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Protocol for Study: M16-291

Rovalpituzumab Tesirine Extension Study

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FULL TITLE: A Multicenter, Long-Term, Rollover Extension Study of Rovalpituzumab Tesirine

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

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1 SYNOPSIS

Title: A Multicenter, Long-Term, Rollover Extension Study of Rovalpituzumab Tesirine	
Background and Rationale:	The purpose of this extension study is to provide ongoing safety and efficacy follow-up of subjects who are participating in a rovalpituzumab tesirine study that has completed the primary analysis and is closing.
Objective and Study Endpoints:	The objective of this study is to provide long-term follow-up for subjects remaining on a rovalpituzumab tesirine study that has completed the primary analysis and is closing. Safety and limited efficacy data on patients retreated with rovalpituzumab tesirine will be collected. There is no formal statistical analysis of safety or efficacy data in this study.
Investigators:	Multicenter
Study Sites:	This extension study will be conducted in ~20 sites in the same countries as the rovalpituzumab tesirine parent studies; including but not limited to, Canada, France, Latvia, Spain, the United Kingdom, and the United States. More study sites and countries may be included as other rovalpituzumab tesirine parent studies complete their primary analyses and close.
Study Population and Number of Subjects to be Enrolled:	Study population includes subjects who were enrolled in rovalpituzumab tesirine treatment studies, but have not yet reached 1 or more endpoints in the parent study at the time of primary analyses. In addition, subjects who were eligible for retreatment based on the criteria written in the parent study will have the option of retreatment in this study.
Investigational Plan:	This is a phase 2 multicenter, long-term, rollover follow-up extension study. The schedule of assessments will depend on whether subjects enter the study in post-treatment follow-up or are receiving ongoing rovalpituzumab tesirine treatment from the parent study. This extension study includes 2 Study Arms: • Arm A: Subjects who enter the extension study while in post-treatment follow-up. This arm includes optional rovalpituzumab tesirine retreatment for those who qualify, based on retreatment criteria written in the parent protocol. Most subjects from all studies will be in this arm. • Arm B: Subjects who enter the extension study while receiving ongoing rovalpituzumab tesirine treatment (e.g., Study SCRX001-007)

Key Eligibility Criteria:	For both Arms A and B; eligibility criteria are that a subject have enrolled, participated in, and received at least 1 dose of rovalpituzumab tesirine in a parent study. Additional eligibility criterion for Arm A is that subjects who discontinued the study drug in the parent study have completed the treatment emergent AE reporting window (e.g., 30 days post last dose for Study SCRX001-002). For subjects who elect optional retreatment in Arm A, below are key eligibility criteria: • Tolerated their initial 2 doses of rovalpituzumab tesirine • Achieved clinical benefit from rovalpituzumab tesirine, defined as stable disease or better, and is determined that the subject would potentially benefit from additional treatment OR • Achieved clinical benefit as defined by stable disease or better and experienced radiographic disease progression at least 12 weeks after last dose of rovalpituzumab tesirine per RECIST 1.1 • Received no other systemic anti-cancer therapy after rovalpituzumab tesirine • Laboratory values meeting the following criteria: • Absolute neutrophil count (ANC) ≥ 1,500/µL; • Platelet count ≥ 75,000/µL; • Hemoglobin ≥ 8.0 g/dL; • Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease; • Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (≤ 5 × ULN if evidence of hepatic involvement by malignant disease); • Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 as calculated by the 4-variable Modification of Diet in Renal Disease study equation (GFR (mL/min/1.73 m^2) = 175 × (serum creatinine [mg/dL])–1.154 × (age [years])–0.203 × 0.742 (if female) × 1.212 (if African American). • Recovery to Grade 1 or baseline of any clinically significant rovalpituzumab tesirine related toxicity (excluding alopecia) prior to initiation of study drug • In subjects with central nervous system (CNS) metastases, documentation of stable or improved status based on brain imaging for at least 2 weeks after completion of definitive treatment and within 2 weeks prior to initiation of retreatment, off or on a stable dose of corticosteroids. (Note: Definitive treatment may include surgical resection, whole brain irradiation, and/or stereotactic radiation therapy.)

Study Drug and Duration of Treatment:	For subjects receiving study drug in this study, rovalpituzumab tesirine (0.3 mg/kg or previously adjusted dose) will be administered as follows: • Arm A (Optional Retreatment): IV once every 6 weeks beginning on Day 1 (day of dosing) for 2 dose (cycles) per subject per retreatment period. • Arm B: IV once every 6 weeks beginning on Day 1 (day of dosing). Subjects will receive rovalpituzumab tesirine on Day 1 of each 6-week cycle, omitting every third cycle until disease progression or study drug discontinuation. • Oral dexamethasone 8 mg (or alternative corticosteroid at equivalent dosing) will be administered twice daily on Day –1, Day 1, and Day 2 for all subjects receiving rovalpituzumab tesirine.
Date of Protocol Synopsis:	20 May 2019

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Rovalpituzumab tesirine is an antibody-drug conjugate (ADC) that targets delta-like protein 3 (DLL3), which is uniquely expressed on the cell surface of neuroendocrine tumor cells, including small cell lung carcinoma (SCLC). It is being developed for the treatment of DLL3-expressing SCLC and being explored for the treatment of other DLL3-expressing solid tumors.

The purpose of this extension study is to provide ongoing safety and efficacy follow-up of subjects who are participating in a rovalpituzumab tesirine study that have completed their primary analyses and are closing and to provide optional retreatment for those who qualify.

Clinical Hypothesis

No clinical hypothesis is being tested.

2.2 Benefits and Risks to Subjects

As of 30 June 2018, a total of 1246 subjects have received study medication in rovalpituzumab tesirine clinical trials.

It is possible that some subjects may not benefit from Rova-T treatment. Subjects with relapsed/recurrent SCLC enrolled in the TAHOE Study *"A Randomized, Open-Label, Multicenter, Phase 3 Study of Rovalpituzumab Tesirine Compared with Topotecan for Subjects with Advanced or Metastatic DLL3^{high} SCLC who have First Disease Progression During or Following Front-Line Platinum-Based Chemotherapy"* had shorter survival in the Rova-T arm compared with the topotecan control arm.

Other preliminary safety and efficacy data from ongoing studies support further development of rovalpituzumab tesirine for subjects with relapsed/refractory DLL3-expressing SCLC and further exploration in other DLL3-expressing solid tumors. For further details, refer to the Rovalpituzumab Tesirine Investigator Brochure.[1]

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

The objective is to provide long-term follow-up for subjects remaining on a rovalpituzumab tesirine study that has completed the primary analysis and is closing. Safety and limited efficacy data on patients retreated with rovalpituzumab tesirine will be collected.

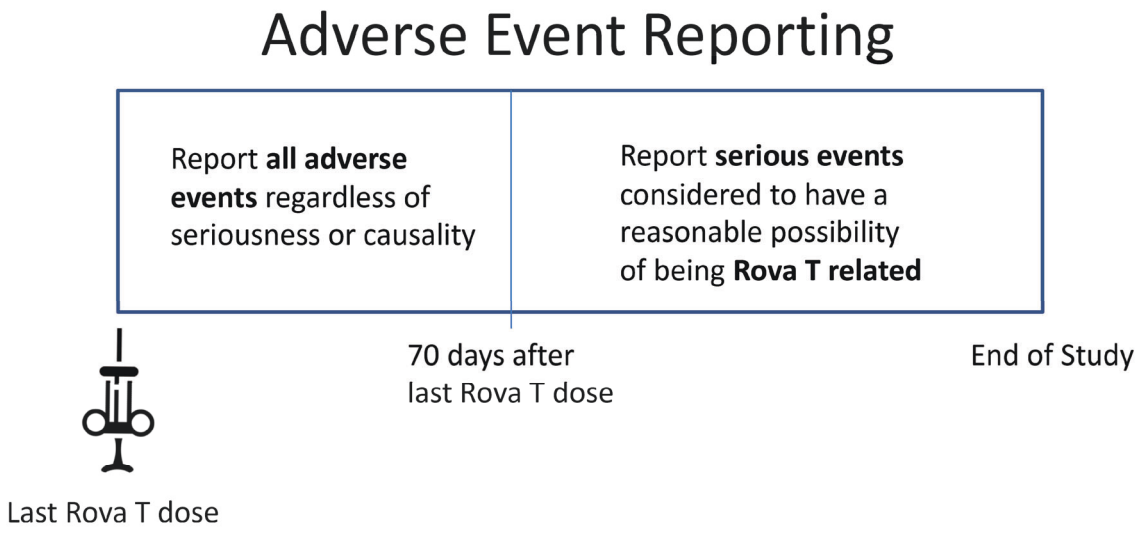
3.2 Efficacy Evaluations

There are no efficacy objectives and endpoints for this extension study. Limited efficacy data will be collected and listed. Aggregate summaries and other statistical analyses of efficacy data are not planned. Efficacy data including radiographic disease response assessment by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1[2] and survival for each subject will be collected and only raw data/listings will be generated.

For efficacy listing information, refer to Section 7.4.

3.3 Safety Evaluations

Safety evaluations include adverse event monitoring, physical examinations, echocardiography, vital sign measurements, performance status, and clinical laboratory testing. Adverse events (AEs) will be collected from the time of enrollment until the end of the study. For subjects receiving treatment/retreatment in this study, all AEs regardless of seriousness or causality, will be reported through 70 days after the last dose of treatment. Only treatment-related serious adverse events (SAEs) will be collected post 70 days of the last dose of rovalpituzumab tesirine received in the study. In those subjects in Arm A who are not receiving treatment, only treatment-related SAEs will be collected. The AE reporting windows are described below in the schema.



Last rovalpituzumab tesirine dose refers to the last dose received by the subject in either the parent study (Arm A, No Retreatment) or this extension study (Arm A Retreatment or Arm B).

Further details on AE reporting are provided in Section 6.1 and the Operations Manual, Section 4. For statistical analysis provided for study disclosure, refer to Section 7.5.

3.4 Pharmacokinetic Evaluations

Collection of samples for pharmacokinetics and anti-therapeutic antibodies is not included in this extension study.

3.5 In Vivo Biomarker and Exploratory Research

Not applicable.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a phase 2, multicenter, long-term, rollover follow-up extension study. It will be conducted in ~20 sites in the same countries as the rovalpituzumab tesirine parent studies; potentially including, but not limited to, Canada, France, Latvia, Spain, the United Kingdom, and the United States. More study sites and countries may be included as other rovalpituzumab tesirine parent studies complete their primary analyses and close.

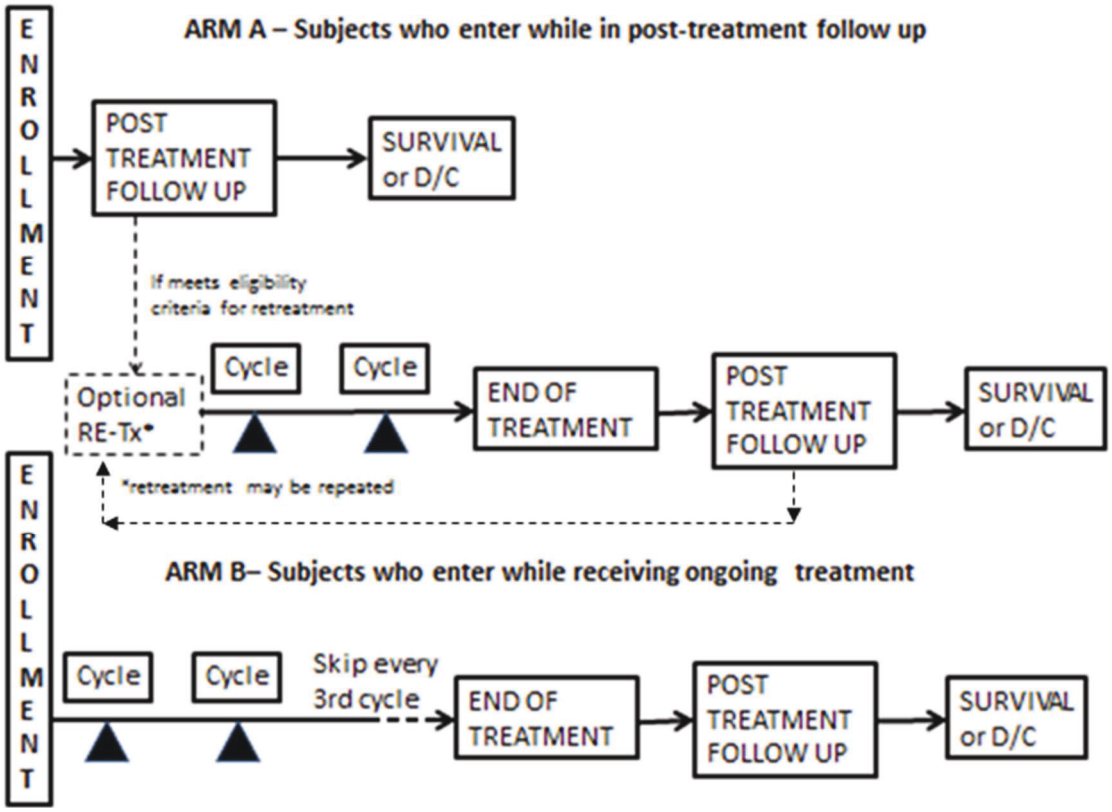
The schedule of assessments will depend on whether subjects enter the study in post-treatment follow-up or receiving ongoing rovalpituzumab tesirine treatment from the parent study.

This extension study includes 2 Study Arms:

- Arm A: Subjects who enter the extension study while in post-treatment follow-up. This arm includes optional rovalpituzumab tesirine retreatment for those who qualify. Most subjects from all studies will be in this arm. These parent studies include, but are not limited to, Study SCRX001-002, Study SCRX001-004, Study SCRX001-006, Study SCRX001-007, and Study M16-289.
- Arm B: Subjects who enter the extension study while receiving ongoing rovalpituzumab tesirine treatment in the parent study (e.g., Study SCRX001-007).

Study specifics for Arms A and B are presented in Figure 1.

Figure 1. Study Schematic



D/C = Study discontinuation; Tx = Treatment

4.2 Discussion of Study Design

Choice of Control Group

There is no control group in this extension study.

Appropriateness of Measurements

Standard clinical and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with SCLC and other indications from parent rovalpituzumab tesirine studies (e.g., Study SCRX001-006).

Suitability of Subject Population

These are all subjects who were enrolled in rovalpituzumab tesirine treatment studies, but have not yet reached 1 or more endpoints in the parent study at the time of primary analyses. In addition, subjects who were eligible for retreatment based on the criteria written in the parent study will have that opportunity in this study.

All subjects must have received at least 1 dose of rovalpituzumab tesirine in the parent study. In order to receive optional retreatment in Arm A, subjects must meet the below eligibility criteria in Section 5.1.

Selection of Doses in the Study

Subjects who receive treatment in this study will receive rovalpituzumab tesirine at a dose of 0.3 mg/kg on Day 1 of every 6 week treatment cycle. If a subject previously required a dose reduction during the parent rovalpituzumab tesirine study, then that reduced dose will be administered for those with ongoing treatment or those electing retreatment. Dose reductions may also occur during treatment or retreatment. If a subject requires a dose reduction, either in the parent rovalpituzumab tesirine study or this extension study, dose re-escalation is not allowed.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Study Entry Criteria

For both Arms A and B; the eligibility criteria are that a subject has enrolled, participated in, and received at least 1 dose of rovalpituzumab tesirine in a parent study.

Arm A Optional Retreatment Criteria

Additional eligibility criterion for Arm A is that subjects who discontinued the study drug in the parent study have completed the treatment emergent AE reporting window (e.g., 30 days post last dose for Study SCRX001-002).

Subjects who elect optional retreatment in Arm A must meet all of the following eligibility criteria before receiving rovalpituzumab tesirine retreatment. Prior to providing retreatment to subjects, study investigators should consult with the AbbVie Medical Monitor.

Demographic and Laboratory Assessments

- 1. Tolerated their initial 2 doses of rovalpituzumab tesirine
- 2. Achieved clinical benefit from rovalpituzumab tesirine, defined as stable disease or better, and is determined that the subject would potentially benefit from additional treatment

  OR

  Achieved clinical benefit as defined by stable disease or better and experienced radiographic disease progression at least 12 weeks after last dose of rovalpituzumab tesirine per RECIST 1.1
- 3. Received no other systemic anti-cancer therapy after rovalpituzumab tesirine treatment
- 4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. See the Operations Manual, Appendix B for conversion of performance status using Karnofsky scales, if applicable
- 5. Minimum life expectancy of at least 12 weeks

- 6. **Laboratory values** meeting the following criteria within the screening period prior to the first dose of study drug:
  - Absolute neutrophil count (ANC) ≥ 1,500/µL;
  - Platelet count ≥ 75,000/µL;
  - Hemoglobin ≥ 8.0 g/dL;
  - Serum total bilirubin ≤ 1.5 × upper limit of normal (ULN) or ≤ 3 × ULN for subjects with Gilbert's disease;
  - Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN (≤ 5 × ULN if evidence of hepatic involvement by malignant disease);
  - Serum creatinine ≤ 1.5 × ULN or estimated glomerular filtration rate (eGFR) ≥ 30 mL/min/1.73 m^2 as calculated by the 4-variable Modification of Diet in Renal Disease study equation (GFR (mL/min/1.73 m^2) = 175 × (serum creatinine [mg/dL])–1.154 × (age [years])–0.203 × 0.742 (if female) × 1.212 (if African American).[3]

Disease Activity

- 7. Recovery to Grade 1 or baseline of any clinically significant rovalpituzumab tesirine related toxicity (excluding alopecia) prior to initiation of study drug
- 8. In subjects with central nervous system (CNS) metastases, documentation of stable or improved status based on brain imaging for at least 2 weeks after completion of definitive treatment and within 2 weeks prior to initiation of retreatment, off or on a stable dose of corticosteroids. (Note: Definitive treatment may include surgical resection, whole brain irradiation, and/or stereotactic radiation therapy)

Contraception

- 9. A **negative urine pregnancy test** for all female subjects (except post-menopausal) at the Screening Visit and a negative urine pregnancy test for all female subjects (except post-menopausal) at baseline prior to the first dose of study drug
- 10. If female, is not pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 6 months after the last dose of study drug
- 11. Females of childbearing potential must have a negative urine pregnancy test result within 7 days prior to the first dose of study drug. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy
- 12. Females of childbearing potential and males who have partners of childbearing potential must agree to use an effective contraception method (see Section 5.2) during the study and for 6 months following the last dose of study drug
- 13. If male, is not considering fathering a child or donating sperm during the study or for approximately 6 months after the last dose of study drug

5.2 Contraception Recommendations

Contraception Requirements for Females

No contraception is required for female subjects of non-childbearing potential, defined as those who are postmenopausal for greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Postmenopausal is 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 a follicle-stimulating hormone (FSH) level > 40 IU/L
- **OR** Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)

Females of childbearing potential must agree to practice at least one of the following methods of birth control at enrollment (or earlier) through at least 6 months after the last dose of study drug. Effective birth control includes:

- Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal) associated with inhibition of ovulation initiated at least 1 month prior to enrollment
- Progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Baseline Day 1
- Bilateral tubal occlusion/ligation (Note: Bilateral tubal occlusion via hysteroscopy [i.e., Essure] is acceptable provided a hysterosalpingogram has confirmed success of the procedure)
- Intrauterine device
- Intrauterine hormone-releasing system
- Vasectomized sexual partner(s): provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the trial participant
- True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (Note: periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Contraception Requirements for Males

No contraception is required for male subjects who are surgically sterile (vasectomy with medical assessment confirming surgical success) or who have a female partner that is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

If a male subject is sexually active with female partner(s) of childbearing potential, he must agree to use condoms until 6 months after the last dose of investigational product. In addition, for such subjects:

- Female partner(s) must use at least one of the contraceptive measures (as defined in the protocol for female study subjects of childbearing potential), or
- Subject must practice true abstinence, defined as refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable)

Further, male subjects must agree not to donate sperm from enrollment through 6 months after the last dose of investigational product.

5.3 Prohibited Medications and Therapy

Not applicable.

5.4 Prior and Concomitant Therapy

For subjects who will receive rovalpituzumab tesirine in this extension study, dexamethasone 8 mg twice daily (BID) or an equivalent corticosteroid will be administered around the time of dosing (Day –1, 1, and 2).

Any medication or vaccine (including over the counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded through the AE reporting window (70 days after last dose). All anti-cancer medication or treatments will be collected for the duration of the study.

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- The subject withdraws consent for participation in the study;
- The Investigator believes it is in the best interest of the subject;
- Subject is significantly non-compliant with study procedures, which would put the subject at risk for continued participation;
- Subject is lost to follow-up or dies;
- The study is terminated by the sponsor.

Subjects who withdraw or discontinue prematurely from the study will not be replaced.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the final status of the subject. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

A subject can:

- withdraw participation in clinic visits, but be included in the follow-up for overall survival by phone call,
- withdraw participation in the overall survival follow-up by phone call, or
- withdraw participation in both clinic visits and overall survival follow-up by phone call

AbbVie may terminate this study prematurely, either in its entirety or at any site. The Investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the Investigator.

Follow-up procedures and survival information collection are described below in Section 5.6.

5.6 Follow-Up for Subject Withdrawal from Study

To minimize missing data for efficacy and safety assessments, subjects who prematurely discontinue study drug treatment should continue to be followed for all regularly scheduled visits, unless subjects have decided to discontinue the study participation entirely (withdrawal of informed consent). Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Termination Follow Up (PTFU visit) should be completed as soon as possible, preferably within 2 weeks. All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate electronic Case Report Form (eCRF) page. 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. Following discontinuation of study drug, the subject will be treated in accordance with the Investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

Subjects no longer undergoing clinical assessments will have survival information collected approximately every 6 weeks 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 addition, if the subject is willing, a 70-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/SAEs have been resolved.

5.7 Study Drug

For subjects receiving study drug, rovalpituzumab tesirine (0.3 mg/kg or adjusted dose) supplied by AbbVie will be administered intravenously (IV) once every 6 weeks beginning on Day 1 (day of dosing) for 2 doses (cycles) per subject in Study Arm A (Optional Retreatment) or once every 6 weeks beginning on Day 1 (day of dosing) omitting every third cycle until disease progression or study drug discontinuation in Study Arm B. Oral dexamethasone 8 mg (or alternative corticosteroid at equivalent

dosing) will be administered twice daily (BID) on Day –1, Day 1, and Day 2 for all subjects receiving rovalpituzumab tesirine.

AbbVie will not routinely supply drug other than rovalpituzumab tesirine. AbbVie will not routinely provide dexamethasone (or its equivalent) unless specified in operational or regulatory requirements (i.e., local site/country-specific requirements). Non-investigational medicinal product (standard of care) must be obtained commercially.

Instructions for drug preparation will be provided by AbbVie. Further details are provided in the Operations Manual, Section 6.

5.8 Randomization/Drug Assignment

As subjects are enrolled in the study, they will be classified into the 2 study arms (A or B), and will be given a unique subject identification number. Rovalpituzumab tesirine will be dispensed using an Interactive Response Technology (IRT) at the study visits, as summarized in Section 5.7, for subjects in Study Arm A (Optional Retreatment) or Study Arm B.

5.9 Protocol Deviations

The Investigator is responsible for complying with all protocol requirements, written instructions and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified), the Investigator is responsible for notifying IEC/IRB (as applicable), regulatory authorities (as applicable) and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

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. Complaints associated with any component of this investigational product must be reported to AbbVie.

Medical Complaints/Adverse Events and Serious Adverse Events

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

The investigators will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

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

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, admission to an outpatient facility, respite, or hospice care.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result 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.

Further details on AEs and SAE are provided in the Operations Manual, Section 4.

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.

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each adverse event as mild (grade 1), moderate (grade 2), severe (grade 3), or life-threatening (grade 4). The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

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

Adverse Events Due to Cancer Progression and Progression of the Underlying Cancer

Certain AEs are anticipated to occur in this study population at some frequency independent of drug exposure. Such events include known consequences of the underlying disease or condition under investigation (e.g., symptoms, disease progression). These AEs may occur alone or in various combinations and are considered expected AEs in subjects and for reporting purposes for this protocol. "Disease progression" should not be captured when reporting AEs or SAEs, even if fatal, as disease progression will be captured as efficacy outcomes in the trial. Rather, symptoms of disease progression should be reported as AEs or SAEs and the distinction on the AE eCRF marked as appropriate.

Deaths Due to Cancer Progression

For SAEs with the outcome of death, the date and cause of death will be recorded on the appropriate eCRF. Further details are provided in the Operations Manual, Section 4.1.

Pregnancy

Pregnancy in a study subject must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who become pregnant during the study must discontinue study drug.

All subjects should be informed that contraceptive measures (refer to Section 5.2) 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 AE. The medical outcome for either mother or infant, meeting any serious criteria including an elective or spontaneous abortion, is considered a SAE and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described in the Operations Manual, Section 4.4. For the purpose of medical management, all AEs and laboratory abnormalities that occur during the study must be evaluated by the investigator. The table of clinical toxicity grades modified from the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 (available on the NCI-CTEP home page, https://nciterms.nci.nih.gov) is to be used in the grading of AEs and laboratory abnormalities that are reported as AEs, each of which will be followed to satisfactory clinical resolution.

A potential drug-related toxicity is an AE or laboratory value outside of the reference range that is judged by the investigator or AbbVie to have either "reasonable possibility" or "no reasonable possibility" of relationship to the study drug. Toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Toxicity is defined as any clinically significant grade 3 or 4 study drug-related toxicity observed in 1 or more subjects. Subjects who develop a study drug-related grade 1 or 2 AE or laboratory abnormality may continue study medications.

If a subject experiences clinically significant toxicity during a cycle, administration of the next scheduled cycle should be delayed until recovery. Specific recommendations are provided in the Operations Manual, Section 4.4. In the event of isolated CNS progression during study treatment, rovalpituzumab tesirine may be withheld while a palliative treatment is administered.

Management of Special Toxicity Concerns

Serosal effusions (pleural or pericardial), alone or in combination with generalized or peripheral edema and/or hypoalbuminemia, have been observed with rovalpituzumab tesirine. These events have the potential to be life-threatening (e.g., pericardial tamponade). As prophylaxis, rovalpituzumab tesirine is administered with dexamethasone 8 mg orally BID on Day –1, Day 1 (the day of dosing), and Day 2 of each treatment cycle.

Development of serosal effusion events or worsening from baseline warrants prompt evaluation by the Investigator or designee. In the event of a grade 2 or higher AE in this group (effusions, edema, hypoalbuminemia) thought to be related to rovalpituzumab tesirine, consider administration of systemic corticosteroids, e.g., a tapered regimen of dexamethasone. Alternatively, nonsteroidal therapies for serositis may be considered, as outlined in the Operations Manual, Section 4.4.

Skin toxicity with rovalpituzumab tesirine may consist of photosensitivity as well as other reactions (e.g., palmar-plantar erythrodysesthesia, erythema multiforme). Development of a cutaneous reaction during treatment warrants prompt evaluation by the Investigator or designee. For skin reactions, refer to the Operations Manual, Section 4.4. All events of cutaneous toxicity should be monitored until resolution or return to baseline.

Potential drug-induced liver injuries (DILIs) are defined in the Operations Manual, along with recommendations for management. All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs.

6.3 TEAE Case Definition/Guidance

To further aid in prospectively identifying treatment-emergent adverse events (TEAEs), refer to the general signs and symptoms coinciding or preceding each TEAE as listed below.

Serosal Effusions

Serosal effusions have been observed with rovalpituzumab tesirine treatment, mainly pleural and pericardial effusions. Possible risk mitigation of serosal effusions includes administration of dexamethasone orally at 8 mg BID given on Day –1, Day 1 (the day of dosing) and Day 2 or each cycle. Pleural and pericardial effusions are considered separate important identified risks for rovalpituzumab tesirine.

Details regarding serosal effusion management are provided in the Operations Manual, Section 4.4.

Pleural Effusions

In general, signs and symptoms coinciding with or preceding pleural effusions may include shortness of breath, chest tightness or pain, cough, and/or weight gain. Monitoring for symptoms of pleural effusions, which include worsening dyspnea, chest tightness or pain, or worsening cough, should occur throughout the treatment and post-treatment period.

If pleural effusion is suspected, additional laboratory and imaging studies should occur per institutional guidelines.

Details regarding pleural effusion management are provided in the Operations Manual, Section 4.4.

Pericardial Effusions

In general, signs and symptoms coinciding with or preceding events of pericardial effusion may include shortness of breath, chest tightness or pain, cough, and/or weight gain. Most patients with pericardial effusions reported preceding or concurrent events of pleural effusions. Monitoring for symptoms of pericardial effusions, which include worsening dyspnea, chest tightness or pain, worsening cough, syncope, or palpitations should occur throughout the treatment and post-treatment period. If pericardial effusion is suspected, additional laboratory and imaging studies including echocardiography should occur per institutional guidelines. Pericardial effusions can result in cardiac tamponade and can be life-threatening.

Details regarding pericardial effusions management are provided in the Operations Manual, Section 4.4.

Generalized Edema

Generalized edema (anasarca) is considered an important identified risk for rovalpituzumab tesirine. In general, signs and symptoms coinciding with or preceding generalized edema may include generalized swelling including extremities or puffiness of the skin, increased abdomen size, and dyspnea. Generalized edema events are infrequent but have resulted in fatal outcomes and are often preceded by events of peripheral edema. Generalized edema can present as unexplained weight gain, thus monitor for signs and symptoms of fluid retention (using the Fluid Retention Questionnaire [Appendix C of the Operations Manual]). The development of new or worsening edema should prompt evaluation for

associated serosal effusions. Signs and symptoms of generalized edema should be monitored throughout treatment with rovalpituzumab tesirine and as part of the follow up period.

If generalized edema is suspected, additional laboratory and imaging investigation should occur. If generalized edema is confirmed, prompt intervention and treatment is warranted.

Details regarding edema management are provided in the Operations Manual, Section 4.4.

Peripheral Edema

Peripheral edema can present as swelling or puffiness of the skin affecting the legs, feet, and ankles, but it can also involve the arms and face. Peripheral edema can present as unexplained weight gain, and thus it is important to monitor for signs and symptoms of fluid retention (using the Fluid Retention Questionnaire [Appendix C of the Operations Manual]). Regular physical examinations should be conducted during treatment, and the development of new or worsening edema should prompt evaluation for associated serosal effusions or generalized edema.

If peripheral edema is suspected, additional laboratory and imaging investigation should occur per institutional guidelines. If peripheral edema is confirmed, please refer to toxicity management section of the Operations Manual, Section 4.4 for dose reduction instructions.

Cutaneous Reactions

Skin reactions have been reported in almost half of the subjects treated with rovalpituzumab tesirine. Most skin reactions consist of photosensitivity reactions, rash, and erythema and mainly occur in sun-exposed regions like the face and arms. Most cutaneous reactions are ≤ grade 2 and do not require intervention. If not clinically consistent with photosensitivity, the cutaneous reaction should be evaluated by a dermatologist, including consideration for skin biopsy to characterize the reaction and guide subsequent treatment and/or disposition of rovalpituzumab tesirine dosing. Development of a cutaneous reaction during treatment with rovalpituzumab tesirine warrants prompt evaluation.

Details regarding cutaneous skin management are provided in the Operations Manual, Section 4.4.

Photosensitivity

Photosensitivity reactions are an important identified risk for rovalpituzumab tesirine. Photosensitivity is characterized by an increase in sensitivity of the skin to sunlight. Minimization measures and management of photosensitivity are included the Operations Manual, Section 4.4. Rovalpituzumab tesirine associated photosensitivity causes redness (erythema) and sunburn-like appearance of the skin. Typical locations include face, v-shaped area of the neck, dorsal arms and legs. Time to onset of photosensitivity varies widely and may occur hours to days after sun exposure.

Details regarding photosensitivity management are provided in the Operations Manual, Section 4.4.

Thrombocytopenia with Bleeding Events

Thrombocytopenia has been observed with rovalpituzumab tesirine. The majority of thrombocytopenia and platelet count decrease observed with rovalpituzumab tesirine have been ≤ grade 3, are asymptomatic, and not associated with an increased risk of bleeding. In general, signs and symptoms

coinciding with or preceding thrombocytopenia with bleeding may include blood in urine or bowel movement, headaches, heavy menstrual periods, or new or worsening bruising.

If thrombocytopenia is suspected, additional laboratory monitoring per institutional guidelines may be necessary.

Details regarding thrombocytopenia management are provided in the Operations Manual, Section 4.4.

Pneumonitis

Pneumonitis has been infrequently reported with rovalpituzumab tesirine but has resulted in fatal outcomes. 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 (ground glass opacities). If pneumonitis is suspected, additional laboratory and imaging investigation per institutional guidelines may be necessary.

6.4 Product Complaints

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

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

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 1 business day of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

As this is an extension study, no Statistical Analysis Plan (SAP) will be written; only data and listings will be produced for future use. No interim analysis will be planned and performed.

7.2 Definition for Analysis Populations

One analysis set will be used for the long-term, rollover extension study that will include subjects who signed an informed consent and met all the eligibility criteria, unless specified otherwise.

7.3 Disposition of Study Subjects

The subject disposition will be presented in listings by subject. Subject disposition listings will include the following:

- Subjects who
  - enrolled
  - prematurely discontinued from the study (including the reasons for discontinuation of study)
- For subjects in Study Arm A (Retreatment) or Study Arm B,
  - The number of subjects who received at least 1 dose of rovalpituzumab tesirine
  - subjects who prematurely discontinued rovalpituzumab tesirine (including the reasons for treatment discontinuation)
- Subject deaths
  - death due to any cause during the study
  - primary reason for death will also be summarized

7.4 Statistical Analyses for Efficacy

No efficacy analyses will be performed. Listings for disease and response assessment, including tumor imaging and brain magnetic resonance imaging (MRI), will be provided for subjects in Study Arms A and B.

7.5 Statistical Analyses for Safety

Adverse events will be coded and summarized by system organ class and preferred term (and severity) according to the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1 or higher. Clinical toxicity grades modified from the NCI CTCAE version 4.0 will be used in the grading of AEs and laboratory abnormalities that are reported as AEs.

No safety analyses will be performed. A listing of data for subjects experiencing AEs will be provided. Laboratory measurements collected on the eCRF will also be listed.

For study disclosure, the following safety data will be summarized:

- For Arm A: Serious adverse events related to treatment will be summarized.
- For Arm B and those who are retreated on Arm A: AEs from enrollment to 70 days after the last dose and SAEs related to rovalpituzumab tesirine from 71 days after the last dose until the end of study will be summarized.

Definitions of AEs are provided in Section 6.1 and the Operations Manual, Section 4.

7.6 Determination of Sample Size

There is no minimum or maximum sample size for this study which depends on the number of subjects who will enroll into the extension study upon completion of primary analysis of the parent rovalpituzumab tesirine studies.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board (IEC/IRB)

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IEC/IRB for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the Investigator are specified in Appendix B.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s).

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

Completion of the study in both arms will be when subjects experience death or discontinue the study for other reasons

12 REFERENCES

1. AbbVie. Rovalpituzumab Tesirine (SC16LD6.5) Investigator's Brochure Edition 7.0. 2018.
2. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45(2):228-47.
3. Levey AS, Coresh J, Green T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247-5.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADC	antibody-drug conjugate
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ANC	absolute neutrophil count
BID	twice daily
CNS	central nervous system
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
DLL3	delta-like protein 3
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
(e)GFR	(estimated) glomerular filtration rate
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Investigational Review Board
IRT	Interactive Response Technology
IV	intravenous/intravenously
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI	National Cancer Institute
PTFU	Premature Termination Follow Up
RECIST	Response Evaluation Criteria for Solid Tumors
SAE	serious adverse event
SAP	Statistical Analysis Plan
SCLC	small cell lung carcinoma
SUSAR	Suspected Unexpected Serious Adverse Reactions

TEAE	treatment-emergent adverse event
ULN	Upper Limit of Normal

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M16-291: Rovalpituzumab Tesirine (Rova-T) Extension Study

Protocol Date: 20 May 2019

Clinical research studies sponsored by AbbVie are subject to the International Council for Harmonisation (ICH) Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
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., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
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 protocol and all of its 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. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	[redacted]	Clinical Program Development
		Clinical Program Development
		Clinical Program Development
		Data and Statistical Sciences
		Medical Writing

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APPENDIX D. ACTIVITY SCHEDULE

The following tables show the required activities across the study arms. The individual activities are described in detail in the **Operations Manual**.

Study Activities: Study Arm A

Arm A: Post-Treatment Follow-Up Activities	Screening/Baseline	Long-Term Follow-Up Visits (Phone Visits) (Additional details provided in the Operations Manual)	End of Study Visit
	Day –1	Every 6 wks, ± 1 wk Until 24 Weeks After 1st Rova T Dose in Parent Study, then Every 12 wks ± 1 wk (Post-Treatment) or 12 wks ± 2 wks (Survival)	
INTERVIEWS & EXAMINATIONS			
Informed consent	✓		
Demographics	✓		
Adverse events (Ongoing adverse events will be transferred from parent study)	✓	✓	
New and ongoing concomitant medications (except in subjects who have already experienced disease progression)	✓	✓	
Survival status/Death (date and cause)		✓	✓
Reason for discontinuation			✓
LOCAL LABS & IMAGING			
Disease/response assessment including tumor imaging and Brain MRI (if clinically indicated)	✓	✓	

Arm A: Retreatment Visit Activities	Subjects from Arm A who elect retreatment will undergo the same schedule of assessments as the subjects in Arm B (see table below) beginning with Day –1. Subjects can receive treatment for no more than 2 cycles per retreatment period. 1 Cycle = starts Day –1 through Post-Cycle Response Assessment Visit (See Arm B table below): **Complete the following assessments ≤ 7 days before initiation of each retreatment period.**
INTERVIEWS & EXAMINATIONS	
Meets eligibility criteria	✓
Physical exam	✓
ECOG status (0-1 required for retreatment)	✓
Vital signs	✓
Adverse events	✓
Ongoing concomitant medications	✓
LOCAL LABS & IMAGING	
Pregnancy test (urine)	✓
Disease/response assessment including tumor imaging and Brain MRI (if clinically indicated)	✓
Echocardiogram	✓
CENTRAL LABS	
Complete blood count	✓
Chemistries	✓
Coagulation test	✓
Urinalysis	✓

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Study Activities: Study Arm B

Time of Activity	Screening	Cycles (Rova-T Treatment) Every 3rd Consecutive Cycle has All Activities EXCEPT Rova-T and Dexamethasone Treatment Post-Cycle Response Assessment if Continuing with Next Rovalpituzumab Tesirine Dose								End of Treatment (if Stopping Treatment)	Long-Term Follow-Up (Additional details provided in the Operations Manual)	End of Study Visit
	Day –7to –1	Day –1	Day 1 (± 2 Days After Previous Treatment Cycle)	Day 2	Day 7 + 2 Days	Day 15 ± 2 Days	Day 22 + 2 Days	Day 29 ± 3 Days	Day 36 + 2 Days	Within 7 Days of Next Rova-T Dose	Day 42 ± 3 Days	Every 6 wks, ± 1 wk Until 24 Weeks After 1st Rova T Dose, Then Every 12 wks ± 1 wk (Post-Treatment) or 12 wks ± 2 wks (Survival)	
INTERVIEWS & EXAMINATIONS													
Informed consent	✓												
Demographics	✓												
Adverse events Ongoing adverse events will be transferred from the parent study	✓		✓			✓		✓		✓	✓	✓	✓
Fluid retention questionnaire			✓			✓		✓		✓	✓		
Fluid retention questionnaire follow-up phone call					✓		✓		✓				
Ongoing concomitant medications	✓		✓			✓		✓		✓	✓	✓	✓
Physical exam	✓	✓	✓	✓		✓		✓		✓	✓		
Vital signs	✓		✓			✓		✓			✓		
ECOG performance status	✓												
Survival status/Death (date and cause)												✓	✓

Time of Activity	Screening	Cycles (Rova-T Treatment) Every 3rd Consecutive Cycle has All Activities EXCEPT Rova-T and Dexamethasone Treatment Post-Cycle Response Assessment if Continuing with Next Rovalpituzumab Tesirine Dose								End of Treatment (if Stopping Treatment)	Long-Term Follow-Up (Additional details provided in the Operations Manual)	End of Study Visit
	Day –7to –1	Day –1	Day 1 (± 2 Days After Previous Treatment Cycle)	Day 2	Day 7 + 2 Days	Day 15 ± 2 Days	Day 22 + 2 Days	Day 29 ± 3 Days	Day 36 + 2 Days	Within 7 Days of Next Rova-T Dose	Day 42 ± 3 Days	Every 6 wks, ± 1 wk Until 24 Weeks After 1st Rova T Dose, Then Every 12 wks ± 1 wk (Post-Treatment) or 12 wks ± 2 wks (Survival)	
LOCAL LABS & IMAGING													
Pregnancy test (urine)	✓		✓								✓		
Echocardiogram (within 7 days before rovalpituzumab tesirine dose)	✓												
Disease/response assessment including tumor imaging and Brain MRI (if clinically indicated)	✓									✓	✓	✓	✓
CENTRAL LABS													
Complete blood cell counts			✓			✓		✓			✓		
Chemistries			✓			✓		✓			✓		
Coagulation tests			✓								✓		
Urinalysis			✓			✓		✓			✓		
TREATMENT (2 Cycles, Skip Every 3rd Cycle)													
Rovalpituzumab tesirine treatment			✓										

Time of Activity	Screening	Cycles (Rova-T Treatment) Every 3rd Consecutive Cycle has All Activities EXCEPT Rova-T and Dexamethasone Treatment Post-Cycle Response Assessment if Continuing with Next Rovalpituzumab Tesirine Dose								End of Treatment (if Stopping Treatment)	Long-Term Follow-Up (Additional details provided in the Operations Manual)	End of Study Visit
	Day –7to –1	Day –1	Day 1 (± 2 Days After Previous Treatment Cycle)	Day 2	Day 7 + 2 Days	Day 15 ± 2 Days	Day 22 + 2 Days	Day 29 ± 3 Days	Day 36 + 2 Days	Within 7 Days of Next Rova-T Dose	Day 42 ± 3 Days	Every 6 wks, ± 1 wk Until 24 Weeks After 1st Rova T Dose, Then Every 12 wks ± 1 wk (Post-Treatment) or 12 wks ± 2 wks (Survival)	
Dexamethasone 8 mg BID (or acceptable corticosteroid alternative) Note: Dosing on Day –1, Day 1, and Day 2		✓	✓	✓									

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	21 March 2018
Version 2.0	29 June 2018
Version 3.0	11 October 2018

The purpose of this Version is to make the following changes:

- Added paragraph stating that some subjects may not benefit from Rova-T treatment (Section 2.2, Benefits and Risks to Subjects)
- Updated number of sites and list of countries involved in the study, added Studies SCRX001-006 and M16-289 to list of parent studies eligible for this extension study (Section 4.1, Overall Study Design and Plan)
- Updated eligibility criteria to allow enrollment of subjects who do not have disease progression but are receiving benefit from study treatment; added instruction that prior to providing retreatment to subjects, investigators should consult with the AbbVie Medical Monitor (Section 5.1, Eligibility Criteria)
- Corrected minor inconsistencies in study follow-up window (Appendix D, Activity Schedule; Operations Manual, Section 2.1 and Section 2.3)

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M16-291

Rovalpituzumab Tesirine Extension Study

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	Rovalpituzumab Tesirine

FULL TITLE: A Multicenter, Long-Term, Rollover Extension Study of Rovalpituzumab Tesirine

1 CONTACTS

Sponsor/ Emergency Contact	[redacted] AbbVie Inc. [redacted] Oncology Clinical Development 1 North Waukegan Road North Chicago, IL 60064 [redacted] **EMERGENCY 24 hour Number:** [redacted]	Mobile : Office: [redacted]
Safety Concerns	Oncology Safety Team AbbVie [redacted] 1 North Waukegan Road North Chicago, IL 60064	Phone: [redacted] Email: [redacted]
SAE Reporting outside of RAVE	Email: [redacted]	Fax: [redacted]
Protocol Deviations	[redacted] Study Project Manager OR [redacted] Study Management Associate	Phone (Mobile): [redacted] Email: [redacted] OR Phone: [redacted] Email
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2 INVESTIGATION PLAN

2.1 Arm A (No Retreatment) Visit Activities

This section presents a list of activities performed for each visit for Arm A. Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

Subjects who enter Arm A of the Extension Study in Long-Term Follow-up and who will not enter Arm A: Retreatment may be eligible for phone call follow-up for ***all*** study visits listed below (in Section 2.1).

SCREENING/BASELINE:

INTERVIEWS	• Informed consent • Adverse events including ongoing adverse events from parent study[a]	• Concomitant medications[a] • Demographics
LOCAL LABS & IMAGING	• Disease/response assessment[b]	

a. New and ongoing from parent study (except in subjects who have already experienced disease progression).

b. Response assessment and brain magnetic resonance imaging (MRI) at baseline to be performed only in subjects who have not yet experienced radiographic disease progression.

LONG TERM FOLLOW-UP VISITS
EVERY 6 WEEKS ± 1 WEEK UNTIL 24 WEEKS AFTER FIRST ROVALPITUZUMAB TESIRINE DOSE IN PARENT STUDY, THEN EVERY 12 WEEKS ± 1 WEEK (FOR POST-TREATMENT FOLLOW-UP) OR EVERY 12 WEEKS ± 2 WEEKS (FOR SURVIVAL FOLLOW-UP)

INTERVIEW	• Adverse events	• Concomitant medications • Survival status/Death (date and cause)
LOCAL LABS & IMAGING	• Disease/response assessment[a]	

a. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

NOTE 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 Response Assessment, then every 6 weeks (± 1 week) until 24 weeks after first dose of rovalpituzumab tesirine, then every 12 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

Survival Follow-Up: 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 24 weeks after first dose of rovalpituzumab tesirine, then every 12 weeks (± 2 weeks) 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). 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.

END OF STUDY VISIT

INTERVIEW	• Survival status/Death (date and cause)	• Reason for discontinuation

2.2 Arm A Retreatment Visit Activities

Subjects in Arm A who elect retreatment will undergo the same schedule of assessments as the subjects in Arm B (Section 2.3), beginning with Day –1. Subjects from Arm A can receive treatment for no more than 2 cycles during each retreatment period with Cycle 1 starting on Day –1 and continuing through the Post-Cycle Response Assessment Visit (see Arm B, Section 2.3).

The following assessments/activities should be completed ≤ 7 days before each retreatment period.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

ADDITIONAL RETREATMENT SCREENING: ≤ 7 DAYS BEFORE INITIATION OF RETREATMENT

INTERVIEW	• Meets eligibility criteria criteria for retreatment[a] • Adverse events • Concomitant medications	• ECOG status (0 – 1 required for retreatment)
EXAMS	• Physical exam	• Vital signs
LOCAL LABS & IMAGING	• Pregnancy test (urine) • Disease/response assessment[b]	• Echocardiogram
CENTRAL LABS	• Complete blood count • Chemistries	• Coagulation tests • Urinalysis

ECOG = Eastern Cooperative Oncology Group

a. Eligibility criteria are provided in the Protocol, Section 5.1.

b. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

2.3 Arm B Ongoing Treatment Visit Activities

This section presents a list of activities performed for each visit for Arm B. Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

SCREENING (DAYS –7 TO –1):

INTERVIEWS	• Informed consent • Demographics	• Adverse events[a] • Concomitant medications[a] • ECOG performance status
EXAMS	• Physical exam	• Vital signs
LOCAL LABS & IMAGING	• Pregnancy test (urine) • Disease/response assessment[b]	• Echocardiogram (≤ 7 days of rovalpituzumab tesirine dose)

a. New and ongoing from parent study except in subjects who have already experienced disease progression.

b. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

Arm B Cycles: The 2 treatment cycles include rovalpituzumab tesirine and dexamethasone. **Every third consecutive cycle is a non-treatment cycle; exams, labs, etc. are all performed.**

TREATMENT CYCLE: DAY –1

EXAMS	• Physical exam
TREATMENT	• Dexamethasone 8 mg BID[a]

NOTES: Every third cycle excludes rovalpituzumab tesirine and dexamethasone treatment.

a. Dexamethasone or corticosteroid equivalent will be administered. Refer to Section 4.4 for details.

TREATMENT CYCLE: DAY 1

INTERVIEW	• Adverse events • Concomitant medications	• Fluid retention questionnaire (see example in Appendix C)[a]
EXAMS	• Physical exam	• Vital signs
LOCAL LABS & IMAGING	• Pregnancy test (urine)	
CENTRAL LABS	• Complete blood count • Chemistries	• Coagulation tests • Urinalysis
TREATMENT	• Dexamethasone 8 mg BID	• Rovalpituzumab tesirine

a. Fluid retention questionnaires are distributed to subjects and are not to be administered during the clinic visit.

NOTES: Day 1 procedures should be performed prior to dosing of study drug (within 1 day); results from local clinical laboratory tests must be available prior to dose; ± 2 day window for Cycle 2 Day 1 and beyond. Day 1 assessment is conducted at a clinic visit.

Every third cycle excludes rovalpituzumab tesirine and dexamethasone treatment.

TREATMENT CYCLE: DAY 2

EXAMS	• Physical exam
TREATMENT	• Dexamethasone 8 mg BID

NOTES: Every third cycle excludes rovalpituzumab tesirine and dexamethasone treatment.

TREATMENT CYCLE: DAY 7 + 2 Days

INTERVIEW	• Fluid retention questionnaire follow-up phone call	

TREATMENT CYCLE: DAY 15 ± 2 DAYS

INTERVIEW	• Adverse events • Concomitant medications	• Fluid retention questionnaire (see example in Appendix C)[a]
EXAMS	• Vital signs	• Physical exam
CENTRAL LABS	• Complete blood count • Chemistries	• Urinalysis

a. Fluid retention questionnaires need to be collected from and discussed with the subject and new questionnaires provided to the subject.

NOTES: Every third cycle excludes rovalpituzumab tesirine and dexamethasone treatment.

TREATMENT CYCLE: DAY 22 + 2 Days

INTERVIEW	• Fluid retention questionnaire follow-up phone call	

TREATMENT CYCLE: DAY 29 ± 3 DAYS

INTERVIEW	• Adverse events • Fluid retention questionnaire (see example in Appendix C)[a]	• Concomitant medications
EXAMS	• Physical exam	• Vital signs
CENTRAL LABS	• Complete blood count • Chemistries	• Urinalysis

a. Fluid retention questionnaires need to be collected from and discussed with the subject and a new questionnaire provided to the subject.

NOTES: Every third cycle excludes rovalpituzumab tesirine and dexamethasone treatment.

TREATMENT CYCLE: DAY 36 + 2 Days

INTERVIEW	• Fluid retention questionnaire follow-up phone call	

POST-CYCLE RESPONSE ASSESSMENT: WITHIN 7 DAYS OF NEXT DOSE OF STUDY DRUG:

INTERVIEW	• Fluid retention questionnaire (see example in Appendix C)[a]	• Adverse events • Concomitant medications
EXAMS	• Physical exam	
LOCAL LABS & IMAGING	• Disease/response assessment[b]	

a. Fluid retention questionnaires need to be collected from and discussed with the subject and new questionnaires provided to the subject.

b. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

NOTE: This appointment is conducted at a clinic visit on Days 35 – 42 of each cycle and is to be conducted if the subject is continuing with rovalpituzumab tesirine treatment.

END OF TREATMENT: 42 DAYS ± 3 DAYS AFTER LAST DOSE (IF SUBJECT IS STOPPING TREATMENT)

INTERVIEW	• Fluid retention questionnaire (see example in Appendix C)[a]	• Adverse events • Concomitant medications
EXAM	• Physical examination	• Vital signs
LOCAL LABS & IMAGING	• Pregnancy test (urine)	• Disease/response assessment[b]
CENTRAL LAB	• Complete blood count • Chemistries	• Coagulation tests • Urinalysis

a. Fluid retention questionnaires need to be collected from and discussed with the subject.

b. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

NOTES: The End of Treatment (EOT) assessment is conducted at a clinic visit. This visit should occur 42 days ± 3 days after last dose, or within 7 days of documentation of the decision to discontinue treatment, whichever is later.

LONG TERM FOLLOW-UP VISITS: EVERY 6 WEEKS ± 1 WEEK UNTIL 24 WEEKS AFTER FIRST ROVALPITUZUMAB TESIRINE DOSE, THEN EVERY 12 WEEKS ± 1 WEEK (FOR POST-TREATMENT FOLLOW-UP) OR EVERY 12 WEEKS ± 2 WEEKS (FOR SURVIVAL FOLLOW-UP)

INTERVIEW[a]	• Adverse events • Concomitant medications • Disease/response assessment[b]	• Survival status/Death (date and cause)
LOCAL LABS & IMAGING		

a. Visit can be a phone call for subjects who have already experienced disease progression.

b. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

NOTE 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 Response Assessment, then every 6 weeks (± 1 week) until 24 weeks after first dose of rovalpituzumab tesirine, then every 12 weeks (± 1 week) until disease progression or initiation of new anti-cancer therapy, whichever occurs first.

Survival Follow-Up: 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 24 weeks after first dose of rovalpituzumab tesirine, then every 12 weeks (± 2 weeks) 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). 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.

END OF STUDY VISIT

INTERVIEW[a]	• Adverse event • Concomitant medications • Disease/response assessment[b]	• Survival status/Death (date and cause)

a. Visit can be a phone call for subjects who have already experienced disease progression.

b. Response assessment and brain MRI (if clinically indicated) to be performed only in subjects who have not yet experienced radiographic disease progression.

3 STUDY PROCEDURES

3.1 Subject Information and Informed 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 or any medications being discontinued by the subject in order to participate in this study, the informed consent statement will be reviewed, 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 signed informed consent 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 benefits 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.

3.2 Demographics

Demographics will be collected at screening visits as described in Section 2 and previously collected information will be transferred electronically directly from the parent study's Electronic Data Capture (EDC) system.

3.3 Physical Examination and Weight

A complete physical examination will be performed at the designated study visits as specified in Section 2. Any significant physical examination findings after the first dose will be recorded as adverse events. All findings, whether related to an adverse event (AE) or part of each subject's medical history, will be captured on the appropriate electronic Case Report Form (eCRF) page.

Height will be measured at screening only, if applicable. Body weight will be measured at scheduled visits as part of the physical examination. The subject will wear lightweight clothing and no shoes during weighing.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the Investigator.

3.4 Vital Signs

Vital sign determinations of body temperature, systolic and diastolic blood pressure, pulse rate, and respirations will be obtained at visits as specified in Section 2. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

3.5 Adverse Event Assessment

Refer to Section 4.2 for details.

3.6 Echocardiogram

An echocardiogram will be performed at the designated study visits as specified in Section 2. The echocardiogram will include assessments of left ventricular ejection fraction and pericardial effusion.

3.7 Dispense Study Drug

Study drug (rovalpituzumab tesirine) will be administered intravenously (IV) to subjects on Day 1 of each treatment cycle, as specified in Section 2. The first dose of study drug will be administered after all other Day 1 procedures are completed. Dexamethasone (or equivalent corticosteroid) will be self-administered twice daily (BID) by subjects on Day –1, Day 1, and Day 2 of each treatment cycle.

Further information on study drug is presented in Section 6.

3.8 Clinical Laboratory Tests

Chemistry

The blood samples for serum chemistry tests should be collected prior to study drug administration. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

Local laboratories can be utilized to process and provide results for the clinical laboratory tests, dosing can occur based on results from local laboratories. Laboratory reference ranges will be obtained prior to the initiation of the study. If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or

- discontinue the subject from the study or require the subject to receive treatment; in this case, the laboratory result will be recorded as an adverse event.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr><td>White blood cell count with five-part differential, to include:
Neutrophils
Lymphocytes
Monocytes
Basophils
Eosinophils
Red Blood Cell (RBC) count
Platelet count (estimate not acceptable)
Hematocrit
Hemoglobin</td><td rowspan="2">Sodium
Potassium
Chloride
Carbon dioxide
Creatinine
Blood Urea Nitrogen (BUN)
Estimated glomerular filtration rate
Glucose
Albumin
Total protein
Liver function tests, to include:
Total and direct bilirubin
Alanine transaminase (ALT)
Aspartate transaminase (AST)
Alkaline phosphatase
Lactate dehydrogenase
Amylase
Lipase</td><td rowspan="2">Coagulation tests to include:
Prothrombin time (PT)
Partial thromboplastin time (PTT)
International normalized ratio (INR)</td></tr>
<tr><th>Urinalysis</th></tr>
<tr><td>Color
Appearance
Specific gravity
pH
Glucose
Bilirubin
Ketones
Occult blood
Protein
Spot urine protein
Creatinine</td><td></td><td></td></tr>
</table>

Urinalysis

Dipstick urinalysis will be completed by the central laboratory at all required visits. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

Pregnancy Tests (Urine)

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study. Determination of postmenopausal status will be made during the screening period based on the subject's history.

A quantitative urine pregnancy test will be performed on site or by local laboratory as specified in Section 2 for all women of child-bearing potential. If the urine pregnancy test is negative, begin or continue dosing.

Additional testing may be done per the investigator.

3.9 Other Assessments

All assessments take place as described in Section 2.

Eastern Cooperative Oncology Group (ECOG) scale will be used to assess performance status at the Screening visits in Arm A retreatment and Arm B. For conversion of performance status using Karnofsky scales to ECOG, see Appendix B.

MRI of the brain (if clinically indicated) should be performed to confirm absence of active central nervous system (CNS) tumor or metastases. Brain MRI may be substituted by computerized tomography (CT) with IV contrast at the discretion of the investigator if MRI testing is clinically contraindicated, not available, or if the subject is unable to tolerate MRI. MRI assessments will be performed at study visits as specified in Section 2.

CT imaging of the chest, abdomen, and pelvis, and neck (if indicated) as well as other relevant imaging, as described via RECIST v1.1, will be used for disease/response assessment. Assessment of response and progression will be determined by the investigator according to RECIST v1.1. These assessments will be conducted at study visits as specified in Section 2. Upon disease progression or initiation of new anticancer therapy, disease/response assessment will consist of subsequent anticancer therapies and dates, date of progression (if not already captured), and survival status. No subsequent radiography is required once disease progression has occurred.

Ongoing concomitant therapies (from subject's parent study) should be recorded at study visits as specified in Section 2 and will include the names of all concomitant medications, blood products, procedures, and radiotherapy, including dates of administration, dose regimen, route of administration, and purpose.

Subjects enrolled in Arm B or Arm A Retreatment will complete fluid retention questionnaires starting on Day 1 through the EOT Visit (refer to Section 2). Subjects will record their daily weights or new edema or dyspnea on the fluid retention questionnaire (Appendix C). Fluid retention questionnaires will be distributed to subjects on Day 1, Day 15, Day 29, and the Post-Cycle Response Assessment Visit. Each questionnaire records up to 7 days of daily weights and subjects should be provided with enough questionnaires to record their daily weight until their next on-site clinic visit.

Sites will call subjects between on-site clinic visits to review completed fluid retention questionnaires. The fluid retention questionnaire follow-up phone calls will be performed at Day 7 + 2 Days,

Day 22 + 2 Days, and Day 36 + 2 Days. Subjects should be instructed to use a consistent weighing device throughout the study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

Adverse Event Reporting in Arm A and B Subjects who Receive Treatment or Retreatment in This Study

Within the 70 Day Follow-Up Period

Treatment-emergent adverse events (TEAEs) and treatment emergent serious adverse events (SAEs) will be collected; TEAEs and treatment emergent SAEs are defined as those that occur or worsen on or after the first dose of study drug until 70 days after the last dose of study drug.

After the 70 Day Follow-Up Period

All SAEs that occur after the safety reporting period that are considered study drug-related in the opinion of the Investigator should also be reported.

Adverse Event Reporting in Arm A subjects who do not Receive Treatment or Retreatment in This Study

All SAEs that are considered study drug-related in the opinion of the Investigator should be reported.

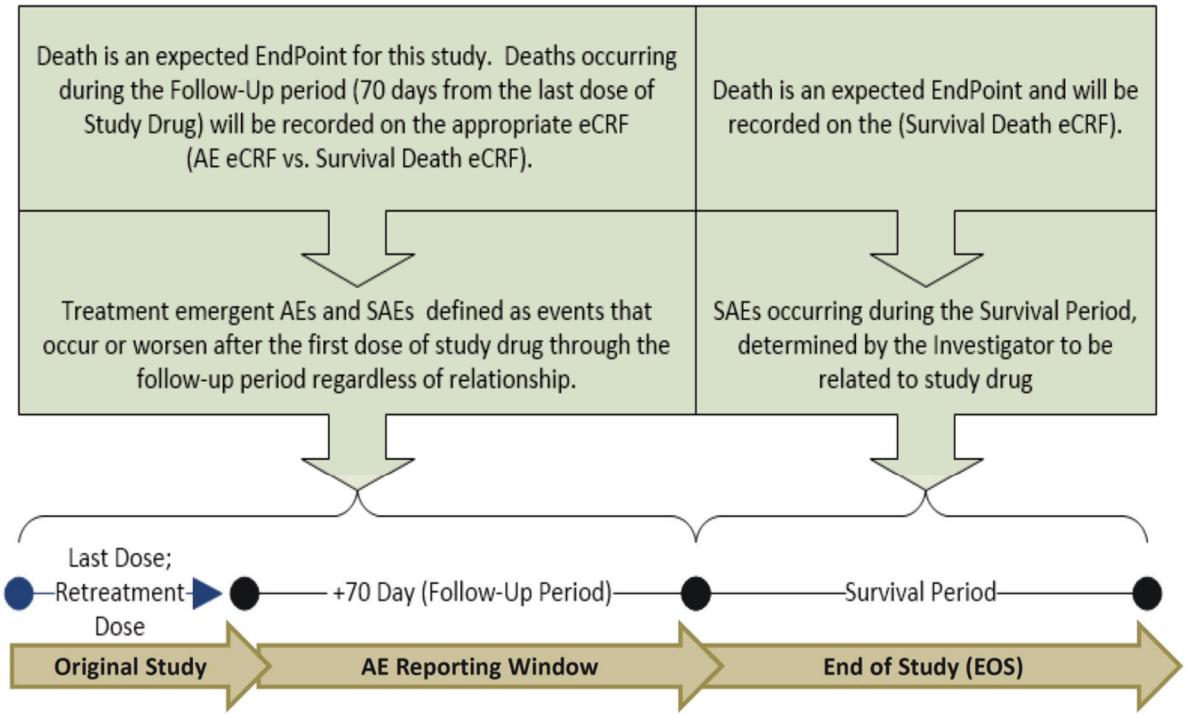
Deaths due to Cancer Progression

Deaths that occur during the protocol specified AE/SAE reporting period (Section 2) that are more likely related to disease progression will therefore be considered as an expected AE and will not be subject to expedited reporting. After the AE reporting period, deaths attributed to progression of disease under study should not be recorded on the AE eCRF, but on the Survival Death 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 1 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 subject 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 subject 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.

The survival status of subjects will be ascertained according to a predetermined follow-up schedule (Section 2). The follow-up schedule is intended to provide for the systematic ascertainment of each subject's survival status (alive, dead, or unknown/lost to follow-up) until the closure of the extension study. For subjects lost to follow-up or whose survival status is unknown, every effort will be made to determine the date such subjects were last known to be alive. Such efforts may include phone calls, certified mail, and the checking of public records.

Information will be collected as the diagram below.



4.2 Recording Data and Analyses of Safety Findings

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The tabulation of the number of subjects with treatment-emergent adverse events by severity grade and relationship to study drug also will be recorded. Subjects reporting more than 1 AE for a given MedDRA preferred term will be documented only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within a System Organ Class (SOC) will be documented only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

In the event of a reportable SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE nonCRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

Email: [redacted]
FAX to: [redacted]

For safety concerns, contact the Oncology Safety Team at:

Oncology Safety Team Dept. [redacted]
1 North Waukegan Road North Chicago, Illinois 60064
Office:
Email: [redacted]

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted]
AbbVie Inc.
[redacted] **Oncology Clinical Development**
1 North Waukegan Road
North Chicago, IL 60064

Contact Information:

Mobile: [redacted]
Office:
Email:

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director 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 Therapeutic Area Medical Director:

HOTLINE: [redacted]

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.

4.4 Toxicity Management

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 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.

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 enrollment, and documentation must exclude active infection. The subject should continue suppressive anti-infectives for the duration of study participation.

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 Therapeutic Area Medical Director in advance, if possible.

In the event of isolated central nervous system (CNS)-only progression during study treatment, investigational product may be withheld while local treatment is administered (e.g., radiotherapy) in accordance with institutional practice. 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 dose of study drug, the subject should undergo a radiographic tumor assessment. If additional sites of progressive disease are present, the subject will be required to discontinue study drug, but may be eligible for retreatment.

Treatment guidelines for hematologic toxicities, and recommended actions regarding rovalpituzumab tesirine dosing, are outlined in Table 1.

Table 1. Guidelines for Managing Hematologic Toxicities

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

Abbreviations: ANC = absolute neutrophil count; ASCO = American Society of Clinical Oncology; National Comprehensive Cancer Network

a. The maximum allowed dose interruption is 6 weeks.

b. Colony stimulating factors include filgrastim or sargramostim.

Special Toxicity Management

Management of Serosal Effusions/Serositis

Serosal effusions (pleural, pericardial), alone or in combination with generalized or peripheral edema and/or hypoalbuminemia, have been observed with rovalpituzumab tesirine. These events have the potential to be life-threatening (e.g., pericardial tamponade), therefore development of any of these events or worsening from baseline warrants prompt evaluation by the investigator or designee.

For serosal effusions considered clinically significant (e.g., grade 2 or higher and considered related to rovalpituzumab tesirine), administration of systemic corticosteroids should be considered (e.g., a tapered regimen of dexamethasone, such as up to 8 mg orally BID for 5 days, followed by 4 mg orally BID for 5 days, then 2 mg orally BID for 5 days). Alternatively, nonsteroidal therapies may be considered, such as non-steroidal anti-inflammatory drugs (e.g., ibuprofen 400 to 600 mg orally 3 to 4 times daily) or colchicine (e.g., 0.6 mg orally 2 to 3 times daily) for 1 to 2 weeks. Symptomatic pleural and pericardial effusions should be drained as appropriate for symptom relief. Effusions can recur/reaccumulate after drainage.

Management of Edema

The majority of the edema events with rovalpituzumab tesirine have been reported as low grade 1 or 2 (mild or moderate); however, a small number of fatal events of generalized edema have been reported with rovalpituzumab tesirine. Physical exams and monitoring of weight gain and signs or symptoms of fluid retention should be conducted during treatment.

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

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

Management of Skin Reactions

Due to the potential for rovalpituzumab tesirine-related skin photosensitivity, subjects should be advised to take the following precautions from Day 1 until 70 days after the last treatment: 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.

All cutaneous reactions that develop warrant prompt evaluation by the Investigator or designee. Recommendations for management of photosensitivity are shown in Table 2. Skin toxicity with rovalpituzumab tesirine may consist of photosensitivity as well as other reactions (e.g., palmar-plantar erythrodysesthesia, erythema multiforme). All events of cutaneous toxicity should be monitored until resolution or return to baseline.

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

Photo-documentation should be available upon request by the Therapeutic Area Medical Director (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 investigational product, and to facilitate the most appropriate terminology for AE reporting.

Table 2. Recommended Management of Photosensitivity

CTCAE v4.03		Treatment Recommendations	Rovalpituzumab Tesirine 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

BSA = body surface area; NSAID = non-steroidal anti-inflammatory drug

Management of 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 event (DILI). All occurrences of potential DILIs meeting the defined criteria must be reported as SAEs.

A potential DILI is defined as:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation > 3 times (3×) upper limit of normal (ULN) and

- Total bilirubin (TBL) > 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 to 72 hours of all 4 of the usual measures (ALT, AST, alkaline phosphatase, and TBL) 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 eCRF. 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, rovalpituzumab tesirine should be discontinued.

Close observation includes:

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

Discontinuation of rovalpituzumab tesirine should be considered if potential DILI is suspected and:

- ALT or AST > 8 × ULN
- ALT or AST > 5 × ULN for more than 2 weeks
- ALT or AST > 3 × ULN and (TBL > 2 × ULN or INR > 1.5)

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

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

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 Sample Retention Requirements

Not applicable for this extension study.

5.2 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the 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 Development Safety Update Report (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.

6 STUDY DRUG

6.1 Treatments Administered

Rovalpituzumab tesirine and dexamethasone (or alternative) will be administered at the visits listed in Section 2. General study drug information for rovalpituzumab tesirine is presented in Table 3.

Table 3. Investigational Products: Rovalpituzumab Tesirine

Investigational Product Name	Rovalpituzumab Tesirine
Route of Administration	IV
Combination Drugs	Not applicable
Formulation	10 mg 15 mg 30 mg
Dosage Form	Powder for solution for infusion in 10 mg, 15 mg, or 30 mg vial (10 mg/mL when reconstituted)
Dose and units	0.3 mg/kg or previously adjusted dose
Drug Preparation	Reconstitution of lyophilized powder with sterile water for injection per EDP
Frequency of administration	Day 1 of every cycle (1 cycle = 42 days/6 weeks); Note: not administered every third cycle in Arm B
Storage Conditions	Stored at refrigerated temperature (2° to 8°C/36° to 46°F), protected from light, and must not be frozen. Specific storage conditions for reconstituted and diluted IP will be provided in a separate document outside of this protocol

Rovalpituzumab Tesirine

Rovalpituzumab tesirine will be supplied as lyophilized drug, as shown in Table 3. Rovalpituzumab tesirine is intended for IV infusion after further dilution in a 50 mL or 100 mL infusion bag (50 mL infusion bag is recommended) containing 0.9% Sodium Chloride Injection, USP, or equivalent, to achieve the desired dose level for administration. Rovalpituzumab tesirine will be infused over 30 minutes (20 - 45 minute infusion window). The rate should be adjusted based on patient tolerability. Further details regarding reconstitution of study drug are provided in the extemporaneous dose preparation (EDP).

Since rovalpituzumab tesirine dosing is based on body weight, multiple vials of reconstituted drug product may be required to achieve the desired dose. Specific dose preparation and documentation details will be provided to the site pharmacy in a separate document.

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

Dexamethasone (or Equivalent Corticosteroid)

Dexamethasone tablets (various formulations) are to be taken orally at a dose of 8 mg BID. Dexamethasone will be self-administered by subjects on Day –1, Day 1, and Day 2 of each cycle when

rovalpituzumab tesirine is taken on Day 1 of the same cycle. The first dose of dexamethasone on Day 1 should be at least 30 minutes but no more than 4 hours prior to the rovalpituzumab tesirine infusion. (Note: If the dose of dexamethasone is vomited within 15 minutes of taking the medication, the subject should retake the medication.) If supplied by AbbVie, dexamethasone will be dispensed through Interactive Response Technology (IRT); if sourced locally, dexamethasone will not be dispensed through IRT.

Alternatives to dexamethasone include corticosteroids administered in equivalent doses (i.e., methylprednisolone, prednisone, etc.).

AbbVie will not routinely provide dexamethasone (or its equivalent) unless specified in operational or regulatory requirements (i.e., local site/country-specific requirements). Non-investigational medicinal product (standard of care) must be obtained commercially from a licensed pharmacy or wholesaler. Each site will be responsible for maintaining drug accountability records, including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

6.2 Packaging and Labeling

Vials of rovalpituzumab tesirine will be packaged in cartons. Each vial and carton will be labeled per country requirements. The labels must remain affixed to the vial and carton. All blank spaces should be completed by site staff prior to dispensing.

Dexamethasone supplied locally will be provided in commercial packaging. If supplied by AbbVie, dexamethasone will be provided in commercial primary packaging with a study label affixed to the primary container and/or secondary packaging. Each bottle, carton and/or blister will be labeled per country requirements. Labels must remain affixed. All blank spaces should be completed by site staff prior to dispensing.

Storage and Disposition of Study Drugs

The lyophilized formulation rovalpituzumab tesirine drug product should be stored at refrigerated temperature (2° to 8°C/36° to 46°F), protected from light, and must not be frozen. Specific storage conditions for reconstituted and diluted investigational product will be provided in a separate document outside of this protocol/operations manual.

For all storage areas and refrigerators, temperature logs will be maintained to document proper storage conditions. The temperature must be recorded on 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 Interactive Response Technology (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.

Dexamethasone supplied by AbbVie should be stored at 15° to 25°C (59° to 77°F), protected from light and moisture, and will be provided in commercial primary packaging with a study label affixed to the primary container and/or secondary packaging. Each bottle, carton, and/or blister will be labeled per country requirements. Labels must remain affixed to the bottle, carton, and/or blister. If dexamethasone is obtained locally from commercial sources, the approved product labeling should be referenced for appropriate storage conditions.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drugs supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use, destroyed on site, or returned to AbbVie in accordance with local regulatory requirements and AbbVie requirements.

6.3 Method of Assigning Subjects to Study Arms

Subjects enrolled into Study M16-291 will be administered a rovalpituzumab tesirine dose based on whether the subject had received a dose reduction in the parent study (details in the Protocol, Section 4.2). Details on study drug information are provided in Section 6.1.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ASCO	American Society of Clinical Oncology
AST	aspartate aminotransferase
AT	aminotransferase
ATEMS	AbbVie Temperature Excursion Management System
BID	twice daily
BSA	body surface area
BUN	blood urea nitrogen
CDSM	Clinical Drug Supply Management
CNS	central nervous system
CT	computerized tomography
DILI	Drug-Induced Livery Injury
DSUR	Development Safety Update Report
ECOG	Eastern Cooperative Oncology Group
EDP	extemporaneous dose preparation
eCRF	electronic Case Report Form
EDC	electronic data capture
EOT	End of Treatment
IMP	Investigational Medicinal Product
INR	international normalized ratio
IRT	Interactive Response Technology
IV	intravenously/intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NSAID	non-steroidal anti-inflammatory drug
PTT	partial thromboplastin time
PT	prothrombin time

RBC	red blood cell
RSI	Reference Safety Information
SAE	serious adverse event
SOC	System Organ Class
SPF	sun protection factor
SUSAR	Suspected Unexpected Serious Adverse Reactions
TA MD	Therapeutic Area Medical Director
TBL	total bilirubin
TEAE	treatment-emergent adverse event
ULN	Upper Limit of Normal

APPENDIX B. 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 C. FLUID RETENTION QUESTIONNAIRE EXAMPLE

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: _____