CLINICAL PROTOCOL

Protocol Number	SCRX001-002
Version and Date	Version 4.0, 18-Nov-2016
Protocol Title	An Open-label, Single-Arm, Phase 2 Study Evaluating the Efficacy, Safety and Pharmacokinetics of Rovalpituzumab Tesirine (SC16LD6.5) for Third-line and Later Treatment of Subjects with Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer (TRINITY)
Investigational Drug	Rovalpituzumab tesirine
Phase	2
IND Number	117510
EUDRACT Number	2015-004506-42
Medical Monitor	[redacted]
Sponsor	
Sponsor Representative	
Sponsor Representative Signature	
SAE Contact Information	See information specified on the SAE reporting manual

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. "AbbVie" shall mean AbbVie Inc. or its affiliate AbbVie Stemcentrx LLC.

SYNOPSIS

TITLE:

An Open-label, Single-Arm, Phase 2 Study of Rovalpituzumab Tesirine (SC16LD6.5) Evaluating the Efficacy, Safety and Pharmacokinetics for Third-line and Later Treatment of Subjects with Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer (TRINITY)

PROTOCOL NUMBER:	SCRX001-002
PHASE OF DEVELOPMENT:	2
INVESTIGATORS AND STUDY CENTERS:	Multicenter

OBJECTIVES:

Primary:

- To investigate the efficacy of rovalpituzumab tesirine as third-line and later treatment for subjects with relapsed or refractory delta-like protein 3 (DLL3)-expressing small cell lung cancer (SCLC)

Secondary:

- To assess duration of response, clinical benefit rate and progression-free survival in subjects with relapsed or refractory DLL3-expressing SCLC treated with rovalpituzumab tesirine
- To assess the safety and tolerability of rovalpituzumab tesirine
- To characterize the pharmacokinetics of rovalpituzumab tesirine and incidence of anti-therapeutic antibodies (ATA)

Exploratory:

- To explore relationship of DLL3 expression to clinical outcome during treatment with rovalpituzumab tesirine
- To explore the efficacy and safety of rovalpituzumab tesirine retreatment when administered to subjects with DLL3-expressing SCLC who previously achieved clinical benefit on rovalpituzumab tesirine
- To explore the effect of rovalpituzumab tesirine on disease biomarkers and pharmacodynamics

TEST PRODUCTS, DOSE, AND MODE OF ADMINISTRATION:

- Rovalpituzumab tesirine 0.3 mg/kg intravenously on Day 1 of each 6-week cycle for 2 cycles
- Dexamethasone 8 mg 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 an open-label, single-arm, Phase 2 study of rovalpituzumab tesirine in DLL3-expressing SCLC subjects with relapsed or refractory disease after receiving at least 2 previous regimens, including at least one platinum-based regimen. Only subjects with tumor cell expression that is DLL3 positive based on an immunohistochemistry (IHC) assay specification will be enrolled in the study. Enrollment will continue until up to approximately 123 DLL3 high, third-line subjects are treated. Enrollment will be carried out in two stages. In Stage 1, up to 60 evaluable, DLL3 high (per IHC assay specification), subjects may be enrolled. If among the 60 evaluable, DLL3 high (per IHC assay specification) subjects, more than 9 subjects achieve complete response or partial response, then enrollment will continue to Stage 2. At least 63 additional subjects that are DLL3 high (per IHC assay specification) will be enrolled in Stage 2. Otherwise enrollment will terminate. Of the enrolled DLL3 positive subjects, less than or equal to 30% can be fourth-line or later.

All enrolled subjects will receive 0.3 mg/kg rovalpituzumab tesirine intravenously (IV) on Day 1 of every six-week treatment cycle for two cycles. An additional two cycles of rovalpituzumab tesirine (retreatment) is permitted for subjects who tolerated their initial two doses of rovalpituzumab tesirine, achieved clinical benefit as defined by stable disease or better, have received no other systemic anti-cancer therapy after rovalpituzumab tesirine as administered per this protocol, and with central radiographic assessment-confirmed disease progression at least 12 weeks after the second dose. Additional retreatment, beyond a total of four cycles will require approval from the Medical Monitor.

All subjects in the long-term follow-up will continue disease assessments every 6 weeks for 6 months, then every 12 weeks thereafter. Subjects will be followed until disease progression per RECIST (version 1.1) or initiation of new anticancer treatment, whichever occurs first; and will afterwards be followed for survival until death or study termination, whichever occurs first.

Blood samples for PK, immunogenicity, biomarker and pharmacodynamics assessments will be collected at protocol-defined time points to support the study endpoints (see Sections 7.3and 7.4).

The primary efficacy endpoints of the study will be the best objective response rate at the end of treatment assessment (42 ± 3 days after last dose) and overall survival. Safety will be assessed by pre- and post-treatment measurements of vital signs and clinical laboratory assessments, and through the recording of adverse clinical events. PK and cytokine data will be collected at select sites only.

An independent Data Monitoring Committee (iDMC) will act in an advisory capacity to monitor subject safety and efficacy data from the study.

MAJOR ELIGIBILITY CRITERIA:

Adult subjects with histologically confirmed advanced DLL3+ SCLC with measurable disease, relapsed/refractory to at least 2 prior systemic regimens, including one platinum-based regimen; ECOG 0-1; adequate hematologic, hepatic and renal function; and no prior exposure to a PBD-based drug (unless retreated with rovalpituzumab tesirine in the context of this protocol).

PLANNED SAMPLE SIZE:

Among the enrolled DLL3 high subjects, at least 123 will be third-line. Of the enrolled, DLL3 positive subjects, less than or equal to 30% can be fourth-line or later.

ENDPOINTS AND OUTCOME MEASURES:

Efficacy Endpoints

Primary:

This study has two co-primary endpoints:

- Objective response rate through the End of Treatment (42 ± 3 days after last dose) for DLL3 high and for DLL3 positive, per IHC assay specification subjects
- Overall survival for DLL3 high and for DLL3 positive, per IHC assay specification subjects

Secondary:

- Duration of response for DLL3 high and for DLL3 positive subjects, per IHC assay specification
- Clinical Benefit Rate for DLL3 high and for DLL3 positive subjects, per IHC assay specification
- Progression-free survival for DLL3 high and for DLL3 positive subjects, per IHC assay specification

Safety Endpoints

Safety assessments include vital signs, body weight, ECOG score, clinical adverse events, laboratory tests (hematology, serum chemistries, urinalysis, and coagulation), ECGs, echocardiogram, fluid retention questionnaire, and monitoring of concomitant therapies.

Pharmacokinetic and Pharmacodynamic Endpoints

Pharmacokinetic 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 of blood samples for tumor markers, [redacted] and soluble biomarkers such as soluble DLL3.

STATISTICAL METHODS:

Sample Size

A response rate of 15% or less is typically observed in this advanced state of the disease. It is assumed that at least 25% of subjects treated with rovalpituzumab tesirine will achieve complete or partial response. In Stage 1, up to 60 evaluable, DLL3 high (per IHC assay specification), subjects may be enrolled. In Stage 2, at least 63 additional subjects that are DLL3 high (per IHC assay specification) will be enrolled, to maintain an 80% power at a one-side significance level of 0.025. The number of subjects evaluated at each stage and the minimum

number of responders to continue from Stage 1 to Stage 2 were estimated using the minimax principle of the Simon two-stage design.

Up to approximately 123 DLL3 high, third-line subjects will be enrolled. The total sample size for this study will be determined by the proportion of enrolled subjects with DLL3 high expression among those who are DLL3 positive.

Efficacy Analysis

The primary efficacy endpoint is objective response rate defined as the proportion of subjects whose best overall response is either complete response (CR) or partial response (PR) according to RECIST (version 1.1). The best overall response is the best recorded response through End of Treatment (42 ± 3 days after last dose). The overall response rate will be estimated based on the maximum likelihood estimator (i.e., crude proportion of subjects with best overall response of CR or PR). The estimate will be accompanied by a two-sided exact 95% binomial confidence interval. [redacted]

Overall survival will be summarized descriptively using the Kaplan-Meier method. [redacted] The proportion of subjects alive at 6, 9, and 12 months from the initiation of study treatment will be estimated and summarized using the Kaplan–Meier approach.

Duration of response and progression-free survival will also be summarized descriptively using the Kaplan-Meier method. The progression-free survival rate at additional landmark time points may also be evaluated (e.g., 6, 9, and 12 months).

For subjects retreated with rovalpituzumab tesirine, both safety and selected efficacy outcomes will be analyzed separately from the outcomes observed following the initial course of treatment.

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DEFINITIONS OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Definition
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
ANA	antinuclear antibodies
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AT	aminotransferase
ATA	anti-therapeutic antibody
AUC	area under the curve
$AUC_{0-\tau}$	AUC within a dosing interval
$AUC_{0-\infty}$	AUC from time 0 extrapolated to infinity
β-hCG	beta-human chorionic gonadotropin
BUN	blood urea nitrogen
CBR	Clinical benefit rate
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum concentration
CL	clearance
CNS	central nervous system
CPK	creatine phosphokinase
CR	complete response
CRF	case report form
CRP	C-reactive protein
CT	computerized tomography
[redacted]	
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	concentration at trough
DILI	drug-induced liver injury
DLL3	delta-like protein 3
DLT	dose-limiting toxicity
DMC	data monitoring committee
DOR	duration of response
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

Abbreviation or Term	Definition
EDC	Electronic data capture
EGF	epidermal growth factor
eGFR	estimated glomerular filtration rate
EOT	end of treatment
ESR	erythrocyte sedimentation rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HNSTD	highest nonseverely toxic dose
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IHR	infusion or hypersensitivity reaction
IL	interleukin
INR	international normalized ratio
IRB	Institutional Review Board
IUD	intrauterine device
IV	intravenous(ly)
LCNEC	large cell neuroendocrine carcinoma
LTFU	long-term follow-up
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MDRD	Modification of Diet in Renal Disease
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NSCLC	non-small cell lung cancer
NSE	neuron-specific enolase
NYHA	New York Heart Association
ORR	objective response rate
OS	overall survival
PBD	pyrrolobenzodiazepine

Abbreviation or Term	Definition
PCR	polymerase chain reaction
PD	progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PO	per os
PR	partial response
PT	prothrombin time
PTT	partial thromboplastin time
q3w	Every 3 weeks
q6wk	Every 6 weeks
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate by Bazett's formula
QTcF	QT interval corrected for heart rate by Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RF	rheumatoid factor
RP2D	recommended phase 2 dose
SAE	serious adverse event
SC-DR002	DNA cross-linking agent also known as D6.5
SC16	Humanized DLL3-specific IgG1 antibody
SCLC	small cell lung cancer
S_{cr}	serum creatinine
SD	stable disease
SPF	sun protection factor
$t_{½}$	terminal half-life
TEAE	treatment-emergent adverse event
T_{max}	time of maximum concentration
TNBC	triple-negative breast cancer
TPC	Tumor perpetuating cell
ULN	upper limit of normal
USP	United States Pharmacopeia
VEGF	vascular endothelial growth factor
V_{ss}	volume of distribution at steady state

1 INTRODUCTION

1.1 Background

1.1.1 Small Cell Lung Cancer

Small cell lung cancer (SCLC) is an important unmet medical need, representing 15–20% of the 220,000 annual new cases of lung cancer in the United States (Govindan 2006, Siegel 2012). These cancers arise from epithelial cells with neuroendocrine differentiation and typically are positive for both cytokeratin and neuroendocrine markers; however, the diagnosis is usually made by morphologic examination. Historically, SCLC has been divided into limited versus extensive stage disease—the former being defined as disease limited to the chest that can be encompassed by a radiation field while the latter includes all other cases. Approximately one-third of newly diagnosed patients will have limited stage disease while the rest will be extensive. Unlike nonsmall cell lung cancer (NSCLC), SCLC is rarely cured with local therapy (surgery and/or radiotherapy); systemic chemotherapy remains the cornerstone of therapy for all stages of disease. Standard initial therapy for all patients with a suitable performance status consists of a platinum salt (carboplatin or cisplatin) in combination with a second agent, usually etoposide. For patients with limited stage disease, concurrent or sequential involved-field thoracic radiotherapy is indicated. Response rates to initial therapy are high, ranging from 70–90% for limited stage and 60–70% for extensive stage; however recurrence rates are also high in the limited group and universal in the extensive group, leading to median survivals of 14–20 months and 9–11 months, respectively (Simon 2004).

Recurrent SCLC is rapidly fatal (median survival less than 6 months). Two groups may be identified: ‘resistant’ patients who recur during or within 2–3 months after completing a course of initial therapy, and ‘sensitive’ patients who recur later following primary therapy. Although many single agents and chemotherapy combinations have shown some transient evidence of activity in recurrent patients, only topotecan has received FDA approval in this setting. The approval for an intravenous (IV) formulation of topotecan was based on response rates of 11-31% in the sensitive population and between 2–7% in the refractory population, with an overall time to progression (TTP) of 3–4 months (Eckardt 2007, Owonikoko 2012). An oral formulation was later approved for patients based on a survival benefit compared with best supportive care (25.9 versus 13.9 weeks, hazard ratio = 0.64). The overall response rate (ORR) in

this study was 7% (O'Brien 2006). There is no approved agent, nor an existing standard of care treatment, for SCLC patients who recur following second-line treatment.

1.1.2 DLL3 and Rovalpituzumab Tesirine

Delta-like protein 3 (DLL3) is an inhibitory ligand of the Notch receptor family. It is highly expressed in SCLC and some neuroendocrine cancers like large cell neuroendocrine carcinoma (LCNEC), including tumor perpetuating cells (TPCs), but with no detectable expression in normal tissues or other non-neuroendocrine tumor types. While the function of DLL3 has not been clearly defined, it has been implicated in the regulation of cell development and fate decisions (Dunwoodie 1997, Chapman 2011).

Rovalpituzumab tesirine is a DLL3-targeted ADC consisting of the humanized DLL3-specific IgG1 antibody SC16; the 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.

Preliminary data from a Phase 1 study with rovalpituzumab tesirine have been encouraging, with an objective response rate (ORR) of 44% and clinical benefit rate (CBR) of 76% in relapsed or refractory $DLL3^{hi}$ SCLC subjects treated in the expansion cohorts of 0.2 mg/kg q3wk and 0.3 mg/kg q6wk, and preserved response rates in the subset of third line subjects (ORR 45%, CBR 73%). In all expansion cohort SCLC subjects, regardless of DLL3 expression, the ORR and CBR were 23% and 68%, respectively (AbbVie data on file).

1.1.3 Rationale for the Study and Anticipated Risks

No approved therapeutic options are available for subjects who have progressive SCLC following treatment with two prior therapies, including at least one involving a platinum-based frontline regimen. Based on the promising efficacy data to date, rovalpituzumab tesirine warrants investigation as a potentially important therapeutic option in the third-line and later setting. This

study will examine the therapeutic utility of rovalpituzumab tesirine in subjects with DLL3+ extensive-stage SCLC after failure of at least two prior systemic regimens, including a platinum-based therapy.

Potential risks with rovalpituzumab tesirine include fatigue, dyspnea, and nausea, which have been the most frequently reported AEs to date. However, remarkable toxicities have included serosal effusions (typically pleural or pericardial), peripheral edema, cutaneous reactions (typically photosensitivity), and thrombocytopenia. In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified the lung and kidney as a potential source of clinical AEs. Accordingly, safety assessments will include regular assessments at protocol-specified time points of routine physical examination, laboratory and imaging tests, as well as echocardiograms, a fluid retention questionnaire, daily weights and spot urine protein testing.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

- To investigate the efficacy of rovalpituzumab tesirine as third-line and later treatment for subjects with relapsed or refractory delta-like protein 3 (DLL3 -expressing small cell lung cancer (SCLC)

2.1.2 Secondary Objectives

- To assess duration of response, clinical benefit rate and progression-free survival in subjects with relapsed or refractory DLL3-expressing SCLC treated with rovalpituzumab tesirine
- To assess the safety and tolerability of rovalpituzumab tesirine
- To characterize the pharmacokinetics of and incidence of anti-therapeutic antibodies (ATA) to rovalpituzumab tesirine

2.1.3 Exploratory Objectives

- To explore relationship of DLL3 expression to clinical outcome during treatment with rovalpituzumab tesirine
- To explore the efficacy and safety of rovalpituzumab tesirine retreatment when administered to subjects with DLL3-expressing SCLC who previously achieved clinical benefit on rovalpituzumab tesirine
- To explore the effect of rovalpituzumab tesirine on disease biomarkers and pharmacodynamics

2.2 Endpoints

2.2.1 Primary Efficacy Endpoints

This study has two primary endpoints:

- Objective response rate through the End of Treatment (42 ± 3 days after last dose) for DLL3 high and for DLL3 positive subjects, per IHC assay specification
- Overall survival for DLL3 high and for DLL3 positive subjects, per IHC assay specification

2.2.2 Secondary Efficacy Endpoints

- Clinical Benefit Rate for DLL3 high and for DLL3 positive subjects, per IHC assay specification

- Duration of response for DLL3 high and for DLL3 positive subjects, per IHC assay specification
- Progression-free survival for DLL3 high and for DLL3 positive subjects, per IHC assay specification

2.2.3 Safety Endpoints

- Adverse Events
- Vital signs
- Laboratory abnormalities
- Electrocardiographic intervals (e.g. QTc)
- Echocardiography
- Components of a fluid retention questionnaire

2.2.4 Pharmacokinetics, Biomarker and Pharmacodynamic Endpoints

- Specific pharmacokinetic parameters of rovalpituzumab tesirine (e.g., C_{max}, AUC)
- Anti-therapeutic antibodies against rovalpituzumab tesirine
- Tumor DLL3 expression
- Inflammatory Markers
- Blood Tumor Markers
- Biomarkers, including soluble DLL3

3 INVESTIGATIONAL PLAN

3.1 Summary of Study Design

This is an open-label, single-arm, multicenter, Phase 2 study of rovalpituzumab tesirine in DLL3-expressing SCLC subjects with relapsed or refractory disease after receiving at least 2 previous regimens, including one platinum-based regimen. Only subjects with tumor cell expression that is DLL3 positive, based on an immunohistochemistry (IHC) assay specification will be enrolled in the study. [redacted]

All enrolled subjects will receive 0.3 mg/kg rovalpituzumab tesirine once every six-week treatment cycle administered intravenously (IV) for up to two cycles. An additional two cycles of rovalpituzumab tesirine (retreatment) is permitted for subjects who tolerated their initial two doses of rovalpituzumab tesirine, achieved clinical benefit as defined by stable disease or better, have received no other systemic anti-cancer therapy after rovalpituzumab tesirine as administered in this protocol, and with central radiographic assessment-confirmed disease progression at least 12 weeks after the second dose. Additional retreatment, beyond a total of four cycles will require approval from the Medical Monitor.

All subjects in LTFU will continue disease assessments every 6 weeks until 6 months, then every 12 weeks. Subjects will be followed until disease progression per RECIST or initiation of new anticancer treatment, whichever occurs first; and will afterwards be followed for survival until death or study termination, whichever occurs first. Blood samples for PK, immunogenicity, biomarker and pharmacodynamics assessments will be collected at protocol-defined time points to support the study endpoints (see Sections 7.3 and 7.4).

The primary efficacy endpoint of the study will be the best objective response rate through the end of treatment assessment (42 ± 3 days after last dose). Safety will be assessed by pre- and post-treatment measurements of vital signs and clinical laboratory assessments, and through the recording of adverse clinical events. PK and cytokine data will be collected at select sites only.

An independent Data Monitoring Committee (iDMC) will act in an advisory capacity to monitor subject safety and efficacy data from the study.

Retreatment with rovalpituzumab tesirine is permitted for subjects who tolerate two doses of rovalpituzumab tesirine, achieve clinical benefit as defined by stable disease or better, have received no other systemic anti-cancer therapy after rovalpituzumab tesirine as administered in this protocol, and with central radiographic assessment-confirmed disease progression at least 12 weeks after the second dose. Retreatment consists of rovalpituzumab tesirine 0.3 mg/kg IV once every 6 weeks for two cycles, or a reduced dose if dose reduction has previously taken place (see Section 5.2.3.2). Additional retreatment, beyond a total of four cycles will require approval from the Medical Monitor.

3.2 Discussion and Rationale for Study Design

3.2.1 Study Design

This is a single-arm, open-label study in third-line and later SCLC. Rovalpituzumab tesirine has previously demonstrated preliminarily promising efficacy and tolerability in both second- and third-line SCLC. Because there is no approved therapy for third-line SCLC, no appropriate active comparator is available. At the same time, the very poor prognosis of subjects in this setting makes placebo comparison inappropriate.

3.2.2 Dose Rationale

The chosen dose regimen, two doses of 0.3 mg/kg administered 6 weeks apart, is based on the safety and efficacy observed in a previous phase 1 study (SCRX16-001), where delayed and/or cumulative toxicities were observed with both q3wk and q6wk schedules and appeared to be related to total dose administered. The total dose was therefore capped at a total cumulative dose of 0.6 mg/kg and the finite dosing regimens of 0.2 mg/kg q3wk for a total of 3 doses (q3wk x 3) and 0.3 mg/kg q6wk for a total of 2 doses (q6wk x 2) were evaluated in expansion cohorts. Because the intended mechanism of action of rovalpituzumab tesirine is to target cancer stem

cells and, more broadly, tumor-initiating cells, limiting the number of doses is hypothesized to affect anti-tumor response only minimally.

The 0.2 mg/kg q3wk x 3 and 0.3 mg/kg q6wk x 2 dosing regimens demonstrated comparable objective response and clinical benefit rates. Both regimens were tolerated, but the 0.3 mg/kg regimen demonstrated a trend towards lower rates of treatment-emergent adverse events (TEAE), related TEAEs, Grade 3/4 TEAEs and related Grade 3/4 TEAEs. In addition, although the 0.3 mg/kg regimen appeared to have a higher incidence of Grade 3/4 thrombocytopenia, such an AE was generally clinically manageable. [redacted] serosal effusions, which may be life threatening such as leading to pericardial tamponade. In addition, objectives responses preliminarily have appeared to be more durable in subjects treated with the 0.3 mg/kg regimen. Finally, the 0.3 mg/kg q6wk x 2 regimen is more conveniently administered than 0.2 mg/kg q3w x 3 and coincides with the timing of radiographic evaluation of tumor size. Therefore, 0.3 mg/kg q6wk x 2 is the chosen dose regimen for this study.

3.2.3 Blinding

This is not a blinded trial. However, sponsor-independent review of efficacy and safety will occur throughout the study (Sections 7.2.1 and 0).

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, subjects must meet all inclusion and exclusion criteria outlined in this section.

4.1 Inclusion Criteria

1. Adult aged 18 years or older
2. Histologically confirmed small-cell lung cancer (SCLC) with documented disease progression after at least 2 prior systemic regimens, including at least one platinum-based regimen
3. DLL3-expressing SCLC based on central immunohistochemistry (IHC) assessment of banked or otherwise representative tumor tissue.
4. Measurable disease, defined as at least 1 tumor lesion ≥10 mm in the longest diameter or a lymph node ≥15 mm in short-axis measurement assessed by CT scan (RECIST v1.1)
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See Appendix 12.2 for conversion of performance status using Karnofsky scales, if applicable
6. Minimum life expectancy of at least 12 weeks
7. Subjects with a history of central nervous system (CNS) metastases must have documentation of stable or improved status based on 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
8. Recovery to Grade 1 of any clinically significant toxicity (excluding alopecia) prior to initiation of study drug administration
9. Satisfactory laboratory parameters:
    a. Absolute neutrophil count (ANC) ≥ 1,500/µL
    b. Platelet count ≥ 75,000/µL

c. Hemoglobin ≥ 8.0 g/dL

d. Serum total bilirubin ≤ 1.5x upper limit of normal (ULN) or ≤ 3x ULN for subjects with Gilbert's disease

e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5x ULN (≤ 5x ULN if evidence of hepatic involvement by malignant disease)

f. Serum creatinine ≤ 1.5x ULN or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 as calculated by the 4-variable Modification of Diet in Renal Disease (MDRD) study equation (GFR (mL/min/1.73 m^2) = 175 × (serum creatinine [mg/dL])–1.154 × (age [years])–0.203 × 0.742 (if female) × 1.212 (if African American; Levey, 2006)

10. 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 (i.e., anti-PD-1, anti-PD-L1, or anti-CTLA-4): 4 weeks

    c. Other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, or T-cell or other cell-based therapies: 4 weeks (2 weeks with documented disease progression)

11. Females of childbearing potential must have a negative beta human chorionic gonadotropin (β-hCG) pregnancy test result within 7 days prior to the first dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy.

    a. Females of childbearing potential and males who have partners of childbearing potential must agree to use an effective contraception method during the study and for 1 year following the last dose of study drug. Effective birth control includes (a) combined, estrogen and progestogen containing, hormonal contraception (oral, intravaginal, transdermal); (b) progestogen-only hormonal contraception (oral, injectable, implantable); (c) intrauterine device (d) intrauterine hormone-releasing system; (e) bilateral tubal occlusion; (f) vasectomised partner; and (g) sexual abstinence.

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 6 months) or neurological disorder (e.g., seizure disorder active within 6 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 (see Appendix 12.3) 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 (per 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. Women who are breastfeeding

5. Systemic therapy with corticosteroids at >20 mg/day prednisone or equivalent within 1 week prior to the first dose of study drug

6. History of another invasive malignancy that has not been in remission for at least 3 years. Exceptions to the 3 year limit include nonmelanoma skin cancer, curatively treated localized prostate cancer, and cervical cancer *in situ* on biopsy or squamous intraepithelial lesion on PAP smear

7. Prior exposure to a pyrrolobenzodiazepine (PBD)-based drug, 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 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.

4.3.1 Discontinuation of Study Drug

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

- Progressive disease (as confirmed by central radiographic assessment; see Section 7.2.1)
- Adverse event (AE)
- Investigator decision
- Subject decision, Non-AE
- Other

4.3.2 Subject Discontinuation from Study

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

- Subject withdrawal of consent
- Adverse event (AE)
- Death
- Investigator decision
- Lost to follow-up
- Significant noncompliance to protocol
- Study termination 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

5.2.1 Description

Rovalpituzumab tesirine (SC16LD6.5) drug product is provided in a sterile clear USP Type I 10 mL glass vial [redacted] The [redacted] drug product is reconstituted with [redacted] sterile water for injection [redacted] The rovalpituzumab tesirine formulation consists of 10 mg/mL rovalpituzumab tesirine in 20 mM histidine hydrochloride, 0.175 M sucrose and 0.4 mg/mL polysorbate 20, pH 6.0. The [redacted] drug product is stored and shipped at 2–8°C prior to its use in clinical trials.

A complete description of the chemistry and formulation may be found in the Investigator's Brochure.

5.2.2 Dose and Administration

Dosing is based on subject actual body weight to the nearest tenth of a kilogram, assessed on Day 1 of each cycle, and administered according to the assigned dose.

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

- Absolute neutrophil count (ANC) ≥ 1,000/μL
- Platelet count ≥ 75,000/μL
- Clinically-significant AEs occurring during the previous cycle (both clinical and laboratory) have resolved to Grade 0 or 1 (or to baseline grade if preexisting)

Rovalpituzumab tesirine should be diluted into 100 mL normal saline (0.9% NaCl). The infusate should be administered over 30 minutes [redacted] See the Pharmacy Instructions for details.

5.2.3 Dose Modifications

5.2.3.1 Treatment Delays Due to Toxicity or Progression

Subjects who experience toxicity during a cycle must have recovered as outlined previously in Section 5.2.2 before the next cycle may proceed. If an AE is still ongoing at the time of the next scheduled cycle, the cycle must be delayed until recovery. Specific recommendations are given below.

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

5.2.3.2 Dose Reduction Guidelines

Rovalpituzumab tesirine dose reduction for specific toxicities should occur as outlined in Table 5-1 and Table 5-2. If toxicities persist despite dose reduction, the dose should be discontinued. Exceptions to the dose modification guidelines may be permitted with written or electronic approval from the Medical Monitor. If a dose is reduced during the previous cycle, the reduced dose will be administered on Day 1 of subsequent cycles.

Table 5-1 Dose Reductions for Rovalpituzumab Tesirine

Starting Dose	First Dose Reduction (reduce dose)	Second Dose Reduction (discontinue dose)
0.3 mg/kg	0.2 mg/kg	Discontinue dosing

Table 5-2 Unacceptable Toxicities Requiring Dose Reduction

Toxicity	Grade [a] / Details
Thrombocytopenia **Thrombocytopenia with bleeding**	Grade 4 thrombocytopenia (or Grade 3 thrombocytopenia with bleeding) lasting more than 7 days and/or requiring platelet transfusion
Neutropenia **Febrile neutropenia**	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)
Laboratory abnormality	Grade 2 or higher hypoalbuminemia (in subject with normal baseline albumin levels) Grade 3 or 4 non-albumin laboratory abnormality considered clinically significant and treatment-related
Nonlaboratory toxicity	Grade 3 or 4 nonlaboratory toxicity (including infusion reactions) with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom
Skin toxicity	Grade 3 or higher cutaneous toxicity or symptom of photosensitivity (refer to Section 5.5.2)
Serosal effusions	Serosal effusions including: Grade 3 or higher pericardial effusion Grade 2 or higher pleural effusion Grade 3 or higher peripheral edema

a) Refer to Appendix 12.5 for definitions of NCI-CTCAE severity grades.

For the purposes of dose reduction, unacceptable toxicity is defined in Table 5-2. If unacceptable toxicity is encountered in Cycle 1, the Cycle 2 dose may be reduced (Table 5-1). If unacceptable toxicity is encountered at the reduced dose level, treatment should be discontinued. If the rovalpituzumab tesirine dose is reduced, the reduced dose level will be used for any subsequent cycles (i.e., retreatment).

Treatment guidelines for hematologic toxicities, and recommended actions regarding rovalpituzumab tesirine dosing, are outlined in Table 5-3.

Table 5-3 Guidelines for Hematologic Toxicities

Toxicity	Recommended Action[a] for Rovalpituzumab Tesirine Doses
Toxicity on Day 1 of Cycle (i.e., predose of Cycle 2)	
Platelets < 75,000/μL	• Hold • With resolution restart at original dose for next cycle • If no resolution, reduce dosing
ANC < 1,000/μL	• Hold • Growth factors are recommended to be used per ASCO/NCCN/institutional guidelines • With resolution restart at original dose for next cycle • If no resolution, reduce dosing
Toxicity on Subsequent Days of Cycle	
Platelets < 25,000/μL for greater than 7 days, OR Thrombocytopenia with bleeding observed in the previous cycle	• Hold • With resolution restart at reduced dose per Table 5-1 for next cycle • If no resolution, discontinue dosing
ANC < 500/μL for greater than 7 days, OR Neutropenic fever (ANC < 1,000/μL and single temperature > 38.3°C or temperature > 38.0°C for more than 1 hour)	• Hold • Growth factors are recommended to be used per ASCO/NCCN/institutional guidelines[b] • With resolution restart at reduced dose per Table 5-1 for next cycle • If no resolution, discontinue dosing

Abbreviations: ANC = absolute neutrophil count.

a) The maximum allowed dose interruption is 6 weeks.

b) Colony stimulating factors include filgrastim or sargramostim

5.2.4 Storage and Handling

Vials of rovalpituzumab tesirine must be stored at 2–8°C. The reconstituted drug product should be used immediately. If not used immediately, the reconstituted rovalpituzumab tesirine vials can be stored at 2–8°C for up to 8 hours. The prepared dosing solution in the infusion bag should be used immediately following preparation. If not used immediately, the bag can be stored at 2–8°C for up to 8 hours.

5.2.5 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.

5.2.6 Preparation

Rovalpituzumab tesirine is a drug product for injection for IV use following reconstitution with sterile water for injection. The reconstituted drug product is further diluted in an infusion bag containing 0.9% Sodium Chloride Injection, USP, or equivalent, to achieve the desired dose level for administration. On visual inspection, the solution for infusion should be clear, colorless and free from visible particulates. Detailed drug preparation instructions are provided in the Pharmacy Instructions.

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. A missed steroid dose can be provided the next day, as clinically appropriate. 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). In countries, where dexamethasone is not available, the equivalent dose of an alternate corticosteroid may be administered in lieu of dexamethasone.

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. Any concomitant therapy given for a study protocol-related adverse event 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 per local institutional standards. Other standard supportive care for symptom control or drug-related toxicity is allowed, such as analgesics, antiemetics, electrolyte replacement, and hydration. Other prescribed medications for non-neoplastic conditions are allowed, as well as vitamins and nutritional supplements.

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 (see 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; 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.

5.4.3 Prohibited Concomitant Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study, other than as allowed in Sections 5.2.3 and 5.4.2.

5.5 Management of Adverse Reactions

5.5.1 Management of Serosal Effusions

Serosal effusions (pleural or pericardial, or ascites) have been observed with rovalpituzumab tesirine, alone or in combination with peripheral edema and/or hypoalbuminemia. These events 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. Alternative causes, such as infection, congestive heart failure, or disease progression, should be ruled out.

In the event of a grade 2 or higher AE in this group (effusions, edema, hypoalbuminemia) considered related to rovalpituzumab tesirine:

- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases. 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 three to four times daily) or colchicine (e.g. 0.6 mg orally two to three 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 Sections 5.2.2 and 5.2.3.

5.5.2 Management of Skin Reactions

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 may be reported as such (using medically accurate and descriptive AE terminology), and managed via application of at least topical steroids (Table 5-4).
- If not clinically consistent with photosensitivity, the following should be done:
  - Photodocumentation to facilitate later review by the sponsor or designee
  - 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.

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

Table 5-4 Recommended Management of Photosensitivity

CTCAE v4.03		Treatment Recommendations	Dose Modifications
Grade 1	Painless erythema and erythema covering <10% Body Surface Area (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 x 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 x 7 days Hospitalization	Reduce dose

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 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. At the same time, subjects will maintain a diary of daily weights. Any study protocol-related adverse event should be recorded from the time of informed consent as well as any concomitant therapies given for treatment of the adverse event. A schedule of events is provided in Appendix 12.1. 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 will follow the same study schedule from Screening through EOT and LTFU.

6.2 Screening Visit (Days -14 to -1)

Informed consent will be obtained prior to the performance of any study procedures and may occur within 30 days of the Day 1 visit. Screening assessments will be completed within 14 days of the Day 1 visit.

- Informed consent – omitted for retreatment subjects
- Demographics (see Section 7.1) – omitted for retreatment subjects
- Study eligibility per inclusion/exclusion criteria (see Section 4)
- Medical and surgical history (see Section 7.1) – omitted for retreatment subjects
- Malignancy history (see Section 7.1) – omitted for retreatment subjects
- Prior anticancer treatments (see Section 7.1) – omitted for retreatment subjects
- Physical examination (see Section 7.6.2)
- Vital signs (see Section 7.6.3)
- Height (see Section 7.6.3)
- Complete blood count (see Section 7.6.4)
- Serum chemistries (see Section 7.6.4)

- Coagulation tests (see Section 7.6.4)
- Urinalysis (see Section 7.6.4)
- Hepatitis B and C tests (see Section 7.6.4) – omitted for retreatment subjects
- Pregnancy test (see Section 7.6.4) for women of child-bearing potential
- Triplicate ECG (see Section 7.6.5)
- ECOG performance status (Appendix 12.2)
- Disease assessment consisting of CT scans of the chest, abdomen, and pelvis (and neck if indicated; see Section 7.2) – 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). For those subjects that are unable to tolerate MRI, a CT scan with contrast can be performed instead (with approval from the Medical Monitor)
- Paraneoplastic assessment (see Section 7.1) – omitted for retreatment subjects
- Tumor tissue, collected upon an archived or fresh specimen (see Section 7.4.1). Previously obtained DLL3 tumor expression results may be substituted if assessed previously via central immunohistochemistry assessment – omitted for retreatment subjects

6.3 Treatment Period

The treatment period for subjects is Day 1 to 42 of each 6 week cycle. Subjects undergoing retreatment as described in Section 3.1 will follow the same study schedule from Screening through EOT and LTFU.

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 for Cycle 2 and Beyond)

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 (complete blood count, 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 chemistry panel) must be available prior to dose.

- Physical examination (see Section 7.6.2)
- Vital signs – within 30 minutes prior to the infusion, and then post-infusion at 30 minutes (±10 minutes), 2 hours (±15 minutes) and 4 hours (±30 minutes; see Section 7.6.3)
- Complete blood count (see Section 7.6.4)
- Chemistry Panel (see Section 7.6.4)
- Coagulation tests (see Section 7.6.4)
- Urinalysis (see Section 7.6.4)
- Pregnancy test (see Section 7.6.4) for women of child-bearing potential
- Triplicate ECG - prior to and after the infusion (see Section 7.6.5)
- Echocardiogram (see Section 7.6.6)
- ECOG performance status (Appendix 12.2)
- Fluid retention questionnaire (see Section 7.6.8
- Blood sample for pharmacokinetics – [redacted]
- Blood sample for anti-therapeutic antibodies
- Blood inflammatory markers (see Section 7.4.2)
- Blood tumor markers (see Section 7.4.3)
- Soluble biomarkers (see Section 7.4.4)
- [redacted]
- 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 (see Section 5.1)

6.3.3 Day 2 (Day after Dosing)

- Subjects will take dexamethasone 8 mg PO twice a day

6.3.4 Day 3 (±1 days)

- Triplicate ECG taken at approximately the same time of day as on Day 1 - prior to blood sample for pharmacokinetics (see Section 7.6.5)
- Blood sample for pharmacokinetics

6.3.5 Day 8 (±2 days)

- Fluid retention questionnaire (see Section 7.6.8) – may be conducted virtually

6.3.6 Day 15 (±2 days)

- Physical examination (see Section 7.6.2)
- Vital signs (see Section 7.6.3)
- Complete blood count (see Section 7.6.4)
- Chemistry panel (see Section 7.6.4)
- Urinalysis (see Section 7.6.4)
- Fluid retention questionnaire (see Section 7.6.8)
- Blood sample for pharmacokinetics

6.3.7 Day 22 (±2 days)

- Fluid retention questionnaire (see Section 7.6.8) – may be conducted virtually

6.3.8 Day 29 (±3 days)

- Physical examination (see Section 7.6.2)
- Vital signs (see Section 7.6.3)
- Complete blood count (see Section 7.6.4)
- Chemistry Panel (see Section 7.6.4)
- Urinalysis (see Section 7.6.4)
- Fluid retention questionnaire (see Section 7.6.8)
- Blood sample for pharmacokinetics

6.3.9 Day 36 (±3 days)

- Fluid retention questionnaire (see Section 7.6.8) – may be conducted virtually

6.3.10 Within 7 days prior to the next dose

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; see Section 7.2)
- MRI of the brain – if clinically indicated (e.g. if CNS progression has been documented previously). For those subjects that are unable to tolerate MRI, a CT scan with contrast can be performed instead (with approval from the Medical Monitor)

6.4 End of Treatment Visit

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

- Physical examination (see Section 7.6.2)
- Vital signs (see Section 7.6.3)
- Complete blood count (see Section 7.6.4)
- Chemistry Panel (see Section 7.6.4)
- Coagulation tests (see Section 7.6.4)
- Urinalysis (see Section 7.6.4)
- Pregnancy test (see Section 7.6.4) for women of child-bearing potential
- Triplicate ECG (see Section 7.6.5)
- Echocardiogram (see Section 7.6.6)
- ECOG performance status (Appendix 12.2)
- Fluid retention questionnaire (see Section 7.6.8)
- 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 (see Section 7.2)
- 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. For those subjects that are unable to tolerate MRI, a CT scan with contrast can be performed instead (with approval from the Medical Monitor)

- Blood sample for pharmacokinetics
- Blood sample for anti-therapeutic antibodies
- Blood inflammatory markers (see Section 7.4.2)
- Blood tumor markers (see Section 7.4.3)
- Soluble biomarkers (see Section 7.4.4)
- [redacted]

6.5 Long-Term Follow-up (LTFU; Every 6-12 weeks ±1 week)

For all subjects without centrally-confirmed disease progression (including those who discontinue study treatment for reasons other than disease progression), 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; see Section 7.2)
- MRI of the brain – if clinically indicated (e.g. if CNS progression has been documented previously). For those subjects that are unable to tolerate MRI, a CT scan with contrast can be performed instead (with approval from the Medical Monitor)
- Survival status

After centrally-confirmed disease progression, 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 will be enrolled in this study.

Absence of active central nervous system tumor or metastases will be confirmed by MRI of the brain. For those subjects that are unable to tolerate MRI, a CT scan with contrast can be performed instead (with approval from the Medical Monitor)

Demographics include age, gender, race, smoking history and status.

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

Malignancy history should include tumor type, stage, sites of metastases, and mutational status.

Paraneoplastic assessment includes documentation of the presence and type of any SCLC-related paraneoplastic syndrome(s) (Appendix 12.6)

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. The central assessment will be relayed to the investigator. All decisions regarding study eligibility will be based upon DLL3 expression adjudicated by this central assessment.

7.2 Response/Efficacy Assessments

Treatment response will be assessed by radiographic tumor evaluation at protocol-specified time points. Diagnostic quality, spiral CT scans are recommended; other methods may be used if performed consistently throughout the study for each individual subject. Scans of the chest, abdomen and pelvis must be obtained; scans of the neck must also be obtained if there is documented or suspected involvement in this region. Positron emission tomography (PET) may be used in an ancillary manner; however, no decisions relating to PD may be made based on PET alone. Clinical response will be determined by the investigator at each assessment according to

RECIST v1.1 (Appendix 12.4 and Eisenhauer 2009) and by Central Radiographic Assessment (Section 7.2.1).

Treatment at Cycle 2 beyond what would be considered progression of disease using RECIST v1.1 is permitted if the following criteria, as assessed by the investigator, are met:

- Ongoing clinical benefit, without rapid disease progression
- 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 disease progression (e.g., central nervous system 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.

7.2.1 Central Radiographic Assessment

Radiological scans will be assessed in real time by a Central Radiographic Assessment Committee. [redacted]

7.3 Pharmacokinetic Assessments

Blood samples for PK and ATA testing will be collected at the time points throughout the study as indicated in Appendix 12.1 for incorporation into an integrated population PK analysis. The population PK analysis will be reported separately.

Sensitive, qualified assays will be used to measure blood concentrations of rovalpituzumab tesirine and SC-DR002, the small molecule component of rovalpituzumab tesirine. A qualified immunoassay will be used to assess ATA against rovalpituzumab tesirine.

7.4 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 Appendix 12.1. See the laboratory manual for additional details.

7.4.1 Tumor Tissue

Tumor tissue, consisting of a representative archived specimen, or a fresh tumor biopsy, will be assessed for expression of DLL3 by methods such as but not necessarily limited to IHC.

[redacted]

7.4.2 Inflammatory Markers

[redacted]

7.4.3 Blood Tumor Markers

[redacted]

7.4.4 Soluble Biomarkers

[redacted]

7.4.5 [redacted]

[redacted]

[redacted]

7.4.6 Serosal Fluid

Any pericardial, pleural and/or ascitic fluid collected as part of routine care (e.g. as part of a therapeutic thoracentesis, pericardiocentsis, or paracentesis) will be procured, where feasible, for possible pharmacokinetic, pharmacodynamic and/or biomarker testing. See the laboratory manual for additional details.

7.5 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 sponsor's future research, including but not limited to the evaluation of additional targets for novel therapeutic agents, the biology of DLL3, and the identification of biomarkers. Blood and tissue samples donated for future research may be retained by sponsor indefinitely. If additional consent is not provided, any remaining biological samples will be destroyed by sponsor or sponsor's representatives following study completion.

7.6 Safety Assessments

The assessment of safety during the course of this study will consist of the surveillance and recording of adverse events (AEs) and serious adverse events (SAEs);recording of concomitant therapies; protocol-specified physical examination findings including vital signs; ECOG performance status; disease assessments; and diagnostic testing including laboratory testing, radiographic imaging, ECGs and echocardiograms, etc..

Safety will be monitored over the course of the study by a DMC.

7.6.1 Adverse Events

7.6.1.1 Definitions

Adverse Event

Per the International Conference on Harmonization (ICH) E2A Guidance, Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH, 1995), and 21 CFR 312.32 IND Safety Reporting, an AE is 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.

The following information should be considered when determining whether or not to record a test result, medical condition, or other incident on the Adverse Events or Pre-existing Conditions case report form (CRF):

- From the time of informed consent through Day 1 prior to dosing, only study protocol-related AEs and serious adverse events (SAEs) should be recorded. A protocol-related AE is defined as an untoward medical event occurring as a result of a protocol mandated procedure.
- All baseline medical conditions present prior to dosing on study Day 1 should be recorded and assessed for grade or severity.
- All AEs (regardless of relationship to study drug) should be recorded from study Day 1 (during and post-dose) through the end of the safety reporting period (see Section 7.6.1.3). Complications that occur in association with any procedure (e.g., biopsy) should be recorded as AEs with assessed grade or severity whether or not the procedure was protocol mandated.
- Changes in baseline medical conditions and AEs (including changes in severity, frequency, or character) during the safety reporting period should be recorded.
- In general, an abnormal diagnostic or laboratory value should not be recorded as an AE unless it is associated with clinical signs or symptoms (i.e. assessed as clinically significant), requires an intervention, results in a serious adverse event (SAE), or results in study termination or interruption/discontinuation of study treatment. When recording an AE resulting from a diagnostic or laboratory abnormality, the medical condition or diagnosis rather than the abnormality itself should be recorded (e.g., record “anemia” rather than “low hemoglobin”).

Serious Adverse Event (SAE)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

Fatal:	Results in death.
Life threatening:	Is life threatening. ***Note:*** The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Hospitalization:	Requires in-patient hospitalization, or resulted in prolongation of an existing hospitalization, (Hospitalizations for elective medical or surgical procedures or treatments planned before the signing of informed consent in the study or routine check-ups are not SAEs by this criterion. Admission to a palliative unit or hospice care facility is not considered to be a hospitalization. Hospitalizations or prolonged hospitalizations for scheduled therapy of the underlying cancer or study target disease need not be captured as SAEs).
Disabling/ incapacitating:	Resulted in a persistent or significant disability/ incapacity or substantial disruption of the subject's ability to conduct normal life functions.
Congenital anomaly or birth defect:	Is a congenital anomaly or birth defect in a child or fetus of a patient/subject who has been exposed to the molecule or study treatment regimen before conception or during pregnancy.
Medically significant:	The AE did not meet any of the above criteria, but could have jeopardized the subject and might have required medical or surgical intervention to prevent one of the outcomes listed above or involves suspected transmission via a medicinal product of an infectious agent.

The following hospitalizations will not be considered SAEs:

- A visit to the emergency room or other hospital department of less than24 hours, that does not result in a hospital admission (unless considered an important medical event or a life-threatening event)
- Elective surgery, that was planned prior to signing consent
- Admissions, per protocol, for a planned medical/surgical procedure
- Scheduled therapy of the underlying cancer or study target disease
- Routine health assessments (e.g., routine colonoscopy)

Admission to a palliative unit or hospice facility is not considered a hospitalization.

Adverse Event Severity

AE severity should be graded using the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. These criteria are provided in the study manual. When CTCAE grade is not available, severity will be used.

AE severity and seriousness are assessed independently. 'Severity' characterizes the intensity of an AE. 'Serious' is a regulatory definition and serves as a guide to the sponsor for defining appropriate regulatory reporting obligations (see definition for Serious Adverse Events).

Relationship of the Adverse Event to Study Treatment

The relationship of each AE to study drug should be evaluated by the investigator using the following criteria:

Related:	There is evidence to suggest a causal relationship between the drug and the AE, such as: – An event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome) – An event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
Unrelated:	Another cause of the AE is more plausible (e.g., due to underlying disease or occurs commonly in the study population), or a temporal sequence cannot be established with the onset of the AE and administration of the study treatment (latency), or a causal relationship is considered biologically implausible

7.6.1.2 Procedures for Eliciting and Recording Adverse Events

Investigator and study personnel will report all AEs and SAEs whether elicited during subject questioning, or discovered during physical examination, laboratory testing and/or other means by recording them on the CRF and/or SAE form, as appropriate.

Eliciting Adverse Events

An open-ended or non-directed method of questioning should be used at each study visit to elicit the reporting of AEs.

Recording Adverse Events

The following information should be recorded on the Adverse Events and Pre-existing Conditions CRF:

- Description using standard medical terminology (with an effort to use the unifying or reached diagnosis), including onset and resolution dates
- Whether the AE met serious criteria
- Severity/Grade
- Relationship to study treatment or other causality
- Outcome

Diagnosis vs. Signs or Symptoms

In general, the use of a unifying or reached diagnosis is preferred to reporting of individual symptoms. Grouping of symptoms into a diagnosis should only be done if each component sign and/or symptom is a medically confirmed component of a diagnosis as evidenced by standard medical practice. If any aspect of a sign or symptom does not fit into a classic pattern of the diagnosis, report the individual symptom as a separate adverse event.

Important exceptions for this study are adverse reactions associated with the infusion of study drug. For infusion-related reactions, do not use the NCI CTCAE terms of 'cytokine release syndrome,' 'acute infusion reaction,' or 'allergic or hypersensitivity reaction.' Instead, record each sign or symptom as an individual AE. If multiple signs or symptoms occur with a given infusion-related event, each sign or symptom should be recorded separately with its own level of severity.

Recording Serious Adverse Events

For SAEs, record the event(s) on both the CRF and an SAE form.

The following should be considered when recording SAEs:

Death is an outcome of an event. Death, per se, in not a reportable event. The event that resulted in the death should be recorded and reported on both an SAE form and CRF.

For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

Progression of the Underlying Cancer

Do not use the term 'disease progression' alone when reporting AEs, including SAEs, because it is too nonspecific. Symptoms of disease progression that meet the criteria for a SAE must be reported. When possible, report the specific disease (clinical) manifestation of the progression (e.g., 'malignant pleural effusion,' 'spinal bone metastases,' 'lymphadenopathy,' 'brain metastases').

Pregnancy

Notification to Drug Safety: Complete a Pregnancy Report Form for all pregnancies that occur from the time of first study drug dose until 6 months after the last dose of study drug(s) received, including any pregnancies that occur in the female partner of a male study subject. Additionally, report pregnancies that occur in a dosed male subject's female partner if the estimated date of conception occurred after the male subject's first dose of study drug. Transmit the form to the Drug Safety Department of the sponsor or designee within 48 hours of becoming aware of the pregnancy. All pregnancies will be monitored for the full duration; all perinatal and neonatal outcomes should be reported. Infants should be followed for a minimum of 8 weeks after their delivery.

Collection of data on the CRF: All pregnancies (as described above) that occur within 30 days of the last dose of study drug(s) will also be recorded on the Adverse Events and Pre-Existing Conditions CRF.

Abortion (whether spontaneous, therapeutic, or planned) should be reported as a SAE. Congenital anomalies or birth defects, as defined by the 'serious' criterion above (see definitions Section 7.6.1.1) should be reported as SAEs.

7.6.1.3 Reporting Periods for Adverse Events and Serious Adverse Events

The safety reporting period for all AEs and SAEs is from study Day 1 (during and post-dosing) up to 30 days after the last study treatment dose. For those undergoing retreatment, the safety reporting period will also include retreatment study Day 1 (during and post-dosing) up to 30 days after the last study retreatment dose. However, all study protocol-procedure related AEs and SAEs are to be recorded from the time of informed consent. Additionally, all SAEs that occur after the safety reporting period that are considered study treatment-related in the opinion of the investigator should also be reported to the sponsor or its designee.

Each SAE must be followed until the SAE is Recovered/Resolved, Not recovered/Not resolved, Recovered/Resolved with sequelae, or the subject dies (the SAE may be assessed as ongoing at the time of death). SAE outcomes may not be possible to collect when a subject withdraws consent and/or is lost to follow-up. All non-serious AEs will be followed through the end of the safety reporting period. Certain non-serious AEs of interest should be followed until resolution, return to baseline, or study closure.

7.6.1.4 Serious Adverse Events Require Immediate Reporting

Within 24 hours of observing or learning of a SAE, investigators are required to report the event to the sponsor or designee, regardless of the relationship of the event to the study treatment regimen.

For initial SAE reports, available case details are to be recorded on a SAE form. At a minimum, the following must be included:

- Identifiable subject with identification number (can also include gender, age at onset)
- Study treatment (suspect medicinal product)
- Identifiable reporting source
- An event or outcome that can be identified as serious, preferably with a description of the event with date of event onset (to reflect latency)
- Causality (relatedness)

The completed SAE form are to be transmitted to the Drug Safety Department of the sponsor or designee (see contact information specified on the SAE report form) within 24 hours.

Relevant follow-up information is to be submitted to the sponsor as soon as it becomes available.

7.6.1.5 Sponsor Safety Reporting to Regulatory Authorities

Investigators are required to report all SAEs, including anticipated SAEs, to the sponsor or designee (see Section 7.6.1.4).

The sponsor or designee will report all SAEs to the appropriate regulatory authorities as required per local regulatory reporting requirements. In the United States, endpoints that assess disease-related mortality or major morbidity as well as other SAEs that are not study endpoints (but are known consequences of the underlying disease or condition that are anticipated to occur in the

study population), should not be reported to the FDA as individual IND safety reports (per the final rule amending the IND safety reporting requirements under 21 CFR 312.32 and the FDA's guidance Safety Reporting Requirements for INDs and BA/BE Studies dated December 2012).

7.6.1.6 Laboratory Test Result Abnormalities

Any laboratory test result abnormality should be reported as an AE or SAE, as appropriate, if it:

- is clinically significant or meets the definition of an SAE
- required the subject to have study drug discontinued or interrupted
- required the subject to receive specific corrective therapy

Wherever possible, the medical diagnosis rather than laboratory term should be used by the reporting Investigator (e.g., use "anemia" rather than "low hemoglobin").

7.6.1.7 Potential Drug-Induced Liver Injury

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to reporting a potential drug-induced liver injury (DILI) event (FDA 2009). 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 times (3X) upper limit of normal (ULN); AND
- Total bilirubin > 2X 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 serum AT to > 3X ULN should be followed by repeat testing within 48-72 hours of all four of the usual serum measures (ALT, AST, alkaline phosphatase, and 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 available to the investigator immediately for review. All data must be recorded on the case report forms. Close observation should be initiated if symptoms persist or repeat testing shows AT >3xULN for subjects with normal baseline

measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure. If close monitoring is not possible, study drug should be discontinued.

Close observation includes:

- Repeating liver enzyme and serum bilirubin tests two or three times weekly. Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the study 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 non-prescription 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; 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., INR, direct bilirubin).
- Considering gastroenterology or hepatology consultations.

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

- ALT or AST > 8x ULN
- ALT or AST > 5x ULN for more than 2 weeks
- ALT or AST > 3x ULN and (TBL > 3x ULN or INR > 1.5)
- ALT or AST > 3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia

All trial subjects showing possible DILI should be followed until all abnormalities return to normal or to the baseline state. Retreatment of subjects who develop possible DILI and have previously discontinued study drug may only be permitted upon approval by the sponsor and medical monitor.

7.6.2 Physical Examination

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

7.6.3 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. Weight will be measured at the times indicated. For adult subjects, 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.

7.6.4 Clinical Laboratory Tests

Laboratory assessments will be performed to evaluate safety at scheduled time points (see Appendix 12.1) during the course of the study. The following assessments will be performed at the local laboratory:

- Complete Blood Count, including white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, hemoglobin, and hematocrit.
- Chemistry panel, including electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate, glucose, albumin, total protein, liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase), amylase, and lipase.
- Coagulation tests, including prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR).
- Urinalysis, including dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot protein and creatinine.
- 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 PCR tests for Hep B and/or C, respectively.
- Pregnancy test, consisting of blood or urine testing for beta-human chorionic gonadotropin (β-hCG).

7.6.5 Electrocardiograms

Throughout the study, subjects will be monitored for changes in cardiac conduction through ECGs (Appendix 12.1). ECGs consist of 12-lead studies, performed within a 5 minute window after at least 10 minutes of quiet rest in a supine position.

7.6.6 Echocardiogram

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

7.6.7 ECOG Performance Status

ECOG performance Status (Appendix 12.2) will be evaluated at protocol-specific time points (Appendix 12.1).

7.6.8 Fluid Retention Questionnaire

Throughout the treatment period, subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix 12.7). This assessment may take place virtually (e.g. by telephone).

7.6.9 Daily Weight Diary

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

7.7 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. Adverse events 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. 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. Pharmacokinetic assessments for drug activity are also common in clinical studies.

8 DATA QUALITY CONTROL AND QUALITY ASSURANCE

8.1 Site Training and Monitoring Procedures

A study manual with 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/package insert
- 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, labeling, dispensing and record keeping
- Subject coding
- Study samples/specimen collection, handling and shipping
- Protocol compliance
- Clinical study record keeping, 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.

8.2 Data Management Procedures

AbbVie or its designee will provide CRF Completion Guidelines for electronic CRF (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.

8.3 Access to Source Data

The investigator will permit the sponsor's representatives to monitor the study as frequently as the sponsor deems necessary 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 available for inspection by representatives of regulatory authorities.

8.4 Accuracy and Reliability of Data

Steps to be taken to assure the accuracy and reliability of data include:

- 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).

- CRFs will be reviewed 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.

8.5 Quality Assurance Procedures

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

8.6 Data Handling and Recordkeeping

8.6.1 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 Electronic Data Capture (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.

8.6.2 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. Records shall be retained for at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least two (2) years have lapsed since the formal 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 shall be transferred to a mutually agreed upon designee, such as another investigator or IRB/IEC. Notice of such transfer will be provided in writing to the sponsor.

9 PLANNED ANALYSES

A full Statistical Analysis Plan will provide specific details on the analytical methods and data displays.

9.1 Determination of Sample Size

9.2 Statistical and Analytical Plans

The statistical and analytical plans presented below summarize the more complete plans to be detailed in the statistical analysis plan (SAP). A change to the data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol. The SAP will be finalized prior to database lock. Any changes to the methods described in the final SAP will be described and justified in the clinical study report.

9.2.1 General Considerations

9.2.1.1 Randomization and Blinding

This is an open-label, non-randomized study. Formal blinding will not be performed.

9.2.1.2 Adjustments for Covariates

Adjustments for covariates are not planned.

9.2.1.3 Handling of Dropouts and Missing Data

With the exception of time-related endpoints, no imputation will be conducted for missing data unless otherwise specified in the SAP. For time-related endpoints (e.g., duration of response), subjects who have no specified event will be censored at the time of the last valid assessment of the endpoint(s).

9.2.1.4 Multiple Comparisons and Multiplicity

No adjustments for multiple comparisons are planned.

9.2.1.5 Data Transformations and Derivations

Time variables based on 2 dates (e.g., Start Date and End Date) will be calculated as (End Date - Start Date + 1) (in days) unless otherwise specified in the planned analysis section. Baseline values used in all statistical analyses will be the most recent measurement prior to the first dose of study drug. For subjects retreated with study drug, separate baseline values will be determined using the most recent measurement prior to the first dose of retreatment.

9.2.1.6 Analysis Sets

Full Analysis Set

The full analysis set includes all subjects who receive any amount of study drug. The full analysis set will be used for the primary analysis of efficacy.

A supplemental analysis set consisting of all subjects who receive at least 1 dose of study drug as retreatment also will be defined. Selected efficacy outcomes (e.g., ORR, DOR, and PFS) for such subjects will be analyzed separately from the outcomes observed following the initial course of treatment.

Safety Population

The safety population includes all subjects who receive any amount of study drug. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after at least 1 dose of study treatment may be required for inclusion in the analysis of a specific safety parameter (e.g., lab shifts from baseline).

A supplemental safety population consisting of all subjects who receive at least 1 dose of study drug as retreatment also will be defined. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after at least 1 dose of retreatment may be required for inclusion in the analysis of a specific safety parameter. The safety outcomes for such subjects will be analyzed separately from the outcomes observed following the initial course of treatment.

Pharmacokinetic-Evaluable Population

The pharmacokinetic population consists of all subjects who receive at least 1 dose of study treatment. A baseline measurement and at least 1 blood sample following a dose of study treatment is required for inclusion in this analysis. The pharmacokinetic data will be used in a population PK analysis that will be reported separately.

9.2.1.7 Examination of Subgroups

Subgroup analyses may be conducted for selected endpoints.

Subgroups will be specified in the Statistical Analysis Plan.

9.2.1.8 Timing of Analyses

See Section 9.2.10.

9.2.2 Subject Disposition

An accounting of study subjects by disposition will be tabulated and the number of subjects in each analysis set will be summarized. Subjects who discontinue study treatment and subjects who withdraw from the study will be summarized with reason for discontinuation or withdrawal.

9.2.3 Subject Characteristics

Captured demographic and baseline characteristics will be summarized.

9.2.4 Prior and Concomitant Therapies

Prior and concomitant therapies will be coded to the generic term using the current version of the World Health Organization Drug Dictionary and will be tabulated and listed by subject.

A summary of the anticancer therapies and interventions received after discontinuing study treatment will be provided.

9.2.5 Treatment Compliance

The dose administered at each cycle will be assessed and dose intensity will be summarized. Details will be provided in the SAP.

9.2.6 Efficacy Analyses

9.2.6.1 Primary Efficacy Analysis:

Primary Efficacy analysis will be performed on subjects that are DLL3 positive, as well as on a subset of subjects that are DLL3 high based on the defined IHC assay specifications.

9.2.6.1.1 Objective Response Rate

The objective response rate defined as the proportion of subjects whose best overall response is either complete response (CR) or partial response (PR) according to RECIST version 1.1. The best overall response is the highest recorded response through end of treatment (42 ± 3 days after last dose).

The objective response rate will be estimated based on the maximum likelihood estimator (i.e., crude proportion of subjects with best overall response of CR or PR). The estimate will be accompanied by a two-sided exact 95% binomial confidence interval (CI).

A supplemental analysis of ORR will be performed based on assessments by the Investigator.

Objective response rate following retreatment with rovalpituzumab tesirine will be reported separately as a secondary, supplemental analysis.

9.2.6.1.2 Overall Survival

Overall survival is defined as the number of months from first dose date (Day 1) to the date of death of any cause. The survival status of subjects will be ascertained according to a predetermined follow-up schedule. The follow-up schedule is intended to provide for the systematic ascertainment of each subject's survival status (alive, dead, or unknown/lost to

follow-up) at the time just prior to database lock for the interim analysis, primary analysis, and subsequent updates (if any) until the closure of the study. For subjects lost to follow-up or whose survival status is unknown, every effort will be made to determine the date such subjects were last known to be alive. Such efforts may include phone calls, certified mail, and the checking of public records. Subjects who are alive or lost to follow-up as of the data analysis cutoff date will be right-censored. The censoring date will be determined from the date the subject was last known to be alive.

The duration of overall survival will be summarized descriptively using the Kaplan-Meier method. Median follow-up and the associated 95% confidence interval for overall survival will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper 1996).

[redacted]

The proportion of subjects alive at 6, 9, and 12 months from the initiation of study treatment will be summarized descriptively based on Kaplan-Meier estimates. The estimates will be accompanied by a two-sided 95% CI.

9.2.6.2 Secondary Efficacy Analyses

All secondary analyses will be performed on subjects that are DLL3 positive, as well as on a subset of subjects that are DLL3 high, based on the defined IHC assay specifications. Additionally, analyses by line of therapy will be reported. Objective response rate and overall survival as described above will be analyzed by the line of therapy.

9.2.6.2.1 Duration of Response

Duration of response will be calculated for subjects who achieve a best overall response of CR or PR. For such subjects, duration of response is defined as the number of weeks from the start date of PR or CR (whichever response is recorded first) and subsequently confirmed to the first date that recurrent or progressive disease or death is documented. In such cases, recurrent or progressive disease will be assessed relative to the smallest tumor measurements recorded since the start of study treatment. The primary analysis of duration of response will be based on the time point responses, best overall response, and PD status that are determined by central review.

A supplemental analysis of duration of response will be performed based on assessments by the Investigator. Median follow-up for duration of response will be estimated according to the Kaplan-Meier estimate of potential follow-up (Schemper 1996). Duration of response at 6, 9, and 12 months from the start date of CR or PR will be summarized descriptively based on Kaplan-Meier estimates. The estimates will be accompanied by a two-sided 95% CI.

Duration of response for subjects who achieve CR or PR following retreatment with rovalpituzumab tesirine will be reported separately as a secondary, supplemental analysis.

9.2.6.2.2 Clinical Benefit Rate

Duration of response will be calculated for subjects who achieve a best overall response of CR, PR or SD. For such subjects, duration of clinical benefit is defined as the number of weeks from the start date of PR, CR or SD (whichever response is recorded first) and subsequently confirmed to the first date that recurrent or progressive disease or death is documented. Clinical benefit rate will be analyzed in a manner similar to the analysis of the objective response rate described above.

9.2.6.2.3 Progression-free Survival

Progression-free survival is defined as the number of weeks from first dose date (Day 1) to the date of earliest of PD or death due to any cause. Disease progression will be assessed using RECIST (version 1.1). Such assessments will be made by both the individual Investigator and by central review. The primary analysis will be based on PFS events determined by independent central review. A supportive analysis of PFS will be performed based on PFS events assessed by the Investigator.

Progression-free survival will be summarized descriptively using the Kaplan-Meier method. The PD and censoring dates for the primary and secondary analyses of PFS will be based on the conventions found in FDA's Guidance for Industry (FDA 2007). For the primary analysis, the PD status (progressed or censored) and the corresponding progression or censoring date will be based on the conventions described in the guidance.

The proportion of subjects who are alive and without disease progression at 6, 9, and 12 months from the initiation of study treatment will be will be summarized descriptively based on Kaplan-

Meier estimates. The estimates will be accompanied by a two-sided 95% CI. The progression-free survival rate at additional landmark time points may also be evaluated.

Progression-free survival (and related outcomes) following retreatment with rovalpituzumab tesirine will be reported separately as a secondary, supplemental analysis.

9.2.7 Pharmacokinetic Analyses

The pharmacokinetic (PK) of rovalpituzumab tesirine will be estimated from concentration-time data using population PK methods. The reporting of PK parameters will be determined based on the final parameter analysis on the available data. The incidence and timing of ATA to study drug will be summarized by descriptive statistics. The possible effects of ATA on pharmacokinetics, efficacy and safety may be explored. Details will be provided in the SAP.

9.2.8 Pharmacodynamic Analyses

Descriptive statistics of the mean, median, absolute number, and percent change from baseline will be visually evaluated for IHC, inflammatory markers, blood tumor markers like NSE, soluble biomarkers such as soluble DLL3, [redacted] and regressions will 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.

9.2.9 Safety Analyses

Unless specified otherwise, the safety analyses will be conducted for the safety population. At least 1 laboratory or other safety-related assessment subsequent to at least 1 dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

A supplemental safety population consisting of all subjects who receive at least 1 dose of study drug as retreatment also will be defined. A baseline measurement and at least 1 laboratory or other safety-related measurement obtained after at least 1 dose of retreatment may be required for inclusion in the analysis of a specific safety parameter. The safety outcomes for such subjects will be analyzed separately from the outcomes observed following the initial course of treatment.

9.2.9.1 Treatment Emergent Adverse Events

Adverse events will be defined as treatment emergent if they are newly occurring or worsen following study treatment. The incidence of treatment-emergent adverse events and treatment-related adverse events will be tabulated. Adverse events will be classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

AEs will be listed and summarized by MedDRA preferred term, severity, and relationship to study drug. In the event of multiple occurrences of the same AE with the same preferred term in one subject, the AE will be counted once as the occurrence, using the event with highest severity grade and strongest causal relationship. The incidence of AEs will be tabulated by preferred term.

9.2.9.2 Deaths and Serious Adverse Events

Serious adverse events will be listed and summarized in the same manner as all AEs. All deaths that occur on study will be reported in a subject listing, which will include the primary cause of death and the number of days between the date of the last dose of study drug and death.

9.2.9.3 Other Safety Analyses

Vital Signs

Summary statistics and change from baseline and/or pre-dose to post-dose may be tabulated where appropriate.

ECOG Status

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

Clinical Laboratory Results

Summary statistics of laboratory results and change from baseline to scheduled post-baseline visits may be tabulated as appropriate.. Directional shifts in laboratory toxicity grades per NCI CTCAE v4.03 will be analyzed using standard shift tables. Shift tables will present directional shifts from baseline to above or below the laboratory standard normal range. . Laboratory values will be listed with grade per NCI CTCAE, v4.03 and out of the normal range flags.

Electrocardiogram

ECG status (normal, abnormal clinically significant, or abnormal not clinically significant) will be summarized for each scheduled ECG, and shifts from baseline may be tabulated. Summary statistics of each ECG parameter results and change from baseline to scheduled post-baseline visits may be tabulated as appropriate.

In addition, mean, median and maximum absolute change from baseline of QTcF will be assessed and summarized, where $QTcF = \frac{QT}{\sqrt[3]{RR}}$.

Categorical outliers (e.g. QTcF > 450 msec, > 480 msec, and > 500 msec or ΔQTcF from baseline > 30 msec and > 60 msec) will be presented.

The relationship between plasma concentration of study drug and SC-DR002 with ΔQTcF will be assessed and described with an appropriate model. Details will be provided in the SAP.

9.2.10 Interim Analyses

An interim analysis will be conducted when End of Treatment assessments from 60 evaluable, DLL3 high (per IHC assay specification), subjects are available. The interim analysis will be based on review of data from the Stage 1 part of the study. Evaluable subjects will be those who have measurable disease per central reader with at least one post-baseline response assessment, which can include the response assessment performed at the end of treatment study visit.

9.2.11 Independent Data Monitoring Committee

An independent Data Monitoring Committee (iDMC) will be formed and constituted according to appropriate regulatory agency guidelines. Detailed information regarding the composition of the iDMC and detailed iDMC procedures will be provided in a separate charter maintained by the sponsor and/or designee. The iDMC will review the efficacy and safety data periodically and

provide recommendations according to the charters. The iDMC will review safety data approximately every 6 months. Otherwise, the iDMC may request further safety analyses.

The iDMC will review data and provide recommendations regarding stopping or continuing the trial in accordance with the DMC charter. The sponsor may attend only selected portions of the iDMC meetings to answer questions as necessary.

10 ETHICAL AND REGULATORY CONSIDERATIONS

This study will be conducted in accordance with the Protocol, ICH Guidance E6 (R1) (ICH, 1996); FDA CFR [21 CFR 50, 56, and 312]), Declaration of Helsinki (Brazil 2013), and all applicable regulatory requirements.

10.1 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 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 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. 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 approved ICF.

Prior to the start of the study, the investigator will provide the sponsor with an ICF approved by the IRB for use during the study that is based on sponsor's model template ICF. The model ICF template prepared by the sponsor may be found in the Study Manual. The authorization for use and disclosure of protected health information must contain the elements required by 45 CFR 164.508(b) for valid authorizations. 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 4.8and 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/EC. The ICF document 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 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.

10.2 Confidentiality of Subject Personal Information

Subjects shall be provided with information in the informed consent process on the confidential treatment of their personal information collected in the study and such information shall be included in the ICF (See Section 10.1). In addition, an authorization for the collection, use, 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.

The investigator will assign a unique identifier or code 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 strictly adhere to professional standards and applicable law concerning the confidential treatment of the subject information.

10.3 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 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 document will contain information on the treatment of subject personal information relating to clinical samples, including, if applicable, the labeling of clinical samples with the subject's unique code.

10.4 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 are provided 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.

10.5 Regulatory Considerations

This study will be conducted in accordance with the protocol and ethical principles stated in the applicable guidelines on good clinical practice, and all applicable local and/or regional laws, rules, and regulations.

10.6 Investigator Information

The contact information and qualifications of the principal investigator and subinvestigators and name and address of the research facilities are included in the investigator file. 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.

10.6.1 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 terminate the study at any time. The IRB/IEC must be advised in writing of study completion or early termination.

10.7 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.

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 (the Authorization). 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.

10.8 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 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 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, 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 two (2) years; or as otherwise approved by sponsor in writing. The investigator will submit to sponsor any proposed publication or presentation along with the name of the applicable scientific journal or presentation forum at least sixty (60) days prior to submission of the publication or presentation. The investigator will comply with sponsor's request to delete references to its confidential information in any paper or presentation and the investigator or institution will withhold publication or presentation for an additional sixty (60) days in order to allow sponsor sufficient time to obtain patent protection on the contents of any publication if deemed necessary by sponsor. 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. Sponsor shall have the unrestricted right to use, share, and copy such publications and portions of such publications for its business purposes.

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12 APPENDICES

12.1 Schedule of Assessments

Item	Day / Window	Screening	Every Treatment Cycle									EOT[1]	LTFU
	Day	–14 to –1	–1	1[2]	2	3	8	15	22	29	36	≤ 7 days prior to next dose[3]	42 days after last dose	q6-12 w thru 4 yr[4]
	Window	–	–	± 2d[2]	–	± 1d	± 2d	± 2d	± 2d	± 3d	± 3d		± 3d	± 1w
Location	Clinic Visit	X		X		X		X		X		X	X	
	Virtual Visit						X		X		X			
	Investigator (MD) present	X		X				X		X			X	
Screening, Baseline, and Safety Assessments	Informed Consent[5]	X												
	Demographics	X												
	Inclusion/Exclusion Criteria	X												
	Medical and Surgical History[6]	X												
	Malignancy History[7]	X												
	Prior Anticancer Treatments[8]	X												
	Physical examination	X		X				X		X			X	
	Vital Signs[9]	X		X				X		X			X	
	Height	X												
	Complete Blood Count[10]	X		X				X		X			X	
	Chemistries[11]	X		X				X		X			X	
	Coagulation Tests[12]	X		X									X	
	Urinalysis[13]	X		X				X		X			X	
	Hepatitis B and C tests[14]	X												
	Pregnancy Test[15]	X		X									X	
	Electrocardiogram (ECG)[16]	X		X		X							X	
	Echocardiogram[17]			X									X	
	Performance Status (ECOG)	X		X									X	
	Fluid Retention Questionnaire[18]			X			X	X	X	X	X		X	
	Daily Weight Diary[19]			Day 1 predose thru EOT or 30 days after last study treatment, whichever is later										
	Adverse Events	Procedure-related only												
	Concomitant Therapies[20]													
Treatment	Rovalpituzumab tesirine			X										
	Dexamethasone		X	X	X									
Response Assessment	Disease/Response Assessment[21, 23]	X										X	X[22]	X
	MRI of the Brain	X										X[24]	X[24]	X[24]
	Paraneoplastic Assessment[25]	X												

Schedule of Assessments Cont.

Item	Day / Window	Screening	Every Treatment Cycle									EOT[1]	LTFU
	Day	–14 to –1	–1	1[2]	2	3	8	15	22	29	36	≤ 7 days prior to next dose[3]	42 days after last dose	q6-12 w thru 4 yr[4]
	Window	–	–	± 2d[2]	–	± 1d	± 2d	± 2d	± 2d	± 3d	± 3d		± 3d	± 1w
PK, PD and Biomarkers	Pharmacokinetics[26]			X		X		X		X			X	
	Anti-therapeutic antibody			X									X	
	Tumor Tissue[27]	X												
	Inflammatory Markers[28]			X									X	
	Blood Tumor Markers[29]			X									X	
	Soluble Biomarkers[30]			X									X	
	[redacted]			X									X	
			Day 1 thru EOT or 30 days after last study treatment, whichever is later											

Table Notes

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 should be performed prior to dosing of study drug (within 1 day); results from local clinical laboratory tests must be available prior to dose; ±2 day window for Cycle 2 Day 1 and beyond.

3) Days 36–42 of each cycle.

4) Follow-up occurs every 6 weeks until 6 months, then every 12 weeks. See Section 6.5.

5) Informed consent will be obtained prior to the performance of any study procedures and may occur within 30 days of the Day 1 visit. Screening assessments will be completed within 14 days of the Day 1 visit.

6) Medical and Surgical History includes descriptions of conditions or procedures, and dates of onset - offset.

7) Malignancy History includes tumor type, stage, sites of metastases, mutational status.

8) Prior Anticancer Treatments include names of specific treatments, dates of administration, response to therapy, and duration of response, if known

9) Vital signs include temperature, blood pressure, pulse, respirations, and weight.

10) Complete Blood Count includes white blood cell count with five-part differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils), red blood cell count, platelet count, hemoglobin, and hematocrit.

11) Chemistries include electrolytes (sodium, potassium, chloride, and carbon dioxide), creatinine, blood urea nitrogen (BUN), estimated glomerular filtration rate, glucose, albumin, total protein, liver function tests (total and direct bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase), amylase, and lipase.

12) Coagulation tests include prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR)

13) Urinalysis includes dipstick results for color, appearance, specific gravity, pH, glucose, bilirubin, ketones, occult blood, and protein; as well as spot urine protein and creatinine.

14) Hepatitis B and C tests include Hep B surface antigen (HBsAg), Hep B surface antibody (HBsAb), Hep B core antibody (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.

15) Pregnancy test consists of blood or urine testing for beta-human chorionic gonadotropin (β-hCG) for women of child-bearing potential. Additional testing may be done per the investigator.

16) Electrocardiogram consists of a 12-lead study taken in triplicate. For Day 3 assessment, evaluate ECGs at approximately the same time of day as on Day 1 – prior to blood sample for pharmacokinetics.

17) Echocardiogram includes assessment of left ventricular ejection fraction (LVEF) and pericardial effusion.

18) Fluid Retention Questionnaire includes queries of daily weights and worsening or new edema or dyspnea.

19) Subjects will maintain a diary of daily weights.

20) Concomitant Therapies include names of all concomitant medications, blood products, procedures and radiotherapy, including dates of administration, dose regimen, route of administration, and purpose.

21) Every 6 weeks until 6 months, then every 12 weeks, until disease progression or initiation of new anticancer therapy. Thereafter, Disease/Response Assessment consists of subsequent anticancer therapies and dates, date of progression (if not already captured on study), and survival status.

22) May be omitted if a Disease/Response Assessment was performed within the preceding 6 weeks.

23) CT imaging of the chest, abdomen, and pelvis, and neck (if indicated), for assessment via RECIST v1.1.

24) MRI of the brain is only required during treatment when clinically indicated (e.g. if CNS progression is documented)

25) Paraneoplastic assessment includes documentation of the presence of a SCLC-related paraneoplastic syndrome, if present.

26) On days of study drug dosing, includes pre-infusion and end of infusion samples.

27) Tumor Tissue 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.

[redacted]

32) Serosal Fluid 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, pericardiocentsis, or paracentesis), for possible pharmacokinetic, pharmacodynamic and/or biomarker testing.

12.2 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.

12.3 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.

12.4 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[a]	Always represents PD
New nonmeasureable 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)

a) 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 no greater than 5 mm)

12.5 CTCAE v4.03 Grading of Some Relevant AEs

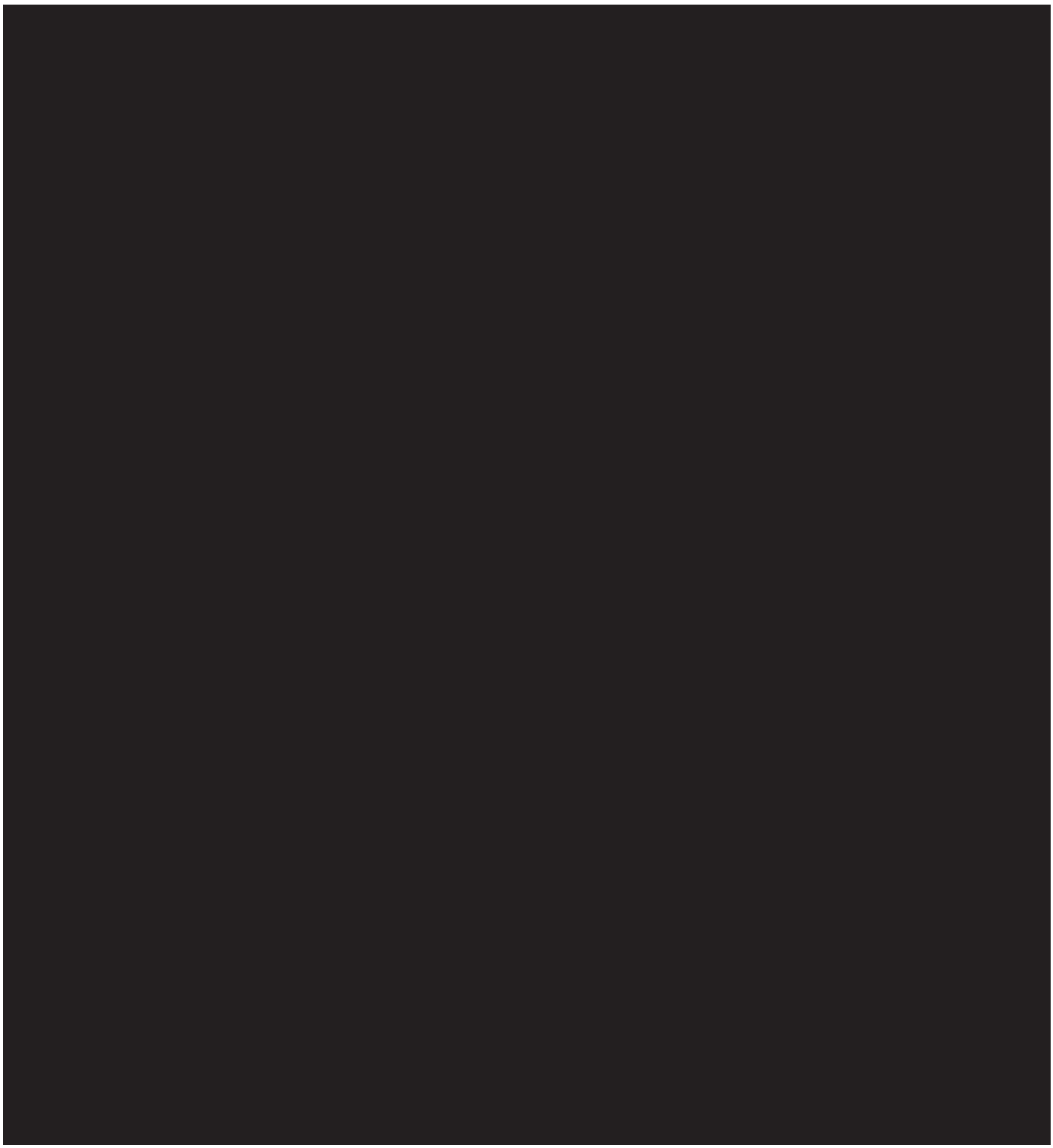
Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Effusions	Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated
	Pericardial Effusion	–	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated
	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
Edema	Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self care ADL	–
	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	–
	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	–
	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	–
	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	–

CTCAE v4.03 Grading of Some Relevant AEs Cont.

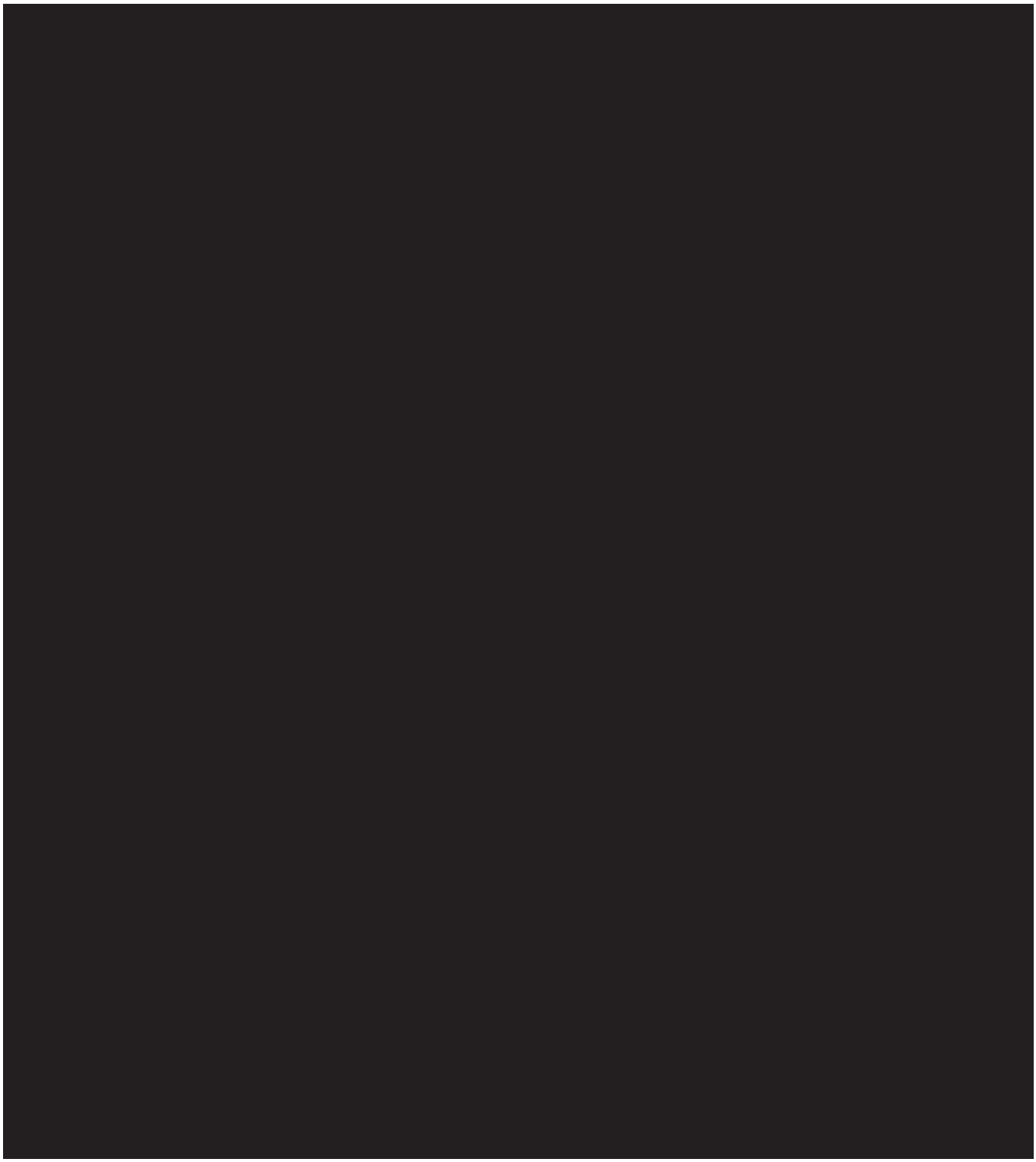
Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Labs	Hypo-albuminemia	<LLN – 3 g/dL; <LLN – 30 g/L	<3 – 2 g/dL; <30 – 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
	Neutrophil count decreased	<LLN – 1500/mm3; <LLN – 1.5 x 10e9 /L	<1500 – 1000/mm3; <1.5 – 1.0 x 10e9 /L	<1000 – 500/mm3; <1.0 – 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
	Platelet count decreased	<LLN – 75,000/mm3; <LLN – 75.0 x 10e9 /L	<75,000 – 50,000/mm3; <75.0 – 50.0 x 10e9 /L	<50,000 – 25,000/mm3; <50.0 – 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L

From CTCAE v4.03

12.6 Paraneoplastic Assessment



12.7 Fluid Retention Questionnaire



12.8 Investigator Signature Page

Investigator Statement and Signature

I have read the attached protocol.

Protocol Number	SCRX001-002
Version and Date	Version 4.0, 18-Nov-2016
Protocol Title	An Open-label, Single-Arm, Phase 2 Study Evaluating the Efficacy, Safety and Pharmacokinetics of Rovalpituzumab Tesirine (SC16LD6.5) for Third-line and Later Treatment of Subjects with Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer (TRINITY)
Investigational Drug	Rovalpituzumab tesirine
Phase	2
IND Number	117510
EUDRACT Number	2015-004506-42

I understand and agree to the provisions of the protocol, and I accept the responsibilities listed above in my role as principal investigator for the study.

Investigator Signature _____ Date _____

Investigator Name, Printed _____

12.9 Document History

Version	Date
Original	23-Sep-2015
Version 2.0	12-Nov-2015
Version 3.0	14-Mar-2016
Version 4.0 (current version)	**18-Nov-2016**

DOCUMENT NAME STUDY NUMBER:	SCRX001-002 (Protocol) An Open-label, Single-Arm, Phase 2 Study Evaluating the Efficacy, Safety and Pharmacokinetics of Rovalpituzumab Tesirine (SC16LD6.5) for Third-line and Later Treatment of Subjects with Relapsed or Refractory Delta-Like Protein 3-Expressing Small Cell Lung Cancer (TRINITY)
VERSION:	4.0
DATE FINAL: DD MMM YYYY	18-Nov-2016

MASTER REVIEW	N/A ☐
☒ Approved as written ☐ Approved with changes ☐ Not approved and must be resubmitted	
Name and Title: [redacted] Signature: [redacted]	

MASTER REVIEW	N/A ☐
☒ Approved as written ☐ Approved with changes ☐ Not approved and must be resubmitted	
Name and Title: [redacted] Signature: [redacted]	

MASTER REVIEW	N/A ☐
☒ Approved as written ☐ Approved with changes ☐ Not approved and must be resubmitted	
Name and Title: [redacted] Signature: [redacted]	