Rexahn Pharmaceuticals, Inc.

Protocol Number: ***Protocol Number RX3117-003***

A Phase 1/2 Open-Label, Safety, Pharmacokinetic, Pharmacodynamic and Efficacy Study of RX-3117 in Combination with Abraxane® in Subjects with Metastatic Pancreatic Cancer

Statistical Analysis Plan

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1.0 PURPOSE

This SAP describes the methods to be used in the analysis of study data from clinical protocol RX3117-003 in order to answer the study objectives and is based on Amendment 03 of the study protocol, dated 08-August-2018.

Populations for analysis, data handling rules, statistical methods, and formats for data presentation are described within this document. The statistical analyses and summary tabulations described in this SAP will provide the basis for the results sections of the CSR for this study. The SAP outlines any differences in data analysis methods relative to those planned in the study protocol. Any changes to the data analysis methods after the SAP is finalized will be described in the CSR.

2.0 ACRONYMS

Below is the list of acronyms that will be used throughout this document.

Abbreviation	Definition
AE	Adverse Event
BQL	Below the Quantifiable Limit
CI	Confidence Interval
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
eCRF	Electronic Case Report Form
EORTC-PAN26	European Organization for Research and Treatment of Cancer – Pancreatic module
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer – Quality of Life Questionnaire
FACT-Hep	Functional Assessment of Cancer Therapy – Hepatobiliary
ECG	Electrocardiogram
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Definition
mITT	Modified Intent-to-Treat
MTD	Maximum Tolerated Dose
NR	No Results/Not Reported
ORR	Objective Response Rate
PD	Progressive Disease or Pharmacodynamic
PFS	Progression-Free Survival
PK	Pharmacokinetic
PR	Partial Response
PT	Preferred Term
QOL	Quality of Life
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	Standard of Care
TEAE	Treatment-Emergent Adverse Events
TTP	Time-to-Progression
TTR	Time-to-Response

3.0 OVERALL STUDY DESIGN AND OBJECTIVE

3.1 Study Objectives

3.1.1 Phase 1 Objectives

- Primary Objectives
  - To evaluate the safety and tolerability of RX-3117 in combination with Abraxane® in subjects with metastatic pancreatic cancer

- To determine the Recommended Phase 2 Dose (RP2D) of RX-3117 when administered orally in combination with Abraxane® to subjects with metastatic pancreatic cancer

- Secondary Objectives
  - To determine the pharmacokinetic (PK) profiles of RX-3117 and Abraxane® on Day 1 (single dose) and Day 15 (steady-state) in Cycle 1
  - To evaluate the antitumor activity of RX-3117 in combination with Abraxane®
- Exploratory Objective
  - 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

3.1.2 Phase 2 Objectives

- Primary Objectives
  - To estimate the antitumor activity of RX-3117 in combination with Abraxane® as first-line therapy in subjects with metastatic pancreatic cancer
- Secondary Objectives
  - To assess additional measures of antitumor activity
  - To characterize the safety profile of RX-3117 in combination with Abraxane®
  - To evaluate the PK of RX-3117 and Abraxane® at the recommended Phase 2 dose (RP2D)
- Exploratory Objective
  - To investigate the effect of RX-3117 in combination with Abraxane® on potential cellular or molecular biomarkers in blood or tumor samples
  - To evaluate the change in tumor burden response
  - To evaluate the effect on Quality of Life (QOL)

3.2 Study Design and Study Procedures

This will be a Phase 1b/2a multicenter 2-stage study. Phase 1 will be conducted as a dose-finding, open-label study of oral RX-3117 administered in combination with Abraxane® to subjects with metastatic pancreatic cancer. The recommended phase 2 dose (RP2D) of RX-3117, in combination with Abraxane®, will be determined based on the safety profile, dose modification,

and PK. Phase 1 will be conducted using a combination of the single MTD for RX-3117 and the Abraxane® dose as per the package insert when Abraxane® is given in combination for subjects with pancreatic cancer. A safety committee will assess the safety and the tolerability of the combination after the first 5 subjects and may make recommendation to confirm the MTD in another 5 subjects.

After completion of the Phase 1 portion, a Phase 2a study will be conducted using a 2-stage, open-label design, of RX-3117 and Abraxane® in combination to treat subjects with metastatic pancreatic cancer as first-line therapy. Approximately 10 subjects will participate in the Stage 1 at the dose identified in Phase 1 (RP2D). Subjects will be treated for up to 8 cycles of combined therapy. An interim analysis will be conducted after 10 evaluable subjects have been treated at the RP2D, have completed a minimum of 4 months/ cycles of therapy, or have discontinued therapy due to progressive disease before completing 4 cycles. If an adequate number of Responders are observed out of the initial 10 evaluable subjects, then 30 evaluable additional subjects will be enrolled to participate in Stage 2. An adequate number of Responders is defined as either at least 2 out of the 10 subjects (20%) having a measured benefit in PFS noted as PFS ≥ 4 months/ cycles or if at least 1 subject (10%) has 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. The study may stop after the interim analysis if an adequate number of Responders are not seen. However, if an adequate number of Responders are seen, approximately 30 evaluable subjects will be enrolled and evaluated. Subjects will be treated for up to 8 cycles of combined therapy.

RX-3117 will be administered orally for 5 consecutive days followed by 2 days off each week for 3 weeks and a 1-week rest in repeated 4-week cycles. Abraxane® will be administered intravenously over 30-40 min. on Days 1, 8, and 15 of each cycle at the dose level assigned in Phase 1 or the RP2D determined for Phase 2. Subjects will receive up to 8 cycles of RX-3117 in combination with Abraxane® or until disease progression (per RECIST 1.1), clinical progression, 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 clinical benefit (as determined by subject care, quality of life, and tumor reduction), additional cycles of RX-3117 in combination with Abraxane® may be administered following discussions with the sponsor and medical monitor.

3.3 Treatments and Assignment to Treatments

The investigational product in this study is RX-3117. RX-3117 will be administered in combination with Abraxane®. During Phase 1, 700 mg or lower doses of RX-3117 may be investigated in combination with Abraxane®. RX-3117 dosing will begin at 700 mg daily/ 5 days consecutively per week with 2 days rest for 3 weeks and then 1 week of rest in each Cycle. The Abraxane® starting dose will be 125 mg/m2 administered on Days 1, 8 and 15 of each cycle. Abraxane® and RX-3117 dose reductions will follow Table 1 below.

Table 1. Dosage Reductions

Dose Level	Abraxane® (mg/m2)	RX-3117 (mg)
Full dose	125	700
1st dose reduction	100	600
2nd dose reduction	75	500

In Phase 1, if 0 or 1 of the first 5 subjects that complete one cycle of treatment experiences a DLT, then the full dose may be confirmed as the RP2D. If 3 or more of the first 5 subjects that complete one cycle of treatment experience a DLT, then there will be a dose reduction and 5 subjects will be treated at the next lowest dose level. If 2 of the first 5 subjects that complete one cycle of treatment experience a DLT, then the safety review committee may recommend an additional 5 subjects are to be treated at the full dose. In this case, if 3 or less of the 10 subjects experience a DLT, then the full dose will be confirmed as the RP2D. Otherwise, if 4 or more of the 10 subjects experience a DLT, then a dose reduction will occur. Additional doses may be recommended by the review committee which includes investigators, medical monitor and sponsor. For Phase 2, the RX-3117 and Abraxane® dosing will be administered based on the RP2D identified after completion of Phase 1.

In the Phase 1 and Phase 2-Stage 1, 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-Stage 2 portion, subjects who are enrolled but not treated will be replaced.

3.4 Determination of Sample Size

For the Phase 1 dose-finding, approximately 10 subjects are planned. The sample size is not based on formal statistical hypothesis testing but will be determined based on observed number of first-cycle DLTs at each dose level. The intent is to limit the number of subjects who are exposed to excessively toxic doses or sub-therapeutic doses of a drug in a Phase 1 evaluation of anticancer agents being used in combination for the first time.

For Phase 2, approximately 40 evaluable subjects are planned. This sample size is not based on statistical hypothesis but rather to further evaluate efficacy and safety endpoints in order to plan future studies. Once the RP2D is identified approximately 10 evaluable subjects will participate in Stage 1. Depending on the results of the interim analysis, approximately 30 evaluable subjects will participate in Stage 2.

4.0 GENERAL ANALYSIS CONVENTIONS

4.1 Study Periods

The study consists of the following periods:

- Screening period: From the date of consent to date of enrollment, up to 14 days or up to 21 days for tumor assessments. Please note: The study allows up to 5 days after enrollment before dosing.
- Treatment period: From first dose of RX-3117 to last dose of RX-3117. Additional cycles are allowed on a per subject basis upon agreement between the Sponsor, Medical Monitor, and Investigator. 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 subject 5 times per week (i.e., for 5 consecutive days followed by 2 days off) for 3 consecutive weeks followed by 1 week of rest in each 4-week cycle. Abraxane® will be administered once a week for 3 weeks on Days 1, 8, and 15 followed by 1 week of rest during each 28-day cycle. End of Treatment visit will be performed when a subject discontinues study treatment.
- Safety follow-up period: From the day after the last dose of RX-3117 to the safety follow-up visit which occurs approximately 37 days after the last dose of RX-3117.

Subject participation is anticipated to be approximately 9 months

4.2 Visit Windows

The visit windows will be analyzed per the protocol and as collected in the eCRF. Study Day will be calculated from the reference start date and used to show start/stop day of the assessments and events as follows:

- For assessments/events on/after the reference start date:

  Study Day= (date of assessment/event – reference start date) +1

- For assessments/events before the reference start date:

  Study Day= (date of assessment/event – reference start date)

5.0 ANALYSIS POPULATIONS

5.1 Intent-to-Treat Population

The Intent-to-Treat (ITT) population will include all subjects who were enrolled in the study regardless of if they actually received any amount of either study medication.

5.2 Modified Intent-to-Treat (mITT)

The Modified Intent-to-Treat (mITT) population includes all subjects who receive ≥ 1 dose of RX-3117, who have measurable tumor, who can be evaluated for tumor response at both baseline and at least one on-study tumor evaluation with the exclusion of any subjects with protocol deviations/violations that would compromise the safety and/or efficacy of the study treatment. Any subjects excluded from this population will be identified and documented prior to database lock.

A subset of the mITT population will be used in the analyses of time to response and duration of response. This subset will include those subjects who achieved a complete response or partial response.

5.3 Safety Population

The Safety population includes all ITT subjects who receive ≥ 1 dose of RX-3117. It is the primary population to be used for safety evaluations such as summaries of baseline characteristics, study drug exposure, subject disposition and assessment of DLTs and MTDs.

5.4 PK Population

The PK Population will be a subset of the Safety population and used in the analysis of PK and Pharmacodynamic (PD) parameters. It will include those

subjects from the Safety population who have baseline and on-study PK/PD measurements to provide interpretable results for specific parameters of interest.

6.0 SUBJECT DISPOSITION

A tabulation of subject disposition will be presented by study phase including the number in each analysis population, reasons for discontinuing treatment, and reasons for discontinuing from the study.

7.0 DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographics and baseline characteristics will be summarized using descriptive statistics by study phase. This includes but is not limited to medical, surgical, and cancer histories plus prior medications and physical examination results

8.0 EFFICACY VARIABLES

8.1 Primary Efficacy Variable

The primary efficacy variable in the study is the adequate number of Responders based on progression free survival (PFS) and/or objective clinical response. This analysis will be performed on the mITT population.

An adequate number of responders is defined as either at least 20% subjects having a measured benefit in PFS noted as PFS ≥ 4 months/ cycles or if at least 10% subject has 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. This definition applies to analyses of data from Stage 1 of Phase 2 (which may include subjects from Phase 1 if they received the RP2D), entire Phase 2, and the entire study overall.

8.2 Secondary Efficacy Variables

The secondary efficacy variables in this study are listed below.

- Time to progression (TTP) is defined as the time from first treatment administration until first documentation of RECIST-defined objective tumor progression. TTP does not include deaths. In the TTP analysis, deaths are

censored, either at the time of death or at an earlier visit representing informative censoring (non-random pattern of loss from the study).

- Objective response rate (ORR) is defined as the rate of a clinical response of complete response (CR) or partial response (PR) at the completion of treatment assessment of tumor control. ORR will be summarized at each tumor assessment as well as a combined summary at the subjects' last assessment on study. Tumor response assessments will be based on the standardized RECIST version 1.1. Tumor response will be documented 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. Subjects with unknown or missing response will be treated as non-responders at the assessment where their response is unknown or missing.
- Duration of response (DOR) defined as the time from the first documentation of RECIST-defined objective tumor response to the first documentation of RECIST-defined objective tumor progression or death. Clinical progression without RECIST-defined objective tumor progression will not be considered the end of response. Responders who discontinue from the study for reasons other than tumor progression or death will be censored at the time of their last responding tumor assessment. This analysis is applicable for responders only and a subset of the mITT.
- Time to response (TTR) is defined as the time from first treatment administration to first documentation of RECIST-defined objective tumor response.
- Progression Free Survival (PFS) is defined as the time from first treatment administration to first documentation of RECIST-defined objective tumor progression or relapse or death from any cause. Clinical progression without RECIST-defined objective tumor progression will not be considered to have progressed and follow-up data utilized or censored.
    - For all the 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.

9.0 EFFICACY ANALYSES

9.1 Primary Efficacy Analysis

The number and percentage of Responders based on progression free survival (PFS) and/or objective clinical response will be summarized for Stage 1 of the Phase 2 portion of the study (on those subjects receiving the RP2D), and for the entire study in the final analysis separately, including a 95% confidence interval for response. The rationale for response being achieved (PFS ≥ 4 months, PR/CR, or both) will also be summarized. A listing of responders will be provided. This analysis will be performed on the ITT population as well as the mITT population.

9.2 Secondary Efficacy Analyses

9.2.1 Time to Progression (TTP)

The TTP analysis will be performed on the mITT population and estimated using the Kaplan-Meier (KM) product limit method. The median TTP time along with 95% confidence interval will be constructed based on a log-log transformed CI for the survival function. Summary statistics of minimum, maximum, and range will be calculated. The results will be displayed graphically in a KM plot as well as provided in a listing.

9.2.2 Objective Response Rate (ORR)

The ORR analysis will be performed on the mITT population and will be summarized by a binomial response rate and its corresponding two-sided exact CI using Clopper-Pearson method. The number and percentage of subjects by response category (CR, PR, SD, PD, NE) will be summarized.

9.2.3 Duration of Response (DOR)

The DOR analysis will be performed on only those subjects with a documented response (CR or PR) as a subset within the mITT population as noted in Section 5.2. The DOR will be estimated using the KM-product limit method. The median DOR time along with 95% confidence interval will be constructed based on a log-log transformed CI for the survival function. Summary statistics of minimum, maximum, and range will be calculated. The DOR results will be provided in a listing inclusive of response category, first response date, date response was lost or censoring, and DOR.

9.2.4 Time to Response (TTR)

The TTR analysis will be performed on only those subjects with a documented response (CR or PR) as a subset within the mITT population as noted in Section 5.2. The TTR will be estimated using the KM-product limit method. The median TTR time along with 95% confidence interval will be constructed based on a log-

log transformed CI for the survival function. Summary statistics of minimum, maximum, and range will be calculated. Summary statistics of minimum, maximum, and range will be calculated. The results will be displayed graphically in a K-M plot as well as provided in a listing.

9.2.5 Progression-Free Survival (PFS)

The PFS analysis will be performed on the mITT population and estimated using the Kaplan-Meier (KM) product limit method. The median PFS time along with 95% confidence interval will be constructed based on a log-log transformed CI for the survival function. Summary statistics of minimum, maximum, and range will be calculated. The results will be displayed graphically in a KM plot as well as provided in a listing.

9.2.6 Disease Control Rate (DCR)

Disease control rate (DCR) is defined as the number of subjects with a best overall response of a CR, PR or SD, divided by the total number of subjects. The DCR analysis will be performed on the mITT population and will be summarized by a binomial response rate and its corresponding two-sided exact CI using Clopper-Pearson method.

9.3 Additional Efficacy Analyses

9.3.1 Tumor burden

The percentage change from baseline in tumor change (burden) will be summarized using summary statistics.

9.3.2 Quality of Life (QOL) Assessments

Each of the three QOL assessments (EORTC QLQ-C30 version 3, EORTC PAN26, and the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) version 4) will each be summarized individually using summary statistics. Each QOL assessment will be scored according to the appropriate scoring manual and summarized overall and for subscales as available. In addition to the values at each timepoint, the percentage change from baseline to each scheduled visit will be summarized.

10.0STATISTICAL/ANALYTICAL ISSUES

10.1 Handling of Dropouts or Missing Data

All summaries and analyses will be based upon the observed data unless methods for handling missing data are specified otherwise. It is not anticipated that any missing data will be imputed with the exceptions below:

- For QOL measurements, missing data will be handled as described in the scoring manuals and/or algorithms.
- For time to event analyses:
    - Subjects without any efficacy evaluations will be considered as censored at time 0.
    - Subjects without the event of interest will be censored on the date they were last known to be event-free.
- For Adverse Events:
    - Missing dates will not be imputed; however, if partial dates are available, they will be used to assess if the AE occurred during the treatment period.
    - Missing severities of AEs will not be imputed and will be considered missing in any tabulations of AE severity.
    - If an AE is missing a response to the question regarding relationship to treatment, the event will be considered to be related.

10.2 Pooling of Centers in Multi-Center Studies

Approximately 3 enrolling sites in the US will participate in the Phase 1 portion of the study and up to 15 enrolling sites in the US will participate in the Phase 2 study. Due to the nature of this early phase study, data from all sites will be pooled for all analyses.

10.3 Multiple Comparisons/Multiplicity

No adjustments for multiple comparisons, and/or multiplicity are planned for this study.

10.4 Examination of Subgroups

No examination of subgroups is planned for this study.

10.5 Interim Analysis and Data Monitoring

The interim analyses that are planned to be conducted in the Phase 1 are related to an informal review of available data during the dose escalation phase of the study. The review consisted of case report reviews, information from the study database, and discussions between the Investigators, Medical Monitor, and Sponsor. The decision to de-escalate to the next dose level will be made after the evaluation of safety data through at least 28 days of the first cycle of the current dose level.

The interim analysis after Stage 1 of the Phase 2 will be performed when the first 10 evaluable subjects have been treated at the recommended Phase 2 dose which may include subjects from Phase 1 on the same dose, are evaluable for response, have the opportunity to complete up to 4 cycles of therapy or have discontinued therapy before 4 cycles. If an adequate number of Responders are observed out of the initial 10 evaluable subjects, subject enrollment will continue with another 30 evaluable subjects enrolled (approximately 40 evaluable subjects combined in Phase 2). An adequate number of Responders is defined as either at least 2 out of the 10 evaluable subjects (20%) having a measured benefit in PFS noted as PFS ≥ 4 months/ cycles or if at least 1 subject (10%) has 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. The study may stop after the interim analysis if an adequate number of Responders are not seen. However, if an adequate number of Responders are seen, an additional 30 evaluable subjects will be enrolled and evaluated.

11.0PHARMACOKINETICS/PHARMACODYNAMICS

All subjects who received study treatment, with available concentration data and no major protocol deviations with an impact on PK will be included in the PK analysis set as shown in Section 5.2.

In order to prepare the PK analysis dataset, all plasma concentration values reported as No Results/Not Reportable (NR) values will be treated as missing and will appear in the dataset as ".". Values below the quantifiable limit (BQL) that occur prior to the first measurable concentration will be treated as zero. All other BQL values will be treated as missing and set to ".".

The following PK parameters will be calculated (Phase 1 and Phase 2 – Stage 1 only) on Day 1 (single dose) and Day 15 (steady-state) for RX-3117 and Abraxane, within Phoenix WinNonlin Version 8.0 or higher, if appropriate:

For Day 1:

- C_{max}: Observed maximum concentration after administration, taken directly from the analytical data
- T_{max}: Time to reach maximum concentration in plasma. (obtained without interpolation)
- Kel: The terminal elimination rate constant will be estimated at terminal phase by linear regression after log-transformation of the concentrations
    - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.

- A minimum number of three descending data points in the terminal phase will be used in calculating Kel with the line of regression starting at any post-C_{max} data point (C_{max} should not be part of the regression slope).
- The adjusted correlation coefficient ($R2_{adj}$) in general should be greater than 0.80.
- An appropriate number of decimal places should be used for Kel to enable the reported value of $t_{1/2}$ to be calculated.

- AUC_{0-t}: Area under the concentration-time curve up to the last observable concentration calculated using linear trapezoidal summation from time 0 to time t, where t is the time of the last measurable concentration (C_t)
- AUC_{0-inf}: Area under the concentration-time curve up to infinity calculated using linear trapezoidal summation from time 0 to time infinity using the linear up log down method, $AUC_{(0-\infty)} = AUC_{(0-t)} + C_t/Kel$, where Kel is the terminal elimination rate constant (the slope of elimination phase of the log-concentration versus time plot) and C_t is the last measurable plasma concentration. AUC_{0-inf} will not be reported if the percentage extrapolated exceeds 20%
- $t_{1/2}$: Terminal half-life time estimated by 0.693/Kel (Kel is determined by the slope of terminal phase of log concentration versus time plot).

For Day 15:

- $C_{max,ss}$: Observed maximum concentration after administration, taken directly from the analytical data;
- $T_{max,ss}$: Time to reach maximum concentration in plasma. (obtained without interpolation);
- Kel: The terminal elimination rate constant, will be estimated at terminal phase by linear regression after log-transformation of the concentrations
  - Only those data points that are judged to describe the terminal log-linear decline will be used in the regression.
  - A minimum number of three descending data points in the terminal phase will be used in calculating Kel with the line of regression starting at any post-$C_{max,ss}$ data point ($C_{max,ss}$ should not be part of the regression slope).
  - The adjusted correlation coefficient ($R2_{adj}$) in general should be greater than 0.80.
  - An appropriate number of decimal places should be used for Kel to enable the reported value of $t_{1/2}$ to be calculated.
- AUC_{tau}: Area under the concentration-time curve up to the last observable concentration calculated using linear trapezoidal summation from time 0 to time tau, where tau is the dosing interval

- $t_{1/2}$: Terminal half-life time estimated by 0.693/Kel (Kel is determined by the slope of terminal phase of log concentration versus time plot).

The mean plasma concentration over time by treatment and day and the individual subject plasma concentration versus time data will be plotted. Nominal times will be used for plotting the mean plasma concentrations over time by treatment and day and actual sampling times will be used for the individual figures and for the non-compartmental analysis.

The PK parameters will be summarized descriptively including the number of observations, arithmetic mean, SD, CV, minimum, median, maximum, geometric mean and geometric CV%.

All PK parameters will be rounded to 3 significant figures except for T_{max} which will be rounded to two decimal places.

Mean SD, median, minimum, maximum, and geometric mean will be presented to 3 significant figures for all PK parameters except T_{max}; T_{max} will be presented to 2 decimal places; CV% and geometric CV% will be presented to 1 decimal place.

12.0DRUG EXPOSURE AND COMPLIANCE

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

- Duration of treatment is defined as last dose date – first dose date + 1 in days.
- RDI for RX-3117 is calculated as:
  - {Actual cumulative dose (mg) / actual treatment duration (day)}/375 (mg/day), where 375 comes from Planned cumulative dose (mg)/ planned treatment duration = 10500mg/28 days.
- RDI for Abraxane is calculated as:
  - {Actual cumulative dose (mg/m^2) / actual # of infusions given per cycle}/{Planned cumulative dose (mg/m^2) / planned # of infusions given per cycle}.
- 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).

13.0SAFETY ANALYSES

13.1 Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.0 and displayed in tables and listings using MedDRA system organ class (SOC) and preferred term (PT). AEs will be graded using CTCAE version 4.03. The incidence rates of treatment-emergent AEs, SAEs, DLTs, AEs of at least Grade 3 in severity, related AEs, and AEs leading to withdrawal of treatment will be tabulated and summarized. Treatment-emergent adverse events (TEAEs) will be those AEs that start or worsen on or after the first day dose of study treatment, through 30 days after last dose; related AEs will be those with an Investigator determination of related to treatment.

AEs with partial dates will be assessed using the available date information to determine if treatment-emergent. AEs with completely missing dates will be assumed to be treatment-emergent. No formal hypothesis-testing of AE incidence rates will be performed.

The causal relationship between the occurrence of an AE and the study drug will be judged by the investigator as not related or related. In the event a subject experiences repeat episodes of the same AE, then the event with the highest severity will be used for purposes of tabulations.

All safety analysis will be performed on the Safety population.

13.2 Treatment-Emergent Adverse Events

The number and percentage of subjects experiencing TEAEs will be tabulated according to the following categories:

- Overall summary of TEAEs
- TEAEs by system organ class and preferred term
- SAEs by system organ class and preferred term
- DLTs by system organ class and preferred term (Phase 1 only)
- TEAEs ≥ Grade 3 by system organ class and preferred term
- TEAEs Related to Study Drug by system organ class and preferred term
- TEAEs leading to treatment discontinuation by system organ class and preferred term
- TEAEs leading to study discontinuation by system organ class and preferred term
- TEAEs by system organ class, preferred term, and AE severity (CTCAE Grade)

- TEAEs by system organ class, preferred term, and AE causality
- TEAEs by preferred term

Listings will be provided for all AEs.

13.3 Death, Serious Adverse Events, and Adverse Events Leading to Discontinuation

The number and percentage of subjects experiencing Deaths, SAEs, and AEs leading to discontinuation will be tabulated according to the following categories:

- Death
- Serious AEs (SAEs) by system organ class and preferred term
- Serious AEs leading to study discontinuation by system organ class and preferred term

Listings will be also provided for SAEs and AEs leading to study discontinuation.

13.4 Dose Limiting Toxicity

DLTs are applicable to only Phase 1 of the study.

A DLT is defined as any of the following adverse events that is considered by the Investigator as possibly, probably or definitely-related to RX-3117, Abraxane or the combination:

- Grade 4 neutropenia (ANC $< 0.5 \times 10^9$/L)
- Grade ≥3 neutropenia (ANC $< 1.0 \times 10^9$/L) with fever greater than 38.5°C (101.3°F)
- Grade 4 thrombocytopenia (platelet count $< 25 \times 10^9$/L)
- Grade 3 nausea or vomiting lasting > 3 days despite optimal management
- Grade 3 fatigue lasting > 7 days
- Grade 4 fatigue
- Treatment interruptions of ≥ 7 days
- Any Grade thrombocytopenia that occurs with clinically significant bleeding

Any other non-hematological Grade ≥ 3 adverse events will be considered DLTs with the exception of the following:

- Alopecia
- Grade 1 or 2 sensory neuropathy

- For subjects with bone or liver metastases and baseline levels of AST or ALT > 2.5 x ULN or alkaline phosphatase > 2x ULN, DLTs do not include elevations in AST, ALT, and alkaline phosphatase unless the following criteria are met:
- AST > 8 x ULN, if the baseline level was between 2.5 to 5 x ULN in subjects with liver metastases
- ALT > 8 x ULN, if the baseline level was between 2.5 to 5 x ULN in subjects with liver metastases
- Alkaline phosphatase > 8 x ULN, if the baseline level was between 2 to 5 x ULN in subjects with bone or liver metastases.

A listing of DLTs that occur during Cycle 1 of Phase 1 will be provided.

13.5 Clinical Laboratory Data

For each analyte in Appendix 15.2, the actual value and percentage change from baseline to each visit timepoint will be summarized to include, but not limited to, hematology, clinical chemistry, coagulation, and biomarker data. In the event of repeat values, the last non-missing value per study day will be used.

Severity of select clinical lab measures will be determined using CTCAE (version 4.03) criteria (e.g., those measures that have a corresponding CTCAE grade classification). Laboratory analytes with CTCAE grades greater than or equal to 3 will be presented in a data listing. Shift tables that present changes from baseline to worst on-study and baseline to last on-study values relative to CTCAE classification ranges will be produced.

13.6 Vital Signs

The actual vital signs values and percentage change from baseline to each visit timepoint will be summarized using summary statistics.

13.7 Electrocardiograms (ECGs)

The ECG parameters (heart rate, PR interval, QRS interval, QT interval, and corrected QT [QTcF] interval) at each visit timepoint recorded as well as the percentage change from baseline will summarized using descriptive statistics. These parameters will be determined electronically by the ECG machine at the clinical site. The QT interval will be corrected by the Fridericia method as follows:

- Fridericia: QTcF = QT/(RR^0.33)

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 baseline will be presented.

Please note: the ECG data was collected on only subjects in Phase 1 and Stage 1 of Phase 2.

13.8 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the WHO Drug Dictionary Enhanced (WHODDE) version March 2017. Concomitant medications will be tabulated by ATC Level 3 term and drug preferred term. Prior medications and concomitant medications will also be presented in the data listings.

14.0QUALITY CONTROL

All analysis will be performed using SAS® Version 9.4 and SAS Enterprise Guide version 7.12. Appropriate SOPs will be followed in the creation and quality control of all tables, listings, figures, and analysis.

All data displays and analyses will adhere to the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline: Structure and Content of Clinical Study Reports (ICH Topic E3). Rexahn will review all tables, listings, and figures prior to final database lock. Final SAS datasets, programs and outputs will be transferred to the Rexahn at project completion.

15.0APPENDICES

15.1 Schedule of Events

Appendix A. Schedule of Assessments Cycle 1

	SCR[a]	Cycle 1					EOT / ET	SFU[c]
Procedures and Treatments **Day**	-14	1	2	8[b]	15	22[b]		
Informed consent	X							
Medical, surgical, cancer and psychiatric histories	X							
Prior medication usage	X[d]	X[e]						
Eligibility review, enrollment	X	X[f]						
Quality of Life measurements[g]		X		X	X	X	X	X
Pregnancy test[h]	X	X						
Physical examination excluding GU including height	X							
Weight	X	X					X	X
ECOG performance status	X	X					X	X
Hematology and serum chemistry	X	X[i]		X	X	X	X	X
Coagulation profile and Urinalysis	X	X[i]		X	X		X	
Vital sign measurements[j,k]	X	X	X	X	X	X	X	X
12-lead electrocardiogram[j,l]	X	X	X					
Pharmacokinetic sampling[j,m]		X			X			
Abraxane® infusion[n]		X		X	X			
RX-3117 drug administration[o]		X	X[p]	X	X			
Dispensing of study drug[q] and diary cards		X[q]	X[q]	X[q]	X[q]			
Unused study drug collection & subject compliance				X	X	X	X	
Tumor assessment(s)[r]	X							X[s]
Tumor marker blood samples	X	X[i]					X	
Adverse event assessment[t]		X	X	X	X	X	X	X
Concomitant med review		X	X	X	X	X	X	X
Archived tumor tissue[u]		X						
Biomarker blood sample[v]		X					X	
Tumor biopsy samples (optional)[w]		X						

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 enrollment, except baseline tumor assessment, which can be evaluated within 21 days before enrollment. ECG must be done within 7 days before 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 RX-3117.
d Medications taken within 28 days before 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 QoL questionnaires must be completed prior to any other study procedure.
h 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 before dosing on Cycle 1 Day 1.

i If screening laboratory tests were performed within 72 hours before Cycle 1 Day 1, they do not need to be repeated on Cycle 1 Day 1.
j The required order of assessments is ECG, followed by vital signs and then PK sampling when applicable.
k Vital signs measurements will include resting heart rate, blood pressure, pulse, respiratory rate, and temperature. Oxygen saturation (by pulse oximetry while subject is breathing room air) will be assessed at Screening only.
l ECG to be assessed pre-dose of Abraxane®, pre-dose of RX-3117 administration, and at 1, 2, 4, and 6 hours after RX-3117 oral administration on Cycle 1 Day 1. (Phase 1 and Phase 2-Stage 1 only)
m In Phase 1 and Phase 2-Stage 1 only, Pharmacokinetic (PK) samples will be collected at Abraxane® pre-dose, at the end of infusion, at RX-3117 pre-dose (no more than 15 minutes before dosing) and at 0.5, 1, 2, 3, 4, and 6 hours after oral administration of RX-3117 on Day 1 in Cycle 1. A sample will also be taken 24 hours after RX-3117 dosing administration on Cycle 1 Day 1.)
n Abraxane® IV infusion over 30-40 minutes on Days 1, 8, and 15. If a dose is administered on the same day as PK sampling (i.e. pre-dose and 24 hours), the PK sample will be collected first.
o RX-3117 will be administered orally after having fasted for a minimum of 8 hours and no earlier than 1 hour after the start of infusion of Abraxane®.
p 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 (i.e., pre-dose and 24 hours), the PK sample will be collected first.
q Study drug and diary cards will be dispensed at 1 week intervals during Cycle 1.
r Tumor assessments will be evaluated using RECIST v1.1 and should include an assessment of all areas of known and suspected malignancy. 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.
s 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.
t 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.
u To be collected within 4 weeks after enrollment
v Biomarker samples will be collected pre-dose
w Tumor biopsies will be taken following enrollment but before first dose of study treatment (optional)

Appendix B. Schedule of Assessments Cycles 2 to 8

	Cycles 2 - 8				EOT/ET	SFU[a]
Procedures and Treatments **Day**	**1**	**8**	**15**	**22**		
Quality of Life measurements[b]	X	X	X	X	X	X
Weight	X				X	X
ECOG performance status	X				X	X
Hematology and serum chemistry	X		X		X	X
Coagulation profile and Urinalysis	X				X	
Vital sign measurements[c]	X	X	X		X	X
Abraxane® infusion[d]	X	X	X			
RX-3117 drug administration [e,f]	X	X	X			
Dispensing of study drug and diary cards[g]	X[g]					
Unused study drug collection & subject compliance				X	X	
Tumor assessment(s)[h]				X[i]	X[j]	X
Tumor marker blood samples	X				X	
Adverse event assessment[l]	X	X	X	X	X	X
Concomitant medication review	X	X	X	X	X	X
Biomarker blood sample	X[m]				X	

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

Footnotes for Schedule of Assessments

a Safety follow-up visit will be between 30 and 37 days after the last dose of study drug.
b EORTC QLQ-C30; EORTC PAN26; FACT-Hep. QoL questionnaires must be completed prior to any other study procedure.
c Vital signs measurements will include resting heart rate, blood pressure, pulse, respiratory rate, and temperature.
d Abraxane® IV infusion over 30- 40 minutes on Days 1, 8, and 15.
e RX-3117 will be administered orally after having fasted for a minimum of 8 hours and no earlier than 1 hour after the start of infusion of Abraxane®.
f Administered for 5 consecutive days followed by 2 days off per week for 3 weeks then 1 week off.
g Study drug and diary cards will be dispensed at least once every cycle thereafter.
h Tumor assessments will be evaluated using RECIST v1.1 and should include an assessment of all areas of known and suspected malignancy. 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.
i Tumor evaluation, including CT/MRI/PET will be performed between Days 22-28 of Cycles 2, 4, 6 and 8. The results of the assessments must be available before the start of the next cycle. Results of the assessment must be available before the start of the next cycle.
j 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.
k 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.

l 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.
m Biomarker samples will be collected predose on Cycle 2 only.

Appendix C. Schedule of Assessments Cycle 9 and beyond

	≥Cycle 9				EOT/ET	SFU[a]
Procedures and Treatments **Day**	**1**	**8**	**15**	**22**		
Quality of Life measurements[b]	X	X	X	X	X	X
Weight	X				X	X
ECOG performance status	X				X	X
Hematology and serum chemistry	X				X	X
Coagulation profile and Urinalysis					X	
Vital sign measurements[c]	X				X	X
Abraxane® infusion[d]	X	X	X			
RX-3117 drug administration[e,f]	X	X	X			
Dispensing of study drug and diary cards[g]	X					
Unused study drug collection & subject compliance				X	X	
Tumor assessment(s)[h]				X[i]	X[j]	X[k]
Tumor marker blood samples	X				X	
Adverse event assessment[l]	X	X	X	X	X	X
Concomitant med review	X	X	X	X	X	X
Biomarker blood sample					X	

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

Footnotes for Schedule of Assessments

a Safety follow-up visit will be between 30 and 37 days after the last dose of study drug.
b EORTC QLQ-C30; EORTC PAN26; FACT-Hep. QoL questionnaires must be completed prior to any other study procedure.
c Vital signs measurements will include resting heart rate, blood pressure, pulse, respiratory rate, and temperature.
d Abraxane® IV infusion over 30-40 minutes on Days 1, 8, and 15 .
e RX-3117 will be administered orally after having fasted for a minimum of 8 hours and no earlier than 1 hour after the start of infusion of Abraxane®.
f Administered for 5 consecutive days followed by 2 days off per week for 3 weeks then 1 week off.
g Study drug and diary cards will be dispensed at least once every cycle.
h Tumor assessments will be evaluated using RECIST v1.1 and should include an assessment of all areas of known and suspected malignancy. 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.
i Tumor evaluation, including CT/MRI will be performed between Days 22-28 of Cycle 10 and every 2 cycles thereafter. The results of the assessments must be available before the start of the next cycle. Results of the assessment must be available before the start of the next cycle.
j 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.
k 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.

l 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.

15.2 Clinical Laboratory Analytes

Chemistry	Urinalysis	Hematology	Other Labs
Sodium	Specific gravity	RBC	Urine β-HCG
Potassium	pH	Hemoglobin	Serum β-HCG
Chloride		ANC	PT; PTT or INR
Bicarbonate	Protein	Platelets	
Magnesium	Glucose	WBC	Blood samples for RX-3117 and metabolite concentration and PK
Calcium	Bilirubin	Differential	
BUN	Ketones	• Eosinophils	
Serum Creatinine	WBC	• Basophils	Blood samples for biomarkers
AST (SGOT)	RBC	• Lymphocytes	Tumor Marker
ALT (SGPT)	Epithelial cells	• Neutrophils	Blood samples for Abraxane® concentration and PK
Alkaline phosphatase	Bacteria (macroscopy only)	• 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

16.0SIGNATURE PAGE

Prepared By:

Name	Role	Signature
L. Stacey Arrambide	*SVP, Biometrics*	Right-click to sign with CoSign

Approved By: *The signature of the document approver means that the approver has read, understood and approved this document.*

Name	Role	Signature	Date
Callie Heaton	*Rexahn Pharmaceuticals, Inc.* *Associate Director, Clinical Operations*		

Document is considered final upon date of last signature.