of pretreatment blood biomarkers
- Recording of adverse events and concomitant medications
- Resting vital signs and weight
- ECOG performance status
- Laboratory tests
- 12-lead electrocardiogram in Cycle 1
- Pharmacokinetic sampling
- Tumor imaging assessments once per cycle for Cycles 1 through 4 and after every 2 cycles of treatment, thereafter
- Collection of blood biomarkers at the time of tumor assessment

Safety Parameters: Adverse events will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA, Version 15.1) and will be graded using the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03). The CTCAE will also be used to grade abnormalities in vital signs, laboratory assessments that include serum chemistry, hematology, coagulation and urinalysis and electrocardiograms (Phase 1).

Statistical Considerations:

Analysis Methods:

In the Phase 1 portion and the Dose Expansion the statistical methods will be descriptive in nature. Appropriate data analysis sets will be defined. The full-analysis set will include data from all subjects who receive $\geq$ 1 dose of study therapy; other data sets (responding and evaluable data sets) will be defined in a separate statistical analysis plan and will include data from subjects who have sufficient baseline and on-study measurements to provide interpretable results for specific parameters of interest.

Subject characteristics and study results will be described and summarized by RX-3117 dose level, schedule and overall for the relevant analysis sets.

Based on the full-analysis set, information regarding study treatment administration, study drug compliance, and safety variables will be described and summarized. Using data from the relevant evaluable data sets, RX-3117 plasma concentrations, pharmacokinetic parameters, and pharmacodynamic markers will also be described and summarized. Calculated pharmacokinetic parameters will be derived using non-compartmental methods.

For endpoints related to tumor assessment, analyses will be done based on the full-analysis, responding, or evaluable data sets, as appropriate. Continuous and categorical variables will be summarized. Changes from baseline in categorical variables and changes from baseline in continuous endpoints will be analyzed using appropriate methods. Time-to-event endpoints will be summarized using Kaplan-Meier methods.

The Phase 2 portion of the study will follow a 2-stage design (Simon, 1989). An interim analysis will be conducted when 10 response-evaluable subjects, treated with the recommended phase 2 dose (RP2D) of RX-3117, in each tumor indication are enrolled and have had the opportunity to complete a minimum of 4 cycles of therapy or have discontinued therapy due to progressive disease (PD). The critical value for evaluation of each tumor type to proceed to the second stage of the Phase 2 is 2 in 10 subjects (20%) measured by a benefit in PFS (stable disease for at least 4 months) or 1 subject with an objective clinical response (partial or complete response) supported by acceptable safety and tolerability reviewed through the conduct of the study by the investigators, medical monitor and sponsor.. In the second stage of the Phase 2 objective clinical

response rate and PFS will be further evaluated, in 40 additional subjects within each of the disease groups that continue beyond the first stage.

Sample Size Calculation:

In this dose-escalation Phase 1 trial designed to determine an MTD for RX-3117, 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 and schedule. The planned accelerated design followed by a sequential 3+3 dose-escalation is consistent with usual oncologic paradigms for dose ranging and schedule finding. The intent is to limit the number of subjects who are exposed to excessively toxic doses of a drug in a Phase 1 evaluation of an anticancer agent. 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 dose group size and dose-escalation rules establish a low probability of increasing the dose if the true rate of DLT is high while there is a high likelihood of escalating or proceeding to the next stage of the study if the true underlying proportion of DLT is low. Once the recommended phase 2 dose or MTD and schedule is identified approximately 12 subjects will be treated in the Dose Expansion.

The maximum number of subjects needed for Phase 2 is approximately 100 (50 per tumor indication). An estimated 20 subjects (10 per indication) will be enrolled in the first stage of the Phase 2 at the recommended dose from the Phase 1. The Dose Expansion subjects who have measurable disease at baseline and at least 1 post-baseline response assessment may be considered as part of the first stage of the Phase 2.

A formal statistical analysis plan will be developed and finalized before database lock.

Study Glossary

Abbreviation	Definition
ANC	Absolute neutrophil count
AUC	Area under the plasma concentration time curve
AUC_{0-t}	area under the plasma concentration-time curve from the time of dosing to the last measurable concentration
$AUC_{0-\tau}$	area under the plasma concentration-time curve from time 0 to the end of the dosing interval
$AUC_{0-\infty}$	area under the plasma drug concentration-time curve from 0 to time extrapolated to infinity
AUC_{0-last}	area under the plasma drug concentration-time curve from 0 to time of the last quantifiable concentration
C_{max}	Maximum observed plasma concentration
CYP	Cytochrome P450
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECG	Electrocardiography, electrocardiogram
ECOG	Eastern Cooperative Oncology Group
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor
GLP	Good Laboratory Practice
HED	Human equivalent dose
IC_{50}	Half maximum inhibitory concentration
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall Response Rate
PD	Progressive disease
PET	Positron emission tomography
PFS	Progression free survival
PR	Partial response
PT	Prothrombin time
PTT	Partial thromboplastin time
QTcF	Corrected QT interval using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RNA	Ribonucleic Acid
SD	Stable disease
T_{max}	Time to maximum observed plasma concentration
TTR	Time to response
UCK	Uridine-cytidine kinase
ULN	Upper limit of normal
Vz	Volume of distribution

Study Definitions

Baseline Value	The “baseline value” is the value measured before first administration of study specified treatment. For variables/assessments not scheduled to be performed on study day 1 or that are missing at baseline, the baseline value is the value from the screening period measured closest to study day 1.
Duration of Response	The time from the date of first documentation of a response to the first documented progressive disease.
End of Study	This visit is planned for approximately 30 days after a subject discontinues investigational product administration.
Investigational Product	RX-3117
On-Study Death	Any death that occurs after receiving protocol directed therapy through 30 days after the last dose of investigational product. The cause of any on-study death will be reported as a serious adverse event.
Overall Response Rate	The number of complete responders and partial responders in the response evaluable population
Progression Free Survival	The time from the date of first study drug administration to the date of documented progressive disease or death due to any cause, whichever occurs first. The progression-free survival rate will also be measured. It is defined as the proportion of subjects with stable disease for at least 4 months.
Safety Follow-up	This period is planned for approximately 30 days after a subject discontinues investigational product administration.
Screen Failure	A subject who signs an informed consent but does not qualify to be enrolled into the study.
Screening Period	The period that occurs between the signing of the informed consent and day of enrollment (14 day maximum).
Study Day 1	The day that the first dose of investigational product is administered.
Study Start	Occurs when the first subject has been enrolled.
Treatment emergent adverse event	An adverse event that occurs following the first administration of study specified treatment.
Time to Progression	The time from the date of first study drug administration to the date of documented progression
Time to Response	The interval from the start of study treatment to the first documentation of CR or PR or other measure of response

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1. OBJECTIVES

1.1 Phase 1 Primary

- To evaluate the safety and tolerability of escalating RX-3117 doses and multiple schedules in subjects with advanced or metastatic solid tumors
- To determine the maximum tolerated dose (MTD) of RX-3117 when administered orally to subjects with advanced solid tumors

1.2 Phase 1 Secondary

- To determine the pharmacokinetic profile of RX-3117
- To evaluate the anti-tumor activity of RX-3117
- To evaluate the potential for QT interval prolongation due to RX-3117

1.3 Phase 1 Exploratory

- To investigate predictive and pharmacodynamic blood or tumor biomarkers suggested from nonclinical studies/literatures which may be predictive of response or resistance to RX-3117 treatment

1.4 Phase 2 Primary

- To estimate the antitumor activity of RX-3117 in subjects with advanced malignancies (relapsed or refractory pancreatic or advanced bladder cancer)

1.5 Phase 2 Secondary

- To assess additional measures of antitumor activity
- To characterize the safety profile associated with RX-3117
- To evaluate population pharmacokinetics using a limited sampling

1.6 Phase 2 Exploratory

- To investigate the effect of RX-3117 on potential biomarkers in blood or tumor samples
- To evaluate changes in tumor burden response

2. BACKGROUND AND RATIONALE

2.1 Disease

According to the latest statistics (American Cancer Society, 2013), cancer causes around 7.6 million deaths worldwide each year. Deaths from cancer are projected to continue rising to an estimated 21.4 million worldwide in 2030 (American Cancer Society, 2011).

For patients presenting with confined local-regional cancer, the development of systemic therapies as adjuvants to primary surgery or irradiation have substantially improved outcomes by delaying recurrence of disease. However, for patients who present with large primary tumors or metastases or who develop recurrent metastatic disease, cancer becomes a life-threatening disorder. Therapy for patients with advanced cancer has focused on the sequential use of systemic treatments to impede the disease progression that leads to disabling symptoms and death. Depending upon the tumor type, hormonal therapies, therapeutic monoclonal antibodies, or tyrosine kinase receptor inhibitors may be employed, and most commonly, cytotoxic chemotherapy in various sequences and combinations is administered.

The development of newer agents in the past 2 decades illustrates that it is still possible to improve outcomes by offering more efficacious, less toxic, and more convenient therapies to patients with cancer. However, for patients with metastatic disease, the acquisition of drug resistance results in less activity with each successive type of treatment, leading to a decrease in the quality and the duration of tumor response with each subsequent therapy. Survival rates for patients with metastatic cancer remain poor because tumor progression leads to death in the majority of patients. Consequently, new therapies with alternative mechanisms of action are needed to offer additional treatment options for patients with advanced cancer.

2.2 Cytidine Analogs in the Therapy of Cancer

Cytidine analogs have been widely used as antivirals and for the treatment of various types of cancer, both hematologic as well as solid tumors. These agents include cytarabine, 5-azacytidine, 5-aza-2'deoxycytidine (decitabine) and gemcitabine.

Among these, gemcitabine is the most broadly used anticancer agent. Initially developed as an antiviral agent, gemcitabine (2',2'-difluoro-2'-deoxycytidine) is structurally similar to cytarabine differing due to a fluorine substitution at position 2' of

the furanose ring. Gemcitabine is a prodrug that requires cellular uptake and intracellular phosphorylation. Within the cell, gemcitabine is phosphorylated to gemcitabine monophosphate (dFdCMP) by deoxycytidine kinase which ultimately is converted to either the di- or triphosphate forms (gemcitabine diphosphate [dFdCDP] and gemcitabine triphosphate [dFdCTP]; Heinemann et al 1992).

Gemcitabine appears to have several intracellular targets. Much of its anticancer properties, however, involve inhibition of deoxyribonucleic acid (DNA) synthesis (Gandhi and Plunkett 1990, Heinemann et al 1990, Hertel et al, 1990). Gemcitabine diphosphate is an inhibitor of DNA polymerase (Gandhi and Plunkett 1990) and is also physically incorporated into DNA which can lead to termination of chain elongation (Huang et al 1991). The nonterminal positioning of dFdCTP in DNA prevents detection and repair of that sequence by repair enzymes, which ultimately induces apoptosis (Gandhi and Plunkett 1990, Schy et al 1993). A metabolite of gemcitabine, which is most likely dFdCTP, can also incorporate into ribonucleic acid (RNA) (Ruiz van Haperen et al 1993). Other activities associated with gemcitabine metabolites include inhibition of cytidine triphosphate synthetase (CTP synthetase) and inhibition of deoxycytidylate deaminase (dCMP deaminase) by dFdCTP (Heinemann et al 1992). Gemcitabine can also affect topoisomerase I, which suggests that induction of topoisomerase I mediated DNA break formation can contribute to the cytotoxic potential of this drug (Pourquier et al 2002).

Initial Phase 2 studies with gemcitabine as a single-agent (800 mg/m^2 weekly for 3 weeks) demonstrated an overall response rate (ORR) in chemotherapy-naive patients with metastatic adenocarcinoma of the pancreas in the range of 6% to 11% (Carmichael et al 1996, Casper et al 1994). Despite this low objective response rate, clinical benefit was derived. In the Phase 2 study that led to Food and Drug Administration (FDA) approval, clinical benefit was defined as improvement in pain, performance status, or weight without deterioration in any other factors (Rothenberg et al 1996). Clinical benefit was reported at 27% as compared to the objective response rate of 11% in 126 patients. In addition to its indication in metastatic pancreatic cancer (Burris, III et al 1997), gemcitabine is used in combination treatment in non-small cell lung cancer (Sandler et al 2000), bladder cancer (von der Maase et al 2000), breast cancer (Albain et al 2004), ovarian cancer, mesothelioma, and head/neck cancers (Mini et al 2006).

Despite the clinical value of gemcitabine, drug resistance is common, which may be due to the loss of transporters and kinases responsible for the first phosphorylation step.

2.2.1 RX-3117 Structure

RX-3117 is a small-molecule, cyclopentyl pyrimidyl nucleoside being developed by Rexahn Pharmaceuticals, Inc. RX-3117 was synthesized as a new oral antimetabolite with the potential to overcome gemcitabine resistance and offer a favorable pharmacologic profile. Its chemical name is 4-amino-1-[(1S,4R,5S)-2-fluoro-4,5-dihydroxy-3-(hydroxymethyl)cyclopent-2-en-1-yl]pyrimidin-2-one. The RX-3117 monohydrate drug substance is a white to yellow crystalline solid. The molecular weight is 257.22 daltons for the anhydrous form and 275.24 daltons for the monohydrate form. Its molecular formula is $C_{10}H_{12}N_3O_4F \bullet H_2O$.

2.2.2 Mechanism of Action and Nonclinical Pharmacology Studies

The mechanism of action of RX-3117 has been investigated extensively. RX-3117 is an antimetabolite that mimics the building blocks of DNA or ribonucleic acid (RNA). Antimetabolites are incorporated into DNA or RNA of cells, where they interfere with cell division. RX-3117 is activated by uridine-cytidine kinase (UCK), and thus differs from gemcitabine, which is activated by deoxycytidine kinase. In addition, gemcitabine is inactivated by cytidine deaminase at a fast rate, whereas RX-3117 is inactivated by cytidine deaminase at a slow rate, thus allowing higher cellular concentrations of RX-3117 to enhance its anticancer activity.

In vitro mechanism studies characterized the effects of RX-3117 on cell cycle, apoptosis, and further elucidated its mode of action. Cell-cycle analysis by flow cytometry demonstrated that RX-3117 inhibited the cell cycle in G1 phase and also induced programmed cell death (apoptosis). The sensitivity of RX-3117 to a variety of antimetabolite-resistant cell lines was tested, and it was shown that RX-3117 was effective in wild-type cells as well as cells with acquired antimetabolite resistance. RX-3117 showed a variable resistance pattern in the cell lines tested, with a marked cross-resistance for the intrinsically gemcitabine-sensitive A2780 and gemcitabine-resistant AG6000 ovarian cancers, a moderate cross-resistance for CCRF-CEM acute lymphoblastic T-cell leukemia cells, and an enhanced sensitivity for gemcitabine-resistant SW1573/G non-small cell lung cancer cells. The effect of RX-3117 on DNA and RNA was evaluated; the majority of cell lines investigated showed a concentration-

dependent inhibition of DNA and RNA synthesis after exposure to RX-3117, and RX-3117 showed inhibition of DNA synthesis more than RNA synthesis in most cell lines. Moreover, RX-3117 inhibited the proliferation of a variety of cancer cell lines of different origins, including bladder, bone, brain, breast, cervical, colon, liver, lung, muscle, ovary, pancreas, prostate, renal, and skin.

Deoxyribonucleic acid methyltransferase 1 (DNMT1) is responsible for the methylation of cytosine residues on newly synthesized DNA and also regulates and maintains methylation patterns. DNMT1 is often overexpressed in cancer cells, potentially resulting in aberrant methylation patterns that can further cancer progression. It has been shown that RX-3117 mediates the down-regulation of DNMT1 protein expression with no effect on DNMT1 messenger RNA (mRNA) levels. While the basis for this activity of RX-3117 on DNMT1 is unclear, this additional action of RX-3117 could contribute to its anti-cancer activity.

In vivo studies in nude mice evaluated the effects of RX-3117 on tumor proliferation/growth. RX-3117 displayed antitumor activity in nude mice implanted with human tumors (COLO 205 colorectal adenocarcinoma, HCT116 colorectal carcinoma, MV-522 and A549 non-small cell lung carcinomas, H460 large-cell lung carcinoma, H69 small-cell lung cancer, Caki-1 renal carcinoma, CTG-0298 and Mia PaCa-2 pancreatic carcinomas, and OVCAR3 ovarian carcinoma).

The efficacy of RX-3117 in subcutaneous xenograft models (Colo-205, H460, H69 and CaSki models), which are moderately sensitive or resistant to gemcitabine, indicates that RX-3117 may have the potential to be used for the treatment of tumors that do not respond to gemcitabine or have become resistant to gemcitabine.

In vitro cross-species myelotoxicity data showed a myelotoxic effect on human and monkey bone marrow, a potential cytotoxic effect on mouse bone marrow, while non-significant myelotoxicity was observed on canine and rat bone marrow.

2.2.3 Nonclinical Safety Pharmacology Studies

Safety pharmacology studies by the oral route evaluated potential functional effects of RX-3117 on the cardiovascular system, respiratory system, and central nervous system. Effects on the central nervous system and the cardiovascular system were also evaluated as part of the 28-day oral repeated dose toxicity study in dogs. In vitro,

RX-3117 displayed no human ether-a-go-go-related gene (hERG) potassium channel inhibition, no cardiac cytotoxicity, and had no effect on spontaneous beating in Cor.At® pure embryonic stem cell derived cardiomyocytes. In vivo, RX-3117 did not elicit any changes in blood pressure parameters, electrocardiography (ECG) parameters, or heart rate in dogs. RX-3117 had no significant effects on respiratory parameters in mice. In addition, RX-3117 had no effects on the central or autonomic nervous systems, or on peripheral motor and sensory systems in both mice and dogs. Finally, RX-3117 had no effects on electroencephalography activity following an intravenous (IV) dose of 100 mg/kg in monkeys.

Further nonclinical safety pharmacology information can be found in the RX-3117 Investigator's Brochure.

2.2.4 Nonclinical Pharmacokinetic and Drug Metabolism Studies

The pharmacokinetic properties of RX-3117 were investigated in mice, dogs, and monkeys in conjunction with toxicity studies, as well as in separate pharmacokinetic studies.

Pharmacokinetic studies indicate that RX-3117 is orally bioavailable in mice and dogs, in contrast to gemcitabine, which can only be administered by the IV route only. RX-3117 is only poorly orally bioavailable in monkeys. For all species investigated in which the drug was orally bioavailable, RX-3117 displayed generally biphasic plasma profiles, with fast absorption and a relatively fast initial distribution phase followed by a slower terminal phase. Nonclinical pharmacokinetic parameters characterize a longer terminal elimination half-life (t½) of RX-3117 than that of gemcitabine. Following repeated administration, although plasma concentrations were detectable before the last dose, the extent of RX-3117 accumulation was minimal, with similar exposure parameters on the first and last days of administration. No sex-related differences of pharmacokinetic parameters were observed in any of the species tested.

In CD-1 mice, RX-3117 displayed dose-dependent pharmacokinetics upon oral administration, with subproportional increase in exposure across dose levels of 100, 300, and 1000 mg/kg. The absorption of RX-3117 following oral administration was fast, resulting in an early time to maximum observed plasma concentration (T_{max}) (0.75-1 hour postdose). Oral bioavailability was determined to be 74%. The t½ values ranged from 3 to 10.3 hours.

In Beagle dogs, linear pharmacokinetic properties were evident following both IV and oral administration, at the dose ranges of 100 to 400 mg/kg and 30 to 300 mg/kg, respectively. The absorption of RX-3117 was fast, resulting in an early T_{max} (0.25 hour postdose). Administration of 10 mg/kg RX-3117 hydrate in hydroxypropylmethyl-cellulose capsules, with and without Avicel PH-102 as excipient, did not significantly affect absorption of RX-3117 in female dogs relative to solution; although T_{max} was slightly delayed (0.5-1 hour postdose), relative exposure was the same. Oral bioavailability was determined to be greater than 100%. The t½ values ranged from 3 to 5.35 to 39 hours following oral administration and 3.25 to 4.7 hours following IV administration.

The pharmacokinetic properties of RX-3117 were investigated in male Cynomolgus monkeys following a single bolus IV administration dose of 2.5 mg/kg (not conducted under Good Laboratory Practice [non-GLP] study), or an IV infusion for 6 minutes at 100 to 300 mg/kg. Monkeys were dosed via IV administration since RX-3117 displayed poor oral bioavailability (11%) in monkeys. Analysis of RX-3117 after IV infusion showed that increasing the dose from 2.5 to 35 mg/kg resulted in a supraproportional increase in exposure (greater than twice the expected value), suggesting nonlinear pharmacokinetics. However, IV administration of RX-3117 between the dose range of 35 to 300 mg/kg displayed linear kinetics. RX-3117 was rapidly eliminated and showed moderate systemic clearance (CL) and volume of distribution (Vz) after low- and moderate-dose IV administration. The t½ values ranged from 1.28 to 11.25 hours.

RX-3117 showed low permeability ($< 5\times10^{-6}$ cm/sec) in Caco-2 cells in both the A-B and B-A directions, and seems to be actively transported from the gastrointestinal tract into the blood, as well as from the blood into tissues, possibly by human equilibrative nucleoside transporter (hENT).

RX-3117 was tested for plasma protein binding in vitro, in mouse, rat, dog, monkey, and human plasma, at concentrations of 1 to 500 µM. No measurable percentage of protein binding was observed in any of the species and concentrations examined.

Early nonclinical pharmacokinetic and toxicokinetic investigations in dogs and monkeys characterized the plasma deaminated metabolite profile of RX-3117. Deamination of RX-3117 was faster in monkeys than in dogs (T_{max}= 2.5 and 5 hours). Relative plasma exposure for the deaminated metabolite was higher in monkeys than in dogs (area under

the plasma drug concentration-time curve from 0 to time of the last quantifiable concentration [$AUC_{0\text{-last}}$] of metabolite and AUC from 0 to time extrapolated to infinity [$AUC_{0\text{-}\infty}$] of RX-3117 were 56% and 30% in monkeys and dogs, respectively), and the observed elimination of the metabolite was slower than the elimination of the drug for both species. Due to its longer t½, the deaminated metabolite exposure following repeated administration equaled or exceeded RX-3117 exposure. In monkeys, the ratio of $AUC_{0\text{-last}}$ of metabolite to $AUC_{0\text{-last}}$ of the parent drug was 197% and 93%, respectively, after 5 daily IV administrations of 35 mg/kg RX-3117 and 4 doses of 150 mg/kg administered IV twice weekly. In dogs, accumulation of the metabolite was less pronounced, with an increase of the exposure ratio to around 50% upon repeated administration.

Interspecies comparison of the in vitro metabolism of RX-3117 in mouse, rat, dog, monkey, and human liver microsomes revealed that RX-3117 does not undergo cytochrome P450 (CYP)-mediated metabolism in any of these species. RX-3117 metabolism was further investigated in human transformed cell lines. It was shown that RX-3117 was not phosphorylated by deoxycytidine kinase, but by UCK, into an active nucleotide form (mono-, bi-, or triphosphorylated RX-3117) and further incorporated into both RNA and DNA. It was also shown that RX-3117 deamination was cytidine deaminase -mediated, although its extent and rate are relatively very low.

RX-3117 excretion was studied using 300 mg/kg of ^{3}H-RX-3117 orally administered to mice. RX-3117 excretion was relatively rapid with about 80% of the radioactivity eliminated during the first 24 hours. Total recovery following 1 week was 94%, with 48% of dose radioactivity excreted in the urine and 46% in the feces.

When tested in vitro in human liver microsomes, RX-3117 at 0.1 to 100 µM did not cause direct or time-dependent inhibition of any of the CYP enzymes tested, namely CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4/5.

When tested in vitro in human transporter-transfected polarized cell monolayer/vesicles, RX-3117 did not inhibit any of the transporters studied, namely organic anion transporter (OAT)1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, breast cancer resistance protein, P-glycoprotein, and bile salt export pump, at clinically relevant concentrations (up to 5 mM). The effect of RX-3117 on CYP induction has not yet been evaluated.

2.2.5 Nonclinical Toxicology Studies

In mice, a single oral administration of RX-3117 at doses up to 1000 mg/kg did not induce toxicity signs on the day of treatment or during a 14-day recovery period, at any of the doses tested. Following daily oral administration of RX-3117 at 180/100 mg/kg/day (male/female mice), 60 and 30 mg/kg/day (both male and female mice) for up to 28 days, mortality occurred at the high dose in male and female mice (180 and 100 mg/kg, respectively) and in the mid-dose female mice (60 mg/kg). Consequently, dosing of the high-dose groups was terminated early. Clinical signs were observed mainly in high-dose groups and included hunched posture, piloerection, decreased activity, lethargy, tremors, semi-closed eyes, and cold to touch. Clinical signs mostly appeared just prior to the death or unscheduled sacrifice of the animals. Marked reductions in body weight and food consumption were observed in high-dose groups and to a lesser extent in mid-dose groups with complete recovery at the end of the recovery period. Hematology investigations showed anemia, thrombocytosis, and leukopenia to be dose dependent, with partial recovery at the end of the recovery period. In clinical chemistry, reductions in glucose, and elevated globulin and creatine kinase levels were seen. At necropsy, atrophy was seen in the thymus, lymph nodes, spleen, and bone marrow. Histopathologic examinations revealed reductions in the normally present intracytoplasmic glycogen contents and single-cell necrosis in the liver, sporadic cases of vacuolation of the epithelium lining the kidney tubules, moderate inflammation of the intestinal mucosa associated with atrophy of the villi, and sporadic presence of ulcers in the cecum and atrophy of the ovary corpora lutea. Partial recovery was seen at the end of the recovery period. The dose of 60 mg/kg/day was considered as the severely toxic dose (STD).

In a non-GLP study in mice in which RX-3117 was given orally 3 times a week at 500, 1000, and 1500 mg/kg for a total of 5 administrations, a similar picture of toxicity appeared, yet at much higher doses as compared with the daily dosing regimen. Mortality occurred in the mid- and the high-dose groups (1000 and 1500 mg/kg, respectively). Clinical signs were observed in the mid- and high-dose groups and included piloerection, hunched posture and decreased activity. Reduction in body weights and food consumption were mainly observed in high-dose groups. Hematologic changes included significant reductions in reticulocytes and anemia, thrombosis, and leukopenia to be dose dependent. The dose of 500 mg/kg/day was considered to be the maximum tolerated dose (MTD) in this study.

In dogs, the main effects following a single oral administration of RX-3117 at doses up to 300 mg/kg were bone marrow toxicity, consisting of significant changes in hematologic parameters, and reductions in weights of the thymus and male sexual glands in mid- (100 mg/kg) and high-dose (300 mg/kg) groups. Following daily oral administration of RX-3117 for up to 28 days at doses of 1, 2.5, and 5 mg/kg, isolated episodes of emesis and liquid feces, along with reductions in body weight and food consumption, were seen in high-dose groups. Hematologic changes were noted in high-dose groups, consisting of decreases in erythrocytes, hemoglobin, hematocrit, reticulocytes, and leucocytes and elevations in platelets, which were fully recoverable by the end of the recovery period. At necropsy, thymus weights were reduced in high-dose groups and mid-dose female dogs, with complete recovery in 3 of 4 animals. Thymus atrophy was noted at histopathologic examinations in 1 male dog given the high dose. The changes seen in the thymus were potentially secondary, related to stress-associated with the administration of high dose.

No changes were observed in weights or histopathology of male sexual glands. The dose of 5 mg/kg/day was determined as the highest nonseverely toxic dose (HNSTD) while the dose of 2.5 mg/kg/day was determined as the no-observed-adverse-effect level (NOAEL).

In a non-GLP study in dogs in which RX-3117 was given orally at doses of 15 and 30 mg/kg 3 times per week for a total of 6 administrations, abnormal feces were observed in the high-dose group but no significant reductions in body weight and food consumption were seen in either dose group. Hematologic changes included reductions in neutrophils, lymphocytes, monocytes, and basophils in both dose groups with full recovery 5 days after the last dose. Overall, the toxicity profile of RX-3117 in this study was similar to that observed during the 28-day repeated dose toxicity study, yet toxic effects were observed at higher doses in the thrice-weekly dosing regimen. The dose of 30 mg/kg/day was considered to be the MTD in this study.

Intravenous administration of high doses of RX-3117 in dogs and monkeys was associated with marked central nervous system toxicity, which was not observed in any of the tested species following dosing by the oral route. In dogs, a single IV dose of 400 mg/kg induced tremors of the head and convulsions 10 hours postdose. No such signs were noted in dogs following a single oral administration of RX-3117 at up to 300 mg/kg, or after 28-days repeated oral administration at doses up to 5 mg/kg/day. In monkeys, a single IV dose of 300 mg/kg induced convulsions, tremors, and behavioral disturbances

(disorientation, incoordination, and falling over), which were observed 8 hours postdose, while a single IV dose of 200 mg/kg or repeated twice weekly doses of 150 mg/kg (given 4 times) were associated with dilated pupils, ataxia, and tremors. Daily IV doses of 35 mg/kg in monkeys (given for 5 consecutive days) were not associated with any signs of central nervous system toxicity.

RX-3117 was tested in a dedicated electroencephalography study in monkeys, in order to set safe doses and exposure levels based on electroencephalography measurements. Following a single IV dose of 100 mg/kg, no effects were noted on electroencephalographic activity and no clinical or electrophysiologic findings suggesting proconvulsant or seizure liability were observed. Exposure levels measured at this safe dose of 100 mg/kg IV were: 200428 ng/mL and 206670 ng/mL (mean maximum observed plasma concentration measured [C_{max}] in male and female monkeys, respectively) and 119,811 ng•hr/mL and 13439 ng•hr/mL (mean AUC from the time of dosing to the last measurable concentration, [AUC_{0-t}] in male and female monkeys, respectively).

RX-3117 was not mutagenic in the Ames in vitro reverse mutation assay using 5 strains of bacteria. However, RX-3117 was mutagenic to mammalian cells, when tested in the mouse lymphoma cell assay.

No studies on reproductive toxicity and carcinogenicity with RX-3117 have been performed.

2.2.6 Exploratory Clinical Study

RX-3117 was evaluated in an exploratory pharmacokinetic study of a single oral dose (50 or 100 mg) or a single IV dose (20 mg) of RX-3117 performed at 2 centers in Hungary. Subjects had advanced solid tumor and had not received any chemotherapy for 2 weeks prior to receiving the study drug.

The primary study objective was to determine the absolute oral bioavailability of RX-3117 from a single dose administered to subjects with solid tumors. The secondary objectives were to evaluate the safety and tolerability of a single dose of RX-3117 administered either orally or IV and to evaluate dose proportionality of 2 single dose levels of RX-3117 administered orally.

Nine subjects (3 subjects in each group [50 mg oral dose, 100 mg oral dose, or 20 mg IV dose]) were administered study drug in this first-in-human, sub-therapeutic, single-dose study. Study drug was administered either orally or IV to the subject in the clinical setting. The in-patient observation period was from Study Day 1 through Study Day 3. After administering the appropriate single dose of RX-3117, blood samples were collected at specific times throughout a 48-hour period. A safety follow-up assessment was performed on Study Day 7. No efficacy or pharmacodynamic endpoints were assessed. Pharmacokinetic and safety results were assessed. Information on concomitant medications was collected.

No subjects were withdrawn from the study for any reason and all subjects completed the study. All 9 subjects were included in the safety and pharmacokinetic analyses.

Following oral administration, RX-3117 exposure parameters for the 50-mg and 100-mg dose levels were not markedly different. For the respective 50- and 100-mg doses, the mean T_{max} was 2.16 and 2.49 hours, the mean C_{max} was 303 ng/mL and 311 ng/mL, the mean $AUC_{0-\infty}$ was 2440 ng•h/mL and 2986 ng•h/mL, and mean t½ values were 14 hours and 21 hours (with the concentration-time profiles after the peak showing an initial distribution phase followed by a slower terminal elimination phase). After a single IV bolus administration of 20 mg RX-3117, plasma concentrations declined rapidly, resulting in a multiphasic profile with a rapid initial decline followed by a slow terminal elimination phase, with mean t½ of 21 hours. The calculated absolute oral bioavailability (F), based on non-crossover data, was 55.7% for the 50-mg dose and 33.4% for the 100-mg dose. The mean Vz calculated was 345 L.

No adverse events, treatment-emergent adverse events, deaths, or other serious adverse events were reported. No significant findings resulted from assessments of clinical laboratory test results, vital sign measurements, ECG, or physical examination findings. No safety issues (including cardiac toxicity) were reported although it should be noted that data were only collected on Days 1 through 3 and Day 7 after the study drug administration.

2.3 Selection of Starting Dose

The starting dosage of RX-3117 selected for this study is 30 mg/day administered in repeated 4-week cycles comprising administration of the drug 3 times per weekly for 3 weeks with a 1-week hiatus. This starting dosage selection is based on the results of

28-day toxicology studies in both mice and dogs and is in compliance with the International Conference on Harmonisation (ICH) S9 guideline.

Repeated oral dose toxicity studies with RX-3117 were conducted up to 28 days in mice and dogs followed by recovery periods of up to 28 days. Dosages evaluated in mice were 180/100 mg/kg/day (male/female mice), 60 mg/kg/day and 30 mg/kg/day (both male and female mice), which were converted into human equivalent doses (HED) of 540/300 mg/m^2, 180 mg/m^2, and 90 mg/m^2, respectively. Dosages evaluated in dogs were 1, 2.5, and 5 mg/kg/day with HEDs of 20 mg/m^2, 50 mg/m^2, and 100 mg/m^2, respectively.

Using data from rodents, the initial starting dose in humans is calculated as 1/10 of the HED that produces severe toxicity in 10% of the animals (STD_{10}). The STD_{10} in mice was determined to be 60 mg/kg, which is converted to an HED of 180 mg/m^2; with application of the 1/10 safety factor, the starting dose in humans would be 18 mg/m^2. For an adult (60 kg) with an average body surface area of 1.6 m^2, this calculates to a dose of 28.8 mg/subject.

Using data from nonrodents, the initial starting dose is calculated as 1/6 of the human equivalent of the HNSTD. In the case of RX-3117, the HED is calculated according to body surface comparison as described by Senderowicz (2010). Thus, the STD_{10} of 5 mg/kg in dogs is converted to a HED of 100 mg/m^2; with application of the 1/6 safety factor, the starting dose based on this species is 16.7 mg/m^2. For an adult (60 kg) with an average body surface area of 1.6 m^2, this calculates to a dose of 26.7 mg/subject.

Therefore, the human starting doses of RX-3117 calculated from 28-day toxicity studies in mice and dogs are comparable, at 28.8 or 26.7 mg/subject, respectively. Thus an appropriate starting dose is 30 mg.

Based on preliminary xenograft modeling in the most sensitive tumor cell line to date, renal cell (Caki-1), 3 times/week dosing was effective (see RX-3117 Investigator's Brochure). Considering toxicity data from nude mice and beagle dogs, clinical administration of repeated therapy cycles comprising drug administration 3 times per week weekly for 3 weeks with a 1-week hiatus appears appropriate to induce tumor cell killing but permit recovery from myelosuppression. However, there are other studies in dogs in which once daily dosing for 5 days was given. Additional studies may suggest daily dosing for 5 days with a 2-day hiatus over a 2-week period with a 2-week period of

no drug for a total 28-day cycle. If the planned treatment schedule is not fully feasible, the study design may be amended to evaluate alternate treatment schedules.

2.4 Dosing Frequency Rationale

Three times per week dosing up to 4500 mg was originally planned for this study. However, following treatment with 1000 to 2000 mg, RX-3117 levels in the blood began to plateau. Based upon this finding more frequent dosing at lower doses is recommended.

To predict the potential exposures resulting from variable doses and schedules, a simulated population PK model was created and then validated with the clinical pharmacokinetic data collected in the current study at 3 times per week dosing administration (doses 30 to 2000 mg 3 times per week). At each dose level, 500 simulated profiles were generated using the RX-3117 population PK model. At most dose levels, the clinically measured concentration profiles were generally within the middle 90% of the simulated profiles and often were close to the median concentration line, thereby providing a positive visual predictive check of the model. Using the population PK model, potential RX-3117 plasma exposures were predicted for proposed 5 and 7 times per week dosing schedules. In the revised dosing schedule (Table 2), the total weekly doses, total weekly exposures (AUCs), and total cycle doses are initially planned not to exceed doses administered previously on a 3 times per week dosing schedule (Table 1).

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a Phase 1, multicenter, open-label, single-agent study of RX-3117 administered orally to subjects with advanced or metastatic solid tumors, with a dose expansion at the MTD or recommended Phase 2 dose and schedule followed by a 2-stage (Simon, 1989) Phase 2 study design in subjects with relapse/refractory pancreatic cancer or advanced bladder cancer. The study consists of a screening period (up to 14 days; up to 21 days for tumor imaging assessments), repeated 28-day treatment cycles for up to 8 cycles, an end-of-treatment visit, and a follow-up visit approximately 30 days after the last dose of RX-3117. Additional cycles of therapy may be provided following discussions with the investigator, sponsor and medical monitor.

The drug will be administered orally in repeated 4-week cycles comprising administration of the drug 3 times per weekly, 5 times per week, or daily (e.g., 7 days per week) for 3 weeks with a 1-week hiatus. These dosing regimens and schedules are supported by non-clinical toxicology studies performed in the mouse and dog, clinical pharmacokinetic data from the current study and pharmacokinetic simulation data.

In the Phase 1, the initial starting dose level of RX-3117 will be 30 mg/day. The dose escalation will begin with an accelerated design in single subjects (Simon et al., 1997). After the occurrence in Cycle 1 of a single ≥ Grade 2 adverse event that is considered related to RX-3117, the study will transition to a standard 3 + 3 design using a modified Fibonacci sequence (see Section 6.2 for details).

In the Phase 1 portion of the study subjects with advanced solid tumor malignancies will be enrolled. During the Phase 1 portion of the study, the maximum tolerated dose (MTD) or a recommended Phase 2 dose (RP2D) and schedule will be determined and the pharmacokinetics of RX-3117 characterized in eligible subjects. Following determination of the MTD or RP2D dose a Phase 1 Dose Expansion will occur. In the Dose Expansion, subjects will be enrolled in 1 of 3 diagnosis groups: relapsed or refractory pancreatic, colorectal or advanced bladder cancers. In the Phase 2 portion, subjects will be enrolled in 1 of 2 diagnosis groups: relapsed or refractory pancreatic or bladder cancers. The Phase 2 part of the study will follow a 2-stage design (Simon, 1989). An interim analysis will be conducted when 10 response evaluable subjects in each tumor indication are enrolled and have had the opportunity to complete a minimum of 4 cycles of therapy or have discontinued therapy due to progressive disease. In the second stage, efficacy will be further evaluated in the disease groups that continue beyond the first stage.

Subjects will receive up to 8 cycles of RX-3117 or until disease progression (per RECIST ver 1.1 see Appendix C), an intolerable RX-3117 related adverse event, withdrawal of consent, pregnancy, substantial noncompliance, or if the principal investigator feels it is in the best interest of the subject to stop treatment. After 8 cycles of therapy if in the opinion of the investigator, a subject is receiving benefit, additional cycles of RX-3117 may be administered following discussions with the sponsor and medical monitor.

The study endpoints are defined in Section 10.1.

3.2 Number of Centers

Approximately 12 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

The number of subjects enrolled into this study may vary depending upon the number of dose levels needed to determine the maximum tolerated dose or recommended Phase 2 dose. It is anticipated that approximately 152 subjects will be enrolled in this study (40 subjects in the Phase 1, 12 subjects in the Phase 1 Dose Expansion, 20 subjects (10 per cancer indication) in Stage 1 of the Phase 2 and 80 subjects (40 per cancer indication) in Stage 2 of the Phase 2.

3.4 Estimated Study Duration

3.4.1 Study Duration for Participants

The study will consist of a screening period (14 days), up to 8 treatment cycles (i.e., cycle = 28 days), an end-of-treatment visit, and a follow-up visit 30 +7 days after the last dose of RX-3117. Subject participation is anticipated to be approximately 10 months.

Subjects may receive RX-3117 until the earliest sign of disease progression (per RECIST ver 1.1 see Appendix C), an intolerable RX-3117-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.

3.4.2 End of Study

The study will end when the last subject treated completes their safety follow-up visit.

4. SUBJECT ELIGIBILITY

This clinical trial can fulfill its objectives only if appropriate participants are enrolled. 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.

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

4.1.1 Disease related

- Confirmed histologic or cytologic evidence of metastatic or locally advanced solid neoplasm that has failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens (Phase 1).

- Confirmed histologic or cytologic evidence of metastatic pancreatic, colorectal or advanced bladder cancer that failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens (Phase 1 Dose Expansion)

- Confirmed histologic or cytologic evidence of metastatic pancreatic or advanced bladder cancer that failed to respond to standard therapy, progressed despite standard therapy or for which standard therapy does not exist. There is no limit on the number of prior treatment regimens (Phase 2)

- Measurable or evaluable disease using Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1.

- Life expectancy of ≥ 3 months

- ECOG performance score 0, 1 or 2 (Phase 1)

- ECOG performance score 0 or 1 (Phase 2)

- Discontinuation of all therapy (including radiotherapy, chemotherapy, immunotherapy, systemic corticosteroids, or investigational therapy) for the treatment of cancer within 2 weeks before the planned start of study therapy.

- All acute toxic effects of any prior antitumor therapy resolved to Grade ≤ 1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], or neurotoxicity [Grade 1 or 2 permitted], or anemia [Grade 2 permitted]).

4.1.2 Demographic

- Males or females who are 18 years or older
- Able to swallow capsules

4.1.3 Laboratory

- Hemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count ≥ 1.5 x 10^9/L
- Platelet count ≥ 100 x 10^9/L
- Serum creatinine ≤ 1.5 times the upper limit of normal OR 24-hour measured urine creatinine clearance ≥ 50 mL/min for subjects with serum creatinine levels > 1.5 times the upper limit of normal
- Serum bilirubin ≤ 1.5 times the upper limit of normal *OR* ≤ 3 times the upper limit of normal in the presence of known liver metastases
- Aspartate aminotransferase (AST; SGOT) and alanine amino transferase (ALT; SGPT) ≤ 2.5 times the upper limit of normal OR ≤ 5 times the upper limit of normal in the presence of known liver metastases
- Alkaline phosphatase ≤ 2.5 times the upper limit of normal OR ≤ 5 times the upper limit of normal in the presence of known liver or bone metastases
- Prothrombin time (PT) < 1.2 times the upper limit of normal unless receiving therapeutic anticoagulation, International normalized ratio (INR) up to 3-4 times the upper limit of normal if on therapeutic anticoagulation and partial thromboplastin time (PTT) < 1.2 times the upper limit of normal unless receiving therapeutic anticoagulation.
- For women of childbearing potential: Negative serum pregnancy test during screening and negative serum or urine pregnancy test at start of study therapy (Cycle1 Day 1)

4.1.4 Reproductive

- For female subjects of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the screening visit throughout the study treatment period and for 30 days following the last dose of study drug (see Section 6.8.6 for definition of child-bearing potential).
- For fertile male subjects having intercourse with females of childbearing potential, willingness to abstain from heterosexual intercourse or use a protocol-recommended method of contraception from the start of study therapy throughout the study treatment period and for 30 days following the last dose of study drug and to refrain from sperm donation from the start of study treatment throughout the study treatment period and for 30 days following the last dose of study drug. (see Section 6.8.6 for definition of male fertility)

4.1.5 Ethical

- In the judgment of the investigator, participation in the protocol offers an acceptable benefit-to-risk ratio when considering current disease status, medical condition, and the potential benefits and risks of alternative treatments for the subject's cancer.

- Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 12.1).

4.3 Exclusion Criteria

4.2.1 Disease Related

- Primary brain tumors or clinical evidence of active brain metastasis

4.2.2 Medications

- Systemic corticosteroid use within 7 days before planned start of study therapy

4.2.3 General

- Active infection requiring parenteral or oral antibiotics within 2 weeks before planned start of study therapy

- Uncontrolled diabetes as assessed by the investigator

- Second malignancy other than curatively resected basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ carcinoma of the cervix, or other cancers treated with curative intent and no known active disease in the 3 years before planned start of study therapy

- QTcF interval greater than 470 msec, with a known history of QTcF prolongation, is taking medications known to prolong QTcF, or has history of torsade de pointes.

- Documented history of hepatitis B, hepatitis C or human immunodeficiency virus

- History of any other concurrent conditions that could preclude the subject's participation in the study, pose an undue medical hazard, or interfere with the interpretation of the study results, including, but not limited to, subjects with congestive heart failure (New York Heart Association [NYHA] Class III or IV), cardiac arrhythmia, or acute coronary syndromes within 6 months before planned start of study therapy

- History of prior allogeneic bone marrow progenitor cell or solid organ transplantation.

- Any other medical, psychiatric, or social condition, which in the opinion of the investigator, would preclude participation in the study, pose an undue medical

hazard, interfere with the conduct of the study, or interfere with interpretation of the study results

- Pregnant, planning a pregnancy or breast feeding during the study
- Concurrent participation in another therapeutic clinical trial
- Has any disorder that may interfere with drug absorption, distribution, metabolism, or excretion (including gastrointestinal surgery, bariatric surgery)
- Has known hypersensitivity to prior gemcitabine, azacytidine or cytosine arabinoside exposure
- Unwilling or unable to comply with study requirements or planned unavailability for follow-up assessments

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, Enrollment and Treatment Assignment

Before subjects may be entered into the study, the sponsor requires a copy of the site's written institutional review board approval of the protocol, informed consent form, and all other subject information and/or recruitment material, if applicable (see Section 12.3).

All subjects must personally sign and date the consent form before study specific procedures are performed during the screening period. 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 of the subject into the study.

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, PET scans, MRIs, etc). In order to obtain a subject number, the site must provide completed eligibility documents to the study sponsor or designee. In order for the subject to begin

study treatment, the study sponsor or designee will provide confirmation of eligibility by either fax or e-mail to the site. Of note, subjects may be rescreened only once for laboratory values not meeting the criteria for study eligibility. A subject will be enrolled when the treatment dose has been assigned.

5.3 Subject Enrollment and Treatment Assignment

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, dosing schedule and a confirmation of enrollment. Ideally subjects will be dosed within 3 days of enrollment.

5.4 Subject Replacement

In the Phase 1, including the Dose Expansion, subjects 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 level and schedule as that for the subject who withdrew.

In the Phase 2 portion, non-evaluable subjects will be replaced.

6. TREATMENT PROCEDURES

The only investigational product in this study is RX-3117. For details on the study drug description, storage and handling see Section 11.

6.1 Study Drug Administration

6.1.1 Dosing Schedule

RX-3117 will be administered on a cyclical basis. A cycle is defined as the period elapsing from the first day of RX-3117 administration through Day 28 of the cycle or to the recovery from any adverse events sufficient that a new cycle can be administered (e.g., on Day 36 or Day 43), whichever occurs later. Once a new cycle is initiated, the prior cycle is considered to be completed.

In each 28-day cycle, RX-3117 will be taken by the study subjects 3 times per week (e.g., Monday, Wednesday, Friday), 5 times per week (i.e., for 5 consecutive days followed by 2 days off) or daily (e.g., 7 days per week) for 3 successive weeks followed by $\geq$ 1-week of washout. Study drug should be taken at approximately the same time

each day (e.g., at ~8 AM on each planned day of dosing). Ideally, doses should be taken at ~48-hour intervals, for 3 times per week, or ~24- hour intervals, for 5 and 7 times per week dosing schedule. While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen should be followed as closely as possible, especially in the clinic.

At specified clinic visits in Cycle 1, the study drug will be administered in the clinic with dosing appropriately timed relative to blood sampling for RX-3117 pharmacokinetics. As detailed in Section 7, clinic staff should record RX-3117 administration information, including the exact time each dose of RX-3117 is administered in the clinic or hospital.

6.1.2 Dose Administration

At each RX-3117 dose administration, the capsule types and numbers corresponding to the appropriate dose of RX-3117 are to be swallowed whole with 100 to 200 mL (~ 4 to 8 ounces) of water. Subjects should be instructed not to bite or chew on the capsules. In case of breakage of the capsules in the oral cavity, additional water should be taken as a rinse.

Subjects will be instructed to refrain from eating for 8 hours before each dose is administered. Subjects may eat ≥ 1 hour after dose administration.

6.2 Dose Escalation and Stopping Rules

Dose escalation in this study will begin with an accelerated design involving single subjects (Simon et al., 1997) until the occurrence of any adverse event of Grade ≥ 2 that is considered related to RX-3117. Thereafter, the dose escalation will transition to a standard 3 + 3 design using a modified Fibonacci sequence. Dose escalation will proceed according to the specified dose escalation scheme described in Tables 1 and 2. The doses will be administered from the least number of capsules available at the time of dosing.

Table 1: Dose Escalation Three times per Week

Dose Group	Capsule Size, mg				Actual dose, mg	Escalation Fold-Increase	Total weekly dose, mg	Total cycle dose, mg
	30	100	200	500				
1	1	0	0	0	30	-	90	270
2	2	0	0	0	60	2.00	180	540
3	0	1	0	0	100	1.67	300	900
4	5	0	0	0	150	1.50	450	1,350
5	0	2	0	0	200	1.33	600	1,800
6	0	1	2	0	500	2.50	1,500	4,500
7	0	0	5	0	1,000	2.00	3,000	9,000
8	0	0	0	3	1,500	1.50	4,500	13,500
9	0	0	0	4	2,000	1.33	6,000	18,000

In the revised dosing schedule, the total weekly doses, total weekly exposures (AUCs), and total cycle doses are initially planned (Table 2, groups 10 through 15) not to exceed doses administered previously on a weekly dosing schedule. Dose groups 16 through 19, if administered, will use all available safety data to make dose escalation decisions between the Sponsor, principal investigators and medical monitor. Subjects receiving doses that are similar based upon total weekly dosing, despite differing schedules, may be enrolled at the same time.

Table 2. Dose Escalation - 5 and 7 Times per Week

Dose Group	Doses per week	Capsule Size, mg			Total daily dose, mg	Total weekly dose, mg	Escalation fold Increase	Total cycle dose, mg
		100	200	500				
10	5	0	0	1	500	2500	-0.83[1]	7500
11	5	0	1	1	700	3500	1.16[1]	10500
12	7	0	0	1	500	3500	1.16[1]	10500
13	7	0	1	1	700	4900	1.08[2]	14700
14	5	0	0	2	1000	5000	-0.83[3]	15000
15	5	0	1	2	1200	6000	1.00[3]	18000
16	7	0	0	2	1000	7000	1.16[4]	21000
17	5	0	0	3	1500	7500	1.07[4]	22500
18	7	0	1	2	1200	8400	1.12[4]	25200
19	5	0	1	3	1700	8500	1.12[4]	25500
20	5	0	0	4	2000	10000	1.17[4]	30000

*Doses will be daily for 5 consecutive days with 2 days off per week (5) or daily for 7 days per week (7)
[1] compared to 3000 mg weekly dose Table 1; [2] compared to 4500 mg weekly Table 1; [3] compared to 6000 mg weekly Table 1, [4] compared to the previous dose in Table 2.

In the accelerated portion, dose-escalation decisions will be made after a single subject has been treated for 1 cycle of therapy (i.e., 3 weeks of treatment followed by ≥ 1 week of rest) and doses will be escalated following review of data from Cycle 1 by the investigators, medical monitor and sponsor. The accelerated design schedule will continue until there is an adverse event of a ≥ Grade 2 in Cycle 1 that the investigator considers related to RX-3117. After the occurrence of such an adverse event in the first subject at that dose level, dose escalation will proceed according to the standard 3+3 design, with 2 to 5 additional subjects to be treated at the same dose level and schedule (depending upon the toxicities observed).

If a DLT occurs at one dose and dosing schedule (i.e., 5 or 7 times per week), that dose and schedule will follow the rules described below for enrolling additional subjects.

Once the standard 3+3 dose escalation is initiated, the following dose-escalation rules will be employed:

- If 0 of the first 3 subjects experience DLT during the first 4 weeks of treatment, then the dose and schedule will be escalated to the next higher dose group in 3 subsequent subjects.

- If 1 of the first 3 subjects experiences DLT at the current dose and schedule during the first 4 weeks of treatment, then 3 more subjects will be accrued at the same dose level and schedule.

- If 0 of the 3 additional subjects experience DLT during the first 4 weeks of treatment, then the dose and schedule will be escalated to the next dose group level in 3 subsequent subjects.

- If ≥ 1 of the 3 additional subjects in a dose group experiences DLT in the first 4 weeks of treatment, the MTD has been exceeded and 3 more subjects will be treated at the next lower dose group (if only 3 subjects were previously treated at that prior dose group).

- If ≥ 2 of 3 or ≥ 2 of 6 subjects experience DLT during the first 4 weeks of treatment, then the MTD has been exceeded and 3 more subjects will be treated at the next lower dose group (if only 3 subjects were previously treated at that prior dose level).

- Each group of 3 subjects within a dose group must be observed for a minimum period of 4 weeks without DLT before subsequent subjects are enrolled at the next higher dose level.

- Escalation to the next dose group 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 and schedule. 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 and schedule is complete and when the next dose level and schedule is open to enrollment.

6.3 Determination of MTD and Recommended Phase 2 Starting Dose

The establishment of the MTD or recommended Phase 2 dose will be based on a review of the overall safety data by the investigators, medical monitor and sponsor. The MTD is the highest dose level and schedule below the dose and schedule associated with first-cycle DLTs in < 33.3% of subjects. Once the MTD is initially established, additional subjects (up to 12 subjects with metastatic pancreatic cancer or advanced bladder cancer) may be enrolled to receive RX-3117 at the MTD or a lower dose and corresponding schedule if further confirmation of the safety profile appears warranted. Selection of a recommended Phase 2 starting dose from within the tested dose range and schedules will be based on evaluation of short- and long-term safety information but also considering findings regarding compliance, pharmacokinetics, pharmacodynamics and antitumor activity, if applicable. The review committee may recommend that a previous dose level and schedule be considered the MTD or recommended Phase 2 dose or that another dose level and schedule between the highest previously tolerated dose level and schedule, and the dose level and schedule exceeding the MTD be tested in additional subjects. While the Phase 2 is ongoing the review committee may

recommend that subjects receiving benefit may also be dosed for 4 weeks without a rest.

6.4 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-3117:

- Grade 4 neutropenia (ANC < 0.5 x 10^9/L)
- Grade ≥ 3 neutropenia (ANC < 1.0 x 10^9/L) with fever greater than 38.5°C (101.3°F)
- Grade 4 thrombocytopenia (platelet count < 25 x 10^9/L)
- Grade ≥ 2 vomiting despite maximal oral antiemetic therapy, or a requirement for IV antiemetics to control RX-3117-related nausea and vomiting
- Other Grade ≥ 3 adverse events or laboratory abnormalities

6.5 Delayed, Missed and Vomited Doses

Subjects receiving RX-3117 at 3 times per week who have a delay in the administration of a dose of RX-3117 of < 12 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of RX-3117 of ≥ 12 hours, the dose should not be taken. RX-3117 administration may continue but the missed dose should not be made up and the planned timing of subsequent RX-3117 dosing should not be altered.

Subjects receiving RX-3117 at 5 times per week who have a delay in the administration of a dose of RX-3117 of ≤ 8 hours should take the planned dose as soon as possible after the intended time of administration. For subjects who have a delay in administration of RX-3117 of ≥ 8 hours, the dose should not be taken. RX-3117 administration may continue but the missed dose should not be made up and the planned timing of subsequent RX-3117 dosing should not be altered.

Subjects receiving RX-3117 daily (e.g., 7 times per week) who have a delay in the administration of a dose of RX-3117 of ≤ 8 hours should take the planned dose as soon

as possible after the intended time of administration. For subjects who have a delay in administration of RX-3117 of ≥ 8 hours, the dose should not be taken. RX-3117 administration may continue but the missed dose should not be made up and the planned timing of subsequent RX-3117 dosing should not be altered.

Vomited doses should not be retaken.

6.6 Dosage Modifications

Whenever possible, dose and scheduling modifications should be discussed between the investigator and the sponsor prior to implementation. The appropriate clinic staff should dispense the study drug for the new dose level or schedule and instruct the subject/caregiver about the change in dose level or schedule.

6.6.1 Dose Modifications During a Cycle

If a subject experiences a RX-3117-related DLT (as defined in Section 6.4) and requires a dose and/or frequency reduction, RX-3117 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-3117 may be reinstituted, but the dose and/or frequency of RX-3117 for the remainder of that cycle should be reduced by 1 dose level or as directed by the Sponsor. Successive adjustments to progressively lower dose levels can be made. If the subject cannot tolerate RX-3117 at Dose Level 1 (30 mg/dose) then the subject should be discontinued from RX-3117 therapy. If necessary, the subject should be instructed to return to the clinic to receive RX-3117 of the appropriate strength(s) for the reduced dose level. Doses during missed days of treatment should not be made up (e.g., if a subject experiences an RX-3117-related adverse event, after 1 week of treatment, and the event lasts for 1 week, the missed doses during week 2 should be omitted and the new reduced dose level should be administered only for the remaining doses so that the total planned cycle duration remains 28 days).

6.6.2 Dose Modifications at the Beginning of the Next Cycle

A new cycle of RX-3117 treatment may begin no earlier than Day 28 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, weekly 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 6.4 in the current cycle of therapy should have the dose and/or frequency in the next cycle of therapy reduced by 1 dose level and/or frequency (see Table 1 and Table 2) or as directed by the Sponsor. Subjects who required an intra-cycle dose and/or frequency reduction, during the current cycle of therapy, should have the dose and/or frequency in the next cycle of therapy administered at no higher than the highest dose and/or frequency tolerated in the current cycle. Successive inter-cycle adjustments to progressively lower dose levels and/or frequencies can be made. If the subject cannot tolerate RX-3117 at Dose Level 1 (30 mg/dose) then the subject should be discontinued from RX-3117 therapy.

Subjects receiving a lower dose and/or frequency but who the principal investigator feels is benefiting from treatment, may after discussions with the Sponsor, receive a higher dose and at more frequent dosing, for which there is already safety data.

6.6.3 Dose Re-Escalation

After a dose and/or frequency is reduced, the dose and/or frequency need not be re-escalated, even if there is minimal or no toxicity with the reduced dose and/or frequency. However, if the subject tolerates a reduced dose and/or frequency of RX-3117 for ≥ 4 weeks then the RX-3117 dose may be increased to the next higher dose level and/or frequency, 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 and/or frequency reduction was not RX-3117-related. Successive adjustments to progressively higher dose and/or frequency levels can be made at 4-week intervals but the dose and/or frequency must not exceed the highest dose and/or frequency level for which there is already Cycle 1 safety data.

6.7 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, investigator and medical monitor. 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 who cannot tolerate RX-3117 at the 30-mg dose level despite appropriate supportive care 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 institutional review board 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.

6.8 Concomitant and Supportive Therapy

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication 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 electronic case report forms (eCRFs).

6.8.1 Analgesics

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

6.8.2 Antibiotics

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 RX-3117 during treatment for the infection.

6.8.3 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.

6.8.4 Antidiarrheals

For subjects who develop diarrhea, causes related 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 the administration of RX-3117 on Cycle 1 Day 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. Subjects should be instructed to begin taking antidiarrheal medication at the first sign of any of the following: (1) poorly formed or loose stool, (2), occurrence of more bowel movements than usual in 1 day, or (3) an unusually high volume or increased liquidity of stool.

A recommended symptomatic antidiarrheal is loperamide, which may be taken in the following manner: 4 mg at the first onset of diarrhea, then 2 mg every 2 hours around the clock until diarrhea-free for at least 12 hours. Subjects may take loperamide 4 mg every 4 hours during the night. Subjects who appear prone to drug-related diarrhea should be provided with loperamide so that they have sufficient supply on hand in case antidiarrheal support is required. Alternate or additional antidiarrheal measures may be used at the discretion of the treating physician. Subjects should be instructed to increase fluid intake to help maintain hydration during episodes of diarrhea.

Depending upon the type and severity of the diarrhea, interruption of RX-3117 and rechallenge at the same or a reduced dose level and with appropriate support care should be considered.

6.8.5 Antiemetics

Antiemetics are not allowed prior the administration of RX-3117 on Cycle 1 Day 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.

At the occurrence of drug-related nausea or vomiting of severity Grade $\geq$ 1, it is suggested that the subject receive an oral or transdermal serotonin antagonist (e.g., dolasetron, granisetron, ondansetron, tropisetron, palonosetron). The neurokinin receptor antagonist, aprepitant, may also be considered. Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines. If possible, systemic corticosteroids should be avoided due to their many non-specific effects.

Depending upon the type and severity of the vomiting, interruption of RX-3117 and rechallenge at the same or a reduced dose level and with appropriate support care should be considered.

6.8.6 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 RX-3117. 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 $\geq$ 55 years with amenorrhea for $\geq$ 6 months). Protocol-recommend 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 (as noted in Table 3; 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-3117 (as noted in Table 3). 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 described in Table 3.

Table 3. Protocol-Recommended Contraceptive Methods

Individual Methods	Combination Methods	
	Hormonal Methods (One method to be used with a barrier method)	**Barrier Methods (Both of these methods to be used OR one of these methods to be used with a hormonal method)**
IUD	Estrogen and progesterone	• Diaphragm with spermicide
• Copper T 380A IUD	• Oral contraceptives	• Male condom (with spermicide)
• LNg 20 IUD	• Transdermal patch	
Tubal sterilization	• Vaginal ring	
Hysterectomy	Progesterone	
	• Injection	
	• Implant	

Abbreviation**:** IUD=intrauterine device

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

6.8.7 Corticosteroids

Systemic or enteric corticosteroids are not allowed prior the administration of RX-3117 on Cycle 1 Day 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

6.8.8 Diet

There are no specific dietary restrictions in the study other than that subjects should refrain from eating for 8 hours before and for 1 hour after each study drug dose is taken.

6.8.9 Drugs with Potential for Interactions with RX-3117

As described in Section 2.2.4, in vitro studies indicate that RX-3117 does not inhibit drug transporters or CYP enzymes at clinically relevant concentrations; thus, it is not expected that RX-3117 would induce interactions with drugs for which absorption or metabolism would be modulated by inhibition of these enzymes.

As also described in Section 2.2.4, the primary metabolic route for disposition of RX-3117 is deamination by cytidine deaminase. These data imply that strong inhibitors or inducers of cytidine deaminase could theoretically increase or decrease RX-3117 plasma concentrations. However, such agents are unlikely to be administered in clinical practice and thus the risk of altered RX-3117 exposure due to such a drug interaction is considered low. The effect of RX-3117 on CYP induction has not been evaluated.

6.8.10 Erythropoietin and Granulocyte Colony-Stimulating Factors

Use of erythropoietic agents (e.g., erythropoietin or darbepoetin alpha) is not permitted during Cycle 1 of therapy. Thereafter, such agents may be administered for Grade $\geq$ 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 in Cycle 1 of therapy. Prophylactic administration of G-CSF and concomitant administration of RX-3117 and G-CSF is not permitted in support of protocol therapy. However, administration of G-CSF may be considered in a subject who, despite RX-3117 dose modification to 30 mg administered 3 times per week, 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).

6.8.11 Immunization

Due to its potential effects on lymphoid cells, RX-3117 might theoretically impair primary or secondary responses to immunization. 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 during RX-3117 therapy, vaccination should not be performed during Cycle 1 or during any other cycle in a period when the patient is experiencing Grade ≥ 2 leukopenia. The safety of immunization with live viral vaccines during RX-3117 has not been evaluated and vaccination with live virus vaccines during study treatment is not recommended.

6.8.12 Radiation Therapy

Radiation therapy is not permitted during Cycle 1 of study treatment. 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.

Since the radiosensitizing properties of RX-3117 have not yet been established, it is recommended that the study drug be stopped ≥ 2 days before radiation and re-started ≥ 2 days after the completion of the course of radiation. Before treatment occurs, the investigator should discuss the method/frequency of radiation administration with the sponsor.

6.8.13 Surgery or Other Invasive Procedures

The effects of RX-3117 on coagulation or wound healing are unknown. Potential RX-3117 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.

6.8.14 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) for an outline of procedures required at each visit. All safety blood and urine samples should be collected and submitted to the local laboratory on the day of collection. Blood for evaluation of RX-3117 pharmacokinetics, any archived tumor tissue, any tumor biopsy samples, and biomarker samples should be prepared and shipped to the central laboratory for analysis.

Unless otherwise specified, all assessments will be done on the planned visit date.

7.1 General Study Procedures

A signed and dated institutional review board 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 that they are still within the screening period.

7.2 Screening Procedures

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

- Written informed consent
- Review of inclusion and exclusion criteria
- Medical, surgical and psychiatric 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
- Prior medication usage within the previous 28 days before planned study drug administration.
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and

oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air)

- ECOG Performance status
- Physical examination including weight and height
- Laboratory tests (for analyte details see Appendix B)
    - Urinalysis
    - Hematology panel
    - Chemistry panel
    - Serum pregnancy test for female subjects of childbearing potential
    - Coagulation: PTT, PTT or INR
    - Tumor marker, if applicable
- 12-lead electrocardiogram will be taken after the subject has been supine or recumbent (same position must be used for all measurements) for at least 5 minutes (within 7 days before enrollment). All electrocardiogram reports must include the HR, QRS, QT, QTc, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor.
- Radiological imaging to assess disease extent. Radiological assessment must include computerized tomography or magnetic resonance imaging of disease sites and the modality selected should be the same throughout the study. Disease assessment should be according to RECIST ver 1.1 (for details see Appendix C) within 21 days before enrollment. Some imaging assessments may be collected for a second review by a central imaging vendor.
- Review of subject eligibility by the study sponsor or assigned designee
- Subject is enrolled and receives treatment assignment from the sponsor or assigned designee

7.3 Treatment Period – Cycle 1 Day 1

7.3.1 Pre-dosing Assessments

The following procedures will be performed within 3 days **before** the 1st dose of RX-3117 is administered on Cycle 1 Day 1, unless otherwise described:

- Review eligibility criteria
- Record concomitant medication(s)
- Weight
- ECOG performance status
- Laboratory tests within 3 days before dosing (for analyte details see Appendix B)

- Hematology panel
- Chemistry panel
- Urinalysis
- Urine pregnancy test for female subjects of childbearing potential must be negative before study drug dosing can occur. If a serum pregnancy test was done and determined negative within 72 hours of dosing a urine pregnancy test is not needed.
- Coagulation tests: PT, PTT or INR
- Tumor marker, if applicable

- Collect a blood sample for pre-dose pharmacokinetics (with recording of the date and actual clock time of blood collection.
- Collect blood samples for biomarker analysis
- Collection of a tumor biopsy sample pre-treatment from eligible subjects (optional)
- 12 lead electrocardiogram taken while the subject is supine or recumbent (same position must be used for all measurements). All electrocardiogram reports in this study must include HR, QRS, QT, QTc, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor. (Phase 1 and Dose Expansion)
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes), and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).

7.3.1 Post-dosing Assessments – Cycle 1 Day 1

The following procedures will be performed **after** the administration of RX-3117:

- The required order of assessments is electrocardiogram, followed by vital signs and pharmacokinetic sampling when applicable.
- 12 lead electrocardiogram taken at 1 hour ± 10 minutes, 2 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes and 8 hours ± 10 minutes after the RX-3117 administration while the subject is supine or recumbent (same position must be used for all measurements). All electrocardiogram reports in this study must include HR, QRS, QT, QTc, and PR intervals. A duplicate printout of the electrocardiogram report must be printed when the assessment is performed for review by a central vendor. (Phase 1 and Dose Expansion)
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air) will be taken whenever a blood sample is collected for RX-3117 pharmacokinetics.

- Blood samples for RX-3117 pharmacokinetics will be collected (Phase 1 and Dose Expansion):
    - At 0.5 hours ± 5 minutes, 1 hour ± 10 minutes, 2 hours ± 10 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes and 8 hours ± 10 minutes, after the oral administration of RX-3117 on Cycle 1 Day 1.
- Collect a blood sample for biomarker analysis at approximately 4 hours ± 15 minutes, after the oral administration of RX-3117 on Cycle 1 Day 1 (Phase 1 and Dose Expansion).
- Recording of concomitant medication(s)
- Record 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.
- Collection of archived tumor samples from eligible treated subjects within 4 weeks of Cycle 1 Day 1.
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards

7.4 Treatment Period – Cycle 1 Day 8

The following procedures and assessments will be performed **before** RX-3117 dosing on Cycle 1 Day 8, unless otherwise described:

- Collection of unused study drug
- Review subject study drug compliance
- Record 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.
- Weight
- Laboratory tests (for details see Appendix B)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Coagulation tests: PT, PTT or INR
- Collect a blood sample for pre-dosing pharmacokinetics.
- Collect blood samples for biomarker analysis.

- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards
- RX-3117 may be taken orally in the clinic or at home.

7.5 Treatment Period – Cycle 1 Day 15

7.5.1 Pre-dosing Assessments

The following procedures will be performed **before** RX-3117 dosing on Cycle 1 Day 15, unless otherwise described:

- Collection of unused study drug
- Review subject study drug compliance
- Record 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.
- Weight
- Laboratory tests within 3 days before dosing (for details see Appendix B)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Coagulation tests: PT, PTT or INR
- Collect blood sample for pre-dose pharmacokinetics (with recording of the date and actual clock time of blood collection.
- Collect blood samples for biomarker analysis
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes), and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).

7.5.2 Post-dosing Assessments – Cycle 1 Day 15

The following procedures will be performed **after** the administration of RX-3117 on Cycle 1 Day 15:

- The required order of assessments is vital signs before pharmacokinetic sampling when applicable.
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air) will be taken whenever a blood sample is collected for RX-3117 pharmacokinetics.
- Blood samples for RX-3117 pharmacokinetics will be collected (Phase 1 and Dose expansion):
    - At 0.5 hours ± 5 minutes, 1 hour ± 10 minutes, 2 hours ± 10 minutes, 3 hours ± 10 minutes, 4 hours ± 10 minutes, 6 hours ± 10 minutes and 8 hours ± 10 minutes, after the oral administration of RX-3117 on Cycle 1 Day 15.
- Collect a blood sample for biomarker analysis at approximately 4 hours ± 15 minutes, after the oral administration of RX-3117 on Cycle 1 Day 15 (Phase 1 and Dose expansion).
- Record 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.
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards
-

7.6 Treatment Period – Cycle 1 Day 22

- Collection of unused study drug
- Review subject study drug compliance
- 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.
- Laboratory tests (for details see Appendix B)
    - Hematology panel
    - Chemistry panel

- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).
- Tumor assessment to be performed between Days 22-28 of Cycle 1. Results of the assessments must be available before the start of the next cycle, including CT/MRI/PET as applicable. Some imaging assessments may be collected for a second review by a central imaging vendor.
- Blood sample for biomarker analysis will be taken around the time of the tumor assessment.
- Dispensing of study drug and instructions for dosing at home, if applicable.
- Dispensing of diary cards, if applicable.

7.7 Treatment Period – Cycles 2 - 8

For subjects receiving treatment beyond Cycle 1 the following procedures will be performed within 3 days **before** dosing on Day 1 of each new cycle, unless otherwise described.

- Collection of unused study drug
- Review subject study drug compliance
- Record 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.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).
- Laboratory tests (for details see Appendix B) on Day 1 and Day 15 of each cycle
    - Hematology panel
    - Chemistry panel
    - Tumor Marker, if applicable (Day 1)
- Tumor assessment, including CT/MRI/PET as applicable between Days 22 and 28 of Cycles 2, 3, 4, 6 and 8. Results of the assessment must be available and reviewed before dosing begins in the next cycle.

- Blood samples for biomarker analysis will be collected on Day 1 of each cycle and around the time of the tumor assessment.
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards

7.8 Treatment Period – ≥ Cycles 9

For subjects receiving treatment beyond Cycle 8 the following procedures will be performed within 3 days **before** dosing on Day 1 of each new cycle, unless otherwise described. Visit schedule deviations may be permitted following discussions with the sponsor.

- Collection of unused study drug
- Review subject study drug compliance
- Record 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.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).
- Laboratory tests (for details see Appendix B) on Day 1 of each cycle
    - Hematology panel
    - Chemistry panel
    - Tumor marker, if applicable
- Tumor Assessment(s) as applicable between Days 22 and 28 of each even numbered cycle before the Day 1 of the next odd numbered cycle. Results to be evaluated before dosing at the next odd numbered cycle. Some imaging assessments may be collected for a review by a central imaging vendor.
- Blood samples for biomarker analysis will be collected on Day 1 of each cycle and around the time of the tumor assessment.
- Dispensing of study drug and instructions for dosing at home
- Dispensing of diary cards

7.9 End of Treatment Visit or Early Termination

The following procedures will be performed unless otherwise described:

- Collect unused study drug
- Review subject study drug compliance
- Record 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.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).
- Laboratory tests (for details see Appendix B)
    - Hematology panel
    - Chemistry panel
    - Urinalysis
    - Coagulation tests: PT, PTT or INR
- Tumor assessment, including CT/MRI/PET as applicable. End of study tumor assessment (if the subject withdraws from the study for reasons other than tumor progression on a routine imaging/scan) should be performed if the last assessment was performed ≥ 4 weeks earlier. Some imaging assessments may be collected for a second review by a central imaging vendor.
- Blood sample for biomarker analysis will be taken around the time of the tumor assessment.

7.9.1 RX-3117 Dosing

RX-3117 will be administered orally, at the assigned dose, with the subject in a fasted state (i.e., ≥ 8 hours after a meal) with 100 to 200 mL (4 to 8 ounces) of water. Food may be taken ≥ 1 hour after the dose has been administered. The time of dosing must be documented.

On days when the subject is scheduled to come into the clinic, RX-3117 will be administered orally in the presence of site personnel, per the assigned dose and schedule. This is important for days when blood is collected for pharmacokinetic analysis

(i.e., Days 1, 8, and 15 of Cycle 1), on those days dosing will occur after that pre-dose pharmacokinetic sample is collected.

When subjects self-administer RX-3117 at home, RX-3117 will be taken orally at approximately the same time every day after fasting for a minimum of 8 hours and with approximately 4-8 ounces of water. Food may be taken approximately 1 hour after the dose has been administered.

7.10 Safety Follow-Up Visit

Subjects will undergo the safety follow-up visit approximately ~30 days (+ 7 days) after the subject receives their last dose of RX-3117.

The following procedures will be performed:

- Recording of concomitant medication(s), including any anticancer therapies administered subsequent to the administration of study drug
- 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.
- Weight
- ECOG performance status
- Resting vital signs: pulse, respiration rate and temperature measurements, blood pressure (i.e., after the subject has been seated for at least 5 minutes) and oxygen saturation (to be assessed by pulse oximetry while subject is breathing room air).
- Laboratory tests
    - Hematology panel
    - Chemistry panel
    - Tumor marker, if applicable
- Tumor assessment, including CT/MRI/PET as applicable. Subjects first meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a Safety Follow-up tumor assessment if the last assessment was performed ≥ 4 weeks, in order to confirm the response based on RECIST ver 1.1 criteria. Some imaging assessments may be collected for a second review by a central imaging vendor.
- Blood sample for biomarker analysis will be taken around the time of the tumor assessment, if applicable.

7.11 Unscheduled Visit(s)

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 the eCRF, as well as any other data obtained (e.g., adverse events, concomitant medications and treatments, and results from procedures or tests).

7.12 Tumor measurements

Radiographic tumor assessment(s) performed during the screening period will be used to prospectively identify all sites of disease present at the start of treatment. Subjects with symptoms suggestive of disease progression should be objectively evaluated for tumor progression.

On-study tumor assessment(s) will be performed by the investigator. Response and progression will be evaluate using modified RECIST ver 1.1 (see Appendix C) after cycles 1 through 4 (e.g, every 4 weeks) and every 8 weeks thereafter or upon early termination if an assessment has not been done in the previous 4 weeks. The results of the tumor assessment must be available before the beginning of the next cycle.

Radiographic tumor assessment(s) must include CT/MRI/PET of chest, abdomen, and pelvis, sufficient to evaluate major sites of disease. Throughout the study, the same method of assessment and the same technique should be used to characterize each identified and reported lesion at screening.

See Appendix C for detailed information on RECIST ver 1.1 to be used in this study. Some imaging assessments may be collected for a second review by a central imaging vendor.

8. Other Assessment(s)

8.1 Predictive and Pharmacodynamic Biomarker

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 treatment with RX-3117 and around the time of tumor assessments to measure biomarkers (e.g., including but not limited to including (but not limited to) concentrative nucleoside transporter (CNT) 2; equilibrative nucleoside transporter (ENT) 1; uridine-cytidine kinase (UCK) 1 and 2; DNA methyltransferase (DNMT) 1, 3a and 3b;, ribonucleotide reductases (RRM) 1 and 2) and RX-3117 incorporation into DNA/RNA.

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).

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

8.2 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-3117. 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 12.4 for subject confidentiality.

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Definitions

9.1.1 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 screening, study drug administration, or follow-up periods.
- Any injury or accident occurring during the screening, 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 9.7.2 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 eCRFs.

- 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.

9.1.2 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

9.2 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. Information regarding DLTs should be recorded on a protocol-designated DLT report form and faxed or emailed 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 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.

9.2.1 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.

9.3 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 9.1.2)
- The start date (date of adverse event onset)
- The stop date (date of adverse event resolution)
- The severity of the adverse event (see Section 9.4)
- A description of the potential relatedness of the adverse event to study drug or a study procedure (see Section 9.5)

- The action taken due to the adverse event
- The outcome of the adverse event

9.4 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 4.

Table 4. 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 9.1.2 above.

9.5 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 ECG) 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.

9.6 Adverse Event Reporting Requirements

9.6.1 Site Reporting Requirements

Classification of an event as serious or nonserious (see Section 9.1.2) determines the reporting procedures to be followed by the site.

Site reporting requirements for adverse events are summarized in Table 5 below.

Table 5. Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Fax or email report on 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 CRF submission procedure	Record and submit information on appropriate CRFs
Nonserious	Per CRF submission procedure	Record and submit information on appropriate CRFs

a See Operations Manual for study contact information
Abbreviations: CRF=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 are provided in the Operations Manual.

9.6.2 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 9.5). For reporting purposes, an adverse event will be considered expected if the study sponsor determines that the event is expected (see Section 9.2).

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 6.

Table 6. 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-3117 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.

9.7 Special Situation Reporting Requirements

9.7.1 Definitions of Special Situations

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

- Information regarding pregnancy is provided in Section 9.7.2.
- 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 11.7). 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.

9.7.2 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 report 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 9.6.1).

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.

9.7.3 Instructions for Reporting Special Situations

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.

Along with information regarding the circumstances of the special situation, any clinical sequelae occurring in association with that situation should be reported as adverse

events or serious adverse events according to the reporting requirements for those events (see Section 9.6). Details of signs or symptoms, clinical management and outcome should be reported, if available defined in this protocol but may be serious adverse events if they meet one or more of the criteria for a serious adverse events (see Section 9.1.2). 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 9.6.1). Recording of a DLT in the relevant CRFs will also be required.

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints

10.1.1 Primary Endpoints – Phase 1

- Overall safety profile characterized by the type, frequency, severity, timing of onset, duration, and relationship to study therapy of any adverse events, or abnormalities of laboratory tests or ECGs

- Enumeration and description of any dose-limiting toxicities (DLTs) occurring during Cycle 1, serious adverse events, or adverse events leading to discontinuation of study treatment

10.1.2 Secondary Endpoints – Phase 1

- Pharmacokinetic parameters (e.g., T_{max}, C_{max}, C_{trough}, AUC) for RX-3117 based on blood sampling performed at initiation of RX-3117 dosing (Day 1) and at steady state (Day 15)

- Indices of anti-tumor activity including:

    - Overall response rate (ORR) – defined as the proportion of subjects who achieve a complete response (CR) or partial response (PR)

    - Time to response (TTR) – defined as the interval from start of study therapy to the first documentation of CR or PR

    - Duration of response (DOR) – defined as the interval from the first documentation of CR or PR to the earlier of the first

documentation of definitive disease progression or death from any cause

- Progression-free survival (PFS) – defined as the interval from the start of study therapy to the earlier of the first documentation of disease progression or death from any cause

10.1.3 Exploratory Endpoints – Phase 1

Biomarker expression/concentration in tumor and blood samples including but not limited to concentrative nucleoside transporter (CNT) 2; equilibrative nucleoside transporter (ENT) 1; uridine-cytidine kinase (UCK) 1 and 2; DNA methyltransferase (DNMT) 1, 3a and 3b; ribonucleotide reductases (RRM) 1 and 2 and RX-3117 incorporation into DNA/RNA.

10.1.4 Primary endpoint – Phase 2

- The primary endpoint is a 20% (2 out of 10 subjects) or higher rate of progression free survival (PFS) benefit (i.e., proportion of subjects with stable disease for at least 4 months) and/or a 10% (1 of 10 subjects) partial response rate or better for each disease indication. This study is not intended to demonstrate differences in treatment outcomes between indications.

10.1.5 Secondary endpoints – Phase 2

- The secondary efficacy parameters include overall response rate, time to progression and duration of response.

  TTP and DOR will be analyzed using standard survival analysis techniques based on the Kaplan-Meier life test method.

  ORR will be tabulated by response marker status for each disease indication, if applicable. Point estimates as well as 95% confidence intervals will be presented.

The efficacy endpoints analyzed for this study will include a progression free survival benefit and measures of disease response (complete response [CR] plus partial response [PR] according to RECIST ver 1.1). For metastatic pancreatic cancer or advanced bladder cancer, the portion of subjects with a 5% or more reduction in target lesions or stable disease for at least 4 months as well as other indicators of clinical benefit including subject reported assessments and other markers of clinical benefit

including tumor markers (CA 19-9 for pancreatic cancer) will also be considered in the response evaluation. When reductions in tumor size, do not qualify as at least a partial response defined by RECIST ver 1.1, those data will be evaluated further by disease specific key opinion leaders.

- Concentration of RX-3117 and its metabolites pre-dose

10.1.6 Exploratory endpoints – Phase 2

- Biochemical levels of drug targets in blood and tumor samples
- Changes in tumor burden

10.2 Analysis Conventions

10.2.1 Analysis Sets

10.2.1.1 Full Analysis Set

The full-analysis set includes all subjects who receive $\geq$ 1 dose of RX-3117. This analysis set will be used in the analyses of subject characteristics, study drug treatment administration, safety (including first-cycle DLTs), overall response rate, and progression free survival.

10.2.1.2 Responding Analysis Set

The responding analysis set includes subjects in the full-analysis set who have measurable tumor, who can be evaluated for tumor response with both baseline and on-study tumor evaluations, and who achieve a complete response or partial response. This analysis set will be used in the analyses of time to response and duration of response.

10.2.1.3 Evaluable Analysis Sets

The evaluable analysis sets include subjects in the full-analysis set who have baseline and on-study measurements to provide interpretable results for specific parameters of interest.

These analysis sets will be used in the analyses of RX-3117 plasma pharmacokinetics, and changes in biomarkers.

10.3 Sample Size Considerations

The sample size calculation for this study has been empirically set. Approximately 40 subjects will be recruited in Phase 1 portion of this trial. During Phase 1 study, dose escalation will be conducted according to a modified dose escalation rule, with potentially 1 subject only per dose and frequency until the appearance of a related grade 2 or greater adverse event or the investigator, medical monitor and sponsor requesting that additional subjects be treated at a dose and/or schedule.

The Dose Expansion of Phase 1 will enroll approximately 12 subjects at the recommended Phase 2 dose or MTD and schedule.

For the Phase 2 portion of the study, the primary objective is to estimate the antitumor activity of RX-3117 in subjects with advanced solid malignancies.

The maximum number of subjects needed for Phase 2 is approximately 100 (50 per solid tumor). An estimated 20 subjects (10 per indication) will be enrolled in the first stage at the recommended Phase 2 dose from the Phase 1 portion. Those dose expansion subjects who have measurable disease at baseline and at least 1 post-baseline response assessment may be included in Stage 1 of the Phase2 if the disease type is one of those to be studied in Phase 2. The goal is the observation of at least 2 subjects with progression free survival for at least 4 months and/or 1 objective clinical response in a specific tumor indication in order for evaluation of that indication to advance to Stage 2.

In Stage 2, the goal is to further evaluate primary and secondary endpoints, of efficacy. The number of subjects to be enrolled in the second stage will be approximately 80 (40 per solid tumor indication).

10.4 Randomization and Stratification

Randomization will not be used in this study. In the Phase 2 part of the study, subjects will be enrolled in a disease group based on their cancer diagnosis. No stratification is planned for this study.

10.5 Interim Analysis and Early Stopping Guidelines

The interim analyses that are planned to be conducted in the Phase 1 are related to the review of available data during the dose escalation phase of the study. The decision to escalate to the next dose level and schedule will be made after the evaluation of safety

data through at least 28 days of the first cycle of the current dose level. Each review will be conducted by the investigators, medical monitor and sponsor.

The interim analysis in Stage 1 of the Phase 2 will be performed when the first 10 subjects have been treated at the recommended Phase 2 dose and schedule, are evaluable for response, have the opportunity to complete up to 4 cycles of therapy or have discontinued therapy before 4 cycles. If 2 responders are observed out of the initial 10 evaluable subjects in one of the specific cancer indication, subject enrollment will continue in that indication.

For the Phase 2, an interim analysis for futility stopping may be conducted to determine whether continuation until study completion is warranted. The investigator-assessed response rate will be used as the endpoint for the interim analysis. Although response evaluations are repeated after every cycle for the first 4 cycles and then every 2 cycles thereafter, all available response data will be included in the interim analysis, a subject can be considered a responder with or without available confirmatory imaging. Each of the 2 major indications enrolled in the Phase 2 portion will be evaluated independently, and could be subject to enrollment hold by individual indication.

The number of subjects to be enrolled in the second stage will be determined as outlined in Section 10.3.

10.5.1 Data Handling Conventions

10.5.1.1 General Methods

By-subject listings will be created for important variables from each eCRF module. Summary tables for continuous variables will contain the following statistics: N (number in population), n (number with data), mean, standard deviation, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include: N, n, percentage, and 95% confidence intervals on the percentage. Unless otherwise indicated, 95% confidence intervals for binary variables will be calculated using the binomial distribution (exact method) and will be 2-sided. Data will be described and summarized by analysis set, dose level, dose schedule and timepoint. As appropriate, changes from baseline to each subsequent timepoint will be described and summarized. Similarly, as appropriate, the best change from baseline during the study will also be described and summarized. Graphical techniques (e.g.,

waterfall plots, Kaplan-Meier curves, line plots) may be used when such methods are appropriate and informative.

The baseline value used in each analysis will be the last (most recent) pre-treatment value. Data from all sites will be pooled for all analyses. Analyses will be based upon the observed data unless methods for handling missing data are specified. If there is a significant degree of non-normality, analyses may be performed on log-transformed data or nonparametric tests may be applied, as appropriate.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

10.5.1.2 Calculation of Pharmacokinetic Variables

Pharmacokinetic parameters for RX-3117 will be calculated using non-compartmental methods. Only plasma concentrations greater than or equal to the validated lower limit of quantitation (LLQ) will be used in the pharmacokinetic analyses. Actual blood sampling times will be used in all pharmacokinetic analyses. Per-protocol times will be used to calculate mean plasma concentrations for graphical displays.

The C_{max} and T_{max} will be taken directly from the subject's data. The elimination rate constant, λz, will be calculated as the negative of the slope of the terminal log-linear segment of the plasma concentration-time curve. The range of data to be used for each subject and treatment will be determined by visual inspection of a semi-logarithmic plot of concentration versus time and will comprise ≥ 3 data points along the elimination phase. Elimination $t_{½}$ will be calculated according to the following equation:

$$t½ = \frac{0.693}{\lambda z}$$

The AUC to the final sample with a concentration ≥LLQ ($AUC_{0\text{-}t}$) will be calculated using the linear trapezoidal method and extrapolated to infinity (AUC_{∞}) using:

$$AUC_{\inf} = AUC_{0-t} + \frac{C_{tf}}{\lambda z}$$

where C_{tf} is the final concentration >LOQ.

Oral clearance (CL/F) and volume of distribution (Vz/F) will be calculated according to

$$CL/F = \frac{Dose}{AUC} \text{ and } Vz/F = \frac{Dose}{\lambda z \times AUC}$$

respectively, where AUC represents AUC_{∞}.

10.5.1.3 Calculation of Tumor Control Variables

Tumor control assessments will be based on the standardized RECIST ver 1.1, as specifically modified for this study (see Appendix C). Tumor control will be documented at each assessment by response category (e.g., CR, PR, SD, PD) as defined for each response parameter, tumor dimension values, percentage change in tumor dimension values from baseline or nadir, date that response is first documented, date that response is confirmed, and date of disease progression.

For time-to-event endpoints, only events occurring ≤ 30 days following the permanent discontinuation of study treatment will be considered as events; for subjects with events occurring > 30 days following the permanent discontinuation of study treatment, the data will be censored. The following censoring conventions will be applied:

- Duration of Response (DOR): Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of tumor progression was objectively documented while on study treatment.

- Progression Free Survival (PFS): Data from surviving, non-progressing subjects will be censored at the earliest of the time of initiation of antitumor treatment other than the study treatment or the last time that lack of tumor progression was objectively documented while on study treatment.

10.6 Analysis Plan

10.6.1 Subject Disposition and Baseline Characteristics

A listing of all full-analysis subjects will be generated to describe site, subject number, first screening date, first treatment date, dose level, dosing schedule, the longest duration of study drug treatment, and the reason for discontinuing study treatment. Available information on subjects who were screened or enrolled but not treated may be listed separately. A table will be created summarizing these categories in terms of number and percent for the full-analysis set.

Subject baseline characteristics (e.g., demographic, disease-related, and prior-treatment-variables) will be listed and summarized by dose level and schedule for the full-analysis set.

10.6.2 Exposure and Safety Analyses

10.6.2.1 Treatment Administration and Study Drug Compliance

Descriptive information will be provided regarding the number of doses of study therapy prescribed, the total number of doses taken, the percent of expected doses taken, the duration of treatment, and the number and timing of prescribed dose reductions, dose interruptions, and dose re-escalations.

RX-3117 compliance will be described in terms of the proportion of study drug actually taken based on subject diaries and returned capsule counts relative to the amount that was dispensed (accounting for physician-prescribed reductions and interruptions).

10.6.2.2 RX-3117 Pharmacokinetics

Plasma concentrations and derived pharmacokinetic parameters (see Section 10.2.2.2) will be listed and graphs of individual subject concentrations by visit will be presented on linear and semi-logarithmic axes. Pharmacokinetic data will be summarized by visit using graphical and tabular methods considering stage, dose level and schedule. The data may be evaluated by baseline variables such as sex, weight, body-mass index, age, and cancer type.

The relationship between the parameters C_{max}, AUC_{inf}, and AUC_{0-24} and dose will be examined using the power model, i.e.,

$$P = a \times Dose^{b}$$

where P represents the parameter and *a* and *b* are constants. A value of *b* of approximately 1 indicates linear pharmacokinetics.

As appropriate, data regarding plasma concentrations and pharmacokinetics parameters for major and/or active metabolites in retained plasma samples will be described.

10.6.2.3 Prior, Concomitant, and Post-Treatment Medication Use

Prior, concomitant, and post-treatment medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) dictionary into Anatomical-Therapeutic-Chemical classification (ATC) codes.

Descriptions of prior medication use will be focused on drugs and regimens used as treatments for cancer. As appropriate and if available, information on the sequencing, and type of prior regimens will be collected.

The type and timing of use of concomitant medications will be listed and summarized. Information regarding the type and use of specific supportive medications (e.g., antiemetics, antidiarrheals, hematopoietic growth factors, corticosteroids) during study treatment will be described.

10.6.2.4 Adverse Events

All adverse events will be listed. The focus of adverse event summarization will be on treatment-emergent adverse events. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period from the first dose of study treatment to 30 days after the last dose of study treatment. Adverse events that occur before the first dose of study treatment or > 30 days after the subject has been discontinued from study treatment will be included in data listings.

Adverse events will be classified using MedDRA (http://www.meddramsso.com) with descriptions by System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 4.03 (*http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf*), whenever possible. If a CTCAE criterion does not exist for a specific type of adverse event, the grade corresponding to the appropriate adjective will be used by the investigator to describe the maximum intensity of the adverse event: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life threatening), or Grade 5 (fatal). The relationship of the adverse event to the study drug will be categorized as related or unrelated.

Treatment-emergent adverse events will be summarized. Summary tables will be presented to show the number of subjects reporting treatment-emergent adverse events

by severity grade and corresponding percentages. A subject who reports multiple treatment-emergent adverse events within the same Preferred Term (or System Organ Class) is counted only once for that Preferred Term (or System Organ Class) using the worst severity grade. Adverse event descriptions will be presented in alphabetical order of System Organ Class, then by decreasing frequency in the "overall" column for a given Preferred Term.

Separate listings and summaries will be prepared for the following types of treatment-emergent adverse events:

- Dose-limiting adverse events occurring in Cycle 1 of therapy
- Study-drug-related adverse events
- Adverse events that are Grade $\geq$ 3 in severity
- Adverse events leading to study drug interruption and/or dose modification
- Adverse events leading to study drug discontinuation
- Serious adverse events (with categorization of the primary reason that the adverse event is considered serious, e.g., death, hospitalization, etc)

10.6.2.5 Laboratory Evaluations

All laboratory data will be listed. Summaries of laboratory data will be based on observed data and will be reported using conventional units. The focus of laboratory data summarization will be on treatment-emergent laboratory abnormalities. A treatment-emergent laboratory abnormality is defined as an abnormality that, compared to baseline, worsens by $\geq$ 1 grade in the period from the first dose of study treatment to 30 days after the last dose of study treatment. If baseline data are missing, then any graded abnormality (i.e., an abnormality that is Grade $\geq$ 1 in severity) will be considered treatment-emergent. Laboratory abnormalities that occur before the first dose of study treatment or > 30 days after the subject has been discontinued from study treatment will be included in data listings.

Hematological, serum biochemistry, and urine data will be programmatically graded according to CTCAE severity grade, when applicable. For parameters for which a CTCAE scale does not exist, reference ranges from the local laboratory will be used to

determine programmatically if a laboratory parameter is below, within, or above the normal range for the subject's age, sex, etc.

Hematological and serum biochemistry and their changes from baseline will be summarized. Summary tables will be presented for each relevant assay to show the number of subjects by CTCAE severity grade with corresponding percentages. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during a period of interest (e.g., during the study or from baseline to a particular visit).

Shift tables for hematology and serum biochemistry will also be presented by showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each visit (normal, low and high [or abnormal]). Tables will be prepared to show frequencies adjusted for baseline values; for this frequency, subjects with the same or worse toxicity grade at baseline are not considered.

Separate listings and summaries will be prepared for laboratory abnormalities that are Grade $\geq$ 3 in severity.

10.6.2.6 Electrocardiography

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and corrected QT [QTc] interval) at each time recorded as well as the change from screening will be listed and summarized. These parameters will be determined electronically by the ECG machine at the clinical site. The QT interval will be corrected by the Fridericia methods as follows:

- Fridericia: $QTcF = QT/(RR)^{1/3}$

The overall ECG assessment will be reported as "Normal" or "Abnormal" with respect to relevant abnormalities by the investigator. A shift table comparing the ECG assessment over the study drug administration period to screening will be presented.

The QTc data obtained by using the Fridericia corrections will be categorized separately into the following classifications and summarized by time after study drug dosing:

- QTc interval > 450 msec and ≤ 480 msec
- QTc interval > 480 msec and ≤ 500 msec
- QTc interval > 500 msec

The change of the QTc values obtained by using the Fridericia's correction will also be categorized separately as follows:

- QTc interval increases from baseline by > 30 msec and ≤ 60 msec
- QTc interval increases from baseline by > 60 msec

QTc data will be presented in shift tables consistent with these categories.

10.6.2.7 Oxygen Saturation Values

All oxygen saturation data will be listed. Summaries of oxygen saturation data will be based on observed data and will be reported as percent (%) saturation. Data and changes from baseline will be summarized. Summary tables will be presented for values below 92% and for declines from baseline of ≥ 5% to show the number of subjects with corresponding percentages. Subjects will be characterized only once for each of these categorizations, based on their lowest value observed during a period of interest (e.g., during the study or from baseline to a particular visit).

10.6.2.8 Other Safety Variables

Vital signs, weight, and performance status data will be appropriately described.

10.6.3 Efficacy Analyses

10.6.3.1 Categorical Endpoints

As appropriate depending up the level of activity and the numbers of patients with individual tumor types that are accrued, ORR, CR and PR rates may be determined and described. In the analyses of ORR, subjects who do not have sufficient baseline or on-study tumor assessment to characterize response will be counted as failures. For all analyses, the corresponding 95% confidence intervals will be presented.

10.6.3.2 Time-to-Event Tumor Control and Survival Endpoints

Time to response, duration of response, and progression free survival will be described in the appropriate analysis set using Kaplan-Meier methods. Medians, ranges, and

corresponding 95% confidence intervals (as calculated using a Cox proportional hazards regression model) will be presented.

10.6.3.3 Continuous Endpoints

Changes in tumor dimension values will be assessed using analysis of covariance (ANCOVA) with baseline values as covariates; in these analyses, both changes from baseline to each subsequent timepoint and best overall on-study changes will be evaluated. Means and standard errors will be presented.

10.6.4 Other Analyses

Data explorations may be performed to evaluate potential associations among subject characteristics, biomarkers, RX-3117 dose, RX-3117 schedule and outcome measures. Explorations may also be performed to assess the potential associations between different outcomes measures (e.g., relationships between pharmacokinetic parameters, biomarkers and adverse event changes in tumor dimensions).

10.7 Statistical Basis for the Dose Escalation Paradigm

In this dose-escalation trial designed to determine an MTD for RX-3117, the sample size for the study is not based on a formal statistical hypothesis but will be determined based on the observed number of first-cycle DLTs at each dose level and its schedule.

To accelerate the early dose escalation and avoid treating excessive numbers of patients with innocuous but ineffective dose levels of RX-3117, the dose escalation will be performed initially with a single patient at each dose level. After the occurrence of at least one Grade $\geq$ 2 adverse event that is considered related to RX-3117, the study will transition to a standard 3 + 3 design in which 3 to 6 subjects will be treated at each of the proposed RX-3117 dose levels and schedules. Based on the planned 3+3 dose-escalation scheme, Table 7 shows the probability of escalating to the next dose level based on the true rate of DLT at the current dose level.

Table 7: Probability of Dose Escalation (N=3+3)	
True Incidence of DLT	**Probability of Escalating**
10%	0.91
20%	0.71
30%	0.49
40%	0.31
50%	0.17
60%	0.08

Abbreviation: DLT=dose-limiting toxicity

Thus, if the true underlying proportion of DLT is low (e.g., ≤ 10% at the current dose level, there is a high probability (≥ 0.91) of dose escalation to the next dose level. Conversely, if the true underlying proportion of DLT is high (e.g., ≥ 60%) at the current dose level, there is a low probability (≤ 0.08) of escalation to the next dose level.

The trial employs the standard NCI definition of MTD (starting dose associated with DLT in < 33.3% of subjects during the first cycle of therapy).

10.8 Timing of Analyses

10.8.1 Interim Analyses

No formal interim analyses are planned in this Phase 1 trial. The sponsor study team (or a specially delegated committee of expert clinicians) and the investigators will collectively discuss study conduct and accumulating safety and other data through teleconferences. It is expected that these discussions will be scheduled at intervals of ~4 weeks unless accrual to the study and the need for decisions regarding dose escalation or stage progression indicate the need for more frequent or less frequent reviews.

10.8.2 Final Analysis

Final study reporting is expected to occur after all subjects have discontinued study treatment and completed the safety follow up visit or 24 weeks after accrual of the final subject. Addenda to the study report may be created to account for subjects still on study at the time of the major analysis of the study.

11. INVESTIGATIONAL PRODUCT

11.1 RX-3117

RX-3117 will be provided as 30-mg, 100-mg, 200 mg and 500 mg capsules intended for oral administration. The capsules contain approximately 32 mg, 107 mg, 215-mg or 540 mg, respectively, of RX-3117 monohydrate with the additional mass above the nominal respective values of 30, 100, 200 or 500 mg accounting for the water of hydration. RX-3117 capsules are filled only with the active pharmaceutical ingredient (API). No other excipients are contained in the formulation.

The capsules will be a hard gelatin hydroxypropylmethyl cellulose capsule. The 30-mg dosage form will be contained in a Size 4 white/yellow capsule, the 100-mg dosage form will be contained in a Size 2 white/white capsule, the 200 mg capsule will be contained in a Size 2 Swedish orange and the 500 mg will be contained in a Size 00 clear capsule.

11.2 Packaging and Labelling

The drug product will be packaged in white, high-density polyethylene (HDPE) bottles with a child-resistant closure and an induction seal. Bottles will contain either 16 capsules of 1 of the relevant dose strengths (30 mg or 100 mg) or 10 capsules of 1 of the relevant dose strengths (200 mg or 500 mg).

All labels for study drug bottles 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.

11.3 Storage and Handling

Bottles containing tablets of RX-3117 should be stored at a controlled refrigerated temperature of 2-8^{o}C (i.e., 36-46^{o} F).

11.4 Source

RX-3117 will be supplied without charge by Rexahn Pharmaceuticals, Inc.

11.5 Dispensing

The site personnel (e.g., pharmacist or other qualified person) will be responsible for dispensing RX-3117. It is planned that the study drug will be dispensed at 1-week intervals during Cycle 1 of treatment and at 4-week intervals thereafter.

The clinic pharmacist or an alternative qualified person will provide each subject with directions regarding drug storage and instructions regarding how many of each size/color of capsule to use at each dosing. The subject number, subject initials, dose assigned, and number of capsules to be taken will be written on the bottle label by site personnel.

11.6 Procedures for Monitoring Subject Compliance

Each study site will be responsible for monitoring subject compliance through subject interviews and counting of unused study drug capsules.

At the time of study drug dispensing, the site personnel will show subjects how to complete a subject diary card with a record of the number of capsules of RX-3117 that they have taken daily at home and how to record any problems with drug administration or reasons for noncompliance. Site personnel will instruct subjects that they must bring the diary card back after each study visit. The site personnel will need to evaluate subjects' diary cards for completeness after each dispensing interval.

In addition, subjects should be instructed to return all bottles (used or unused) and any unused study medication to the study site at the end of each dispensing interval. The quantity of RX-3117 and the date when it is returned by the subject should be recorded in the study drug accountability records. All RX-3117 returned by the subject should be retained for review by the study site monitor prior to return to the study sponsor or destruction.

If it is determined that a subject is substantially noncompliant with the study protocol in circumstances that increase risk or substantially compromise the interpretation of study results, the investigator and the sponsor should determine whether the subject should be withdrawn from study treatment. If the subject is withdrawn for noncompliance, the institutional review board should be notified.

11.7 Drug Accountability

The disposition of all RX-3117 should be documented from the time of receipt at the site through dispensing to study subjects, drug return, or drug destruction. All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

Study personnel must ensure that all study drug is kept in a secure locked area with access limited to authorized personnel. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics, or allow the study drug to be used other than as directed by this protocol.

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by the study sponsor or its designee, including, but not limited to: the date received, lot number, amount received, condition of the study drug, and the disposition of all study drug. Study drug accountability records must also be maintained that include the subject number to whom the study drug was dispensed; the date, quantity and lot number of the study drug dispensed; and the identity of the person dispensing the medication.

Depending upon the decision of the study sponsor, remaining unused study drug supply will be returned to the study sponsor or its designee after the study is completed or will be discarded or destroyed at the clinical site. Drug may be returned or destroyed on an ongoing basis during the study if appropriate. If the study drug is discarded or destroyed at the clinical site, standard institutional policy should be followed. Records documenting the date of study drug return or destruction, relevant lot numbers, and the amount returned or destroyed should be maintained.

11.8 Overdose Precautions

There is limited prior clinical experience with RX-3117. Administration of very high single IV doses of RX-3117 to monkeys induced convulsions, tremors, and lack of coordination. Myelotoxicity is a known dose-dependent consequence of anti-metabolite administration.

In this protocol, an overdose is defined as administration of more than the prescribed daily dose of RX-3117. In a subject who experiences an overdose, consideration should be given as to whether RX-3117 administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and hematological parameters should be followed closely (consistent with the protocol or

more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated.

The study sponsor should be contacted if a study drug overdose occurs. Cases of study drug overdose will result in specific reporting requirements (see Section 9.6.1).

11.9 Inadvertent Exposure and Spill Precautions

Based on available data from nonclinical studies, RX-3117 may be acutely toxic and genotoxic. It is not anticipated that the study drug would be irritative at levels that are likely to result from inadvertent exposure to the contents of broken capsules.

Personnel handling the drug should use reasonable precautions to avoid ingestion of the study drug product or eye contact, skin contact, or inhalation of the study drug substance. Study subjects should be strongly advised to store the drug appropriately, keep the drug in a secure place out of the reach of children and to avoid mixing study drug capsules with other medications.

For further information regarding inadvertent exposure and spill precautions, please consult the RX-3117 investigator brochure.

12. REGULATORY OBLIGATIONS

12.1 Informed Consent

An initial generic informed consent form will be provided to the investigator for preparing the informed consent document to be used at his or her site. Updates to the template will be communicated in writing from the sponsor or designee to the investigator. The written informed consent document should be prepared in the language(s) of the potential subject population.

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 products are administered.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician 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). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or legally acceptable representative

12.2 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 institutional review board for written approval. A copy of the written approval of the protocol and informed consent form must be received by the sponsor before recruitment of subjects into the study and shipment of investigational product.

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

The investigator will be responsible for obtaining annual institutional review board approval/renewal throughout the duration of the study. Copies of the investigator's reports and the institutional review board continuance of approval must be sent to the sponsor or designee.

12.3 Prestudy Documentation Requirements

The investigator is responsible for forwarding the following documents to the sponsor or designee for review before study initiation 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 institutional review board approval of the protocol, consent form, and subject information sheet
- Up-to-date curricula vitae of principal investigator and all sub-investigators
- Institutional review board 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 Food and Drug Administration (FDA) form 1572
- Financial disclosure document

12.4 Subject Confidentiality

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

In compliance with Federal regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the institutional review board 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.

12.5 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 the sponsor, 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

13. ADMINISTRATIVE AND LEGAL OBLIGATIONS

13.1 Protocol Amendments and Study Termination

Protocol amendments, except where necessary to eliminate an immediate hazard to subjects, must be made only with the prior approval of the sponsor. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The institutional review board must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the institutional review board to Rexahn.

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

13.2 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 electronic case report forms will be included on the sponsor's Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's electronic case report form 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 the sponsor and/or applicable regulatory authorities. Elements should include:

- Subject files containing completed electronic case report forms, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, investigator's brochure, copies of prestudy documentation (see Section 12.3), and all correspondence to and from the institutional review board and the sponsor

- 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 electronic case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the sponsor 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 the sponsor in writing of the new responsible person and/or the new location.

13.3 Study Monitoring and Data Collection

The sponsor's 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., electronic case report forms and other pertinent data) provided that subject confidentiality is respected.

The sponsor's monitor is responsible for verifying the electronic case report forms at regular intervals approximately every 4 to 6 weeks or more frequently if needed 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 electronic case report forms.

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 electronic case report forms, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by sponsor or its designee. 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.

To ensure the quality of clinical data across all subjects and sites, a data management review will be performed on subject data received at the sponsor or designee. During

this review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and good clinical practice. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications will be sent to the site for completion and returned to the sponsor or designee.

The principal investigator will electronically sign and date the indicated places on the electronic case report form. These signatures will indicate that the principal investigator inspected or reviewed the data on the electronic case report form, the data queries, and the site notifications, and agrees with the content.

13.4 Language

All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

13.5 Publication Policy

To coordinate dissemination of data from this study, the sponsor encourages the formation of a publication committee consisting of several principal investigators and appropriate sponsor staff. The committee is expected to solicit input and assistance from other investigators and the sponsor staff as appropriate. Membership on the committee (both for investigators and the sponsor's staff) does not guarantee authorship—the criteria described below should be met for every publication.

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 the sponsor for corporate review. The Clinical Study Agreement among the institution, principal investigator, and the sponsor will detail the procedures for, and timing of, the sponsor's review of publications.

13.6 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.

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15. APPENDICES

Appendix A. Schedule of Assessments

	SCR[a]	Cycle 1				Cycles 2-6	≥Cycle 8	EOT/ ET	SFU[c]
Procedures and Treatments Day	-14	1	8[b]	15	22[b]	1[c]	1		
Informed consent	X								
Medical, surgical, cancer and psychiatric histories	X								
Prior medication usage[d]	X	X[e]							
Eligibility review, enrollment	X	X[f]							
Pregnancy test	X[g]	X[g]							
Physical examination including height	X								
Weight	X	X	X	X		X	X	X	X
ECOG performance status	X	X				X	X	X	X
Tumor biopsy samples (optional)[h]		X							
Hematology and serum chemistry	X	X[i]	X	X	X	X[j]	X	X	X
Coagulation profile and Urinalysis	X	X[i]	X	X				X	
Vital sign measurements[k,l]	X	X	X	X	X	X		X	X
12-lead electrocardiogram[k,m]	X[a]	X							
Pharmacokinetic sampling[k,n]		X[n]	X[n]	X[n]					
Study drug administration - 3 times per week[o,p]		X	X	X		X	X		
Study drug administration - 5 times per week[o,q]		X	X	X		X	X		
Dispensing of study drug[r]		X[r]	X[r]	X[sr]	X	X[r]	X		
Unused study drug collection & subject compliance			X		X	X	X	X	
Tumor assessment(s)[s]	X[a]				X[t]	X[t]	X[t]	X[t]	X[u]
Tumor Marker, if applicable	X	X[i]				X	X	X	
Adverse event assessment[v]		X	X	X	X	X	X	X	X
Concomitant med review		X	X	X	X	X	X	X	X
Archived tumor tissue[w]		X							
Biomarker blood sample		X[x]	X[x]	X[x]	X[y]	X[y]	X[y]	X[y]	X[y]

ECOG = Eastern Cooperative Oncology Group; ET = Early Termination; EOT = End of Treatment; SFU = Safety Follow up; SCR = Screening

Footnotes for Schedule of Assessments

a Screening procedures will be performed within 14 days of Cycle 1 Day 1, except baseline tumor assessment, which can be evaluated within 21 days of Cycle 1 Day 1. ECG must be done within 7 days of enrollment.
b The Cycle 1 Day 8 and Day 22 visits may occur on Days 8 or 22 (+1 day).
c Safety follow-up visit will be between 30 and 37 days after the last dose of study drug.
d Medications taken within 28 days Cycle 1 Day 1.
e Review prior medication usage for any medications started since the screening visit.
f Confirm that the subject is still is eligible for enrollment in the study.
g A serum pregnancy test will be performed at screening (for women of childbearing potential). A serum pregnancy test or urine pregnancy test will be performed at baseline (day 1 of cycle 1) unless the screening serum pregnancy test was performed within 72 hours of dosing on Cycle 1 Day 1.
h Tumor biopsies will be taken following enrollment but before first dose of study treatment (optional)
i 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.
j Hematology and chemistry will be assessed on Days 1 and 15 in Cycles 2 through 8 and Day 1 for Cycles > 8.
k The required order of assessments is ECG, followed by vital signs and then PK sampling when applicable
l Vital signs measurements will include resting blood pressure, pulse, respiratory rate, pulse oximetry, and temperature.
m ECG to be assessed pre dose, 1, 2, 4, 6, and 8 hours after RX-3117 oral administration on Cycle 1 Day 1 (Phase 1 and Dose Expansion).
n Pharmacokinetic (PK) samples will be collected pre-dose and 0.5, 1, 2, 3, 4, 6 and 8 hours after oral administration on Days 1 and 15 in Cycle 1 for Phase 1 and Dose Expansion. PK will be collected pre-dose only in Cycle 1 on Days 1, 8 and 15 in Phase 2.
o Orally after having fasted for a minimum of 8 hours.
p Administered 3 times per week (preferably Monday, Wednesday and Friday) followed by 2 days off each week for 3 weeks then 1 week off. If a dose is administered on the same day as PK sampling, the PK sample will be collected first.
q Administered for 5 consecutive days followed by 2 days off per week for 3 weeks then 1 week off. If a dose is administered on the same day as PK sampling, the PK sample will be collected first.

r Study drug and diary cards will be dispensed at 1 week intervals during Cycle 1 and at least once every cycle thereafter.
s Tumor assessments will be evaluated using RECIST v1.1 between Days 22-28 of cycles. The results of the assessments must be available before the start of the next cycle. Depending on the tumor type, specific assessments may include CT (preferred for lung lesions) or MRI scans and any other appropriate radiographic or scintigraphic procedures and/or physical examinations. The method of assessment for an individual tumor or lesion that was used at baseline must be used consistently throughout the study and follow-up visit.
tu Tumor evaluation, including CT/MRI/PET will be performed between Days 22-28 of cycles. The results of the assessments must be available before the start of the next cycle. For subjects who end treatment on a cycle for which response assessments are not planned (i.e., cycle 5 or 7) and if an assessment has not been done in the previous 4 weeks.

uv Subjects meeting criteria for complete response or partial response at the last on-treatment tumor assessment should have a Safety Follow-up tumor assessment if the last assessment was performed ≥ 4 weeks, to confirm the response based upon RECIST.
vw Adverse events include all worsening of pre-existing conditions from the time the subject receives study treatment. All adverse events attributed to study drug will be assessed until resolved or returned to baseline.
wx To be collected within 4 weeks after enrollment
xy Biomarker samples will be collected pre-dose on Days 1, 8 and 15 of Cycle 1 and also post-dose at 4 hours ± 15 minutes on Day 1 and Day 15 of Cycle 1 during Phase 1 and the Dose Expansion.
yz Biomarker samples will be collected pre-dose on Day 1 of Cycle n, and when tumor assessments are done.

Appendix B. Analytes

Chemistry	Urinalysis	Hematology	Other Labs
Sodium	Specific gravity	RBC	Urine β-HCG
Potassium	pH	Hemoglobin	Serum β-HCG
Chloride	Hemoglobin	ANC	PT; PTT or INR
Bicarbonate	Protein	Platelets	PK
Magnesium	Glucose	WBC	Blood samples for RX-3117 and its metabolites concentration
Calcium	Bilirubin	Differential	
BUN	Ketones	• Eosinophils	
Serum Creatinine	WBC	• Basophils	Blood samples for biomarkers
AST (SGOT)	RBC	• Lymphocytes	Tumor Marker, if applicable
ALT (SGPT)	Epithelial cells	• Neutrophils	
Alkaline phosphatase	Bacteria	• Monocytes	
Lactate dehydrogenase			
Total bilirubin			
Creatine phosphokinase			
Total protein			
Albumin			
Glucose			

β-HCG = beta human chorionic gonadotropin; ALT = alanine amino transferase; ANC = absolute neutrophil count; AST aspartate amino transferase; BUN = blood, urea, nitrogen, INR = international normalized ratio; PT = prothrombin time; PTT = Partial prothrombin time; RBC = red blood cells; WBC = white blood cells

Appendix C. Response Evaluation Criteria in Solid Tumors

(Eisenhauer et al, 2009)

- **Definitions**

  At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

  - **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 that can be accurately measured in at least one dimension with longest diameter ≥ 20 mm using chest X-ray or ≥ 10 mm with CT scan.
  - **Non-measurable Lesions** - all other lesions, including small lesions (longest diameter <20 mm with chest X-ray or ≥ 10 but < 15 mm with CT scan), i.e., bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, and also abdominal masses that are not confirmed and followed by imaging techniques; and.

- 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 never more than 28 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 (e.g., skin nodules and palpable lymph nodes) will only be considered measurable target lesions when they ≥ 15 mm. For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- Lymph nodes that are < 10 mm will be considered non-pathological

Methods of Measurement

- CT and MRI are the best currently available and reproducible methods to measure target lesions selected for response assessment. Conventional CT and MRI should be performed with cuts no greater than 5 mm in slice thickness contiguously. This applies to tumors of the chest, abdomen and pelvis. Head and neck tumors and those of extremities usually require specific protocols.
- When the primary endpoint of the study is objective response evaluation, ultrasound should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.
- The utilization of endoscopy and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require

sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

- Cytology and histology can be used to differentiate between partial response and complete response in rare cases (e.g., 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 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured during screening.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).
- A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- 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.

Response Criteria

Evaluation of Target Lesions

* Complete Response (CR):	Disappearance of all target lesions. Any pathologic lymph nodes (whether target or non-target) mush 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 diameters
* Progressive Disease (PD):	At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum diameters recorded since the treatment started or the appearance of one or more new lesions. In addition the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. Appearance of one or more new lesions is also considered progression.
* Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

* Complete Response (CR):	Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (i.e., < 10 mm short axis)
* Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s)
* Progressive Disease (PD):	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (1)

(1) Although a clear progression of “non target” lesions only is exceptional, in such circumstances, the opinion of the treating physician should prevail.

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 subject'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	Not Evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = compete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable

- Subjects 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

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- 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, follow-up measurements must have met the SD criteria no earlier than 49 days after the date of enrollment/randomization during the study.

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.