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CLINICAL PROTOCOL SCRX001-006

Protocol Title	An Open-Label Study of Rovalpituzumab Tesirine in Subjects with Delta-Like Protein 3-Expressing Advanced Solid Tumors
AbbVie Investigational Product:	Rovalpituzumab tesirine (SC16LD6.5)
Development Phase:	1/2
IND Number:	117510
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Previous Version and Date	**Version 1.0 27 January 2016**

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.
*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

Synopsis

TITLE:

An Open-Label Study of Rovalpituzumab Tesirine in Subjects with Delta-Like Protein 3-Expressing Advanced Solid Tumors

PROTOCOL NUMBER: SCRX001-006

PHASE OF DEVELOPMENT: 1/2

INVESTIGATORS AND STUDY CENTERS: Multicenter

OBJECTIVES:

Primary

- To assess the safety and tolerability of rovalpituzumab tesirine in subjects with specific delta-like protein 3 (DLL3)-expressing advanced solid tumors.

Secondary

- To explore the antitumor activity of rovalpituzumab tesirine in subjects with specific DLL3-expressing advanced solid tumors.
- To study the pharmacokinetics (PK) of and incidence of anti-therapeutic antibodies (ATA) against rovalpituzumab tesirine in subjects with specific DLL3-expressing advanced solid tumors.

Exploratory

- To explore the expression of DLL3 in specific DLL3-expressing advanced solid tumors, and its relationship to clinical outcome during treatment with rovalpituzumab tesirine.
- To explore the effect of rovalpituzumab tesirine on disease biomarkers and pharmacodynamics.
- To assess change in patient reported outcomes (PRO) within the expansion cohorts (Part B) utilizing the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) questionnaire and EuroQoL Five Dimension Questionnaire (EQ-5D-5L) during treatment with rovalpituzumab tesirine.

TEST PRODUCTS, DOSE, AND MODE OF ADMINISTRATION:

- Rovalpituzumab tesirine 0.2–0.4 mg/kg will be administered intravenously (IV) on Day 1 of each 6-week cycle, or according to other dosing regimens recommended by the Safety Monitoring Committee (SMC).
- Dexamethasone 8 mg will be administered orally (PO) twice daily on Day -1, Day 1 (the day of dosing), and Day 2 of each 6-week cycle.

STUDY DESIGN AND METHODOLOGY:

This is a multicenter, open-label study involving multiple specific advanced solid tumor types. This study consists of a Part A dose escalation followed by a Part B expansion. Cancer subtypes will be studied in separate disease-specific cohorts in both study parts, A and B. Seven separate cohorts will enroll the following cancer types:

1. Malignant melanoma
2. Medullary thyroid cancer (MTC)
3. Glioblastoma (GBM)
4. Large cell neuroendocrine carcinoma (LCNEC) of any origin
5. Neuroendocrine prostate cancer (NEPC)
6. High-grade gastroenteropancreatic neuroendocrine carcinoma (GEP NEC)
7. Other neuroendocrine carcinoma (NEC), and high grade neuroendocrine tumors (NET)
8. Solid tumors other than the above

As of protocol version 4.0, cohort 3 (GBM) is closed to enrollment.

Part A Dose Escalation

Rovalpituzumab tesirine will be initially administered on Day 1 of each 6-week cycle, following a standard 3+3 dose-escalation approach. For each cohort in Part A, dose escalation is planned to proceed until a single maximum tolerated dose (MTD) (dose level and dosing interval inclusive) is determined.

The SMC will monitor the safety of the trial and may make dose-escalation and dosing-interval recommendations. The SMC may also recommend further evaluation of the safety at a given dose, investigation of alternative dose regimens (including a dose level that is intermediate to the planned dose levels), modification of the dosing interval, or limitation to the maximum number of doses. For instance, based on dose-limiting toxicities (DLTs) and/or adverse event (AE)-related dose delays, enrollment may change at the same dose to a different dosing schedule (e.g., up to 12-week cycles, in which rovalpituzumab tesirine is administered on Day 1 of each cycle of up to 84 days). The SMC may also recommend the elimination or cancellation of a dose level(s) in a cohort based on the experience in other cohorts. For instance, if 3 or more initially-enrolled cohorts establish the same dose level as MTD, the remaining cohorts may forgo escalation to higher dose levels.

Response will be assessed by radiographic imaging at protocol-specified time points determined by the subject's dosing schedule. In the 6-week cycle schedule, response assessments will be conducted between Days 36–42 of Cycles 1-4, and every 2 cycles thereafter. Prostate cancer-specific assessments are described in Appendix 13.6.

Part B Expansion Cohorts

To explore the recommended dosing regimen for distinct disease subsets, subjects will be enrolled in disease-specific expansion cohorts in Part B. The dose regimen(s) to be examined in the disease-specific cohorts will be at the MTD determined in Part A or a lower dose(s) and/or regimen(s), depending on the cumulative data. For example, a lower dose regimen may consist of a finite number of doses and/or a mixed-dose regimen, with all doses at or below MTD, but varying based on the cycle. The dose(s), regimen(s), and schedule(s) for the expansion cohorts will be determined by the Sponsor in consultation with the SMC.

In Part B, up to approximately 174 subjects may be enrolled, including approximately 19 subjects in each of the 5 disease-specific cohorts and up to 30 subjects each for Cohort 7 and Cohort 8. The goal of the Part B expansion is to provide further safety data and preliminary efficacy data for the selected dose regimens.

Response will be assessed by radiographic imaging at protocol-specified time points determined by the subject's dosing schedule. In the 6-week cycle schedule, tumor response will be assessed every 6 weeks during active study treatment until 24 weeks, then every 12 weeks, thereafter. Prostate cancer-specific assessments are described in Appendix 13.6.

MAJOR ELIGIBILITY CRITERIA:

Subjects with a histologically confirmed, DLL3-expressing advanced solid tumor with measurable disease, that is relapsed/refractory to prior standard systemic therapy; ECOG 0–1; adequate hematologic, hepatic and renal function; and no prior exposure to a pyrrolobenzodiazepine (PBD)-based drug. Prostate cancer-specific criteria are provided in Appendix 13.6.

PLANNED SAMPLE SIZE:

Up to approximately 318 subjects are expected to participate in this two-part trial. Study accrual in Part A is approximately 144 subjects (depending on the number of cohorts required to reach the MTD). For Part B, approximately 174 subjects may be enrolled. The "Other NEC/NET" and "Other Solid Tumor" cohorts will each enroll 30 subjects. The rationale for the sample size is based on the assumption that an objective response rate (ORR) of around 15% would be indicative of efficacy worthy of further investigation, given the advanced cancers and extensive treatment history in this study population. Conversely, response rates less than 5% would indicate lack of efficacy. A sample size of 25 subjects would produce a 90% two-tailed confidence interval (CI) of 5.7% to 33.0% around an observed response rate of 16.0%.

STUDY TESTS AND OBSERVATIONS:

Safety assessments include physical examinations, vital signs, body weight, Eastern Cooperative Oncology Group (ECOG) score, monitoring of AEs, laboratory tests (hematology, serum chemistries, urinalysis, and coagulation), electrocardiograms (ECGs), echocardiograms (ECHOs), fluid retention questionnaire, and monitoring of concomitant medications.

Efficacy assessments will consist of radiographic imaging. Responses will be categorized by Response Evaluation

Criteria in Solid Tumors (RECIST v1.1) (Eisenhauer 2009). Prostate cancer subjects will also be categorized by Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria (Scher 2016), including the use of bone scintigraphy and prostate-specific antigen (PSA) testing, as described in Appendix 13.6.

PK assessments will include blood samples for rovalpituzumab tesirine and anti-therapeutic antibodies (ATAs).

Pharmacodynamic and biomarker assessments will include analyses of tumor tissue for DLL3 expression, and blood samples for tumor markers, circulating tumor cells, and soluble biomarkers, such as soluble DLL3.

Changes from baseline in PROs, utilizing the EORTC QLQ-C30 and EQ-5D-5L, will be assessed.

STATISTICAL METHODS:

As a general strategy, data will be analyzed by disease, cohort, and dose regimen.

Safety analysis will include summaries by disease, by cohort, and/or by dose level of: AEs, laboratory measures, physical examinations, ECGs, and vital signs using data from subjects in the Safety Analysis set. The incidence of DLTs will be summarized using data from the DLT-Evaluable Set (defined as all subjects who receive any amount of study drug and either experienced a DLT, or were followed for the full DLT evaluation period).

The ORR will be reported with category counts, percentage, and 90% two-tailed CI. Duration of response (DOR), progression-free survival (PFS), and overall survival (OS) will be evaluated using Kaplan-Meier estimates, and curves will be generated based on these estimates.

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Definitions of Abbreviations and Terms

ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AR	accumulation ratios for exposure-related PK parameters
AST	aspartate aminotransferase
AT	aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the curve
$AUC_{0-\tau}$	AUC within a dosing interval
β-hCG	beta-human chorionic gonadotropin
BRAF	proto-oncogene B-Raf and v-Raf murine sarcoma viral oncogene homolog B
BSA	body surface area
BUN	blood urea nitrogen
C1D1	Cycle 1 Day 1
CBC	complete blood count
CBR	clinical benefit rate
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CgA	chromogranin A
CI	confidence interval
CL	plasma clearance
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRF	case report form
CRP	C-reactive protein
CT	computerized tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	cytotoxic T-lymphocyte antigen 4
C_{trough}	concentration at trough
D6.5	the deoxyribonucleic acid (DNA) cross-linking agent SC-DR002
DILI	drug-induced liver injury
DLL3	delta-like protein 3
$DLL3^{hi}$	delta-like protein 3 positive in ≥50% tumor cells
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid

DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic CRF
EDC	electronic data capture
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
EOT	end of treatment
EOS	end of study
EORTC	European Organization for Research and Treatment of Cancer
EQ-5D-5L	EuroQoL Five Dimension Questionnaire
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
FMTC	familial medullary thyroid carcinoma
FSH	follicle stimulating hormone
GBM	glioblastoma
GCP	Good Clinical Practice
GEP	gastroenteropancreatic
GEP NEC	gastroenteropancreatic neuroendocrine carcinoma
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IAC	intermediate atypical carcinoma
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IHC	immunohistochemistry or immunohistochemical
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous(ly)
KIT	proto-oncogene c-Kit
LCNEC	large cell neuroendocrine carcinoma

LDH	lactate dehydrogenase
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEK	mitogen-activated protein kinase
MEN	multiple endocrine neoplasia
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
MTD	maximum tolerated dose
NASH	non-alcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NEC	neuroendocrine carcinoma
NEPC	neuroendocrine prostate cancer
NET	neuroendocrine tumor
NSAIDs	non-steroidal anti-inflammatory drugs
NSE	neuron-specific enolase
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBD	pyrrolobenzodiazepine
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Clinical Trials Working Group 3
PD	progressive disease or disease progression
PD-1	programmed death receptor-1
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	per os (by mouth, orally)
PR	partial response
PRO	patient reported outcomes
PSA	prostate-specific antigen
PT	prothrombin time
PTT	partial thromboplastin time
Q3wk	every 3 weeks
Q6wk	every 6 weeks
QLQ-C30	Quality of Life Questionnaire-Core 30 questionnaire
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate by Fridericia's formula
RANO	Response Assessment in Neuro-Oncology
RECIST	Response Evaluation Criteria in Solid Tumors

RET	rearranged during transfection receptor tyrosine kinase
rova-T	rovalpituzumab tesirine
RP2D	recommended Phase 2 dose
RF	rheumatoid factor
S100B	S-100 calcium-binding protein B
SAE	serious adverse event
SC16	humanized DLL3-specific IgG1 monoclonal antibody
SAP	Statistical Analysis Plan
SC16	humanized DLL3-specific IgG1 monoclonal antibody
SCLC	small cell lung cancer
SD	stable disease
SMC	Safety Monitoring Committee
SPF	sun protection factor
SRS	stereotactic radiosurgery
TEAE	treatment-emergent adverse event
TKI	tyrosine kinase inhibitor
T_{max}	time of maximum concentration
TPC	tumor perpetuating cells
$t_{½}$	terminal half-life
ULN	upper limit of normal
USP	United States Pharmacopeia
VAS	visual analog scale
VEGF	vascular endothelial growth factor
$V_{dβ}$	volume of distribution
WOCBP	woman of childbearing potential
WHODRUG	World Health Organization Drug

1. Introduction

1.1 Delta-like Protein 3

Delta-like protein 3 (DLL3) is an inhibitory ligand of the Notch receptor family. It is highly expressed in high-grade tumors of neuroendocrine origin such as small cell lung cancer (SCLC), including its tumor perpetuating cells (TPCs), but with no detectable expression in normal tissues or non-neuroendocrine tumor types (Saunders 2015; Stemcentrx data on file). While the function of DLL3 has not been clearly defined, it has been implicated in the regulation of cell development and fate decisions (Chapman 2011; Dunwoodie 1997).

1.2 Rovalpituzumab Tesirine

Rovalpituzumab tesirine (SC16LD6.5) is a DLL3-targeted antibody-drug conjugate (ADC) consisting of the humanized DLL3-specific IgG1 monoclonal antibody SC16; the deoxyribonucleic acid (DNA) cross-linking agent SC-DR002 (D6.5); and a protease-cleavable linker that covalently links SC-DR002 to SC16. The primary mechanism of rovalpituzumab tesirine is binding of the ADC to DLL3 on target-expressing cells, followed by internalization of the ADC-DLL3 complex and release of SC-DR002 via proteolytic cleavage in late endosomes. Interstrand crosslinks of cellular DNA induced by intercalated SC-DR002 leads to cellular cytotoxicity. ADCs like rovalpituzumab tesirine represent a potential advantage over traditional chemotherapy by delivering cytotoxic agents to specific target cells, resulting in an improved safety profile.

In a Phase 1 study (Study SCRX16-001), rovalpituzumab tesirine dosed at 0.2 – 0.4 mg/kg exhibited encouraging efficacy in recurrent SCLC, achieving a 31% (8/26) and 85% (22/26) central review-adjudicated confirmed objective response rate (ORR) and clinical benefit rate (CBR), respectively, in subjects whose tumors expressed DLL3 in ≥ 50% of cells. Median overall survival was 7.7 months in DLL3 ≥ 50% subjects at all dose levels, with a 1-year survival rate of 30%. The most frequent grade 3 or worse treatment-related adverse events in 74 patients with small-cell lung cancer were thrombocytopenia (11%), pleural effusion (8%), and increased lipase (7%). Drug-related serious adverse events occurred in 28 (38%) of 74 patients. The recommended phase 2 dose and schedule is 0·3 mg/kg every 6 weeks (AbbVie Stemcentrx, data on file).

In a Phase 2 SCRX001-002 (TRINITY) study in patients with SCLC recurrent after at least two systemic chemotherapy regimens, rovalpituzumab tesirine dosed at 0.3 mg/kg every 6 weeks for two cycles (with an option for additional two cycles upon progression occurring ≥ 12 weeks after the second dose) had shown confirmed objective response rate of 16%, progression-free survival of 3.9 months and overall survival of 5.6 months in 3rd line DLL3^{High} patients. Of note, prolonged stable disease with target lesion size reduction has been observed in a considerable number of patients receiving additional post-progression cycles of rovalpituzumab tesirine. Drug related grade 3 or above treatment emergent adverse events that occurred in at least 10 subjects include thrombocytopenia (11%), photosensitivity reactions (7%), anemia (4%), fatigue (4%),

and pleural effusion (4%). Adverse events leading to study treatment discontinuation occurred in7% of subjects (AbbVie Stemcentrx, data on file).

1.3 DLL3-Expressing Cancers Other than Small Cell Lung Cancer

Several other cancers of neuroendocrine origin appear to express DLL3 in a significant proportion, including melanoma (~25%), medullary thyroid carcinoma (MTC; >50%), glioblastoma (GBM, ~70%), and neuroendocrine cancers, including large-cell neuroendocrine carcinoma (LCNEC, ~80%), neuroendocrine prostate cancer (NEPC, ~10%), and high-grade gastroenteropancreatic neuroendocrine carcinoma (GEP NEC, ~20%) (Saunders 2015; Stemcentrx data on file). Novel therapeutic approaches continue to be needed for each of these cancers, as described below.

1.3.1 Metastatic Melanoma

Although most cases of cutaneous melanoma are diagnosed at an early stage when surgical excision can be curative, some patients have metastatic disease at presentation (2–5%), and/or develop metastases after initial definitive treatment. Primary treatment for metastatic melanoma currently involves immunotherapy, consisting of programmed death receptor-1 (PD-1) inhibitors (e.g., nivolumab, pembrolizumab), typically in combination with a cytotoxic T-lymphocyte antigen 4 (CTLA4) inhibitor (e.g., ipilimumab), and/or kinase inhibitors (e.g., BRAF inhibition with vemurafenib or dabrafenib, MEK inhibition with trametinib, or KIT inhibition with imatinib) in patients with corresponding driver mutations (e.g., in *BRAF* or *KIT*). Nonetheless, recurrence remains virtually inevitable despite these therapies, with median durations of response (DORs) of only 5–6 months and progression-free survival (PFS) generally less than 1 year (National Comprehensive Cancer Network, NCCN Melanoma 2016; Dummer 2015).

1.3.2 Medullary Thyroid Carcinoma

Medullary thyroid carcinoma (MTC) accounts for approximately 1–2% of thyroid cancers. MTC is characterized by the production of calcitonin, and is often associated with mutations in the *RET* proto-oncogene, either sporadically or as a component of the type 2 multiple endocrine neoplasia (MEN) syndromes, MEN2A and MEN2B, and the related syndrome, familial MTC (FMTC). Most localized MTC responds to locoregional therapies, including surgery and/or radiation therapy, but metastatic disease is present in 10–15% of patients at the time of diagnosis, and may develop after failure of definitive therapy. Frontline systemic therapy in this setting typically involves a tyrosine kinase inhibitor (TKI) such as vandetanib or cabozantinib, where clinical benefit (partial response [PR] or stable disease [SD]) in 50–60% of subjects has been observed. However, benefit duration is generally limited to about 12–24 months, with toxicities often requiring drug withdrawal or dose reduction (NCCN Thyroid 2015; Wells 2015).

1.3.3 Glioblastoma

Glioblastoma (GBM), the most common primary malignant adult brain tumor, accounts for about 54% of all gliomas, and may arise *de novo* (primary GBM), usually in older patients, or evolve from a low-grade glioma (secondary GBM). Initial treatment typically includes a combination of surgery and radiation therapy, including adjunct local nitrosourea chemotherapy (carmustine). The alkylating agent temozolomide has emerged as the standard of care, in conjunction with postoperative radiation therapy for younger patients with good performance status. Nonetheless, the prognosis for GBM remains poor and it remains the most lethal brain tumor: nearly all GBMs recur, with only one-third of patients surviving for 1 year and less than 5% beyond 5 years. (NCCN CNS 2015; Stupp 2014).

1.3.4 Neuroendocrine Carcinomas

The neuroendocrine tumors (NETs) comprise a rare, but broad family, often sporadic, but sometimes arising in the context of inherited genetic syndromes, such as MEN types 1 and 2. Poorly-differentiated tumors are high grade neuroendocrine carcinomas (NECs) with clinical behavior distinct from well-differentiated NETs, and may occur in a wide variety of organs, including lung, intestine and pancreas, and prostate. Early-stage cancers may sometimes be amenable to surgical resection and chemotherapy, with or without radiotherapy. Otherwise, radiotherapy in combination with chemotherapy or chemotherapy alone is generally considered for unresectable locoregional or metastatic disease, respectively — typically following SCLC guidelines. SCLC regimens, such as cisplatin or carboplatin in combination with etoposide, are commonly used for primary chemotherapy, although somatostatin analogues are sometimes considered for symptom control in hormone-secreting or scintigraphy-positive cases (NCCN NEC 2015; Oberg 2012; Oberg, Knigge 2012). Nonetheless, prognosis remains poor, with most series describing overall survival (OS) less than 18 months (e.g., Hainsworth 2006; Sorbye 2013; Yamaguchi 2014).

1.4 Rationale for the Study and Anticipated Risks

Rovalpituzumab tesirine may be effective in multiple cancers that express DLL3. This study will explore further the safety, tolerability, and potential therapeutic utility of rovalpituzumab tesirine in subjects with such non-SCLC DLL3+ tumors, with the intent to provide the basis for further development of rovalpituzumab tesirine in one or more of these evaluated indications.

As of 30 June 2016, 104 subjects (SCLC or LCNEC) had received at least one dose of rovalpituzumab tesirine at doses ranging from 0.05 mg/kg to 0.8 mg/kg on an every 3 weeks (Q3wk) schedule (34 subjects) and 0.3 mg/kg to 0.4 mg/kg on an every 6 weeks (Q6wk) schedule (70 subjects).

The most frequently reported treatment-emergent adverse event (TEAE) terms in all treated subjects were fatigue (49%), pleural effusion (34%), and dyspnea (31%); the most frequently reported TEAE terms considered related to rovalpituzumab tesirine by the Investigator were fatigue (35%), pleural effusion (28%), and peripheral edema (26%).

The most frequently reported Grade 3/4 TEAEs were dyspnea (14%), pleural effusion (12%), and fatigue (11%); the most frequently reported Grade 3/4 TEAEs considered related to rovalpituzumab tesirine were pleural effusion and thrombocytopenia (10% each), and fatigue and increased lipase (6% each).

Serious adverse events (SAEs) were reported in 49 subjects (47%), 26 (25%) were considered related to rovalpituzumab tesirine by the Investigator. The most common SAE was pleural effusion, occurring in 18 subjects (17%); all occurrences were considered related to rovalpituzumab tesirine. The second most common related SAE was pericardial effusion, in 8 subjects (8%). Six subjects experienced a fatal AE, 2 of which were considered related to rovalpituzumab tesirine (acute kidney injury and tumor hemorrhage).

Preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified the bone marrow, lung, and kidney as a potential source of clinical adverse events (AEs) (refer to Section 4.3.1 of the current Rovalpituzumab Tesirine Investigator's Brochure [IB]; Stemcentrx data on file). Accordingly, safety assessments will include regular assessments at protocol-specified time points of routine physical examination, laboratory and imaging tests, as well as echocardiograms (ECHOs), a fluid retention questionnaire, daily weights, and untimed (spot) analysis of protein.

2. Objectives

2.1 Primary Objective

- To assess the safety and tolerability of rovalpituzumab tesirine in subjects with specific delta-like protein 3 (DLL3)-expressing advanced solid tumors.

2.2 Secondary Objectives

- To explore the antitumor activity of rovalpituzumab tesirine in subjects with specific DLL3-expressing advanced solid tumors.
- To study the pharmacokinetics (PK) of and incidence of anti-therapeutic antibodies (ATA) against rovalpituzumab tesirine in subjects with specific DLL3-expressing advanced solid tumors.

2.3 Exploratory Objectives

- To explore the expression of DLL3 in specific delta-like protein 3-expressing advanced solid tumors, and its relationship to clinical outcome during treatment with rovalpituzumab tesirine.
- To explore the effect of rovalpituzumab tesirine on disease biomarkers and pharmacodynamics.
- To assess change in patient reported outcomes (PRO) within the expansion cohorts (Part B) utilizing the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ-C30) questionnaire and EuroQoL Five Dimension Questionnaire (EQ-5D-5L) during treatment with rovalpituzumab tesirine.

2.4 Endpoints

2.4.1 Safety Endpoints

- Adverse events (AEs)
- Vital signs
- Physical examination
- Body weight
- Laboratory abnormalities
- Electrocardiographic parameters (e.g., QT interval corrected for heart rate [QTc], QT interval corrected for heart rate by Fridericia's formula [QTcF])
- ECHO
- Components of a fluid retention questionnaire

2.4.2 Efficacy Endpoints

- Response assessments according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1) (Eisenhauer 2009), including ORR and CBR
- DOR
- PFS
- PFS status after 6 months from the initiation of study treatment
- OS
- Prostate cancer only:
  - Response assessments according to Prostate Cancer Clinical Trials Working Group 3 (PCWG3), including prostate-specific antigen (PSA) response rate, DOR, and radiographic PFS
  - Circulating tumor cell (CTC) conversion rate (e.g., ≥5 CTCs/7.5 mL to <5 CTCs/ 7.5 mL)
- GBM only:
  GBM will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria. (Appendix 13.3.4)

2.4.3 Patient Reported Outcomes Endpoint

- Change in PROs (based on the EORTC QLQ-C30 and EQ-5D-5L questionnaires)

2.4.4 Pharmacokinetics, Biomarker, and Pharmacodynamic Endpoints

- Specific PK parameters of rovalpituzumab tesirine (e.g., maximum concentration [C_{max}], area under the curve [AUC])
- ATA against rovalpituzumab tesirine
- Tumor DLL3 expression
- Inflammatory markers (locally tested)
- Blood tumor markers
- Biomarkers, including soluble DLL3
- CTCs

3. Investigational Plan

3.1 Summary of Study Design

This is a multicenter, open-label study of rovalpituzumab tesirine in subjects with DLL3-expressing advanced solid tumors. The study will include 7 cohorts of subjects with the following cancers:

1. Malignant melanoma
2. Medullary thyroid cancer (MTC)
3. Glioblastoma
4. Large cell neuroendocrine carcinoma (LCNEC) of any origin
5. Neuroendocrine prostate cancer (NEPC)
6. High-grade gastroenteropancreatic neuroendocrine carcinoma (GEP NEC)
7. Other neuroendocrine carcinoma (NEC) and high grade neuroendocrine tumors (NET)
8. Solid tumors other than the above

As of protocol version 4.0, cohort 3 (Glioblastoma) is closed to enrollment. Specific guidance for cohort 3 (Glioblastoma) subjects (protocol version 3.0) are provided in Appendix 13.3.

Each disease-specific cohort will include two parts:

- Part A – Dose-Regimen Finding: Will involve disease-specific dose escalation, and possible dose-interval modification, to define the maximum tolerated dose (MTD) and/or possible recommended Phase 2 dose(s) (RP2Ds).
- Part B – Expansion Cohorts: Disease-specific expansion cohorts may be enrolled. Subjects in the expansion cohorts will be treated with a dose regimen(s) at or below the MTD and/or RP2D determined in Part A.

Dose limiting toxicities (DLTs) will be assessed during the DLT Evaluation Period (Section 3.1.3) for subjects in Part A, the dose regimen finding portion of the trial.

Safety will be monitored throughout the trial by the Safety Monitoring Committee (SMC) consisting at least of a Medical Monitor, Investigators, and the study biostatistician. The SMC will meet routinely to review the emerging safety, select pharmacodynamic and efficacy data, and may make dose-escalation and dosing-interval recommendations. The SMC may recommend further evaluation of safety at a given dose level, investigation of alternative dose regimens, including a dose level that is intermediate to the planned dose levels, modification of the dosing interval, limitation to the maximum number of doses, and/or elimination or cancellation of a dose level(s) in a cohort based on the experience in other cohorts. The SMC will also review cumulative safety data in order to identify safety concerns that may emerge due to cumulative exposure beyond the DLT window. The process for dose-escalation decisions and dose-interval recommendations, and the roles and responsibilities of the SMC may be detailed separately.

Tumor response will be assessed every 6 weeks during active study treatment until 24 weeks, and then every 12 weeks thereafter. Treatment decisions by the Investigator will be based on RECIST v1.1 (and/or PCWG3 for prostate cancer; Appendix 13.7).

Subjects will be eligible to continue treatment until unacceptable toxicity, disease progression (PD), withdrawal of consent, study termination, or completion of a planned course of treatment (if a regimen with a limited number of doses is selected), whichever occurs first. Subjects who discontinue study treatment prior to PD will be evaluated for response every 6 weeks until 24 weeks, then every 12 weeks until PD or initiation of new anticancer treatment, whichever occurs first, and will afterwards be followed for survival until death or study termination, whichever occurs first. Appendix 13.7 includes specific additional guidance for prostate cancer subjects.

Blood samples for PK, immunogenicity, biomarker and pharmacodynamics assessments will be collected at protocol-defined time points to support the study endpoints (Sections 7.4 and 7.5).

3.1.1 Part A Dose-Regimen Finding

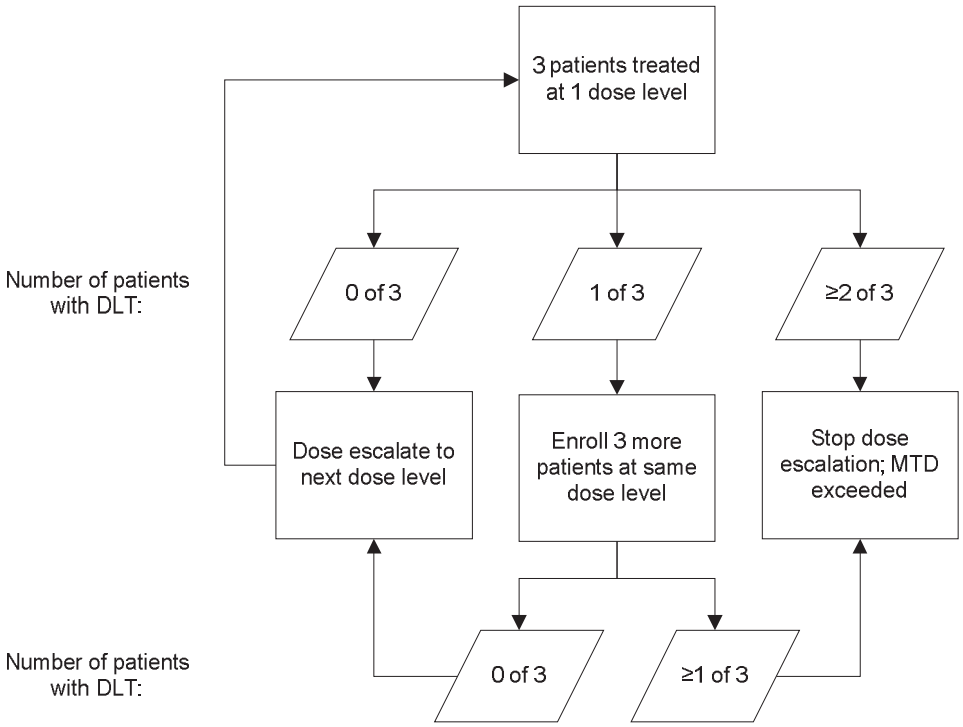
For Part A, the planned dose levels of rovalpituzumab tesirine are presented in Table 3-1. Initially, rovalpituzumab tesirine will be administered according to the Schedule Q6wk, on Day 1 of each 6-week cycle, continuous dosing. If the MTD is determined to be 0.3 mg/kg in the initial 3 dose levels, further dose escalation will be stopped.

Table 3-1 Planned Dose Levels in Part A

Dose Level	Dose Level Schedule Q6wk (every 6 weeks)
1	0.2 mg/kg
2	0.3 mg/kg
3	0.4 mg/kg

A standard 3+3 dose-escalation approach will be utilized (Figure 3-1). Subjects will be enrolled in groups of 3.

Figure 3-1 Dose-Escalation Decision Summary



During 3+3 dose escalation, DLTs will be assessed during the DLT Evaluation Period (Section 3.1.3). If 0 of 3 subjects experience a DLT in a cohort, the next dose level will be opened for enrollment. If ≥2 of 3 subjects in a cohort experience a DLT, the MTD will have been exceeded and dose escalation will stop. If 1 of 3 subjects in a cohort experiences a DLT, an additional 3 subjects will be treated at that same dose level for a total of 6 subjects. If none of the 3 additional subjects experiences a DLT (1 of 6 subjects with a DLT), dose escalation will continue to the next higher dose level. If 1 or more of the 3 additional subjects experiences a DLT (≥2 of 6 subjects with a DLT), the MTD will have been exceeded and dose escalation will not continue. Subjects who do not complete the DLT-evaluation period due to non-DLT reasons will not be considered DLT-evaluable and will be replaced for the DLT evaluation.

The MTD and RP2D will be determined by the Sponsor in consultation with the SMC after a review of all available data. At least 6 subjects must be treated at the putative MTD or RP2D, with no more than 1 incident of DLT.

If 3 or more disease-specific cohorts clear the 0.3 mg/kg or 0.4 mg/kg dose level and the Q6wk schedule, then the SMC may evaluate all the data available to determine an appropriate RP2D and the Part B expansion may proceed for all the cohorts in the study at these dose(s) and schedule.

During dose escalation, additional subjects may be enrolled at a dose level previously declared to be tolerated in order to explore further the safety and tolerability of the regimen. For instance, if

all 3 or 6 subjects necessary for DLT evaluation have been enrolled in a cohort, but have not yet completed the DLT evaluation period, additional subjects may be enrolled at a lower dose level(s), with approval of the Medical Monitor and Sponsor.

3.1.2 Part B Expansion Cohorts

To explore the recommended dosing regimen for distinct disease subsets, subjects will be enrolled in disease-specific expansion cohorts in Part B. The dose regimen(s) to be examined in the disease-specific cohorts will be the MTD determined in Part A or a lower dose(s) and/or regimen(s), depending on the cumulative data. For example, a lower dose regimen may consist of a finite number of doses and/or a mixed-dose regimen, with all doses at or below MTD, but varying based on the cycle. The dose(s), regimen(s) and schedule(s) for each expansion cohort will be determined by the Sponsor in consultation with the SMC. For Part B, approximately 174 subjects may be enrolled. The "Other NEC/NET" and "Other Solid Tumor" cohorts will each enroll 30 subjects. Additional information regarding sample size is provided in Section 10.1, Determination of Sample Size.

3.1.3 Definition of Dose-Limiting Toxicities

The DLT evaluation period is the first 3 weeks of the first cycle of treatment for all subjects in Part A. DLTs are defined as any of the following in the DLT evaluation period, graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03:

- Grade 4 thrombocytopenia (or Grade 3 thrombocytopenia with bleeding) lasting more than 7 days and/or requiring platelet transfusion
- Grade 4 neutropenia lasting more than 7 days, and/or requiring hematopoietic growth factor rescue, or any febrile neutropenia (Grade 3 or 4 neutropenia with concurrent fever ≥38.3°C)
- Grade 4 anemia unrelated to underlying disease
- Clinically-significant Grade 3 or 4 non-hematologic laboratory abnormality that does not resolve to Grade 0/1 or baseline within 7 days
- Grade 3 or 4 non-laboratory AE with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom

The following events will not be considered DLTs:

- Any AE ≥ Grade 3 clearly determined to be unrelated to study drug (e.g., PD)
- ≥Grade 3 isolated alkaline phosphatase, amylase or lipase laboratory abnormality of any duration

3.1.4 Retreatment

Retreatment with rovalpituzumab tesirine may be permitted, with Medical Monitor and Sponsor approval, for subjects who tolerate all doses of rovalpituzumab tesirine, achieve clinical benefit

as defined by stable disease or better, receive no other systemic anti-cancer therapy after rovalpituzumab tesirine as administered in accordance with this protocol, and then experience PD at least 12 weeks after the most recent dose of rovalpituzumab tesirine. The retreatment dose level and regimen for each subject will be determined by the Medical Monitor, Sponsor or designee and the site Investigator, not to exceed the MTD.

3.2 Discussion and Rationale for Study Design

3.2.1 Study Design

This is the first clinical study with rovalpituzumab tesirine that will have cohorts dedicated to specific tumor types other than SCLC. Since the safety and tolerability of rovalpituzumab tesirine in tumor types other than SCLC has not been well-studied, separate dose escalations are planned for each cohort. In addition, some NEC cancer types warrant specific considerations in trial design, such as the utility of bone scintigraphy and PSA in prostate cancer (Kulke 2011; Scher 2016), and the safety and tolerability of rovalpituzumab tesirine may differ in cancers of different primary organs (Stemcentrx data on file). Therefore, some specific NECs will be enrolled and analyzed in distinct cohorts in this study, including LCNEC, NEPC, and high-grade GEP NEC (Section 3.1; Appendix 13.7).

Each Part A dose escalation will utilize a traditional rule-based design, including 3+3 cohorts at anticipated active doses to evaluate the safety and tolerability of multiple dose levels in a disease-specific fashion (Le Tourneau 2009), and will allow definition of the MTD, if one can be identified. In Part B, potential therapeutic doses (i.e., the MTD and/or lower doses as guided by the cumulative clinical experience in Part A) may be studied in expansion cohorts of subjects with specific solid tumor types.

Evaluation of the study endpoints will inform the safety profile of rovalpituzumab tesirine in advanced solid tumors and may provide evidence of antitumor activity that could influence the trial design of subsequent studies.

3.2.2 Method of Assigning Subjects to Treatment Groups

Upon approval of subject registration, the Sponsor or designee will assign each subject to a disease-specific cohort. The cohort assignment decisions will be documented in the clinical trial master file.

3.2.3 Rationale for Selection of Doses

In a Phase 1 study with rovalpituzumab tesirine, the MTD was established at 0.4 mg/kg Q3wk based on the incidence of Cycle 1 toxicities, while the RP2D in SCLC was chosen as 0.3 mg/kg Q6wk based on the toxicity and efficacy profile during multiple cycle dosing (Stemcentrx data on file). For this study, dosing will begin with 0.2 mg/kg Q6wk, a dose level -1 relative to the

RP2D (that was determined for SCLC), and dose escalation is planned to continue through 0.4 mg/kg Q6wk, the MTD in SCLC.

3.2.4 Blinding

This is not a blinded trial.

4. Study Population

Subjects must meet all of the enrollment criteria to be eligible for this study. Eligibility criteria may not be waived by the Investigator and are subject to review in the event of Good Clinical Practice (GCP) audit and/or appropriate health regulatory authority inspection.

To be eligible for retreatment as described in Section 3.1.4, subjects must meet all inclusion and exclusion criteria outlined in this section.

4.1 Inclusion Criteria

1. Ability to provide written informed consent.
2. Histologically confirmed, unresectable advanced solid malignancy other than SCLC.
   Note: Subjects with prostate cancer must also meet the additional prostate-specific criteria in Appendix 13.7.
3. Measurable disease, defined as at least one tumor lesion ≥10 mm in the longest diameter, or a lymph node ≥15 mm in short-axis measurement, assessed by computerized tomography (CT) scan (by RECIST v1.1).
4. Disease refractory to standard therapy or for which standard or curative therapy does not exist or is not considered appropriate by the Investigator.
5. DLL3-expressing malignancy based on central immunohistochemical (IHC) testing of representative baseline tumor tissue (archived tissue or on-study biopsy). Positive is defined as staining in ≥1% of tumor cells.
6. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Refer to Appendix 13.3 for conversion of performance status using Karnofsky scales, if applicable.
7. Minimum life expectancy of at least 12 weeks.
8. Subjects with a history of central nervous system (CNS) metastases must have documentation of stable or improved brain imaging for at least 2 weeks after completion of definitive treatment and within 2 weeks prior to first dose of Study Drug, off or on a stable dose of corticosteroids. Definitive treatment may include surgical resection, whole brain irradiation, and/or stereotactic radiation therapy. (Applicable to tumor types of non-CNS primary origin only).
9. Recovery to Grade 1 of any clinically significant toxicity (excluding alopecia) prior to initiation of study drug administration.
10. Satisfactory laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥1,500/μL.
    b. Platelet count ≥75,000/μL.
    c. Hemoglobin ≥8.0 g/dL.
    d. Total bilirubin ≤1.5× upper limit of normal (ULN) or ≤3× ULN for subjects with Gilbert's disease.

e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5× ULN (≤5× ULN if evidence of hepatic involvement by malignant disease).
f. Creatinine ≤1.5× ULN or estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73m^2.
g. Serum albumin ≥3.0 g/dL

11. Last dose of any prior therapy administered by the following time intervals before the first dose of study drug:
    a. Chemotherapy, small molecule inhibitors, radiation, and/or other investigational anticancer agents (excluding investigational monoclonal antibodies): 2 weeks.
    b. Immune-checkpoint inhibitors (e.g., anti-PD-1, anti-PD-L1, or anti-CTLA-4), monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or T-cell or other cell-based therapies: 4 weeks (2 weeks with documented disease progression).
12. If female, subject must be either postmenopausal defined as:
    - Age >55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤55 years with no menses for 12 or more months without an alternative medical cause AND follicle stimulating hormone (FSH) level >40 IU/L.
      OR
    - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)
      OR
    - A Woman of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 4.3.1) starting at Study Day 1 through at least 6 months after the last dose of study drug.
13. If the male subject is sexually active, he must agree, from Study Day 1 through at least 6 months after the last dose of study drug, to practice the protocol specified contraception (Section 4.3.2).
14. Females of childbearing potential must have a negative serum pregnancy test result at screening and a pre-dose negative urine pregnancy test on Cycle 1 Day 1 (C1D1). Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 4.3) at screening do not require pregnancy testing.

4.2 Exclusion Criteria

1. Any significant medical condition, including any suggested by screening laboratory findings that, in the opinion of the Investigator or Sponsor, may place the subject at undue risk from the study, including but not necessarily limited to uncontrolled hypertension and/or diabetes, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease

requiring hospitalization within 3 months) or neurological disorder (e.g., seizure disorder active within 3 months).

2. Documented history of a cerebral vascular event (stroke or transient ischemic attack), unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III–IV (refer to Appendix 13.5) within 6 months prior to their first dose of study drug.
3. Recent or ongoing serious infection, including:
    a. Any active Grade 3 or higher (according to NCI CTCAE version 4.03) viral, bacterial, or fungal infection within 2 weeks of the first dose of the study drug. Routine antimicrobial prophylaxis is permitted.
    b. Known seropositivity for or active infection by human immunodeficiency virus (HIV).
    c. Active Hepatitis B (by surface antigen expression or polymerase chain reaction) or Hepatitis C (by polymerase chain reaction) infection or on hepatitis-related antiviral *therapy within 6 months of first dose of study drug.*
4. Female subject who is pregnant, breastfeeding, or is considering becoming pregnant during the study or for approximately 6 months after the last dose of study drugs.
5. Male subject who is considering fathering a child or donating sperm during the study for approximately 6 months after the last dose of study drugs.
6. Systemic therapy with corticosteroids at >20 mg/day prednisone or equivalent within 1 week prior to the first dose of study drug.
7. History of another invasive malignancy that has not been in remission for at least 3 years. Exceptions to the 3year limit include non-melanoma skin cancer, curatively treated localized prostate cancer, ductal carcinoma *in situ*, and cervical cancer *in situ* on biopsy or squamous intraepithelial lesion on PAP smear.
8. Prior exposure to a pyrrolobenzodiazepine (PBD)-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity to rovalpituzumab tesirine or excipient contained in the drug formulation, unless undergoing retreatment with rovalpituzumab tesirine in the context of this protocol.

4.3 Contraception Recommendations

In WOCBP, pregnancy testing will be conducted at scheduled time points during screening and the course of the study (refer to Appendix 13.1). Pregnancy testing guidelines are outlined in Section 7.2.9.

4.3.1 Contraception for Female Subjects

If female, subject must be either postmenopausal or permanently surgically sterile (refer to Inclusion Criteria 12) OR a WOCBP, practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 6 months after the last dose of study drug.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
- Bilateral tubal occlusion/ligation.
-
- Vasectomized partner(s), provided the vasectomized partner verbally confirms receipt of medical assessment of the surgical success, and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable].

4.3.2 Contraception for Male Subjects

Male subjects who are sexually active with a WOCBP, even if the male subject has undergone a successful vasectomy, must agree from Study Day 1 through at least 6 months after the last dose of study drug to use condoms and his female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential).

Male subject agrees not to donate sperm from Study Day 1 through at least 6 months after the last dose of study drug.

4.4 Removal of Subjects from Therapy or Assessment

The Sponsor or its designee must be notified if a subject is withdrawn from study treatment or from the study. The reason(s) for withdrawal must be documented in the subject's medical records and case report form (CRF). When a subject withdraws from treatment, all safety data normally required at the end of the study (i.e., the end-of-treatment visit and long-term follow-up) will be obtained if possible.

4.4.1 Discontinuation of Study Drug

Treatment with study drug may be discontinued for any of the following reasons:

- Progressive disease (PD) per RECIST 1.1
- Adverse event
- Physician decision
- Study terminated by sponsor
- Withdrawal by subject
- Other

4.4.2 Subject Discontinuation from Study

Any subject may be discontinued from the study for any of the following reasons:

- Withdrawal by subject
- Death
- Physician decision
- Lost to follow-up
- Study terminated by Sponsor
- Other

5. Treatments

5.1 Treatments Administered

Rovalpituzumab tesirine, the investigational agent under study in this protocol, is an ADC. Detailed information describing the preparation, administration, and storage of rovalpituzumab tesirine is located in the Pharmacy Binder.

5.2 Investigational Product: Rovalpituzumab Tesirine

5.2.1 Description

Rovalpituzumab tesirine drug product is provided in a sterile clear USP Type I 10 mL glass vial and includes histidine hydrochloride, sucrose and polysorbate 20. A complete description of the chemistry and formulation are provided in the Investigator's Brochure.

5.2.2 Packaging and Labeling

Rovalpituzumab tesirine is provided in sterile clear USP Type I, 10 mL glass vials. The vials and/or primary vial carton will have labels bearing the appropriate label text as required by governing regulatory agencies.

5.2.3 Dosing

The actual dose is based on the subject's actual body weight on C1D1 to the nearest kilogram, and administered according to the assigned dose. If the subject's actual weight at subsequent cycles is within 10% of the C1D1 weight, the dose will not be adjusted due to weight changes. Otherwise, the dose will be adjusted based on the actual body weight to the nearest kilogram at that cycle. Rovalpituzumab tesirine will be administered intravenously (IV) over 30 minutes (treatment window: 20 to 40 minutes) on Day 1 of each 6-week cycle.

Subjects must meet all of the following on each dosing day before receiving study drug:

- ANC ≥1,000/μL
- Platelet count ≥75,000/μL
- Resolution to Grade 0 or 1, or to baseline grade if pre-existing, of any clinically-significant AEs or laboratory abnormalities occurring during the previous cycle

5.2.4 Dose Modifications

Information and guidelines regarding Part A dose-regimen finding, including information regarding DLTs and the methods for determination of the MTD, are provided in Section 3.1.1. Information regarding Part B expansion cohorts is provided in Section 3.1.2.

Instructions for dose modifications for individual subjects in the Part A dose-regimen finding and Part B expansion groups are the same. No intrasubject dose escalation will be permitted. Adjustments to Dose Modification Guidelines may occur based on the clinical judgment of the Investigator with approval from the Medical Monitor.

5.2.4.1 Dose Holds or Delays

Subjects who experience DLT in Cycle 1 should not receive further treatment with study drug unless clinical benefit is demonstrated with adequately managed toxicity and there is approval from the Medical Monitor and/or Sponsor. The subsequent dose level will be defined by the Medical Monitor and/or Sponsor in discussion with the site Investigator in the context of the type of AE observed.

If a subject has a clinically significant, unresolved AE on Day 1 of Cycle 2 or beyond, the start of the cycle may be delayed for up to 12 weeks. Longer dose delays may be permitted with the approval of the Medical Monitor if there was no documented PD. The AE must resolve to baseline or ≤Grade 1 prior to proceeding with treatment, unless the AE is determined to be clearly unrelated to study drug, or toxicity has been adequately managed.

Serosal effusions (e.g., pleural, pericardial, or ascites) that have been drained should remain stable or improved for at least 2 weeks prior to resumption of dosing (refer to Table 5-1, below).

5.2.4.2 Clinical Monitoring of Grade 3 or Grade 4 Adverse Events

Subjects who experience Grade 3 or 4 non-laboratory AEs will require weekly or more frequent clinical assessments, as appropriate. The assessments should include review of AEs, concomitant medications, vital signs, weight, physical examination, ECOG performance status, laboratory and other testing, as clinically appropriate.

Subjects who experience Grade 3 or 4 hematologic AEs should have repeat complete blood count (CBC) assessment at least every 3 days or more frequently, as clinically appropriate, until resolution of hematologic toxicity to Grade 2 or lower.

Subjects who experience Grade 3 or 4 non-hematologic laboratory AEs will require more frequent laboratory assessments, as clinically appropriate, until resolution of the AEs.

Subjects who experience Grade 3 or 4 laboratory abnormalities may require more frequent laboratory assessments, as clinically appropriate.

5.2.4.3 Dose Reductions Due to Adverse Events

Subjects who experience a Grade 3 or 4 AE (unless the AE is determined to be clearly unrelated to study drug) should have a dose reduction in subsequent treatment cycles to dose level -1 or -2, or as suggested following discussion with the Medical Monitor and/or Sponsor. If the Grade 3 or 4 AE recurs after dose reduction, study treatment must be permanently discontinued. Table 5-1 displays specific toxicities requiring dose reduction and/or discontinuation. Adjustments to these guidelines may occur based on the clinical judgment of the Investigator and with approval of the Medical Monitor.

Table 5-1 Toxicities Requiring Dose Reduction

Toxicities Requiring 1 Dose Level Reduction at First Occurrence – **2nd occurrence = 2nd dose level reduction** – ***Discontinue after 2 dose level reductions***	
Serosal Effusions and Edema	• Grade 2 or higher pericardial effusion • Grade 2 or higher pleural effusion • Grade 2 or higher ascites • Grade 2 or higher peripheral edema
Hematology	• Grade 3 thrombocytopenia (platelets <50.0–25.0 × 10^9/L) • Grade 4 neutropenia (ANC <0.5 × 10^9/L) lasting more than 7 days • Grade 3 or higher febrile neutropenia (with ANC <1.0 × 10^9/L) (concurrent fever ≥38.3° C)
Laboratory Abnormalities	• Clinically significant Grade 3 or higher non-hematologic laboratory abnormality that does not resolve to Grade 0/1 or baseline within 7 days • Any other Grade 3 or 4 laboratory abnormality considered clinically significant and treatment-related; adjustments to these guidelines may occur based on the clinical judgment of the Investigator and with approval of the Medical Monitor and Sponsor • Grade 2 hypoalbuminemia
Other Adverse Events	• Grade 3 photosensitivity reaction (Section 5.5.2) • Grade 3 or Grade 4 nonlaboratory treatment-related toxicity, with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom
Toxicities Requiring 2 Dose Level Reductions at First Occurrence – ***Discontinue at second occurrence***	
• Grade 3 serosal effusions (pleural effusions, pericardial effusions, and ascites) and edema • Grade 2 capillary syndrome • Grade 4 thrombocytopenia/ Grade 3 thrombocytopenia with bleeding/ Need for platelet transfusion • Grade 4 febrile neutropenia • Grade 4 (>20.0 × ULN) ALT or AST or Grade 3 (>5.0–20.0 × ULN) ALT or AST elevation with concomitant total bilirubin Grade 2 or higher (>1.5 ULN) • Grade 3 or higher hypoalbuminemia (<2 g/dL) • Grade 2 pneumonitis	

Toxicities Requiring Discontinuation of Investigational Product at First Occurrence
• Grade 4 photosensitivity or skin reaction (Section 5.5.2) • Drug induced liver injury is confirmed (refer to Section 5.5.3 for definition) • Life threatening Infusion related reaction or hypersensitivity • Grade ≥3 pneumonitis

Abbreviations: ALT = alanine aminotransferase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; DILI = drug induced liver injury; INR = International normalized ratio; ULN = upper limit of normal.

5.3 Required Premedication and Postmedication

All subjects enrolled will receive premedication consisting of dexamethasone orally (PO) at 8 mg twice daily given on Day –1, Day 1 (the day of dosing), and Day 2 of each cycle. Dexamethasone will be provided through a subject's local prescription by Investigator or other provider (i.e., dexamethasone will not be provided by the Sponsor). When dexamethasone is not available, the glucocorticoid-equivalent dose of an alternate corticosteroid may be administered. Parenteral (e.g., IV) administration may be substituted for PO at the discretion of the Investigator.

5.4 Concomitant Therapy

All concomitant medications, blood products, procedures and radiotherapy administered will be recorded from Day 1 (predose) through the safety reporting period (Section 7.2 and Appendix 13.1). Any concomitant therapy given for a study protocol-related AE should be recorded from the time of informed consent.

5.4.1 Required Concomitant Therapy

Other than dexamethasone (Section 5.3), there are no required concomitant therapies. However, due to the potential for rovalpituzumab tesirine-related skin photosensitivity, subjects should be advised to avoid unprotected sun exposure and use a broad spectrum sunscreen (sun protection factor [SPF] of at least 30), protective clothing, a broad-brimmed hat, and sunglasses when outdoors or when driving or riding in the car for more than 1 hour, with re-application of sunscreen as activity-appropriate.

5.4.2 Allowed Concomitant Therapy

Standard supportive care for drug-related toxicity is permitted, including growth factors and blood product transfusions in accordance with local institutional standards. Other standard supportive care for symptom control or drug-related toxicity is allowed, such as analgesics, anti-emetics, electrolyte replacement, and hydration. Bone modifying agents for bone metastases are also permitted in accordance with local institutional standards. Other prescribed medications for non-neoplastic conditions are allowed, as well as vitamins and nutritional supplements.

Further ongoing treatments may be permitted for prostate cancer subjects according to Appendix 13.7.

Concomitant prednisone (or equivalent) may be used at a dose of ≤20 mg/day. The use of intermittent high-dose corticosteroid treatment to prevent or manage hypersensitivity reactions, serosal effusions (refer to Section 5.5.1), or other non-cancer-related symptoms, including premedication for known hypersensitivity reactions to contrast for scans is allowed.

Routine prophylaxis with vaccines is permitted; however, vaccines used should not contain live micro-organisms.

If the subject is taking chronic suppressive anti-infectives (antiviral, antifungal, or antibacterial), appropriate investigation must be completed prior to registration and documentation must exclude active infection. The subject should continue suppressive anti-infectives for the duration of study participation.

Palliative radiation therapy is permitted. Study drug must be held during therapy. If more than 6 weeks have elapsed since the previous dose of study drug, the subject should undergo a radiographic tumor assessment before restarting study drug. If PD is detected in new sites, the subject will be required to discontinue study treatment (but may be eligible for re-treatment according to Section 3.1.4).

5.4.2.1 Treatment of Isolated Central Nervous System Progression

In the event of isolated CNS progression during study treatment, study drug may be withheld while palliative treatment is administered, e.g., a standard course of whole brain radiotherapy or stereotactic radiosurgery (SRS) in accordance with institutional practice, and restarted within 1 week after completion of radiotherapy. During this time the subject should be fully evaluated for other sites of progression. If more than 6 weeks have elapsed since the previous dose of study drug, the subject should undergo a radiographic tumor assessment before restarting study drug. If additional sites of PD are present, the subject will be required to discontinue study treatment (but may be eligible for re-treatment according to Section 3.1.4).

5.4.3 Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, or systemic anti-neoplastic therapy during the study, other than as allowed in Sections 4, 5.2.4, and 5.4.2, and Appendix 13.7.

5.5 Management of Adverse Reactions

5.5.1 Serosal Effusions

Serosal effusions (pleural or pericardial, or ascites) have been observed with rovalpituzumab tesirine, and have the potential to be life-threatening (e.g., pericardial tamponade). Therefore,

development of any of these events, or worsening from baseline, warrants prompt evaluation by the Investigator or designee. Cytology analysis should be done for pleural and pericardial effusion as appropriate. Alternative causes, such as infection, congestive heart failure, or PD, should be ruled out. When appropriate, a unifying diagnosis or reached diagnosis should be reported (e.g., "heart failure," not simply "pleural effusion" and "edema limbs"). When considered clinically significant (e.g., Grade 2 or higher and considered related to study drug):

- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases. The Investigator should consider a tapering regimen, such as dexamethasone up to 8 mg orally twice a day for 5 days, followed by 4 mg orally twice a day for 5 days, then 2 mg orally twice a day for 5 days. Alternatively, nonsteroidal therapies for serositis may be considered, such as non-steroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen 400–600 mg orally 3 to 4 times daily) or colchicine (e.g., 0.6 mg orally 2 to 3 times daily) given for 1–2 weeks.
- Until clinical experience suggests otherwise, guidance for dose delay and/or reduction, as well as criteria for ongoing dosing, should follow Section 5.2.4.

5.5.2 Skin Reactions

Recommendations for management of photosensitivity reactions are outlined below in Table 5-2.

Photosensitivity was reported in patients treated with Rova-T including severe events. Photosensitivity reactions may occur hours to days after sun exposure. The median time to onset was 30 days (range 1 to 247 days). Patients should be advised to avoid direct and indirect sun exposure as much as possible during Rova-T treatment and for 30 days after the last dose. If unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). 31 – 90 days after last dose, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher. Skin reactions should be evaluated promptly and treated with topical or systemic steroids as indicated (refer to Table 5-2). Rova-T dose should be delayed, reduced or discontinued as necessary (refer to Table 5-1)

All cutaneous reactions which develop during treatment warrant prompt evaluation. Skin toxicity with rovalpituzumab tesirine may consist of photosensitivity but possibly other reactions such as palmar-plantar erythrodysesthesia or erythema multiforme. As such, development of a cutaneous reaction during treatment warrants prompt evaluation by the Investigator or designee:

- If clinically consistent with photosensitivity, the AE should be reported as such (using medically accurate and descriptive AE terminology), and managed as described below in Table 5-2.

- For clinically more severe cases of photosensitivity or if clinically not consistent with photosensitivity, photodocumentation to facilitate later review by the Sponsor or designee may occur.
  - Formal evaluation by a dermatologist, including possible skin biopsy to rule out alternative etiologies, such as erythema multiforme which may warrant discontinuation of study drug, and to facilitate the most appropriate terminology for AE reporting, is recommended.
  - Photodocumentation of skin toxicity, if available, may be requested by the TAMD. The investigative site will take measures to protect the identity of the patient. These measures include taking the photograph very close to the affected skin region to exclude facial features, or if facial features cannot be excluded due to the location of the skin reaction, covering identifying features (such as the eyes) with a black rectangle.

All events of cutaneous toxicity should be monitored until resolution or return to baseline.

Table 5-2 Recommended Management of Photosensitivity

CTCAE v4.03		Treatment Recommendations	Dose Modifications
Grade 1	Painless erythema and erythema covering <10% BSA	Low-potency topical steroid (face) High-potency topical steroid (body)	–
Grade 2	Tender erythema covering 10–30% BSA	Low-potency topical steroid (face) High-potency topical steroid (body) Nonsteroidal anti-inflammatory agents orally as needed	–
Grade 3	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Low-potency topical steroid (face) High-potency topical steroid (body) Prednisone 0.5 mg/kg × 7 days	Reduce dose
Grade 4	Life-threatening consequences; urgent intervention indicated	Low-potency topical steroid (face) High-potency topical steroid (body) Prednisone 0.5 mg/kg × 7 days Hospitalization	Reduce dose

BSA = body surface area; CTCAE = Common Terminology Criteria for Adverse Events; NSAIDs = non-steroidal anti-inflammatory drug.

5.5.3 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury (DILI) event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug-induced liver injury is defined as:

- ALT or AST elevation >3× ULN; ***and***
- Concurrent total bilirubin >2× ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase), ***and***
- No other immediately apparent possible causes of aminotransferase (AT) elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease or tumor(s), or the administration of other drug(s) known to be hepatotoxic

In general, an increase of AT to >3× ULN should be followed by repeat testing within 48–72 hours of all four of the usual measures (ALT, AST, alkaline phosphatase, total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. Inquiry regarding symptoms should also be made (e.g., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash). Subjects may be retested locally, but normal laboratory ranges should be recorded and results made to the Investigator immediately. All data must be recorded in the CRF. If symptoms persist or repeat testing shows AT >3× ULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, close observation should be initiated. If close monitoring is not possible, study drug should be discontinued.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests 2 or 3 times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio [INR], direct bilirubin)
- Considering gastroenterology or hepatology consultations

Discontinuation of study drug should be considered if potential DILI is suspected and:

- ALT or AST >8× ULN
- ALT or AST >5× ULN for more than 2 weeks

- ALT or AST >3× ULN and (TBL >2× ULN or INR >1.5)
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia

All subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state.

5.5.4 Monitoring and Management of Edema

- The majority of the edema events with rovalpituzumab tesirine have been reported as low grade 1 or 2 (mild or moderate); however, a small number of fatal events of generalized edema have been reported with rovalpituzumab tesirine. Physical exams and monitoring of weight gain and signs or symptoms of fluid retention should be conducted during treatment.
- Consistent with institutional guidelines or standard practice, the use of diuretics with or without albumin may be considered in subjects with clinically significant edema and hypoalbuminemia. The selection and use of diuretics in subjects should be based on individual clinical characteristics and include monitoring of electrolyte status and signs or symptoms of intravascular volume depletion such as hypotension and impaired renal function.
- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases.

5.5.5 Monitoring and Management of Pneumonitis:

- Pneumonitis has been infrequently reported with rovalpituzumab tesirine but has resulted in fatal outcomes. Although the causal role of rovalpituzumab tesirine could not be ruled out, the reports of pneumonitis had one or more confounders including underlying pulmonary disease/cancer, prior thoracic radiation, prior cytotoxic chemotherapy or clinical evidence suggestive of an alternative diagnosis including pneumonia.
- Heavily pretreated SCLC patients and patients with a history of pneumonitis may be at increased risk, and careful monitoring for signs and symptoms of pneumonitis is important. The risk of pneumonitis is increased with prior radiation to lung.
- In general signs and symptoms coinciding with or preceding pneumonitis may include new or worsening cough, chest pain and/or shortness of breath, fever, and radiographic changes (reticular markings, ground glass opacities). Protocol defined disease assessments provide for the opportunity for on study pulmonary monitoring for detection of pneumonitis. The protocol allows for additional imaging per physician discretion for signs and symptoms of pulmonary toxicity.

- The diagnosis of drug induced pneumonitis is one of exclusion. Other etiologies including infection, which is a common cause of pulmonary infiltrates with clinical and radiographic appearance similar to drug-induced pneumonitis, need to be carefully considered and excluded before the diagnosis of drug induced pneumonitis can be established.
- If pneumonitis is suspected, close monitoring including additional laboratory and imaging investigation per institutional guidelines may be necessary. Systemic corticosteroids may be beneficial for rapidly progressive or more severe pneumonitis.

For Grade 1 pneumonitis, monitor closely. For dose modification, please see Table 5-1 of the protocol.

5.6 Treatment Compliance

Study drug administration must be performed by study site staff and documented in source documents and the CRF.

6. Study Activities

6.1 Enrollment

Once screening procedures have been completed for the subject, the Registration and Enrollment Form will be completed and submitted to the Sponsor or designee to confirm eligibility. Refer to the study manual for the enrollment form, contact numbers, and other details of enrollment.

AEs and concomitant therapies will be recorded from Day 1 (predose) through the safety reporting period (Section 7.2 and Appendix 13.1). At the same time, subjects will maintain a diary of daily weights, which will be recorded in the CRF. Any study protocol-related AE should be recorded from the time of informed consent as well as any concomitant therapies given for treatment of the AE. Schedules of events are provided in Appendices 13.1 and 13.2. Study activities are listed by visit in this section and descriptions of all study assessments are presented in Section 7.

Subjects undergoing retreatment as described in Section 3.1.4 will follow the same study schedule from screening through end of treatment (EOT) and long-term follow-up (LTFU).

6.2 Screening Visit (Days -15 to -1)

- Informed consent – omitted for retreatment subjects
- Demographics (Section 7.1) – omitted for retreatment subjects
- Study eligibility – according to Inclusion/Exclusion Criteria (Section 4)
- Medical and surgical history (Section 7.1) – omitted for retreatment subjects
- Malignancy history (Section 7.1) – omitted for retreatment subjects
- Prior anticancer treatments (Section 7.1) – omitted for retreatment subjects
- Physical examination (Section 7.2.1)
- Vital signs (Section 7.2.2)
- Height (Section 7.2.2)
- PRO questionnaires EORTC QLQ-C30 and EQ-5D-5L – for subjects in Part B of the study only (Section 7.3.2)
- Complete blood count (Section 7.2.3)
- Serum chemistries (Section 7.2.3)
- Coagulation tests (Section 7.2.3)
- Urinalysis (Section 7.2.3)
- Hepatitis B and C tests (Section 7.2.3) – omitted for retreatment subjects
- Pregnancy test (Section 7.2.9) – for women of childbearing potential
- Electrocardiogram (ECG) in triplicate (Section 7.2.4)
- ECHO – the screening ECHO should be done any time before the first dose of study drug.

- ECOG performance status (Appendix 13.3)
- Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated; Section 7.3) – may be omitted for retreatment subjects if recent scans demonstrating PD are within 2 weeks of study drug dosing (Day 1 of the first cycle of retreatment).
- MRI of the brain – may be omitted for retreatment subjects if recent scans demonstrating PD are within 2 weeks of study drug dosing (Day 1 of the first cycle of retreatment). CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.
- Tumor tissue – Collected upon an archived or fresh specimen (Section 7.5.1). Previously obtained DLL3 tumor expression results may be substituted if assessed previously via central immunohistochemistry assessment – omitted for retreatment subjects.
- Prostate cancer subjects only:
  - Serum total testosterone – omitted for retreatment subjects
  - 99mTc Bone Scintigraphy (Section 7.3) – may be omitted at initial screening if scans have been performed within 2 weeks. May be omitted for retreatment subjects if recent scans demonstrating PD are within 2 weeks of study drug dosing (Day 1 of the first cycle of retreatment).

6.3 Treatment Period

The treatment period for subjects in Schedule Q6wk is Day 1 to 42 of each 6-week cycle.

6.3.1 Day -1 (Day before Dosing)

- Subjects will take dexamethasone 8 mg PO twice a day

6.3.2 Day 1 (±2 Days)

If screening visit activities occur within 1 day prior to Cycle 1, Day 1, the following pre-dose assessments do not need to be repeated at the Cycle 1, Day 1 visit: physical examination, ECOG performance status, and local safety labs (CBC, chemistries, coagulation tests, urinalysis, pregnancy test; if obtained within 1 calendar day).

Day 1 procedures may be performed within 1 calendar day prior to dosing of study drug. Results from local clinical laboratory tests (at least CBC with differential and serum chemistry panel) must be available prior to dose.

- Physical examination (Section 7.2.1)
- Vital signs – within 30 minutes prior to the infusion, then post-infusion at 30 minutes after start of infusion (±10 minutes), 2 hour (±15 minutes) and 4 hour (±30 minutes; Section 7.2.2)

- PRO questionnaires EORTC QLQ-C30 and EQ-5D-5L – for subjects in Part B of the study only; to occur at screening, Cycle 2 (Days 1 and 29), and EOT (Section 7.3.2)
- CBC (Section 7.2.3)
- Serum chemistries (Section 7.2.3)
- Coagulation tests (Section 7.2.3)
- Urinalysis (Section 7.2.3)
- Pregnancy test (Section 7.2.9) – for women of childbearing potential
- ECG in triplicate – within 180 minutes prior to infusion, and then post-infusion at 30 minutes (±10 minutes; Section 7.2.4)
- ECHO (Section 7.2.5) – The screening ECHO should be done any time before the first dose of study drug; all ECHOs after C1D1 should be conducted within 4 days before the next dosing.
- ECOG performance status (Section 7.2.6)
- Fluid retention questionnaire (Section 7.2.7)
- Blood sample for PK – Should be drawn within 30 minutes prior to the infusion, and then post-infusion at 30 minutes after start of infusion (±10 minutes). In Cycles 1 and 2, an additional sample will be taken at 6 hour (±30 minutes). The 6 hour PK sample is required for Cycles 1 and 2 only - omitted for retreatment subjects.
- Blood sample for ATA
- Blood inflammatory markers (Section 7.5.2)
- Blood tumor markers (Section 7.5.3)
- Soluble biomarkers (Section 7.5.4)
- Circulating tumor cells (CTCs), collected at Cycle 1 Day 1. (Section 7.5.5)
- Subjects will take dexamethasone 8 mg PO twice a day (the first dose of the day should be at least 30 minutes, but no more than 4 hours, prior to the rovalpituzumab tesirine dose)
- Administration of rovalpituzumab tesirine (Section 5.1)

6.3.3 Day 2

- Subjects will take dexamethasone 8 mg PO twice a day

6.3.4 Day 3 (Window +1 Day) of Cycles 1, 2, and 4 Only

- ECG in triplicate (Section 7.2.4)
- Blood sample for PK for Cycles 1 and 2 only – omitted for retreatment subjects

6.3.5 Days 8 and 15 (± 2 Days) and 29 (± 3 Days)

- Physical examination (Section 7.2.1)
- Vital signs (Section 7.2.2)

- PRO questionnaires EORTC QLQ-C30 and EQ-5D-5L – for subjects in Part B of the study only; to occur at screening, Cycle 2 (Days 1 and 29), and EOT (Section 7.3.2)
- CBC (Section 7.2.3)
- Serum chemistries (Section 7.2.3)
- Urinalysis (Section 7.2.3)
- Fluid retention questionnaire (Section 7.2.7)
- Blood sample for PK for Cycles 1 and 2 only – omitted for retreatment subjects

In Cycles 5 and higher, the Day 8 visit may be reduced to a virtual visit consisting only of the Fluid retention questionnaire (similar to visits on Days 22 and 36, Section 6.3.6), but only if the previous 4 consecutive cycles lacked any clinically significant AEs. Visits on Days 15 and 29 must consist of all above procedures in all cycles.

6.3.6 Days 22 (± 2 Days) and 36 (± 3 Days)

- Fluid retention questionnaire (Section 7.2.7) – may be conducted virtually

6.3.7 Disease Assessment

- Disease assessment consists of CT scans of the chest, abdomen, and pelvis (and neck if indicated; Section 7.3). Tumor response will be assessed every 6 weeks counting from Cycle 1 Day 1, preferably before each dosing if possible, until 24 weeks, then every 12 weeks, thereafter.
- MRI of the brain – if clinically indicated (e.g., if CNS progression has been documented previously). CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator. CNS lesion will be assessed every 6 weeks counting from Cycle 1 Day 1, preferably before each dosing if possible, until 24 weeks, then every 12 weeks, thereafter.
- Prostate cancer subjects only: 99 mTc Bone Scintigraphy, will be assessed every 6 weeks counting from Cycle 1 Day 1, preferably before each dosing if possible, until 24 weeks, then every 12 weeks, thereafter (Section 7.3).).

6.4 End-of-Treatment Visit

The EOT visit occurs 42 ±3 days after the last dose of study drug or within 7 days of documentation of the decision to discontinue treatment, whichever is later.

- Physical examination (Section 7.2.1)
- Vital signs (Section 7.2.2)
- PRO questionnaires EORTC QLQ-C30 and EQ-5D-5L – for subjects in Part B of the study only; to occur at screening, Cycle 2 (Days 1 and 29), and EOT (Section 7.3.2)
- CBC (Section 7.2.3)
- Serum chemistries (Section 7.2.3)

- Coagulation tests (Section 7.2.3)
- Urinalysis (Section 7.2.3)
- Pregnancy test (Section 7.2.9) for women of child-bearing potential
- ECG in triplicate (Section 7.2.4)
- ECHO (Section 7.2.5) – The EOT ECHO should be conducted on EOT (±3 days) (Appendix 13.1).
- ECOG performance status (Appendix 13.3)
- Fluid retention questionnaire (Section 7.2.7)
- Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated) – may be omitted if a Disease/Response Assessment was performed within the last 6 weeks (Section 7.3)
- MRI of the brain – if clinically indicated (e.g., if CNS progression has been documented previously); may be omitted if a Disease/Response Assessment was performed within the last 6 weeks. CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.
- Blood sample for PK
- Blood sample for ATA
- (Optional) fresh tumor tissue, collected at PD (Section 7.3)
- Blood inflammatory markers (Section 7.5.2)
- Blood tumor markers (Section 7.5.3)
- Soluble biomarkers (Section 7.5.4)
- CTCs (Section 7.5.5)
- Prostate cancer subjects only: 99mTc Bone Scintigraphy – may be omitted if performed within the last 6 weeks (Section 7.3)

6.5 Long-Term Follow-up (LTFU; Every 6 to 12 Weeks ±1 Week)

For all subjects without PD (including those who discontinue study treatment for reasons other than PD), the first follow-up visit will occur at 6 weeks (±1 week) after the last dose of study drug, then every 6 weeks (±1 week) until 6 months, then every 12 weeks (±1 week), consisting of:

- Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated; Section 7.3)
- MRI of the brain – if clinically indicated (e.g., if CNS progression has been documented previously). CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.
- Blood tumor markers (Section 7.5.3)
- Circulating tumor cells (Section 7.5.5)

- Prostate cancer subjects only: 99mTc Bone Scintigraphy (Section 7.3)
- Survival status

At progression, an optional collection of fresh tumor tissue may be conducted (Section 7.3).

After PD, subjects who are not retreated will be followed for subsequent anticancer therapies and dates, as well as survival status, similarly every 6 weeks (±1 week) until 6 months, then every 12 weeks (±1 week).

6.6 End of Study/End of Follow-Up

The date the subject met criteria for study discontinuation and the reason for study discontinuation will be recorded. Where available, subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status will be recorded.

7. Study Assessments

7.1 Screening/Baseline Assessments

Only subjects who meet all inclusion and exclusion criteria specified in Section 4 (and Appendix 13.7, for prostate cancer subjects) will be enrolled in this study.

Absence of active CNS tumor or metastases will be confirmed by MRI of the brain. CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.

Demographics include age, gender, and race.

Subject medical history includes a thorough review of significant past medical history, current conditions, smoking history, any diagnosis and treatment for prior malignancies, including response to treatment, and any concomitant therapies.

Malignancy history should include tumor type, stage, grade and grading system, sites of metastases, and mutational status. The latter should include, at least, status of *BRAF* for melanoma subjects, and *RET* for MTC subjects.

Standard of Care procedures completed prior to the subject signing ICF, but within the study screening window, may be used as screening procedures.

7.1.1 Central Immunohistochemistry Assessment

For all subjects, tumor tissue representative of the qualifying malignancy must be submitted to a central laboratory for determination of DLL3 expression. An archived tumor specimen, or a fresh specimen, obtained via on-study biopsy, may be used. DLL3 positivity, for purposes of eligibility, will be defined as staining in ≥1% tumor cells. The central assessment will be definitive regarding DLL3 expression, which will be relayed to the Investigator. All decisions regarding study eligibility will be based upon DLL3 expression adjudicated by this central assessment.

7.2 Safety Assessments

In addition to the surveillance and recording of AEs, the assessment of safety during the course of this study will consist of the recording of concomitant therapies, protocol-specified physical examination findings including vital signs, daily weight diary, ECOG performance status, disease assessments, and diagnostic testing (including laboratory testing, radiographic imaging, ECGs and ECHOs).

Safety will be monitored over the course of the study by an SMC.

7.2.1 Physical Examination

Physical examinations will include assessments of the head and neck, heart, lungs, abdomen, extremities, neurological and skin.

7.2.2 Vital Signs, Weight and Height

Vital signs will include heart rate, respirations, blood pressure, temperature, and weight. All vital signs should be measured after the subject has been sitting/resting for at least 5 minutes. For adult subjects (>18 years), measurements of height obtained within the prior 6 months may be utilized. In the event of an infusion reaction or hypersensitivity reaction, vital signs should be monitored more frequently than originally scheduled and as clinically indicated.

Weight will be measured at the times indicated, preferably without outer garments such as hats, coats or shoes. Measurements while in light indoor clothing only, or undergarments only, are acceptable; but every effort should be made to measure subjects in the same or similar clothing, including any accessories or jewelry, at each assessment.

7.2.3 Clinical Laboratory Tests

Laboratory assessments will be performed to evaluate safety at scheduled time points (refer to Appendix 13.1) during the course of the study. The following assessments will be performed at the local laboratory:

- CBC, including white blood cell (WBC) count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell (RBC) **count**, platelet count, hemoglobin, and hematocrit.
- Chemistry panel, including electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, blood urea nitrogen (BUN), calcium, phosphorus, magnesium, estimated glomerular filtration rate, glucose, albumin, total protein, amylase, lipase, and liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase [LDH]).
- Coagulation tests, including prothrombin time (PT), activated partial thromboplastin time (aPTT)/partial thromboplastin time (PTT), and INR.
- Urinalysis, including dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as untimed (spot) analysis of protein and creatinine for ratio.
- Hepatitis B and C tests include Hep B surface antigen (HBsAg), Hep B surface antibody (HBsAb), Hep B core antibody (HBcAb) and hepatitis C virus (HCV) antibody. Results that may be consistent with chronic or active infection, and/or subjects with known prior active hepatitis B or C infection, should undergo polymerase chain reaction (PCR) tests for Hep B and/or C, respectively.
- Pregnancy test, consisting of blood or urine testing for beta-human chorionic gonadotropin (β-hCG). Repeat testing may be performed as requested by the Investigator.

7.2.4 Electrocardiograms

Throughout the study, subjects will be monitored for changes in cardiac conduction through ECGs. ECGs will be done in triplicate at the times indicated in Appendices 13.1 and 13.2.

7.2.5 Echocardiogram

ECHOs will be performed at the indicated times (Appendix 13.1) to assess any pericardial effusions, if present, as well as cardiac function (left ventricular ejection fraction, LVEF).

7.2.6 ECOG Performance Status

ECOG performance Status (Appendix 13.3) will be evaluated at protocol-specific time points (Appendix 13.1).

7.2.7 Fluid Retention Questionnaire

Throughout the treatment period, subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix 13.9). This assessment may take place virtually (e.g., by phone).

7.2.8 Daily Weight Diary

Throughout the treatment period, subjects will maintain a diary of daily weights.

7.2.9 Pregnancy Testing

In WOCBP, pregnancy testing will be conducted at scheduled time points during screening and the course of the study (refer to Appendix 13.1). Contraception recommendations are outlined in Section 4.3.

7.3 Radiographic Response/Efficacy Assessments

Radiographic evaluations at protocol-specified time points include:

- CT scans of the chest, abdomen and pelvis (scans of the neck must also be obtained for MTC and/or if there is documented or suspected involvement in this region)
- MRI of the brain, if indicated. CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.
- Whole-body technetium-99m (99mTc) bone scintigraphy (prostate cancer subjects only)

Diagnostic quality, spiral CT scans are recommended; other methods may be used if performed consistently throughout the study for each individual subject. Positron emission tomography (PET) and/or octreotide/somatostatin scans may be used in an ancillary manner; however, no decisions relating to PD may be made based on PET or octreotide/somatostatin scans alone. Clinical response will be determined by the Investigator at each assessment according to RECIST v1.1 (Appendix 13.6; Eisenhauer 2009), and/or for prostate cancer subjects, PCWG3 criteria (Appendix 13.7).

For tumors to be assigned a status of responder (PR or CR), changes in tumor measurements must be confirmed by repeat assessments performed no less than 4 weeks, but preferably not more than 6 weeks, after the criteria for response are first met; i.e., two consecutive assessments of PR or CR are required. In instances where a follow-up visit is not otherwise scheduled to occur for more than 6 weeks, repeat radiographic disease assessments should be conducted at least 4 but not more than 6 weeks after the criteria for response are first met, in order to confirm response, whether or not a formal follow-up visit is conducted at the same time.

7.3.1 Radiographic Disease Progression

Radiographic PD will be defined as either of the following:

- PD by RECIST v1.1 (refer to Appendix 13.6)
- Confirmed PD by Bone Scan (for prostate cancer subjects using PCWG3 criteria; Appendix 13.7)

Treatment beyond what would be considered PD using RECIST v1.1 or PCWG3 is permitted if the following criteria, as assessed by the Investigator, are met:

- Ongoing clinical benefit, without rapid PD
- Subject continues to meet all other study protocol eligibility criteria
- Tolerance of study drug
- Stable ECOG performance status

Treatment beyond progression must not delay an imminent intervention to prevent serious complications of PD (e.g., CNS metastases).

Subjects' clinical data must be available for CRF source verification. Copies of tumor images must be made available for review by the Sponsor or its designee upon request.

7.3.2 Patient Reported Outcomes

PROs will be evaluated for subjects in Part B of the study (only) by assessment of health-related quality of life and symptoms using the EORTC QLQ-C30 and EQ-5D-5L questionnaires. The questionnaires will be completed during screening, Cycle 2 (Days 1 and 29), and EOT (as outlined in the Schedule of Assessments Appendix 13.1). Additional details regarding the questionnaires are provided in Section 10.3.9.

7.4 Pharmacokinetic Assessments

Blood samples for PK and ATA testing will be collected throughout the study as indicated in Appendices 13.1 and 13.2.

Sensitive, qualified assays will be used to measure plasma concentrations of rovalpituzumab tesirine ADC (SC16LD6.5). Plasma concentrations of rovalpituzumab total antibody and blood concentrations of SC-DR002, the small molecule component of rovalpituzumab tesirine, may

also be measured if deemed necessary and appropriate. A qualified immunoassay will be used to assess ATA against rovalpituzumab tesirine.

7.5 Pharmacodynamic and Biomarker Assessments

Blood and/or tissue samples for pharmacodynamics and biomarker testing will be collected at the time points throughout the study as indicated in Appendices 13.1 and 13.2. Refer to the laboratory manual for additional details.

AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on rovalpituzumab tesirine (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion, or per local requirement.

7.5.1 Tumor Tissue

Tumor tissue, consisting of a representative archived specimen, or a fresh tumor biopsy, will be assessed at baseline for expression of DLL3 by methods such as but not necessarily limited to immunohistochemistry (Section 7.1.1). Additional studies, such as routine hematoxylin and eosin for morphology and histological classification, IHC for confirmation of diagnosis (e.g., for synaptophysin, chromogranin-A, or CD56 for neuroendocrine tumors, or HMB45, S100, or MART-1 for melanoma), or scoring of immune infiltrates (e.g., IHC for CD3+, CD4+, CD8+, and Foxp3+ cells) may be performed. Tumor material may also be utilized for exploratory research that includes assessments of nucleic acid or protein based biomarkers of drug sensitivity, resistance, or disease biology and development of a companion diagnostic assay.

At PD, an optional tumor biopsy may be performed for the assessment of expression of DLL3 and/or execution of additional studies, such as but not necessarily limited to scoring of immune infiltrates or assessment of molecular pathways related to the response to rovalpituzumab tesirine. Tumor material may also be utilized for exploratory research that includes assessments of nucleic acid or protein based biomarkers of drug sensitivity, resistance, or disease biology and development of a companion diagnostic assay. Additional instructions will be provided in the laboratory manual.

7.5.2 Inflammatory Markers

At the indicated times, blood will be collected for local testing of inflammatory markers, including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), and rheumatoid factor (RF).

7.5.3 Blood Tumor Markers

At the indicated times, blood will be collected for testing of tumor-specific biomarkers, including but not necessarily limited to, the disease-specific biomarkers in Table 7-1.

Table 7-1 Disease-Specific Blood Tumor Markers

Note: Blood tumor markers are NOT collected for Cohort 8, Other Solid Tumors.

Tumor	Calcitonin	CEA	CgA	LDH	NSE	PSA	S100B
Melanoma				X			X
MTC	X	X					
All NECs (Cohorts 4, 5, 6, and 7)		X	X		X	X[a]	

Abbreviations: CEA = carcinoembryonic antigen; CgA = chromogranin A; LDH = lactate dehydrogenase; MTC = medullary thyroid carcinoma; NEC = neuroendocrine carcinoma; NSE = neuron-specific enolase; PSA = prostate-specific antigen; S100B = S-100 calcium-binding protein B.

[a] Required for prostate cancer subjects only.

7.5.4 Soluble Biomarkers

At the indicated times, blood samples will be collected for possible testing of biomarkers that may be related to the pharmacodynamics effects of rovalpituzumab tesirine, such as but not necessarily limited to, soluble DLL3, or circulating chemokines or cytokines such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), interleukin (IL)-6 or IL-8.

7.5.5 Circulating Tumor Cells

At the indicated times, blood samples from subjects with neuroendocrine prostate cancer will be collected for assessment and characterization of CTC as a possible reflection of disease burden for central processing at all sites. A sample for exploratory analyses of CTC-associated biomarkers, such as DLL3, will be collected from subjects with large cell neuroendocrine carcinoma (cohort 4), neuroendocrine prostate cancer (cohort 5), and high-grade gastroenteropancreatic neuroendocrine carcinoma (cohort 6).

7.5.6 Serosal Fluid

Any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis) will be procured, where feasible, for possible PK, pharmacodynamic and/or biomarker testing. Refer to the laboratory manual for additional details. For clinical serosal effusions, refer to Section 7.2.3.

7.5.7 Biospecimen Repository

For subjects who provide additional written consent, remaining de-identified unused clinical samples (blood and/or tissue) will be retained by the Sponsor and used for the Sponsor's future research, including, but not limited to, the evaluation of DLL3 and of additional targets for novel therapeutic agents, the biology of DLL3, and to identify biomarkers. Blood and tissue samples donated for future research may be retained by the Sponsor or its designee indefinitely or as permitted by the applicable laws and regulations in the relevant country in which the study is conducted. If additional written consent is not provided, any remaining biological samples will be destroyed by Sponsor or its designee following study completion.

8. Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

The investigational product in this study is defined as rovalpituzumab tesirine. Complaints associated with any component of this investigational regimen must be reported to the Sponsor (Section 8). For AEs, please refer to Section 8.1. For product complaints, please refer to Section 8.2.

8.1 Medical Complaints

The Investigator will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The Investigator will assess and record any AE in detail, including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the AE to study drugs, and any action(s) taken. For SAEs considered as having "no reasonable possibility" of being associated with study drugs, the Investigator will provide another cause of the event. For AEs to be considered intermittent, the events must be of similar nature and severity. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All AEs will be followed to a satisfactory conclusion.

8.1.1 Definitions

8.1.1.1 Adverse Events

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE.

Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention (including interruption/dose reduction of study drug, starting or discontinuing medication, etc.), meets protocol specific criteria (refer to Sections 5.5 and 8.1 regarding toxicity management) and/or if the Investigator considers them to be AEs.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

All protocol-related AEs must be collected from the signing of the study specific informed consent until study drug administration.

In addition, AEs with onset or worsening reported by a subject from the time that the first dose of study drug is administered until 70 days have elapsed following discontinuation of study drug administration will be considered as TEAEs.

8.1.1.2 Serious Adverse Events

If an AE meets any of the criteria outlined in Table 8-1, the AE is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE.

Table 8-1 Criteria for a Serious Adverse Event (SAE)

Death of Subject	An event that results in the death of a subject.
Life Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility, or hospitalization for respite care.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Note: For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate CRF.

8.1.1.3 Adverse Events Expected Due to Cancer Progression

The term "disease progression" alone should not be used when reporting AEs or SAEs, due to its lack of specificity. Rather, symptoms of disease progression (PD) should be collected under the unifying diagnosis of "malignant neoplasm progression;" symptoms of progression may be subsumed under this diagnosis.

8.1.2 Adverse Event Severity

The Investigator will rate the severity of each AE according to the NCI CTCAE v4.03. If a reported AE **increases** in severity, the initial AE should be given an outcome date and a new AE reported on a different date from the end date of the previous AE to reflect the change in severity. For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect the change in severity.

When CTCAE criteria cannot be used, the event should be graded as defined below:

Grade 1	The adverse event is transient and easily tolerated by the subject (mild).
Grade 2	The adverse event causes the subject discomfort and interrupts the subject's usual activities (moderate).
Grade 3/4	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life threatening (severe).
Grade 5	The adverse event resulted in death of the subject (severe).

8.1.3 Relationship to Study Drug

The Investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility	After consideration of factors, including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors, including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the Investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

If an Investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the Investigator for the SAE.

8.1.4 Deaths

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

Deaths that occur during the protocol specified AE reporting period (Section 8.1.5) that are more likely related to PD will therefore be considered as an expected AE and will not be subject to expedited reporting to regulatory agencies. These SAEs should be reported as "malignant neoplasm progression" and also recorded on the AE eCRF. After the AE reporting period, deaths attributed to PD under study should be recorded only on the end of study (EOS) eCRF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

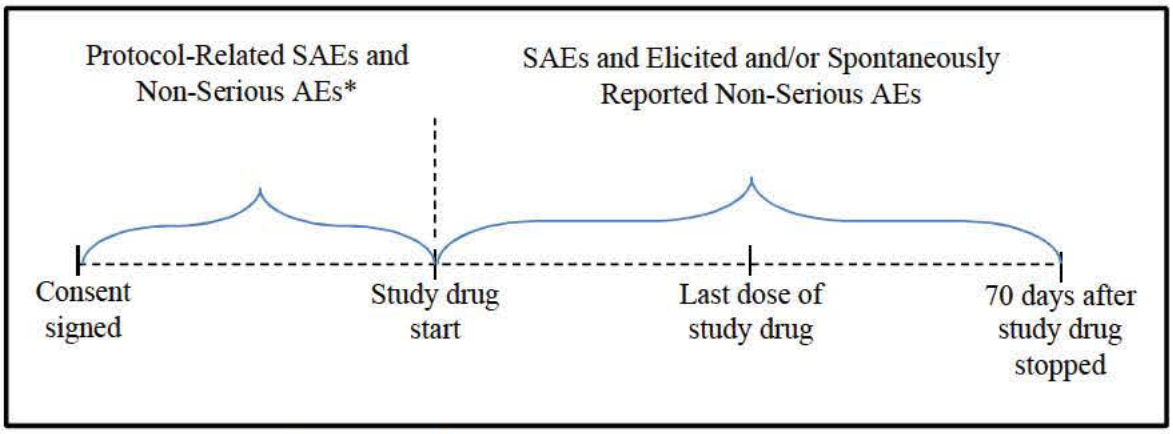
8.1.5 Adverse Event Collection Period

All AEs reported from the time of study drug administration until 70 days following discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious and non-serious AEs will be collected from the time the subject signed the study-specific informed consent.

Serious and non-serious AEs occurring after the study-specific informed consent is signed but prior to the initial dose of study drug will be collected **only** if they are considered by the Investigator to be causally related to the study-required procedures.

AE information will be collected as shown in Figure 8-1.

Figure 8-1 Adverse Event Collection



AE = adverse event; SAE = serious adverse event.
* Only if considered by the Investigator to be causally related to study-required procedures.

8.1.6 Adverse Event Reporting

In the event of an SAE, whether associated with study drug or not, the Investigator will notify Pharmacovigilance and Patient Safety (PPS) by documenting the event on the SAE Non-CRF form that is then emailed (preferred route) or faxed to PPS within 24 hours of the site being made aware of the SAE according to the details in the box below. The same procedure should be followed for SAEs that occur prior to the site having access to electronic data capture (EDC) system, or if the EDC is not operable. Within 10 days of the SAE reporting, the site is also instructed to enter the SAE data onto the AE log in the EDC system, and to mark the event as "Serious".

Email: [redacted]

FAX to: [redacted]

For safety concerns, contact the Oncology Safety Management Team at:

AbbVie Oncology Safety Team
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Email: [redacted]

For any subject safety concerns, please contact the study Medical Monitor listed below:

[redacted], MD, PhD
Novella Clinical
1700 Perimeter Park Drive
Morrisville, NC 27560 USA
Telephone Contact Information:
Phone: [redacted]
[redacted]

In emergency situations involving study subjects when the Medical Monitor is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: [redacted]

8.1.7 Pregnancy Reporting

Pregnancy in a study subject must be reported to the Sponsor within 24 hours of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued.

All subjects should be informed that contraceptive measures (refer to Section 4.3 Contraception Recommendations) should be taken throughout the study and for at least 6 months after the last dose of study drug. Male subjects should be informed that contraceptive measures should be taken by their female partner.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome. In the event a study subject or the partner of an enrolled subject delivers a baby, they will be asked to provide information including the following will be requested: date of delivery, birth weight and length, boy or girl, problems during pregnancy or delivery, and if the baby has any birth defects.

Pregnancy in a study subject is not considered an AE. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

8.2 Product Complaint

8.2.1 Definition

A Product Complaint is any Complaint (refer to Section 8 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

8.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with AEs will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the Investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

8.2.3 Events Commonly Associated in Study Population with Advanced Solid Tumors and/or Progression of Underlying Malignancy

Certain AEs are anticipated to occur in the study population at some frequency independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, PD).

A list of AEs associated with advanced solid tumors is provided in Appendix 13.10. These AEs are preferred terms coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary; the AEs may occur alone or in various combinations and are considered expected for reporting purposes for this protocol. Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, if these AEs meet serious criteria these SAEs must be reported to AbbVie within 24 hours of the site

being made aware of the SAE (as required in Section 8.1.6). For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form (CRF), but the event will not be expedited as an Individual Case Safety Report (ICSR) to regulatory authorities (Section 8.1.4).

8.3 Appropriateness of Measurements

The safety measures that will be used in this trial are considered standard procedures for evaluating the potential adverse effects of study medications. AEs and, when applicable, clinical laboratory data will be graded using NCI CTCAE, version 4.03.

Response will be assessed according to RECIST v1.1 (Eisenhauer 2009), which includes standard criteria for evaluating response in solid tumors. Prostate cancer is assessed by PCWG3 criteria. The intervals of evaluation in this protocol are appropriate for disease management.

Standard tests will be performed to detect the possible presence of specific antibodies to study drug. PK assessments for drug activity are also common in clinical studies.

9. Data Quality Control and Quality Assurance

9.1 Site Training and Monitoring Procedures

A study manual that includes instructions for study compliance and CRF completion will be provided. Prior to the enrollment of subjects at the site, the Sponsor or its designated clinical and medical personnel will review the following items with the Investigator and clinic staff:

- The protocol, study objectives, eligibility requirements, study procedures, registration and withdrawal processes
- Current Investigator's brochure
- Recording and reporting AEs and SAEs
- Enrollment goals and study timelines
- The CRF completion process and source documentation requirements
- Monitoring requirements
- Institutional Review Board/Independent Ethics Committee (IRB/IEC) review and approval process
- Informed consent process
- Good Clinical Practice guidelines and related regulatory documentation requirements
- Key study team roles and responsibilities
- Investigational product storage, accountability, labelling, dispensing and recordkeeping
- Subject coding
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study recordkeeping, document retention, and administrative requirements

Monitoring visits will occur periodically, with frequency dependent on the rate of enrollment and workload at each site. During monitoring visits, the Sponsor representative will review regulatory documentation, CRFs, source documentation, investigational product storage, preparation, and accountability. The CRFs will be reviewed for completeness, adherence to the provided guidelines, and accuracy compared to the source documents. The Investigators must ensure that the monitor is allowed to inspect all source documents pertinent to study subjects, and must cooperate with the monitor to ensure that any problems noted in the course of the trial are resolved. The Investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor or its designated monitors and by quality assurance auditors, or representatives of regulatory authorities.

9.2 Data Management Procedures

The Sponsor or its designee will provide CRF Completion Guidelines for eCRF data entry. Study specific data management procedures will be maintained in the data management plan. Queries

resulting from edit checks and/or data verification procedures will be posted electronically in the eCRF.

9.3 Access to Source Data

The Investigator will permit the Sponsor's representatives to monitor the study as frequently as the Sponsor deems necessary during or after the completion of the study to determine that protocol adherence and data recording are satisfactory. Appropriate measures to protect subject confidentiality are to be employed during monitoring. The CRFs and related source documents will be reviewed in detail by the monitor at each site visit. Original source documents or certified copies must be provided to the Sponsor for review. This review includes inspection of data acquired as a requirement for participation in this study and other medical records as required to confirm that the information contained in the CRFs, such as disease assessments, AEs, and concomitant therapies, is complete and correct. Other study records, such as correspondence with the Sponsor and the IRB/IEC and screening and drug accountability logs will also be inspected. All source data and study records must also be made available during or after completion of the study for inspection by representatives of regulatory authorities. In the event of an inspection by regulatory authorities, the Sponsor may be available to assist in any preparations. All pertinent study data must be made available as requested to the regulatory authority for verification, audit, or inspection purposes.

9.4 Accuracy and Reliability of Data

The Sponsor or its designee shall take steps to assure the accuracy and reliability of data, including:

- The selection of qualified Investigators and appropriate study centers.
- Review of protocol procedures with the Investigators and associated personnel prior to the study.
- Periodic monitoring visits by the designated monitor(s).
- Review of CRFs for accuracy and completeness by the designated monitor(s) during monitoring visits to the study centers. Any discrepancies will be resolved with the Investigator or designees as appropriate.

9.5 Quality Assurance Procedures

The Quality Assurance group or its designee may conduct audits at the clinical site or other study-related facilities and organizations during or at any time after the study. Audit reports will be retained by the Sponsor's Quality Assurance group or its designee as part of the written record.

9.6 Data Handling and Recordkeeping

9.6.1 Data Handling

It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs and in all required reports. The CRFs should be captured in the Sponsor EDC system within ten (10) business days of the subject's visit to the site. Data reported on the CRF that is derived from source documents should be consistent with the source documents or the discrepancies must be explained.

Any change or correction to a CRF must be maintained in an audit trail within the electronic data capture system. Data changes may only be made by those individuals so authorized. The Investigator must retain records of the changes and corrections, written and/or electronic. Prior to database lock the Investigator must review and approve the completed electronic CRFs to verify their accuracy.

9.6.2 Investigator Record Retention

The Investigator shall retain study drug disposition records and all source documentation (such as original ECG tracings, laboratory reports, and in-patient or office patient records) for the maximum period required by the country and institution in which the study will be conducted, or for the following periods, whichever is longer: for at least 2 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or for at least 2 years after the relevant authority has been informed of the discontinuation of clinical development of the study drug. The Investigator may not destroy any records associated with the study without obtaining the prior, written consent of the Sponsor. If the Investigator withdraws from the study (due to relocation, retirement, etc.), the records will be transferred to a mutually agreed upon designee, such as another Investigator or IRB/IEC. No records shall be transferred without prior, written authorization from the Sponsor or its designee.

10. Data Analysis and Statistical Methods

This section provides the key details of the statistical analyses to be performed using data captured according to this protocol. Further details on planned analyses for the data captured in this protocol will be provided in the Statistical Analysis Plan (SAP).

10.1 Determination of Sample Size

Up to approximately 318 subjects are expected to participate in this two-part trial.

In Part A, up to approximately 144 subjects may be enrolled, assuming 3 dose-escalation cohorts of 6 subjects each (18 subjects) across 8 disease cohorts. The exact number will depend on the number of cohorts required to reach the MTD in each disease, and the number of subjects enrolled in each disease-specific cohort.

In Part B, up to approximately 174 subjects may be enrolled, including approximately 19 subjects in each of the 5 disease-specific cohorts. The rationale for the sample size is based on the assumption that an ORR of around 15% would be indicative of efficacy worthy of further investigation given the advanced cancers and extensive treatment history in this study population. Additionally, an ORR below 5% would provide evidence of an ineffective treatment. The goal of the efficacy analyses is to provide a preliminary signal that the response rate may potentially be within that target range.

When Part B is enrolled, each disease-specific cohort will have approximately 25 subjects treated at the RP2D, including the Part A and Part B subjects. Table 10-1 presents the 90% two-tailed lower exact confidence limits for selected response rates.

Table 10-1 Lower Exact 90% Two-Tailed Confidence Limits for Selected Objective Response Rate Results for 25 Subjects

Number of Responses	Response Rate	Lower Confidence Limit
1	4.0%	0.2%
2	8.0%	1.4%
3	12.0%	3.4%
4	16.0%	5.7%

The final decision to pursue the clinical development of any disease-specific cohort will be based on safety evaluations, the complete results of the study, and other factors; fewer than 3 responses could be considered a discouraging result. When 3 or more responses are observed, there is approximately a 75% probability this occurs when the true rate is 15%, but less than 13% when the true rate is 5%. When 4 responses are observed, a 5% rate is excluded by the 90% confidence interval (CI) lower bound.

An interim futility analysis is planned for each cohort, which may have an impact on the number of subjects ultimately enrolled in Part B. The futility analysis is described in Section 10.3.6.

- The Other NEC/NET and Other Solid Tumor cohorts will enroll subjects until all other disease cohorts complete enrollment, and are expected to enroll approximately 30 subjects each by the time of study completion.
- Details will be provided in the SAP.

10.2 Analysis Populations

The following populations will be considered:

- Full Analysis Set: All enrolled subjects who receive any amount of study drug.
- Safety Set: All subjects who receive any amount of study drug and have at least one post-baseline safety evaluation.
- DLT-Evaluable Set: All subjects who receive any amount of study drug and either experienced a DLT or were followed for the full DLT evaluation period.
- Pharmacokinetic-Evaluable Set: All subjects who receive at least 1 dose of study drug and for whom a baseline measurement and at least one blood sample following a dose of study treatment are available.

Based on the actual deviations, the criteria for exclusion of subjects from the different data sets will be specified and updated, if necessary, prior to database lock.

10.3 Planned Analyses

As a general strategy, continuous efficacy and safety endpoints will be summarized using the five-number summary (mean, standard deviation, median, minimum, and maximum). Frequency distributions (counts and percentages) will be used to summarize categorical endpoints.

10.3.1 Disposition of the Study Subjects

The disposition of subjects will be described with summaries by disease and cohort of the number of subjects enrolled, the number of subjects treated, the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation), and the number of subjects who discontinued early from the study.

10.3.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized and compared by disease and cohort. Results will be reported using subjects in the full analysis set.

10.3.3 Exposure to Study Treatment and Compliance

Frequency distributions of the number of received doses will be presented by disease and cohort. Treatment duration and treatment compliance for all randomized subjects will be described by

disease and cohort.

10.3.4 Analysis of Primary Efficacy Endpoints

The first primary efficacy endpoints are the best objective response rate based on RECIST v1.1 and/or, for prostate cancer subjects, PCWG3 criteria. It is defined as the proportion of subjects whose best overall response is either CR or PR according to RECIST v1.1 or PCWG3. The best overall response is the highest recorded response through End of Treatment. The number and percentage of responders along with the corresponding 90% two-tailed CI will be provided for each disease and cohort.

10.3.5 Analysis of Secondary Efficacy Endpoints

The analysis of the secondary efficacy endpoints will be conducted using data from the Full Analysis set.

Burden of disease will be analyzed in a way similar to the analysis of the best ORR (described in the previous section).

DOR will be summarized for responders (*i.e.*, subjects with CR or PR only) by disease and cohort. PFS and OS will be summarized by disease and cohort. The PFS rate at additional time points may also be evaluated (e.g., 26, 39 and 52 weeks). DOR, and PFS, will be obtained by using the Kaplan-Meier approach similar to OS described in the previous section.

Details of the analysis of secondary efficacy endpoints will be described in the Statistical Analysis Plans.

10.3.6 Futility Analysis

A non-binding futility analysis is planned for each cohort when 12 subjects have at least 2 evaluable tumor response evaluations after starting therapy. This analysis is designed to give a timely preliminary signal of response to consider along with cohort safety data to assess the advisability of continuing to enroll the cohort. Reported probabilities are based on exact calculations. There is a 54% chance that a result of 0 responses is observed when the true response rate is 5%. When the response rate in the population is the target rate of interest (15%); the chance of 0 responses is 14%, 1 response 30%, and 1 or more responses 96%. Therefore, observing 1 or more responses at the interim analysis would be supportive of further enrollment.

10.3.7 Safety Analysis

Safety endpoints will be summarized using data from the Safety Set. Safety analyses will involve examination of the incidence, severity, and type of TEAEs reported, changes in vital signs and laboratory test results from baseline (the assessment prior to first dose) to specified time points throughout the study, and concomitant medications use.

10.3.7.1 Treatment Emergent Adverse Events

TEAEs reported during the study will be coded using a Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Incidence of TEAEs will be summarized by disease and cohort and the following:

- System organ class and preferred term
- System organ class, preferred term and severity

These summaries will be presented for the following subsets:

- Serious adverse events
- All adverse events
- Drug-related adverse events
- Adverse events leading to treatment discontinuation

For tables reporting AEs by severity, if a subject has multiple occurrences of an AE with the same organ class and preferred term, the most severe event will be presented.

10.3.7.2 Clinical Laboratory Evaluation

Laboratory parameters will be summarized by disease and cohort at each visit. Each summary will include the values of the laboratory parameters and their change from baseline. Shift tables from baseline will be presented for laboratory values in the chemistry and hematology panels. Parameters will be classified according to the laboratory reference normal ranges. A listing will be provided for out of normal range as well as clinically significant abnormal lab values.

10.3.7.3 Vital Signs

Vital signs, including pulse, blood pressure, temperature, height, and body weight will be summarized by disease and cohort and time point. For each assessment of vital signs, change and percent change in vital signs from baseline will be summarized by disease and cohort.

10.3.7.4 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be summarized for each visit by disease and cohort. Shifts from baseline to the best and worst post-baseline score may be tabulated.

10.3.7.5 Electrocardiogram

Electrocardiogram status will be summarized for each scheduled visit by disease and cohort. Shifts from baseline may be tabulated. Additionally, ECG parameters will be described using the five-number summary.

10.3.7.6 Concomitant Medications

Concomitant medications will be classified according to the anatomical therapeutic chemical codes in the World Health Organization Drug (WHODRUG) dictionary. The incidence rate of

each coded concomitant medication will be tabulated by disease and cohort. The table will be sorted by the incidence use of the entire sample.

10.3.8 Pharmacokinetic and Pharmacodynamics Analyses

Data from the Pharmacokinetic-Evaluable Set will be used in the analysis of PK and Pharmacodynamics endpoints. The PK of rovalpituzumab tesirine will be estimated from concentration-time data using non-compartmental methods. The reporting of PK parameters will be determined based on the final parameter analysis on the available data. The PK parameters that may be assessed include, as appropriate:

- C_{max} Maximum plasma concentration
- AUC Area under the plasma concentration-time curve
- T_{max} Time of C_{max}
- C_{trough} Plasma concentrations at trough
- $t_{1/2}$ (Apparent) terminal half-life
- CL Plasma clearance
- $V_{d\beta}$ Volume of distribution

The above parameters will be summarized by descriptive statistics.

The incidence and timing of ATA to study drug will be summarized by descriptive statistics. The possible effects of ATA on PK, efficacy and safety may be explored. Details will be provided in the SAP.

The five-number summary will be used to describe absolute and percent change from baseline in IHC, blood tumor markers (like NSE), soluble biomarkers (such as soluble DLL3) and circulating tumor cells. Regressions may be performed as appropriate. Exploratory analyses may be performed to evaluate a possible correlation between each of these endpoints and disease response and/or toxicities. Additional analyses may also be performed. Details will be provided in the SAP.

10.3.9 Patient Reported Outcomes (PROs)

PROs will be evaluated for subjects in Part B of the study (only) by assessment of health-related quality of life and symptoms using the EORTC QLQ-C30 and EQ-5D-5L questionnaires. The questionnaires will be completed according to Section 7.3.2 (and as outlined in the Schedule of Assessments, Appendix 13.1). The EORTC QLQ-C30 is a cancer-specific instrument that has 30 items and 5 functional domain scales: Physical, Role, Emotional, Social, and Cognitive; 2 items evaluate global quality of life. The EQ-5D-5L is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L is composed of 5 questions and a visual analog scale (VAS) assessing overall health that can be converted into a single health status or

"utility" score for use in an economic evaluation to adjust life-years gained by the subject's health-related quality of life.

Details of the analysis of PROs will be described in the SAP.

11. Ethical and Regulatory Considerations

This study will be conducted in accordance with ICH Guidance E6 (R1) (ICH 1996); FDA CFR [21 CFR Parts 50, 56, and 312]); Declaration of Helsinki World Medical Association Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, as it may be amended; applicable data protection laws and regulations; and all laws, rules, and regulations applicable to the study or the study drug in jurisdictions in which the Investigator conducts the study.

11.1 Informed Consent

The Investigator is responsible for presenting the risks and benefits of study participation, along with the aims and methods of the study, to the subject in terms understandable to the subject using the IRB/IEC approved Informed Consent Form (ICF). The Investigator will also instruct the subjects that they are free to withdraw their consent and discontinue their participation in the study at any time without prejudice. The Investigator or his/her designee shall re-consent subjects when the ICF is updated during the study, if required. The Investigator will ensure that written informed consent is obtained from each subject or their legally authorized representative, if applicable to this study, by obtaining the signature and date on the ICF prior to the performance of protocol evaluations or procedures.

The ICF will document the study-specific information the Investigator or his/her designee provides to the subject and the subject's agreement to participate in the study and to comply with the instructions of the Investigator and study staff. Informed consent will be verified and countersigned by the Investigator or their designee. If informed consent is obtained from a legally authorized representative for a subject who is unable to provide informed consent at study entry but the subject is later able to provide informed consent, the Investigator must obtain written informed consent from the subject using the IRB/IEC approved ICF.

Prior to the start of the study, the Investigator will provide the Sponsor with an ICF approved by the IRB/IEC for use during the study that is based on Sponsor's model template ICF. The model ICF template prepared by the Sponsor will be provided in the study manual. The proposed ICF and the informed consent process must comply with US regulations 21 CFR Part 50.25 as well as other applicable national and international laws, rules and regulations. The proposed ICF should contain the 20 elements of the informed consent described in ICH E6 4.8 and adhere to the ethical principles of the Declaration of Helsinki. The ICF must have been reviewed and approved by the Sponsor and the study IRB prior to initiation of the study. In addition, any amendments to the ICF will need to be approved by the Sponsor and the IRB/IEC. The ICF must contain, or subjects must separately be provided with, an authorization for use and disclosure of protected health information and include the elements required by 45 CFR Part 164.508(b) for valid authorizations.

Each subject will be given a copy of the signed ICF. The source documents for each subject shall document that the informed consent was obtained prior to participation.

11.2 Confidentiality of Subject Personal Information

During the informed consent process, subjects shall be provided with information in the ICF regarding the confidential treatment of their personal information collected in the study. In addition, an authorization for the collection, use, storage, disclosure, and transfer of subject personal information (an "Authorization") in compliance with applicable laws, rules, and regulations of the jurisdiction where the study is conducted, must be obtained from each subject, either as part of the ICF or as a separate signed document, for example, in the United States a Health Insurance Portability and Accountability Act (HIPAA) Authorization, approved by the IRB and the Sponsor, will be used. Such Authorization shall include the use of personal information by the Sponsor, its representatives, collaborators, licensees and assigns for purposes of conducting and monitoring the study, regulatory submissions and conducting future research related to the diseases or study drug covered by this protocol.

A unique identifier or code will be assigned to each subject to be used in lieu of the subject's name in study documentation and in reporting of AEs for the purpose of ensuring the confidential treatment of the study participant's personal and health information. The Investigator will maintain a master key to the subject identifier list in a secure location at the study site consisting of the unique subject identifiers, subject names, and dates of birth to allow unambiguous identification of each subject included in the study.

Subject personal information that is collected for the study may be transferred to countries outside the country where the study is conducted for purposes relating to the study, including regulatory submissions by the Sponsor. The Authorization will include information on any potential transfer of subject personal information, including, if applicable, a statement that the laws governing the treatment of personal data in countries to which subject personal data is transferred may not be as stringent as those of the country where the study is being conducted.

Researchers, monitors, and auditors shall be required to adhere strictly to professional standards and applicable law concerning the confidential treatment of the subject information.

11.3 Biospecimens

Clinical samples donated by subjects in the study (blood, urine, tissue, etc.) comprise study results of the Sponsor and will be collected and processed in accordance with this protocol and delivered to the Sponsor or Sponsor's designee, as instructed by Sponsor. Clinical samples shall not be retained or used by the Investigator or institution except as expressly permitted by Sponsor in writing. The ICF will contain information on the handling of subject personal

information relating to clinical samples, including, if applicable, the labeling of clinical samples with the subject's unique code.

11.4 Ethics Approval

The Investigator will provide the Sponsor or its designee with documentation of the IRB/IEC approval of the protocol and the ICF before the study may begin at the investigative site(s). The name and address of the reviewing ethics committee will be included in the Investigator file.

The Investigator will supply the following to the investigative site's IRB/IEC:

- Protocol and amendments
- ICF and updates
- Clinical Investigator's Brochure and updates
- Relevant curricula vitae, if required
- Required safety and SAE reports
- Any additional submissions required by the site's IRB/IEC

The Investigator must provide the following documentation to the Sponsor or its designee:

- The IRB/IEC periodic (e.g., quarterly, annual) re-approval of the protocol.
- The IRB/IEC approvals of any amendments to the protocol or revisions to the ICF.
- The IRB/IEC receipt of safety and SAE reports, as appropriate.

11.5 Investigator and Study Personnel Information

The contact information and qualifications of the Principal Investigator, Subinvestigators and name and address of the research facilities shall be included in the Investigator file. The Investigator is responsible for the supervision of study conduct in accordance with this protocol, including collection of and maintenance of adequate and appropriate study documentation. The Investigator may delegate some of the work involved in the conduct of the study to study staff under his/her supervision. The Investigator shall ensure that all study staff are qualified by education, experience, and training to perform their specific responsibilities in relation to the study. The Investigator has final responsibility for the accuracy and authenticity of all study data.

Each Investigator and Subinvestigator (as designated on the Form FDA 1572) will provide a signed Financial Disclosure Form in accordance with 21 CFR Part 54. Each Investigator will notify the Sponsor or its authorized representative of any relevant changes to the information included on such Financial Disclosure Form during the conduct of the study and for 1 year after the study has been completed.

If the study site is located in the European Union, the Principal Investigator and any Subinvestigators must provide their express authorization for the Sponsor's collection, use, transfer (including to countries outside of the country where the study is conducted and the EU) and storage of their personal data, including their name, address, phone number for: review by

governmental authorities with regard to Sponsor's regulatory submissions related to the study; fulfilling regulatory or legal requirements; and publication of the study on the www.clinicaltrials.gov website.

11.6 Protocol Amendments and Study Termination

Any Investigator-initiated changes to the protocol (with the exception of changes to eliminate an immediate hazard to a study subject) must be approved by the Sponsor prior to seeking approval from the IRB/IEC, and prior to implementing. The Investigator is responsible for enrolling subjects who have met protocol eligibility criteria. Protocol deviations must be reported to the Sponsor and the local IRB/IEC in accordance with IRB/IEC policies.

The Sponsor may close a cohort at their discretion, or terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

11.7 Study Documentation, Privacy and Records Retention

To protect the safety of participants in the study and to ensure accurate, complete, and reliable data, the Investigator will keep records of laboratory tests, clinical notes, and subject medical records in the subject files as original source documents for the study. If requested, the Investigator will provide the Sponsor, its licensees and collaborators, applicable regulatory agencies, and applicable IRB/IEC with direct access to original source documents and certified copies within no more than ten (10) days of request by Sponsor (or sooner if required by a regulatory authority).

Records containing subject medical information and other personal data must be handled in accordance with local and national laws, rules, and regulations and consistent with the terms of the subject Authorization contained in the ICF for the study. Care should be taken to ensure that such records are not shared with any person or for any purpose not contemplated by the Authorization. Furthermore, CRFs and other documents to be transferred to the Sponsor should be completed in strict accordance with the instructions provided by the Sponsor, including the instructions regarding the coding of subject identities.

In compliance with local and/or regional regulations, this trial may be registered and trial results may be posted on public registries, such as ClinicalTrials.gov.

11.8 Clinical Trial Agreement

A separate written clinical trial agreement covering the obligations of the Sponsor and of the institution and Investigator in relation to the study is required before the study site is initiated. The clinical trial agreement will include terms for payments by the Sponsor to Investigators and institutions conducting the trial, requirements for Investigators' and institutions' insurance, provisions for reimbursement of the treatment of subject injuries attributable to the study or the study drug, the publication of clinical trial data, and other relevant provisions.

The Investigator and the institution shall collect and record all data and results of the study, including all information, CRFs, laboratory work sheets, slides, biospecimens, findings and reports ("Results") as required by this protocol, the Sponsor's instructions and the clinical trial agreement. Results are the exclusive property of Sponsor and are deemed its confidential information. Subject medical records and other source documentation are not included in Results. The written permission of the Sponsor is required prior to disclosure by the Investigator or the study sites of Results or any other information related to the study or the study drug. After conclusion of the study at all study sites, the Investigator may publish or present the Results that have been generated at the institution, provided that, the Results of the overall study have already been published or disclosed with Sponsor's permission in an abstract, manuscript or presentation; or the overall study has been completed at all sites for at least 2 years; or as otherwise approved by Sponsor in writing. The Investigator will submit to Sponsor for review any proposed publication or presentation along with the name of the applicable scientific journal or presentation forum prior to its submission for publication or presentation. The Investigator will comply with the Sponsor's request to delete references to its confidential information in any proposed publication or presentation and the Investigator or institution will withhold publication or presentation for an additional time period in order to allow the Sponsor to obtain patent protection. Investigators will conduct all interactions with third parties, including journal editors and reviewers, in a manner consistent with the confidentiality provisions of the clinical trial agreement in place with Sponsor. The foregoing shall not operate to restrict publication but is intended solely to ensure the accuracy and completeness of data intended for publication, to provide an opportunity to share with the Investigator any new and/or unpublished information of which he/she may be unaware and to ensure that Sponsor's confidential information is not disclosed.

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13. Appendices

13.1 Schedule of Assessments

		Screening[24]		Treatment (Each Cycle)								EOT[1]	LTFU
		Day –15 to –1	Day –1	Day 1[2]	Day 2	Day 3[3]	Day 8[4]	Day 15	Day 22	Day 29	Day 36	42 days (6 weeks) after last dose	Every 6–12 weeks thru 4 years[6]
	Window	–	–	±2 d	–	+1 d	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	
Location	Clinic Visit	X		X		X	X	X		X		X	
	Virtual Visit				X				X		X		
	Investigator (MD) present[7]	X		X			X	X		X		X	
Screening, Baseline, and Safety Assessments	Informed Consent	X											
	Demographics	X											
	Inclusion/Exclusion Criteria	X											
	Medical and Surgical History[8]	X											
	Malignancy History[9]	X											
	Prior Anticancer Treatments[10]	X											
	Physical examination	X		X			X	X		X		X	
	Vital Signs[11]	X		See 13.2			X	X		X		X	
	Height	X											
	Complete Blood Count[12]	X		X			X	X		X		X	
	Chemistries[13]	X		X			X	X		X		X	
	Coagulation Tests[14]	X		X								X	
	Urinalysis[15]	X		X			X	X		X		X	
	Hepatitis B and C tests[16]	X											
	Pregnancy Test[17]	X		X								X	
	Electrocardiogram (ECG)[18]	X		See 13.2		X						X	
	Echocardiogram[19]	X		X								X	
	Performance Status (ECOG)	X		X								X	

		Screening[24]		Treatment (Each Cycle)								EOT[1]	LTFU
		Day –15 to –1	Day –1	Day 1[2]	Day 2	Day 3[3]	Day 8[4]	Day 15	Day 22	Day 29	Day 36	42 days (6 weeks) after last dose	Every 6–12 weeks thru 4 years[6]
	Window	–	–	±2 d	–	+1 d	±2 d	±2 d	±2 d	±3 d	±3 d	±3 d	
	Fluid Retention Questionnaire[20]			X			X	X	X	X	X	X	
	Daily Weight Diary[21]			Day 1 predose thru EOT or 30 days after last study treatment, whichever is later									
	Adverse Events	Procedure-related only											
	Concomitant Medications[22]												
Treatment	Rovalpituzumab tesirine			X									
	Dexamethasone		X	X	X								
Response Assessment	Disease/Response Assessment[23]	X		Subjects will be assessed for response every 6 weeks (± 1 week) counting from C1D1 until week 24, and then every 12 weeks thereafter (± 1 week)									
	MRI of the Brain[25]	X		CNS lesions will be assessed every 6 weeks (± 1 week) counting from Cycle 1 Day 1 until week 24, then every 12 weeks, thereafter (± 1 week).[26]									
	Survival Status												X
	PRO[27]	X		X						X		X	
PK and PD	Pharmacokinetics			See 13.2		X[5]	X[5]	X[5]		X[5]		X	
	Anti-therapeutic antibody			X								X	
	Tumor Tissue[28]	X										X[29]	X[29]
	Blood Inflammatory Markers[30]			X								X	
	Blood Tumor Markers[31]			X								X	X
	Soluble Biomarkers[32]			X								X	
	Circulating Tumor Cells[33]			X								X	X
	Serosal Fluid[34]			Day 1 thru EOT or 30 days after last study treatment, whichever is later									
Prostate Cancer Only	Serum Total Testosterone	X											
	99mTc Bone Scintigraphy	X		Bone lesions will be assessed every 6 weeks (± 1 week) counting from Cycle 1 Day 1 until week 24, then every 12 weeks, thereafter (± 1 week).									

Abbreviations for Schedules of Assessments (Table and Footnotes): AE = adverse event; ALT = alanine aminotransferase; ANA = antinuclear antibodies; aPPT = activated partial thromboplastin time; AST = aspartate aminotransferase; β-hCG = beta-human chorionic gonadotropin; BUN = blood urea nitrogen; C = Cycle; CBC = complete blood count; CNS = central nervous system; CRP = C-reactive protein; CT = computerized tomography; CTC = circulating tumor cells; d = Day; DLL3 = delta-like protein 3; ECG = electrocardiogram; ECHO = echocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; ESR = erythrocyte sedimentation rate; HBcAb = Hepatitis B core antibody; HBsAb = Hepatitis B surface antibody, HBsAg,= Hepatitis B surface antigen; HCV = Hepatitis C virus; INR = international normalized ratio; LTFU = long-term follow-up; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; PD = progressive disease; PRO = patient reported outcomes; PT = prothrombin time; PTT = partial thromboplastin time; RF = rheumatoid factor; RECIST = Response Evaluation Criteria in Solid Tumors; RBC = red blood cell; WBC = white blood cell.

Table Footnotes

1) EOT occurs 42 ±3 days after last dose, or within 7 days of documentation of the decision to discontinue treatment, whichever is later.
2) Day 1 procedures may be performed within 1 day prior to dosing of study drug in Cycle 1; results from local clinical laboratory tests must be available prior to dose. Dexamethasone will be administered on Day -1 to Day 2 of rovalpituzumab dosing.
3) Assessments are to occur during Cycles 1, 2, and 4, only.
4) In Cycles 5 and higher, this visit may be reduced to a virtual visit consisting of Fluid Retention Questionnaire only if the previous 4 consecutive cycles lacked any clinically significant AEs.
5) The PK sample is to be drawn Cycles 1 and 2 only – omitted for retreatment subjects
6) LTFU occurs every 6 weeks until 6 months, then every 12 weeks until PD or initiation of new anticancer therapy, whichever occurs first. Afterwards, Disease/Response Assessment consists of subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status. Subjects will be followed for survival until death or study termination, whichever occurs first.
7) Assessments after CXD1 can be done by MD or by PA/NP with MD supervision. Assessments during screening, C1D1, and EOT should be done by an MD.
8) Medical and Surgical History includes descriptions of conditions or procedures, and dates of onset - offset.
9) Malignancy History includes tumor type, stage, sites of metastases, mutational status.
10) Prior Anticancer Treatments include recording of names of specific treatments, dates of administration, response to therapy, and DOR, if known
11) Vital signs include temperature, blood pressure, pulse, respirations, and weight. On treatment days, weight is only assessed once, pre-infusion.
12) CBC includes WBC count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), RBC count, platelet count, hemoglobin, and hematocrit.
13) Chemistries include electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, calcium , phosphorus, magnesium, BUN, estimated glomerular filtration rate, glucose, albumin, total protein, amylase, lipase, and liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase).
14) Coagulation tests include PT, aPTT, PTT, and INR
15) Urinalysis includes dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot analysis of protein and creatinine for ratio.
16) Hepatitis B and C tests include HBsAg, HBsAb, HBcAb and HCV antibody. Results that may be consistent with chronic or active infection must be confirmed by PCR tests for Hep B and/or C.
17) Pregnancy test consists of blood or urine testing for β-hCG in women of child-bearing potential. Repeat testing may be done as requested by the Investigator.

18) ECG consists of a 12-lead study. ECGs will be done in triplicate at the indicated times.
19) ECHO includes assessment of left LVEF and pericardial effusion. The screening ECHO should be done any time before the first dose of study drug, either during screening or pre-dose on C1D1; all ECHOs after C1D1 should be conducted within 4 days before the next dosing.
20) Fluid Retention Questionnaire includes queries of daily weights and worsening or new edema or dyspnea.
21) Subjects will maintain a diary of daily weights.
22) Concomitant medications include names of all concomitant therapies, including dates of administration, dose regimen, route of administration, and purpose
23) CT imaging of the chest, abdomen, and pelvis, and neck (if indicated) for all subjects, for assessment via RECIST v1.1. Subjects who achieve a partial or complete response must undergo confirmatory assessment(s) as described in Section 7.3.
24) Standard of Care procedures completed prior to the subject signing ICF, but within the study screening window, may be used as screening procedures.
25) CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.
26) MRI of the brain is only required after screening when clinically indicated (e.g., if CNS progression is documented).
27) PRO assessments (questionnaires) are required for subjects in Part B of the study (only) at screening, and also on Cycle 2 Day 1, Cycle 2 Day 29, and EOT.
28) Tumor tissue assessment consists of procurement for DLL3 testing of archived, representative tumor tissue, or an optional fresh tumor biopsy, if accessible. With consent from the subject, tumor tissue may be obtained prior to the screening period and tested for DLL3 expression. Optional: collection of tumor tissue at progression to better understand mechanisms of resistance and expression of DLL3**.**
29) Optional collection of tumor tissue at progression
30) Inflammatory markers will be assessed locally and will include ESR, CRP, ANA, and RF.
31) Blood Tumor Markers include soluble tumor-specific biomarkers specific to the tumor type (Section 7.5).
32) Soluble Biomarkers consists of blood collection for possible future analysis of soluble factors such as chemokines or cytokines which may have prognostic or pharmacodynamic importance in cancer and/or with rovalpituzumab tesirine, e.g., soluble DLL3.
33) CTC assessment includes 1 sample collected from subjects with neuroendocrine prostate cancer for central assessment of CTC and a sample for exploratory analyses of CTC-associated biomarkers such as DLL3 collected from subjects with large cell neuroendocrine carcinoma (cohort 4), neuroendocrine prostate cancer (cohort 5), and high-grade gastroenteropancreatic neuroendocrine carcinoma (cohort 6). Both CTC samples are collected at the following time points: C1D1, EOT, Long Term Follow-Up 2 (12 weeks), and time of progression (if not already collected).
34) Clinical assessments should include the following (refer also to Section 7.2.3): Serosal fluid assessment entails procurement, where feasible, of any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis), for possible PK, pharmacodynamic and/or biomarker testing.

13.2 Schedule of Day 1 Peridosing Assessments

	Predose		Dosing	Postdose		
Time	**–**	**0**	**+30 Minutes post SOI***	**+2 Hours post SOI***	**+4 Hours post SOI***	**+6 Hours post SOI***
Window	**–30 to 0 Minutes**	**–**	**±10 Minutes**	**±15 Minutes**	**±30 Minutes**	**±30 Minutes**
Rovalpituzumab Tesirine Administration		X				
Vital Signs[1]	X		X	X	X	
Electrocardiogram[2]	X		X			
Pharmacokinetic sample	X		X			X[3]

*SOI = Start of infusion

1) Vital signs according to Appendix 13.1.
2) ECG (in triplicate) according to Appendix 13.1; up to 180 minutes predose.
3) The 6 hour PK sample is to be drawn Cycles 1 and 2 only – omitted for retreatment subjects.

13.3 Previous Protocol (version 3.0) Cohort 3 (Glioblastoma) Specific Guidance

Protocol version 3.0 included eight separate cohorts enrolling in the following cancer types:

1. Malignant melanoma
2. Medullary thyroid cancer (MTC)
3. Glioblastoma (GBM)
4. Large cell neuroendocrine carcinoma (LCNEC) of the lung
5. Neuroendocrine prostate cancer (NEPC)
6. High-grade gastroenteropancreatic neuroendocrine carcinoma (GEP NEC)
7. Other neuroendocrine carcinoma (NEC), and high grade neuroendocrine tumors (NET)
8. Solid tumors other than the above

13.3.1 Efficacy Endpoint

Response will be assessed by radiographic imaging at protocol-specified time points. Tumor response assessments will be conducted every 6 weeks during active study treatment until 24 weeks, then every 12 weeks, thereafter. GBM cancer-specific assessments are described below, in Section 13.3.4.

For GBM subjects only, efficacy will be assessed using Response Assessment in Neuro-Oncology (RANO) criteria.

13.3.2 Inclusion Criteria

Measurable disease, defined as at least one tumor lesion ≥10mm in the longest diameter, or a lymph node ≥15mm in short-axis measurement, assessed by computerized tomography (CT) scan (by RECIST v1.1). Subjects with GBM must have measurable disease by RANO criteria: Measurable disease is defined as bidimensionally contrast enhancing lesions with clearly defined margins by CT or magnetic resonance imaging (MRI) scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0 mm skip.

13.3.3 Study Activities

Subjects enrolled in cohort 3 (GBM) will follow the study activities for subjects in cohorts 1-8, as outlined in Section 6 of the protocol (version 4.0), as well as the Schedule of Assessments for cohort 1-8 subjects (Table 13.1). Specific considerations for cohort 3 subjects are provided in this section 13.3.

13.3.4 Blood Tumor Markers

Blood tumor markers are NOT collected for Cohort 3, Glioblastoma.

13.3.4 Response Assessment in Neuro-Oncology Criteria

Tumor assessments will be assessed using the RANO criteria as outlined below according to Wen, et al, "Updated Response Assessment Criteria for High-Grade Gliomas: Response Assessment in Neuro-Oncology Working Group."

Table 13-1 Criteria for Determining First Progression Depending on Time from Initial Chemoradiotherapy

First Progression	Definition
Progressive disease <12 weeks after completion of chemoradiotherapy	Progression can only be defined using diagnostic imaging if there is new enhancement outside of the radiation field (beyond the high-dose region or 80% isodose line) or if there is unequivocal evidence of viable tumor on histopathologic sampling (e.g., solid tumor areas [i.e., > 70% tumor cell nuclei in areas], high or progressive increase in MIB-1 proliferation index compared with prior biopsy, or evidence for histologic progression or increased anaplasia in tumor). Note: Given the difficulty of differentiating true progression from pseudoprogression, clinical decline alone, in the absence of radiographic or histologic confirmation of progression, will not be sufficient for definition of progressive disease in the first 12 weeks after completion of concurrent chemoradiotherapy.
Progressive disease ≥12 weeks after chemoradiotherapy completion	1. New contrast-enhancing lesion outside of radiation field on decreasing, stable, or increasing doses of corticosteroids. 2. Increase by ≥25% in the sum of the products of perpendicular diameters between the first post-radiotherapy scan, or a subsequent scan with smaller tumor size, and the scan at 12 weeks or later on stable or increasing doses of corticosteroids. 3. Clinical deterioration not attributable to concurrent medication or comorbid conditions is sufficient to declare progression on current treatment but not for entry onto a clinical trial for recurrence. 4. For patients receiving anti-angiogenic therapy, significant increase in T2/FLAIR non-enhancing lesion may also be considered progressive disease. The increased T2/FLAIR must have occurred with the patient on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy and not be a result of comorbid events (e.g., effects of radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects).

FLAIR = fluid-attenuated inversion recovery

Pseudoprogression and Radiation Effects

The proposed new response criteria suggest that within the first 12 weeks of completion of radiotherapy, when pseudoprogression is most prevalent, progression can only be determined if the majority of the new enhancement is outside of the radiation field (for example, beyond the high-dose region or 80% isodose line) or if there is pathologic confirmation of progressive disease. It is recognized that the proposed histologic criteria have important limitations, but they provide guidance on the type of findings that are suggestive of progressive disease. For patients in whom pseudoprogression cannot be differentiated from true tumor progression, enrollment onto trials for recurrent gliomas should not be permitted. Patients who remain clinically stable and/or are suspected to have pseudoprogression based on metabolic or vascular imaging should continue with their current therapy.

Enhancement as a Result of Surgery and Other Therapies

Increased enhancement often develops in the wall of the surgical cavity 48 to 72 hours after surgery. To avoid interpretation of postoperative changes as residual enhancing disease, a baseline MRI scan should ideally be obtained within 24 to 48 hours after surgery and no later than 72 hours after surgery. The inclusion of diffusion weighted imaging in the immediate post-operative MRI scan can be helpful in determining whether new enhancement developing in the subsequent weeks or months is caused by sequelae of ischemia or by tumor recurrence. In addition, a transient increase in enhancement that can be difficult to distinguish from recurrent disease can also occur after locally administered therapies. These include chemotherapy wafers, immunotoxins delivered by convection enhanced delivery, regionally administered gene and viral therapies, immunotherapies, and focal irradiation with brachytherapy and stereotactic radiosurgery. Imaging modalities such as perfusion imaging, magnetic resonance spectroscopy, and positron emission tomography scans may sometimes be helpful in differentiating treatment effects from recurrent tumor. However, no imaging modality currently has sufficient specificity to conclusively differentiate recurrent tumor from treatment effects, and surgical sampling may occasionally be needed to obtain a definitive diagnosis.

Definition of Clinical Deterioration

The definition of clinical deterioration is left to the discretion of the treating physician, but it is recommended that a decline in the KPS from 100 or 90 to 70 or less, a decline in KPS of at least 20 from 80 or less, or a decline in KPS from any baseline to 50 or less, for at least 7 days, be considered neurologic deterioration unless attributable to comorbid events or changes in corticosteroid dose. Similarly, a decline in the Eastern Cooperative Oncology Group and WHO performance scores from 0 or 1 to 2 or 2 to 3 would be considered neurologic deterioration.

For those subjects who have measurable disease post resection, RANO criteria for assessment of CR, PR, SD and PD can be applied. See the below tables for the definitions to be used.

Definition of Radiographic Response

Radiographic response should be determined in comparison to the tumor measurement obtained at pretreatment baseline for determination of response, and the smallest tumor measurement at either pretreatment baseline should be used for determination of progression. Table 1 lists the criteria for radiographic changes after therapy. In the event that the radiographic changes are equivocal and it is unclear whether the patient is stable or has developed progressive disease, it is permissible to continue treatment and observe the patient closely, for example at 4-week intervals. If subsequent imaging studies demonstrate that progression has occurred, the date of progression should be the date of the scan at which this issue was first raised. The determination of radiographic response after treatment with agents that affect vascular permeability is particularly difficult. In these patients, consideration should be given to performing a second scan at 4 weeks to confirm the presence of response or stable disease. All measurable and nonmeasurable lesions should be assessed using the

same techniques as at baseline. Ideally, patients should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

Patients with nonmeasurable enhancing disease whose lesions have significantly increased in size and become measurable (minimal bidirectional diameter of ≥10 mm and visible on at least two axial slices that are preferably, at most, 5 mm apart with 0 mm skip) will also be considered to have experienced progression. The transition from a nonmeasurable lesion to a measurable lesion resulting in progression can theoretically occur with relatively small increases in tumor size (e.g., a 9 × 9 mm lesion [nonmeasurable] increasing to a 10 × 11 mm lesion [measurable]). Ideally, the change should be significant (>5 mm increase in maximal diameter or ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions). In general, if there is doubt about whether the lesion has progressed, continued treatment and close follow-up evaluation will help clarify whether there is true progression. If there is uncertainty regarding whether there is progression, the patient may continue on treatment and remain under close observation (e.g., evaluated at 4-week intervals). If subsequent evaluations suggest that the patient is in fact experiencing progression, then the date of progression should be the time point at which this issue was first raised.

Table 13-2 Criteria for Response Assessment Incorporating MRI and Clinical Factors

Response	Criteria
Complete Response	Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a complete response; the best response possible is stable disease.
Partial Response	Requires all of the following: ≥50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Patients with nonmeasurable disease only cannot have a partial response; the best response possible is stable disease.
Stable Disease	Requires all of the following: does not qualify for complete response, partial response, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
Progression	Defined by any of the following: ≥25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy* not caused by comorbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection, and so on) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

MRI = magnetic resonance imaging; FLAIR = fluid-attenuated inversion recovery

* Stable doses of corticosteroids include patients not on corticosteroids.

Note: All measurable and nonmeasurable lesions must be assessed using the same techniques as at baseline.

13.4 Performance Status Scales Conversion

ECOG		Karnofsky	
Score	**Description**	**Percent**	**Description**
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

13.5 New York Heart Association (NYHA) Classification

Class I	Patients with no limitation of activities; they suffer no symptoms from ordinary activities.
Class II	Patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.
Class III	Patients with marked limitation of activity; they are comfortable only at rest.
Class IV	Patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest.

13.6 Response Evaluation Criteria for Solid Tumors (RECIST) v1.1

Term	Definition
Complete response (CR)	Disappearance of all target lesions. Any pathological lymph nodes must have reduction in short axis to <10 mm.
Partial response (PR)	A ≥30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 0.5 cm. The 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 PD, taking as reference the smallest sum diameters while on study.
New measureable lesions*	Always represents PD.
New nonmeasurable lesions	Always represents PD.
Non-index lesions	Changes contribute to defining best overall response of CR, PR, SD, and PD.

From RECIST v1.1 (Eisenhauer 2009)

* Measureable lesion must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT scan (CT slice thickness ≤5 mm).

13.7 Guidance for Subjects with Prostate Cancer

For subjects with prostate cancer, the following prostate-specific guidelines will apply.

Additional Study Population Criteria

The following additional inclusion criteria will be applied to the main study criteria (Section 4):

1. Prostate cancer of predominantly small cell neuroendocrine (NEPC) and/or intermediate atypical carcinoma (IAC) histologic differentiation in a primary or metastatic tumor specimen.
2. Progressive disease by PCWG3 (Scher 2016), RECIST v1.1 (Eisenhauer 2009), or both criteria during or within 4 weeks following completion of at least one prior systemic therapy delivered in the metastatic disease setting, including at least one of the following:
    a. Progression of nodal or visceral metastasis (computed tomography [CT] scan or magnetic resonance imaging [MRI] according to RECIST v1.1).
    b. Development of new sites of visceral or nodal metastases. Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed.
    c. Progression of bone disease (at least 2 new bone lesions as measured by bone scan).
3. Surgically or medically castrated with serum testosterone <50 ng/dL (1.7 nM) at screening. Any medical castration therapy (subjects who have not undergone orchiectomy) must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must be continued throughout the duration of the study. Subjects with de novo primary small cell carcinoma of the prostate are exempt from this criterion.

Duration of Treatment

Subjects will be eligible to continue treatment until unacceptable toxicity, no longer clinically beneficial according to PCWG3, withdrawal of consent, or study termination, whichever occurs first. In accordance with PCWG3 guidelines, early changes in PSA should not be acted on without other evidence of PD, and treatment should be continued for at least 12 weeks to ensure adequate drug exposure.

Allowed Concomitant Therapy

For prostate cancer subjects, ongoing treatment with luteinizing hormone-releasing hormone (LHRH) agonists or antagonists, denosumab, or bisphosphonates (e.g., zoledronic acid) is allowed.

13.7.1 Additional Assessments for Subjects with Prostate Cancer

- Tumor assessments will be performed according to RECIST v1.1 for soft tissue lesions and/or the PCWG3 for bone lesions
- PSA levels will be measured and monitored according to the PCWG3 guidance for PSA

PCWG3 Guidance for Bone Lesions

Assessment of bone lesions will be based on radionuclide scans. The outcome of bone scans should be recorded as either "new lesions" or "no new lesions."

- For the first scheduled reassessment, new lesions will require a confirmatory bone scan 6 or more weeks later. If new lesions are confirmed, the subject will be defined as disease progression in accordance with PCWG3, with progression dated as of the first "new lesion" scan.
- For subsequent scheduled reassessments, new lesions will define the subject as disease progression in accordance with PCWG3, with progression dated as of the scan.

PCWG3 Guidance for PSA

A PSA progression is defined as the time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second PSA value at least 4 weeks later (i.e., a confirmed rising trend).

13.8 CTCAE v4.03 Grading of Some Relevant AEs

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Effusions	Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated
	Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity.				
	Pericardial effusion	–	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.				
	Pericardial tamponade	–	–	–	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.				
	Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention, including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
	Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.				
Edema	Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.				
	Edema limbs	5–10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	>10–30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	>30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL	–

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
	Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.				
Edema cont.	Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.				
	Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.				
	Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	–
	Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.				
Labs	Hypo-albuminemia	<LLN–3 g/dL; <LLN–30 g/L	<3–2 g/dL; <30–20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.				
	Neutrophil count decreased	<LLN–1500/mm^3; <LLN–1.5 x 10e9/L	<1500–1000/mm^3; <1.5–1.0 x 10e9/L	<1000–500/mm^3; <1.0–0.5 x 10e9/L	<500/mm^3; <0.5 x 10e9/L
	Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.				
	Platelet count decreased	<LLN–75,000/mm^3; <LLN–75.0 x 10e9/L	<75,000–50,000/mm^3; <75.0–50.0 x 10e9/L	<50,000–25,000/mm^3; <50.0–25.0 x 10e9/L	<25,000/mm^3;<25.0 x 10e9/L
	Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Erythema multiforme	Target lesions covering <10% BSA and not associated with skin tenderness	Target lesions covering 10-30% BSA and associated with skin tenderness	Target lesions covering >30% BSA and associated with oral or genital erosions	Target lesions covering >30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated
	Definition: A disorder characterized by target lesions (a pink-red ring around a pale center).				
Skin cont.	Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	–
	Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.				
	Photosensitivity	Painless erythema and erythema covering <10% BSA	Tender erythema covering 10-30% BSA	Erythema covering >30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by an increase in sensitivity of the skin to light.				
	Rash maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10-30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self-care ADL	–
	Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.				

From CTCAE v4.03

13.9 Fluid Retention Questionnaire

[EXAMPLE: Refer to the study binder for the actual document]

Fluid Retention Questionnaire for Study SCRX001-006

Subject ID:_____

Over the past 7 days, or since the last time this questionnaire was asked:

1. What have your daily weights been?

   - Please weigh yourself at the same time each day and record the date and your weight for that day below. Weights should be taken without outer garments such as hats, coats or shoes. Measurements while in light indoor clothing only, or undergarments only, are acceptable; however, please try to use the same or similar clothing (including any accessories or jewelry) from day to day when measuring weights.
   - Please complete one questionnaire for every 7 day/1 week period.

Date (DD/MMM/YYYY)	Weight (circle one: lb or kg)
	lb or kg
	lb or kg
	lb or kg
	lb or kg
	lb or kg
	lb or kg
	lb or kg

2. Have you noticed any new or worsening edema – e.g., swelling of the ankles or legs during the days above?

   ☐Yes or ☐No

3. Have you noticed any new or worsening shortness of breath during the days above?

   ☐Yes or ☐No

4. Please sign below to confirm that you have completed this questionnaire.

   _____ Date: _____

13.10 Disease Related Events Associated with Solid Tumors

Abdominal pain
Asthenia
Back pain
Bone pain
Cough
Decreased appetite
Deep vein thrombosis
Dysphagia
Dysphonia
Dyspnea
Esophageal obstruction
Fatigue
General physical health deterioration
Horner's syndrome
Ileus
Infection*
Jaundice
Lymphadenopathy
Malaise
Malignant pleural effusion
Malignant ascites
Metastasis
Nausea
Non-cardiac chest pain
Opportunistic infection*
Paraneoplastic syndrome
Pathological fracture
Pneumonia*
Pruritus
Pulmonary embolism
Pyrexia
Sepsis*
Septic shock*
Small intestinal obstruction
Superior vena cava syndrome
Tumor pain
Vocal cord paralysis
Vomiting
Weight decreased

* Includes life threatening or fatal events.

13.11 Investigator Signature Page

Investigator Statement and Signature

I have read the attached protocol entitled "An Open-Label Study of Rovalpituzumab Tesirine in Subjects with Delta-Like Protein 3-Expressing Advanced Solid Tumors."

I understand and agree to the provisions of the protocol. I accept the responsibilities included herein in my role as Principal Investigator for the study and I will ensure that all Subinvestigators and study personnel comply with the provisions of this protocol.

Investigator Signature	Date

Investigator Name, Printed

13.12 Document History

Version	Date
Version 1	27 January 2016
Version 2	21 July 2016
Version 3	06 September 2017
Version 4	**19 October 2018**

13.12.1 Protocol Amendment Version 4.0: Summary of Change

Protocol Title:	**An Open-Label Study of Rovalpituzumab Tesirine in Subjects with Delta-Like Protein 3-Expressing Advanced Solid Tumors**
Protocol Number:	**SCRX001-006**
Amendment Version 4.0:	**19 October 2018**
Supersedes Amendment Version 3.0:	**06 September 2017**

Main Changes to the Protocol:

The main purposes of this amendment are:

1) Close enrollment to Cohort 3 (Glioblastoma)
2) Clarify enrollment criteria for cohort 4 (large cell neuroendocrine carcinoma)
3) Clarify response assessment schedule
4) Add guidance for the monitoring and management of Edema;
5) Add guidance for the monitoring and management of Pneumonitis;
6) Add guidance for the monitoring and management of Skin Reactions;
7) Clarify photodocumentation requirements for skin reactions;
8) Clarify pregnancy reporting requirements for pregnant study subjects and partners;
9) Clarify AE reporting requirements including for deaths related to disease progression;
10) Update PK sample collection requirements;
11) Clarify CTC sample collection;
12) Clarify research tests associated with tumor tissue specimens;
13) Clarify sample collection requirements for retreatment subjects;
14) Clarify sample collection schedule for Blood Inflammatory Markers, Blood Tumor Markers, and Soluble Biomarkers;
15) Clarify sample retention guidelines;
16) Clarify that CT imaging of the chest, abdomen, and pelvis, and neck (if indicated), for assessment via RECIST v1.1 should be completed for all subjects;
17) Updates to align with the Recommended Phase 2 Dose (RP2D);
18) Clarify that Standard of Care procedures completed prior to the subject signing ICF, but within the screening window, may be used as screening procedures;
19) Update sponsor name to AbbVie Inc.;
20) Update Medical Monitor contact phone number;
21) Remove AbbVie Safety contact phone number;
22) Clarify that the sponsor can close a cohort at their discretion;
23) Relocate the cohort 3 (Glioblastoma) inclusion criteria, study activities, response assessment criteria, and other applicable language to the Appendix;
24) Make administrative changes of typographical errors, minor language and word revision as needed throughout the document;

All substantive changes to protocol are summarized below; wherever possible, new text is **bold** and deleted text is shown by strike through text.

Additional editorial and administrative changes were made to reflect current administrative details, correct typographical errors, and add clarity; such changes are not itemized below.

Section	Revision	Rationale
Cover Page	*Revised Medical Monitor Contact Number*: [redacted], MD, PhD Novella Clinical 1700 Perimeter Park Drive Morrisville, NC 27560 USA Phone: [redacted]	Updated to provide new Medical Monitor contact information.
Synopsis	The Synopsis has been updated to reflect the changes made throughout the protocol body.	Updated to align with the revised protocol body.
Definitions of Abbreviations and Terms	The List of Abbreviations has been updated to reflect the changes made throughout the protocol.	Updated to align with the revised protocol body.
Section 1.2 Royalpituzumab Tesirine	*Revised Paragraph 2*: **In a Phase 1 study (Study SCRX16-001), rovalpituzumab tesirine dosed at 0.2 – 0.4 mg/kg exhibited encouraging efficacy in recurrent SCLC, achieving a 31% (8/26) and 85% (22/26) central review-adjudicated confirmed objective response rate (ORR) and clinical benefit rate (CBR), respectively, in subjects whose tumors expressed DLL3 in ≥ 50% of cells. Median overall survival was 7.7 months in DLL3 ≥ 50% subjects at all dose levels, with a 1-year survival rate of 30%%. The most frequent grade 3 or worse treatment-related adverse events in 74 patients with small-cell lung cancer were thrombocytopenia (11%), pleural eff usion (8%), and increased lipase (7%). Drug-related serious adverse events occurred in 28 (38%) of 74 patients. The recommended phase 2 dose and schedule is 0.3 mg/kg every 6 weeks.% (AbbVie Stemcentrx, data on file).** ~~A Phase 1 study with rovalpituzumab tesirine, SCRX16-001, has demonstrated encouraging results with an objective response rate (ORR) of 44% and a clinical benefit rate (CBR) of 78% in relapsed or refractory DLL3hi (delta-like protein 3-positive in ≥50% tumor cells) SCLC subjects treated in the expansion cohorts of 0.2 mg/kg Q3wk (every 3 weeks) and 0.3 mg/kg Q6wk (every 6 weeks). In all expansion cohort SCLC subjects, regardless of DLL3 expression, the ORR and CBR were 23% and 66%, respectively (Stemcentrx data on file). Therefore, rovalpituzumab tesirine appears to be an active anticancer therapy.~~ ***New Paragraph 3:*** **In a Phase 2 SCRX001-002 (TRINITY) study in patients with SCLC recurrent after at least two systemic chemotherapy regimens, rovalpituzumab tesirine dosed at 0.3 mg/kg every 6 weeks for two cycles (with an option for additional two cycles upon progression occurring ≥ 12 weeks after the second dose) had shown confirmed objective response rate of 16%, progression-free survival of 3.9 months and overall survival of 5.6 months in 3rd line DLL3High patients. Of note, prolonged stable disease with target lesion size reduction has been observed in a considerable number of patients receiving additional post-progression cycles of rovalpituzumab**	Updated the section based on updated data/information now available.

	tesirine. Drug related grade 3 or above treatment emergent adverse events that occurred in at least 10 subjects include thrombocytopenia (11%), photosensitivity reactions (7%), anemia (4%), fatigue (4%), and pleural effusion (4%). Adverse events leading to study treatment discontinuation occurred in7% of subjects (AbbVie Stemcentrx, data on file).	
Section 3.1 Summary of Study Design	*Revised Paragraph 1:* This is a multicenter, open-label study of rovalpituzumab tesirine in subjects with DLL3 expressing advanced solid tumors. The study will include ~~8~~ **7** cohorts of subjects with the following cancers: *Revised Bullet 4:* Large cell neuroendocrine carcinoma (LCNEC) **of any origin** *Added Paragraph 2:* **As of protocol version 4.0, cohort 3 (Glioblastoma) is closed to enrollment. Specific guidance for cohort 3 (Glioblastoma) subjects (protocol version 3.0) are provided in Appendix 13.3.**	Updated to align with the closure of cohort 3 (Glioblastoma). Updated to allow enrollment of LCNEC from tumor types of any origin. Updated to clarify closure of cohort 3 (Glioblastoma) and note that specific guidance for glioblastoma subjects has been moved to the Appendix.
Section 4.1 Inclusion Criteria	*Revised Bullet 3:* Measurable disease, defined as at least one tumor lesion ≥10 mm in the longest diameter, or a lymph node ≥15 mm in short-axis measurement, assessed by computerized tomography (CT) scan (by RECIST v1.1). ~~Subjects with GBM must have measurable disease by RANO criteria: Measurable disease is defined as bidimensionally contrast enhancing lesions with clearly defined margins by CT or magnetic resonance imaging (MRI) scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0 mm skip.~~	Updated to align with the closure of cohort 3 (Glioblastoma).
Section 4.3.1 Contraception for Female Subjects	*Removed Bullet 4:* ~~Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.~~	Updated to align with current requirements for contraception.
Section 4.4.1 Discontinuation of Study Drug	*Revised Bullets 1-5:* • Progressive disease (PD) **per RECIST 1.1** • Adverse event (~~AE~~) • ~~Investigator~~ **Physician** decision • **Study terminated by sponsor** ~~Subject decision, Non-AE~~ • **Withdrawal by subject** • Other	Updated bullets to align with language present in EDC
Section 4.4.2 Subject Discontinuation from Study	*Revised Bullets 1-2, 4, 6-7:* • **Withdrawal by subject** ~~Subject withdrawal of consent~~ • ~~AE~~ • Death • ~~Investigator~~ **Physician** decision • Lost to follow-up • ~~Significant noncompliance to protocol~~ • Study terminat**ed**~~ion~~ by Sponsor • Other	Updated bullets to align with language present in EDC

Table 5-1 Toxicities Requiring Dose Reduction	*Updated Serosal Effusions and Edema, Toxicities Requiring 2 Dose Level Reductions at First Occurrence, and Toxicities Requiring Discontinuation of Investigational Product at First Occurrence Subsections:*		Updated to align with recent safety updates
	Toxicities Requiring 1 Dose Level Reduction at First Occurrence – 2nd occurrence = 2nd dose level reduction – *Discontinue after 2 dose level reductions*		
	Serosal Effusions and Edema	• Grade 2 or higher pericardial effusion • Grade **2** ~~3~~ or higher pleural effusion • Grade **2** ~~3~~ or higher ascites • Grade **2** ~~3~~ or higher peripheral edema	
	Hematology	• Grade 3 thrombocytopenia (platelets <50.0–25.0 × 10^9/L) • Grade 4 neutropenia (ANC <0.5 × 10^9/L) lasting more than 7 days • Grade 3 or higher febrile neutropenia (with ANC <1.0 × 10^9/L) (concurrent fever ≥38.3° C)	
	Laboratory Abnormalities	• Clinically significant Grade 3 or higher non-hematologic laboratory abnormality that does not resolve to Grade 0/1 or baseline within 7 days • Any other Grade 3 or 4 laboratory abnormality considered clinically significant and treatment-related; adjustments to these guidelines may occur based on the clinical judgment of the Investigator and with approval of the Medical Monitor and Sponsor • Grade 2 hypoalbuminemia	
	Other Adverse Events	• Grade 3 photosensitivity reaction (Section 5.5.2) • Grade 3 or Grade 4 nonlaboratory treatment-related toxicity, with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom	
	Toxicities Requiring 2 Dose Level Reductions at First Occurrence – *Discontinue at second occurrence*		
	• **Grade 3 serosal effusions (pleural effusions, pericardial effusions, and ascites) and edema** • **Grade 2 capillary syndrome** • Grade 4 thrombocytopenia/ Grade 3 thrombocytopenia with bleeding/ Need for platelet transfusion • **Grade 4 febrile neutropenia** • Grade 4 (>20.0 × ULN) ALT or AST or Grade 3 (>5.0–20.0 × ULN) ALT or AST elevation with concomitant total bilirubin Grade 2 or		

	higher (>1.5 ULN) • Grade 3 or higher hypoalbuminemia (<2 g/dL) • **Grade 2 pneumonitis** <u>Toxicities Requiring Discontinuation of Investigational Product at First Occurrence</u> • Grade 4 photosensitivity or skin reaction (Section 5.5.2) • Drug induced liver injury is confirmed (refer to Section 5.5.3 for definition) • Life threatening Infusion related reaction or hypersensitivity • **Grade ≥3 pneumonitis**	
Section 5.5.2 Skin Reactions	*Added Paragraph 1:* **Photosensitivity was reported in patients treated with Rova-T including severe events. Photosensitivity reactions may occur hours to days after sun exposure. The median time to onset was 30 days (range 1 to 247 days). Patients should be advised to avoid direct and indirect sun exposure as much as possible during Rova-T treatment and for 30 days after the last dose. If unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). 31 – 90 days after last dose, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher. Skin reactions should be evaluated promptly and treated with topical or systemic steroids as indicated (refer to Table 5-2). Rova-T dose should be delayed, reduced or discontinued as necessary (refer to Table 5-1).** *Revised Paragraph 2:* **All cutaneous reactions which develop during treatment warrant prompt evaluation.** Skin toxicity with rovalpituzumab tesirine may consist of photosensitivity but possibly other reactions such as palmar-plantar erythrodysesthesia or erythema multiforme. As such, development of a cutaneous reaction during treatment warrants prompt evaluation by the Investigator or designee: *Revised Bullets 1 and 2 :* • If clinically consistent with photosensitivity, the AE ~~may~~ **should** be reported as such (using medically accurate and descriptive AE terminology), and managed as described below in Table 5 2. • ~~If not~~**For clinically more severe cases of photosensitivity or if**~~If not~~ **clinically not** consistent with photosensitivity, ~~the following should be done, :~~ ~~Photodocumentation~~P**photodocumentation** to facilitate later review by the Sponsor or designee **may occur**. *Revised Sub Bullet 1:* • Formal evaluation by a dermatologist, including possible skin biopsy to rule out alternative etiologies, such as erythema multiforme which may warrant discontinuation of study drug, and to facilitate the most appropriate terminology for AE reporting, **is recommended.** *Added Sub Bullet 2:* **• Photodocumentation of skin toxicity, if available, may be requested by the TAMD. The investigative site will take measures to protect the**	Updated to align with recent safety updates Updated to align with recent safety updates Clarifies photodocumentation guidelines for photosensitivity Clarifies photodocumentation guidelines for photosensitivity Clarifies photodocumentation guidelines for photosensitivity

	identity of the patient. These measures include taking the photograph very close to the affected skin region to exclude facial features, or if facial features cannot be excluded due to the location of the skin reaction, covering identifying features (such as the eyes) with a black rectangle.	
Section 5.5.4 Monitoring and Management of Edema	*Added New Section; refer to protocol body Section 5.5.4*	Update to align with recent safety updates
Section 5.5.5 Monitoring and Management of Pneumonitis	*Added New Section; refer to protocol body Section 5.5.5*	Update to align with recent safety updates
Section 6.3.2 Day 1 (±2 Days)	*Revised Bullet 13:* • Blood sample for PK – Should be drawn within 30 minutes prior to the infusion, and then post infusion at 30 minutes after start of infusion (±10 minutes). In Cycles 1 and~~, 2, and 4 of subjects in Part A~~, an additional sample will be taken at 6 hour (±30 minutes). **The 6 hour PK sample is required for Cycles 1 and 2 only - omitted for retreatment subjects**. *Revised Bullet 18:* • Circulating tumor cells (CTCs), **collected at Cycle 1 Day 1**. (Section 7.5.5)	Clarify PK sample collection Clarify CTC sample collection
Section 6.3.4 Day 3 (Window +1 Day) of Cycles 1, 2, and 4 Only	*Revised Bullet 2:* • Blood sample for PK **for Cycles 1 and 2 only – omitted for retreatment subjects**	Clarify PK sample collection
Section 6.3.5 Days 8 and 15 (±2 Days) and 29 (±3 Days)	*Revised Bullet 8:* • Blood sample for PK **for Cycles 1 and 2 only – omitted for retreatment subjects**	Clarify PK sample collection
Section 6.3.7 Within 7 Days Prior to the Next Dose	*Removed Section:* ~~The following assessments should be performed within the time frame and at a frequency determined by the subject's dosing schedule:~~ ~~• Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated; Section 7.3)~~ ~~• MRI of the brain – if clinically indicated (e.g., if CNS progression has been documented previously). CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator.~~ ~~• Blood inflammatory markers (Section 7.5.2)~~ ~~• Blood tumor markers (Section 7.5.3)~~ ~~• Soluble biomarkers (Section 7.5.4)~~ ~~• CTCs (Section 7.5.5)~~ ~~• Prostate cancer subjects only: 99 mTc Bone Scintigraphy, as clinically indicated in accordance with the institutional standard of care, but at a minimum of every 12 weeks (Section 7.3).~~	Corrected the sample collection to align with protocol schedule of assessments. Moved scans to a new section 6.3.7 to align with updated guidance.
Section 6.3.7 Disease Assessment	*Added Section:* **• Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated; Section 7.3). Tumor response will be assessed every 6 weeks counting from Cycle 1 Day 1, preferably before each dosing if possible, until 24 weeks, then every 12 weeks, thereafter.** **• MRI of the brain – if clinically indicated (e.g., if CNS progression has been documented previously). CT of the brain with intravenous**	Clarify response assessment schedule to allow for consistency in response assessment collection

	contrast may be substituted at the discretion of the Investigator. CNS lesion will be assessed every 6 weeks counting from Cycle 1 Day 1, preferably before each dosing if possible, until 24 weeks, then every 12 weeks, thereafter. **• Prostate cancer subjects only: 99 mTc Bone Scintigraphy, will be assessed every 6 weeks counting from Cycle 1 Day 1, preferably before each dosing if possible, until 24 weeks, then every 12 weeks, thereafter (Section 7.3).).**	
Section 7.1 Screening/Baseline Assessments	*Added a Note to the Section:* Only subjects who meet all inclusion and exclusion criteria specified in Section 4 (and Appendix 13.6, for prostate cancer subjects) will be enrolled in this study. Absence of active CNS tumor or metastases will be confirmed by MRI of the brain. CT of the brain with intravenous contrast may be substituted at the discretion of the Investigator. Demographics include age, gender, and race. Subject medical history includes a thorough review of significant past medical history, current conditions, smoking history, any diagnosis and treatment for prior malignancies, including response to treatment, and any concomitant therapies. Malignancy history should include tumor type, stage, grade and grading system, sites of metastases, and mutational status. The latter should include, at least, status of BRAF for melanoma subjects, and RET for MTC subjects. **Standard of Care procedures completed prior to the subject signing ICF, but within the study screening window, may be used as screening procedures.**	Clarify window associated with SOC screening assessments.
Section 7.3 Radiographic Response/Efficacy Assessments	*Revised Paragraph 2:* Diagnostic quality, spiral CT scans are recommended; other methods may be used if performed consistently throughout the study for each individual subject. Positron emission tomography (PET) and/or octreotide/somatostatin scans may be used in an ancillary manner; however, no decisions relating to PD may be made based on PET or octreotide/somatostatin scans alone. Clinical response will be determined by the Investigator at each assessment according to RECIST v1.1 (Appendix 13.5; Eisenhauer 2009), and/or for prostate cancer subjects, PCWG3 criteria (Appendix 13.6). ~~GBM will be assessed using RANO criteria (refer to Appendix 13.7).~~	Updated to align with the removal of cohort 3 (Glioblastoma)
Section 7.4 Pharmacokinetic Assessments	*Revised Paragraphs 1-2:* Blood samples for PK and ATA testing will be collected at ~~the time points~~ throughout the study as indicated in Appendices 13.1 and 13.2 ~~for incorporation into an integrated population PK analysis. A population PK analysis may be reported separately.~~ Sensitive, qualified assays will be used to measure ~~blood~~ **plasma** concentrations of rovalpituzumab tesirine ADC (SC16LD6.5) ~~and)~~. **Plasma concentrations of rovalpituzumab total antibody and blood concentrations of** SC-DR002, the small molecule component of rovalpituzumab tesirine, **may also be measured if deemed necessary and appropriate**. A qualified immunoassay will be used to assess ATA against rovalpituzumab tesirine.	Clarify PK sample collection
Section 7.5 Pharmacodynamic and Biomarker Assessments	*Added Paragraph 2:* **AbbVie (or people or companies working with AbbVie) will store the samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on rovalpituzumab tesirine (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after**	Clarify sample retention guidelines

	study completion, or per local requirement.	
Section 7.5.1 Tumor Tissue	*Revised Paragraphs 1-2:* Tumor tissue, consisting of a representative archived specimen, or a fresh tumor biopsy, will be assessed at baseline for expression of DLL3 by methods such as but not necessarily limited to immunohistochemistry (Section 7.1.1). Additional studies, such as routine hematoxylin and eosin for morphology and histological classification, IHC for confirmation of diagnosis (e.g., for synaptophysin, chromogranin-A, or CD56 for neuroendocrine tumors, or HMB45, S100, or MART-1 for melanoma), or scoring of immune infiltrates (e.g., IHC for CD3+, CD4+, CD8+, and Foxp3+ cells) may be performed. **Tumor material may also be utilized for exploratory research that includes assessments of nucleic acid or protein based biomarkers of drug sensitivity, resistance, or disease biology and development of a companion diagnostic assay.** ~~When fresh tumor biopsies are performed, tissue may also be collected for exploratory studies, such as but not necessarily limited to assays of drug sensitivity or resistance.~~ At PD, an optional tumor biopsy may be performed for the assessment of expression of DLL3 and/or execution of additional studies, such as but not necessarily limited to scoring of immune infiltrates or assessment of molecular pathways related to the response to rovalpituzumab tesirine. **Tumor material may also be utilized for exploratory research that includes assessments of nucleic acid or protein based biomarkers of drug sensitivity, resistance, or disease biology and development of a companion diagnostic assay.** Additional instructions will be provided in the laboratory manual.	Clarify potential uses for collected tumor tissue specimens
Table 7-1 Disease-Specific Blood Tumor Markers	*Revised Table Note:* Note: Blood tumor markers are NOT collected for ~~Cohort 3, Glioblastoma, or~~ Cohort 8, Other Solid Tumors.	Updated to align with the removal of cohort 3 (Glioblastoma)
Section 7.5.5 Circulating Tumor Cells	*Revised Section:* At the indicated times, blood samples from subjects with neuroendocrine prostate cancer will be collected for assessment and characterization of CTC as a possible reflection of disease burden for central processing at all sites. A second sample for exploratory analyses of CTC-associated biomarkers, such as DLL3, will be collected from subjects **with large cell neuroendocrine carcinoma (cohort 4), neuroendocrine prostate cancer (cohort 5), and high-grade gastroenteropancreatic neuroendocrine carcinoma (cohort 6)** ~~at specific sites based on feasibility.~~	Clarify CTC sample collection
Section 8.1.1.1 Adverse Events	*Revised Paragraph 3:* Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention **(including interruption/dose reduction of study drug, starting or discontinuing medication, etc.)**, ~~[~~meets protocol specific criteria (refer to Sections 5.5 and 8.1 regarding toxicity management)~~]~~ and/or if the Investigator considers them to be AEs.	Clarify medical intervention as it requires to AEs
Section 8.1.4 Deaths	*Revised Paragraph 2:* Deaths that occur during the protocol specified AE reporting period (Section 8.1.5) that are more likely related to PD will therefore be considered as an expected AE and will not be subject to expedited reporting~~.~~ **to regulatory agencies**. These **SAEs** ~~events~~ should be ~~captured~~ **reported** as "~~disease progression~~**malignant neoplasm progression**" and **also** recorded on the AE eCRF. After the AE reporting period, deaths attributed to PD under study should be recorded only on the end of study	Clarify reporting requirements for deaths related to disease progression

	(EOS) eCRF.	
Section 8.1.6 Adverse Event Reporting	*Removed AbbVie Safety Contact Number:* For safety concerns, contact the Oncology Safety Management Team at: AbbVie Oncology Safety Team [redacted] 1 North Waukegan Road North Chicago, IL 60064 ~~Office:~~ [redacted] Email: *Revised Medical Monitor Contact Number*: [redacted], MD, PhD Novella Clinical 1700 Perimeter Park Drive Morrisville, NC 27560 USA Phone: [redacted]	Updated to provide current AbbVie Safety contact information Updated to provide new Medical Monitor contact information.
Section 8.1.7 Pregnancy Reporting	*Revised Paragraph 3:* Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome. **In the event a study subject or the partner of an enrolled subject delivers a baby, they will be asked to provide information including the following will be requested: date of delivery, birth weight and length, boy or girl, problems during pregnancy or delivery, and if the baby has any birth defects.**	Clarify pregnancy reporting requirements for study subject or pregnant partner
Section 8.2.3 Events Commonly Associated in Study Population with Advanced Solid Tumors and/or Progression of Underlying Malignancy	*Revised Paragraph 2:* A list of AEs associated with advanced solid tumors is provided in Appendix 13.10. These AEs are preferred terms coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary; the AEs may occur alone or in various combinations and are considered expected for reporting purposes for this protocol. Although exempted from expedited reporting to Health Authorities and IRBs as individual cases, **if these AEs meet serious criteria** these SAEs must be reported to AbbVie within 24 hours of the site being made aware of the SAE (as required in Section 8.1.6). For deaths related to disease progression (coded to malignant neoplasm progression), the date and cause of death will be recorded on the appropriate case report form (CRF), but the event will not be expedited as an Individual Case Safety Report (ICSR) to regulatory authorities (Section 8.1.4).	Clarify reporting requirements for AEs related to disease progression
Section 8.3 Appropriateness of Measurements	*Revised Paragraph 2:* Response will be assessed according to RECIST v1.1 (Eisenhauer 2009), which includes standard criteria for evaluating response in solid tumors. Prostate cancer is assessed by PCWG3 criteria ~~and GBM will be assessed according to RANO Criteria~~. The intervals of evaluation in this protocol are appropriate for disease management.	Updated to align with the removal of cohort 3 (Glioblastoma)
Section 10.1	*Revised Paragraph 2:*	Updated to align

Determination of Sample Size	In Part B, up to approximately 174 subjects may be enrolled, including approximately 19 subjects in each of the ~~56~~ disease-specific cohorts. The rationale for the sample size is based on the assumption that an ORR of around 15% would be indicative of efficacy worthy of further investigation given the advanced cancers and extensive treatment history in this study population. Additionally, an ORR below 5% would provide evidence of an ineffective treatment. The goal of the efficacy analyses is to provide a preliminary signal that the response rate may potentially be within that target range.	with the removal of cohort 3 (Glioblastoma)
Section 10.3.8 Pharmacokinetic and Pharmacodynamics Analysis	*Revised Paragraph 1:* Data from the Pharmacokinetic-Evaluable Set will be used in the analysis of PK and Pharmacodynamics endpoints. The PK of rovalpituzumab tesirine will be estimated from concentration-time data using non-compartmental methods. The reporting of PK parameters will be determined based on the final parameter analysis on the available data. The PK parameters **that may** ~~to~~ be assessed ~~may~~ include, as appropriate: *Revised Bullets 2, 5, 6, and 8:* • Cmax Maximum plasma concentration • $AUC_{0-\tau}$ Area under the plasma concentration-time curve ~~within a dosing interval~~ • Tmax Time of Cmax • Ctrough Plasma concentrations at trough • ~~T1~~**t1/2** (Apparent) ~~Terminal~~ **terminal** half-life • ~~AR Accumulation ratios for exposure related PK parameters~~ • CL Plasma clearance • ~~Vss~~**Vdβ** ~~Steady state v~~**Volume** of distribution *Revised Continued Paragraph 1:* The above parameters will be summarized **by descriptive statistics** ~~using the five number summary~~	Clarify PK sample analysis
Section 11.6 Protocol Amendments and Study Termination	*Revised Paragraph 2:* The Sponsor may **close a cohort at their discretion, or** terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.	Clarify Sponsor option for cohort closure
Appendix 13.1 Schedule of Assessments	*Revised Appendix 13.1.* *Revised Footnote 19:* ECHO includes assessment of left LVEF and pericardial effusion. The screening ECHO should be done any time before the first dose of study drug, **either during screening or pre-dose on C1D1**; all ECHOs after C1D1 should be conducted within 4 days before the next dosing. *Revised Footnote 23:* CT imaging of the chest, abdomen, and pelvis, and neck (if indicated) **for all subjects**, for assessment via RECIST v1.1. Subjects who achieve a partial or complete response must undergo confirmatory assessment(s) as described in Section 7.3.	Updated to align with the revised protocol body Clarify collection requirements for the screening ECHO Clarify collection requirements for CT imaging of the chest, abdomen, pelvis, and neck (if indicated)

	Revised Footnote 33: CTC assessment includes 1 sample collected from subjects with neuroendocrine prostate cancer for central assessment of CTC, implemented at all sites, and a ~~second~~ sample for exploratory analyses of CTC-associated biomarkers such as DLL3, ~~implemented only at specific sites based on feasibility~~ **collected from subjects with large cell neuroendocrine carcinoma (cohort 4), neuroendocrine prostate cancer (cohort 5), and high-grade gastroenteropancreatic neuroendocrine carcinoma (cohort 6). Both CTC samples are collected at the following time points: C1D1, EOT, Long Term Follow-Up 2 (12 weeks), and time of progression (if not already collected).**	Clarify CTC sample collection
Appendix 13.2 Schedule Day 1 Peridosing Assessments	*Revised Footnote 3;* **The 6 hour PK sample** ~~PK sample~~ is to be drawn Cycles 1 **and**~~,~~ 2~~, and 4~~ only. – **omitted for retreatment subjects.**	Updated to align with the revised protocol body
Appendix 13.3 Previous Protocol (version 3.0) Cohort 3 (Glioblastoma) Specific Guidance	*Added New Appendix; refer to Appendix 13.3*	Moved cohort 3 (Glioblastoma) guidance associated with protocol version 3 to the appendix as a reference for those GBM subjects still on study