

Statistical Analysis Plan

Product: Rovalpituzumab tesirine (SC16LD6.5)
Indication: Small Cell Lung Cancer
Protocol Title: Document Date 14 February 2018
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)
Protocol Number: SCRX001-002
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Prepared by:

Change of History

Version Number	Brief description of changes made
Version 2.0	
Version 2.1	
Version 3.0	

Version 3.0



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ABBREVIATIONS AND ACRONYMS

Abbreviation	Meaning
ADC	Antibody Drug Conjugate
AE	Adverse Event
ALT	Alanine Transaminase
ANC	Absolute neutrophil count
AST	Aspartate Transaminase
ATA	Anti-Therapeutic Antibodies
AUC	Area Under the Curve
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBR	Clinical Benefit Rate
Cmax	Maximum Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
D6.5	Stemcentrx's drug toxin, a PBD cytotoxic agent
DAR	Drug-to-Antibody Ratio
DLL3	Delta-Like Ligand 3
DOCB	Duration of Clinical Benefit
DOT	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group (ECOG)
ESA	Erythropoiesis-Stimulating Agent
FDA	Food and Drug Administration
HR	Heart Rate
ICF	Informed Consent Form
IHC	Immunohistochemistry
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Radiology Committee (also Central Radiographic Assessment Committee)
IC50	Concentration at 50% inhibition
IV	Intravenous
kg	Kilogram
LCNEC	Large Cell Neuroendocrine Carcinoma
µM	Micromolar

MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram(s)
Min	Minute(s)
mL	Millilitre(s)
msec	Millisecond
μ	Micro
NCI	National Cancer Institute
NSCLC	Non Small Cell Lung Cancer
ORR	Objective Response Rate
PD	Progression Disease
PDc	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PR	Partial Response
RP2D	Recommended Phase II Dose
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SC16LD6.5	Stemcentrx's Antibody Drug Conjugate
SCLC	Small Cell Lung Cancer
SCRI	Sarah Cannon Research Institute
SCRX	Stemcentrx
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
ULN	Upper Limit of Normal

1. BACKGROUND

Rovalpituzumab tesirine (SC16LD6.5) is an antibody-drug conjugate (ADC) consisting of a humanized monoclonal antibody against delta-like ligand 3 (DLL3) conjugated to a pyrrolobenzodiazepine (PBD) dimer (D6.5) via a serum stable linker. It is constructed utilizing a maleimide group for conjugation to the antibody, a PEG linker that serves as a spacer, and a serum stable valine-alanine dipeptide, which serves as a cathepsin B cleavage site for release of the cytotoxic drug (D6.5). Upon binding to DLL3, SC16LD6.5 internalizes and D6.5 is released via proteolysis of the cathepsin B cleavage site. ADCs theoretically enable the precise delivery of highly potent cytotoxic agents to cells expressing the target antigen, thereby combining the best characteristics of biologics (target specificity) and chemotherapy (potent killing activity) and improving the therapeutic index.

In this document, the statistical methods to be implemented to analyze the data captured according to protocol number SCRX001-002, “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 dated 18 Nov 2016 are described. This trial was registered on ClinicalTrials.gov (see <https://clinicaltrials.gov/show/NCT02674568>).

2. STUDY OBJECTIVES

The objectives of the study are:

2.1 *Primary objective*

The primary objective of the study is to investigate the efficacy, as measured by objective response rate (ORR) and overall survival (OS), 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).

2.2 *Secondary objectives*

- To assess duration of response (DOR), clinical benefit rate (CBR) and progression-free survival (PFS) 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)

2.3 *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

3. STUDY DESIGN

3.1 *General Description*

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 (Ventana mouse assay, SCRX16.65) will be enrolled in the study.



3.2 *Determination of Sample Size*





3.3 Methods of Assigning Subjects to Treatment and Stratification

SCRX001-002 is a Phase II open-label, single-arm, non-comparative, multicenter 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. Subjects will be screened and identified as eligible for the study by the Investigator at each site. 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. Eligible subjects will be registered to the study centrally by the CRO, PPD.

No stratification is required.

4. STUDY ENDPOINTS AND COVARIATES

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4.1 Demographic and Baseline Characteristics

- Demography includes: Age at baseline (years), sex, ethnicity, race, weight at baseline (kg), height (cm) and countries/sites
- Baseline Characteristics include: ECOG Performance Status at baseline, history of brain metastases, presence of brain metastases at baseline, baseline tumor burden, smoking history status and pack years of smoking for previous and current smokers, renal function at baseline, and hepatic function at baseline
- Disease History: stage at initial diagnosis, stage at study entry, history of paraneoplastic syndrome, number of metastatic sites, sites of metastatic disease, and time from initial diagnosis to first dose (months)
- Prior therapy information include:
 - Prior lines of systemic therapy (2, 3, 4 or more)
 - Response to frontline therapy (sensitive, refractory, resistant)
 - Prior systemic therapies drug categories
 - Best overall response of prior systemic therapies
 - Time from diagnosis to the last progression (months)
 - Time to progression on second line (2L) therapy
 - Prior Radiation Therapy (Yes, No) and number of radiation sites (0, 1, 2, 3 or more)
 - Prior Cancer Surgery (Yes, No) and number of surgeries (0, 1, 2, 3 or more)
- Medical History

4.2 DLL3 Expression

[REDACTED]
[REDACTED]
All patients enrolled in the TRINITY study are
DLL3 positive by [REDACTED]

[REDACTED]

[REDACTED]



If multiple scores are available for a subject, then the score with the latest sample date is used. If there are multiple scores available at the latest date then the highest value is used.

4.3 Primary Efficacy Endpoint

This study has two primary endpoints:

- Objective response rate (ORR) through the initial treatment period
- Overall survival (OS)

4.4 Secondary Efficacy Endpoints

- Best Overall Response of CR or PR Rate
- Clinical benefit rate (CBR)
- Duration of Response (DOR)
- Progression-free Survival (PFS)

4.5 Safety Endpoints

- Adverse Events
- Vital signs
- Laboratory abnormalities
- Electrocardiographic intervals (e.g. QTc)
- Echocardiography

- Components of a fluid retention questionnaire

The fluid retention questionnaire serves as a tool for patient management on site.

Data from the questionnaire will not be entered into the EDC and will not be analyzed.

4.6 Pharmacokinetic Pharmacodynamic, and Biomarker Endpoints

Pharmacokinetic Endpoints

- Specific pharmacokinetic parameters of rovalpituzumab tesirine (e.g. C_{max} , AUC)
- Anti-therapeutic antibodies against rovalpituzumab tesirine

Pharmacodynamic and Biomarker Endpoints

- Tumor DLL3 expression
- Inflammatory Markers
- Blood Tumor Markers
- Biomarkers, including soluble DLL3

Analyses of DLL3

expression and other biomarkers for the purpose of the Clinical Study Report are outlined in Section 7.7 of this document.

5. ANALYSIS POPULATIONS AND SUBGROUP

Analyses of ORR, DOR, CBR, DOCB, and PFS will be performed using response assessments by IRC, and by investigators.

5.1 Analysis Population

The modified intent-to-treat (ITT) population includes all subjects who received any amount of study drug. The modified ITT population is the same as the safety analysis population. The modified ITT population is the primary analysis population for efficacy,

unless otherwise specified, and efficacy analyses will be performed in the following analysis sets:

- All DLL3 High subjects in the modified ITT population
- All DLL3 Positive subjects in the modified ITT population

In addition, efficacy analyses will be performed for the modified ITT population regardless DLL3 status. [REDACTED]

The efficacy-evaluable population includes subjects in the modified ITT who had at least one post-baseline response assessment, or those that did not have a post-baseline response assessment and died within 42 days due to underlying disease progression. Analyses based on investigator responses will include subjects meeting the above definition based on investigator-assessed post-baseline responses. Similarly, analyses based on IRC responses will include subjects meeting the above definition based on IRC-assessed post-baseline responses. The efficacy-evaluable population may be used in supportive analyses of efficacy. Analyses of ORR and CBR will be also performed in the following analysis sets:

- All DLL3 High subjects in the efficacy-evaluable population
- All DLL3 Positive subjects in the efficacy-evaluable population

DOR and DOCB would be analyzed in the subsets of patients who achieved CR/PR and CR/PR/SD, respectively, in the above analysis sets.

The safety analysis population includes all subjects who receive any amount of study drug. A baseline measurement and at least one post-baseline 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).

Pharmacokinetic analysis population consists of all subjects who receive at least 1 dose of study treatment and at least 1 post-baseline blood sample following a dose of study treatment. The pharmacokinetic data will be used in a population PK analysis that will be reported separately.

Retreatment analysis population consists of all subjects who receive at least 1 dose of study drug as retreatment. This population is defined for supplemental analyses. Selected efficacy outcomes (e.g., ORR and PFS) for such subjects during retreatment may be analyzed separately from the outcomes observed during the initial course of treatment. Adverse events reported during retreatment will be summarized separately from those observed during the initial course of treatment. Time to retreatment will also be summarized.

5.2 Efficacy Analysis by Line of Therapy

Efficacy analyses will include analysis by current line of therapy (3rd line and ≥3rd line) in the modified ITT population. Efficacy analyses by current line of therapy (3rd line and ≥3rd line) in the efficacy evaluable population will be included for all endpoints except for overall survival.

5.3 Subgroup Analyses for Primary Endpoints

The following subgroup analyses will be performed for the primary endpoints of ORR and OS for DLL3 high and DLL3 positive subjects in the modified ITT population.

- Current line of therapy (3rd, 4th, >4th)
 - Determined based on regimen. It will be the last regimen number +1
- Response to frontline therapy (sensitive, refractory, resistant, and resistant/refractory)
- Prior systemic therapies (drug categories) that may include the following:
 - Topotecan
 - Immunotherapy (Yes, No; includes PD-1 inhibitor and other immunotherapy)
- Prior cancer surgery (Yes, No)
- Prior radiation therapy (Yes, No)
- History of brain metastases (Yes, No)
- Presence of brain metastases at baseline (Yes, No)
- ECOG at baseline (0, 1, >1)
- Baseline tumor burden (<Q1, Q1- Q3 inclusive, > Q3; where Q1 and Q3 are the quartile values of the baseline sum of the longest diameters of target lesions per IRC assessment)
- Gender (Male, Female)
- Grouped race (White, Non-White)
- Age group (<65, ≥65 years)

- U.S. vs non-U.S. sites



In addition to above subgroups, subgroup analysis of OS will also be performed by

- Objective response (determined by IRC and investigator assessments) to rovalpituzumab tesirine therapy (CR/PR, Non-CR/PR)
- Best overall response (determined by IRC and investigator assessments) to rovalpituzumab tesirine therapy (CR/PR, Non-CR/PR and the subcategories of SD, PD, NE/Early Death/Indeterminate)
- Clinical benefit (determined by IRC and investigator assessments) to rovalpituzumab tesirine therapy (Yes, No)
- Time to progression on second line (2L) therapy, defined as time from start of 2L therapy to the last progression on 2L therapy (≤ 3 months, > 3 months).

6. ANALYTIC DEFINITIONS

Initial Treatment Period includes all assessments prior to the retreatment period or the start of new anti-cancer therapy, whichever occurs earlier. For subjects who will not be retreated, the initial treatment period will include assessments till the start of new anti-cancer therapy or the end of study, whichever occurs earlier.

Baseline Evaluation is the last available evaluation prior to receiving first dose of study drug. This will include any unscheduled evaluation prior to first dose. For subjects receiving retreatment, baseline for that period is the last available evaluation prior to receiving first dose of study drug for retreatment.

Change from Baseline is defined as the difference between the baseline value as defined above and the value at the respective time point. Negative values represent decreases from baseline; positive values will reflect increases from baseline.

Percent Change from Baseline is defined as the change from baseline divided by the baseline value times 100%. That is

$$100x (\text{Post-baseline value} - \text{baseline value}) / (\text{baseline value}).$$

Age at Baseline (in years) is defined from date of birth to date of first dose.

Last Evaluable Disease Assessment, for purpose of censoring, will be the last assessment with a response that is determined to be CR, PR, SD, PD, or Not Evaluable (NE).

Treatment-Emergent Adverse Event during this period is defined as any adverse event occurring on or after initiation of therapy and prior to the earlier of the start of retreatment period for those received Rova-T retreatment and the start of a subsequent anti-cancer therapy. Any adverse event with onset on or after the first dose of retreatment till the start of the next retreatment period or the start of a subsequent anti-cancer therapy will be considered treatment-emergent for that retreatment period.

Concomitant Medication is defined as a medication or treatment other than the study drug is considered concomitant if it is taken at any time on or after the first dose date. A medication taken prior to first dose date and continuing past first dose date is considered concomitant. Concomitant medications that stopped prior to first dose of retreatment will only be included in the initial treatment period. Medications started after the first of retreatment will be considered concomitant during the retreatment period.

Cumulative Actual Dose (in mg) is the sum of actual dose. Cumulative dose will be summarized for both initial treatment period and retreatment period.

Treatment Duration (in cycles) is defined as number of cycles begun where rovalpituzumab tesirine dose is greater than zero.

Response to Frontline Therapy (sensitive, refractory, resistant)

- Refractory: For 1st Regimen if response is 'PD' (if first Regimen is 'NE' then 'NE')
- Sensitive: If not Refractory and not 'NE' and if (First of Regimen 2 start date – Last of Regimen 1 End Date, excluding placebo) +1 \geq 90 days
- Resistant: If not Refractory and not 'NE' and if (First of Regimen 2

start date – Last of Regimen 1 End Date) +1 < 90 days

- Note: Impute partial date of start or stop date as follows: If month and day both missing for one of the two dates in comparison and the year is different, the duration considered >= 90 days. If the year is the same then response is considered ‘Undetermined’
- If only Day is missing then based on the month and year derive the months of duration to compare with 3 months duration and determine sensitive or resistant

Note: If the response for the first regimen is ‘NE’ then the response to frontline therapy for that subject is classified as a ‘Not Evaluable’

Pack Years of Smoking is defined as:

(Number of cigarettes smoked per day/20) * Number of years smoked

QTcF is defined as:

$$QTcF = QT / (\sqrt[3]{RR})$$

Tumor Burden is based on the sum of the target lesions at baseline, where baseline is defined as the last lesion measurement on or prior to first dose.

7. STATISTICAL METHODS AND ANALYSIS OF THE INITIAL TREATMENT

Analyses for the initial treatment period (defined in Section 6) will be performed based on the modified ITT population as defined in Section 5.1, unless otherwise specified. Outputs will display summaries for subjects with DLL3 high and DLL3 positive (per Ventana rabbit SP347 IHC assay specification), respectively.

7.1 *Subject Disposition*

The number and percent of subjects in each analysis population group will be summarized. The number and percentage of treated subjects, subjects discontinuing from study treatment during initial treatment, including the reasons for study drug discontinuation during initial treatment, subjects discontinuing the study, including the

reasons for discontinuation from the study, and subjects in the follow-up or retreatment period will be presented. Detailed information will be listed.

7.2 Study Conduct

Protocol violations and major protocol deviations will be summarized.

7.3 Demographics, Baseline Characteristics and Prior Therapies

Demographic characteristics including age, sex, race and ethnicity; as well as baseline characteristics including height, weight, ECOG performance status, history of brain metastases, presence of brain metastases at baseline, and smoking history will be summarized and listed. Summaries of subgroups included in Section 5.3 will also be provided.

Disease history data, including stage at initial diagnosis and at study entry, history of paraneoplastic syndrome, number of metastatic sites, location of metastatic sites, and time from diagnosis to first dose will be summarized and listed.

Medical history being coded with MedDRA will be summarized by system organ class and preferred term. Medical history will be listed as well.

Prior systemic therapy, prior radiation, and prior surgery defined in Section 4.1 will be summarized and listed.

7.4 Treatment Exposure and Compliance

Exposure to study treatment will be summarized and listed:

- Cumulative actual dose (mg)
- Treatment duration (cycles)

The number and percent of subjects with at least one dose modification (reduced, interrupted or delayed) will be summarized, which will include dose modification due to AE and other reasons. Dose modifications and study treatment discontinuation due to adverse events captured on AE CRF will be summarized in separate adverse event tables.

7.5 *Analysis of Primary Efficacy Endpoint*

All analyses of primary efficacy endpoints will be summarized for the modified ITT and efficacy evaluable populations defined in Section 5.

7.5.1 Objective Response Rate

Overall Response at each visit post-baseline is assessed based on a subject's lesion measurements or assessments. Overall Response is assessed as CR, PR, SD, PD, or NE as defined by RECIST version 1.1. An additional category of Early Death will also be included which is defined as subjects who died prior to any post-baseline response assessment. Amongst all the Overall Responses, the best Overall Response is then determined. The best Overall Response will be ordered as CR, PR, SD, PD, or NE; with CR being the best. A subject will be considered to have a best overall response of SD if there is a minimum interval of 42 days between the date of assessment and (-7 days to allow for scheduled visit window per the protocol) the first dose date. Subjects who died prior to the first post-baseline lesion assessment are included in the Early Death category. The Not Evaluable (NE) category includes subjects who are not evaluable as indicated by the IRC or by the Investigator, in analyses of overall response per IRC and investigator, respectively. Subjects who discontinued the study prior to obtaining a post-baseline scan for lesion assessment will be categorized as Indeterminate.

Objective Response is defined as a subject with the best Overall Response of Complete Response (CR) or Partial Response (PR) prior to receiving any subsequent anticancer therapy and retreatment, and is confirmed by a consecutive response assessment at least 4 (28 days) from the initial determination of CR/PR per RECIST v 1.1 as described in Table 1:

Table 1 – Confirmed partial and complete response

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR ^a
CR	SD	SD (if minimum duration for SD met), otherwise, PD
CR	PD	SD (if minimum duration for SD met), otherwise, PD

CR	NE	SD (if minimum duration for SD met), otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD (if minimum duration for SD met), otherwise, PD
PR	NE	SD (if minimum duration for SD met), otherwise, NE
NE	NE	NE

Note: In case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 42 days (-7 days to allow for scheduled visit window per the protocol).

a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met.

Only assessments within the initial treatment period will be included if a subject had retreatment. ORR is defined as the proportion of subjects with Objective Response. Best Overall Response Rate is defined as the proportion of subjects with a response of CR or PR (regardless of confirmation) prior to receive any subsequent anticancer therapy or retreatment.

ORR will be presented as a number and percentage with two-sided exact 95% binomial confidence interval (CI). Any subjects not exhibiting a response (CR or PR) as defined above are considered non-responders.

Similar analyses as described above will include:

- Best Overall response of CR or PR determined by the IRC
- ORR determined by the Investigator
- Best Overall response of CR or PR determined by the Investigator

7.5.2 Overall Survival

OS is defined as the time in months from the first day of study drug administration (Day 1) to death. Subjects who are alive at the end of study will be censored at the date of last contact. OS primary analysis includes all follow-up data, including follow-up data in the retreatment period or after the start of subsequent anti-cancer therapy. Date of death will be obtained from the AE CRF page, or End of Study CRF page, or the Survival Status CRF page.

Censoring of OS will be performed as detailed in [Table 2](#).

Table 2 – Overall Survival Censoring Methodology

Situation	Date of Death or Censoring	Outcome*
Death	Date of death	Event
No documented death	Date last known alive	Censored

*Time (month) = (Date of Death or Censoring – Date of first study drug administration + 1)/ 30.44

OS will be estimated using the Kaplan-Meier method. In addition to the range, the median OS and its 2-sided 95% confidence interval using the method by Klein and Moeschberger; 1997) with complementary log-log transformation will be produced. Additionally, proportion of subjects alive at 6, 9 and 12 months from the initiation of study treatment using the Kaplan-Meier method and corresponding 2-sided 95% confidence intervals using complementary log-log transformation will be estimated.

7.5.3 Sensitivity and Subgroup Analysis

Subgroup analyses of ORR and OS will include all subgroups defined in Section 5.3.

Additional sensitivity analyses may be performed if deemed appropriate.

7.6 Analysis of Secondary Efficacy Endpoints

All secondary efficacy analyses will be summarized for the efficacy analysis populations defined in Section 5.

7.6.1 Duration of Response

Duration of objective response is defined as the time in months from the initial CR or PR to the time of disease progression or death on study, whichever occurs first during the initial treatment period. Only subjects with a confirmed response of CR or PR will be included.

For subjects who are alive and have not experienced disease progression on the study, duration of objective response will be censored at the day of the last tumor assessment during the initial treatment period. If no tumor assessment after the initial response is available, then the duration of response will be one day. Censoring rules for duration of response will be performed as detailed in [Table 3](#). If multiple visits exist, the latest

evaluable assessment date will be used for censoring except for PD, which will use the earliest assessment date when PD was recorded. Symptomatic deterioration will not be considered PD since a lesion assessment will need to be performed to verify disease progression. If there are multiple scans with multiple dates provided for a visit, the lesion assessment date will be the last scan date recorded for that visit to define baseline and the earliest scan date within the visit to determine the lesion assessment date post-baseline.

Table 3 - Duration of Response Censoring Methodology

Situation	Date of Progression/Death or Censoring	Outcome*
Death or disease progression per RECIST 1.1 at any time during initial treatment period	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
Progression caused by new lesion during initial treatment period	Date new lesion is detected	Event
Progression caused by worsening of non-target lesion(s) or target lesion(s) during initial treatment period	First assessment date documenting the increase in target lesion(s) meeting criteria for progression, or the worsening non-target lesion(s)	Event
Progression caused by multiple causes (e.g. new lesions and worsening of non-target lesions) during initial treatment period	First date among the multiple sources of PD	Event
Subsequent anti-cancer treatment started before death or without documentation of disease progression beforehand	Date of last evaluable disease assessment prior to start of subsequent anti-cancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments during initial treatment period	Date of last evaluable disease assessment visit without documentation of disease progression that is before the missed visit	Censored
Alive and without documentation of disease	Date of last evaluable	Censored

progression during initial treatment period	disease assessment during initial treatment period	
---------------------------------------------	----------------------------------------------------	--

*Time (month) = (Date of Progression/Death or Censoring – Date of first response (CR or PR) + 1)/ 30.44.

For Duration of Objective Response, only subjects with a confirmed response of CR or PR will be included.

Duration of objective response will be estimated using the Kaplan-Meier method. The median duration of objective response and the corresponding 2-sided 95% confidence interval will be produced in addition to the range. The proportion of responders who have not yet experienced disease progression or death 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 best overall response will also be summarized. This analysis will include subjects with a response of CR or PR, regardless of confirmation.

Duration of objective response and duration of best overall response will be summarized based on IRC assessments, as well as investigator assessments.

7.6.2 Clinical Benefit Rate

Clinical Benefit is defined as the achievement within a subject of a Best Overall Response of CR, PR or SD with SD of a minimum duration of 42 days (-7 days to allow for scheduled visit window per the protocol) from the first dose date, prior to receiving any subsequent anticancer therapy and retreatment; as defined by RECIST version 1.1. CBR is defined as the proportion of subjects with clinical benefit. CBR will be presented as a number and percentage with two-sided exact 95% binomial confidence interval (CI). CBR will be summarized based on IRC assessments, and based on investigator assessments, respectively.

7.6.3 Duration of Clinical Benefit

DOCB [CR, PR, or SD with SD of a minimum duration of 42 days (-7 days to allow for scheduled visit window per the protocol from the first dose date)] is defined as time in months from the initial CR, PR, or SD to the time of disease progression or death on

study, whichever occurs first during the initial treatment period. Only subjects with the response of CR, PR, or SD are included.

For subjects who are alive and have not experienced disease progression on the study, DOCB will be censored at the day of the last tumor assessment during the initial treatment period. Censoring rules for duration of clinical benefit will be performed as detailed in Table 3 above. If multiple visits exist, the latest evaluable assessment date will be used for censoring except for PD, which will use the earliest assessment date when PD was recorded. Symptomatic deterioration will not be considered PD since a lesion assessment will need to be performed to verify disease progression.

DOCB will be estimated using the Kaplan-Meier method. The median duration of clinical benefit and the corresponding 2-sided 95% confidence interval will be produced in addition to the range.

Calculation of DOCB will be based on IRC assessments, as well as investigator assessments.

7.6.4 Progression-Free Survival

PFS is defined as the time in months from the first day of study drug administration (Day 1) to disease progression or death on study, whichever occurs first during the initial treatment period.

For subjects who are alive and have not experienced disease progression during the initial treatment period, PFS will be censored on the day of the last tumor assessment during the initial treatment. Subjects with no post-baseline response assessment PFS will be censored and have a PFS duration of one day. Censoring rules for PFS will be performed as detailed in Table 4 below. If multiple dates exist for a given visit, the latest evaluable assessment date will be used for censoring except for PD, which will use the earliest assessment date when PD was recorded. Symptomatic deterioration will not be considered PD since a lesion assessment will need to be performed to verify disease progression.

Table 4 – Progression-Free Survival Censoring Methodology

Situation	Date of Progression/Death or Censoring	Outcome*
Death or disease progression per RECIST 1.1 at any time during initial treatment period	Date of death or first disease assessment showing disease progression, whichever occurs first	Event
Death before first planned disease assessment	Date of death	Event
Progression caused by new lesion during initial treatment period	Date new lesion is detected	Event
Progression caused by worsening of non-target lesion(s) or target lesion(s) during initial treatment period	First assessment date documenting the increase in target lesion(s) meeting criteria for progression, or the worsening non-target lesion(s)	Event
Progression caused by multiple causes (e.g. new lesions and worsening of non-target lesions) during initial treatment period	First date among the multiple sources of PD	Event
Subsequent anti-cancer treatment started before death or without documented disease progression	Date of last evaluable disease assessment prior to start of non-protocol anticancer treatment	Censored
Death or disease progression after missing two or more consecutively scheduled disease assessments during initial treatment period	Date of last evaluable disease assessment visit without documentation of disease progression that is before the missed visit	Censored
Alive and without documentation of disease progression during initial treatment period	Date of last evaluable disease assessment during initial treatment period	Censored

*Time (month) = (Date of Progression/Death or Censoring – Date of first dose + 1) / 30.44

PFS will be estimated using the Kaplan-Meier method. The median duration of PFS and the corresponding 2-sided 95% confidence interval will be produced in addition to the range.

Proportion of subjects alive and without PD at 6, 9 and 12months from the initiation of study treatment will be summarized based on Kaplan-Meier estimates, with the corresponding 2-sided 95% confidence intervals.

7.6.5. Subgroup Analysis of Secondary Endpoints

Subgroup analyses of secondary endpoints of DOR, CBR, DOCB and PFS may include the subgroups described in Section 5.3. For example, DOR may be analyzed in the DLL3 subgroups defined in Section 5.3 by current line of therapy (3L vs 3L+), if there are sufficient number of responders in each subgroup. Subgroup analysis of PFS by DLL3 subgroups will be performed by current line of therapy (3L vs 3L+).

Additional analysis of the secondary endpoints in the modified ITT population, regardless of the DLL3 score, will be included.



7.7 Analysis of Safety Endpoints

Unless otherwise stated, all safety analyses will be carried out in the safety analysis population by initial treatment period and retreatment period. No formal statistical inference or missing data imputations are planned.



and for all dosed subjects combined regardless of the DLL3 score.

7.7.1 Treatment Emergent Adverse Events

All adverse events will be coded using the MedDRA dictionary. Safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events (TEAE) and serious adverse events as reported by the investigators. A treatment-emergent adverse event (TEAE)/treatment emergent serious adverse event is defined in Section 6. An applicable AE/SAE is considered ‘related’ if its relationship to study drug was judged by the investigator. Ongoing adverse events that have a change in severity, action taken with study drug, or outcome will be recorded multiple times with the

changes. If a subject has multiple occurrences of an adverse event with the same system organ class, the most severe event will be chosen. Similarly, if a subject has multiple occurrences of an adverse event with the same preferred term, the most severe event will be chosen. If a partial date does not provide enough information to determine the onset date relative to first dosing date, then the adverse event will be assumed as treatment-emergent, otherwise partial dates will be imputed relative to the first dose date. TEAEs will be summarized by system organ class and preferred term. These summaries will be presented by system organ class and preferred term for the following subsets:

- All TEAEs (All grades, and for maximum grade of 3 or 4)
- All TESAEs (All grades, and for maximum grade of 3 or 4)
- All TEAEs leading to study drug discontinuation (All grades, and for maximum grade of 3 or 4)
- All TEAEs leading to death

All drug-related TEAEs, and all drug-related TESAEs will also be summarized. The above tables will also be categorized by gender and age group (<65, \geq 65 years). For tables classifying TEAEs by severity, if a subject has multiple occurrences of an adverse event with the same system organ class, the most severe event will be chosen. Similarly, if a subject has multiple occurrences of an adverse event with the same preferred term, the most severe event will be chosen.

Adverse events of special interest (AESI) identified by the specific search criteria outlined in Appendix F will be summarized by System Organ Class (SOC) and Preferred Term (PT) [REDACTED]

Tabulation of TEAEs will be based on subjects in safety analysis population. The number and percent of subjects with an adverse event will be displayed. In general, the denominator for the percent of subjects with an adverse will be the number of subjects in the safety analysis population or the number of subjects in safety analysis population within a subgroup if a subgroup is summarized.

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.

TEAE that occurred during retreatment period will be summarized separately for those who receive retreatment, provided there is sufficient number of subjects who received retreatment; otherwise listings will be provided. Adverse events that occurred after the start of subsequent anti-cancer therapy, if not included in the retreatment period, will be summarized separately by system organ class and preferred term, provided there is sufficient number of subjects; otherwise listings will be provided. Adverse events with onset prior to first dose date will be considered pre-treatment. All pre-treatment adverse events will be summarized by system organ class and preferred term, provided there is sufficient number of subjects; otherwise listings will be provided for pre-treatment adverse events. Listing of all AEs, SAEs, AEs leading to study drug discontinuation, and death will be reported.

7.7.2 Laboratory Tests

Clinical laboratory assessments for this study include: hematology, blood chemistry and liver function tests (LFT). Most hematology, blood chemistry and LFT parameters will be graded according to NCI-CTCAE version 4.03, as applicable. Numeric values will be analyzed after conversion into standard international units, where applicable. A complete listing of all laboratory parameters with normal ranges in standard international units is included in Appendix 5. Laboratory values with grade 3 or above will be listed. For subjects with grade 3 or higher values, all values of that lab test will be listed.

Continuous clinical laboratory results will be summarized by analyte and by visit after conversion into standardized SI results. Summary statistics for the change from baseline to end-of-treatment (EOT), where end-of-treatment will be summarized using the last non-missing post-baseline result no more than 45 days after treatment discontinuation or initiation of subsequent therapy (whichever is first, if applicable), will be tabulated. The largest change from baseline (increase or decrease) will be summarized in a shift table based on the CTCAE grade which will include both scheduled and unscheduled visits.

Laboratory-based summaries will be provided as follows:

- Observed, change from baseline, and percent change from baseline at each scheduled visit and EOT in parameter results

- Shift from baseline to maximum post-baseline CTCAE grade for hematology laboratory results
- Shift from baseline to maximum post-baseline CTCAE grade for chemistry laboratory results
- Elevations in AST, ALT, total bilirubin, and alkaline phosphatase as outlined in the FDA Guidance for Industry pertaining to premarketing clinical evaluations for drug-induced liver injury (DILI):
 - Elevations of AST, ALT, and either ALT or AST: 3x-, 5x-, 10x-, and 20xULN
 - Elevations of bilirubin defined as total bilirubin >2 xULN
 - Elevations of alkaline phosphatase >1.5 xULN
 - Elevations of ALT or AST (>3 xULN) accompanied by elevated total bilirubin (>1.5 xULN, >2 xULN)

In addition, a listing of potential Hy's Law cases (i.e., subjects with AST or ALT >3 xULN in combination with bilirubin >2 xULN) will be also presented. Results from unscheduled or repeated assessments will be included in the DILI evaluations, with elevations of AST or ALT in combination with total bilirubin at the same unscheduled or repeat assessment.

7.7.3 Vital Signs

Vital signs (weight, pulse rate, systolic blood pressure, diastolic blood pressure, and temperature) will be summarized and listed. The summaries include:

- Observed values
- Change from baseline by scheduled visit (including mean, median, standard deviation, maximum, and minimum)
- Percentage change from baseline at each scheduled visit through treatment discontinuation

7.7.4 Analyses of ECG Change

ECG parameter will be summarized by test and by visit. Summary statistics for the change from baseline at end-of-treatment (EOT), where end-of-treatment will be summarized using the last non-missing post-baseline result no more than 45 days after treatment discontinuation or initiation of subsequent therapy (whichever is first, if applicable), will be tabulated. In the case of multiple assessments at a visit, baseline will

be the last value prior to dosing. Observed values, change from baseline, and percent change from baseline at each scheduled visit and EOT in parameter results will be summarized. One-sided 95% confidence interval for the change from baseline will be provided for each visit.

The QTcF triplicate will be summarized and tabulated by maximum QTcF (msec) increase from baseline and QTcF (msec) value at any time during treatment:

- Maximum QTcF (msec) increase from baseline on treatment:
 - $\Delta\text{QTcF} > 10$ msec
 - $\Delta\text{QTcF} > 20$ msec
 - $\Delta\text{QTcF} > 30$ msec
 - $\Delta\text{QTcF} > 60$ msec
- QTcF on treatment:
 - $\text{QTcF} > 450$ msec
 - $\text{QTcF} > 480$ msec
 - $\text{QTcF} > 500$ msec

7.7.5 Echocardiography

The presence of pericardial effusion will be summarized using the shift table at each scheduled visit.

7.7.6 ECOG Performance Status

ECOG scores will be summarized using the shift table at each scheduled visit and listed. Maximum shift of ECOG performance status from baseline will also be summarized.

7.7.7 Concomitant Medications

World Health Organization (WHO) Drug Dictionary will be used for coding medication terms. Medications taken prior to the first dose of study medication through 30 days following the last dose of study medication or medications taken after the first dose of study medication through 30 days following the last dose of study medication will be considered as concomitant medications, which will be listed and summarized (frequency and percentage of subjects) by preferred name. Subjects will be counted once per each unique medication.

7.8 Analysis of Pharmacokinetic, Pharmacodynamic, and Biomarker Endpoints

Pharmacokinetic Endpoints

Rovalpituzumab tesirine ADC concentrations will be listed by patient and summarized descriptively (arithmetic mean, standard deviation, minimum, median, maximum). Concentrations below the lower limit of quantification of the assay will be treated as missing. Results of the population PK analysis, including rovalpituzumab tesirine pharmacokinetic parameters (e.g. Cmax, AUC), will be reported separately.

Pharmacodynamic and Biomarker Endpoints

Summary statistics will be generated for tumor expression of DLL3 in dosed subjects. Exploratory analyses of other pharmacodynamics and biomarker endpoints (e.g. inflammatory markers, blood tumor markers, [REDACTED] soluble DLL3) may be performed if deemed necessary and appropriate.

8. INTERIM ANALYSIS

An interim analysis will be conducted when at least one post-baseline response assessment from 60 evaluable subjects with DLL3 high expression per IHC assay specification are available. 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. This interim analysis will be used to determine if there is sufficient response as described in Section 3.1.

An independent Data Monitoring Committee (iDMC) will be formed to review the efficacy and safety data periodically and provide recommendations. 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. The iDMC may request further safety analyses.

9. VISIT WINDOWS

Efficacy analyses based on response assessment will include all scans, including those from unscheduled visits. All data will be tabulated according to scheduled visits, unless otherwise specified. No visit windows will be developed for the safety analysis of this study. Unscheduled visits will be used to determine baseline, the last post-baseline value, maximum change from baseline in shift tables, or determination of response.

10. HANDLING OF MISSING DATA

Standard clinical monitoring and data management practices will be used to ensure the integrity of the data. All start and end dates, where applicable, for study drug exposure, safety, efficacy evaluation and study milestones must be complete dates (i.e., day, month and year must be present). Any exceptions will be footnoted on applicable tables, figures or listings. Dates associated with prior medications, prior therapies, and other historical data, whether complete or not, that typically are not involved in direct calculations affecting safety or efficacy will be listed in the manner of their recording on the eCRF. However, prior medications will be considered as concomitant medications, and AE will be considered as treatment-emergent adverse event if the missing date makes the categorization undoable.

A. STUDY OVERVIEW

The design of the study is described in Section 3.1 of the protocol.

B. SCHEDULE OF ASSESSMENTS

Item	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
Location	Window	-	-	± 2d ²	-	± 1d	± 2d	± 2d	± 2d	± 3d	± 3d	± 3d	± 3d
Clinic Visit	X			X		X		X		X		X	
Virtual Visit						X		X		X		X	
Investigator (MD) present	X			X				X		X		X	
Informed Consent ⁵	X							X		X		X	
Screening, Baseline, and Safety Assessments	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	
	Vital Signs ⁹	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	
	Hepatitis B and C tests ¹⁴	X											

Item	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
Day	Window	-	-	± 2d ²	-	± 1d	± 2d	± 2d	± 2d	± 3d	± 3d	± 3d	± 1w
Pregnancy Test ¹⁵	X	X										X	
Electrocardiogram (ECG) ¹⁶	X	X										X	
Echocardiogram ¹⁷		X										X	
Performance Status (ECOG)	X											X	
Fluid Retention Questionnaire ¹⁸		X					X	X	X	X	X	X	
Daily Weight Diary ¹⁹													
Adverse Events	Procedure-related only												
Concomitant Therapies ²⁰													
Treatment	Rovalpituzumab tesirine		X										
	Dexamethasone		X	X	X								
Response Assessment	Disease/Response Assessment ²¹	X										X ²²	X ²³
	MRI of the Brain		X									X ²⁴	X ²⁴
	Paraneoplastic Assessment ²⁵	X											

	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	42 days after last dose
Day	Window	-	-	± 2d ²	-	± 1d	± 2d	± 2d	± 2d	± 3d	± 3d	± 3d	± 1w

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 d 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 of the protocol
- 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 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) ECG 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) [REDACTED]

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.

28) [REDACTED]

29) [REDACTED]

30) [REDACTED]

31) [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, pericardiocentesis, or paracentesis), for possible pharmacokinetic, pharmacodynamic and/or biomarker testing.

C. RANDOMIZATION ALGORITHM

Not Applicable

D. SAS ROUTINES

Endpoint	Test	SAS Code
ORR, CBR	95% Exact confidence interval for the proportion calculated using the exact binomial method	[REDACTED]
PFS, OS,	Kaplan-Meier method and 95% confidence interval for median calculated using the complementary log-log transformation	[REDACTED]

E. POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY VALUES CRITERIA

No potentially clinically significant lab values criteria except the ones identified in section 7.6.2 were identified. The following normal ranges were used to identify values classified as High or Low.

Laboratory Test	Standard Result Unit	Normal Range Low	Normal Range High
Albumin	g/dL	3.5	5
Alkaline Phosphatase	U/L	30	120
ALT (SGPT)	U/L	10	40
AST (SGOT)	U/L	10	30
Basophils	10 ⁹ /L	0	0.2
Total Bilirubin	mg/dL	0.292	1.228
Blasts	%	0	0
Blood Urea Nitrogen	mmol/L	2.9	8.2
Calcium	mg/dL	8.2	10.2
Chloride	mmol/L	96	106
Carbon Dioxide	mmol/L	20	28
Serum Creatinine	mg/dL	0.6	1.2
Eosinophils	10 ⁹ /L	0	0.45
Glucose	mg/dL	70	110
Hematocrit	%	41	50
Hemoglobin	g/dL	14	17.5
Potassium	mmol/L	3.5	5
Lactate Dehydrogenase	U/L	100	200
Lymphocytes	10 ⁹ /L	1	4.8
Monocytes	10 ⁹ /L	0	0.8
Neutrophils	10 ⁹ /L	1.8	7.8
Platelets	10 ⁹ /L	150	350
Total Protein	g/dL	6	8
Sodium	mmol/L	136	142
WBC	10 ⁹ /L	4.5	11

F. ADVERSE EVENTS OF SPECIAL

Specific treatment-emergent adverse events of special interest (AESI) will be identified by the following search criteria:

Adverse Event of Special Interest

MedDRA Search Criteria / Codes







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	15-Feb-2018 06:17:07 AM	Approver
	15-Feb-2018 05:07:01 PM	Approver
	15-Feb-2018 05:51:01 PM	Author
	15-Feb-2018 07:12:23 PM	Approver
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