1.0 Title Page

Clinical Study Protocol M16-298

A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)

Incorporating Amendments 1, 2, 3 and 4

AbbVie Investigational Product:	Rovalpituzumab tesirine (Rova-T)
Date:	05 March 2019
Development Phase:	3
Study Design:	A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)
EudraCT Number:	2016-003503-64
Investigators:	Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc.*
Sponsor/Emergency Contact:	[redacted] Senior Medical Director AbbVie 1 North Waukegan Road North Chicago, IL 60064 USA Phone: Cell Phone: Fax: Email: [redacted]

* 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.

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.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	13 October 2016
Amendment 1	03 February 2017
Amendment 2	20 April 2017
Amendment 3	09 May 2017

The purpose of this amendment is to:

- Modified Section 1.0 Sponsor/Emergency Contact

  Rationale: *Modification of the emergency contact for the study.*
- Update Section 1.2, Synopsis, Section 4.0, Study Objectives, Section 5.3.3.2, Section 5.3.3.3, Section 5.3.3.4, Section 8.1.4 Primary Efficacy Endpoints, Section 8.1.5 Secondary Efficacy Endpoints, Section 8.1.6 Exploratory Efficacy Endpoints to clarify the DLL3^{high} population, secondary endpoints updated to include, OS, PFS and PRO endpoints to be tested in all randomized patient population and prioritize these ahead of other efficacy endpoints such as ORR, CBR and DOR. Exploratory endpoints were added.

  Rationale: *This clarifies the population for primary endpoints (unchanged from prior protocol version) and allows evaluation of Rova-T efficacy on OS, PFS, and PRO in all enrolled patient population in secondary endpoint. ORR, CBR etc., are clinically less relevant than PFS, OS and PRO and thus, will be tested as exploratory endpoints.*
- Modified Section 1.2, Synopsis Study sites and Section 5.1 Overall Study Design to Approximately 300 from 275.

  Rationale: *The number of study sites has increased since the last amendment.*
- Update Section 1.2 Synopsis, Section 5.2.1, Inclusion criteria 1 to add the option of the subject's legally accepted representative as a person that can sign consent on the subject's behalf.

  Rationale: *To align with the approved informed consent language.*

- Updated Section 1.2 Synopsis, Section 5.2.1, Inclusion criteria 3 to say 'Histologically or cytologically confirmed ED SCLC (extensive stage disease at initial diagnosis) with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).'

  Rationale: *Clarify that intended patient population is ED SCLC as per staging performed at the initial diagnosis and not any other time point.*

- Updated Section 1.2 Synopsis, Section 5.2.1, Inclusion criteria 5 to say 'Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy.'

  Rationale: *Clarify intended window between front-line therapy and randomization.*

- Updated Section 1.2 Synopsis, Section 5.2.1, Inclusion criteria 9f to add 'modified' to say 'Calculated creatinine clearance ≥ 30 mL/min by the modified Cockroft-Gault formula (Refer to Appendix E).'

  Rationale: *Clarify required method for assessment of calculated creatinine clearance.*

- Updated Section 1.2 Synopsis, Section 5.2.2, Exclusion criteria 1 to remove 'the disease under study' and replace it with 'SCLC.'

  Rationale: *Further clarify that subjects who received prior treatment for LD-SCLC are excluded*

- Updated Section 1.2 Synopsis, Section 5.2.2, Exclusion criteria 2 to add 'palliative radiotherapy to a radiographically documented non-progressing lesion for symptom control.'

  Rationale: *Clarify that palliative radiotherapy is allowed for non-progressing lesions.*

- Updated Section 1.2 Synopsis, Section 5.2.2, Exclusion criteria 4 to change the reference from Appendix E to Appendix F.

  Rationale: *Correcting a typo from the previous amendment.*

- Updated Section 1.2 Synopsis Statistical Methods section, Section 8.1 Statistical and Analytical Plans, Section 8.4, Section 8.5 and Section 8.6 to

remove the efficacy interim analysis after observing 75% of the final OS events and to add a futility analysis at 50% of the final OS events.

Rationale: *Enable earlier stopping of the trial in the event of futility and improve statistical properties at final OS.*

- LD SCLC defined in List of Abbreviations as Limited-stage disease small cell lung cancer

  Rationale: *Definition added to clarify the different disease states for SCLC.*

- Modified Section 3.3 Rovalpituzumab Tesirine to provide updated data.

  Rationale: *Latest data added from ongoing Rova-T studies.*

- Modified Section 3.5 Benefits and Risks to update safety language.

  Rationale: *To provide updated safety information*

- Modified Section 5.1 Overall Study Design, Footnote number 3 under Figure 1 to include the following updated language- 'Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy.'

  Rationale: *To be consistent with the update to Inclusion Criteria 5.*

- Modified Section 5.2 Selection of Study Population to include the LD and ED SCLC definition.

  Rationale: *Modified to include the definition per IASLC/VA for LD and ED SCLC.*

- Modified Section 5.2.3.1 Prior therapy to be consistent with changes to Inclusion Criteria 3 and 5.

  Rationale: *To be consistent with the update to Inclusion Criteria 3 and 5.*

- Modified Section 5.2.3.2 Concomitant Therapy to add additional safety guidelines regarding sun exposure.

  Rationale: *To provide updated* guidelines regarding sun exposure *and to maintain consistent with the Toxicity Management language in Section 6.1.8.2.*

- Modified Section 5.3.1.1 Study Procedures, Vital signs, to address weight increases of 5% or greater and add 'actual' prior to 'weight.'

  Rationale: *To ensure accurate determination of dose in the event of blinded investigational product-related weight gain due to fluid retention*

- Modified Section 5.3.1.1 Study Procedures, Echocardiogram, the following language has been changed: 'Echocardiograms will be performed per Appendix C, Study Activities to **rule out** pericardial effusion (**or assess**, if present), as well as **assess** cardiac function (left ventricular ejection fraction, LVEF).'

  Rationale: *Clarifying the purpose of on-study Echocardiograms.*

- Modified Section 5.3.1.1 Study Procedures, Disease/Response Assessment (Radiographic Imaging), language has been added to advise sites on the need to discuss with TA MD regarding the gaps between tumor assessments and doses in certain cases of dose delays.

  Rationale: *Modified to address the planning of CTs in cases of treatment delays.*

- Modified Section 5.3.1.1 Study Procedures, MRI/CT of the Brain and Footnote t under Appendix C to clarify that the MRI/CT of the brain is required at screening and when clinically indicated thereafter.

  Rationale: *Modified to clarify when MRI/CT of the brain is required on study.*

- Modified Section 5.3.1.1 Study Procedures, Fluid Retention Questionnaire (Including Subject Daily Weight), the following language has been added: 'The site will advise subjects to contact the site in cases where sudden weight gain **(5% or greater)** is observed for possible assessment in the clinic.'

  Rationale: *Modified to clarify the definition of weight gain that requires additional assessment by the site.*

- Modified Section 5.3.1.1 Study Procedures, End of Treatment (EOT) Visit, the following language has been added: 'The EOT procedures should be done within 7 days of documented decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.'

  Rationale: *Modified to fix conflicted language in the protocol.*

- Modified Section 5.3.3.2 Primary Variables to add '…determined by a Central Radiographic Assessment Committee (CRAC) **per RECIST v. 1.1** and overall survival (OS) **in DLL3^{high} population.'**

  Rationale: *To clarify the version of RECIST used for this study and to clarify that the DLL3^{high} subjects are analyzed.*

- Modified Section 5.5.1 Treatment Administration to add 'placebo' after 'dexamethasone' in the last sentence of the first paragraph

  Rationale: *Modified to be consistent with the rest of the paragraph.*

- Modified Section 5.5.2.1 Packing and Labeling, Rovalpituzumab Tesirine and Placebo to include updated Hazardous Drug packing and shipping standards.

  Rationale: *Added to clarify packaging and shipping requirements as per applicable regulations.*

- Modified Section 5.5.2.2 Storage and Disposition of Blinded Investigational Product(s) and Section 5.5.2.3 Preparation/Reconstitution of Dosage Form(s) to note specific instructions for reconstituted and diluted IP will be found in an outside document.

  Rationale: *Site awareness for a separate document that contains additional information on IP storage and disposition.*

- Modified Section 5.5.4.1 Dosing to add fluid retention weight gain guidance.

  Rationale: *To instruct sites on cases of weight gain due to fluid retention.*

- Modified Table 5 to include:

Grade 2 pneumonitis	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade ≥ 3 pneumonitis	Discontinue Rova-T	N/A

- Addition of footnote b.

  Rationale: *Update dose modification guidelines to align with safety profile for Rova-T as described in the IB v.7.*

- Modified Section 5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC) to update the change from an interim analysis to a futility analysis.

  Rationale: *To align with the updated statistical plan.*

- Modified Section 5.5.7 Drug Accountability to update classification of Rova-T as a dangerous good/hazardous material.

  Rationale: *Added to clarify classification as well as packaging and shipping requirements as per applicable regulations.*

- Modified Section 6.1.1.3 to update guidance on capturing disease progression and fatal events for AEs and SAEs in the CRF.

  Rationale: *To clarify on AE/SAE reporting regarding events due to disease progression.*

- Modified Section 6.1.4 Deaths to add language about capturing these events in the CRF.

  Rationale*: To provide guidance on capturing deaths during AE/SAE reporting period in EDC.*

- Modified Section 6.1.5 Adverse Event Collection Period, to say 'All adverse events reported from the time of blinded investigational product administration until 70 days following **the last dose** of blinded investigational product will be collected, whether solicited or spontaneously reported by the subject.'

  Rationale: *To clarify AE collection period from last dose of blinded IP.*

- Modified Section 6.1.6 Adverse Event Reporting to update the emergency contact for the study and add updated language regarding SUSARs and guidelines for the Reference Safety Information (RSI).

  Rationale: *Modification of the emergency contact for the study and current information regarding SUSAR reporting.*

- Modified Section 6.1.8 Toxicity Management to add additional safety guidance on serosal effusions, skin reactions, edema, and pneumonitis.

  Rationale: *Provide additional guidance to investigators and subjects for awareness and guidance to align with IBv7.*

- Updated Section 7.0 Protocol Deviations-Primary and Alternate contact information.

  Rationale: *To provide sites with current AbbVie contact information.*

- Modified Section 8.1.3 Efficacy Endpoints and Analyses to delete the first sentence.

  Rationale: *Align with updated analysis plan as outlined above.*

- Updated Section 8.1.7 to Patient Reported Outcomes (PRO) and add the following language, 'Physical functioning scale score in EORTC QLQ-C30 is the **key secondary** endpoint.'

  Rationale: *Align with updated analysis plan as outlined above.*

- Changed Section Planned Sensitivity and Subgroup Analysis to 8.1.8 and delete the first, third and last sentence of the section.

  Rationale: *Align with updated analysis plan as outlined above.*

- Changed Section Pharmacokinetic and Exposure-Response Analyses to 8.1.9. Modified Synopsis Section 1.2 Criteria for Evaluation, Pharmacokinetic, Section 5.3.5 Pharmacokinetic Variables and Section 8.1.9 Pharmacokinetic and Exposure-Response Analyses to change 'plasma' to 'serum.'

  Rationale*: To update numbering in the section of the protocol and align with the lab manual.*

- Modified Section 8.3 Type I Error Adjustment Procedure for Multiple Testing to include the $DLL3^{high}$ set, update the null hypotheses and level of significance. Figure 3 was also added. This is outlined above in the Synopsis section.

  Rationale: *Align with updated analysis plan as outlined above.*

- Modified Section 10.1 Source Documents to clarify that the Investigator Awareness date of a SAE should be noted in the source, not the EDC.

  Rationale: *This data point cannot be captured in the EDC.*

- Added the following addition to References, '19. AbbVie. Rovalpituzumab Tesirine Dear Rova-T Investigator Letter. 05 December 2018.'

  Rationale: *Added reference due to new safety data.*

- Modified Appendix B: List of Protocol Signatories

  Rationale: *Updated new team members since last amendment.*

- Modified Appendix C: Echocardiogram. Now a required assessment listed under Screening.

  Rationale: *To provide a bigger window for sites to complete the assessment.*

- Modified Footnote b under Appendix C to say, 'End of Treatment Visit **procedures should be done** within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.'

  Rationale: *Updated to be consistent with EOT treatment language.*

- Modified Footnote e under Appendix C to add the following language, 'Cycle 1 Day 1 procedures, **with the exception of weight**.'

  Rationale: *Updated to clarify when weight should be done to be used for dosing decisions.*
- Modified Footnote n under Appendix C to clarify when Echocardiograms are required throughout the study and in relation to pericardial effusion assessments.

  Rationale: *To allow for a larger window for the assessment to be completed.*
- Modified Footnote q under Appendix C to advise sites on the need to contact TA MD for the gaps in tumor assessments.

  Rationale: *Updated to indicate when the TA MD should be consulted.*
- Make administrative changes of typographical errors, minor language and word revision as needed throughout the document.

  Rationale: *Clarifies and ensures consistency throughout.*

An itemized list of all changes made to this protocol under this amendment can be found in Appendix K.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M16-298
Name of Study Drug: rovalpituzumab tesirine (Rova-T)	**Phase of Development:** 3
Name of Active Ingredient: rovalpituzumab tesirine	**Date of Protocol Synopsis:** 05 March 2019
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)	
Objectives: Primary • To evaluate if rovalpituzumab tesirine improves progression-free survival, assessed by a Central Radiographic Assessment Committee (CRAC) according to RECIST v1.1, and overall survival in subjects with extensive-stage small cell lung cancer (ED SCLC) tumors with a high level of DLL3 expression ($DLL3^{high}$) who have ongoing clinical benefit (SD, PR, or CR) following first-line platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo. Secondary • To evaluate if rovalpituzumab tesirine improves progression-free survival by CRAC and overall survival in all randomized subjects compared to placebo. • To assess change in patient reported outcomes (PRO) with physical functioning as measured by the EORTC QLQ-C30 questionnaire in all randomized subjects compared to placebo. Exploratory • To evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), and duration of responses (DOR) by CRAC and Investigator assessment in $DLL3^{high}$ and in all randomized subjects. • To evaluate if rovalpituzumab tesirine improves progression-free survival by Investigator assessment compared to placebo in $DLL3^{high}$ and in all randomized subjects. • To assess change from baseline in all patient reported outcomes (PRO) domains (except physical functioning) measured by EORTC QLQ-C30/LC13 and EQ-5D-5L. • To characterize the pharmacokinetics and incidence of anti-therapeutic antibodies (ATAs) against rovalpituzumab tesirine. • To evaluate pharmacodynamic and predictive biomarkers in blood and tumor for association with sensitivity, efficacy and safety. • To explore DLL3 expression in circulating tumor cells (CTCs) for association with efficacy.	
Investigators: Multicenter, International	
Study Sites: Approximately 300	
Study Population: Subjects with extensive-stage Small Cell Lung Cancer (ED SCLC) with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based chemotherapy (cisplatin or carboplatin in combination with etoposide or irinotecan).	

Number of Subjects to be Enrolled: Up to approximately 740 SCLC subjects, to obtain approximately 480 subjects with DLL3^{high} expression in tumor (DLL3^{high}). DLL3^{high} is defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.

Methodology:

This is a Phase 3, randomized, double-blinded, placebo-controlled, multinational, and multicenter study.

ED SCLC subjects who meet all the inclusion criteria and none of the exclusion criteria, and demonstrate ongoing clinical benefit (SD, PR, or CR) at the completion of 4 cycles of first-line platinum-based chemotherapy (such benefit must be ongoing at the last re-staging assessment prior to randomization), will be randomly assigned in a 1:1 ratio to receive 0.3 mg/kg rovalpituzumab tesirine or placebo, and will receive their assigned therapy on Day 1 of each 6-week cycle, omitting every third cycle. Upon completion of first-line chemotherapy, eligible subjects must be offered prophylactic cranial irradiation (PCI), if offering this procedure is not contradictory to country or institutional guidelines. Subjects receiving PCI must complete it prior to randomization into the study. Subjects will also receive 8 mg orally (PO) of dexamethasone or placebo twice daily on Day –1, Day 1, and Day 2 of each 6-week cycle, omitting every third cycle. Randomization will be stratified by RECIST v1.1 response after completion of first-line platinum-based chemotherapy at screening assessment (SD vs. PR/CR), DLL3 expression, (Unknown vs. 0% to < 25% vs. 25% to < 75% vs. 75% or above), history of central nervous system (CNS) metastases (Yes vs. No), and for subjects with no history of CNS metastases, PCI vs. no PCI.

Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject or the subject's legally acceptable representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.
2. Subject must be ≥ 18 years of age.
3. Histologically or cytologically confirmed ED SCLC (extensive stage disease at initial diagnosis), with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).
4. Subjects with a history of CNS metastases prior to the initiation of first-line platinum-based chemotherapy must have received definitive local treatment and have documentation of stable or improved CNS disease status based on brain imaging within 28 days prior to randomization, off or on a stable dose of corticosteroids.
5. Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy
6. Availability of archived or representative tumor material for assessment of DLL3 expression.
7. Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1.
8. Recovery to ≤ Grade 1 of any clinically significant toxicity (excluding alopecia) prior to randomization.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

9. Subject must have adequate bone marrow, renal and hepatic function as follows:
   a. Absolute neutrophil count (ANC) ≥ 1,000/μL
   b. Platelet count ≥ 75,000/μL
   c. Hemoglobin ≥ 8.0 g/dL
   d. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
   e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5× ULN if evidence of hepatic involvement by malignant disease)
   f. Calculated creatinine clearance ≥ 30 mL/min by the modified Cockroft-Gault formula (Refer to Appendix E).
   g. Albumin ≥ 3g/dL
10. If female, subject must be either postmenopausal as defined as:
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

      OR
    - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

    OR a Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control, starting at randomization through at least 6 months after the last dose of blinded investigational product.

    If the male subject is sexually active, he must agree, from randomization through at least 6 months after the last dose of blinded investigational product, to practice the protocol specified contraception.
11. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at randomization.

    Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the protocol) at Screening do not require pregnancy testing.

Main Exclusion:

1. Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in Inclusion Criteria 3 – 5 for SCLC.
2. Any disease-directed radiotherapy (except, PCI, palliative radiotherapy to a radiographically documented non-progressing lesion for symptom control, or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.
3. 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.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

4. Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III – IV heart failure (refer to Appendix F) within 6 months prior to randomization.
5. Documented history of capillary leak syndrome.
6. Grade 2 or higher pleural or pericardial effusion within 4 weeks of randomization or earlier history of recurrent Grade 2 or higher effusions with ongoing requirement for pericardiocentesis or thoracentesis.
7. Serious infection within 2 weeks prior to randomization, including any Grade 3 or higher (per NCI CTCAE version 4.0) viral, bacterial, or fungal infection.
8. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 6 months after the last dose of blinded investigational product.
9. Male subject who is considering fathering a child or donating sperm during the study or for approximately 6 months after the last dose of blinded investigational product.
10. Systemic therapy with corticosteroids at > 10 mg/day prednisone or equivalent within 1 week prior to randomization.
11. Subject has a history of active malignancies other than SCLC within the past 2 years prior to study entry, with the exception of in situ cancer which was curatively treated.
12. Any prior exposure to a pyrrolobenzodiazepine (PBD-based)-or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.
13. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.

Investigational Products:	Rovalpituzumab tesirine or Placebo Dexamethasone or Placebo
Doses:	Rovalpituzumab tesirine/Placebo: 0.3 mg/kg, Day 1 of each 6-week cycle, omitting every third cycle. Dexamethasone/Placebo 8 mg orally (PO) twice daily on Day –1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle.
Mode of Administration:	Rovalpituzumab tesirine/Placebo: Intravenous Dexamethasone/Placebo: Oral

Duration of Treatment: Subjects will receive rovalpituzumab tesirine/placebo in combination with dexamethasone/placebo on Day 1 of a 6-week cycle, omitting every third cycle until disease progression.

Criteria for Evaluation:

Efficacy: Efficacy assessments will consist of evaluations for tumor progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will be based on a Central Radiographic Assessment Committee (CRAC) review of medical images, as outlined in the Schedule of Assessments. Additionally, efficacy will be assessed by overall survival.

Pharmacokinetic: Serum concentrations of rovalpituzumab tesirine ADC and the presence of anti-therapeutic antibodies (ATA) will be determined.

Criteria for Evaluation (Continued):

Biomarkers: Pharmacodynamic and predictive biomarker assessments will include analyses of tumor material and circulating tumor cells for DLL3 expression, blood samples for inflammatory, tumor, and soluble markers. Samples may also be used for other nucleic acid or protein based exploratory biomarkers to understand the sensitivity or resistance to rovalpituzumab tesirine and biology of SCLC.

Safety: Safety assessments include physical exam, vital signs, body weight, ECOG score, clinical adverse events, laboratory tests (hematology, serum chemistries, urinalysis, and coagulation), ECGs, echocardiogram, fluid retention questionnaire, radiographic images review for fluid retention, and monitoring of concomitant medications.

Patient Reported Outcome (PRO):

Changes in the patient reported outcomes (PROs) EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L from baseline will be assessed.

Statistical Methods:

Efficacy:

Progression-free survival (PFS) per CRAC and overall survival (OS) in patients with DLL3^{high} ED SCLC are the two primary efficacy endpoints. To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) for comparisons of rovalpituzumab tesirine arm versus placebo arm with respect to progression-free survival (PFS) per CRAC in DLL3^{high} patients, overall survival (OS) in DLL3^{high} patients, PFS per CRAC in randomized patients, OS in randomized patients, and physical functioning scale score (EORTC QLQ-C30) in the randomized set.

The following null hypotheses are considered:

Two hypotheses in H_{01} are H_{01a} and H_{01b}.

H_{01a}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in DLL3^{high} set.

H_{01b}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in DLL3^{high} set.

H_{02}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in randomized set.

H_{03}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in randomized set.

H_{04}: Rovalpituzumab tesirine arm is not superior to placebo arm in physical functioning scale score (EORTC QLQ-C30) in randomized set.

The null hypotheses will be tested in a fixed sequence of {H_{01a}, H_{01b}, H_{02}, H_{03}, and H_{04}} in order. To maintain the family-wise type I error for the study, the null hypotheses in H01 (H_{01a} and H_{01b}) will be first tested with an alpha-split approach. The one-sided alpha of 0.25% and 2.25% will be assigned for PFS and OS hypothesis in H_{01}, respectively. Out of one-sided alpha of 2.25% allocated to OS hypothesis (H_{01b}), the one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis. If the hypothesis for PFS in H_{01} (H_{01a}) is rejected the one-sided alpha of 0.25% will be recycled to the OS hypothesis in H_{01} (H_{01b}). Hence, the hypothesis for OS in H_{01} (H_{01b}) will be tested either at a one-sided 2.4999% or one-sided 2.2499% level of significance depending on the PFS hypothesis in H_{01} a is rejected or not.

If either PFS or OS endpoint reaches statistical significance, the study is considered positive. No further tests will be performed if the OS endpoint in DLL3^{high} population (H_{01b}) does not reach statistical significance.

Statistical Methods (Continued):

The hypothesis in H_{02} will be tested if the hypothesis in H_{01b} is rejected. If the hypothesis in H_{02} is rejected, then, either (i) H_{03} and H_{04} will be tested sequentially if the PFS endpoint in DLL3^{high} subjects (H_{01a}) is also rejected or (ii) only H_{04} will be tested if the PFS endpoint in DLL3^{high} subjects (H_{01a}) is not rejected.

Futility Analysis:

Unblinded interim data will be analyzed and reviewed by the IDMC. A futility analysis will be conducted when approximately 160 deaths in subjects with DLL3^{high} ED SCLC (approximately 50% of the planned deaths) are observed. The trial may be stopped for futility if the estimated Overall Survival Cox HR of Rova-T to Placebo at this analysis exceeds 0.9. The one-sided alpha of 10^{-6} will be spent for the early look at the efficacy data for futility analysis.

Sample Size:

There are two primary efficacy endpoints for this study: Progression-free survival (PFS) based on the CRAC and overall survival (OS) in subjects with DLL3^{high} ED SCLC. To maintain the overall 1-sided type I error at a 2.5% for this study, the type I error will be split, assigning 0.25% to progression-free survival and the remaining 2.25% to overall survival. However, the OS endpoint will be tested at a one-sided 2.2499% significance level as a one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis.

The sample size of the study is primarily determined by the analysis of OS. It is assumed, taking into account the expected patient population for the study, that median overall survival in the placebo and rovalpituzumab tesirine arm will be around 9 months and 13 months, respectively. The increase of median OS in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.69, i.e., a reduction in the hazard of death by 31%. With all these assumptions, a total of 319 deaths among subjects with DLL3^{high} are needed to achieve a 90% power based on a log-rank test at a one-sided significance level of 0.022499. Assuming a 19-month accrual period and the last enrolled subject followed for 12 months, at least 480 subjects with DLL3^{high} are expected to be randomized (240 subjects in each arm). A total of 740 subjects regardless of DLL3 expression level (including 480 subjects with DLL3^{high}) will enroll in the study, assuming an approximate prevalence of 65% for subjects with DLL3^{high}. For one-sided significance level of 0.022499, it is projected that an observed hazard ratio of 0.799 or less, corresponding to a 2.3 months or greater improvement in median OS, would result in a statistically significant improvement in the primary analysis of OS.

The primary endpoints of OS and PFS in DLL3^{high} patients will be analyzed at the same time after observing at-least 319 OS event. It is expected at approximately 420 PFS events will be observed at the time of the primary analysis.

It is assumed, taking into account the expected patient population for the study, that median progression-free survival for the placebo and rovalpituzumab tesirine arm will be approximately 3 months and 4.5 months, respectively. The increase of median progression-free survival in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.667. With all these assumptions, a total of 420 PFS events assessed by the CRAC for the subjects with DLL3^{high} are needed to achieve a 91% power based on a log-rank test at a one-sided significance level of 0.0025. It is projected that an observed hazard ratio of 0.760 or less, corresponding to approximately 1 month or greater improvement in median PFS, would result in a statistically significant improvement in the PFS.

Statistical Methods (Continued):

Pharmacokinetic:

Individual concentrations of rovalpituzumab tesirine ADC will be tabulated and summarized for subjects treated with the active regimen and summary statistics provided. The incidence of ATA will be summarized.

Biomarkers:

Biomarkers will be measured at baseline and post-treatment and analyses performed to identify markers associated with rovalpituzumab tesirine response, pharmacodynamics, PK, or safety.

Safety:

The safety of rovalpituzumab tesirine will be assessed by evaluating the study drug exposure, adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse event
ALT	Alanine aminotransferase
ANA	Anti-nuclear antibodies
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCL1	Achaete-scute homolog 1
ASRO	American Society for Radiation Oncology
AST	Aspartate aminotransferase
AT	Aminotransferase
ATA	Anti-therapeutic antibody
ATC	Anatomical therapeutic chemical (codes)
β-hCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
CBR	Clinical benefit rate
CDSM	Clinical Drug Supply Management
CFR	Code of Federal Regulations
CNS	Central nervous system
CR	Complete response
CRAC	Central Radiographic Assessment Committee
CRP	C-reactive protein
CSC	Cancer stem cell
CT	Computerized tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating Tumor DNA
CYP3A4	Cytochrome P450 3A4
DILI	Drug-induced liver injury
DLL3	Delta-like protein 3
$DLL3^{high}$	DLL3 high expression in tumor defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay

DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EDC	Electronic data capture
ED SCLC	Extensive-stage disease small cell lung cancer
EFNS	European Federation of Neurological Societies
EGF	Epidermal growth factor
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment
EQ-5D-5L	EuroQoL Five Dimensions Questionnaire
ESMO	European Society for Medical Oncology
ESR	Erythrocyte sedimentation rate
EU	European Union
FDA	US Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
Gy	Gray
HDPE	High-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IL	Interleukin
IMP	Investigational Medicinal Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive response technology
IUD	Intrauterine device
IV	Intravenous(ly)

JSMO	Japanese Society of Medical Oncology
LCNEC	Large cell neuroendocrine cancer
LDH	Lactate dehydrogenase
LD SCLC	Limited-stage disease small cell lung cancer
LFT	Liver function test
LVEF	Left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
nAb	Neutralizing antibodies
NASH	Non-alcoholic steatohepatitis
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NEUROD1	Neurogenic differentiation 1
NSAID	Non-steroidal anti-inflammatory drug
NSE	Neuron-specific enolase
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PBD	Pyrrolobenzodiazepine
PCI	Prophylactic cranial irradiation
PD	Progressive disease
PDX	Patient-derived xenografts
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetics
PO	Per os (by mouth)
PR	Partial response
PRO	Patient reported outcome
PT	Prothrombin time
PTFU	Post-treatment follow up
q6wk	Every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RF	Rheumatoid factor

Rova-T	Rovalpituzumab tesirine
RPTD	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SC-DR002	DNA cross-linking agent also known as D6.5
SC16	Humanized DLL3-specific IgG1 antibody
SCLC	Small cell lung cancer
SD	Stable disease
SIADH	Syndrome of Inappropriate Anti-Diuretic Hormone
SMPC	Summary of product characteristics
SPF	Sun protection factor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TEAE	Treatment-emergent adverse event
TIC	Tumor-initiating cells
TNM	Tumor, node, metastases
TTP	Time to progression
ULN	Upper limit of normal
VA	Veterans Administration
VEGF	Vascular endothelial growth factor
WHODRUG	World Health Organization Drug (Dictionary)
WOCBP	Women of childbearing potential

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3.0 Introduction

3.1 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.[1,2] SCLC arises from epithelial cells with neuroendocrine differentiation. Historically, SCLC has been staged using the Veterans Administration (VA) staging system as 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. Systemic chemotherapy remains the cornerstone of therapy for all stages of SCLC. Standard initial chemotherapy for all patients with a suitable performance status consists of a platinum salt (carboplatin or cisplatin) in combination with a second agent, usually etoposide or irinotecan. 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, responses are typically not durable and recurrence rates are high in the limited stage disease and nearly universal in the extensive stage disease, leading to median survivals of 14 – 20 months and 9 – 11 months, respectively.[3]

Extensive stage disease subjects achieving SD or better during first-line platinum-based therapy have median progression-free survival (PFS) of approximately 2.1 – 2.3 months and median OS of approximately 6.9 – 8.9 months from the completion of first-line therapy.[4,5] Exploration of clinical benefit maintenance strategies in extensive disease SCLC with the goal of prolonging PFS and OS after completion of first-line standard therapies is therefore warranted.

3.2 Delta-Like Protein 3

Delta-like protein 3 (DLL3) is an atypical, inhibitory ligand of the Notch receptor family, discovered by AbbVie Stemcentrx scientists as a novel therapeutic target in SCLC and

other high-grade neuroendocrine carcinomas. It was identified by whole transcriptome sequencing of tumor initiating cells (TICs) isolated from SCLC and large cell neuroendocrine cancer (LCNEC) patient-derived xenografts (PDXs), and found to be expressed in the majority of SCLC and LCNEC tumors, but with no detectable protein expression in normal tissues or non-neuroendocrine tumor types.[6] DLL3 has been implicated in the regulation of cell fate decisions during development, and likely acts as an oncogene in high-grade neuroendocrine tumors where it is a downstream transcriptional target of the achaete-scute homolog 1 (ASCL1) transcription factor in SCLC tumor cells, and acts to inhibit the Notch receptor pathway, thereby facilitating neuroendocrine tumorigenesis.[6-8]

3.3 Rovalpituzumab Tesirine

Rovalpituzumab tesirine (SC16LD6.5) is a DLL3-targeted antibody-drug conjugate (ADC) consisting of the humanized DLL3-specific IgG1 monoclonal antibody SC16; the 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.

In the Phase 1 first in human study of rovalpituzumab tesirine (Study SCRX16-001), the best overall response (confirmed) for all SCLC subjects (dose escalation, retreatment, and maintenance cohorts) was retrospectively assessed by the Independent Review Committee (IRC) by RECIST v1.1 criteria. The ORR (confirmed) was 16% (95% CI: 7.35, 27.42), with 12% achieving PR. The clinical benefit rate (CBR) was 59% (95% CI: 44.93, 71.40). The median duration of response by the IRC was 1.7 months (95% CI: 0.03, 3.06). The median progression-free survival by the IRC was 3.0 months (95% CI: 2.56, 3.84), with a probability of progression-free survival at 12 weeks of 52% (95% CI: 39, 63). The median overall survival was 4.3 months (95% CI: 3.22, 5.65). The probability of overall survival at 12 weeks was 69% (95% CI: 52, 81). In DLL3-positive (≥ 1%

tumor cells staining positive for DLL3 with murine anti-DLL3 antibody assay) subjects, the ORR was 23% (95% CI: 10.42, 40.14), and the CBR was 77% (95% CI: 59.86, 89.58). A slightly higher ORR (27%) and CBR (87%) were observed in DLL3-high (≥ 50% tumor cells staining positive for DLL3 with murine anti-DLL3 antibody assay) subjects.

In the Phase 2 Study SCRX001-002 (TRINITY) in patients with SCLC recurrent after at least two systemic chemotherapy regimens, rovalpituzumab tesirine dosed at 0.3 mg/kg every 6 weeks for two cycles (with an option for additional two cycles upon progression occurring ≥ 12 weeks after the second dose) resulted in the following:

- In DLL3^{high} (≥ 75% tumor cells staining positive for DLL3 with VENTANA Rabbit IHC (SP347) DLL3 assay) subjects, ORR of 14% per IRC assessment, median OS of 5.7 months and median PFS of 3.8 months
- In DLL3^{high} subjects, the clinical benefit rate was 74% with a median duration of clinical benefit of 3.0 months per IRC assessment

Additionally, DLL3 positive (≥ 25% tumor cells staining positive for DLL3 with VENTANA Rabbit IHC (SP347) DLL3 assay) and DLL3^{high} groups had comparable response rates given highly overlapping populations where approximately 85% of DLL3 positive subjects were also DLL3^{high}.

In December 2018, enrollment in Study M16-289 TAHOE ("A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3high Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy") was discontinued at the recommendation of the Independent Data Monitoring Committee (IDMC) after review of available efficacy data which demonstrated shorter overall survival in the rovalpituzumab tesirine arm compared with the topotecan control arm. At the time enrollment was halted, 444 DLL3^{high} (≥ 75% tumor cells staining positive for DLL3 with VENTANA Rabbit IHC (SP347) DLL3 assay) subjects had enrolled on the trial. The IDMC recommended that investigators and

subjects make individual decisions as to whether or not to continue treatment based on patient level response. The results of the TAHOE study did not adversely impact the safety profile for rovalpituzumab tesirine.[19]

3.4 Differences Statement

This is the first randomized, double-blind, multicenter, Phase 3 study comparing rovalpituzumab tesirine versus placebo as maintenance therapy following first-line platinum-based therapy in subjects with extensive-stage SCLC.

3.5 Benefits and Risks

Although response rates to first-line platinum-based chemotherapy in ED SCLC are high, SCLC nearly invariably recurs, which may be attributed to the relative resistance of cancer stem cells (CSCs)/TICs to conventional chemotherapy. Rovalpituzumab tesirine has been found to reduce the frequency of TICs in low passage SCLC patient-derived xenograft models significantly more than platinum-based SOC therapy.[6] By targeting this resistant, residual cell population, rovalpituzumab tesirine has a unique mechanistic rationale for benefit in post-chemotherapy maintenance setting. Rovalpituzumab tesirine had shown promising clinical activity in subjects with recurrent/relapsed SCLC (Section 3.3), and it is likely that the observed benefit will translate into maintenance setting. This study will assess the efficacy, tolerability, and safety of rovalpituzumab in subjects with extensive-stage SCLC who have ongoing clinical benefit (SD, PR, or CR) following first-line platinum-based chemotherapy (cisplatin or carboplatin in combination with etoposide or irinotecan).

As of 30 June 2018, 1246 subjects have received study medication in the rovalpituzumab tesirine clinical program; an estimated 1039 subjects (with SCLC or other DLL3-expressing solid tumors) have received at least 1 dose of rovalpituzumab tesirine at doses ranging from 0.05 mg/kg to 0.8 mg/kg on a q3w schedule and 0.3 mg/kg to 0.4 mg/kg on a q6w schedule.

Among subjects with SCLC treated with rovalpituzumab tesirine 0.3 mg/kg q6w, 96.8% of subjects reported at least 1 adverse event. The most frequently reported adverse events among subjects with SCLC treated with rovalpituzumab tesirine 0.3 mg/kg q6w were decreased appetite (28.0%), photosensitivity reaction (27.7%), oedema peripheral (27.2%), dyspnoea (26.6%), and nausea (25.6%). Important identified risks following treatment with rovalpituzumab tesirine include: pleural effusions (33.9%), pericardial effusions (16.7%), generalized edema (2.7%) and photosensitivity reactions (27.7%). Important potential risks following treatment with rovalpituzumab tesirine include pneumonitis (1%). The following adverse events of special interest have also been identified: cutaneous reactions (48.7%), thrombocytopenia and hemorrhage events (28%), edema (33.8%), hypoalbuminemia (16.2%), hepatotoxicity (19.3%), nephrotoxicity (5.9%), anemia (19.7%), neutropenia (9.2%) and infusion related reaction (0.2%). In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified bone marrow, lung, and kidney as potential sources of clinical adverse events (AEs) (AbbVie Investigator Brochure v7). Accordingly, safety assessments will include regular assessments at protocol-specified time points of routine physical examination, laboratory and imaging tests including CT/MRI assessments and echocardiograms, a fluid retention questionnaire, and daily weights (Section 5.3.1.1). The timing and frequency of these assessments are designed so that potential rovalpituzumab tesirine-related toxicities are identified prior to additional drug doses, limiting the risk of toxicity exacerbation. The dose delay/reduction/discontinuation protocol guidelines provide additional level of risk mitigation for subjects enrolled in this study.

It is thus considered that the study has acceptable benefit/risk profile for subjects with ED SCLC and stable disease or better following completion of four cycles of platinum-based standard front line treatment, taking into account short progression-free and overall survival of these subjects.[4]

4.0 Study Objectives

The primary objective of this study is to evaluate if rovalpituzumab tesirine improves progression-free survival, assessed by CRAC, and overall survival in subjects with

extensive-stage SCLC tumors with a high level of DLL3 expression (DLL3^{high}) who have ongoing clinical benefit (SD, PR, or CR) following the completion of 4 cycles of first-line, platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

The secondary objectives are:

- To evaluate if rovalpituzumab tesirine improves progression-free survival by CRAC and overall survival in all randomized subjects compared to placebo.
- To assess change in patient reported outcomes (PRO) with physical functioning as measured by the EORTC QLQ-C30questionnaire in all randomized subjects compared to placebo.

The exploratory objectives are:

- To evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), and duration of responses (DOR) by CRAC and investigator assessment in DLL3^{high} and in all randomized subjects.
- To evaluate if rovalpituzumab tesirine improves progression-free survival by investigator assessment compared to placebo in DLL3^{high} and in all randomized subjects.
- To assess change from baseline in all patient reported outcomes (PRO) domains (except physical functioning) measured by EORTC QLQ-C30/LC13 and EQ-5D-5L.
- To characterize the pharmacokinetics and incidence of anti-therapeutic antibodies (ATAs) against rovalpituzumab tesirine.
- To evaluate pharmacodynamic and predictive biomarkers in blood and tumor for association with sensitivity, efficacy and safety.
- To explore the DLL3 expression in circulating tumor cells (CTCs) for association with efficacy.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

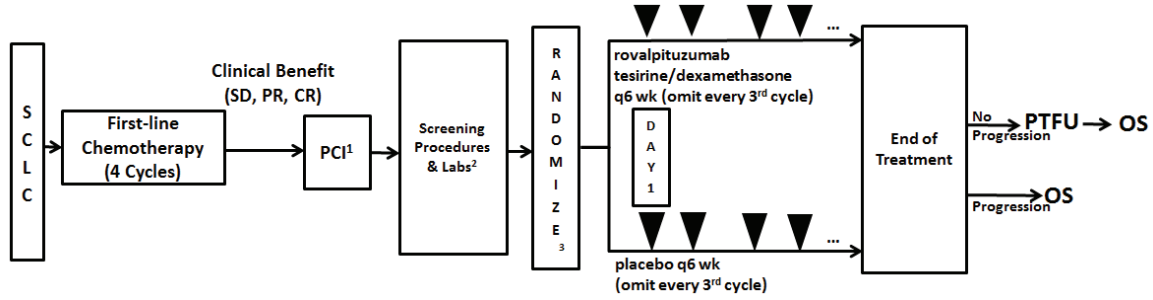
The study is designed to enroll approximately 740 SCLC subjects to obtain approximately 480 subjects with DLL3^{high} expression in tumor (DLL3^{high}) and to meet scientific and regulatory objectives without enrolling an undue number of subjects in alignment with ethical considerations. DLL3^{high} is defined as ≥ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.

This is a Phase 3, randomized, double-blinded, placebo-controlled, multinational, and multicenter study. Approximately 300 clinical sites will participate.

Eligible subjects will be randomly assigned in a 1:1 ratio to receive 0.3 mg/kg rovalpituzumab tesirine or placebo, and will receive their assigned therapy on Day 1 of each 6-week cycle, omitting every third cycle. Subjects will also receive 8 mg orally (PO) of dexamethasone or placebo twice daily on Day –1, Day 1 (the day of dosing), and Day 2 of each 6-week cycle, omitting every third cycle. Subjects will be stratified by RECIST v1.1 response after completion of first-line platinum-based chemotherapy at screening assessment (SD vs. PR/CR), DLL3 expression (Unknown vs. 0% to < 25% vs. 25% to < 75% vs. 75% or above), history of central nervous system (CNS) metastases (Yes vs. No), and for subjects with no history of CNS metastases, PCI vs. no PCI. Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first.

A schematic of the study is provided in Figure 1, Study Schema.

Figure 1. Study Schema



Arrowheads = blinded investigational product administration; CR = complete response; OS = overall survival; PR = partial response; PTFU = post-treatment follow-up; SD = stable disease

1. Upon completion of first-line platinum-based chemotherapy, eligible subjects must be offered prophylactic cranial irradiation (PCI), if offering this procedure is not contradictory to country or institutional guidelines. Subjects receiving PCI must complete it prior to randomization into the study.
2. Collection of tumor material for DLL3 testing will be provided any time after the signing of the informed consent and prior to randomization.
3. Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy.

On study disease assessments, for the purposes of efficacy assessments will be performed by a Central Radiographic Assessment Committee (CRAC) blinded to study treatment information and independent of Investigators and personnel who are involved in conducting the study (Section 5.3.1.1).

5.2 Selection of Study Population

Current standard of care after first-line platinum-based chemotherapy consists primarily of observation until disease progression, at which time second line chemotherapy, such as with topotecan, may be instituted. No therapy is approved for use or routinely used as maintenance or consolidation after first-line platinum-based chemotherapy in extensive stage SCLC. Rovalpituzumab tesirine may be beneficial in this setting, but no prior studies have formally explored its potential. Therefore, this study will involve a comparison of rovalpituzumab tesirine against placebo.

For the purposes of study eligibility, limited stage disease SCLC (LD-SCLC) is defined as a disease confined to the hemithorax of origin, with or without the involvement of regional lymph nodes, including ipsilateral and contralateral hilar, ipsilateral and contralateral mediastinal, and ipsilateral supraclavicular nodes. Extensive stage disease SCLC (ED-SCLC) is defined as all other SCLC.

Subjects must meet all of the inclusion and none of the exclusion 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 a Good Clinical Practice (GCP) audit and/or regulatory authority inspection.

5.2.1 Inclusion Criteria

1. Subject or the subject's legally acceptable representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.
2. Subject must be ≥ 18 years of age.
3. Histologically or cytologically confirmed ED SCLC (extensive stage disease at initial diagnosis), with ongoing clinical benefit (SD, PR, or CR per RECIST v.1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).
4. Subjects with a history of CNS metastases prior to the initiation of first-line platinum-based therapy must have received definitive local treatment and have documentation of stable or improved CNS disease status based on brain imaging within 28 days prior to randomization, off or on a stable dose of corticosteroids.
5. Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy.

6. Availability of archived or representative tumor material for assessment of DLL3 expression.
7. Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1 (Refer to Appendix D).
8. Recovery to ≤ Grade 1 of any clinically significant toxicity (excluding alopecia) prior to randomization.
9. Subject must have adequate bone marrow, renal and hepatic function as follows:
    a. Absolute neutrophil count (ANC) ≥ 1,000/µL
    b. Platelet count ≥ 75,000/µL
    c. Hemoglobin ≥ 8.0 g/dL
    d. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
    e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5 × ULN if evidence of hepatic involvement by malignant disease)
    f. Calculated creatinine clearance ≥ 30 mL/min by the modified Cockroft-Gault formula (Refer to Appendix E)
    g. Albumin ≥ 3 g/dL
10. If female, subject must be either postmenopausal as defined as:
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

      OR
    - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

OR a Woman of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at randomization through at least 6 months after the last dose of blinded investigational product.

If the male subject is sexually active, he must agree, from randomization through at least 6 months after the last dose of blinded investigational product, to practice the protocol specified contraception (Section 5.2.4).

11. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at randomization.

    Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing.

Rationale for Inclusion Criteria

1	In accordance with Harmonized Good Clinical Practice (GCP)
2 – 7	To select and/or collect data on the subject population
8 – 9	For the safety of the subjects
10 – 11	The impact of rovalpituzumab tesirine on pregnancy in humans is unknown

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in Inclusion Criteria 3 – 5 for SCLC.

2. Any disease-directed radiotherapy (except PCI, palliative radiotherapy to a radiographically documented non-progressing lesion for symptom control, or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.
3. 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.
4. Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III – IV heart failure (refer to Appendix F) within 6 months prior to randomization.
5. Documented history of capillary leak syndrome.
6. Grade 2 or higher pleural or pericardial effusion within 4 weeks of randomization or earlier history of recurrent Grade 2 or higher effusions with ongoing requirement for pericardiocentesis or thoracentesis.
7. Serious infection within 2 weeks prior to randomization, including any Grade 3 or higher (per NCI CTCAE version 4.0)[11] viral, bacterial, or fungal infection.
8. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 6 months after the last dose of blinded investigational product.
9. Male subject who is considering fathering a child or donating sperm during the study or for approximately 6 months after the last dose of blinded investigational product.
10. Systemic therapy with corticosteroids at > 10 mg/day prednisone or equivalent within 1 week prior to randomization.
11. Subject has a history of active malignancies other than SCLC within the past 2 years prior to study entry, with the exception of in situ cancer which was curatively treated.

12. Any prior exposure to a pyrrolobenzodiazepine (PBD-based) or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.
13. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.

Rationale for Exclusion Criteria

1, 10 – 13	To select the appropriate subject population
2 – 7	For the safety of the subjects
8 – 9	The impact of rovalpituzumab tesirine on pregnancy in humans is unknown

5.2.3 Prior and Concomitant Therapy

Any concomitant medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of study drug administration or receives during the study through the safety reporting period (Section 6.1.5), must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

Any concomitant therapy given for a protocol-related AE should be recorded from the time of informed consent.

The AbbVie TA MD should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior Therapy

Subjects will have received first-line platinum-based chemotherapy consisting of 4 cycles of treatment with combination of either cisplatin or carboplatin with etoposide or

irinotecan; administration of Day 1 of the last cycle of first-line chemotherapy must be at least 3 weeks but no more than 9 weeks prior to randomization. Subjects previously treated for LD-SCLC are not eligible.

Subjects with central nervous system (CNS) metastases present prior to the initiation of first-line chemotherapy will have completed definitive local treatment (e.g., surgery or radiotherapy). Upon completion of first-line chemotherapy, subjects without a history of CNS metastases must have been offered prophylactic cranial irradiation (PCI), if offering this procedure is not contradictory to country or institutional guidelines. Subjects receiving PCI must complete it prior to randomization into the study. PCI regimen must be consistent with those endorsed by the National Comprehensive Cancer Network (NCCN) or European Society for Medical Oncology (ESMO).

5.2.3.2 Concomitant Therapy

All subjects enrolled will receive premedication consisting of dexamethasone/placebo. Refer to Section 5.5.1, Treatments Administered for details.

There are no other required concomitant therapies. However, due to the potential for rovalpituzumab tesirine-related skin photosensitivity, patients should be advised to avoid direct and indirect sun exposure as much as possible from Cycle 1 Day 1 until 30 days after the final dose. When sun exposure is unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). Thirty-one to ninety days after last dose of Rova-T/placebo, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher.

5.2.3.2.1 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, anti-emetics, electrolyte replacement, and hydration. Bone modifying agents

(e.g., bisphosphonates, denosumab) for bone metastases are also permitted per local institutional standards. 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 ≤ 10 mg/day. The use of intermittent high-dose corticosteroid treatment to prevent or manage infusion reactions, serosal effusions (see Section 6.1.8.1), or other non-cancer-related symptoms including premedication for known hypersensitivity reactions to contrast for scans is allowed.

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

If the subject is taking chronic suppressive anti-infectives (antiviral, antifungal, or antibacterial), appropriate investigation must be completed prior to randomization, and documentation must exclude active infection. After exclusion of active infection, otherwise eligible subjects should complete or continue suppressive anti-infectives as prescribed.

If a subject requires palliative radiation during the study (e.g., symptomatic worsening of a bone lesion) diagnostic imaging has to be performed to assess for radiographic progression prior to radiation, and documentation of non-progressive status by radiography will be captured in the eCRF. Any cancer-directed therapy a subject receives due to disease improvement should be discussed with the TA MD in advance, if possible.

In the event of isolated CNS-only progression during study treatment, blinded investigational product may be withheld while local treatment is administered (e.g., radiotherapy) in accordance with institutional practice. Blinded investigational product may be restarted 1 week after the completion of local CNS disease-directed therapy.

5.2.3.3 Prohibited Therapy

Subjects may not receive other investigational drugs, immunosuppressive medications, radiotherapy, or systemic anti-neoplastic therapy during the study, other than as allowed in Section 5.2.3.2 and Section 5.2.3.2.1. Additionally, strong inhibitors of cytochrome P450 3A4 (CYP3A4) should be avoided (refer to Table 1).

Table 1. Examples of Strong CYP3A4 Inhibitors

Enzyme/Transporter	Strong Inhibitor Examples[10]
CYP3A4	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir and ritonavir, diltiazem, elvitegravir and ritonavir, idelalisib, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, nefazodone, nelfinavir paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, troleandomycin, voriconazole

(CYP) Cytochrome P450.

Note: This is not an exhaustive list; so if in question, please refer to the appropriate product label.

5.2.4 Contraception Recommendations

If female, subject must be either postmenopausal or permanently surgically sterile (refer to inclusion criteria for definitions of both) OR a Woman of Childbearing Potential (WOCBP), practicing at least one of the following methods of birth control, on randomization (or earlier) through at least 6 months after the last dose of blinded investigational product.

- Combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) associated with the inhibition of ovulation, initiated at least 1 month prior to randomization.
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation, initiated at least 1 month prior to randomization.

- Bilateral tubal occlusion/ligation.
- Bilateral tubal occlusion via hysteroscopy (i.e., Essure), provided a hysterosalpingogram confirms success of the procedure.
- Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
- Intrauterine device (IUD).
- Intrauterine hormone-releasing system (IUS).
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

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

Male subject agrees not to donate sperm from randomization through at least 6 months after the last dose of blinded investigational product.

5.3 Efficacy, Pharmacokinetic, Biomarker, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C, Study Activities.

5.3.1.1 Study Procedures

Unless otherwise stated, the baseline measurement for any given variable will be defined as the last value obtained for the variable prior to the first dose of blinded investigational product.

Screening procedures must be performed within 21 days prior to randomization, with the exception of radiographic assessments (CT scan or MRI including the head, chest, and abdomen) which may be performed within 28 days prior to randomization. The collection of tumor material for DLL3 testing will be provided any time after the signing of the informed consent and prior to randomization. Randomization may occur within 3 days prior to C1D1.

Subsequent study procedures should be performed within 3 days prior to the scheduled treatment visits, within a ±3 day window during the non-treatment visits, and within a ±1 week window during the post-treatment follow up, and survival follow up phase unless otherwise indicated.

The results of all screening and evaluations at the time of randomization must be within clinically acceptable limits, upon review by the investigator, before a subject can be randomized. Subjects will not be randomized in the study if laboratory or other screening results are unacceptable. Subjects are allowed to rescreen and have laboratory samples redrawn to meet eligibility within the same 21 day screening window. Subjects who meet the inclusion criteria and do not meet any of the exclusion criteria may be randomized.

Informed Consent

Signed informed consent will be obtained from the subject before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 21-day screening window. For the optional tumor biopsy procedure at time of disease progression an optional tumor material biopsy procedure informed consent should be

completed. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Subjects will be considered screen failures if the informed consent has been signed and a study-specific procedure has been performed (e.g., central laboratories drawn), but subject does not randomize into the study. The reason for screen failure will be documented in the source and will be captured in the eCRF.

Tumor Material at Screening

For all subjects, archived or fresh tumor material must be submitted to the AbbVie designated central IHC laboratory for determination of DLL3 expression prior to randomization, as per Appendix C, Study Activities.

Tumor material testing for DLL3 status may occur at any time after initial diagnosis for subjects who provide consent. These subjects must be registered in IRT. Eligibility will depend on the fulfillment of all other inclusion and exclusion criteria and the trial status (whether the study is still open for accrual).

For purposes of the study, "unknown" status is possible if all available samples were tested and failed due to unforeseen technical or logistical reasons; subject with no tumor sample will not be eligible for the trial or subject with sample not fulfilling sponsor's specifications (different method of tissue fixation, known necrotic, too few cells etc.) will not be eligible.

Medical and Surgical History (Including Malignancy History); Adverse Event and Prior/Concomitant Medication Assessment

The following will be collected during the Screening Visit:

- Medical history, including demographics and documentation of any clinically significant medical condition and/or surgical history
- History of tobacco and alcohol use:

- **current smoker** [subject who has > 100 smoking events in their lifetime and has smoked within the last 12 months]
- **past smoker** [subject who has > 100 smoking events in their lifetime and has not smoked in past 12 months]
- **never smoked** [subject with ≤ 100 smoking events in lifetime]

- Detailed oncology history including:
  - Histology
  - Date of initial cancer diagnosis
  - TNM Stage at diagnosis, if available
  - Veterans Administration (VA) Stage at diagnosis
  - Sites of metastases
    - Absence of active CNS metastases will be confirmed by MRI or CT of the brain
  - Mutational status, if performed or applicable
  - Any surgical procedures
  - Treatments administered (including dates and type of modality)
- Detailed prior and concomitant medication usage including dates of usage and dosing information for all medications and supplements taken

Any changes observed from the Screening assessments (prior to dosing) will be recorded in the subject's medical history. At each visit, including the End of Treatment Visit, the subject's medical history will be reviewed and any changes from baseline will be recorded on the adverse event eCRF.

All medication (prescription or over-the-counter, including vitamins and/or herbal supplements) will be recorded from the first study drug administration through the 70 days following the last dose of blinded investigational product.

Physical Examination

A physical examination will be performed per Appendix C, Study Activities. If the Screening assessment is performed within 21 days of C1D1, it is not required to be repeated on C1D1 unless clinically indicated. Clinically significant changes from baseline will be documented in the source documentation and eCRFs as adverse events.

Height will be measured at the Screening visit only. For height assessments, the subject should not wear shoes.

Investigators will assess subjects for pleural and pericardial effusion prior to dosing of blinded investigational product on Day 1 of each cycle.

Physical exam will include cardiac, pulmonary (including cardiopulmonary exam for serosal effusions), evaluation of extremities for peripheral edema, neurological (sensory, motor, cranial nerves), head and neck, lymphatic, hepatobiliary, gastrointestinal, genitourinary, and skin evaluation per local standard of care.

Vital Signs

Vital signs will be performed per Appendix C, Study Activities. Vital signs include actual weight, sitting blood pressure, heart rate and body temperature. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections.

Actual weight will be collected in the clinic prior to dosing at each cycle and the recorded weight will be utilized for dosing calculations. For weight assessments, the subject should not wear shoes. In the event of a 5% or greater increase in weight within 2 consecutive visits or compared to baseline which ever has the shorter interval, a prompt workup for fluid retention (e.g., edema, effusions, etc.) should be conducted. If weight gain is due to proven or suspected fluid retention related to study drug, and dosing is not prohibited per Section 5.5.4, dose should be calculated based on actual weight before the event of fluid retention.

Vital signs should be collected prior to the infusion.

12-Lead Electrocardiogram (ECG)

A resting 12-lead ECG will be performed per Appendix C, Study Activities. ECGs consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

A qualified physician will determine whether any findings outside of normal physiological variation are clinically significant (in consultation with a cardiologist if necessary). The physician will document whether findings are clinically significant (CS) or not clinically significant (NCS) on the tracing and sign and date the tracing. The original annotated ECG tracing containing the physician's assessment will be retained in the subject's records at the study site.

Echocardiogram

Echocardiograms will be performed per Appendix C, Study Activities to rule out pericardial effusion (or assess, if present), as well as assess cardiac function (left ventricular ejection fraction, LVEF).

ECOG Performance Status

The ECOG performance status will be documented according to Appendix C, Study Activities. Refer to Appendix D, Performance Status Scales Conversion for details.

If the Screening assessment is performed within 21 days of C1D1, it is not required to be repeated on C1D1 unless clinically indicated.

Documentation of Non-Childbearing Status and Pregnancy Testing

For each female subject, the Investigator will document non-childbearing status (surgically sterile or post-menopausal for at least 1 year) or potential childbearing status.

Should a female study subject become pregnant or suspect she is pregnant while participating in this study, she should inform the treating Investigator immediately (Section 6.1.6).

For female subjects of childbearing potential, the laboratory will perform pregnancy testing according to Appendix C, Study Activities. A serum pregnancy test will be performed at Screening and the results must be available prior to the administration of the first dose of blinded investigational product on C1D1. Subjects with borderline pregnancy tests at Screening must have a serum pregnancy test ≥ 3 days later to document continued lack of a positive result. Urine pregnancy tests will be performed at Day 1 of each cycle, the Non-Treatment cycle, End of Treatment Visit, and PTFU until 6 months after the last dose of blinded investigational product.

Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have an FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the Investigator.

Clinical Laboratory Tests

Samples for chemistry, hematology, coagulation, and urinalysis will be collected per Appendix C, Study Activities. Specific laboratory assessments are outlined in Table 2, Clinical Laboratory Tests.

If the Screening assessment is performed within 7 days of C1D1, it is not required to be repeated on C1D1 unless clinically indicated. Starting at Cycle 2, lab assessments may be performed 3 days prior to Day 1 visits. All laboratory samples will be assessed using a certified central laboratory and these data will be used for all data analysis. The central laboratory will provide instructions regarding the collection, processing, and shipping of samples. All laboratory samples will be shipped to the central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care.

Qualified medical staff at the site will review, initial and date all local and central laboratory results. Any laboratory value outside the reference range that is considered clinically significant by the Investigator will be followed as appropriate. Clinically significant laboratory values will be recorded as adverse events if they meet the criteria as specified in Section 6.1.1.

Table 2. Clinical Laboratory Tests

Hematology	**Clinical Chemistry**	**Urinalysis (Dipstick)**
Hematocrit Hemoglobin Red blood cell (RBC) count White blood cell (WBC) count Neutrophils Bands (if indicated) Lymphocytes Monocytes Basophils (if indicated) Eosinophils (if indicated) Platelet count (estimate not acceptable) Mean corpuscular volume Mean corpuscular hemoglobin concentration RBC distribution width	Blood urea nitrogen (BUN) Serum creatinine Total bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Total protein Glucose Albumin Magnesium Chloride Amylase Lipase Lactate dehydrogenase (LDH)	Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase
Coagulation		**Serum Pregnancy Test**
Activated Partial Thromboplastin Time (aPTT) Prothrombin time (PT) International Normalized Ratio (INR)		Beta-Human Chorionic Gonadotropin (β-hCG) (if applicable) Follicle-stimulating hormone (FSH) (if applicable)

Disease/Response Assessment (Radiographic Imaging)

Treatment response will be assessed by radiographic tumor evaluation per RECIST v1.1 at protocol-specified time points as outlined in the Appendix C, Study Activities. Diagnostic quality, spiral CT scan with contrast is recommended for all anatomic areas except brain (MRI is recommended for brain imaging); other CT methods or MRI for

respective anatomic areas may be used if performed consistently throughout the study for each individual subject and only under the circumstances described in Appendix G. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening radiographic assessment must include brain MRI/CT. Diagnostic/baseline pre-first-line scans through screening scans will be reviewed by the investigator to determine disease response status per RECIST v1.1 for eligibility and stratification. On study disease response will be determined by the Investigator at each assessment according to RECIST v1.1 (Appendix G, Response Evaluation Criteria for Solid Tumors (RECIST) v 1.1)[12] and independently reviewed by Central Radiographic Assessment Committee (described below). Disease/Response Assessment may be performed within 7 days prior to the Day 1 visit.

Effusion (pleural, pericardial, etc.) assessments will be performed by a radiologist at each on-study radiographic assessment and any new findings communicated to the Investigator prior to the next dose of blinded investigational product. Effusions should contribute to disease status assessment per RECIST v 1.1 only if confirmed malignant by cytology or otherwise clearly disease-related; if disease progression is suspected solely based on the appearance of new or increase of existing effusions, confirmation of malignant nature of such effusions is strongly recommended due to known adverse event profile of rovalpituzumab tesirine. If collected, effusion fluid must be tested for cytology if disease progression due to appearance/worsening of effusion is suspected.

Isolated CNS-only progression will not require removal of the subject from therapy. Refer to Section 5.2.3.2.1, Allowed Concomitant Therapy for details associated with CNS only progression.

The EOT assessment may be omitted if the previous assessment was performed within the preceding 6 weeks.

Scheduled tumor assessments should not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method

throughout the study every 6 weeks after randomization, unless evidence of tumor progression warrants otherwise. In some cases, mandatory dose delays due to toxicity will lead to a gap between tumor assessment and dosing. In cases where this gap exceeds 1 week, the TAMD should be contacted for guidance.

Subjects who discontinue treatment for reasons other than radiographic disease progression will continue to be followed every 6 weeks from randomization to determine the extent of tumor burden, until disease progression occurs.

MRI/CT of the Brain

MRI of the brain will be performed at protocol-specified time points as outlined in Appendix C, Study Activities. Brain MRI may be substituted by CT with intravenous contrast at the discretion of the Investigator. MRI/CT of the brain is required at screening and when clinically indicated (e.g., if CNS progression is suspected) thereafter.

Central Radiographic Assessment Committee (CRAC)

In addition to being reviewed by the investigator and/or site staff, radiological scans will be assessed by a Central Radiographic Assessment Committee (CRAC), as outlined in the Appendix C, Study Activities. Sites will collect the appropriate scans and ship by courier or submit electronically to the central facility at each subject's disease assessment. If, in addition to protocol-specified disease assessment modalities other modalities were used to assess disease (e.g., FDG-PET, X-ray), imaging should also be transferred to the central facility.

The EOT assessment may be omitted if the previous assessment was performed within the preceding 6 weeks.

Subject treatment management will be based on review by the local investigator and/or site staff. The investigator should treat according to clinical judgment and the CRAC will make the definitive decision on tumor response or progression in regards to the PFS endpoint.

Randomization and Subject Number Assignment

An Interactive Response Technology system (IRT) will be utilized to register subjects. Subjects who complete all Screening procedures and meet the eligibility criteria will proceed to randomization. Refer to Section 5.5.3 for details associated with subject assignment to treatment arms.

Health Resource Utilization

Health Resource Utilization will be documented at each clinic visit per Appendix C, Study Activities. Information regarding hospitalizations, emergency room visits, and physician office visits will be collected since the last study visit.

Patient Reported Outcomes (PRO)

Health-related quality of life and symptom assessments will be performed per Appendix C, Study Assessments using the EORTC QLQ-C30, the EORTC QLQ-LC13, and the European Quality of Life-5 Dimensions (EQ-5D-5L). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30)[13] is used as general cancer-specific instrument. The EORTC QLQ-C30 has 30 items and 5 functional domain scales: Physical, Role, Emotional, Social, and Cognitive; two items evaluate global quality of life. The EORTC QLQ-C30 core questionnaire can be supplemented by the additional lung module EORTC QLQ-LC13, resulting in a 43-item disease and cancer site-specific quality of life and symptom questionnaire. The EORTC QLQ-LC13 module items evaluate symptoms such as cough, haemoptysis, shortness of breath, sore mouth or tongue, dysphagia, tingling hands or feet, hair loss, and pain. The EuroQol 5 Dimensions 5 Level (EQ-5D-5L) is a generic preference instrument that has been validated in numerous populations. The EQ-5D-5L is composed of 5 questions and a visual analog scale (VAS) assessing overall health that can be converted into a single health status or "utility" score for use in an economic evaluation to adjust life-years gained by the subject's health-related quality of life.

Fluid Retention Questionnaire (Including Subject Daily Weight)

Throughout the treatment period as outlined in the Appendix C, Study Activities, subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix I, Fluid Retention Questionnaire). The assessments on Days 8, 15, 29, and 36 may take place by phone, with the site contacting the subject and reviewing the questionnaire.

Starting on Day 1 through the EOT visit, subjects will maintain a diary of daily weights (captured on the Fluid Retention Questionnaire). Subjects should be instructed to use a consistent device throughout the study. The site will advise subjects to contact the site in cases where sudden weight gain (5% or greater) is observed for possible assessment in the clinic.

Non-Treatment Cycle Visit

In order to establish 12 weeks of non-treatment after two dosing cycles, every third cycle of treatment should be omitted and a clinic visit conducted, as outlined in Appendix C, Study Activities. The visit should be performed after the Disease Response/Assessment has been conducted and reviewed by the Investigator. The subject should continue to complete the Fluid Retention Questionnaire, including conducting daily weight assessments, and the site should contact the subject weekly during this 42 day non-treatment cycle to review the questionnaire and assess for any adverse events or changes in concomitant medications. The following cycle of treatment may be resumed 42 days ± 3d if the subject has not met any reason for study treatment discontinuation as outlined in Section 5.4.

End of Treatment (EOT) Visit

The visit at which an investigator identifies disease progression or a subject meets other criteria for study treatment discontinuation will be considered the End of Treatment Visit. The EOT procedures should be done within 7 days of documented decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible. The

EOT visit is the last visit during the treatment phase before subjects begin the Post Treatment Follow Up and/or Survival Follow Up phase. The reason(s) for the discontinuation from study treatment will be recorded and assessments will be performed per Appendix C, Study Activities.

Disease/Response Assessment, CT/MRI of the brain (if applicable), and submission of scans to the CRAC, may be omitted if performed within the last 6 weeks.

Post-Treatment Follow Up

For all subjects 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 Disease Response/Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first. Refer to Appendix C, Study Activities for details of required assessments.

At disease progression, an optional collection of fresh tumor material may be conducted (Section 5.3.1.2, Collection and Handling of Biomarker and Optional Exploratory Research has details regarding Tumor Material at Time of Disease Progression).

Survival Follow Up (OS)

After disease progression or if subjects stop treatment and decline further study radiographic assessments prior to the endpoint of disease progression, subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis). If the subject withdraws from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations. Refer to Appendix C, Study Activities for details of required assessments.

5.3.1.2 Collection and Handling of Biomarker and Optional Exploratory Research Samples

Biomarker Samples

Blood, tumor material, and serosal fluid will be collected as noted in Appendix C, Study Activities and may be utilized to evaluate known and/or novel markers (nucleic acids, peptides/proteins and/or metabolites) of disease status, related conditions or to evaluate the association with pharmacokinetics, safety or efficacy. Samples will also be utilized for the development of Companion Diagnostics in conjunction with rovalpituzumab tesirine clinical development. The biomarker rationale is discussed in the Biomarker Research Variables Section (Section 5.3.6).

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual.

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

Tumor Material at Screening

For all subjects, tumor material representative of the qualifying malignancy must be submitted to a central laboratory for determination of DLL3 expression. An archived tumor specimen or fresh tumor material (obtained via on-study biopsy procedure if archival tumor specimen is unavailable) may be used for DLL3 expression evaluation by methods such as but not necessarily limited to immunohistochemistry (IHC). Additional analyses, such as routine hematoxylin and eosin for morphology, IHC for confirmation of diagnosis (e.g., for synaptophysin, chromogranin-A, or CD56), or scoring of immune infiltrates (e.g., IHC for CD3+, CD4+, CD8+, and Foxp3+ cells) may be performed.

Material may also be utilized for exploratory biomarkers research of drug sensitivity, resistance, or disease biology.

Blood (Plasma) for Inflammatory Markers and Circulating Tumor DNA (ctDNA)

At the indicated times noted in Appendix C, Study Activities, blood will be collected, processed to plasma for testing of inflammatory markers including erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), rheumatoid factor (RF), and ctDNA. On Day 1 (–3 day window is permitted) of each cycle, the collection will be pre-infusion. A sample will also be collected at the EOT or at the time of disease progression.

Blood (Serum) for Tumor and Soluble Markers

At the indicated times noted in Appendix C, Study Activities, blood will be collected, processed as serum for possible testing of tumor-specific biomarkers that may reflect disease burden such as but not necessarily limited to neuron-specific enolase (NSE) and biomarkers that may be related to the pharmacodynamics effects of rovalpituzumab tesirine such as but not necessarily limited to soluble DLL3, circulating chemokines, or cytokines such as vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), interleukin (IL)-6, or IL-8. Other biomarkers based on emerging science may also be assessed. On Day 1 (–3 day window is permitted) of each cycle, the collection will be pre-infusion. A sample will also be collected at the EOT or at the time of disease progression.

Blood for Circulating Tumor Cells

At the indicated times noted in Appendix C, Study Activities, blood samples will be collected for assessment and characterization of circulating tumor cells (CTCs) as a possible reflection of disease burden and DLL3 expression to study association with efficacy. Whole blood sample will be collected for CTC analysis at pre-dose on Cycle 1 Day 1 (–3 days window is permitted) and EOT only at specific sites based on feasibility.

Serosal Fluid

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

Pharmacogenetic Samples

A whole blood sample for DNA isolation will be collected on Cycle 1 Day 1 (pre-infusion) and End of Treatment Visit from each subject. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies.

Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Instructions for the preparation and shipment of the pharmacogenetic exploratory research samples will be provided in a laboratory manual.

Optional Exploratory Research Samples

Subjects will have the option to provide samples for exploratory research. Subjects may still participate in the main study even if they decide not to participate in this optional exploratory research.

AbbVie (or people or companies working with AbbVie) will store the exploratory research samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on rovalpituzumab tesirine (or drugs of this class) or this disease and related conditions continues, but for no longer than 20 years after study completion. The procedure for obtaining and documenting informed consent for exploratory research samples is discussed in Section 9.3.

Tumor Material at the Time of Disease Progression

An optional tumor material collection by biopsy procedure may be obtained at the time of disease progression, from subjects who consent to undergo biopsy procedure to better

understand mechanisms of resistance and expression of DLL3. Other nucleic acid or protein based biomarkers related to the response to rovalpituzumab tesirine and SCLC biology may be assessed.

Samples will be shipped to AbbVie or a designated laboratory for long-term storage. Instructions for the preparation and shipment of the biomarker exploratory research samples will be provided in a laboratory manual.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Approximately 6 mL of blood will be collected by venipuncture for pharmacokinetic (PK), Anti-therapeutic antibody (ATA), and neutralizing antibodies (nAb) testing as indicated in Appendix C, Study Activities. Two samples will be collected at each treatment cycle. The pre-infusion sample will be collected prior to dosing on Day 1 (–3 days window is allowed) and the second sample will be collected within 60 minutes post-infusion. Only one collection will be required at the Non-Treatment Cycle visit and EOT visit. Blood will be processed to serum and three aliquots generated, each containing approximately 0.8 mL of serum.

The date and time of each sample collected will be recorded to the nearest minute.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood/serum samples and subsequent preparation and storage of the samples for the assays will be provided by the central laboratory, AbbVie, or its designee.

5.3.2.3 Disposition of Samples

The frozen serum samples for the rovalpituzumab tesirine ADC, rovalpituzumab tesirine ADC ATA, and neutralizing antibodies (nAb) assays will be packed in dry ice sufficient to last during transportation and shipped from the study site to the central laboratory.

An inventory of the included samples will accompany the package and an electronic copy of the manifests (including subject number, study day, the time of sample collection and barcode) will be sent to the contact person at gprd_lupet@abbvie.com.

5.3.2.4 Measurement Methods

Serum concentrations of rovalpituzumab tesirine ADC and relative titers of rovalpituzumab tesirine ADC ATA will be determined using validated methods. Any additional related analytes may be analyzed using non-validated methods. Serum samples collected for the PK, ATA and nAb analysis may be used for future assay development or validation activities. Rovalpituzumab tesirine ADC nAb samples upon request may be used for the analysis of neutralizing anti-drug antibodies in a validated assay.

5.3.3 Efficacy Variables

5.3.3.1 Definition of Disease Progression

Disease progression will be defined as radiographic progression of disease by RECIST version 1.1. Refer to Appendix G, Response Evaluation Criteria for Solid Tumors (RECIST) version 1.1 for Tumor Response.[12] Effusions (pleural, pericardial, etc.) will contribute to disease response assessment only if confirmed malignant by cytology or otherwise clearly disease-related; if disease progression is suspected solely based on the appearance of new or increase of existing effusions, confirmation of malignant nature of such effusions is strongly recommended prior to making the decision on treatment discontinuation due to known adverse event profile of rovalpituzumab tesirine. If collected, effusion fluid must be tested centrally and/or locally for cytology if disease progression due to appearance/worsening of effusion is suspected.

5.3.3.2 Primary Variables

The primary endpoints are progression-free survival (PFS) determined by a Central Radiographic Assessment Committee (CRAC) per RECIST v. 1.1 and overall survival (OS) in $DLL3^{high}$ population.

5.3.3.3 Secondary Variables

The secondary variables are progression-free survival (PFS) determined by a Central Radiographic Assessment Committee (CRAC) per RECIST v. 1.1 and overall survival (OS) in randomized set population. Change in patient reported outcome (PRO) with physical functioning as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in randomized set population is also a secondary endpoint in this study.

5.3.3.4 Exploratory Variables

The exploratory variables are progression-free survival (PFS) based on investigator assessment, objective response rate (ORR) per the CRAC and investigator assessment, respectively, clinical benefit rate (CBR) per the CRAC and investigator assessment, respectively, and the duration of response (DOR) per the CRAC and investigator assessment, respectively. Response assessment will be based on RECIST v1.1. Changes in patient reported outcomes (PROs) as measured by EQ-5D-5L and all other PRO domains (except for physical functioning) as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13) are also exploratory endpoints in this study.

5.3.4 Safety Variables

AbbVie will assess adverse events, laboratory data, ECGs and vital signs throughout the study. Adverse events intensity and laboratory evaluation changes will be assessed by utilizing NCI CTCAE Version 4.0.[11]

During the conduct of the study, the AbbVie medical and safety team will be monitoring blinded, subject laboratory results and serious adverse event data as they are reported.

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

5.3.5 Pharmacokinetic Variables

Serum concentrations of rovalpituzumab tesirine ADC as well as the timing and incidence of ATAs will be tabulated and summarized.

5.3.6 Biomarker and/or Optional Exploratory Research Variables

Biomarker Research Variables

Blood, serosal fluid, and tumor material samples will be collected to conduct analyses to investigate biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites.

Tumor specimen and CTCs will be tested for DLL3 expression and analyses will be performed to correlate the expression levels to rovalpituzumab tesirine response.

Enumeration of CTCs, soluble DLL3 in plasma, or markers that are related to the disease or to drug response will be measured at baseline and post-treatment. The information learned from analyzing these samples may be used to investigate factors influencing response to treatment, pharmacodynamics, PK, safety, scientific questions related to SCLC, and/or in the development of new therapies and diagnostic tests. The results of biomarker testing may not be included with the study summary.

Whole blood for pharmacogenetic analysis may include but not be limited to DLL3, ASCL1, or NEUROD1.

Exploratory Research Variables

Optional samples may be collected to conduct exploratory investigations into known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. The samples may be analyzed as part of a multi-study assessment of factors influencing the subjects' response to the blinded investigational product (or drugs of the same or similar class) or the development and progression of the subjects' disease or related conditions. The samples may also be

used to develop new diagnostic tests, therapies, research methods or technologies. The results from these analyses are exploratory in nature and may not be included with the study report.

In the event a subject withdraws consent to participate from the study, stored biomarker samples will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research of samples, the subject may request for samples to be withdrawn. Once AbbVie receives the request, remaining samples will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain part of the overall research data.

5.4 Removal of Subjects from Therapy or Assessment

Each subject has the right to withdraw from study treatment at any time. In addition, the Investigator may discontinue a subject from the study treatment at any time for any reason if the Investigator considers it necessary. Each subject will be withdrawn from the study or study treatment (as applicable) per Section 5.4.1 if any of the following occur:

- The subject has radiographic progression according to RECIST v1.1 (with the exception of CNS-only progression).
- The subject requires cancer-directed radiotherapy or surgery related to clinical disease progression, or alternate anti-cancer agents during the study period. (Refer to Section 5.2.3.2.1, Allowed Concomitant Therapy for exceptions from this criterion).
- The subject experiences treatment toxicity which, in the Investigator's opinion, prohibits further therapy or the Investigator believes it is otherwise in the best interest of the subject.
- Subject is pregnant or begins breastfeeding during the treatment portion of the study.
- The subject decides to withdraw consent for any reason.
- Any other medical reason that AbbVie or the study Investigator deems appropriate.
- Significant non-compliance to the protocol.

Discontinued subjects will not be replaced.

5.4.1 Discontinuation of Individual Subjects

When subject discontinuation from study treatment (without reaching a protocol-defined endpoint) is planned, the Investigator is to notify the AbbVie Therapeutic Area Medical Director (TA MD) or the clinical team representative (Section 7.0) via telephone as soon as possible (provided, in each case, subject care and safety are not compromised). If not notified prior to discontinuation, the AbbVie TA MD may contact the site to discuss the reason for withdrawal from the study.

The visit at which an investigator identifies disease progression or a subject meets other criteria for study treatment discontinuation will be considered the End of Treatment Visit. The reason(s) for the discontinuation from study treatment will be recorded and assessments will be performed per Appendix C, Study Activities. It is preferable that End of Treatment Visit procedures be conducted prior to the initiation of another anti-cancer therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition.

If a subject is discontinued with an ongoing adverse event or an unresolved clinically significant laboratory result, the site will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory results or adverse event is achieved.

Subjects no longer undergoing clinical assessments will have survival information collected at every 6 weeks (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first.

In the event that a positive result is obtained on a pregnancy test for a subject during the study, the administration of blinded investigational product to that subject must be

discontinued immediately. The site must report the positive pregnancy test result by completing the appropriate eCRF within 24 hours of becoming aware of the pregnancy.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will notify the investigator and provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

Rovalpituzumab tesirine, the investigational agent under study in this protocol, is an ADC. All subjects randomized will receive premedication consisting of dexamethasone/placebo orally (PO) at 8 mg twice daily on Day –1, Day 1 (the day of dosing), and Day 2 of each cycle in which rovalpituzumab tesirine/placebo is administered. Dexamethasone/placebo dosing should occur such that there are approximately 12-hours (i.e., 10 – 14 hours) between AM and PM doses. The first dose of the dexamethasone/placebo on the day of dosing should be at least 30 minutes but no more than 4 hours prior to the rovalpituzumab tesirine/placebo infusion. If the dose of dexamethasone/placebo is vomited within 15 minutes of taking the medication, the subject should retake the medication.

In the event that a subject arrives for rovalpituzumab tesirine/placebo administration on Day 1, but has not taken any or all required dexamethasone/placebo doses on Day –1 and/or Day 1, rovalpituzumab tesirine/placebo administration may not proceed, and rovalpituzumab tesirine/placebo will be held until the required dexamethasone/placebo dosing has occurred.

5.5.2 Identity of Investigational Product(s)

Table 3. Identity of Investigational Products

Investigational Product	Rovalpituzumab Tesirine	Placebo for Rovalpituzumab Tesirine	Dexamethasone*	Placebo for Dexamethasone
Dosage Form	Powder for solution for infusion in vials	Powder for solution for infusion in vials	Capsules	Placebo capsules
Strength	10 mg/ml when reconstituted with 3.2 ml of sterile water for injection	N/A	8 mg	N/A
Route of Administration	Intravenous	Intravenous	Oral	Oral

* Commercially-available Dexamethasone tablets are over-encapsulated to maintain study blinding.

AbbVie will supply rovalpituzumab tesirine/placebo and dexamethasone/placebo.

Each site will be responsible for maintaining drug accountability records, including product description, manufacturer, and lot numbers for all investigational products dispensed by the site.

5.5.2.1 Packaging and Labeling

Rovalpituzumab Tesirine and Placebo

Vials of rovalpituzumab tesirine/placebo will be packaged in cartons. Each vial and carton will be labeled per country requirements. Labels must remain affixed to the vial and carton. Rova-T drug product is classified as a Dangerous Goods/Hazardous Material and is packaged and shipped by AbbVie according to US Department of Transportation (DOT) and International Air Transport Association (IATA) certified regulations.

Dexamethasone and Placebo

Dexamethasone/placebo will be packaged in high-density polyethylene (HDPE) bottles according to the study needs. The bottles will be labeled per country requirements. Labels must remain affixed to the containers.

5.5.2.2 Storage and Disposition of Blinded Investigational Product(s)

For all storage areas and refrigerators, temperature logs will be maintained to document proper storage conditions. The temperature must be recorded on the temperature logs to verify proper function on each business day. Temperature excursions must be reported to AbbVie immediately.

Sites should use the AbbVie Temperature Excursion Management System (ATEMS) module via IRT, if available, or fax copies of the temperature log indicating the extent of the excursion (time, duration of the temperature excursion, min/max values and study drugs affected) to AbbVie Clinical Drug Supply Management (CDSM) including the Storage Temperature Excursion Reporting Form.

In case of a temperature excursion, study medication should be quarantined and not dispensed until AbbVie CDSM or ATEMS deems the medication as acceptable.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the destruction facility.

Rovalpituzumab Tesirine/Placebo

Rovalpituzumab tesirine/placebo must be stored refrigerated at 2° to 8°C (36° to 46°F), protected from light, and must not be frozen. Specific storage conditions for reconstituted and diluted rovalpituzumab tesirine/placebo will be provided in a separate document outside of this protocol.

Dexamethasone/Placebo

Dexamethasone/placebo should be stored at 15° to 25°C (59° to 77°F) and protected from light. For Australia, dexamethasone/placebo should be stored below 25°C and protected from light.

5.5.2.3 Preparation/Reconstitution of Dosage Form(s)

Both rovalpituzumab tesirine and matching placebo will be supplied as a lyophilized powder in a vial. Each vial of rovalpituzumab tesirine or placebo will be reconstituted with 3.2 mL of sterile water for injection. When reconstituted, vial of rovalpituzumab tesirine will contain 10 mg/mL (30 mg total per vial). The rovalpituzumab tesirine drug product is dosed based on actual body weight. The contents of two or more vials of reconstituted drug product may be required to accomplish the desired dose. The total volume administered treatment arm will be dependent upon the assigned dose. The rovalpituzumab tesirine drug product and placebo solution(s) will be administered via intravenous (IV) infusion. Rovalpituzumab tesirine drug product and placebo solution(s) will be added to 50 mL or 100 mL of 0.9% normal saline with an infusion over 30 minutes (20 – 45 minute infusion window). The rate should be adjusted based on patient tolerability. Specific dose preparation and documentation details will be provided to the site pharmacy in a separate document. A complete description of the chemistry and formulation may be found in the Investigator's Brochure.[14]

5.5.3 Method of Assigning Subjects to Treatment Arms

All subjects in the study will be randomized using an IRT system. Before the study is initiated, directions for the IRT will be provided to each site. The site will contact the IRT to obtain a Screening (subject) number once the subject has signed the informed consent and a study-specific procedure has been performed (i.e., central laboratory samples drawn). Once the screening number is assigned, if the subject is not randomized into the study, the reason for screen failure will be documented in the source document and in the eCRF. For others, the site will access the system and a unique randomization number will be provided.

The IRT will randomize subjects in a 1:1 ratio, with one-half of the subjects being randomized to the rovalpituzumab tesirine treatment arm and the other one-half to the placebo arm. The stratification factors used for the randomization should be the last values on or prior to the date of randomization.

5.5.4 Selection and Timing of Dose for Each Subject

5.5.4.1 Dosing

Dosing is based on actual body weight of the subject to the nearest kilogram, assessed in the clinic prior to dosing at each cycle, and administered according to the calculated dose. In cases of weight gain due to fluid retention, dosing should be based on most recent pre-fluid retention actual weight.

Subjects must meet all of the following criteria on each dosing day before receiving blinded investigational product:

- Absolute neutrophil count (ANC) ≥ 1,000/μL
- Platelet count ≥ 75,000/μL
- Resolution of blinded investigational product-related AEs, including findings indicative of pleural or pericardial effusions, and clinically-significant laboratory abnormalities to Grade 0 or 1 (excluding ANC and alopecia), or to baseline grade.

5.5.4.2 Dose Modifications

5.5.4.2.1 Dose Treatment Delays due to Toxicity or Progression

Subjects who experience blinded investigational product-related toxicity during a cycle must have recovered as specified above before the next cycle may proceed. Any dose modifications except those indicated as mandatory below (including dose delay, reduction, resumption, and discontinuation) are to be performed at the discretion of the Investigator. Further guidelines suggesting dose modifications based on prior studies of rovalpituzumab tesirine are provided in Section 5.5.4.2.2, Dose Reduction Guidelines.

In cases of treatment delays of > 28 days, the TA MD should be contacted regarding the subject's continuation of treatment.

In the event of isolated CNS-only progression during study treatment, blinded investigational product will be withheld while local treatment is administered (e.g., radiotherapy) in accordance with institutional practice. Blinded investigational product may be restarted 1 week after the completion of local CNS disease-directed therapy. If more than 6 weeks have elapsed since the previous radiographic tumor assessment, the subject must undergo a radiographic tumor assessment to evaluate extra-cranial disease status prior to resuming blinded treatment. If additional sites of PD are present, the subject will be required to discontinue blinded investigational product.

5.5.4.2.2 Dose Reduction Guidelines

Blinded investigational product dose reductions and discontinuation of blinded investigational product for specific toxicities should occur as outlined in Table 4, Dose Reductions for Blinded Investigational Product (IP) and Table 5, Dose Reductions and Discontinuation for Unacceptable Toxicities. Dose reductions for unacceptable toxicities described in Table 5 are mandatory. Reduced dose levels are described in (Table 4). Generally, if unacceptable toxicity recurs after two dose reductions, treatment will be discontinued (for further details, refer to Table 5). If the blinded investigational product dose is reduced, no re-escalation will be allowed. If different unacceptable toxicities occur in sequential treatment cycles (e.g., Grade 3 LFT after the first dose and Grade 3 thrombocytopenia lasting more than 7 days after the second dose), dose reduction will proceed to the next lower dose level. If different unacceptable toxicities occur within one cycle, maximum specified dose reduction will be implemented. Dose reductions and discontinuation are not planned for dexamethasone/placebo. If full dose of dexamethasone/placebo cannot be administered due to an AE, the blinded infusion should be delayed until dexamethasone/placebo can be administered.

Exceptions to the dose modification guidelines should be discussed with the TA MD prior to implementation.

Details of toxicity management are further outlined in Section 6.1.8, Toxicity Management.

Table 4. Dose Reductions for Blinded Investigational Product (IP)

Starting Dose	First Dose Reduction (Reduce Dose)	Second Dose Reduction (Reduce Dose)
0.3 mg/kg	0.2 mg/kg	0.1 mg/kg

Table 5. Dose Reductions and Discontinuation for Unacceptable Toxicities

Toxicity[a]	First Occurrence	Second Occurrence
Grade 3 thrombocytopenia lasting more than 7 days	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 4 thrombocytopenia/Grade 3 thrombocytopenia with bleeding/Need for platelet transfusion	Reduce dose to 0.1.mg/kg	Discontinue Blinded IP
Grade 4 neutropenia lasting more than 7 days	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 3 febrile neutropenia	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 4 febrile neutropenia	Reduce dose to 0.1.mg/kg	Discontinue Blinded IP
Grade 3 Liver Function Tests (LFTs)	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 4 LFTs or Grade 3 LFTs with concomitant Bilirubin Grade 2 or higher[b]	Reduce dose to 0.1.mg/kg	Discontinue Blinded IP
Potential DILI (Drug-induced liver injury)	See Section 6.1.8.3	See Section 6.1.8.3
Grade 3 or 4 hypoalbuminemia	Reduce dose to 0.1 mg/kg	Discontinue Blinded IP
Any other Grade 3 or 4 laboratory abnormality considered clinically significant and treatment-related	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg
Grade 2 serosal effusions or edema	Reduce to 0.2 mg/kg	Reduce to 0.1 mg/kg
Grade 3 serosal effusions or edema or Grade 2 capillary leak syndrome	Reduce dose to 0.1.mg/kg	Discontinue Blinded IP
Grade 4 serosal effusions or edema or Grade ≥ 3 capillary leak syndrome	Discontinue Blinded IP	N/A
Grade 3 photosensitivity reaction	Reduce dose to 0.2 mg/kg See Section 6.1.8.2	Reduce dose to 0.1 mg/kg See Section 6.1.8.2
Grade 4 photosensitivity reaction	Discontinue Blinded IP	N/A
Grade 2 pneumonitis	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade ≥ 3 pneumonitis	Discontinue Rova-T	N/A
Any other Grade 3 or Grade 4 non-laboratory treatment-related toxicity with the exception of fatigue, asthenia, nausea, or other manageable constitutional symptom	Reduce dose to 0.2 mg/kg	Reduce dose to 0.1 mg/kg

a. Refer to Appendix H, CTCAE v 4.0 Grading of Relevant AEs for definitions of NCI-CTCAE severity grades and for definition of serosal effusions and edema.

b. If potential DILI is suspected please follow guidelines of Section 6.1.8.3.

5.5.5 Blinding

5.5.5.1 Blinding of Investigational Product

AbbVie, the Investigator, the study site personnel, and subject will remain blinded to each subject's treatment with rovalpituzumab tesirine or placebo and dexamethasone or placebo and throughout the course of the study.

The IRT system will provide access to blinded subject treatment information during the study. AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)

An Independent Data Monitoring Committee (IDMC) will be formed and constituted according to appropriate regulatory guidelines. The IDMC will review the unblinded data from the study with respect to subject accrual, pretreatment characteristics of accrued subjects, the frequency and severity of toxicities and morbidity, and provide recommendations according to the charter. Detailed information regarding the composition of the committee and procedures including frequency of meetings and scope of reviews will be documented in a separate charter. For the futility analysis, OS, other efficacy and safety data will be analyzed and reviewed by the IDMC for recommendation.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense blinded investigational product only to subjects randomized in the study in accordance with the protocol. The blinded investigational product must not be used for reasons other than that described in the protocol.

Blinded investigational product administration must be performed by study site staff and documented in source documents and the eCRF.

5.5.7 Drug Accountability

The site will record the dose of rovalpituzimab tesirine/placebo and dexamethasone/placebo given to each subject in the source documents and on the eCRF.

Upon receipt of a shipment of rovalpituzimab tesirine/placebo and dexamethasone/placebo, the representative at each site will (1) open and inspect the shipment; (2) verify that the rovalpituzimab tesirine/placebo has been received intact, in the correct amounts and at the correct address; (3) sign and date the Proof of Receipt (POR) or similar documentation accompanying the shipment; (4) register the shipment as received via the IRT. All blinded investigational products must be retained in the designated secure area under proper storage conditions. This will be documented by signing and dating the Proof of Receipt (POR) or similar document or via direct recording in the IRT.

An overall accountability of the blinded investigational product will be performed and verified by the site monitor throughout the study and at the study site closeout visit. An accurate running inventory of rovalpituzimab tesirine/placebo and dexamethasone/placebo will be maintained utilizing the IRT drug accountability module and, if required, according to your institutional policy and will include the lot number, POR number(s), the bottle/kit numbers, and the date blinded investigational product was dispensed for each subject.

Upon completion or termination of the study, all original bottles/cartons containing unused rovalpituzimab tesirine/placebo and dexamethasone/placebo (empty containers will be defaced and discarded on site) will be returned to the Destruction Facility according to AbbVie's instructions, or if pre-arranged between the sponsor and site, destruction of used and unused bottles will be performed at the site. Rova-T is classified as a Dangerous Good/Hazardous Material according to US Department of Transportation (DOT) and International Air Transport Association (IATA). Dangerous Goods/Hazardous Materials must be packaged and shipped according to applicable regulations.

The study Investigator or his/her designated representative agrees not to supply study medication to any persons not enrolled in the study or not named as a sub-investigator listed on the FDA 1572 or Investigator Information and Agreement (IIA) form.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

Phase 1 data described in Section 3.0 and proposed mechanism of action suggest that rovalpituzumab tesirine may improve outcome of SCLC patients by extending clinical benefit following first-line platinum-based chemotherapy. This randomized, double-blind, placebo controlled phase 3 study will evaluate the effect of rovalpituzumab tesirine as maintenance therapy following first-line platinum-based chemotherapy of extensive stage SCLC. Primary endpoints of PFS and OS are well established in solid tumor trials and in SCLC specifically.

A randomized, double-blind, placebo controlled study such as described here is optimal for assessing the treatment effect of rovalpituzumab tesirine versus current standard, best supportive care to a current standard treatment (placebo is required to allow for blinding).

5.6.2 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 4.0.[11]

Response will be assessed according to RECIST v1.1,[12] 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 blinded investigational product. Pharmacokinetic assessments for drug activity are also common in clinical studies.

5.6.3 Suitability of Subject Population

Although response rates to first-line chemotherapy remain high with platinum-based regimens, time to disease recurrence is short in extensive-stage SCLC. Rovalpituzumab tesirine has demonstrated anti-tumor activity in relapsed/refractory SCLC population. Exploring rovalpituzumab tesirine in ED SCLC subjects with stable disease or objective response following first-line chemotherapy is acceptable considering observed activity/toxicity profile of rovalpituzumab tesirine, and that the standard approach in this setting is no treatment until progression.

5.6.4 Selection of Doses in the Study

In a recent Phase 1 study (SCRX16-001) with rovalpituzumab tesirine, the maximum tolerated dose (MTD) was established at 0.4 mg/kg every 3 weeks based on the incidence of Cycle 1 toxicities, while the recommended Phase 2 dose (RPTD) in SCLC was chosen as 0.3 mg/kg every 6 weeks for a total of two doses with the allowance to retreat at the same dose level and schedule upon progression. The RPTD is based on the toxicity and efficacy profile during multiple cycles dosing (AbbVie Stemcentrx data on file). This experience included multiple doses of rovalpituzumab tesirine at a) 0.2 mg/kg every 6 weeks, b) 0.3 mg/kg every 6 weeks or c) 0.3 mg/kg every 6 weeks for a total of two doses and then at 0.1 mg/kg every 6 weeks thereafter. Based on the totality of the experience with rovalpituzumab tesirine and taking into consideration its pharmacokinetic characteristics, dosing of 0.3 mg/kg q6wk for 2 cycles, omitting every third cycle will be used in this study. This study will not exceed a maximum dose of 1.5 mg/kg at each dose.

6.0 Complaints

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

The investigational product in this study is defined as rovalpituzumab tesirine or placebo and dexamethasone or placebo. Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For AEs, please refer to Sections 6.1.1 through 6.1.6. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

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

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

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

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

Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol specific criteria (see Section 6.1.8 regarding toxicity management) and/or if the investigator considers them to be adverse events.

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

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

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

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as an SAE within 24 hours of the site being made aware of the SAE:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an

	outpatient facility or hospitalization for respite care.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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

6.1.1.3 Adverse Events Expected Due to SCLC or Progression of SCLC

Adverse events that may be expected from primary SCLC lesions, compression of adjacent thoracic structures or distant metastases are presented in Appendix J, Adverse Events Expected Due to SCLC or Progression of SCLC of the protocol.

These adverse events may occur alone or in various combinations and are considered expected adverse events in SCLC subjects.

Although exempted from expedited reporting to Health Authorities and Institutional Review Boards (IRBs) as individual cases, these SAEs must be reported to the Sponsor within 24 hours of the site being made aware of the SAE.

AEs or SAEs should not be reported as "Disease progression," even if fatal, as PD is an efficacy endpoint for the study. Rather, report the specific disease (clinical) manifestation of the progression (eg, 'malignant pleural effusion,' 'spinal bone metastases,' 'lymphadenopathy,' 'brain metastases') or if not possible, report "malignant neoplasm progression" as the AE or SAE as appropriate.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4.0).[11] If a reported adverse event **increases** in severity, the initial adverse event should be given an outcome date and a new adverse event reported on a different date from the end date of the previous adverse event to reflect the change in severity. For all reported serious adverse events that increase in severity, the supplemental eCRFs also need to be updated to reflect the change in severity.

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

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

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of blinded investigational products:

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

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

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

6.1.4 Deaths

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

Deaths that occur during the protocol specified AE reporting period (Section 6.1.6) that are more likely related to disease progression will therefore be considered as an expected SAE and will not be subject to expedited reporting. These events should be recorded on the AE eCRF as described in Section 6.1.1.3. After the AE reporting period, deaths attributed to progression of disease under study should not be recorded on the AE eCRF.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the AE eCRF. Generally, only one such event should be reported. The term "sudden death" should only be used for the occurrence of an abrupt and unexpected death

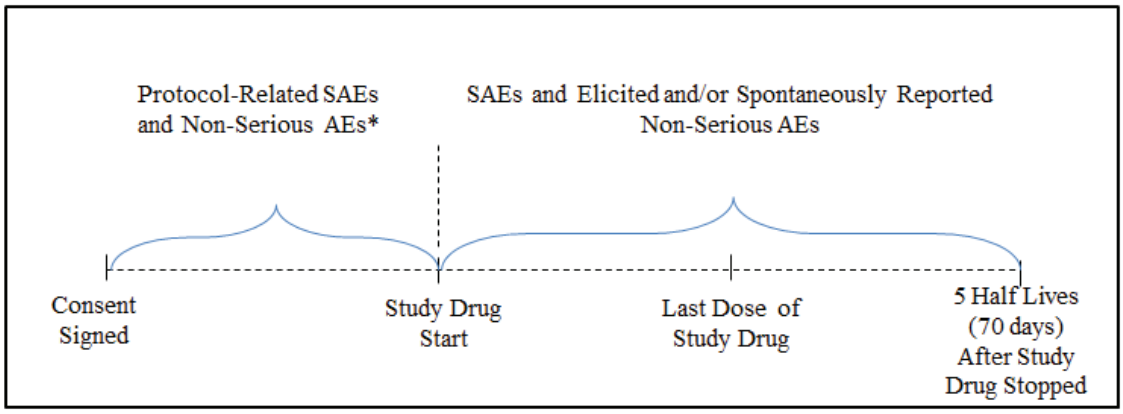
due to presumed cardiac causes in a patient with or without pre-existing heart disease, within 1 hour of the onset of acute symptoms or, in the case of an unwitnessed death, within 24 hours after the patient was last seen alive and stable. If the cause of death is unknown and cannot be ascertained at the time of reporting, "unexplained death" should be recorded on the AE eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of death.

6.1.5 Adverse Event Collection Period

All adverse events reported from the time of blinded investigational product administration until 70 days following the last dose of blinded investigational product will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related serious adverse events and non-serious adverse events will be collected from the time the subject signed the study-specific informed consent, only if considered by the Investigator to be causally related to study-required procedures.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



* Only if considered by the Investigator to be causally related to study-required procedures.

6.1.6 Adverse Event Reporting

In the event of a serious adverse event, whether associated with blinded investigational product or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: [redacted]

FAX to: [redacted]

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

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

Office:
Email: [redacted]

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
Senior Medical Director
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

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

Phone: [redacted]

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

In Japan, the principal investigator will provide documentation of all serious adverse events to the Director of the investigative site and the Sponsor.

6.1.7 Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 24 hours of the investigative site becoming aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.4).

All subjects should be informed that contraceptive measures (refer to Section 5.2.4, Contraception Recommendations and Pregnancy Testing for the details on contraception) should be taken throughout the study and for at least 6 months after the last dose of study drug. Male subjects should be informed that contraceptive measures should be taken by their female partner.

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected. In the event of a pregnancy occurring in the partner of an enrolled subject, written informed consent for release of medical information from the partner must be obtained prior to the collection of any pregnancy-specific information, and the pregnancy will be followed to outcome.

Pregnancy in a study subject is not considered an adverse event. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.1.8 Toxicity Management

Subjects will be monitored continuously for toxicity while on study treatment. Toxicity will be assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.0.[11] If a subject has an AE possibly related to blinded investigational product administration, then dose interruptions/holds with possible modifications as described below may be implemented. Adjustments to these guidelines may occur based on the clinical judgment of the investigator with notification to the TA MD. Dose modifications for toxicities as described in Section 5.5.4.2.2 are mandatory.

6.1.8.1 Management of Serosal Effusions/Serositis

Serosal effusions (pleural or pericardial, or ascites) have been observed with rovalpituzumab tesirine and have the potential to be life-threatening (e.g., cardiac 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. When appropriate, a unifying diagnosis should be reported, e.g., "heart failure," not the signs and symptoms "pleural effusion" and "edema limbs." Effusion events were reported during treatment and may occur up to several months after last Rova-T dose. As a result, subjects should be advised of signs and symptoms of fluid retention and contact treating physician if they arise during this time.

When considered clinically significant (e.g., Grade 2 or higher and considered related to blinded investigational product):

- Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases. The Investigator should consider a tapering regimen, such as dexamethasone up to 8 mg orally twice a day for 5 days, followed by 4 mg orally twice a day for 5 days, then 2 mg orally twice a day for 5 days. Alternatively, nonsteroidal therapies for serositis may be considered, such as non-steroidal anti-inflammatory drugs (NSAIDs, e.g., ibuprofen 400 – 600 mg orally 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 Section 5.5.4.2.

6.1.8.2 Management of Skin Reactions

All cutaneous reactions which develop during treatment warrant prompt evaluation. Skin toxicity with rovalpituzumab tesirine may consist of photosensitivity but possibly other reactions such as palmar-plantar erythrodysesthesia or erythema multiforme. As such,

development of a cutaneous reaction during treatment warrants prompt evaluation by the Investigator or designee.

Photosensitivity reactions may occur hours to days after sun exposure. Patients should be advised to avoid direct and indirect sun exposure as much as possible from Cycle 1 Day 1 until 30 days after the final dose. When sun exposure is unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). Thirty-one to ninety days after last dose of Rova-T/placebo, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher. Subjects with a grade 3 photosensitivity reaction should dose reduce Rova-T/placebo to 0.2 mg/kg after the first occurrence and following a second grade 3 photosensitivity reaction, reduce Rova-T/placebo to 0.1 mg/kg. Subjects with a grade 4 photosensitivity reaction must permanently discontinue Rova-T/placebo.

If clinically consistent with photosensitivity, the AE should be reported as such (using medically accurate and descriptive AE terminology), and managed as described in Table 6.

Photo-documentation of skin toxicity should be available upon request by the TA MD. The investigative site will take measures to protect the identity of the patient. These measures include taking the photograph very close to the affected skin region to exclude facial features, or if facial features cannot be excluded due to the location of the skin reaction, covering identifying features (such as the eyes) with a black rectangle.

Formal evaluation by a dermatologist, including possible skin biopsy to rule out alternative etiologies such as erythema multiforme, which may warrant discontinuation of blinded investigational product, and to facilitate the most appropriate terminology for AE reporting.

All events of cutaneous toxicity should be monitored until resolution or return to baseline. Recommendations for management of photosensitivity reactions are outlined in Table 6.

Table 6. Recommended Management of Photosensitivity

	CTCAE v4.0	Treatment Recommendations	Dose Modifications
Grade 1	Painless erythema and erythema covering < 10% BSA	Low-potency topical steroid (face) High-potency topical steroid (body)	–
Grade 2	Tender erythema covering 10 – 30% BSA	Low-potency topical steroid (face) High-potency topical steroid (body) Nonsteroidal anti-inflammatory agents orally as needed	–
Grade 3	Erythema covering > 30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Low-potency topical steroid (face) High-potency topical steroid (body) Prednisone 0.5 mg/kg × 7 days	Reduce dose
Grade 4	Life-threatening consequences; urgent intervention indicated	Low-potency topical steroid (face) High-potency topical steroid (body) Prednisone 0.5 mg/kg × 7 days Hospitalization	Discontinue

In order to simplify the collection of detailed Safety Data associated with dermatological issues, prior to the verification of a specific diagnosis the general term of "Skin Toxicity" should be recorded on the Adverse Event eCRF and the corresponding details should be captured on the Skin Toxicity Supplemental eCRF (as outlined in the form). Once a final dermatological diagnosis is verified, the AE eCRF should be updated to reflect the specific diagnosis.

6.1.8.3 Management of Potential Drug-Induced Liver Injury

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

A potential DILI is defined as:

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

In general, an increase of AT to > 3 × ULN should be followed by repeat testing within 48 – 72 hours of all four of the usual measures (ALT, AST, alkaline phosphatase, and total bilirubin) to confirm the abnormalities and to determine if they are increasing or decreasing. An 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. All data must be recorded in the CRF. If symptoms persist or repeat testing shows AT > 3 × ULN for subjects with normal baseline measures or 2-fold increases above baseline values for subjects with elevated values before drug exposure, close observation should be initiated. If close monitoring is not possible, blinded investigational product 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 trial drug has been discontinued and the subject is asymptomatic.
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets

- Ruling out acute viral hepatitis types A, B, C, D, and E; autoimmune or alcoholic hepatitis; non-alcoholic steatohepatitis (NASH); hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtaining a history of exposure to environmental chemical agents
- Obtaining additional tests to evaluate liver function, as appropriate (e.g., international normalized ratio [INR], direct bilirubin)
- Considering gastroenterology or hepatology consultations

Blinded investigational product will be discontinued if potential DILI is suspected and:

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

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

Any hepatic related adverse event should be recorded and the Hepatic Adverse Event eCRF triggered from the Adverse Event page.

6.1.8.4 Monitoring and Management of Edema

The majority of the edema events with rovalpituzumab tesirine have been reported as low grade 1 or 2 (mild or moderate); however, a small number of fatal events of generalized edema have been reported with rovalpituzumab tesirine. Physical exams and monitoring of weight gain and signs or symptoms of fluid retention should be conducted during treatment. Edema events were reported during treatment and may occur up to several months after last Rova-T dose. As a result subjects should be advised of signs and symptoms of fluid retention as well as monitor their weight and contact treating physician if they arise during this time.

Consistent with institutional guidelines or standard practice, the use of diuretics with or without albumin may be considered in subjects with clinically significant edema and hypoalbuminemia. The selection and use of diuretics in subjects should be based on individual clinical characteristics and include monitoring of electrolyte status and signs or symptoms of intravascular volume depletion such as hypotension and impaired renal function.

Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases.

Reported Term	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Generalized edema (Anasarca)	Noted on exam; 1+ pitting edema	Interfering with instrumental ADLs; oral therapy initiated	Interferes with self care ADL; intravenous therapy indicated; skin breakdown	Life-threatening consequences
Definition: A disorder characterized by fluid accumulation in the tissues of the body including the skin.				
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.				
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	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities				

6.1.8.5 Pneumonitis

Pneumonitis has been infrequently reported with rovalpituzumab tesirine but has resulted in fatal outcomes. Although the causal role of rovalpituzumab tesirine could not be ruled out, the reports of pneumonitis had one or more confounders including underlying pulmonary disease/cancer, prior thoracic radiation, prior cytotoxic chemotherapy or clinical evidence suggestive of an alternative diagnosis including pneumonia.

Heavily pretreated SCLC patients and patients with a history of pneumonitis may be at increased risk, and careful monitoring for signs and symptoms of pneumonitis is important. The risk of pneumonitis is increased with prior radiation to lung.

In general, signs and symptoms coinciding with or preceding pneumonitis may include new or worsening cough, chest pain and/or shortness of breath, fever, and radiographic changes (reticular markings, ground glass opacities). Protocol defined disease assessments provide the opportunity for on study pulmonary monitoring with "gold standard" diagnostic method for detection of pneumonitis. The protocol allows for additional imaging per physician discretion for signs and symptoms of pulmonary toxicity.

The diagnosis of drug induced pneumonitis is one of exclusion. Other etiologies including infection, which is a common cause of pulmonary infiltrates with clinical and radiographic appearance similar to drug-induced pneumonitis, need to be carefully considered and excluded before the diagnosis of drug induced pneumonitis can be established.

If pneumonitis is suspected, close monitoring including additional laboratory and imaging investigation per institutional guidelines may be necessary. Systemic corticosteroids may be beneficial for rapidly progressive or more severe pneumonitis. For events of Grade 1 pneumonitis close monitoring is recommended; while dose modifications for Grade 2 and discontinuation of Rova-T for Grades 3 and 4 are required. Please see Table 5.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product.

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

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

6.2.2 Reporting

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

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

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

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s):

Primary Contact:

[redacted]
Study Project Manager II
AbbVie Corporation
8401 Trans-Canada Highway
Saint-Laurent, Québec
H4S 1Z1
Canada

Phone: [redacted]
Fax:
Email:

Alternate Contact:

[redacted]
Study Project Manager I
AbbVie s.r.o.
METRONOM BUSINESS CENTER
Bucharova 2817/13, Stodulky,
158 00 Praha 5
Czech Republic

Phone: [redacted]
Fax:
Email:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

In Japan, the Investigator will record all protocol deviations in the appropriate medical records at site.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

This section describes the planned statistical analyses to be performed using data captured according to this protocol. A complete statistical analysis plan (SAP) describing in more detail all planned analyses will be finalized prior to database lock.

The primary endpoints of OS and progress free survival (PFS) assessed by a Central Radiographic Assessment Committee (CRAC) according to RECIST v1.1 in DLL3^{high} patients will be analyzed at the same time after observing at least 319 OS events. It is expected at approximately 420 PFS events will be observed at the time of the primary analysis.

The following analysis sets are considered:

- **DLL3^{high} Set:** It includes all randomized subjects with DLL3^{high} ED SCLC. Subjects will be classified according to the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The DLL3^{high} set will be the analysis set for the analysis of the primary efficacy endpoints of OS and PFS. All the exploratory efficacy endpoints will be analyzed based on the DLL3^{high} set unless the OS and PFS based on the randomized set are statistically significant.
- **Randomized Set:** It includes all randomized subjects, with subjects grouped according to the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The randomized set will be the analysis set for key secondary efficacy endpoints of OS and PFS, and key secondary endpoint of EORTC QLQ-C30 physical functioning domain. All the exploratory efficacy endpoints will be analyzed based on the randomization set if the OS and PFS based on the randomization set are statistically significant.
- **Per Protocol Set:** It includes all subjects in the randomized set without any major protocol violations which may affect the evaluation of the primary

efficacy endpoint. Major protocol violations will be defined in the SAP prior to the database lock. Subjects will be classified according to treatment assigned at the time of randomization. The per protocol set will be used for supportive analysis of efficacy endpoints.

- **Safety Set:** It includes all subjects who received at least one dose of study drug and subjects will be classified according to treatment received. Thus a subject who is randomized to the rovalpituzumab tesirine arm but does not receive rovalpituzumab tesirine will be considered in the placebo arm for safety analysis. Dexamethasone treatment will not be taken into consideration for subjects' classification in the Safety set.
- **Pharmacokinetic-Evaluable Set:** It consists of all subjects who receive at least one dose of study drug, with subjects classified according to the actual treatment received. A baseline measurement and at least one blood sample following a dose of study treatment is required for inclusion in this analysis.

8.1.1 Disposition of Study Subjects

The disposition of subjects will be summarized by treatment arm in the randomized set. The subject disposition includes the number of subjects for whom study drug was permanently discontinued (including the reasons for discontinuation), and the number of subjects who discontinued early from the study.

8.1.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized in the DLL3^{high} set and randomized set.

8.1.3 Efficacy Endpoints and Analyses

Assessment of response and progression will be determined by the CRAC according to RECIST v1.1.

8.1.4 Primary Efficacy Endpoints

Progression-free survival (PFS) and overall survival (OS) in subjects with DLL3^{high} ED SCLC are the two primary efficacy endpoints.

PFS will be defined as the number of months from randomization to disease progression, as assessed by the CRAC per RECIST v1.1, or death of any cause, whichever occurs first. Disease progression and censoring rules will be based on published conventions.[15] If a subject neither experienced disease progression nor died, then the data will be censored at the last date of post-baseline radiographic assessment. If a subject with no post-baseline assessment did not experience disease progression nor died, then the data will be censored at the date of randomization.

Differences between the treatment arm and the placebo arm in PFS will be assessed by a log-rank test stratified by the randomization stratification factors, testing the null hypothesis (rovalpituzumab tesirine arm is not superior to placebo arm in PFS). The hazard ratios of the treatment arm over the placebo arm will be calculated by a Cox's proportional hazards regression model adjusting for the main-effects of the stratification factors. Median PFS and 95% confidence intervals will be estimated using Kaplan-Meier survival methodology, with the Kaplan-Meier survival curves presented to provide a visual description. PFS rates at 3, 6, 9, and 12 months after randomization with 95% confidence intervals will be reported. Estimates of the treatment effect will be expressed as hazard ratio including 95% confidence intervals estimated through a Cox proportional-hazards regression model adjusting for the main-effects of the stratification factors.

Overall survival will be defined as the number of months from randomization to death of any cause. OS and censoring rules will be based on published conventions.[15] If a subject has not died, the data will be censored at the last date documented to be alive.

Differences between the treatment arm and the placebo arm in OS will be assessed by a log-rank test stratified by the randomization stratification factors, testing the null hypothesis (rovalpituzumab tesirine arm is not superior to placebo arm in OS). The

hazard ratios of the treatment arm over the placebo arm will be calculated by a Cox's proportional hazards regression model adjusting for the main-effects of the stratification factors. Median OS and 95% confidence intervals will be estimated using Kaplan-Meier survival methodology, with the Kaplan-Meier survival curves presented to provide a visual description. OS rate at 6, 12, 18, and 24 months and corresponding 95% confidence intervals will be reported. Estimates of the treatment effect on will be expressed as hazard ratio including 95% confidence intervals estimated through Cox proportional-hazards regression models adjusting for the main-effects of the stratification factors.

8.1.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints in the randomized set are:

- OS
- PFS per the CRAC based on RECIST v1.1
- EORTC QLQ-C30 physical functioning domain

Secondary time-to-event endpoints (PFS and OS) will be analyzed using the similar statistical methods described for the primary endpoints.

8.1.6 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in both DLL3^{high} and randomization set are:

- Objective response rate (ORR) per the CRAC based on RECIST v1.1
- PFS per investigator assessment based on RECIST v1.1
- ORR per investigator assessment based on RECIST v1.1
- Clinical benefit rate (CBR) per the CRAC and investigator assessment, respectively, based on RECIST v1.1
- Duration of response (DOR) per CRAC and investigator assessment, respectively

- Change from baseline in all PRO domains (except physical functioning) measured by EORTC QLQ-C30/LC13 and EQ-5D-5L

ORR is defined as the proportion of patients with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) by CRAC review according to RECIST v1.1.

CBR is defined as the proportion of patients with a BOR of CR or PR, or SD by CRAC review according to RECIST v1.1.

ORR and CBR in treatment arms will be compared using Cochran-Mantel-Haenszel test stratified by randomization stratification factors. Rates and 95% confidence intervals will be reported for each treatment arm.

The duration of overall response for a given subject will be defined as the number of months from the day the criteria are met for confirmed complete response (CR) or partial response (PR) by CRAC (whichever is recorded first) to the date of progressive disease or death, whichever comes first. If a subject is still responding (i.e., has not progressed nor died after CR or PR), then the subject's data will be censored at date of the last radiographic assessment by CRAC. For subjects who never experienced CR or PR, these subjects' data will not be included in the duration of response analysis. Distribution of the duration of response will be estimated for each treatment arm using Kaplan-Meier methodology. Median duration of overall response with corresponding 95% CI for each treatment arm will be provided.

8.1.7 Patient Reported Outcomes (PRO)

The EORTC QLQ-C30/LC13[13] scoring manual will be used to transform the raw scores into the domain scores (global heath, functional scales, symptom scales/items). Physical functioning scale score in EORTC QLQ-C30 is the key secondary endpoint. Change from baseline of the items and domains of the QLQ-C30/LC13 will be summarized by treatment arm. The EQ-5D-5L manual and the published weights will be used to convert the individual items to the utility scores. Change from baseline of the EQ-5D-5L utility

score and VAS will be summarized by treatment arm. The treatment group differences will be evaluated by analyzing the change from baseline using a one-way analysis of variance (ANOVA) model.

8.1.8 Planned Sensitivity and Subgroup Analyses

Efficacy analyses for the primary endpoints (PFS per CRAC and OS) will be performed in the per-protocol set.

In the DLL3^{high} and randomized sets, treatment effects for the primary endpoints (PFS per CRAC and OS) will be assessed in the following subgroups:

- RECIST v1.1 response after completion of first-line platinum-based therapy at screening assessment (SD vs. PR/CR)
- DLL3 expression (Unknown vs. 0% to < 25% vs. 25% to < 75% vs. 75% or above) for the randomized set only
- History of CNS metastases (Yes vs. No)
- For subjects with no history of CNS metastases, PCI vs. No PCI
- Lactate dehydrogenase (LDH), ≤ ULN vs. > ULN
- Number of metastatic sites, 0 – 1 vs. > 1
- Age group (age < 40 vs. 40 to < 60 vs. 60 or older)
- Gender
- Race
- ECOG (0 vs. 1)

Differences between rovalpituzumab tesirine arm and the placebo arm for time-to-event endpoints will be assessed by an unstratified log-rank test for each subgroup. Hazard ratios of treatment arm over the placebo arm will be calculated by a Cox's model.

8.1.9 Pharmacokinetic and Exposure-Response Analyses

Serum concentrations of rovalpituzumab tesirine ADC as well as the incidence and timing of ATA formation will be tabulated and summary statistics will be computed. Serum

concentration and ATA data from this study may be combined with data from other studies and analyzed using population pharmacokinetic methodologies.

The relationship between pharmacokinetics (e.g., exposure) and clinical trial findings including, but not limited to demographics, efficacy, and/or safety measures may also be explored. Additional analyses will be performed if useful. Results of the population pharmacokinetic and exposure-response analyses will be provided in a separate report.

8.2 Safety Analyses

Safety endpoints will be summarized using data from the Safety set. Safety analyses will involve examination of the incidence, severity, and type of treatment-emergent adverse events (TEAEs) reported, changes in vital signs and laboratory test results from baseline (the assessment prior to first dose) to specified time points throughout the study, and concomitant medications used. NCI CTCAE version 4.0 will be used in the grading of adverse events and laboratory abnormalities that are reported as adverse events.

8.2.1 Treatment-Emergent Adverse Events (TEAEs)

TEAEs reported during the study will be coded using a MedDRA[16] dictionary. Incidence of TEAEs will be summarized by treatment arm and the following:

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

These summaries will be presented for the following subsets:

- Serious TEAEs
- All TEAEs
- Drug-related TEAEs

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

8.2.2 Clinical Laboratory Evaluation

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

8.2.3 Vital Signs

Vital signs including pulse, blood pressure, temperature, and body weight will be summarized by treatment arm and time point. For each assessment of vital signs, change from baseline will be summarized by treatment arm.

8.2.4 ECOG Performance Status

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

8.2.5 Electrocardiogram

ECG status will be summarized for each scheduled visit by treatment arm. Shifts from baseline may be tabulated.

8.2.6 Concomitant Medications

Concomitant medications will be classified according to the anatomical therapeutic chemical (ATC) codes in the World Health Organization Drug (WHODRUG) dictionary. The incidence rate of each coded concomitant medication will be tabulated by treatment arm. The table will be sorted by the incidence use of the entire sample.

8.3 Type I Error Adjustment Procedure for Multiple Testing

To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) to one-sided 0.025 level for comparisons of

rovalpituzumab tesirine arm versus placebo arm with respect to progression-free survival (PFS) per CRAC in DLL3^{high} set, overall survival (OS) in DLL3^{high} set, PFS per CRAC in randomized set, OS in randomized set, and physical functioning scale score (EORTC QLQ-C30) in randomized set.

The following null hypotheses are considered:

Two hypotheses in H_{01} are H_{01a} and H_{01b}.

H_{01a}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in DLL3^{high} set.

H_{01b}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in DLL3^{high} set.

H_{02}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in randomized set.

H_{03}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in randomized set.

H_{04}: Rovalpituzumab tesirine arm is not superior to placebo arm in physical functioning scale score (EORTC QLQ-C30) in randomized set.

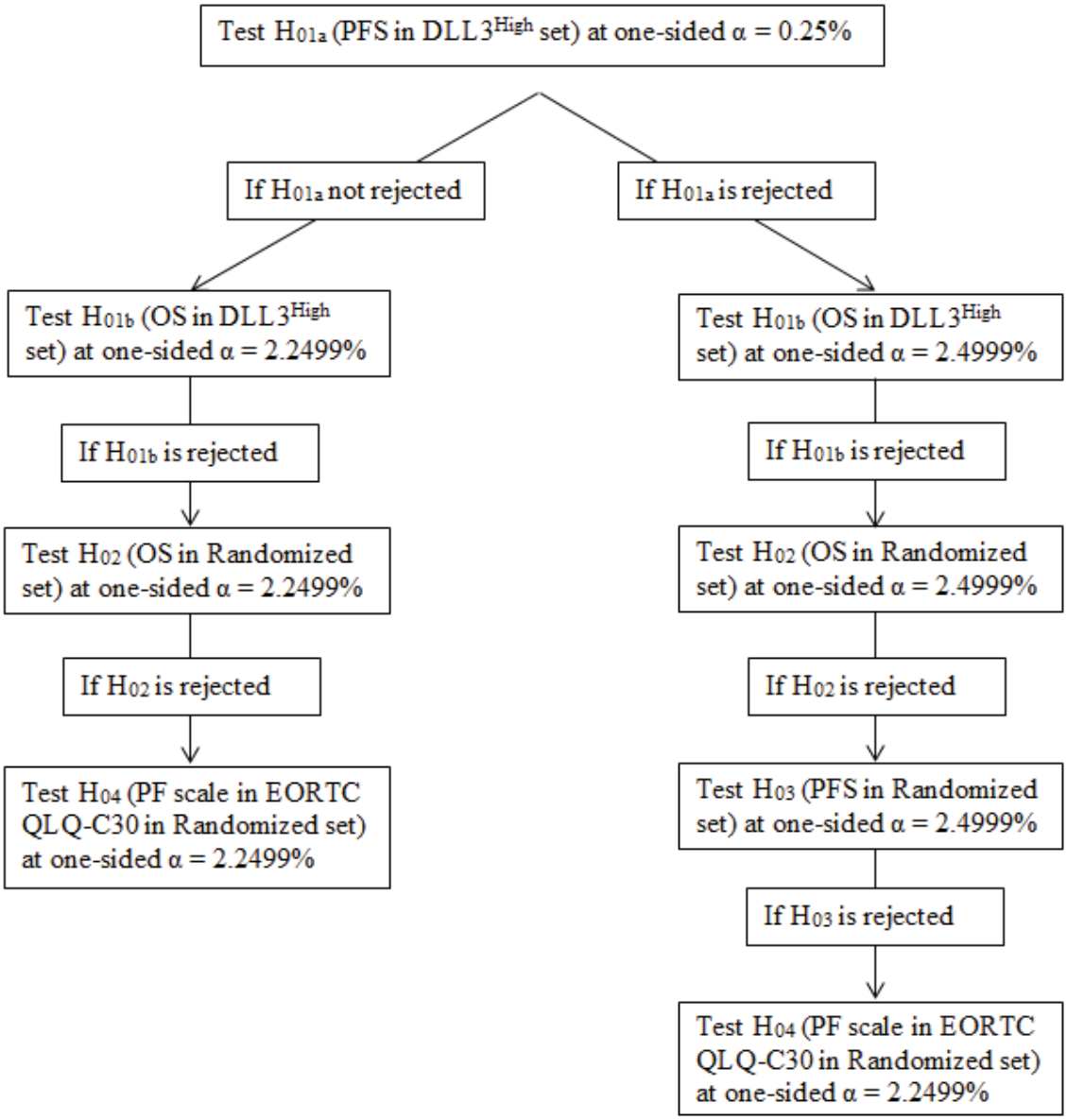
The null hypotheses will be tested in a fixed sequence of {H_{01a}, H_{01b}, H_{02}, H_{03}, and H_{04}} in order. To maintain the family-wise type I error for the study, the null hypotheses in H_{01} (H_{01a} and H_{01b}) will be first tested with an alpha-split approach. The one-sided alpha of 0.25% and 2.25% will be assigned for PFS and OS hypothesis in H_{01}, respectively. Out of one-sided alpha of 2.25% allocated to OS hypothesis (H_{01b}), the one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis. If the hypothesis for PFS in H_{01} (H_{01a}) is rejected the one-sided alpha of 0.25% will be recycled to the OS hypothesis in H_{01} (H_{01b}). Hence, the hypothesis for OS in H_{01} (H_{01b}) will be tested either at a one-sided 2.4999% or one-sided 2.2499% level of significance depending on the PFS hypothesis in H_{01a} is rejected or not.

If either PFS or OS endpoint reaches statistical significance, the study is considered positive. No further tests will be performed if the OS endpoint in DLL3^{high} population (H_{01b}) does not reach statistical significance.

The hypothesis in H_{02} will be tested if the hypothesis in H_{01b} is rejected. If the hypothesis in H_{02} is rejected, then, either (i) H_{03} and H_{04} will be tested sequentially if the PFS endpoint in DLL3^{high} subjects (H_{01a}) is also rejected or (ii) only H_{04} will be tested if the PFS endpoint in DLL3^{high} subjects (H_{01a}) is not rejected.

Diagram of Hierarchical Testing of Primary and Secondary Endpoints is described in Figure 3.

Figure 3. Diagram of Hierarchical Testing of Primary and Secondary Endpoints



8.4 Determination of Sample Size

There are two primary efficacy endpoints for this study: Progression-free survival (PFS) based on the CRAC and overall survival (OS) in DLL3^{high} ED SCLC patients. To maintain the overall 1-sided type I error at a 2.5% for this study, the type I error will be split, assigning 0.25% to progression-free survival and the remaining 2.25% to overall survival. However, the OS endpoint will be tested at a one-sided 2.2499% significance level as a one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis.

The sample size of the study is primarily determined by the analysis of OS. It is assumed, taking into account the expected patient population for the study, that median overall survival in the placebo and rovalpituzumab tesirine arm will be around 9 months and 13 months, respectively. The increase of median OS in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.69, i.e., a reduction in the hazard of death by 31%. With all these assumptions, a total of 319 deaths among subjects with DLL3^{high} are needed to achieve a 90% power based on a log-rank test at a one-sided significance level of 0.022499. Assuming a 19-month accrual period and the last enrolled subject followed for 12 months, at least 480 subjects with DLL3^{high} are expected to be randomized (240 subjects in each arm). A total of 740 subjects regardless of DLL3 expression level (including 480 subjects with DLL3^{high}) will enroll in the study, assuming an approximate prevalence of 65% for subjects with DLL3^{high}. For one-sided significance level of 0.022499, it is projected that an observed hazard ratio of 0.799 or less, corresponding to a 2.3 months or greater improvement in median OS, would result in a statistically significant improvement in the primary analysis of OS.

The primary endpoints of OS and PFS in DLL3^{high} patients will be analyzed at the same time after observing at-least 319 OS event. It is expected at approximately 420 PFS events will be observed at the time of the primary analysis.

It is assumed, taking into account the expected patient population for the study, that median progression-free survival for the placebo and rovalpituzumab tesirine arm will be

approximately 3 months and 4.5 months, respectively. The increase of median progression-free survival in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.667. With all these assumptions, a total of approximately 420 PFS events assessed by the CRAC for the subjects with $DLL3^{high}$ are needed to achieve a 91% power based on a log-rank test at a one-sided significance level of 0.0025. It is projected that an observed hazard ratio of 0.760 or less, corresponding to approximately 1 month or greater improvement in median PFS, would result in a statistically significant improvement in the PFS.

8.5 Futility Analysis

A futility analysis will be conducted when approximately 160 deaths in subjects with $DLL3^{high}$ ED SCLC (approximately 50% of the planned deaths) are observed. The trial may be stopped for futility if the estimated Overall Survival Cox HR of Rova-T to Placebo in the $DLL3^{high}$ set at futility analysis exceeds 0.9. The one-sided alpha of 10^{-6} will be spent for the early look at the efficacy data for futility analysis.

Unblinded interim data will be analyzed and reviewed by the IDMC. The trial may be considered for early stopping for futility and the Sponsor will be unblinded to the aggregated data by randomized treatment arms if the IDMC makes such a recommendation after consideration of the OS results and other supportive evidence including other relevant efficacy and safety data.

Details for the futility analysis will be provided in the IDMC charter.

8.6 Accrual/Study Duration Considerations

On average, it is expected that accrual rates are 1, 7, 27, 36, and 42 with $DLL3^{high}$ subjects per month at study initiation, 3, 6, 9, and 12 month and thereafter, respectively. The total study duration and accrual duration are projected to be 31 months and 19 months with a 5% rate of loss to follow-up, respectively. A total of 740 subjects regardless of DLL3 expression level in tumor are expected to enroll during the accrual period. It is projected that 480 subjects with $DLL3^{high}$ ED SCLC will have enrolled for the primary analysis by

the time approximately 420 PFS events per CRAC and at least 319 OS events should be observed in DLL3^{high} subjects after approximately 8 - 10 months of follow-up.

8.7 Randomization Methods

The randomization numbers of the study will assign subjects in a 1:1 ratio to either receive 0.3 mg/kg rovalpituzumab tesirine or placebo, on Day 1 of each 6-week cycle, omitting every third cycle. Randomization will be stratified by RECIST v1.1 response after completion of first-line platinum-based therapy at screening assessment (SD vs. PR/CR), DLL3 expression (Unknown vs. 0% to < 25% vs. 25% to < 75% vs. 75% or above), history of CNS metastases (Yes vs. No), and for subjects with no history of CNS metastases, PCI vs. no PCI.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure,[14] the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB (Competent Authority, if applicable) approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory

Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines[17,18] applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the informed consent form will be given to the subject and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Tumor material obtained by biopsy procedure at the time of disease progression (for exploratory research) is optional and will only be performed if the subject has voluntarily signed and dated an optional tumor material biopsy procedure informed consent, approved by an IEC/IRB, after the nature of the testing has been explained and the subject has had

an opportunity to ask questions. If the subject does not consent to the optional informed consent, it will not impact the subject's participation in the study.

In the event a subject withdraws consent to participate from the study, stored biomarker and tumor specimen for exploratory research will continue to be used for research and analysis. In the event that a subject would like to withdraw consent for research using these samples, the subject may request that their samples be withdrawn. Once AbbVie receives the request, remaining biomarker and tumor specimen for exploratory research will be destroyed. If the subject changes his/her consent, and the samples have already been tested, those results will still remain as part of the overall research data.

9.3.1 Informed Consent Form and Explanatory Material

In Japan, the principal investigator will prepare the consent form and explanatory material required to obtain subject's consent to participate in the study with the cooperation of the sponsor and will revise these documents as required. The prepared or revised consent forms and explanatory material will be submitted to the sponsor. Approval of the IRB will be obtained prior to use in the study.

9.3.2 Revision of the Consent Form and Explanatory Material

In Japan, when important new information related to the subject's consent becomes available, the principal investigator will revise the consent form and explanatory material based on the information without delay and will obtain the approval of the IRB prior to use in the study. The investigator will provide the information, without delay, to each subject already participating in the study, and will confirm the intention of each subject to continue the study or not. The investigator shall also provide a further explanation using the revised form and explanatory material and shall obtain written consent from each subject of their own free will to continue participating in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The Investigator Awareness Date of SAE should be noted in the source.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

Patient reported data must be completed for each subject screened/enrolled in this study. Some of these data are being collected with an Electronic Patient Reported Outcome (ePRO) system called Trialmax, provided by the technology vendor CRF Health of Plymouth Meeting, PA, USA. The ePRO system is in compliance with Title 21 CFR Part 11. The documentation related to the system validation of the ePRO system is available through the vendor, CRF Health, while the user acceptance testing of the study-specific PRO design will be conducted and maintained at AbbVie.

The subject will be entering the data on an electronic device; these data will be uploaded to a server. The data on the server will be considered source, and maintained and managed by CRF Health.

Internet access to the ePRO data will be provided by CRF Health for the duration of the study. This access will be available for the duration of the study to the site investigator, as well as delegated personnel. Such access will be removed from investigator sites

following the receipt of the study archive. Data from the ePRO system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's ePRO data. It will be possible for the investigator to make paper print-outs from that media.

The (instrument/scale) will be collected electronically via a Tablet/Laptop device into which the patient will directly enter the required pieces of information. The electronic device will be programmed to allow data entry for only the visits specified in the protocol and will not allow for patients to complete more than one of the same assessment at any one visit. All data entered on the device will be immediately stored to the device itself and (manually/automatically) uploaded to a central server administrated by (ePRO Vendor). The Investigator and delegated staff will be able to access all uploaded patient entered data via a password protected website, up until the generation, receipt and confirmation of the study archive.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any research that may be done using optional exploratory research samples from this study will be experimental in nature and the results will not be suitable for clinical decision making or patient management. Hence, the subject will not be informed of individual results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate data from optional exploratory research may be provided to investigators and used in scientific publications or presented at medical conventions. Optional exploratory research information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator (Director of the Site in Japan) and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator (Director of the Site in Japan) and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator (Director of the Site in Japan) must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator (Director of the Site in Japan) is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit, or the date of the last subject's last survival follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for rovalpituzumab tesirine and the product labeling for dexamethasone.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)
Protocol Date:	05 March 2019

Signature of Principal Investigator

Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not making any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Clinical
		Clinical
		Pharmacokinetics
		Clinical Drug Supply Management
		Statistics
		Bioanalysis

Appendix C. Study Activities

Category	Description	Screening	Treatment (Each Cycle)								Non-Treatment Cycle Visit[a]		End of Treatment[b]	PTFU[c]	Survival FU (OS)[d]
		Day –21 to Day –1	Day –1	Day 1[e] (–3d)	Day 2	Day 8	Day 15	Day 22 (–3d)	Day 29	Day 36	Day 1 (±3d)	Weekly (Day 8, 15, 22, 29, 36) (±3d)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (±1wk)	q6 Weeks (±1wk)
Location	Clinic Visit	X		X				X			X		X	X	
	Phone Contact					X	X		X	X		X			X
Safety Assessments	Informed Consent[f]	X													
	Inclusion/Exclusion Criteria	X													
	Medical and Surgical History including Malignancy History[g]	X													
	Physical examination[h]	X		X				X			X		X		
	Vital Signs[i]	X		X				X			X		X		
	Hematology and Serum Chemistry[j]	X		X[k]				X			X		X		
	Coagulation Tests[j]	X		X[k]							X		X		

Category	Description	Screening	Treatment (Each Cycle)								Non-Treatment Cycle Visit[a]		End of Treatment[b]	PTFU[c]	Survival FU (OS)[d]
		Day –21 to Day –1	Day –1	Day 1[e] (–3d)	Day 2	Day 8	Day 15	Day 22 (–3d)	Day 29	Day 36	Day 1 (±3d)	Weekly (Day 8, 15, 22, 29, 36) (±3d)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (±1wk)	q6 Weeks (±1wk)
Safety Assessments (cont.)	Urinalysis[j]	X		X[k]				X			X		X		
	Pregnancy Test[l]	X		X							X		X	X	
	Electrocardiogram (ECG)[m]	X											X		
	Echocardiogram[n]	X		X									X		
	Performance Status (ECOG)	X		X							X		X		
	Fluid Retention Questionnaire[o]			X		X	X	X	X	X	X	X	X		
	SAE/Adverse Events	SAE/ Procedure -related only	X	X		X	X	X	X	X	X	X	X[p]	X[p]	
	Concomitant Medications			X		X	X	X	X	X	X	X	X	X[p]	X[p]

Category	Description	Screening	Treatment (Each Cycle)								Non-Treatment Cycle Visit[a]		End of Treatment[b]	PTFU[c]	Survival FU (OS)[d]
		Day –21 to Day –1	Day –1	Day 1[e] (–3d)	Day 2	Day 8	Day 15	Day 22 (–3d)	Day 29	Day 36	Day 1 (±3d)	Weekly (Day 8, 15, 22, 29, 36) (±3d)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (±1wk)	q6 Weeks (±1wk)
Treatment	rovalpituzumab tesirine or placebo			X											
	dexamethasone or placebo		X	X	X										
Response Assessment	Disease/Response Assessment (Radiographic Imaging)[q]	X		X							X		X[r]	X	
	Central Radiographic Assessment Committee (CRAC) Review[s]	X		X							X		X[r]	X	
	MRI/CT of the Brain	X[t]													
	Health Resource Utilization			X				X			X		X	X	
	Patient Reported Outcome (PRO)[u]	X		X							X		X	X	
	Survival Status														X

Category	Description	Screening	Treatment (Each Cycle)								Non-Treatment Cycle Visit[a]		End of Treatment[b]	PTFU[c]	Survival FU (OS)[d]
		Day –21 to Day –1	Day –1	Day 1[e] (–3d)	Day 2	Day 8	Day 15	Day 22 (–3d)	Day 29	Day 36	Day 1 (±3d)	Weekly (Day 8, 15, 22, 29, 36) (±3d)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (±1wk)	q6 Weeks (±1wk)
Pharmacokinetic (PK), Biomarkers, and Pharmacogenetic (PG)	Pharmacokinetics (PK), Anti-therapeutic Antibody (ATA), and neutralizing antibodies (nAb)[v]			X							X		X		
	Tumor Material at Screening[w]	X													
	Tumor Material at Time of Disease Progression[f]												X	X	
	Blood (plasma) for Inflammatory Markers & ctDNA[x]	X		X									X	X[x]	
	Blood (serum) for Tumor & Soluble Markers[x]	X		X									X	X[x]	
	Circulating Tumor Cells[y]			X									X		
	Pharmacogenetics[z]			X									X		
	Serosal Fluid[aa]			Cycle 1 Day 1 through 70 days after last blinded study treatment											

a. Every third cycle of treatment should be omitted and a clinic visit conducted. The visit should be performed after the Disease Response/Assessment has been conducted and reviewed by the Investigator. The subject should continue to complete the Fluid Retention Questionnaire, including conducting daily weight assessments, and the site should contact the subject weekly during this 42 day non-treatment cycle to review the questionnaire. The following cycle of treatment may be resumed 42 days ± 3d if the subject has not met any reason for study treatment discontinuation as outlined in Section 5.4.

b. End of Treatment Visit procedures should be done within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

c. For subjects who discontinue blinded investigational product for reasons other than disease progression, the first follow-up visit will occur at 6 weeks (± 1 week) after the last Disease Response Assessment, then every 6 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

d. Subjects will be followed for subsequent anti-cancer therapies (dates and responses), as well as survival status, every 6 weeks* (± 1 week) until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first (*or as requested by AbbVie to support data analysis).

e. Cycle 1 Day 1 procedures, with the exception of weight, do not need to be repeated if performed within 21 days of randomization unless clinically indicated. Randomization may occur within 3 days prior to C1D1. Starting at C2D1, study assessments may be performed within 3 days prior to the visit. Disease/Response Assessment and CRAC Review may be performed within 7 days prior to the Day 1 visit.

f. Signed informed consent will be obtained from the subject before any study-specific procedures are undertaken or before any prohibited medications are withheld from the subject in order to participate in this study. Informed consent may be obtained before the 21-day screening window. Informed consent is also required for the optional tumor biopsy at time of disease progression. The sample can be collected at the EOT or at the time of disease progression.

g. Medical and Surgical History includes demographics and documentation of clinically significant medical condition, surgical history, and malignancy history.

h. Height will be collected at the Screening visit only. For height assessments, the subject should not wear shoes.

i. Vital signs include weight, sitting blood pressure, heart rate and body temperature. Weight will be collected in the clinic prior to dosing at each cycle and the recorded weight will be utilized for dosing calculations. If possible, blood pressure and heart rate measurements should not immediately follow scheduled blood collections. Vital signs should be collected prior to the infusion.

j. All laboratory samples will be assessed using a certified central laboratory. A qualified (e.g., certification or accreditation) local laboratory may be used to perform laboratory analyses for treatment decisions as per standard of care. Refer to Table 2, Clinical Laboratory Tests for details.

k. The screening clinical laboratory tests do not need to be repeated on C1D1 if performed within 7 days of randomization and meet eligibility criteria, unless clinically indicated. Starting at Cycle 2, lab assessment may be performed 3 days prior to Day 1 visits.

l. For female subjects of childbearing potential, a serum pregnancy test will be performed at Screening and the results must be available prior to the administration of the first dose of blinded investigational product on C1D1. Urine pregnancy tests will be performed at Day 1 of each cycle, End of Treatment Visit, and PTFU until 6 months after the last dose of blinded investigational product. Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in Section 5.2.4) at Screening do not require pregnancy testing. Post-menopausal female subjects ≤ 55 years of age must have an FSH level > 40 IU/L and will have FSH performed at Screening and assessed by the Investigator.

m. A resting 12-lead ECG will consist of a single 12-lead study performed within a 5-minute window after at least 5 minutes of quiet rest in a supine position. Additional ECG monitoring may occur as clinically indicated during the study.

n. Echocardiograms are required at Screening, Day 1 of each cycle starting C2D1, and EOT. Screening echocardiogram will be performed within 7 business days of randomization to assess for the presence of any pericardial effusion as well as cardiac function (left ventricular ejection fraction, LVEF). Subsequent echocardiograms should be performed within –3 business days of dosing visit to assess for the presence of any pericardial effusion. Additional echocardiogram monitoring may occur as clinically indicated during the study.

o. Subjects will be asked about the development of any new or worsening peripheral edema or dyspnea (Appendix I, Fluid Retention Questionnaire). The assessments on Days 8, 15, 29, and 36 may take place by phone, with the site contacting the subject and reviewing the questionnaire. Starting on Day 1 and through the EOT visit, subjects will maintain a diary of daily weights (captured on the Fluid Retention Questionnaire).

p. Collection of SAE/AE and Concomitant Medications may be required at this visit in order to meet the collection window requirement of Day 1 of study treatment through 70 days after last treatment. Any ongoing SAE/AE that require appropriate standard of care should also be conducted.

q. Diagnostic quality, spiral CT scan with contrast is recommended for all anatomic areas except brain (MRI is recommended for brain imaging); other CT methods or MRI for respective anatomic areas may be used if performed consistently throughout the study for each individual subject and only under circumstances described in Appendix G. Scans of the chest and abdomen must be obtained; scans of the neck and pelvis must also be obtained if there is documented or suspected involvement in these regions. Screening scans may be performed within 28 days prior to randomization. Disease response will be determined by the Investigator at each assessment according to RECIST v1.1. Effusion (pleural, pericardial, and etc.) assessments will be performed by a radiologist at each radiographic assessment and any new findings communicated to the Investigator prior to the next dose of blinded investigational product. Effusions should contribute to disease status assessment per RECIST v1.1 only if confirmed malignant by cytology or otherwise clearly disease-related. Whenever possible, scheduled tumor assessments should not be affected by delays in therapy and/or drug holidays. In some cases, mandatory dose delays due to toxicity will lead to a gap between tumor assessment and dosing. In cases where this gap exceeds 1 week, the TAMD should be contacted for guidance. Subjects will continue to be monitored by the same diagnostic method throughout the study every 6 weeks after randomization.

r. May be omitted if previous assessment was performed within the preceding 6 weeks.

s. Site will collect the appropriate scans and ship by courier or submit electronically to the central facility at each subject's disease assessment.

t. MRI/CT of the brain is required at screening and when clinically indicated (e.g., if CNS progression is suspected) thereafter.

u. PRO assessments are required at Screening, only C2D1, the first Non-Treatment Cycle, EOT, and PTFU (if applicable).

v. Approximately 6 mL of blood will be collected by venipuncture for pharmacokinetic (PK), Anti-therapeutic antibody (ATA), and neutralizing antibodies (nAb) testing. The pre-infusion sample will be collected prior to dosing on Day 1 (–3 days window is permitted) and the second sample will be collected within 60 minutes post-infusion. Only one collection will be required at the Non-Treatment Cycle visit and EOT visit. The date and time of each sample collected will be recorded to the nearest minute.

w. Archived or fresh tumor material must be submitted to the AbbVie designated central IHC laboratory for determination of DLL3 expression prior to randomization.

x. On Day 1 (–3 days window is permitted) of each cycle, the collection will be pre-infusion. A sample will also be collected at the EOT or at the time of disease progression.

y. Whole blood sample will be collected for CTC analysis at pre-dose on Cycle 1 Day 1 (–3 days window is permitted) and EOT only at specific sites based on feasibility.

z. Pharmacogenetic collection should occur unless precluded by local or national regulations or policies. Pharmacogentic sample collected pre-infusion on Day 1 of Cycle 1.

aa. Any pericardial, pleural, and/or ascitic fluid collected as part of routine care (e.g., as part of a therapeutic thoracentesis, pericardiocentesis, or paracentesis) will be procured for testing for any AE starting from C1D1 through 70 days after the last blinded study treatment. Collected fluid must also be tested locally for cytology if disease progression due to appearance/worsening of effusion is suspected.

Appendix D. 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.

Appendix E. Calculated Creatinine Clearance Using Modified Cockcroft-Gault Equation

MODIFIED COCKCROFT AND GAULT FORMULA

For the calculation of estimated creatinine clearance rate (eCCR) using Ideal Body Mass [IBM] instead of Mass.

$$eCCr = \frac{(140 - Age) \bullet IBM\ (kg) \bullet [0.85\ if\ Female]}{72 \bullet Serum\ Creatinine\ (mg/dL)}$$

Or, if serum creatinine is in µmol/L:

$$eCCr = \frac{(140 - Age) \bullet IBM\ (kg) \bullet [1.23\ if\ Male,\ 1.04\ if\ Female]}{Serum\ Creatinine\ (\mu mol/L)}$$

Ideal Body Mass should be used:

$$IBM\ (kg) = [(height\ cm - 154) \bullet 0.9] + (50\ if\ Male,\ 45.5\ if\ Female)$$

Appendix F. New York Heart Association 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.

Appendix G. Response Evaluation Criteria for Solid Tumors (RECIST) v 1.1 for Tumor Response

Response criteria will be assessed using RECIST (version 1.1).[12] Changes in the measurable lesions over the course of therapy must be evaluated using the criteria listed below.

Measurability

Measurable Lesions	Lesions accurately measured in at least one dimension with a minimum size of: • Longest diameter ≥ 10 mm (CT scan slice thickness no greater than 5 mm) • 10 mm caliper measurement by clinical exam
Non-Measurable Lesions	All other lesions, including small lesions (longest diameter < 10 mm) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung and also abdominal masses that are not confirmed and followed by imaging techniques.
Measurable Malignant Lymph Nodes	To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable Malignant Lymph Nodes	Pathological lymph nodes with ≥ 10 to < 15 mm short axis.
Special Considerations Regarding Lesion Measurability	Bone lesions Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as MRI/CT can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.

Blastic bone lesions are non-measurable.

Cystic lesions

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment

Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

All measurements should be taken and recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 28 days before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers. For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended.

Methods of Measurement

Spiral CT should be performed with cuts of 5 mm or less in slice thickness contiguously. This applies to tumors of the chest and abdomen. A scale should be incorporated into all radiographic measurements. MRI can be performed if required by local law or if CT is contraindicated, and should be documented in the subject's source.

If prior to enrollment, it is known a subject is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI should be used to evaluate the subject at baseline and follow-up should be guided by the tumor type under investigation and the anatomic location of the disease. For subjects who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI should be made based upon discussion with the AbbVie TA MD.

For accurate objective response evaluation, ultrasound (US) should not be used to measure tumor lesions.

The utilization of endoscopy and laparoscopy for objective tumor evaluation is not advised. However, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases.

Baseline Documentation of "Target" and "Non-Target" Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. Tumor lesions situated in a previously irradiated area, or in an area subjected to other

loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the longest diameter (LD) for all target lesions will be calculated and reported as the baseline sum LD. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence (stable, increasing or decreasing) or absence of each should be noted throughout follow-up.

Evaluation of Target Lesions

Complete Response (CR):

The disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR):

At least 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 the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started (baseline or after) or the appearance of one or more new lesions. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Stable Disease (SD):

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started (baseline or after).

Assessment of Target Lesions:

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

All lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (< 5 mm). However, sometimes target lesions or lymph nodes become too small to measure. If it is in the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present, but too small to measure, a default value of 5 mm should be assigned (as derived from the 5 mm CT slice

thickness). The measurement of these lesions is potentially non-reproducible; therefore providing this default value will prevent false responses or progression based upon measurement error.

Evaluation of Non-Target Lesions

Complete Response (CR):

The disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD:

Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD):

Unequivocal progression of existing non-target lesions.

In this setting, to achieve 'unequivocal progression' on the basis of non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease. While there are no specific criteria for the identification of new radiographic lesions, the findings of a new lesion should be unequivocal; i.e., not attributable to differences in scanning technique, timing of scanning, phase of contrast administration, change in imaging modality or finding thought

to represent something other than tumor (e.g., some 'new' bone lesions may be simply healing or flare of pre-existing lesions). A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal (e.g., too small to measure), continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is a new lesion, then progression should be declared using the date of the initial scan.

Appendix H. CTCAE v 4.0 Grading of Relevant AEs

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Serosal Effusions	Ascites	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; medical intervention indicated	Severe symptoms; invasive intervention indicated	Life-threatening consequences; urgent operative intervention indicated
	Definition: A disorder characterized by accumulation of serous or hemorrhagic fluid in the peritoneal cavity.				
	Pericardial effusion	–	Asymptomatic effusion size small to moderate	Effusion with physiologic consequences	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by fluid collection within the pericardial sac, usually due to inflammation.				
	Pericardial tamponade	–	–	–	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by an increase in intrapericardial pressure due to the collection of blood or fluid in the pericardium.				
	Pleural effusion	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; intervention indicated (e.g., diuretics or limited therapeutic thoracentesis)	Symptomatic with respiratory distress and hypoxia; surgical intervention including chest tube or pleurodesis indicated	Life-threatening respiratory or hemodynamic compromise; intubation or urgent intervention indicated
	Definition: A disorder characterized by an increase in amounts of fluid within the pleural cavity. Symptoms include shortness of breath, cough and marked chest discomfort.				
	Capillary leak syndrome	–	Symptomatic; medical intervention indicated	Severe symptoms; intervention indicated	Life-threatening consequences; urgent intervention indicated

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Serosal Effusions (cont.)	Definition: A disorder characterized by leakage of intravascular fluids into the extravascular space. This syndrome is observed in patients who demonstrate a state of generalized leaky capillaries following shock syndromes, low-flow states, ischemia-reperfusion injuries, toxemias, medications, or poisoning. It can lead to generalized edema and multiple organ failure.				
Edema	Edema face	Localized facial edema	Moderate localized facial edema; limiting instrumental ADL	Severe swelling; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation in facial tissues.				
	Edema limbs	5 – 10% inter-limb discrepancy in volume or circumference at point of greatest visible difference; swelling or obscuration of anatomic architecture on close inspection	> 10 – 30% inter-limb discrepancy in volume or circumference at point of greatest visible difference; readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	> 30% inter-limb discrepancy in volume; gross deviation from normal anatomic contour; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities.				
	Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Edema (cont.)	Localized edema	Localized to dependent areas, no disability or functional impairment	Moderate localized edema and intervention indicated; limiting instrumental ADL	Severe localized edema and intervention indicated; limiting self-care ADL	–
	Definition: A disorder characterized by swelling due to excessive fluid accumulation at a specific anatomic site.				
	Periorbital edema	Soft or non-pitting	Indurated or pitting edema; topical intervention indicated	Edema associated with visual disturbance; increased intraocular pressure, glaucoma or retinal hemorrhage; optic neuritis; diuretics indicated; operative intervention indicated	
	Definition: A disorder characterized by swelling due to an excessive accumulation of fluid around the orbits of the face.				
Labs	Hypo-albuminemia	< LLN – 3 g/dL; < LLN – 30 g/L	< 3 – 2 g/dL; < 30 – 20 g/L	< 2 g/dL; < 20 g/L	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by laboratory test results that indicate a low concentration of albumin in the blood.				
	Neutrophil count decreased	< LLN – 1500/mm^3; < LLN – 1.5 × 10^9/L	< 1500 – 1000/mm^3; < 1.5 – 1.0 × 10^9/L	< 1000 – 500/mm^3; < 1.0 – 0.5 × 10^9/L	< 500/mm^3; < 0.5 × 10^9/L
	Definition: A finding based on laboratory test results that indicate a decrease in number of neutrophils in a blood specimen.				
	Platelet count decreased	< LLN – 75,000/mm^3; < LLN – 75.0 × 10^9/L	< 75,000 – 50,000/mm^3; < 75.0 – 50.0 × 10^9/L	< 50,000 – 25,000/mm^3; < 50.0 – 25.0 × 10^9/L	< 25,000/mm^3; < 25.0 × 10^9/L
	Definition: A finding based on laboratory test results that indicate a decrease in number of platelets in a blood specimen.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Erythema multiforme	Target lesions covering < 10% BSA and not associated with skin tenderness	Target lesions covering 10 – 30% BSA and associated with skin tenderness	Target lesions covering > 30% BSA and associated with oral or genital erosions	Target lesions covering > 30% BSA; associated with fluid or electrolyte abnormalities; ICU care or burn unit indicated
	Definition: A disorder characterized by target lesions (a pink-red ring around a pale center).				
	Palmar-plantar erythrodysesthesia syndrome	Minimal skin changes or dermatitis (e.g., erythema, edema, or hyperkeratosis) without pain	Skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting instrumental ADL	Severe skin changes (e.g., peeling, blisters, bleeding, edema, or hyperkeratosis) with pain; limiting self-care ADL	–
	Definition: A disorder characterized by redness, marked discomfort, swelling, and tingling in the palms of the hands or the soles of the feet.				
	Photosensitivity	Painless erythema and erythema covering < 10% BSA	Tender erythema covering 10 – 30% BSA	Erythema covering > 30% BSA and erythema with blistering; photosensitivity; oral corticosteroid therapy indicated; pain control indicated (e.g., narcotics or NSAIDs)	Life-threatening consequences; urgent intervention indicated
	Definition: A disorder characterized by an increase in sensitivity of the skin to light.				

Group	Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4
Skin (cont.)	Rash maculo-papular	Macules/papules covering < 10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 – 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering > 30% BSA with or without associated symptoms; limiting self-care ADL	–
	Definition: A disorder characterized by the presence of macules (flat) and papules (elevated). Also known as morbillform rash, it is one of the most common cutaneous adverse events, frequently affecting the upper trunk, spreading centripetally and associated with pruritus.				

Cross reference: NCI CTCAE version 4.0[11]

Appendix I. Fluid Retention Questionnaire

Fluid Retention Questionnaire for Study M16-298

Subject ID: _____

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

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

Date (DD/MMM/YYYY)	Weight (Circle One: lb or kg)
	lb or kg
	lb or kg
	lb or kg
	lb or kg
	lb or kg
	lb or kg
	lb or kg

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

   ☐Yes or ☐No

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

   ☐Yes or ☐No

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

_____ Date: _____

Appendix J. Adverse Events Expected Due to SCLC or Progression of SCLC

Preferred Term (MedDRA Version 19.1)
Pleural effusion
Malignant pleural effusion
Metastases to pleura
Dyspnoea
Cough
Non-cardiac chest pain
Haemoptysis*
Oesophageal obstruction
Pneumonia*
Vocal cord paralysis
Dysphonia
Dysphagia
Superior vena cava syndrome
Horner's syndrome
Myasthenic syndrome
Metastases to bone
Metastases to lymph nodes
Metastases to liver
Metastases to spine
Metastases to the mediastinum
Metastases to pleura
Metastases to adrenals
Metastases to meninges
Metastases to central nervous system
Cancer pain
Inappropriate Anti-Diuretic Hormone (SIADH) secretion
Tumour pain
Fatigue
Asthenia
Pulmonary embolism*
Shock*
Septic shock*

Preferred Term (MedDRA Version 19.1)
Deep vein thrombosis*
Lower respiratory tract infection*
Respiratory tract infection*
Upper respiratory tract infection*
Opportunistic infection*
Viral infection*
Fungal infection*
Bacterial infection*
Pulmonary haemorrhage*
Lung abscess*
Empyema*
Sepsis*
Lymphadenopathy
Decreased appetite
Malaise
Weight decreased
Headache
Pain excluding chest pain
Pyrexia

* Includes life threatening or fatal events.

Appendix K. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Section 1.0 Title Page

"Sponsor/Emergency Contact:" previously read:

[redacted]
Therapeutic Area Medical Director
AbbVie
200 Sidney Street
Cambridge, MA 02139

Phone: [redacted]
Fax:

Has been changed to read:

[redacted]
Senior Medical Director
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Phone:
Cell Phone
Fax:
Email: [redacted]

Section 1.2 Synopsis

Previously read:

AbbVie Inc.	**Protocol Number:** M16-298
Name of Study Drug: rovalpituzumab tesirine (Rova-T)	**Phase of Development:** 3
Name of Active Ingredient: rovalpituzumab tesirine	**Date of Protocol Synopsis:** 09 May 2017
Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)	

Objectives:

Primary

- To evaluate if rovalpituzumab tesirine improves progression-free and overall survival in subjects with extensive-stage small cell lung cancer (ED SCLC) who have ongoing clinical benefit (SD, PR, or CR) following first-line platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

Secondary

- To evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), and duration of responses (DOR)
- To assess change in patient reported outcomes (PRO) with EORTC QLQ-C30/LC13 questionnaires.

Exploratory

- To characterize the pharmacokinetics and incidence of anti-therapeutic antibodies (ATAs) against rovalpituzumab tesirine
- To evaluate pharmacodynamic and predictive biomarkers in blood and tumor for association with sensitivity, efficacy and safety
- To explore DLL3 expression in circulating tumor cells (CTCs) for association with efficacy
- To assess EQ-5D-5L during treatment with rovalpituzumab tesirine.

Investigators: Multicenter, International

Study Sites: Approximately 275

Study Population: Subjects with extensive-stage Small Cell Lung Cancer (ED SCLC) with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based chemotherapy (cisplatin or carboplatin in combination with etoposide or irinotecan).

Number of Subjects to be Enrolled: Up to approximately 740 SCLC subjects, to obtain approximately 480 subjects with DLL3 high expression in tumor ($DLL3^{high}$). $DLL3^{high}$ is defined as $\geq$ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.

Methodology:

This is a Phase 3, randomized, double-blinded, placebo-controlled, multinational, and multicenter study.

ED SCLC subjects who meet all the inclusion criteria and none of the exclusion criteria, and demonstrate ongoing clinical benefit (SD, PR, or CR) at the completion of 4 cycles of first-line platinum-based chemotherapy (such benefit must be ongoing at the last re-staging assessment prior to randomization), will be randomly assigned in a 1:1 ratio to receive 0.3 mg/kg rovalpituzumab tesirine or placebo, and will receive their assigned therapy on Day 1 of each 6-week cycle, omitting every third cycle. Upon completion of first-line chemotherapy, eligible subjects must be offered prophylactic cranial irradiation (PCI), if offering this procedure is not contradictory to country or institutional guidelines. Subjects receiving PCI must complete it prior to randomization into the study. Subjects will also receive 8 mg orally (PO) of dexamethasone or placebo twice daily on Day –1, Day 1, and Day 2 of each 6-week cycle, omitting every third cycle. Randomization will be stratified by RECIST v1.1 response after completion of first-line platinum-based chemotherapy at screening assessment (SD vs. PR/CR), DLL3 expression, (Unknown vs. 0% to < 25% vs. 25% to < 75% vs. 75% or above), history of central nervous system (CNS) metastases (Yes vs. No), and for subjects with no history of CNS metastases, PCI vs. no PCI.

Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.
2. Subject must be ≥ 18 years of age.
3. Histologically or cytologically confirmed extensive-stage SCLC with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).
4. Subjects with a history of CNS metastases prior to the initiation of first-line platinum-based chemotherapy must have received definitive local treatment and have documentation of stable or improved CNS disease status based on brain imaging within 28 days prior to randomization, off or on a stable dose of corticosteroids.
5. At least 3 but no more than 9 weeks between the administration of the last cycle of platinum-based chemotherapy and randomization.
6. Availability of archived or representative tumor material for assessment of DLL3 expression.
7. Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1.
8. Recovery to ≤ Grade 1 of any clinically significant toxicity (excluding alopecia) prior to randomization.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

9. Subject must have adequate bone marrow, renal and hepatic function as follows:
   a. Absolute neutrophil count (ANC) ≥ 1,000/μL
   b. Platelet count ≥ 75,000/μL
   c. Hemoglobin ≥ 8.0 g/dL
   d. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
   e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5× ULN if evidence of hepatic involvement by malignant disease)
   f. Calculated creatinine clearance ≥ 30 mL/min by the Cockroft-Gault formula
   g. Albumin ≥ 3g/dL
10. If female, subject must be either postmenopausal as defined as:
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

      OR
    - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

    OR a Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control, starting at randomization through at least 6 months after the last dose of blinded investigational product.

    If the male subject is sexually active, he must agree, from randomization through at least 6 months after the last dose of blinded investigational product, to practice the protocol specified contraception.
11. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at randomization.

    Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the protocol) at Screening do not require pregnancy testing.

Main Exclusion:

1. Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in Inclusion Criteria 3 – 5 for the disease under study.
2. Any disease-directed radiotherapy (except PCI or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.
3. 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.
4. Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III – IV heart failure within 6 months prior to randomization.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

5. Documented history of capillary leak syndrome.
6. Grade 2 or higher pleural or pericardial effusion within 4 weeks of randomization or earlier history of recurrent Grade 2 or higher effusions with ongoing requirement for pericardiocentesis or thoracentesis.
7. Serious infection within 2 weeks prior to randomization, including any Grade 3 or higher (per NCI CTCAE version 4.0) viral, bacterial, or fungal infection.
8. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 6 months after the last dose of blinded investigational product.
9. Male subject who is considering fathering a child or donating sperm during the study or for approximately 6 months after the last dose of blinded investigational product.
10. Systemic therapy with corticosteroids at > 10 mg/day prednisone or equivalent within 1 week prior to randomization.
11. Subject has a history of active malignancies other than SCLC within the past 2 years prior to study entry, with the exception of in situ cancer which was curatively treated.
12. Any prior exposure to a pyrrolobenzodiazepine (PBD)- or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.
13. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.

Investigational Products:	Rovalpituzumab tesirine or Placebo Dexamethasone or Placebo
Doses:	Rovalpituzumab tesirine/Placebo: 0.3 mg/kg, Day 1 of each 6-week cycle, omitting every third cycle. Dexamethasone/Placebo 8 mg orally (PO) twice daily on Day –1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle.
Mode of Administration:	Rovalpituzumab tesirine/Placebo: Intravenous Dexamethasone/Placebo: Oral

Duration of Treatment: Subjects will receive rovalpituzumab tesirine/placebo in combination with dexamethasone/placebo on Day 1 of a 6-week cycle, omitting every third cycle until disease progression.

Criteria for Evaluation:

Efficacy: Efficacy assessments will consist of evaluations for tumor progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will be based on a Central Radiographic Assessment Committee (CRAC) review of medical images, as outlined in the Schedule of Assessments. Additionally, efficacy will be assessed by overall survival.

Pharmacokinetic: Plasma concentrations of rovalpituzumab tesirine ADC and the presence of anti-therapeutic antibodies (ATA) will be determined.

Criteria for Evaluation (Continued):

Biomarkers: Pharmacodynamic and predictive biomarker assessments will include analyses of tumor material and circulating tumor cells for DLL3 expression, blood samples for inflammatory, tumor, and soluble markers. Samples may also be used for other nucleic acid or protein based exploratory biomarkers to understand the sensitivity or resistance to rovalpituzumab tesirine and biology of SCLC.

Safety: Safety assessments include physical exam, vital signs, body weight, ECOG score, clinical adverse events, laboratory tests (hematology, serum chemistries, urinalysis, and coagulation), ECGs, echocardiogram, fluid retention questionnaire, radiographic images review for fluid retention, and monitoring of concomitant medications.

Patient Reported Outcome (PRO):

Changes in the patient reported outcomes (PROs) EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L from baseline will be assessed.

Statistical Methods:

Efficacy:

Progression-free survival (PFS) and overall survival (OS) are the two primary efficacy endpoints. No order of testing of these two endpoints is specified. To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) for comparisons of rovalpituzumab tesirine arm versus placebo arm with respect to progression-free survival (PFS) per CRAC, and overall survival (OS), ORR per CRAC, and physical functioning scale score (EORTC QLQ-C30).

The following null hypotheses are considered for subjects with $DLL3^{high}$:

H1: Rovalpituzumab tesirine arm is not superior to placebo arm in both PFS and OS.

H2: Rovalpituzumab tesirine arm is not superior to placebo arm in ORR per CRAC.

H3: Rovalpituzumab tesirine arm is not superior to placebo arm in physical functioning scale score (EORTC QLQ-C30).

The null hypotheses will be tested in a fixed sequence of {H1, H2, H3} in order. To maintain the family-wise type I error for the study, the null hypothesis H1 will be first tested with an alpha-split approach. The hypothesis for PFS will be tested at a one-sided 0.25% level of significance and the hypothesis for OS at a one-sided 2.25% level of significance. If either PFS or OS endpoint reaches statistical significance, the study is considered positive. No further tests will be performed if H1 is not rejected. Each hypothesis of H2 and H3 will be tested in order specified above if H1 is rejected and the preceding hypothesis shows statistically significant results at the 1-sided 2.5% level of significance. Otherwise testing in the hierarchical sequence will stop.

Interim Analysis:

An interim efficacy analysis is planned for overall survival after at least 239 deaths in subjects with $DLL3^{high}$ (i.e., 75% of planned deaths are observed) using a one-sided log-rank test. The O'Brien-Fleming method will be implemented to protect the type I error rate of 0.0225 for OS. A one-sided alpha spending of 0.0084 for the interim will be allocated for declaring statistical superiority in OS at the time of the interim analysis. The final analysis of OS will be performed at a one-sided nominal alpha level of 0.01998, adjusting for the interim look at OS data.

Statistical Methods (Continued):

Interim Analysis (Continued):

Unblinded interim data will be analyzed and reviewed by the IDMC. The trial may be considered for early stopping for superiority and the Sponsor will be unblinded to the aggregated data by randomized treatment arms if the IDMC makes such a recommendation after consideration of the PFS and OS results, and all supportive evidence including other efficacy endpoints and safety.

Sample Size:

The sample size of the study is primarily determined by the analysis of OS. It is assumed, taking into account the expected patient population for the study, that median overall survival in the placebo arm will be around 9 months. Based on a log-rank test, at a one sided significance level of 0.0225 and a power of 90%, a total of 319 deaths among subjects with $DLL3^{high}$ are needed to detect an increase of median OS to 13 months in rovalpituzumab tesirine arm, corresponding to a hazard ratio of 0.69 (i.e., a reduction in the hazard death of 31%). Assuming a 19-month accrual period and the last enrolled subject followed for 12 months, at least 480 subjects with $DLL3^{high}$ are expected to be randomized (240 subjects in each arm). A total of 740 subjects regardless of DLL3 expression level (including 480 subjects with $DLL3^{high}$) will enroll in the study, assuming an approximate prevalence of 65% for subjects with $DLL3^{high}$. It is projected that an observed hazard ratio of 0.795 or less, corresponding to a 2.3 months or greater improvement in median OS, would result in a statistically significant improvement in the final analysis of OS.

It is assumed, taking into account the expected patient population for the study, that median progression-free survival for the placebo arm will be approximately 3 months. Treatment with rovalpituzumab tesirine is hypothesized to increase median progression-free survival to 4.5 months (i.e., a hazard ratio of 0.667). With approximately 407 PFS events assessed by the CRAC for subjects with $DLL3^{high}$, the study provides a 90% power to detect a hazard ratio of 0.667 in PFS at a one-sided significance level of 0.0025. It is projected that an observed hazard ratio of 0.757 or less, corresponding to approximately 1 month or greater improvement in median PFS, would result in a statistically significant improvement in the PFS.

Pharmacokinetic:

Individual concentrations of rovalpituzumab tesirine ADC will be tabulated and summarized for subjects treated with the active regimen and summary statistics provided. The incidence of ATA will be summarized.

Biomarkers:

Biomarkers will be measured at baseline and post-treatment and analyses performed to identify markers associated with rovalpituzumab tesirine response, pharmacodynamics, PK, or safety.

Safety:

The safety of rovalpituzumab tesirine will be assessed by evaluating the study drug exposure, adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M16-298
Name of Study Drug: rovalpituzumab tesirine (Rova-T)	**Phase of Development:** 3

Name of Active Ingredient: rovalpituzumab tesirine	**Date of Protocol Synopsis:** 05 March 2019

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Rovalpituzumab Tesirine as Maintenance Therapy Following First-Line Platinum-Based Chemotherapy in Subjects with Extensive Stage Small Cell Lung Cancer (MERU)

Objectives:

Primary

- To evaluate if rovalpituzumab tesirine improves progression-free survival, assessed by a Central Radiographic Assessment Committee (CRAC) according to RECIST v1.1, and overall survival in subjects with extensive-stage small cell lung cancer (ED SCLC) tumors with a high level of DLL3 expression ($DLL3^{high}$) who have ongoing clinical benefit (SD, PR, or CR) following first-line platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

Secondary

- To evaluate if rovalpituzumab tesirine improves progression-free survival by CRAC and overall survival in all randomized subjects compared to placebo.
- To assess change in patient reported outcomes (PRO) with physical functioning as measured by the EORTC QLQ-C30 questionnaire in all randomized subjects compared to placebo.

Exploratory

- To evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), and duration of responses (DOR) by CRAC and Investigator assessment in $DLL3^{high}$ and in all randomized subjects.
- To evaluate if rovalpituzumab tesirine improves progression-free survival by Investigator assessment compared to placebo in $DLL3^{high}$ and in all randomized subjects.
- To assess change from baseline in all patient reported outcomes (PRO) domains (except physical functioning) measured by EORTC QLQ-C30/LC13 and EQ-5D-5L.
- To characterize the pharmacokinetics and incidence of anti-therapeutic antibodies (ATAs) against rovalpituzumab tesirine.
- To evaluate pharmacodynamic and predictive biomarkers in blood and tumor for association with sensitivity, efficacy and safety.
- To explore DLL3 expression in circulating tumor cells (CTCs) for association with efficacy.

Investigators: Multicenter, International

Study Sites: Approximately 300

Study Population: Subjects with extensive-stage Small Cell Lung Cancer (ED SCLC) with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based chemotherapy (cisplatin or carboplatin in combination with etoposide or irinotecan).

Number of Subjects to be Enrolled: Up to approximately 740 SCLC subjects, to obtain approximately 480 subjects with $DLL3^{high}$ expression in tumor ($DLL3^{high}$). $DLL3^{high}$ is defined as $\geq$ 75% tumor cells staining positive according to the VENTANA DLL3 (SP347) IHC Assay.

Methodology:

This is a Phase 3, randomized, double-blinded, placebo-controlled, multinational, and multicenter study.

ED SCLC subjects who meet all the inclusion criteria and none of the exclusion criteria, and demonstrate ongoing clinical benefit (SD, PR, or CR) at the completion of 4 cycles of first-line platinum-based chemotherapy (such benefit must be ongoing at the last re-staging assessment prior to randomization), will be randomly assigned in a 1:1 ratio to receive 0.3 mg/kg rovalpituzumab tesirine or placebo, and will receive their assigned therapy on Day 1 of each 6-week cycle, omitting every third cycle. Upon completion of first-line chemotherapy, eligible subjects must be offered prophylactic cranial irradiation (PCI), if offering this procedure is not contradictory to country or institutional guidelines. Subjects receiving PCI must complete it prior to randomization into the study. Subjects will also receive 8 mg orally (PO) of dexamethasone or placebo twice daily on Day –1, Day 1, and Day 2 of each 6-week cycle, omitting every third cycle. Randomization will be stratified by RECIST v1.1 response after completion of first-line platinum-based chemotherapy at screening assessment (SD vs. PR/CR), DLL3 expression, (Unknown vs. 0% to < 25% vs. 25% to < 75% vs. 75% or above), history of central nervous system (CNS) metastases (Yes vs. No), and for subjects with no history of CNS metastases, PCI vs. no PCI.

Survival Follow-up will continue until the endpoint of death, the subject becomes lost to follow-up or withdraws consent, or termination of the study by AbbVie, whichever occurs first.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Subject or the subject's legally acceptable representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.
2. Subject must be ≥ 18 years of age.
3. Histologically or cytologically confirmed ED SCLC (extensive stage disease at initial diagnosis), with ongoing clinical benefit (SD, PR, or CR per RECIST v1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).
4. Subjects with a history of CNS metastases prior to the initiation of first-line platinum-based chemotherapy must have received definitive local treatment and have documentation of stable or improved CNS disease status based on brain imaging within 28 days prior to randomization, off or on a stable dose of corticosteroids.
5. Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy
6. Availability of archived or representative tumor material for assessment of DLL3 expression.
7. Eastern Cooperative Oncology Group (ECOG) performance score of 0 or 1.
8. Recovery to ≤ Grade 1 of any clinically significant toxicity (excluding alopecia) prior to randomization.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Inclusion (Continued):

9. Subject must have adequate bone marrow, renal and hepatic function as follows:
   a. Absolute neutrophil count (ANC) ≥ 1,000/μL
   b. Platelet count ≥ 75,000/μL
   c. Hemoglobin ≥ 8.0 g/dL
   d. Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease
   e. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN (≤ 5× ULN if evidence of hepatic involvement by malignant disease)
   f. Calculated creatinine clearance ≥ 30 mL/min by the modified Cockroft-Gault formula (Refer to Appendix E).
   g. Albumin ≥ 3g/dL
10. If female, subject must be either postmenopausal as defined as:
    - Age > 55 years with no menses for 12 or more months without an alternative medical cause.
    - Age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND an FSH level > 40 IU/L.

      OR
    - Permanently surgical sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

    OR a Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control, starting at randomization through at least 6 months after the last dose of blinded investigational product.

    If the male subject is sexually active, he must agree, from randomization through at least 6 months after the last dose of blinded investigational product, to practice the protocol specified contraception.
11. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at randomization.

    Females of non-childbearing potential (either postmenopausal or permanently surgically sterile as defined in the protocol) at Screening do not require pregnancy testing.

Main Exclusion:

1. Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in Inclusion Criteria 3 – 5 for SCLC.
2. Any disease-directed radiotherapy (except, PCI, palliative radiotherapy to a radiographically documented non-progressing lesion for symptom control, or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.
3. 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.

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued):

Main Exclusion (Continued):

4. Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III – IV heart failure (refer to Appendix F) within 6 months prior to randomization.
5. Documented history of capillary leak syndrome.
6. Grade 2 or higher pleural or pericardial effusion within 4 weeks of randomization or earlier history of recurrent Grade 2 or higher effusions with ongoing requirement for pericardiocentesis or thoracentesis.
7. Serious infection within 2 weeks prior to randomization, including any Grade 3 or higher (per NCI CTCAE version 4.0) viral, bacterial, or fungal infection.
8. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 6 months after the last dose of blinded investigational product.
9. Male subject who is considering fathering a child or donating sperm during the study or for approximately 6 months after the last dose of blinded investigational product.
10. Systemic therapy with corticosteroids at > 10 mg/day prednisone or equivalent within 1 week prior to randomization.
11. Subject has a history of active malignancies other than SCLC within the past 2 years prior to study entry, with the exception of in situ cancer which was curatively treated.
12. Any prior exposure to a pyrrolobenzodiazepine (PBD-based)-or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.
13. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells.

Investigational Products:	Rovalpituzumab tesirine or Placebo Dexamethasone or Placebo
Doses:	Rovalpituzumab tesirine/Placebo: 0.3 mg/kg, Day 1 of each 6-week cycle, omitting every third cycle. Dexamethasone/Placebo 8 mg orally (PO) twice daily on Day –1, Day 1 (the day of dosing), and Day 2 of each 6 week cycle, omitting every third cycle.
Mode of Administration:	Rovalpituzumab tesirine/Placebo: Intravenous Dexamethasone/Placebo: Oral

Duration of Treatment: Subjects will receive rovalpituzumab tesirine/placebo in combination with dexamethasone/placebo on Day 1 of a 6-week cycle, omitting every third cycle until disease progression.

Criteria for Evaluation:

Efficacy: Efficacy assessments will consist of evaluations for tumor progression using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and will be based on a Central Radiographic Assessment Committee (CRAC) review of medical images, as outlined in the Schedule of Assessments. Additionally, efficacy will be assessed by overall survival.

Pharmacokinetic: Serum concentrations of rovalpituzumab tesirine ADC and the presence of anti-therapeutic antibodies (ATA) will be determined.

Criteria for Evaluation (Continued):

Biomarkers: Pharmacodynamic and predictive biomarker assessments will include analyses of tumor material and circulating tumor cells for DLL3 expression, blood samples for inflammatory, tumor, and soluble markers. Samples may also be used for other nucleic acid or protein based exploratory biomarkers to understand the sensitivity or resistance to rovalpituzumab tesirine and biology of SCLC.

Safety: Safety assessments include physical exam, vital signs, body weight, ECOG score, clinical adverse events, laboratory tests (hematology, serum chemistries, urinalysis, and coagulation), ECGs, echocardiogram, fluid retention questionnaire, radiographic images review for fluid retention, and monitoring of concomitant medications.

Patient Reported Outcome (PRO):

Changes in the patient reported outcomes (PROs) EORTC QLQ-C30, EORTC QLQ-LC13, and EQ-5D-5L from baseline will be assessed.

Statistical Methods:

Efficacy:

Progression-free survival (PFS) per CRAC and overall survival (OS) in patients with DLL3^{high} ED SCLC are the two primary efficacy endpoints. To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) for comparisons of rovalpituzumab tesirine arm versus placebo arm with respect to progression-free survival (PFS) per CRAC in DLL3^{high} patients, overall survival (OS) in DLL3^{high} patients, PFS per CRAC in randomized patients, OS in randomized patients, and physical functioning scale score (EORTC QLQ-C30) in the randomized set.

The following null hypotheses are considered:

Two hypotheses in H_{01} are H_{01a} and H_{01b}.

H_{01a}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in DLL3^{high} set.

H_{01b}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in DLL3^{high} set.

H_{02}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in randomized set.

H_{03}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in randomized set.

H_{04}: Rovalpituzumab tesirine arm is not superior to placebo arm in physical functioning scale score (EORTC QLQ-C30) in randomized set.

The null hypotheses will be tested in a fixed sequence of {H_{01a}, H_{01b}, H_{02}, H_{03}, and H_{04}} in order. To maintain the family-wise type I error for the study, the null hypotheses in H01 (H_{01a} and H_{01b}) will be first tested with an alpha-split approach. The one-sided alpha of 0.25% and 2.25% will be assigned for PFS and OS hypothesis in H_{01}, respectively. Out of one-sided alpha of 2.25% allocated to OS hypothesis (H_{01b}), the one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis. If the hypothesis for PFS in H_{01} (H_{01a}) is rejected the one-sided alpha of 0.25% will be recycled to the OS hypothesis in H_{01} (H_{01b}). Hence, the hypothesis for OS in H_{01} (H_{01b}) will be tested either at a one-sided 2.4999% or one-sided 2.2499% level of significance depending on the PFS hypothesis in H_{01} a is rejected or not.

If either PFS or OS endpoint reaches statistical significance, the study is considered positive. No further tests will be performed if the OS endpoint in DLL3^{high} population (H_{01b}) does not reach statistical significance.

Statistical Methods (Continued):

The hypothesis in H_{02} will be tested if the hypothesis in H_{01b} is rejected. If the hypothesis in H_{02} is rejected, then, either (i) H_{03} and H_{04} will be tested sequentially if the PFS endpoint in DLL3^{high} subjects (H_{01a}) is also rejected or (ii) only H_{04} will be tested if the PFS endpoint in DLL3^{high} subjects (H_{01a}) is not rejected.

Futility Analysis:

Unblinded interim data will be analyzed and reviewed by the IDMC. A futility analysis will be conducted when approximately 160 deaths in subjects with DLL3^{high} ED SCLC (approximately 50% of the planned deaths) are observed. The trial may be stopped for futility if the estimated Overall Survival Cox HR of Rova-T to Placebo at this analysis exceeds 0.9. The one-sided alpha of 10^{-6} will be spent for the early look at the efficacy data for futility analysis.

Sample Size:

There are two primary efficacy endpoints for this study: Progression-free survival (PFS) based on the CRAC and overall survival (OS) in subjects with DLL3^{high} ED SCLC. To maintain the overall 1-sided type I error at a 2.5% for this study, the type I error will be split, assigning 0.25% to progression-free survival and the remaining 2.25% to overall survival. However, the OS endpoint will be tested at a one-sided 2.2499% significance level as a one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis.

The sample size of the study is primarily determined by the analysis of OS. It is assumed, taking into account the expected patient population for the study, that median overall survival in the placebo and rovalpituzumab tesirine arm will be around 9 months and 13 months, respectively. The increase of median OS in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.69, i.e., a reduction in the hazard of death by 31%. With all these assumptions, a total of 319 deaths among subjects with DLL3^{high} are needed to achieve a 90% power based on a log-rank test at a one-sided significance level of 0.022499. Assuming a 19-month accrual period and the last enrolled subject followed for 12 months, at least 480 subjects with DLL3^{high} are expected to be randomized (240 subjects in each arm). A total of 740 subjects regardless of DLL3 expression level (including 480 subjects with DLL3^{high}) will enroll in the study, assuming an approximate prevalence of 65% for subjects with DLL3^{high}. For one-sided significance level of 0.022499, it is projected that an observed hazard ratio of 0.799 or less, corresponding to a 2.3 months or greater improvement in median OS, would result in a statistically significant improvement in the primary analysis of OS.

The primary endpoints of OS and PFS in DLL3^{high} patients will be analyzed at the same time after observing at-least 319 OS event. It is expected at approximately 420 PFS events will be observed at the time of the primary analysis.

It is assumed, taking into account the expected patient population for the study, that median progression-free survival for the placebo and rovalpituzumab tesirine arm will be approximately 3 months and 4.5 months, respectively. The increase of median progression-free survival in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.667. With all these assumptions, a total of 420 PFS events assessed by the CRAC for the subjects with DLL3^{high} are needed to achieve a 91% power based on a log-rank test at a one-sided significance level of 0.0025. It is projected that an observed hazard ratio of 0.760 or less, corresponding to approximately 1 month or greater improvement in median PFS, would result in a statistically significant improvement in the PFS.

Statistical Methods (Continued):

Pharmacokinetic:

Individual concentrations of rovalpituzumab tesirine ADC will be tabulated and summarized for subjects treated with the active regimen and summary statistics provided. The incidence of ATA will be summarized.

Biomarkers:

Biomarkers will be measured at baseline and post-treatment and analyses performed to identify markers associated with rovalpituzumab tesirine response, pharmacodynamics, PK, or safety.

Safety:

The safety of rovalpituzumab tesirine will be assessed by evaluating the study drug exposure, adverse events, all deaths, as well as changes in laboratory determinations and vital sign parameters.

Section 1.3 List of Abbreviations and Definition of Terms

Subsection Abbreviations

Add:

LD SCLC	Limited-stage disease small cell lung cancer

Section 3.3 Rovalpituzumab Tesirine

Last paragraph Previuosly read:

In a Phase 1 study (SCRX16-001), rovalpituzumab tesirine dosed at 0.2 – 0.4 mg/kg exhibited encouraging efficacy in recurrent SCLC, achieving a 31% (8/26) and 85% (22/26) central review-adjudicated confirmed objective response rate (ORR) and clinical benefit rate (CBR), respectively, in subjects whose tumors expressed DLL3 in ≥ 50% of cells. Median overall survival was 7.7 months in DLL3 ≥ 50% subjects at all dose levels, with a 1-year survival rate of 30%.[9] Therefore, rovalpituzumab tesirine appears to be an active anti-cancer therapy.

Has been changed to read:

In the Phase 1 first in human study of rovalpituzumab tesirine (Study SCRX16-001), the best overall response (confirmed) for all SCLC subjects (dose escalation, retreatment, and maintenance cohorts) was retrospectively assessed by the Independent Review Committee (IRC) by RECIST v1.1 criteria. The ORR (confirmed) was 16% (95% CI: 7.35, 27.42),

with 12% achieving PR. The clinical benefit rate (CBR) was 59% (95% CI: 44.93, 71.40). The median duration of response by the IRC was 1.7 months (95% CI: 0.03, 3.06). The median progression-free survival by the IRC was 3.0 months (95% CI: 2.56, 3.84), with a probability of progression-free survival at 12 weeks of 52% (95% CI: 39, 63). The median overall survival was 4.3 months (95% CI: 3.22, 5.65). The probability of overall survival at 12 weeks was 69% (95% CI: 52, 81). In DLL3-positive (≥ 1% tumor cells staining positive for DLL3 with murine anti-DLL3 antibody assay) subjects, the ORR was 23% (95% CI: 10.42, 40.14), and the CBR was 77% (95% CI: 59.86, 89.58). A slightly higher ORR (27%) and CBR (87%) were observed in DLL3-high (≥ 50% tumor cells staining positive for DLL3 with murine anti-DLL3 antibody assay) subjects.

In the Phase 2 Study SCRX001-002 (TRINITY) in patients with SCLC recurrent after at least two systemic chemotherapy regimens, rovalpituzumab tesirine dosed at 0.3 mg/kg every 6 weeks for two cycles (with an option for additional two cycles upon progression occurring ≥ 12 weeks after the second dose) resulted in the following:

- In $DLL3^{high}$ (≥ 75% tumor cells staining positive for DLL3 with VENTANA Rabbit IHC (SP347) DLL3 assay) subjects, ORR of 14% per IRC assessment, median OS of 5.7 months and median PFS of 3.8 months
- In $DLL3^{high}$ subjects, the clinical benefit rate was 74% with a median duration of clinical benefit of 3.0 months per IRC assessment

Additionally, DLL3 positive (≥ 25% tumor cells staining positive for DLL3 with VENTANA Rabbit IHC (SP347) DLL3 assay) and $DLL3^{high}$ groups had comparable response rates given highly overlapping populations where approximately 85% of DLL3 positive subjects were also $DLL3^{high}$.

In December 2018, enrollment in Study M16-289 TAHOE ("A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3high Small Cell Lung Cancer (SCLC) who have First Disease Progression During or Following Front-Line Platinum-Based

Chemotherapy") was discontinued at the recommendation of the Independent Data Monitoring Committee (IDMC) after review of available efficacy data which demonstrated shorter overall survival in the rovalpituzumab tesirine arm compared with the topotecan control arm. At the time enrollment was halted, 444 DLL3^{high} (≥ 75% tumor cells staining positive for DLL3 with VENTANA Rabbit IHC (SP347) DLL3 assay) subjects had enrolled on the trial. The IDMC recommended that investigators and subjects make individual decisions as to whether or not to continue treatment based on patient level response. The results of the TAHOE study did not adversely impact the safety profile for rovalpituzumab tesirine.[19]

Section 3.5 Benefits and Risks
Add: new second paragraph

As of 30 June 2018, 1246 subjects have received study medication in the rovalpituzumab tesirine clinical program; an estimated 1039 subjects (with SCLC or other DLL3-expressing solid tumors) have received at least 1 dose of rovalpituzumab tesirine at doses ranging from 0.05 mg/kg to 0.8 mg/kg on a q3w schedule and 0.3 mg/kg to 0.4 mg/kg on a q6w schedule.

Section 3.5 Benefits and Risks
Second paragraph, first and second sentence previously read:

The most frequent treatment-emergent adverse event (TEAE) terms considered related to rovalpituzumab tesirine have included fatigue (35%), pleural effusion (31%) and peripheral edema (27%), while the most frequent, related TEAE groups of Grade 3 or higher have included thrombocytopenia (12%), serosal effusions (11%), and skin reactions (8%).[9] In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified bone marrow, lung, and kidney as potential sources of clinical adverse events (AEs) (AbbVie Stemcentrx data on file).

Has been changed to read:

Among subjects with SCLC treated with rovalpituzumab tesirine 0.3 mg/kg q6w, 96.8% of subjects reported at least 1 adverse event. The most frequently reported adverse events among subjects with SCLC treated with rovalpituzumab tesirine 0.3 mg/kg q6w were decreased appetite (28.0%), photosensitivity reaction (27.7%), oedema peripheral (27.2%), dyspnoea (26.6%), and nausea (25.6%). Important identified risks following treatment with rovalpituzumab tesirine include: pleural effusions (33.9%), pericardial effusions (16.7%), generalized edema (2.7%) and photosensitivity reactions (27.7%). Important potential risks following treatment with rovalpituzumab tesirine include pneumonitis (1%). The following adverse events of special interest have also been identified: cutaneous reactions (48.7%), thrombocytopenia and hemorrhage events (28%), edema (33.8%), hypoalbuminemia (16.2%), hepatotoxicity (19.3%), nephrotoxicity (5.9%), anemia (19.7%), neutropenia (9.2%) and infusion related reaction (0.2%). In addition, preclinical toxicology studies conducted in the rat and the cynomolgus monkey have identified bone marrow, lung, and kidney as potential sources of clinical adverse events (AEs) (AbbVie Investigator Brochure v7).

Section 4.0 Study Objectives
Previously read:

The primary objective of this study is to evaluate if rovalpituzumab tesirine improves progression-free and overall survival in subjects with extensive-stage SCLC who have ongoing clinical benefit (SD, PR, or CR) following the completion of 4 cycles of first-line, platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

The secondary objectives are to evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), and duration of responses (DOR), and to assess change in patient reported outcomes (PRO) with EORTC QLQ-C30/LC-13 questionnaires.

The exploratory objectives are to characterize the pharmacokinetics and incidence of anti-therapeutic antibodies (ATAs) against rovalpituzumab tesirine, to evaluate pharmacodynamic and predictive biomarkers in blood and tumor for association with sensitivity, efficacy and safety, to explore the DLL3 expression in circulating tumor cells (CTCs) for association with efficacy, and to assess EQ-5D-5L during treatment with rovalpituzumab tesirine.

Has been changed to read:

The primary objective of this study is to evaluate if rovalpituzumab tesirine improves progression-free survival, assessed by CRAC, and overall survival in subjects with extensive-stage SCLC tumors with a high level of DLL3 expression ($DLL3^{high}$) who have ongoing clinical benefit (SD, PR, or CR) following the completion of 4 cycles of first-line, platinum-based chemotherapy (cisplatin or carboplatin plus irinotecan or etoposide) compared to placebo.

The secondary objectives are:

- To evaluate if rovalpituzumab tesirine improves progression-free survival by CRAC and overall survival in all randomized subjects compared to placebo.
- To assess change in patient reported outcomes (PRO) with physical functioning as measured by the EORTC QLQ-C30questionnaire in all randomized subjects compared to placebo.

The exploratory objectives are:

- To evaluate rovalpituzumab tesirine anti-tumor activity by determining objective response rate (ORR), clinical benefit rate (CBR), and duration of responses (DOR) by CRAC and investigator assessment in $DLL3^{high}$ and in all randomized subjects.
- To evaluate if rovalpituzumab tesirine improves progression-free survival by investigator assessment compared to placebo in $DLL3^{high}$ and in all randomized subjects.

- To assess change from baseline in all patient reported outcomes (PRO) domains (except physical functioning) measured by EORTC QLQ-C30/LC13 and EQ-5D-5L.
- To characterize the pharmacokinetics and incidence of anti-therapeutic antibodies (ATAs) against rovalpituzumab tesirine.
- To evaluate pharmacodynamic and predictive biomarkers in blood and tumor for association with sensitivity, efficacy and safety.
- To explore the DLL3 expression in circulating tumor cells (CTCs) for association with efficacy.

Section 5.1 Overall Study Design and Plan: Description
Second paragraph, last sentence previously read:

Approximately 275 clinical sites will participate.

Has been changed to read:

Approximately 300 clinical sites will participate.

Figure 1. Study Schema
Footnote "3." previously read:

At least 3 but no more than 9 weeks between the administration of the last cycle of platinum-based chemotherapy and randomization.

Has been changed to read:

Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy.

Section 5.2 Selection of Study Population
Add: new second paragraph

For the purposes of study eligibility, limited stage disease SCLC (LD-SCLC) is defined as a disease confined to the hemithorax of origin, with or without the involvement of regional lymph nodes, including ipsilateral and contralateral hilar, ipsilateral and contralateral mediastinal, and ipsilateral supraclavicular nodes. Extensive stage disease SCLC (ED-SCLC) is defined as all other SCLC.

Section 5.2.1 Inclusion Criteria
Criterion 1, 3, and 5 previously read:

1. Subject must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.
3. Histologically or cytologically confirmed extensive-stage SCLC with ongoing clinical benefit (SD, PR, or CR per RECIST v.1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).
5. At least 3 but no more than 9 weeks between the administration of the last cycle of platinum-based chemotherapy and randomization.

Has been changed to read:

1. Subject or the subject's legally acceptable representative must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures and should be willing and able to comply with parameters as outlined in the protocol.

3. Histologically or cytologically confirmed ED SCLC (extensive stage disease at initial diagnosis), with ongoing clinical benefit (SD, PR, or CR per RECIST v.1.1) following completion of 4 cycles of first-line platinum-based therapy (cisplatin or carboplatin in combination with etoposide or irinotecan).

5. Subject is eligible to be randomized at least 3 but no more than 9 weeks from Day 1 of the fourth cycle of first-line platinum-based chemotherapy.

Section 5.2.1 Inclusion Criteria
Criterion 9f previously read:

Calculated creatinine clearance ≥ 30 mL/min by the Cockroft-Gault formula (Refer to Appendix E)

Has been changed to read:

Calculated creatinine clearance ≥ 30 mL/min by the modified Cockroft-Gault formula (Refer to Appendix E)

Section 5.2.2 Exclusion Criteria
Criterion 1, 2, 4, and 12 previously read:

1. Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in Inclusion Criteria 3 – 5 for the disease under study.

2. Any disease-directed radiotherapy (except PCI or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.

4. Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association

(NYHA) Class III – IV heart failure (refer to Appendix E) within 6 months prior to randomization.

12. Any prior exposure to a pyrrolobenzodiazepine (PBD)- or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.

Has been changed to read:

1. Any prior systemic chemotherapy, small molecule inhibitors, immune checkpoint inhibitors, other monoclonal antibodies, antibody-drug conjugates, radioimmunoconjugates, T-cell or other cell-based or biologic therapies, or any other anti-cancer therapy than that described in Inclusion Criteria 3 – 5 for SCLC.
2. Any disease-directed radiotherapy (except PCI, palliative radiotherapy to a radiographically documented non-progressing lesion for symptom control, or pre-planned radiotherapy for CNS metastases present prior to start of first-line therapy and non-progressing) after last dose of first-line chemotherapy.
4. Documented history of a cerebral vascular event, unstable angina, myocardial infarction, or cardiac symptoms consistent with New York Heart Association (NYHA) Class III – IV heart failure (refer to Appendix F) within 6 months prior to randomization.
12. Any prior exposure to a pyrrolobenzodiazepine (PBD-based) or indolinobenzodiazepine-based drug, prior participation in a rovalpituzumab tesirine clinical trial, or known hypersensitivity or other contraindications to rovalpituzumab tesirine or excipient contained in the drug formulation.

Section 5.2.3.1 Prior Therapy
First paragraph previously read:

Subjects will have received first-line platinum-based chemotherapy consisting of 4 cycles of treatment with combination of either cisplatin or carboplatin with etoposide or irinotecan; administration of the last cycle of first-line chemotherapy must be at least 3 weeks but no more than 9 weeks prior to randomization.

Has been changed to read:

Subjects will have received first-line platinum-based chemotherapy consisting of 4 cycles of treatment with combination of either cisplatin or carboplatin with etoposide or irinotecan; administration of Day 1 of the last cycle of first-line chemotherapy must be at least 3 weeks but no more than 9 weeks prior to randomization. Subjects previously treated for LD-SCLC are not eligible.

Section 5.2.3.2 Concomitant Therapy
Last paragraph, last sentence previously read:

However, due to the potential for rovalpituzumab tesirine-related skin photosensitivity, subjects should be advised during treatment and for 30 days after last treatment to avoid unprotected sun exposure, use a broad spectrum sunscreen with a sun protection factor (SPF) of at least 30 and re-apply sunscreen as activity-appropriate, and wear protective clothing, a broad-brimmed hat, and sunglasses when outdoors or when driving or riding in a car for more than 1 hour.

Has been changed to read:

However, due to the potential for rovalpituzumab tesirine-related skin photosensitivity, Patients should be advised to avoid direct and indirect sun exposure as much as possible from Cycle 1 Day 1 until 30 days after the final dose. When sun exposure is unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). Thirty-one to ninety days after last dose of

Rova-T/placebo, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher.

Section 5.2.3.2.1 Allowed Concomitant Therapy
First paragraph, third sentence previously read:

Bone modifying agents for bone metastases are also permitted per local institutional standards.

Has been changed to read:

Bone modifying agents (e.g., bisphosphonates, denosumab) for bone metastases are also permitted per local institutional standards.

Section 5.3.1.1 Study Procedures
Subsection Vital Signs
First paragraph, second sentence previously read:

Vital signs include weight, sitting blood pressure, heart rate and body temperature.

Has been changed to read:

Vital signs include actual weight, sitting blood pressure, heart rate and body temperature.

Section 5.3.1.1 Study Procedures
Subsection Vital Signs
Second paragraph previously read:

Weight will be collected in the clinic prior to dosing at each cycle and the recorded weight will be utilized for dosing calculations. For weight assessments, the subject should not wear shoes.

Has been changed to read:

Actual weight will be collected in the clinic prior to dosing at each cycle and the recorded weight will be utilized for dosing calculations. For weight assessments, the subject should not wear shoes. In the event of a 5% or greater increase in weight within 2 consecutive visits or compared to baseline which ever has the shorter interval, a prompt workup for fluid retention (e.g., edema, effusions, etc.) should be conducted. If weight gain is due to proven or suspected fluid retention related to study drug, and dosing is not prohibited per Section 5.5.4, dose should be calculated based on actual weight before the event of fluid retention.

Section 5.3.1.1 Study Procedures
Subsection Echocardiogram
Previously read:

Echocardiograms will be performed per Appendix C, Study Activities to assess any pericardial effusion, if present, as well as cardiac function (left ventricular ejection fraction, LVEF).

Has been changed to read:

Echocardiograms will be performed per Appendix C, Study Activities to rule out pericardial effusion (or assess, if present), as well as assess cardiac function (left ventricular ejection fraction, LVEF).

Section 5.3.1.1 Study Procedures
Subsection Disease/Response Assessment (Radiographic Imaging)
Last paragraph previously read:

Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study every 6 weeks after randomization, unless evidence of tumor metastases warrants otherwise. Subjects who discontinue treatment for reasons other than

radiographic disease progression will continue to be followed every 6 weeks from C1D1 to determine the extent of tumor burden, until disease progression occurs.

Has been changed to read:

Scheduled tumor assessments should not be affected by delays in therapy and/or drug holidays. Subjects will continue to be monitored by the same diagnostic method throughout the study every 6 weeks after randomization, unless evidence of tumor progression warrants otherwise. In some cases, mandatory dose delays due to toxicity will lead to a gap between tumor assessment and dosing. In cases where this gap exceeds 1 week, the TAMD should be contacted for guidance.

Subjects who discontinue treatment for reasons other than radiographic disease progression will continue to be followed every 6 weeks from randomization to determine the extent of tumor burden, until disease progression occurs.

Section 5.3.1.1 Study Procedures
Subsection MRI/CT of the Brain
Last sentence previously read:

MRI/CT of the brain is only required at screening and when clinically indicated (e.g., if CNS progression is suspected).

Has been changed to read:

MRI/CT of the brain is required at screening and when clinically indicated (e.g., if CNS progression is suspected) thereafter.

Section 5.3.1.1 Study Procedures
Subsection Fluid Retention Questionnaire (Including Subject Daily Weight)
Last paragraph, last sentence previously read:

The site will advise subjects to contact the site in cases where sudden weight gain is observed for possible assessment in the clinic.

Has been changed to read:

The site will advise subjects to contact the site in cases where sudden weight gain (5% or greater) is observed for possible assessment in the clinic.

Section 5.3.1.1 Study Procedures
Subsection End of Treatment (EOT) Visit
Add: new second sentence

The EOT procedures should be done within 7 days of documented decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

Section 5.3.1.1 Study Procedures
Subsection End of Treatment (EOT) Visit
Delete: third sentence

The visit should occur within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

Section 5.3.3.2 Primary Variables
Previously read:

The primary endpoints are progression-free survival (PFS) determined by a Central Radiographic Assessment Committee (CRAC) and overall survival (OS).

Has been changed to read:

The primary endpoints are progression-free survival (PFS) determined by a Central Radiographic Assessment Committee (CRAC) per RECIST v. 1.1 and overall survival (OS) in $DLL3^{high}$ population.

Section 5.3.3.3 Secondary Variables
Previously read:

The secondary variables are progression-free survival (PFS) based on investigator assessment, objective response rate (ORR) per the CRAC and investigator assessment, respectively, and clinical benefit rate (CBR) per the CRAC and investigator assessment, respectively, and the duration of response (DOR) per the CRAC and investigator assessment, respectively. Response assessment will be based on RECIST v1.1. Changes in patient reported outcomes (PROs) as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13) are also secondary endpoints in this study.

Has been changed to read:

The secondary variables are progression-free survival (PFS) determined by a Central Radiographic Assessment Committee (CRAC) per RECIST v. 1.1 and overall survival (OS) in randomized set population. Change in patient reported outcome (PRO) with physical functioning as measured by European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in randomized set population is also a secondary endpoint in this study.

Section 5.3.3.4 Exploratory Variables
Add: new section title and text

5.3.3.4 Exploratory Variables

The exploratory variables are progression-free survival (PFS) based on investigator assessment, objective response rate (ORR) per the CRAC and investigator assessment, respectively, clinical benefit rate (CBR) per the CRAC and investigator assessment, respectively, and the duration of response (DOR) per the CRAC and investigator assessment, respectively. Response assessment will be based on RECIST v1.1. Changes in patient reported outcomes (PROs) as measured by EQ-5D-5L and all other PRO domains (except for physical functioning) as measured by European Organization for

Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) and Lung Cancer Module (QLQ-LC13) are also exploratory endpoints in this study.

Section 5.3.5 Pharmacokinetic Variables
Previously read:

Plasma concentrations of rovalpituzumab tesirine ADC as well as the timing and incidence of ATAs will be tabulated and summarized.

Has been changed to read:

Serum concentrations of rovalpituzumab tesirine ADC as well as the timing and incidence of ATAs will be tabulated and summarized.

Section 5.5.1 Treatments Administered
First paragraph, last sentence previously read:

If the dose of dexamethasone is vomited within 15 minutes of taking the medication, the subject should retake the medication.

Has been changed to read:

If the dose of dexamethasone/placebo is vomited within 15 minutes of taking the medication, the subject should retake the medication.

Section 5.5.2.1 Packaging and Labeling
Subsection <u>Rovalpituzumab Tesirine and Placebo</u>
Add: new last sentence

Rova-T drug product is classified as a Dangerous Goods/Hazardous Material and is packaged and shipped by AbbVie according to US Department of Transportation (DOT) and International Air Transport Association (IATA) certified regulations.

Section 5.5.2.2 Storage and Disposition of Blinded Investigational Product(s)
Subsection Rovalpituzumab Tesirine/Placebo
Add: new last sentence

Specific storage conditions for reconstituted and diluted rovalpituzumab tesirine/placebo will be provided in a separate document outside of this protocol.

Section 5.5.2.3 Preparation/Reconstitution of Dosage Form(s)
Fourth sentence previously read:

The rovalpituzumab tesirine drug product is dosed based on body weight.

Has been changed to read:

The rovalpituzumab tesirine drug product is dosed based on actual body weight.

Section 5.5.2.3 Preparation/Reconstitution of Dosage Form(s)
Add: new tenth sentence

Specific dose preparation and documentation details will be provided to the site pharmacy in a separate document.

Section 5.5.4.1 Dosing
First paragraph
Add: new last sentence

In cases of weight gain due to fluid retention, dosing should be based on most recent pre-fluid retention actual weight.

Table 5. Dose Reductions and Discontinuation for Unacceptable Toxicities
Toxicity "Grade 4 LFTs or Grade 3 LFTs with concomitant Bilirubin Grade 2 or higher" previously read:

Grade 4 LFTs or Grade 3 LFTs with concomitant Bilirubin Grade 2 or higher

Has been changed to read:

Grade 4 LFTs or Grade 3 LFTs with concomitant Bilirubin Grade 2 or higher[b]

Table 5. Dose Reductions and Discontinuation for Unacceptable Toxicities
Add: new toxicity "Grade 2 pneumonitis" and "Grade ≥ 3 pneumonitis"

Grade 2 pneumonitis	Reduce dose to 0.1 mg/kg	Discontinue Rova-T
Grade ≥ 3 pneumonitis	Discontinue Rova-T	N/A

Table 5. Dose Reductions and Discontinuation for Unacceptable Toxicities
Add: new footnote "b."

b. If potential DILI is suspected please follow guidelines of Section 6.1.8.3.

Section 5.5.5.2 Blinding of Data for Independent Data Monitoring Committee (IDMC)
Last sentence previously read:

Final PFS data with interim OS data will be analyzed and reviewed by the IDMC for recommendation.

Has been changed to read:

For the futility analysis, OS, other efficacy and safety data will be analyzed and reviewed by the IDMC for recommendation.

Section 5.5.7 Drug Accountability
Fourth paragraph
Add: new last sentence

Rova-T is classified as a Dangerous Good/Hazardous Material according to US Department of Transportation (DOT) and International Air Transport Association (IATA).

Dangerous Goods/Hazardous Materials must be packaged and shipped according to applicable regulations.

Section 6.1.1.3 Adverse Events Expected Due to SCLC or Progression of SCLC
Last paragraph previously read:

"Disease progression" should not be captured when reporting AEs or SAEs, even if fatal, as disease progression is an efficacy endpoint for the trial. Rather, symptoms of disease progression should be reported as AEs or SAEs as appropriate.

Has been changed to read:

Although exempted from expedited reporting to Health Authorities and Institutional Review Boards (IRBs) as individual cases, these SAEs must be reported to the Sponsor within 24 hours of the site being made aware of the SAE.

AEs or SAEs should not be reported as "Disease progression," even if fatal, as PD is an efficacy endpoint for the study. Rather, report the specific disease (clinical) manifestation of the progression (eg, 'malignant pleural effusion,' 'spinal bone metastases,' 'lymphadenopathy,' 'brain metastases') or if not possible, report "malignant neoplasm progression" as the AE or SAE as appropriate.

Section 6.1.4 Deaths
Second paragraph previously read:

Deaths that occur during the protocol specified AE reporting period (Section 6.1.6) that are more likely related to disease progression will therefore be considered as an expected AE and will not be subject to expedited reporting. These events should be captured as disease progression and recorded on the AE eCRF. After the AE reporting period, deaths attributed to progression of disease under study should not be recorded on the AE eCRF.

Has been changed to read:

Deaths that occur during the protocol specified AE reporting period (Section 6.1.6) that are more likely related to disease progression will therefore be considered as an expected SAE and will not be subject to expedited reporting. These events should be recorded on the AE eCRF as described in Section 6.1.1.3. After the AE reporting period, deaths attributed to progression of disease under study should not be recorded on the AE eCRF.

Section 6.1.5 Adverse Event Collection Period
First paragraph, first sentence previously read:

All adverse events reported from the time of blinded investigational product administration until 70 days following discontinuation of blinded investigational product administration will be collected, whether solicited or spontaneously reported by the subject.

Has been changed to read:

All adverse events reported from the time of blinded investigational product administration until 70 days following the last dose of blinded investigational product will be collected, whether solicited or spontaneously reported by the subject.

Section 6.1.6 Adverse Event Reporting
"Primary Therapeutic Area Medical Director:" previously read:

[redacted]
Therapeutic Area Medical Director
AbbVie
200 Sidney Street
Cambridge, MA 02139

Telephone Contact Information:
Office:
Mobile:
Email:

Has been changed to read:

[redacted]
Senior Medical Director
AbbVie
1 North Waukegan Road
North Chicago, IL 60064
USA

Telephone Contact Information:
Office:
Mobile:
Email: [redacted]

Section 6.1.6 Adverse Event Reporting
Fifth paragraph previously read:

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure[14] and the most current version of the Summary of Product Characteristics (SmPC).

Has been changed to read:

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

Section 6.1.8.1 Management of Serosal Effusions/Serositis
First paragraph, first sentence previously read:

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

Has been changed to read:

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

Section 6.1.8.1 Management of Serosal Effusions/Serositis
First paragraph
Add: new fifth and sixth sentence

Effusion events were reported during treatment and may occur up to several months after last Rova-T dose. As a result, subjects should be advised of signs and symptoms of fluid retention and contact treating physician if they arise during this time.

Section 6.1.8.2 Management of Skin Reactions
Add: new second paragraph

Photosensitivity reactions may occur hours to days after sun exposure. Patients should be advised to avoid direct and indirect sun exposure as much as possible from Cycle 1 Day 1 until 30 days after the final dose. When sun exposure is unavoidable, patients should wear protective clothing and sunglasses, and use a broad-spectrum sunscreen and lip balm (SPF 30 or greater). Thirty-one to ninety days after last dose of Rova-T/placebo, the patient may resume outdoor activities with appropriate sun protection including broad brimmed hat, protective clothing and sunscreen SPF 30 or higher. Subjects with a grade 3 photosensitivity reaction should dose reduce Rova-T/placebo to 0.2 mg/kg after the first occurrence and following a second grade 3 photosensitivity reaction, reduce Rova-

T/placebo to 0.1 mg/kg. Subjects with a grade 4 photosensitivity reaction must permanently discontinue Rova-T/placebo.

Section 6.1.8.2 Management of Skin Reactions
Second paragraph previously read:

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

Has been changed to read:

If clinically consistent with photosensitivity, the AE should be reported as such (using medically accurate and descriptive AE terminology), and managed as described in Table 6.

Section 6.1.8.2 Management of Skin Reactions
Third paragraph, first sentence previously read:

Photo-documentation should be available upon request by the TA MD.

Has been changed to read:

Photo-documentation of skin toxicity should be available upon request by the TA MD.

Section 6.1.8.4 Monitoring and Management of Edema
Add: new section title and text

6.1.8.4 Monitoring and Management of Edema

The majority of the edema events with rovalpituzumab tesirine have been reported as low grade 1 or 2 (mild or moderate); however, a small number of fatal events of generalized edema have been reported with rovalpituzumab tesirine. Physical exams and monitoring of weight gain and signs or symptoms of fluid retention should be conducted during treatment. Edema events were reported during treatment and may occur up to several

months after last Rova-T dose. As a result subjects should be advised of signs and symptoms of fluid retention as well as monitor their weight and contact treating physician if they arise during this time.

Consistent with institutional guidelines or standard practice, the use of diuretics with or without albumin may be considered in subjects with clinically significant edema and hypoalbuminemia. The selection and use of diuretics in subjects should be based on individual clinical characteristics and include monitoring of electrolyte status and signs or symptoms of intravascular volume depletion such as hypotension and impaired renal function.

Systemic corticosteroids, when initiated promptly, have been reported to be beneficial in some prior cases.

Reported Term	Grade 1	Grade 2	Grade 3	Grade 4
Generalized edema (Anasarca)	Noted on exam; 1+ pitting edema	Interfering with instrumental ADLs; oral therapy initiated	Interferes with self care ADL; intravenous therapy indicated; skin breakdown	Life-threatening consequences
Definition: A disorder characterized by fluid accumulation in the tissues of the body including the skin.				
Edema trunk	Swelling or obscuration of anatomic architecture on close inspection	Readily apparent obscuration of anatomic architecture; obliteration of skin folds; readily apparent deviation from normal anatomic contour; limiting instrumental ADL	Gross deviation from normal anatomic contour; limiting self care ADL	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the trunk area.				
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	-
Definition: A disorder characterized by swelling due to excessive fluid accumulation in the upper or lower extremities				

Section 6.1.8.5 Pneumonitis

Add: new section title and text

6.1.8.5 Pneumonitis

Pneumonitis has been infrequently reported with rovalpituzumab tesirine but has resulted in fatal outcomes. Although the causal role of rovalpituzumab tesirine could not be ruled out, the reports of pneumonitis had one or more confounders including underlying pulmonary disease/cancer, prior thoracic radiation, prior cytotoxic chemotherapy or clinical evidence suggestive of an alternative diagnosis including pneumonia.

Heavily pretreated SCLC patients and patients with a history of pneumonitis may be at increased risk, and careful monitoring for signs and symptoms of pneumonitis is important. The risk of pneumonitis is increased with prior radiation to lung.

In general, signs and symptoms coinciding with or preceding pneumonitis may include new or worsening cough, chest pain and/or shortness of breath, fever, and radiographic changes (reticular markings, ground glass opacities). Protocol defined disease assessments provide the opportunity for on study pulmonary monitoring with "gold standard" diagnostic method for detection of pneumonitis. The protocol allows for additional imaging per physician discretion for signs and symptoms of pulmonary toxicity.

The diagnosis of drug induced pneumonitis is one of exclusion. Other etiologies including infection, which is a common cause of pulmonary infiltrates with clinical and radiographic appearance similar to drug-induced pneumonitis, need to be carefully considered and excluded before the diagnosis of drug induced pneumonitis can be established.

If pneumonitis is suspected, close monitoring including additional laboratory and imaging investigation per institutional guidelines may be necessary. Systemic corticosteroids may be beneficial for rapidly progressive or more severe pneumonitis. For events of Grade 1 pneumonitis close monitoring is recommended; while dose modifications for Grade 2 and discontinuation of Rova-T for Grades 3 and 4 are required. Please see Table 5.

Section 7.0 Protocol Deviations

Contact Information previously read:

Primary Contact:	Alternate Contact:
[redacted] Study Management Associate III AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064 Office: [redacted] Fax: Email:	[redacted] Study Project Manager I AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: [redacted] Fax: Email:

Has been changed to read:

Primary Contact:	Alternate Contact:
[redacted] Study Project Manager II AbbVie Corporation 8401 Trans-Canada Highway Saint-Laurent, Québec H4S 1Z1 Canada Phone: [redacted] Fax: Email:	[redacted] Study Project Manager I AbbVie s.r.o. METRONOM BUSINESS CENTER Bucharova 2817/13, Stodulky, 158 00 Praha 5 Czech Republic Phone: [redacted] Fax: Email:

Section 8.1 Statistical and Analytical Plans

Second paragraph previously read:

Two analyses are planned for this study. The first will be performed when at least 407 progression-free survival (PFS) events, assessed by a Central Radiographic

Assessment Committee (CRAC) according to RECIST v1.1, and at least 239 deaths have occurred in subjects with DLL3^{high}. The second analysis will be performed when at least 319 deaths have occurred in subjects with DLL3^{high}.

Has been changed to read:

The primary endpoints of OS and progress free survival (PFS) assessed by a Central Radiographic Assessment Committee (CRAC) according to RECIST v1.1 in DLL3^{high} patients will be analyzed at the same time after observing at least 319 OS events. It is expected at approximately 420 PFS events will be observed at the time of the primary analysis.

Section 8.1 Statistical and Analytical Plans
First and second bullet previously read:

- **DLL3^{high} Set:** It includes all randomized subjects with DLL3^{high}. Subjects will be classified according to the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The DLL3^{high} set will be the primary analysis set for the analysis of efficacy endpoints.
- **Randomized Set:** It includes all randomized subjects, with subjects grouped according to the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The randomized set will be used for supportive analysis of efficacy endpoints.

Has been changed to read:

- **DLL3^{high} Set:** It includes all randomized subjects with DLL3^{high} ED SCLC. Subjects will be classified according to the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The DLL3^{high} set will be the analysis set for the analysis of the primary efficacy endpoints of OS and PFS. All the exploratory efficacy endpoints will be analyzed based on the DLL3^{high} set unless the OS and PFS based on the randomized set are statistically significant.
- **Randomized Set:** It includes all randomized subjects, with subjects grouped according to the treatment arm to which they are randomized regardless the actual treatment received, following intent-to-treat principle. The randomized set will be the analysis set for key secondary efficacy endpoints of OS and PFS, and key secondary endpoint of EORTC QLQ-C30 physical functioning domain. All the exploratory efficacy endpoints will be analyzed based on the randomization set if the OS and PFS based on the randomization set are statistically significant.

Section 8.1.3 Efficacy Endpoints and Analyses
Delete: first sentence

Unless specified otherwise, efficacy analyses will be performed in the DLL3^{high} set.

Section 8.1.4 Primary Efficacy Endpoints
First paragraph previously read:

Progression-free survival (PFS) and overall survival (OS) are the two primary efficacy endpoints. No order of testing of these two endpoints is specified.

Has been changed to read:

Progression-free survival (PFS) and overall survival (OS) in subjects with DLL3^{high} ED SCLC are the two primary efficacy endpoints.

Section 8.1.4 Primary Efficacy Endpoints
Third paragraph, second sentence previously read:

The hazard ratios of the treatment arm over the placebo arm will be calculated by a Cox's proportional hazards model stratified by randomization stratification factors.

Has been changed to read:

The hazard ratios of the treatment arm over the placebo arm will be calculated by a Cox's proportional hazards regression model adjusting for the main-effects of the stratification factors.

Section 8.1.4 Primary Efficacy Endpoints
Third paragraph, last sentence previously read:

Estimates of the treatment effect will be expressed as hazard ratio including 95% confidence intervals estimated through a Cox proportional-hazards analysis stratified by randomization stratification factors.

Has been changed to read:

Estimates of the treatment effect will be expressed as hazard ratio including 95% confidence intervals estimated through a Cox proportional-hazards regression model adjusting for the main-effects of the stratification factors.

Section 8.1.4 Primary Efficacy Endpoints
Last paragraph, third sentence previously read:

The hazard ratios of the treatment arm over the placebo arm will be calculated by a Cox's proportional hazards model stratified by randomization stratification factors.

Has been changed to read:

The hazard ratios of the treatment arm over the placebo arm will be calculated by a Cox's proportional hazards regression model adjusting for the main-effects of the stratification factors.

Section 8.1.4 Primary Efficacy Endpoints
Last paragraph, last sentence previously read:

Estimates of the treatment effect on will be expressed as hazard ratio including 95% confidence intervals estimated through a Cox proportional-hazards analysis stratified by randomization stratification factors.

Has been changed to read:

Estimates of the treatment effect on will be expressed as hazard ratio including 95% confidence intervals estimated through Cox proportional-hazards regression models adjusting for the main-effects of the stratification factors.

Section 8.1.5 Secondary Efficacy Endpoints
Previously read:

8.1.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints in the DLL3^{high} set are:

- Objective response rate (ORR) per the CRAC based on RECIST v1.1
- Change in patient reported outcomes (PROs) – physical functioning domain
- PFS per investigator assessment based on RECIST v1.1
- ORR per investigator assessment based on RECIST v1.1
- Clinical benefit rate (CBR) per the CRAC and investigator assessment, respectively, based on RECIST v1.1
- Duration of response (DOR) per CRAC and investigator assessment, respectively

The following endpoints in the randomized set are also included in the secondary efficacy endpoints:

- OS
- PFS per the CRAC based on RECIST v1.1
- ORR per the CRAC based on RECIST v1.1

Secondary time-to-event endpoints (PFS and OS) will be analyzed using the similar statistical methods described for the primary endpoints.

The duration of overall response for a given subject will be defined as the number of months from the day the criteria are met for complete response (CR) or partial response (PR) by CRAC (whichever is recorded first) to the date of progressive disease or death, whichever comes first. If a subject is still responding (i.e., has not progressed nor died after CR or PR), then the subject's data will be censored at date of the last radiographic assessment by CRAC. For subjects who never experienced CR or PR, these subjects' data will not be included in the duration of response analysis. Distribution of the duration of response will be estimated for each treatment arm using Kaplan-Meier methodology. Median duration of overall response with corresponding 95% CI for each treatment arm will be provided.

ORR and CBR in the treatment arm will be compared using Cochran-Mantel-Haenszel test stratified by randomization stratification factors. Rates and 95% confidence intervals will be reported for each treatment arm.

Has been changed to read:

8.1.5 Secondary Efficacy Endpoints

The secondary efficacy endpoints in the randomized set are:

- OS

- PFS per the CRAC based on RECIST v1.1
- EORTC QLQ-C30 physical functioning domain

Secondary time-to-event endpoints (PFS and OS) will be analyzed using the similar statistical methods described for the primary endpoints.

8.1.6 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints in both DLL3^{high} and randomization set are:

- Objective response rate (ORR) per the CRAC based on RECIST v1.1
- PFS per investigator assessment based on RECIST v1.1
- ORR per investigator assessment based on RECIST v1.1
- Clinical benefit rate (CBR) per the CRAC and investigator assessment, respectively, based on RECIST v1.1
- Duration of response (DOR) per CRAC and investigator assessment, respectively
- Change from baseline in all PRO domains (except physical functioning) measured by EORTC QLQ-C30/LC13 and EQ-5D-5L

ORR is defined as the proportion of patients with a best overall response (BOR) of confirmed complete response (CR) or partial response (PR) by CRAC review according to RECIST v1.1.

CBR is defined as the proportion of patients with a BOR of CR or PR, or SD by CRAC review according to RECIST v1.1.

ORR and CBR in treatment arms will be compared using Cochran-Mantel-Haenszel test stratified by randomization stratification factors. Rates and 95% confidence intervals will be reported for each treatment arm.

The duration of overall response for a given subject will be defined as the number of months from the day the criteria are met for confirmed complete response (CR) or partial

response (PR) by CRAC (whichever is recorded first) to the date of progressive disease or death, whichever comes first. If a subject is still responding (i.e., has not progressed nor died after CR or PR), then the subject's data will be censored at date of the last radiographic assessment by CRAC. For subjects who never experienced CR or PR, these subjects' data will not be included in the duration of response analysis. Distribution of the duration of response will be estimated for each treatment arm using Kaplan-Meier methodology. Median duration of overall response with corresponding 95% CI for each treatment arm will be provided.

Section 8.1.6 Patient Reported Outcomes (PRO)
First sentence previously read:

Physical functioning scale score in EORTC QLQ-C30 is the primary PRO endpoint.

Has been changed to read:

Physical functioning scale score in EORTC QLQ-C30 is the key secondary endpoint.

Section 8.1.7 Planned Sensitivity and Subgroup Analyses
Delete: first paragraph

Efficacy analyses for PFS per investigator assessment and ORR per investigator assessment will be performed in the randomized set.

Section 8.1.7 Planned Sensitivity and Subgroup Analyses
Delete: third paragraph

The physical functioning scale score (EORTC QLQ-C30) will be evaluated using an ANOVA model in the randomized set.

Section 8.1.7 Planned Sensitivity and Subgroup Analyses
Delete: last paragraph

In the DLL3^{high} and randomized sets, CRAC assessed ORR will be compared between the 2 arms, using a chi-square test for each subgroup. Odds ratios will be presented.

Section 8.1.8 Pharmacokinetic and Exposure-Response Analyses
First paragraph previously read:

Plasma concentrations of rovalpituzumab tesirine ADC as well as the incidence and timing of ATA formation will be tabulated and summary statistics will be computed. Plasma concentration and ATA data from this study may be combined with data from other studies and analyzed using population pharmacokinetic methodologies.

Has been changed to read:

Serum concentrations of rovalpituzumab tesirine ADC as well as the incidence and timing of ATA formation will be tabulated and summary statistics will be computed. Serum concentration and ATA data from this study may be combined with data from other studies and analyzed using population pharmacokinetic methodologies.

Section 8.3 Type I Error Adjustment Procedure for Multiple Testing
Previously read:

To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) for comparisons of rovalpituzumab tesirine arm versus placebo arm with respect to progression-free survival (PFS) per CRAC, overall survival (OS), ORR per CRAC, and physical functioning scale score (EORTC QLQ-C30).

The following null hypotheses are considered for subjects with DLL3^{high}:

H1: Rovalpituzumab tesirine arm is not superior to placebo arm in both PFS and OS.

H2: Rovalpituzumab tesirine arm is not superior to placebo arm in ORR per CRAC.

H3: Rovalpituzumab tesirine arm is not superior to placebo arm in physical functioning scale score (EORTC QLQ-C30).

The null hypotheses will be tested in a fixed sequence of {H1, H2, H3} in order. To maintain the family-wise type I error for the study, the null hypothesis H1 will be first tested with an alpha-split approach. The hypothesis for PFS will be tested at a one-sided 0.25% level of significance and the hypothesis for OS at a one-sided 2.25% level of significance. If either PFS or OS endpoint reaches statistical significance, the study is considered positive. No further tests will be performed if H1 is not rejected. Each hypothesis of H2 and H3 will be tested in order specified above if H1 is rejected and the preceding hypothesis shows statistically significant results at the 1-sided 2.5% level of significance. Otherwise testing in the hierarchical sequence will stop.

The secondary efficacy endpoints, e.g., PFS per investigator assessment, ORR per investigator assessment, CBR per CRAC, CBR per investigator assessment, DOR per CRAC, DOR per investigator assessment, and PRO evaluations in the $DLL3^{high}$ set will be tested at a one-sided 2.5% level of significance. Similarly, OS, PFS per CRAC, and ORR per CRAC in the randomized set will be tested at a one-sided 2.5% level.

Has been changed to read:

To meet global regulatory requirements, a multiple testing strategy will be implemented to control the family-wise type I error (alpha) to one-sided 0.025 level for comparisons of rovalpituzumab tesirine arm versus placebo arm with respect to progression-free survival (PFS) per CRAC in $DLL3^{high}$ set, overall survival (OS) in $DLL3^{high}$ set, PFS per CRAC in randomized set, OS in randomized set, and physical functioning scale score (EORTC QLQ-C30) in randomized set.

The following null hypotheses are considered:

Two hypotheses in H_{01} are H_{01a} and H_{01b}.

H_{01a}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in $DLL3^{high}$ set.

H_{01b}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in $DLL3^{high}$ set.

H_{02}: Rovalpituzumab tesirine arm is not superior to placebo arm in OS in randomized set.

H_{03}: Rovalpituzumab tesirine arm is not superior to placebo arm in PFS per CRAC in randomized set.

H_{04}: Rovalpituzumab tesirine arm is not superior to placebo arm in physical functioning scale score (EORTC QLQ-C30) in randomized set.

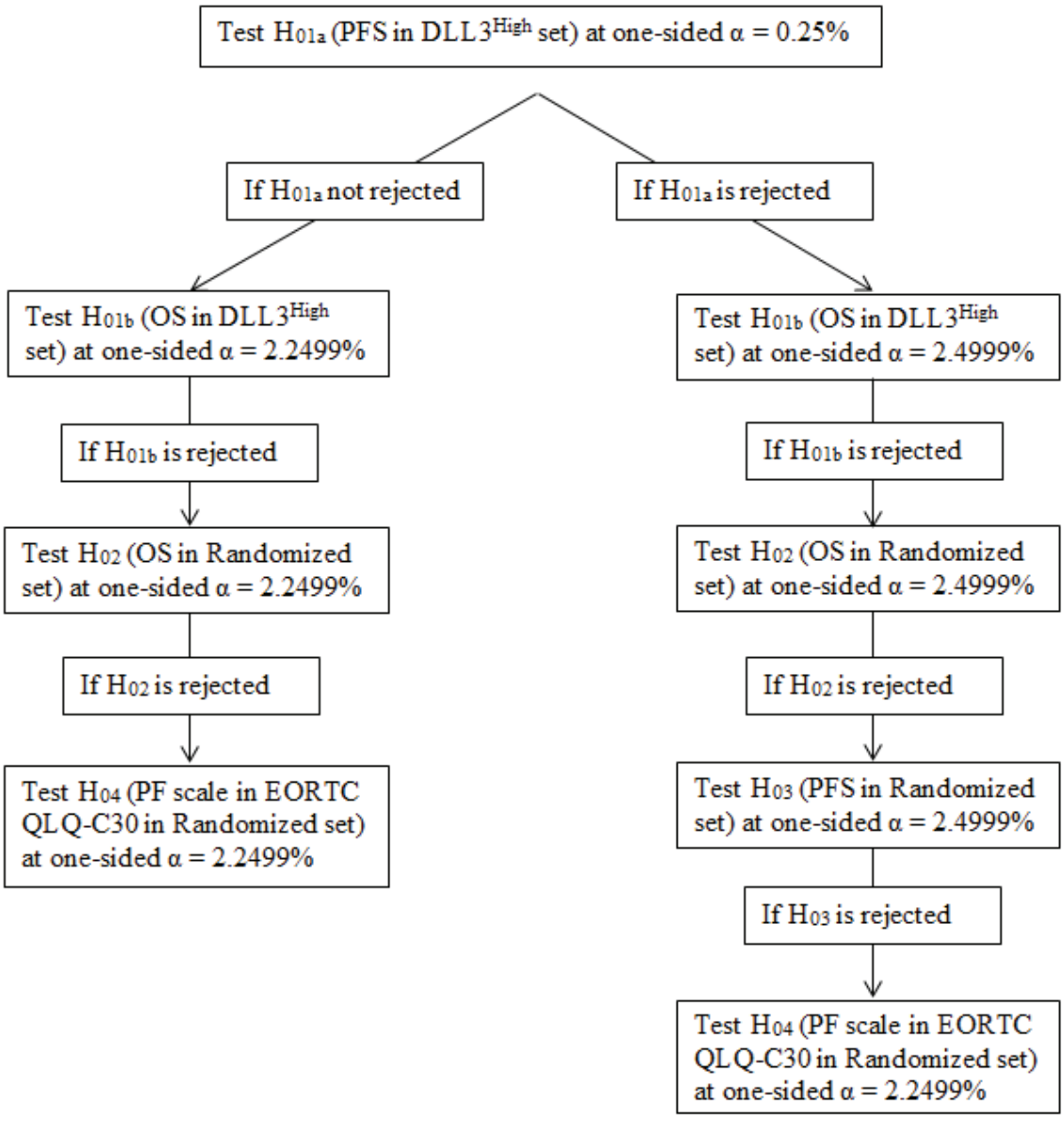
The null hypotheses will be tested in a fixed sequence of {H_{01a}, H_{01b}, H_{02}, H_{03}, and H_{04}} in order. To maintain the family-wise type I error for the study, the null hypotheses in H_{01} (H_{01a} and H_{01b}) will be first tested with an alpha-split approach. The one-sided alpha of 0.25% and 2.25% will be assigned for PFS and OS hypothesis in H_{01}, respectively. Out of one-sided alpha of 2.25% allocated to OS hypothesis (H_{01b}), the one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis. If the hypothesis for PFS in H_{01} (H_{01a}) is rejected the one-sided alpha of 0.25% will be recycled to the OS hypothesis in H_{01} (H_{01b}). Hence, the hypothesis for OS in H_{01} (H_{01b}) will be tested either at a one-sided 2.4999% or one-sided 2.2499% level of significance depending on the PFS hypothesis in H_{01a} is rejected or not.

If either PFS or OS endpoint reaches statistical significance, the study is considered positive. No further tests will be performed if the OS endpoint in $DLL3^{high}$ population (H_{01b}) does not reach statistical significance.

The hypothesis in H_{02} will be tested if the hypothesis in H_{01b} is rejected. If the hypothesis in H_{02} is rejected, then, either (i) H_{03} and H_{04} will be tested sequentially if the PFS endpoint in $DLL3^{high}$ subjects (H_{01a}) is also rejected or (ii) only H_{04} will be tested if the PFS endpoint in $DLL3^{high}$ subjects (H_{01a}) is not rejected.

Diagram of Hierarchical Testing of Primary and Secondary Endpoints is described in Figure 3.

Figure 3. Diagram of Hierarchical Testing of Primary and Secondary Endpoints



Section 8.4 Determination of Sample Size
Previously read:

There are two primary efficacy endpoints for this study: Progression-free survival (PFS) based on the CRAC and overall survival (OS). To maintain the overall 1-sided type I error at a 2.5% for this study, the type I error will be split, assigning 0.25% to progression-free survival and the remaining 2.25% to overall survival.

The sample size of the study is primarily determined by the analysis of OS. It is assumed, taking into account the expected patient population for the study, that median overall survival in the placebo arm will be around 9 months.[4,5] Based on a log-rank test, at a one-sided significance level of 0.0225 and a power of 90%, a total of 319 deaths among subjects with $DLL3^{high}$ are needed to detect an increase of median OS to 13 months in rovalpituzumab tesirine arm, corresponding to a hazard ratio of 0.69 (i.e., a reduction in the hazard death of 31%). Assuming a 19-month accrual period and the last enrolled subject followed for 12 months, at least 480 subjects with $DLL3^{high}$ are expected to be randomized (240 subjects in each arm). A total of 740 subjects regardless of DLL3 expression level (including 480 subjects with $DLL3^{high}$) will enroll in the study, assuming an approximate prevalence of 65% for subjects with $DLL3^{high}$. It is projected that an observed hazard ratio of 0.795 or less, corresponding to a 2.3 months or greater improvement in median OS, would result in a statistically significant improvement in the final analysis of OS.

It is assumed, taking into account the expected patient population for the study, that median progression-free survival for the placebo arm will be approximately 3 months.[4,5] Treatment with rovalpituzumab tesirine is hypothesized to increase median progression-free survival to 4.5 months (i.e., a hazard ratio of 0.667). With approximately 407 PFS events assessed by the CRAC for subjects with $DLL3^{high}$, the study provides a 90% power to detect a hazard ratio of 0.667 in PFS at a one-sided significance level of 0.0025. It is projected that an observed hazard ratio of 0.757 or less, corresponding to approximately

1 month or greater improvement in median PFS, would result in a statistically significant improvement in the PFS.

The primary analysis of PFS will take place when at least 407 CRAC assessed PFS events and at least 239 deaths (an interim efficacy analysis of OS with approximately 75% of targeted 319 deaths) have occurred in subjects with $DLL3^{high}$. When both conditions specified for the numbers of PFS and OS events are satisfied, the primary analysis of PFS and the interim efficacy analysis of OS will be performed at the same time. The final analysis of OS is projected to be approximately 31 months from first subject enrolled when approximately 319 deaths have occurred in subjects with $DLL3^{high}$.

Has been changed to read:

There are two primary efficacy endpoints for this study: Progression-free survival (PFS) based on the CRAC and overall survival (OS) in $DLL3^{high}$ ED SCLC patients. To maintain the overall 1-sided type I error at a 2.5% for this study, the type I error will be split, assigning 0.25% to progression-free survival and the remaining 2.25% to overall survival. However, the OS endpoint will be tested at a one-sided 2.2499% significance level as a one-sided alpha of 10^{-6} will be spent for the early look at the OS data for futility analysis.

The sample size of the study is primarily determined by the analysis of OS. It is assumed, taking into account the expected patient population for the study, that median overall survival in the placebo and rovalpituzumab tesirine arm will be around 9 months and 13 months, respectively. The increase of median OS in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.69, i.e., a reduction in the hazard of death by 31%. With all these assumptions, a total of 319 deaths among subjects with $DLL3^{high}$ are needed to achieve a 90% power based on a log-rank test at a one-sided significance level of 0.022499. Assuming a 19-month accrual period and the last enrolled subject followed for 12 months, at least 480 subjects with $DLL3^{high}$ are expected to be randomized (240 subjects in each arm). A total of 740 subjects regardless of DLL3 expression level (including 480 subjects with $DLL3^{high}$) will enroll in the study, assuming an approximate

prevalence of 65% for subjects with DLL3^{high}. For one-sided significance level of 0.022499, it is projected that an observed hazard ratio of 0.799 or less, corresponding to a 2.3 months or greater improvement in median OS, would result in a statistically significant improvement in the primary analysis of OS.

The primary endpoints of OS and PFS in DLL3^{high} patients will be analyzed at the same time after observing at-least 319 OS event. It is expected at approximately 420 PFS events will be observed at the time of the primary analysis.

It is assumed, taking into account the expected patient population for the study, that median progression-free survival for the placebo and rovalpituzumab tesirine arm will be approximately 3 months and 4.5 months, respectively. The increase of median progression-free survival in rovalpituzumab tesirine arm corresponds to a hazard ratio of 0.667. With all these assumptions, a total of approximately 420 PFS events assessed by the CRAC for the subjects with DLL3^{high} are needed to achieve a 91% power based on a log-rank test at a one-sided significance level of 0.0025. It is projected that an observed hazard ratio of 0.760 or less, corresponding to approximately 1 month or greater improvement in median PFS, would result in a statistically significant improvement in the PFS.

Section 8.5 Interim Analysis
Section title and text previously read:

8.5 Interim Analysis

An interim efficacy analysis is planned for overall survival after at least 239 deaths in subjects with DLL3^{high} (i.e., 75% of planned deaths are observed) using a one-sided log-rank test.

The O'Brien-Fleming method will be implemented to protect the type I error rate of 0.0225 for OS. A one-sided alpha spending of 0.0084 for the interim will be allocated for declaring statistical superiority in OS at the time of the interim analysis. The final analysis of OS will be performed at a one-sided nominal alpha level of 0.01998, adjusting

for the interim look at OS data. If the interim analysis of OS meets the O'Brien-Fleming boundary for statistical significance, the final OS analysis will be considered descriptive.

Unblinded interim data will be analyzed and reviewed by the IDMC. The trial may be considered for early stopping for superiority and the Sponsor will be unblinded to the aggregated data by randomized treatment arms if the IDMC makes such a recommendation after consideration of the PFS and OS results, and all supportive evidence including other efficacy endpoints and safety.

In the event that the IDMC recommends continuing the study due to lack of evidence for superiority, the unblinded interim results will be kept confidential to the investigators, subjects, sponsors, and personnel involved in the conduct of the study until the end of the study, since the final analyses of OS and all other endpoints will be performed in an inferentially seamless manner. Subjects already enrolled in the study will continue rovalpituzumab tesirine or placebo treatment in a blinded fashion to obtain more mature OS data for a robust characterization of treatment effect.

Details for the interim efficacy analysis will be provided in the IDMC charter.

Has been changed to read:

8.5 Futility Analysis

A futility analysis will be conducted when approximately 160 deaths in subjects with $DLL3^{high}$ ED SCLC (approximately 50% of the planned deaths) are observed. The trial may be stopped for futility if the estimated Overall Survival Cox HR of Rova-T to Placebo in the $DLL3^{high}$ set at futility analysis exceeds 0.9. The one-sided alpha of 10^{-6} will be spent for the early look at the efficacy data for futility analysis.

Unblinded interim data will be analyzed and reviewed by the IDMC. The trial may be considered for early stopping for futility and the Sponsor will be unblinded to the aggregated data by randomized treatment arms if the IDMC makes such a

recommendation after consideration of the OS results and other supportive evidence including other relevant efficacy and safety data.

Details for the futility analysis will be provided in the IDMC charter.

Section 8.6 Accrual/Study Duration Considerations
Last sentence previously read:

It is projected that 480 subjects with DLL3^{high} will have enrolled for the interim analysis by the time at least 407 PFS events per CRAC and at least 239 OS events should be observed in subjects with DLL3^{high}, and subjects have completed approximately 5 months of follow-up.

Has been changed to read:

It is projected that 480 subjects with DLL3^{high} ED SCLC will have enrolled for the primary analysis by the time approximately 420 PFS events per CRAC and at least 319 OS events should be observed in DLL3^{high} subjects after approximately 8 - 10 months of follow-up.

Section 10.1 Source Documents
First paragraph, fourth and fifth sentence previously read:

The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

Has been changed to read:

The Investigator Awareness Date of SAE should be noted in the source.

Section 15.0 References

Add: new Reference 19

AbbVie. Rovalpituzumab Tesirine Dear Rova-T Investigator Letter. 05 December 2018.

Appendix B. List of Protocol Signatories

Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Clinical
		Pharmacokinetics
		Clinical Drug Supply Management
		Statistics
		Bioanalysis

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	Clinical
		Clinical
		Pharmacokinetics
		Clinical Drug Supply Management
		Statistics
		Bioanalysis

Appendix C. Study Activities

Category "Echocardiogram[n]" previously read:

Category	Description	Screening	Treatment (Each Cycle)								Non-Treatment Cycle Visit[a]		End of Treatment[b]	PTFU[c]	Survival FU (OS)[d]
		Day –21 to Day –1	Day –1	Day 1[e] (–3d)	Day 2	Day 8	Day 15	Day 22 (–3d)	Day 29	Day 36	Day 1 (±3d)	Weekly (Day 8, 15, 22, 29, 36) (±3d)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (±1wk)	q6 Weeks (±1wk)
Safety Assessments	Echocardiogram[n]			X									X		

Has been changed to read:

Category	Description	Screening	Treatment (Each Cycle)								Non-Treatment Cycle Visit[a]		End of Treatment[b]	PTFU[c]	Survival FU (OS)[d]
		Day –21 to Day –1	Day –1	Day 1[e] (–3d)	Day 2	Day 8	Day 15	Day 22 (–3d)	Day 29	Day 36	Day 1 (±3d)	Weekly (Day 8, 15, 22, 29, 36) (±3d)	Within 7 Days of Decision to Discontinue Treatment	q6 Weeks (±1wk)	q6 Weeks (±1wk)
Safety Assessments	Echocardiogram[n]	X		X									X		

Appendix C. Study Activities
Table note "b." previously read:

End of Treatment Visit occurs within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

Has been changed to read:

End of Treatment Visit procedures should be done within 7 days of documentation of the decision to discontinue treatment and prior to subjects beginning any new anti-cancer therapy if possible.

Appendix C. Study Activities
Table note "e.," first sentence previously read:

Cycle 1 Day 1 procedures do not need to be repeated if performed within 21 days of randomization unless clinically indicated.

Has been changed to read:

Cycle 1 Day 1 procedures, with the exception of weight, do not need to be repeated if performed within 21 days of randomization unless clinically indicated.

Appendix C. Study Activities
Table note "n." previously read:

Echocardiogram will be performed to assess any pericardial effusion, if present, as well as cardiac function (left ventricular ejection fraction, LVEF).

Has been changed to read:

Echocardiograms are required at Screening, Day 1 of each cycle starting C2D1, and EOT. Screening echocardiogram will be performed within 7 business days of randomization to

assess for the presence of any pericardial effusion as well as cardiac function (left ventricular ejection fraction, LVEF). Subsequent echocardiograms should be performed within –3 business days of dosing visit to assess for the presence of any pericardial effusion. Additional echocardiogram monitoring may occur as clinically indicated during the study.

Appendix C. Study Activities
Table note "q.," seventh sentence previously read:

Scheduled tumor assessments will not be affected by delays in therapy and/or drug holidays.

Has been changed to read:

Whenever possible, scheduled tumor assessments should not be affected by delays in therapy and/or drug holidays. In some cases, mandatory dose delays due to toxicity will lead to a gap between tumor assessment and dosing. In cases where this gap exceeds 1 week, the TAMD should be contacted for guidance.

Appendix C. Study Activities
Table note "t." previously read:

MRI/CT of the brain is only required at screening and when clinically indicated (e.g., if CNS progression is suspected).

Has been changed to read:

MRI/CT of the brain is required at screening and when clinically indicated (e.g., if CNS progression is suspected) thereafter.