Phase 1 Study of APR-246 in Combination with Venetoclax and Rituximab Therapy in Patients with Richter's Transformed Non-Hodgkin's Lymphomas

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Sponsor:	Aprea Therapeutics, Inc. [redacted]
Responsible Medical Officer:	Eyal C. Attar, M.D.
Medical Monitor:	[redacted]
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INVESTIGATOR'S STATEMENT

1. I have carefully read this protocol entitled "Phase 1 Study of APR-246 in Combination with Venetoclax and Rituximab Therapy in Patients with Richter's Transformed Non-Hodgkin's Lymphomas" and agree that it contains all the necessary information required to conduct the study. I agree to conduct this study as outlined in the protocol.
2. I understand that this study will not be initiated without approval of the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), and that all administrative requirements of the governing body of the Institution will be complied with fully.
3. Informed written consent will be obtained from all participants in accordance with institutional guidelines, Food and Drug Administration (FDA) requirements as specified in Title 21 Code of Federal Regulations (CFR), Part 50, the European Union Directive 2001/20/European Commission (EC) and its associated Detailed Guidances, European Union Good Clinical Practice (GCP) Directive 2005/28/EC, the International Council for Harmonization (ICH) Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013).
4. I will only enroll participants who meet the protocol criteria for entry.
5. I understand that my signature on each completed electronic Case Report Form (eCRF) indicates that I have carefully reviewed the complete set of eCRFs and accept full responsibility for the contents thereof.
6. I understand that the information presented in this study protocol is confidential, and I hereby assure that no information based on the conduct of the study will be released without prior consent from the Sponsor unless this requirement is superseded by the FDA, a Competent Authority of the European Union or another Regulatory Authority.

Protocol Version 7.0: 31 January 2022

Name: _____ Telephone: _____

_____ _____

Address: _____

_____

Signature: _____ Date: _____

Sponsor/Representative:

[redacted] Date: _____

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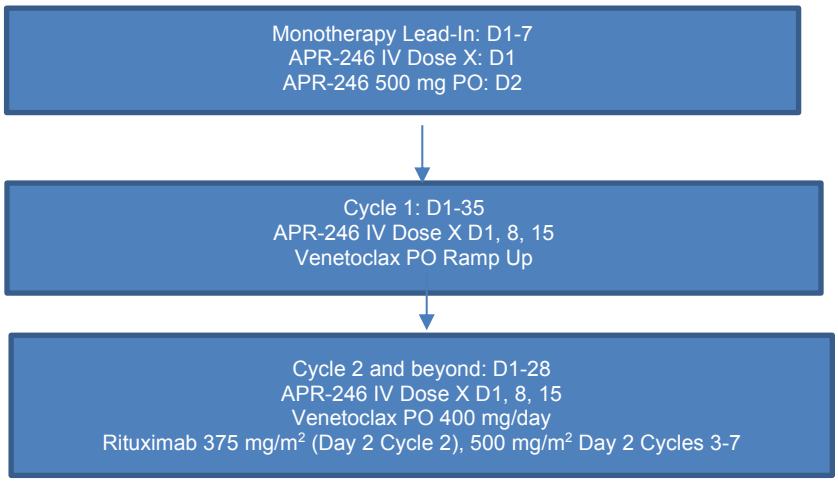
CLINICAL STUDY SYNOPSIS

Title	Phase 1 Study of APR-246 in Combination with Venetoclax and Rituximab Therapy in Patients with Richter's Transformed Non-Hodgkin's Lymphomas (NHL)
Sponsor	Aprea Therapeutics, Inc.
Monitor/ Contract Research Organization (CRO)	[redacted]
Number of Study Centers	Up to 10
Clinical Phase	1
Investigational Agent	APR-246 (eprenetapopt)
Study Design	This is a phase 1, open-label study to determine the pharmacologically active dose range of APR-246 in combination with venetoclax and rituximab in patients with Richter's Transformed NHL (RT) and to select a recommended dose for further development. The study includes a dose escalation design (Figure 1). It is preceded by a brief APR-246 monotherapy lead-in to establish a baseline pharmacokinetic (PK) / pharmacodynamic (PD) profile after intravenous (IV) dosing in each patient and to obtain APR-246 PK after a single dose of APR-246 administered orally (PO). The recommended dose will be based on the safety, tolerability, PK and PD profile of APR-246 in combination with venetoclax and rituximab therapy in patients with RT. Once the recommended dose of APR-246 in combination with venetoclax and rituximab is established, further explorations in expansion arms may be pursued following a protocol amendment. Patients with RT will receive APR-246 administered IV at the assigned cohort dose with standard doses of venetoclax and rituximab. Dose escalation will proceed in a standard 3 + 3 dose escalation design.  X = assigned cohort dose **Figure 1:** Clinical Trial Schema

	The intended three dose levels of APR-246 are: 1.5 g/day, 3.0 g/day, and 4.0 g/day administered as an IV infusion over 6 hours. The dose escalation will proceed until a pharmacologically active dose level is achieved. It will be stopped if maximum tolerated dose (MTD) is reached at a dose level below the maximum planned dose of 4.0 g/day. For the determination of MTD the following rules will be applied: • Three patients will be enrolled to Dose Level 1. • If 0 patients out of 3 experience a dose limiting toxicity (DLT) at Dose Level 1 (1.5 g/day of APR-246), the dose will advance to the next level (Dose Level 2, 3.0 g/day). • If 1 of the first 3 patients at Dose Level 1 experiences a DLT, 3 additional patients will be recruited and treated at the same dose level (1.5 g/day of APR-246). • If ≥2 patients out of 3-6 patients in a cohort experience a DLT at Dose Level 1 (1.5 g/day of APR-246), the study will temporarily discontinue enrollment and the Data Review Team (DRT) will consider further enrollment and possible dose/schedule adjustments. • If <2 patients out of 6 experiences a DLT at Dose Level 1 (1.5 g/day), dose escalation will proceed to the next cohort level (Dose Level 2, 3.0 g/day). • For each cohort, if there are 0 DLTs in the first 3 patients enrolled, the cohort will advance to the next level. If there is 1 DLT in the first 3 patients enrolled to a cohort, the cohort will enroll an additional 3 patients. If there are ≥2 DLTs in a cohort, the prior lower dose level will be declared the MTD. • If there are ≤1 DLT in the first 3 patients enrolled at Dose Level 3, 4.0 g/day APR-246, the study will enroll 3 additional patients at Dose Level 3. If there are ≤1 DLTs in 6 patients enrolled at Dose Level 3, 4.0 g/day APR-246 will be declared the MTD. Upon determination of the pharmacologically active dose or MTD, or when the maximally intended dose is reached, up to 10 additional patients may be enrolled at this dose level to confirm the assessment and to collect additional safety, PK and PD data to aid in determining the recommended dose of APR-246 in combination with venetoclax and rituximab. Prior to initiation of study treatment with APR-246 administered IV in combination with venetoclax and rituximab (during treatment cycles 2-7), patients will receive APR-246 alone on Day 1 and Day 2 of the 7-day monotherapy lead-in period, during which PK and PD of APR-246 following IV and PO administration will be evaluated. On Day 1 of the monotherapy lead-in period, APR-246 will be administered IV at the assigned cohort dose. On Day 2, APR-246 will be administered PO at the dose of 500 mg. This dose may be increased based on emerging PK data to determine dose linearity after oral dosing. Patients will be required to fast for at least 10 hours prior to APR-246 PO administration. Furthermore, a sub-group of patients may receive an oral dose of APR-246 in combination with a standard high-fat meal to determine the effect of food on APR-246 absorption.
Study Objectives	**Primary objective:** To evaluate the PD, safety and tolerability of APR-246 administered IV in combination with venetoclax and rituximab in patients with RT to determine the recommended dose of APR-246. **Secondary objectives:** 1. To investigate PD markers of APR-246 activity, including in peripheral blood malignant cells, using flow cytometry and other techniques. 2. To investigate PD markers of APR-246 activity in monotherapy, including in peripheral blood malignant cells, using flow cytometry and other techniques (*PK/PD Substudy of APR-246 Monotherapy*). 3. To determine the PK profile of APR-246.

	4. To investigate the PK of APR-246 administered PO (*PK/PD Substudy of APR-246 Monotherapy*). 5. To assess preliminary clinical activity of APR-246 in combination with venetoclax and rituximab therapy. **Exploratory objectives:** To explore the exposure response relationship of APR-246 with safety and/or efficacy when combined with venetoclax and rituximab therapy.
Study Endpoints	**Primary endpoints:** 1. PD analysis of circulating peripheral blood cells to determine effects of APR-246 on cellular viability and apoptosis. 2. Frequency of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) related to APR-246 in combination with venetoclax and rituximab therapy. 3. The highest tested dose of APR-246 with acceptable toxicity (the dose producing <33% of DLT). **Secondary endpoints:** 1. PK parameters: maximum concentration (C_{max}), area under the curve (AUC), volume of distribution (V_d) and clearance (CL) of APR-246; and C_{max}, time to maximum concentration (T_{max}), and AUC of venetoclax. 2. PD analysis of circulating peripheral blood cells to determine effects of APR-246 on cellular viability and apoptosis *(PK/PD Substudy of APR-246 Monotherapy*). 3. PK parameters after oral dosing: C_{max}, T_{max}, AUC, relative bioavailability (F), apparent volume of distribution (V_d/F) and apparent clearance (CL/F) of APR-246, *(PK/PD Substudy of APR-246 Monotherapy*). 4. Complete remission (CR) rate, defined as the proportion of patients who achieve CR as per response criteria. 5. Objective response rate (ORR), defined as the proportion of patients achieving a response, as per response criteria. 6. Duration of response (DOR), defined as the time from documentation of tumor response to disease progression or death as a result of any cause. 7. Progression-free survival (PFS), defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurs first). **Exploratory endpoints:** The exposure response relationship for safety and efficacy of APR-246 when combined with venetoclax and rituximab therapy.
Criteria for Inclusion	**Inclusion criteria:** 1. Patient is able to understand the study requirements and is willing and able to comply with them and provide written informed consent. 2. Patients with documented histologic diagnosis of RT by World Health Organization criteria who have relapsed and/or refractory disease following at least one line of prior therapy for RT. 3. Prothrombin time (or international normalized ratio) and partial thromboplastin time not to exceed 1.2 × the institution's normal range (patients with an elevated prothrombin time and known lupus anticoagulant may be eligible for participation after consulting the Medical Monitor).

4. Adequate bone marrow (BM) function independent of growth factor or transfusion support, per local laboratory reference range at screening as follows:
   a. Platelet count ≥75,000/mm^3
   b. Absolute neutrophil count ≥1,000/mm^3 unless cytopenia is clearly due to marrow involvement from NHL
   c. Total hemoglobin ≥9 g/dL (without transfusion support within 2 weeks of screening)

   If any of the above-mentioned cytopenia (a-c) are present due to BM involvement with disease (requiring transfusion or granulocyte colony-stimulating factor [G-CSF] support) NHL patients may proceed with enrollment after discussion with the Medical Monitor. Cytopenia may not be due to evidence of myelodysplastic syndrome (MDS) or hypoplastic BM.
5. Adequate organ function as defined by the following laboratory values:
   a. Creatinine CL ≥60 mL/min (by Cockcroft-Gault method, Appendix I)
   b. Total serum bilirubin ≤1.5 × upper limit of normal (ULN) unless due to Gilbert's syndrome, NHL organ involvement, controlled immune hemolysis or considered an effect of regular blood transfusions
   c. Alanine aminotransferase and aspartate aminotransferase ≤2.5 × ULN, unless due to NHL organ involvement
6. Age ≥18 years at the time of signing the informed consent form.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (APPENDIX II).
8. Projected life expectancy of ≥12 weeks.
9. Female patients must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test at screening, on a serum sample obtained within 7 days prior to initiation of study treatment.
10. Women of childbearing potential and men with female partners of childbearing potential must be willing to use an effective form of contraception (Appendix III).
11. Patients should use an effective form of contraception for up to 6 months after the last dose of APR-246 in combination with venetoclax or up to 12 months after the last dose of rituximab, whichever time period is longer.

Exclusion criteria:

1. Patients with known allergies to xanthine oxidase inhibitors or rasburicase.
2. Prior allergy to rituximab, defined as a clinically significant infusion-related reaction (IRR) in the opinion of the Investigator.
3. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that, in the opinion of the Investigator, may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.
4. Concomitant anticancer therapies, immunotherapies, cellular, or radiotherapy; major surgery within 3 weeks prior to first dose of study treatment. Washout period for chemotherapy is 14 days. Washout period for targeted agents is 2 weeks or 5 half-lives ($T_{1/2}$) (whichever is shorter). Washout period for antibody-based immunotherapies or cellular therapies is 4 weeks. Washout period for radiotherapy is 7 days (limited field) and 28 days (extended field that includes BM). Washout period must be completed prior to any treatment administration.
5. Uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia.
6. Consumption of grapefruit, grapefruit products, Seville oranges, or star fruit within 7 days of starting study treatment.

	7. Concomitant steroids for disease related pain control are allowed at any dose but must be discontinued prior to any study treatment initiation. Chronic use of corticosteroids is allowed up to ≤20 mg prednisone daily for non-cancer related conditions at the time of study start. 8. History of allogeneic or autologous stem cell transplant or chimeric antigen receptor T-cell therapy (CAR-T) within the last 30 days or with any of the following: a. Active graft versus host disease b. Cytopenia from incomplete blood cell count recovery post-transplant c. Need for anti-cytokine therapy for residual symptoms of neurotoxicity grade >1 from CAR-T d. Ongoing immunosuppressive therapy. 9. Known history of human immunodeficiency virus (HIV) serum positivity. 10. Active hepatitis B/C. Patients with prior exposure to hepatitis B (i.e., positive anti-hepatitis B core antibody) must demonstrate hepatitis B polymerase chain reaction to be negative during screening period and undergo prophylaxis and monitoring for hepatitis B according to institutional guidelines. 11. Known central nervous system (CNS) involvement by lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable and without evidence of disease may be eligible if a compelling clinical rationale is provided to sponsor. 12. Known neurologic disorder or residual neurologic toxicities that may put patients at increased risk of neurologic toxicity in the opinion of the Investigator. 13. Any of the following cardiac abnormalities: a. Myocardial infarction within six months prior to enrollment b. New York Heart Association Class III or IV heart failure (Appendix IV) or known left ventricular ejection fraction <40% c. A history of familial long QT syndrome d. Symptomatic atrial or ventricular arrhythmias not controlled by medications e. Corrected QT interval by Fridericia formula (QTcF) ≥470 msec, unless due to underlying bundle branch block and/or pacemaker and with the approval of the Medical Monitor. 14. Concomitant malignancies or previous malignancies with less than a 1-year disease-free interval at the time of signing consent. Patients with adequately treated basal or squamous cell carcinoma of the skin, or adequately treated carcinoma *in situ* (e.g., cervix) may enroll irrespective of the time of diagnosis. Patients with controlled, advanced prostate cancer are permitted. 15. Female patients who are pregnant or breast-feeding. 16. Active uncontrolled systemic infection. 17. Received an investigational agent within 30 days or within 5 $T_{1/2}$, whichever is shorter prior to the first dose of study treatment. 18. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption. 19. Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp or breast cancer resistance protein inhibitors (see Appendix VI).
Treatment Plan	Treatment will be administered on an outpatient basis but may be administered in the inpatient setting for patients who are hospitalized and meet criteria for study enrollment. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's disease under study. *Monotherapy Cycle* There is a 7-day monotherapy cycle where patients receive APR-246 IV on Day 1 and

	APR-246 PO on Day 2. The primary purpose of the monotherapy cycle is to obtain peripheral blood for monotherapy PK and PD analyses following IV and PO administration of APR-246. Patients will start treatment with APR-246 IV as a single agent administered on Day 1 of a single 7-day monotherapy cycle at the assigned cohort dose level, prior to Cycle 1 Day 1 of combination therapy. On Day 2 of the 7-day monotherapy lead-in period, patients will receive a single dose of APR-246 administered PO at the dose of 500 mg. After review of oral PK data from at least 6 patients, a decision can be made whether to increase the PO dose of APR-246 and/or administer APR-246 with a standard high-fat meal to investigate, respectively, dose linearity in PK and/or the effect of food on oral absorption of APR-246. Dose escalation of the oral dose or switching to administration with food will be determined by PK to ensure that the APR-246 exposure levels after oral dosing do not exceed the exposure levels after IV administration in terms of C_{max} and AUC. *Combination Treatment* After the APR-246 monotherapy lead-in, study treatment will consist of APR-246 administered as an IV infusion, at the same assigned dose that was used during the monotherapy lead-in period, once weekly, on Days 1, 8 and 15 of each cycle, concurrently with venetoclax for the 5-week ramp-up at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5. Beginning Cycle 2 Day 1, venetoclax will be administered at 400 mg (or tolerable dose following 5-week ramp up) PO daily. IV rituximab will be initiated at 375 mg/m^2 on Cycle 2, Day 2 and then administered at 500 mg/m^2 on Day 2 of Cycles 3-7. After 6 cycles of treatment with APR-246 in combination with venetoclax + rituximab, APR-246 + venetoclax will continue to be administered starting at Cycle 8 for up to a total of 24 cycles. The safety assessment (DLT) period will occur in the monotherapy lead-in and throughout Cycles 1, 2, and 3 of combination treatment. Patients with RT will receive APR-246 administered IV as the assigned cohort dose with standard doses of venetoclax and rituximab. Dose escalation will proceed in a standard 3 + 3 dose escalation design. Patients who miss >25% of APR-246 doses for a nonmedical reason (patient's preference) or noncompliance will be replaced. Patients who receive at least 3 cycles of study treatment at the assigned dose of APR-246 may proceed to the next dose level of APR-246 that has been demonstrated as safe and tolerable by the DRT in at least 3 patients, provided the dose increase is considered to be in the patient's best interest by the Investigator. Responses will be assessed according to response criteria for RT (Appendix V) via blood, BM, and imaging (positron emission tomography [PET]/computed tomography [CT]). Response assessments are to be performed every 3 cycles and PET-CT scanning is recommended. For patients who achieve CR, imaging may be omitted, and minimal residual disease (MRD) assessment will be completed using flow cytometry and/or molecular techniques from the BM and/or peripheral blood.
Duration of Follow-Up	Patients will be followed as per the Schedule of Study Assessments for up to 26 months through the end of trial visit and then will enter into long-term follow-up per Section 6.10. After a patient is removed or withdrawn from study treatment, the patient will be followed in the study until death or withdrawal of consent for study participation, whichever occurs first.

	Off-treatment data on overall survival (OS) will be updated every 3 months or until death or withdrawal of consent for study participation, whichever occurs first. If a patient is removed from the study due to unacceptable adverse event(s) (AEs), the event(s) will be followed until resolution or stabilization. Patients who respond and discontinue study treatment for reasons other than disease progression should have response assessments, and survival should be collected every 2 months until disease progression, withdrawal of consent for study participation, or death, whichever occurs first. After disease progression, data for survival should be collected every 3 months until death or withdrawal of consent for study participation. *Criteria for Removal from Study Treatment* Study treatment can continue for patients deriving clinical benefit in the opinion of the Investigator, unless one or more withdrawal criteria are met, or at the patient's discretion, or if the study is terminated. Study Treatment Discontinuation 1. Study treatment must be discontinued if: • Evidence of disease progression is observed. Note that patients who have disease progression but are continuing to derive clinical benefit in the opinion of the Investigator may continue to receive study treatment. • A female patient becomes pregnant. • A patient is non-compliant with the requirements of the protocol. • A patient has an adverse experience that would, in the Investigator's judgment, make continued participation in the study an unacceptable risk. • The patient starts new treatment for their disease under study. 2. Patient Withdrawal from Study Treatment If the patient is permanently withdrawn from study treatment, but does not withdraw consent from the study, the Investigator should make every effort to have the patient complete all withdrawal assessments at the time of withdrawal and complete all scheduled follow-up visits. 3. Study Completion A patient must be taken off the study if: • The patient dies during the study. • The patient is lost to follow-up. • The patient withdraws consent for study participation. 4. Patient Withdrawal from Study A patient may voluntarily withdraw from study treatment or withdraw consent from study participation at any time. The Investigator may also, at his or her discretion, discontinue a patient from study treatment at any time. The Investigator and/or designated staff will record the date and the reason for patient withdrawal from the study.
Statistics	This is a phase 1, open-label study to determine the pharmacologically active dose range of APR-246 in combination with venetoclax and rituximab and to select a recommended dose for further development. The recommended dose of APR-246 in combination with venetoclax and rituximab will be defined as the dose determined to be producing the greatest level of cellular apoptosis in circulating peripheral blood malignant cells in the monotherapy portion. Dose escalation will be stopped when either the MTD or the intended maximum dose of the study is reached.

Definition of DLT
All TEAEs are relevant to the determination of DLTs unless they are clearly and solely due to the disease under study. The DLT evaluation period will be up to 91 days (7 days of APR-246 monotherapy plus 84 days for Cycle 1–3 with combination therapy) after the first dose of APR-246 is administered. A DLT is defined as any of the following TEAEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), as follows:

- Any neurologic toxicity of grade 4
- Any grade ≥3 non-hematologic toxicity except for:
    - First occurrence of grade 3 electrolyte abnormalities and/or creatinine CL decrease resolving to grade 2 (or baseline if baseline is grade ≥2) within 48 hours with supportive treatment.
    - Grade 3 fatigue, nausea, vomiting, diarrhea or other manageable constitutional symptom(s) that is/are responsive to supportive therapy.
    - Grade 3 infection responding to appropriate antimicrobial therapy.
    - Any neurologic toxicity of grade 3 that does not return to grade ≤1 or baseline within 7 days.
- Any grade ≥3 hematologic toxicity will be considered a DLT except for:
    - Grade 3 neutropenia without fever
    - Grade 4 neutropenia without fever lasting 8 days or less
    - Grade 3 thrombocytopenia that does not result in bleeding or transfusion
    - Grade 3/4 lymphopenia/lymphocytosis
    - Grade 3/4 white blood cell (WBC) decreased
    - Grade 3/4 WBC increased

Any toxicity, regardless of the NCI-CTCAE v5.0 grade, resulting in discontinuation, dose reduction or treatment with less than 75% of planned doses of APR-246 study drug, will be reviewed by the DRT, and will be considered a DLT unless clearly and solely related to the disease under study. The DRT will consist of the Medical Monitor, Site Principal Investigators, and other clinical research personnel that the Sponsor may deem appropriate.

G-CSF support for the management of neutropenia and prophylactic antimicrobial therapy are allowed, including during the DLT period.

TEAEs that meet the above criteria but that occur after the DLT evaluation period will not be defined as DLTs and will be reported as AEs/SAEs and will be reviewed across all cohorts during the study to help determine the AE profile for the respective treatment regimens under study. A patient that discontinues APR-246 therapy before completion of Cycle 3 without DLT is considered evaluable for the purpose of safety review by the DRT only if at least 75% of the scheduled doses of APR-246 were administered in Cycles 1 through 3.

The study will implement the following stopping criteria:

- Any death occurring between receipt of the first dose of APR-246 through 30 days of last dose of study treatment which is not clearly and solely due to underlying disease,
- A medically equivalent SAE experienced by >1 patient, which is not clearly and solely due to underlying disease,
- A severe AE (NCI-CTCAE toxicity grade >3) experienced by >2 patients that does not return to grade ≤1 or baseline within 7 days ,
- A grade ≥3 neurologic AE that does not return to grade ≤1 or baseline within 7 days.

	If a stopping criterion is met, enrollment will be temporarily suspended until the DRT has performed a prompt cumulative review of safety data and the circumstances of the event(s) in question, to determine whether dosing and/or the protocol should be modified. *Determination of Sample Size* This trial assumes a sample size of up to 48 patients in total, with up to 6 patients in each of the 3 cohorts and an additional 10 patients added at the MTD, or maximum tolerated dose, to gain further confidence in the recommended dose of APR-246. If Dose Level 3 is determined to be the MTD, up to 10 additional patients may be added and treated at both Dose Levels 1 and 2 to obtain additional safety, PK, and/or PD information. No sample size and power calculations are performed for this phase 1 study. Patients who miss >25% of APR-246 doses for a nonmedical reason (patient's preference) or noncompliance in the safety lead-in cohorts will be replaced. *Recommended Dose* The recommended dose of APR-246 in combination with venetoclax and rituximab represents the dose of APR-246 at or below the maximum tested dose, or the MTD, that results in the greatest apoptosis of circulating malignant cells in the monotherapy cycle. *Analysis Populations* Safety population: Patients will be evaluable for safety if they receive at least one dose of APR-246. The safety population will be the primary analysis population used for all analyses such as patient disposition, patient demographics, exposure, safety parameters and efficacy parameters. The safety population will be the primary analysis population for efficacy. Efficacy evaluable (EE) population: All patients who complete at least one treatment cycle of APR-246 and venetoclax and rituximab and who have at least one post-treatment clinical response assessment. The EE population will be the secondary analysis population for efficacy. PD population: Patients will be evaluable for PD if at least one sample for PD evaluation has been obtained after administration of APR-246. PK population: Patients will be evaluable for PK if at least one sample for PK evaluation has been obtained. *Efficacy Analyses* CR rate will be summarized for the safety and EE patients as the proportion (%) of patients with CR. In addition to presenting the CR rate, its associated exact 95% confidence intervals (CI) will also be presented. DOR is defined as the time from the date when criteria for response are met to the date of disease progression or death due to any cause, whichever occurs first. Patients alive with no disease progression will have their DOR censored at the date of the last clinical assessment. The duration of CR will be summarized by providing the median DOR together with associated 95% CI, using Kaplan-Meier methodology. ORR will be summarized in number (%) of patients in each category of responses and ORR will be analyzed by using a similar method to the one used for the CR rate. ORR is defined as the number of patients who achieve CR and partial remission.

	Survival data are collected at treatment and follow-up periods. Patients will be followed until death or withdrawal of consent from the study, whichever occurs first. OS is defined as the number of days from the first day of treatment to the date of death due to any cause. Kaplan-Meier methodology will be utilized. PFS is defined as the time from the first day of treatment to disease progression or death due to any cause, whichever occurs first. If neither event occurs, PFS will be censored at the date of the last clinical assessment. Kaplan-Meier methodology will be utilized. *Safety Analyses* Safety data including AEs, vital signs, laboratory data, electrocardiogram, and physical exam findings will be tabulated for the safety population. AEs will be tabulated by System Organ Class, preferred term, severity, and relationship to treatments. The tabulation of laboratory parameters will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range. Laboratory parameters will also be tabulated by maximum NCI-CTCAE v5.0 severity grade. *Pharmacodynamic Analysis* PD analysis will be conducted using flow cytometry of circulating chronic lymphocytic leukemia (CLL)/RT cells before and after treatment with APR-246 during monotherapy and the first day of combination treatment ramp-up, to assess viability and apoptosis. Descriptive statistics (mean, standard deviation, coefficient of variation (CV%) mean, geometric mean, CV% geometric mean) will be utilized to compare the post- and pre-treatment samples and the differences at each dose cohort level will be tested for relationship to dose. *Pharmacokinetic Analysis* During the APR-246 monotherapy lead-in period, PK sampling for APR-246 will be performed on Days 1 - 3. Noncompartmental PK analysis will be used to determine C_{max}, T_{max}, AUC and bioavailability after oral dosing for decision making on dose escalation of the oral dose. PK sampling for APR-246 will be performed during Cycle 2, on Day 1, 8 and 15 and on Day 1 from Cycle 3 onwards. PK sampling for venetoclax and rituximab will not be performed for this study. The PK of APR-246 will be summarized using descriptive statistics (mean, standard deviation, CV% mean, geometric mean, CV% geometric mean). The concentration data for APR-246 will be evaluated using population PK analysis in combination with data from other studies. APR-246 AUC and C_{max} will then be tested for association with signs of efficacy and safety. If an observable trend exists, a PK/PD model will be developed to evaluate the exposure-response relationship between APR-246 plasma exposure and outcome measures. Demographic and clinical data (ethnicity, current age, body weight, sex, disease status, etc.) will be utilized to assess interpatient variability in the PK and PK/PD relationships.

LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AIHA	Autoimmune hemolytic anemia
AML	Acute myeloid leukemia
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the curve
BBB	Bundle branch block
Bcl-2	B-cell lymphoma-2
βhCG	Beta-human chorionic gonadotrophin
BM	Bone marrow
BUN	Blood urea nitrogen
CAR-T	Chimeric antigen receptor T-cell therapy
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CIT	Chemoimmunotherapy
CL	Clearance
CLL	Chronic lymphocytic leukemia
C_{max}	Maximum concentration
CNS	Central nervous system
CR	Complete remission
CRO	Contract Research Organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CV%	Coefficient of variation
CYP3A4	Cytochrome P450 3A4
DLT	Dose limiting toxicity
DOR	Duration of response
DRM	Data review meeting
DRT	Data Review Team
EC	European Commission
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EE	Efficacy evaluable
EOI	End of infusion
ER	Endoplasmic reticulum
FDA	Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HBV	Hepatitis B virus
HBsAg	Hepatitis B surface antigen
HGSOC	High-grade serous ovarian cancer

HIV	Human immunodeficiency virus
IB	Investigator's Brochure
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRR	Infusion-related reaction
IV	Intravenous(ly)
LBM	Lean body mass
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MDS	Myelodysplastic syndrome
MQ	2-methylene-quinuclidin-3-one
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NGS	Next-generation sequencing
NHL	Non-Hodgkin's lymphoma
OS	Overall survival
ORR	Objective response rate
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PET	Positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PLD	Pegylated liposomal doxorubicin
PML	Progressive multifocal leukoencephalopathy
PO	Orally *(per os)*
popPK	Population pharmacokinetics
PR	Partial remission
PRBC	Packed red blood cells
QTcF	Corrected QT interval by Fridericia formula
RT	Richter's transformed NHL
SAE	Serious adverse event
SOC	System organ class
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
T_{max}	Time to maximum concentration
TrxR1	Thioredoxin reductase 1
$T_{1/2}$	Half-life
ULN	Upper limit of normal
US	United States
USPI	United States Prescribing Information
VAF	Variant allele frequency
V_d	Volume of distribution
WBC	White blood cell

WHO	World Health Organization

1.0 GENERAL INFORMATION

1.1 Protocol Number and Title of the Study

Protocol No. A20-11197

Protocol Title: Phase 1 Study of APR-246 in Combination with Venetoclax and Rituximab Therapy in Patients with Richter's Transformed Non-Hodgkin's Lymphomas

1.2 Sponsor

Aprea Therapeutics, Inc.
[redacted]

1.3 Medical Monitor

[redacted]

1.4 Signature Authorization

The protocol will be signed by Aprea Therapeutics.

2.0 BACKGROUND INFORMATION

2.1 Disease Background

Non-Hodgkin's lymphomas (NHL) are lymphoid malignant neoplasms with diverse biological and clinical behavior, variously derived from the clonal expansion of B cells, T cells, natural killer cells or precursors of these cells.

Chronic lymphocytic leukemia (CLL) is one of the most common types of B-cell NHL, characterized by a progressive accumulation of functionally incompetent monoclonal lymphocytes[1]. The incidence rates among men and women in the United States (US) are approximately 6.75 and 3.65 cases per 100,000 population per year, respectively[2,3].

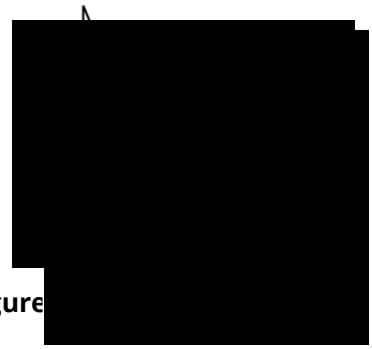
CLL is associated with a highly heterogeneous disease course, with some patients surviving for more than 10 years without needing treatment, and others experiencing rapid disease progression and poor outcomes despite effective chemoimmunotherapy (CIT)[4–8]. This heterogeneity is partly explained by the diverse genetic aberrations identified in approximately 80% of CLL patients[9–12], including a deletion in chromosome 13q14.3 (del(13q)), del(11q), del(17p) and trisomy 12, associated with an intermediate prognosis. Del(13q) is the most common chromosomal alteration, evident in >50% of patients, and is associated with favorable prognosis[13]. Del(17p) is found in 7% of patients and is associated with loss of the tumor suppressor gene *TP53*[14], whereas del(11q) is found in 18% of patients

and is often associated with alterations in ATM; each of these chromosomal alterations is associated with adverse clinical outcome[9,15]. Deletions in chromosome 17p [del(17p)] resulting in loss of the *TP53* gene, which encodes the tumor-suppressor protein p53, belong to the strongest prognostic and predictive markers guiding treatment decisions in CLL, and are associated with markedly decreased survival and impaired response to CIT[16–20]. CLL patients with alterations of *TP53* have inferior outcomes with all CLL directed therapies, in particular CIT combinations, and these patients (if fit) were historically considered for referral for allogeneic hematopoietic stem cell transplantation in first remission[21–25]. New small-molecule inhibitors that are efficacious in patients harboring *TP53* mutations are now available, including the BTK inhibitors ibrutinib and acalabrutinib, the phosphatidylinositol 3-kinase inhibitors idelalisib and duvelisib, and the B cell lymphoma-2 (Bcl-2) inhibitor venetoclax[26–34].

Despite the introduction of targeted agents, 5-10% of previously treated CLL patients undergo transformation into high-grade lymphoma, a condition known as Richter's transformed NHL (RT). These patients typically present with an aggressive disease course and have poor response to traditional chemotherapy used to treat de novo diffuse large B-cell lymphoma and similar or shorter overall survival (OS) (median 3-11 months)[35,36]. Based on clonal relationship of large cell component to CLL, 2 distinct subtypes could be identified: clonally-related RT which carries a worse outcome, and clonally-unrelated RT where the outcomes are similar to de novo diffuse large B-cell lymphoma[37]. Specific risk factors for the development of RT in a patient with CLL have yet to be identified; however, *TP53* disruption, c-MYC abnormalities, unmutated immunoglobulin heavy chain <2%, non-del13q cytogenetics, CD38 gene polymorphisms, stereotypy, and VH4-39 gene usage may predispose to RT[35,37,38]. The CLL-International Prognostic Index aids in predicting time to first therapy among previously untreated patients[38]. The prognosis of patients with RT generally is poor, particularly for those who are heavily pretreated for CLL and/or who have transformation involving lymphocytes that are clonally related to the underlying CLL[39].

There is no standard of care for patients with RT, which represents a disease with unmet medical needs. Development of rituximab-containing intensive chemotherapy regimens and chemo-immunotherapy regimens have improved response rates but have not clearly affected long-term outcomes[35]. CIT remains the treatment of choice, though the outcomes remain suboptimal, with the median survival of less than 1 year.

2.2 APR-246



Figure

2.3 APR-246 Preclinical Studies

2.3.1 Pharmacology and Mode of Action

2.3.2 Safety Pharmacology

[redacted]

2.3.3 Pharmacokinetics and Metabolism in Animals

[redacted]

2.3.4 Toxicology

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

In[redacted]

[redacted]**246 Clinical Studies**

[redacted]

2.4.1 Phase 1/2 Study in Solid and Hematological Malignancies

[redacted]

2.4.2 Phase 1/1b Study in Refractory Hematologic Malignancies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

2.4.6 Phase 1 Study in Combination with Venetoclax and Azacitidine in *TP53*-Mutant Myeloid Neoplasms

[redacted]

[redacted]

2.4.7 APR-246 CNS Safety Overview

[redacted]

[redacted].

2.4.8 APR-246 Cardiac Safety Overview

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]246 Pharmacokinetics in Humans

[redacted]

[redacted]

Table 1. Average Exposure After Infusion of a Fixed Dose of 4.5 g of APR-246 for 6 hours in Males and Females

		Males	Females
[redacted]			

[redacted]

[redacted]

[redacted]				
[redacted]				
[redacted]				

[redacted]

[redacted]

2.5 Venetoclax

Venetoclax is a Bcl-2 inhibitor that was approved by the U.S. FDA for the treatment of adult patients with CLL or small lymphocytic lymphoma in the front line and relapsed/refractory settings.

In the phase 3 study comparing venetoclax plus rituximab with bendamustine plus rituximab in relapsed and/or refractory CLL (MURANO), the 2-year rates of progression-free survival (PFS) were significantly higher in the venetoclax-rituximab group (84.9%) than in the bendamustine–rituximab group (36.3%)[46]. The benefit was maintained across all clinical and biologic sub-groups, including the sub-group of patients with chromosome 17p deletion, where the 2-year rate of PFS among patients with chromosome 17p deletion was 81.5% in the venetoclax–rituximab group versus 27.8% in the bendamustine–rituximab group (hazard ratio, 0.13; 95% CI, 0.05 to 0.29).

The most common adverse reactions (≥20%) of any grade in patients receiving venetoclax monotherapy are neutropenia, diarrhea, nausea, anemia, upper respiratory tract infection, thrombocytopenia, and fatigue. Serious adverse reactions were reported in 43.8% of patients. The most frequent serious adverse reactions (≥2%) were pneumonia, febrile neutropenia, pyrexia, autoimmune hemolytic anemia (AIHA), anemia, and tumor lysis syndrome (TLS). More detailed information about the safety profile of venetoclax in combination with rituximab may be found in the United States prescribing information (USPI) for venetoclax[47].

Following multiple doses under fed conditions, C_{max} of venetoclax is reached 5 – 8 hours after dose. It is recommended that venetoclax be administered with a meal as food increases the absorption after oral administration. Venetoclax is cleared from systemic circulation via hepatic elimination. The $T_{1/2}$ is approximately 26 hours. The PK of venetoclax does not change over time. Venetoclax is predominantly metabolized by CYP3A4/5. CYP3A4 inhibitors and inducers as well as P-gp inhibitors cause clinically relevant drug-drug interactions with venetoclax. For the same reason certain food must be avoided: grapefruit, grapefruit juice, Seville oranges (often used in marmalades), starfruit (CYP3A inhibiting), and St John's wort (CYP3A inducing). Based on their metabolic profiles, a PK drug-drug interaction of venetoclax with APR-246 is considered unlikely.

2.6 Rituximab

Rituximab is a monoclonal antibody that targets the CD20 antigen expressed on the surface of pre-B and mature B-lymphocytes. Upon binding to CD20, rituximab mediates B-cell lysis. Possible mechanisms of cell lysis include complement dependent cytotoxicity and antibody dependent cell mediated cytotoxicity. B cells are believed to play a role in the pathogenesis of rheumatoid arthritis and associated chronic synovitis. In this setting, B cells may be acting at multiple sites in the autoimmune/inflammatory process, including through production of rheumatoid factor and other autoantibodies, antigen presentation, T-cell activation, and/or proinflammatory cytokine production.

In NHL patients, administration of rituximab resulted in depletion of circulating and tissue-based B cells. Among 166 patients in NHL Study 1 (NCT000168740), circulating CD19-positive B cells were depleted within the first three weeks with sustained depletion for up to 6 to 9 months post treatment in 83% of patients. B-cell recovery began at approximately 6 months and median B-cell levels returned to normal by 12 months following completion of treatment. There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following rituximab administration; 14% of patients had IgM and/or IgG serum levels below the normal range[48].

The PK was characterized in 203 NHL patients receiving 375 mg/m^2 rituximab weekly by IV infusion for 4 doses. Rituximab was detectable in the serum of patients 3 to 6 months after completion of

treatment. Based on a population PK (popPK) analysis of data from 298 NHL patients who received rituximab once weekly or once every three weeks, the estimated median $T_{1/2}$ was 22 days (range, 6.1 to 52 days). Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher CL. However, dose adjustment for pretreatment CD19 count or size of tumor lesion is not necessary. Age and gender had no effect on the PK of rituximab[48].

As rituximab is a monoclonal antibody, no PK drug-drug interaction is expected with APR-246.

2.7 Rationale for Combinations of APR-246 with Venetoclax + Rituximab

[redacted]

2.8 Rationale for Dose of APR-246 in Combination with Venetoclax and Rituximab

[redacted]

venetoclax and rituximab.

2.9 Rationale for Oral Dose of APR-246 in the Monotherapy Cycle

[redacted]

2.10 Potential Risks and Benefits

2.10.1 Potential Risks

[redacted]

[redacted]

2.10.2 Potential Benefits

The purpose of this clinical trial is to define the PD, safety and tolerability of APR-246 in combination with venetoclax and rituximab in patients with RT and to determine preliminary efficacy. Considering the lack of effective treatment options in these patients, the benefit/risk assessment supports the use of APR-246 in this trial.

2.11 Characteristics of a Well-Conducted Trial

The following characteristics of an adequate and well-conducted trial will be implemented:

1. The Investigators will be well qualified by scientific training and experience.
2. Detailed electronic Case Report Forms (eCRFs) will be completed for every patient.
3. Requirements for institutional ethics review as set forth by the appropriate Institutional Review Board/Independent Ethics Committee (IRB/IEC), Title 21 Code of Federal Regulations (CFR) Part 56, the European Union Directive 2001/20/European Commission (EC) and its associated Detailed Guidances, European Union Good Clinical Practice (GCP) Directive 2005/28/EC, the International Council for Harmonization (ICH) Guideline for GCP, Sections 3 and 4, and the terms of the Declaration of Helsinki (2013), will be followed.
4. Requirements for informed consent in accordance with institutional guidelines, FDA requirements as specified in Title 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013), will be followed.
5. Safety data will be recorded and evaluated.
6. Routine monitoring visits will be conducted by the Sponsor's representative to ensure data accuracy.
7. Drug accountability will be strictly maintained.
8. This trial will be conducted according to GCP, the protocol and applicable regulatory requirements.

2.12 Patient Population

This study will enroll adult male and female patients of ≥18 years of age with documented histologic diagnosis of RT by WHO criteria who have relapsed and/or refractory disease following at least one line of prior therapy for RT.

3.0 TRIAL OBJECTIVES AND PURPOSE

3.1 Primary Objective

To evaluate the PD, safety and tolerability of APR-246 administered IV in combination with venetoclax and rituximab in patients with RT to determine the recommended dose of APR-246.

3.2 Secondary Objectives

1. To investigate a pharmacologically active dose of APR-246 by using PD markers of APR-246 activity,

including in peripheral blood malignant cells, using flow cytometry and other techniques.
2. To investigate PD markers of APR-246 activity in monotherapy, including in peripheral blood malignant cells, using flow cytometry and other techniques (*PK/PD Substudy of APR-246 Monotherapy*).
3. To determine the PK profile of APR-246.
4. To investigate the PK of APR-246 administered PO (*PK/PD Substudy of APR-246 Monotherapy*).
5. To assess preliminary clinical activity of APR-246 in combination with venetoclax and rituximab therapy.

3.3 Exploratory Objectives

To explore the exposure response relationship of APR-246 with safety and/or efficacy when combined with venetoclax and rituximab therapy.

4.0 TRIAL DESIGN

4.1 Overview of Trial Design

Treatment will be administered on an outpatient basis but may be administered in the inpatient setting for patients who are hospitalized and meet criteria for study enrollment. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's disease under study.

Monotherapy Cycle
There is a 7-day monotherapy cycle where patients receive APR-246 IV on Day 1 and APR-246 PO on Day 2. The primary purpose of the monotherapy cycle is to obtain peripheral blood for monotherapy PK and PD analyses following IV and PO administration of APR-246.

Patients will start treatment with APR-246 IV as a single agent administered on Day 1 of a single 7-day monotherapy cycle at the assigned cohort dose level, prior to Cycle 1 Day 1 of combination therapy. On Day 2 of the 7-day monotherapy lead-in period, patients will receive a single dose of APR-246 administered PO at the dose of 500 mg. After review of oral PK data from at least 6 patients, a decision can be made whether to increase the PO dose of APR-246 and/or administer APR-246 with a standard high-fat meal to investigate, respectively, dose linearity in PK and/or the effect of food on oral absorption of APR-246. Dose escalation of the oral dose or switching to administration with food will be determined by PK to ensure that the APR-246 exposure levels after oral dosing do not exceed the exposure levels after IV administration in terms of C_{max} and AUC.

Combination Treatment
After the APR-246 monotherapy lead-in, study treatment will consist of APR-246 administered as an IV infusion at the same assigned dose that was used during the monotherapy lead-in period once weekly, on Days 1, 8 and 15 of each cycle, concurrently with venetoclax for the 5-week ramp-up at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5. Beginning Cycle 2 Day 1, venetoclax will be administered at 400 mg (or tolerable dose following 5-week ramp up) PO daily. IV rituximab will be initiated at 375 mg/m^2 on Cycle 2, Day 2 and then administered at 500 mg/m^2 on Day 2 of Cycles 3-7. After 6 cycles of treatment with APR-246 in combination with venetoclax + rituximab, APR-246 + venetoclax will continue to be

administered starting at Cycle 8 for up to a total of 24 cycles. Cycle 1 will consist of 35 days. Cycles 2 and beyond will be 28 days. The safety assessment (DLT) period begins at the start of treatment and extends to the end of Cycle 3.

Patients with RT will receive APR-246 administered IV at the assigned cohort dose with standard doses of venetoclax and rituximab. Dose escalation will proceed in a standard 3 + 3 dose escalation design.

The intended three dose levels of APR-246 are: 1.5 g/day, 3.0 g/day, and 4.0 g/day administered as an IV infusion over 6 hours. The dose escalation will proceed until a pharmacologically active dose level is achieved. It will be stopped if the maximum tolerated dose (MTD) is reached at a dose level below the maximum planned dose of 4.0 g/day. For the determination of MTD the following rules will be applied:

- Three patients will be enrolled to Dose Level 1.
- If 0 patients out of 3 experience a DLT at Dose Level 1 (1.5 g/day of APR-246), the dose will advance to the next level (Dose Level 2, 3.0 g/day).
- If 1 of the first 3 patients at Dose Level 1 experiences a DLT, 3 additional patients will be recruited and treated at the same dose level (1.5 g/day of APR 246).
- If ≥2 patients out of 3-6 patients in a cohort experience a DLT at Dose Level 1 (1.5 g/day of APR-246), the study will temporarily discontinue enrollment and the Data Review Team (DRT) will consider further enrollment and possible dose/schedule adjustments.
- If <2 patients out of 6 experiences a DLT at Dose Level 1 (1.5 g/day), dose escalation will proceed to the next cohort level (Dose Level 2, 3.0 g/day).
- For each cohort, if there are 0 DLTs in the first 3 patients enrolled, the cohort will advance to the next level. If there is 1 DLT in the first 3 patients enrolled to a cohort, the cohort will enroll an additional 3 patients. If there are ≥2 DLTs in a cohort, the prior lower dose level will be declared the MTD.
- If there are ≤1 DLT in the first 3 patients enrolled at Dose Level 3, 4.0 g/day APR-246, the study will enroll 3 additional patients at Dose Level 3. If there are ≤1 DLTs in 6 patients enrolled at Dose Level 3, 4.0 g/day APR-246 will be declared the MTD.

Upon determination of the pharmacologically active dose or MTD, or when the maximally intended dose is reached, up to 10 additional patients may be enrolled at this dose level to confirm the assessment and to collect additional safety, PK and PD data to aid in determining the recommended dose of APR-246 in combination with venetoclax and rituximab.

Table 3. APR-246 Dose Levels

Dose Modification	APR-246 Dose
Dose Level 1	APR-246 1.5 g/day 0.5 g (for first 45 minutes) + 1.0 g (for 5 hours 15 minutes)
Dose Level 2	APR-246 3.0 g/day 1.0 g (for first 45 minutes) + 2.0 g (for 5 hours 15 minutes)
Dose Level 3	APR-246 4.0 g/day 1.33 g (for the first 45 minutes) + 2.66 g (for 5 hours 15 minutes)

Prior to initiation of study treatment with APR-246 administered IV in combination with venetoclax and rituximab (during treatment cycles 2-7), patients will receive APR-246 alone on Day 1 and Day 2 of the 7-day monotherapy lead-in period, during which PK and PD of APR-246 following IV and PO administration will be evaluated. On Day 1 of the monotherapy lead-in period, APR-246 will be administered IV at the assigned cohort dose. On Day 2, APR-246 will be administered PO at the dose of 500 mg. This dose may be increased based on emerging PK data to determine dose linearity after oral dosing. Patients will be required to fast for at least 10 hours prior to APR-246 PO administration. Furthermore, a sub-group of patients may receive an oral dose of APR-246 in combination with a standard high-fat meal to determine the effect of food on APR-246 absorption.

Additional dose levels may be explored if warranted based on emerging DLT, safety, PK, and/or PD data. In addition, patients who have received at least 3 cycles of therapy at the assigned dose cohort level may advance to the next higher dose level once the next higher dose level has been declared safe by the DRT.

Responses will be assessed according to response criteria for RT (Appendix V) via blood, BM, and imaging (positron emission tomography [PET]/computed tomography [CT]). Response assessments are to be performed every 3 cycles and PET-CT scanning is recommended. For patients who achieve CR, imaging may be omitted, and minimal residual disease (MRD) assessment will be completed using flow cytometry and/or molecular techniques from the BM and/or peripheral blood.

Patients may continue treatment as long as toxicity remains acceptable, the patient has not withdrawn consent and is deriving clinical benefit in the opinion of the Investigator while receiving study treatment according to the treatment durations specified for the agents in Section 4.4. Response and disease progression will be assessed based on the Revised Criteria for Response Assessment of Hodgkin's and Non-Hodgkin's Lymphoma (Lugano Criteria; see Appendix V), as outlined in the Schedule of Study Evaluations.

4.2 End of Study

The end of the study is defined as the date of the last visit of the last patient undergoing the trial.

4.3 Drug Products

4.3.1 APR-246

[redacted]

[redacted]

4.3.2 Venetoclax

Chemical Name: 4-{4-[(4'-chloro-5,5-dimethyl[3,4,5,6-tetrahydro[1,1'-biphenyl]]-2-yl)methyl] piperazin-1-yl}-N-(3-nitro-4-{[(oxan-4-yl)methyl]amino}benzene-1-sulfonyl)-2-[(1H-pyrrolo[2,3-b]pyridine-5-yl)oxy]benzamide.

Formulation, preparation, storage and stability: Please see venetoclax USPI[52].

Route of Administration: Venetoclax should be taken PO, with food, at a dose of 400 mg daily once the ramp-up phase is completed. During the 5-week ramp-up in Cycle 1, venetoclax is given PO at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5. Use of posaconazole and strong CYP inhibitors is contraindicated in the ramp up phase. For patients receiving a steady daily dose of venetoclax, the dose of venetoclax should be modified accordingly to account for changes in concomitant use of posaconazole and CYP inhibitors in accordance with the venetoclax USPI[52].

4.3.3 Rituximab

Chemical Name: Immunoglobulin G1 (human-mouse monoclonal IDEC-C2B8 gamma 1-chain anti-human antigen CD 20), disulfide with human-mouse monoclonal IDEC-C2B8 kappa-chain, dimer

Formulation, preparation, storage and stability: Rituximab injection is a sterile, preservative-free, clear, colorless solution for IV infusion. Store rituximab vials refrigerated at 2°C to 8°C (36°F to 46°F) and protect from direct sunlight. Do not freeze or shake. Please see Rituximab USPI[48].

Route of administration: Rituximab is administered as an IV infusion with starting dose of 375 mg/m^2 in Cycle 2 and then 500 mg/m^2 in Cycles 3−7.

4.4 Duration of Therapy

Patients may remain on study treatment to the end of the trial visit while deriving clinical benefit, unless unacceptable toxicity, progression, death or patient withdrawal occurs. Rituximab may be given for up to 6 cycles and venetoclax for up to 2 years. Patients may remain on study treatment after disease progression if they are continuing to derive clinical benefit in the opinion of the Investigator.

4.5 Trial Discontinuation

The Sponsor may terminate this study prematurely. Written notification of the termination is required. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure of the Investigator to enter patients at an acceptable rate.
- Insufficient adherence to protocol requirements (non-compliance).
- Lack of evaluable and/or complete data.
- Decision to modify the developmental plan of the drug.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

The Sponsor reserves the right to discontinue the study for clinical or administrative reasons at any time. If the site does not recruit at a reasonable rate, the study may be discontinued at that site. Should the study be terminated and/or the site closed for whatever reason, all documentation and study drug pertaining to the study must be returned to the Sponsor or its representative, and the Investigators, IRB/IEC and Regulatory Authorities will be promptly informed of the termination and the reason for the decision. The Investigator should promptly inform the patients and ensure appropriate therapy and follow-up. Patients should then be withdrawn from the study.

4.6 Drug Accountability/Disposition of Experimental Drug Supplies

The Investigator or designee will maintain accurate records of receipt and the condition of the study drug supplied for this study, including dates of receipt. In addition, accurate records will be kept of when and how much study drug is dispensed and administered to each patient in the study. Any reasons for departure from the protocol dispensing regimen must also be recorded.

At the completion of the study, there will be a final reconciliation of all study drugs.

4.7 Inclusion Criteria

1. Patient is able to understand the study requirements and is willing and able to comply with them and provide written informed consent.
2. Patients with documented histologic diagnosis of RTby WHO criteria who have relapsed and/or refractory disease following at least one line of prior therapy for RT.
3. Prothrombin time (or international normalized ratio) and partial thromboplastin time not to exceed 1.2 × the institution's normal range (patient with an elevated prothrombin time and known lupus anticoagulant may be eligible for participation after consulting the Medical Monitor).
4. Adequate BM function independent of growth factor or transfusion support, per local laboratory reference range at screening as follows:
    a. Platelet count ≥75,000/mm^3
    b. Absolute neutrophil count ≥1,000/mm^3 unless cytopenia is clearly due to marrow involvement from NHL
    c. Total hemoglobin ≥9 g/dL (without transfusion support within 2 weeks of screening)

If any of the above-mentioned cytopenia (a-c) are present due to significant BM involvement with disease (requiring transfusion or granulocyte colony stimulating factor [G-CSF] support) NHL patients may proceed with enrollment after discussion with the Medical Monitor. Cytopenia may not be due to evidence of MDS or hypoplastic BM.

5. Adequate organ function as defined by the following laboratory values:
   a. Creatinine CL ≥60 mL/min (by Cockcroft-Gault method, Appendix I)
   b. Total serum bilirubin ≤1.5 × upper limit of normal (ULN) unless due to Gilbert's syndrome, NHL organ involvement, controlled immune hemolysis or considered an effect of regular blood transfusions
   c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5 × ULN, unless due to NHL organ involvement
6. Age ≥18 years at the time of signing the informed consent form.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1 or 2 (Appendix II).
8. Projected life expectancy of ≥12 weeks.
9. Female patient must be surgically sterile, postmenopausal (for at least 1 year), or have negative results for a pregnancy test performed at screening, on a serum sample obtained within 7 days prior to initiation of study treatment.
10. Women of childbearing potential and men with female partners of childbearing potential must be willing to use an effective form of contraception (Appendix III).
11. Patients should use an effective form of contraception for up to 6 months after the last dose of APR-246 in combination with venetoclax or up to 12 months after the last dose of rituximab, whichever time period is longer.

4.8 Exclusion Criteria

1. Patients with known allergies to xanthine oxidase inhibitors or rasburicase.
2. Prior allergy to rituximab, defined as a clinically significant infusion-related reaction (IRR) in the opinion of the Investigator.
3. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that, in the opinion of the Investigator, may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and/or would make the patient inappropriate for enrollment into this study.
4. Concomitant anticancer therapies, immunotherapies, cellular, or radiotherapy; major surgery within 3 weeks prior to first dose of study treatment. Washout period for chemotherapy is 14 days. Washout period for targeted agents is 2 weeks or 5 $T_{1/2}$ (whichever is shorter). Washout period for antibody-based immunotherapies or cellular therapies is 4 weeks. Washout period for radiotherapy is 7 days (limited field) and 28 days (extended field that includes BM). Washout period must be completed prior to any treatment administration.
5. Uncontrolled AIHA or immune thrombocytopenia.
6. Consumption of grapefruit, grapefruit products, Seville oranges, or star fruit within 7 days of starting study treatment.
7. Concomitant steroids for disease related pain control are allowed at any dose but must be discontinued prior to any study treatment initiation. Chronic use of corticosteroids is allowed up to ≤20 mg prednisone daily for non-cancer related conditions at the time of study start.
8. History of allogeneic or autologous stem cell transplant (SCT) or chimeric antigen receptor T-cell therapy (CAR-T) within the last 30 days or with any of the following:
   a. Active graft versus host disease

   b. Cytopenia from incomplete blood cell count recovery post-transplant
   c. Need for anti-cytokine therapy for residual symptoms of neurotoxicity grade >1 from CAR-T
   d. Ongoing immunosuppressive therapy.
9. Known history of human immunodeficiency virus (HIV) serum positivity.
10. Active hepatitis B/C. Patients with prior exposure to hepatitis B (i.e., positive anti-hepatitis B core antibody) must demonstrate hepatitis B polymerase chain reaction (PCR) to be negative during screening period and undergo prophylaxis and monitoring for hepatitis B according to institutional guidelines.
11. Known CNS involvement by lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable and without evidence of disease may be eligible if a compelling clinical rationale is provided to sponsor.
12. Known neurologic disorder or residual neurologic toxicities that may put patients at increased risk of neurologic toxicity in the opinion of the Investigator.
13. Any of the following cardiac abnormalities:
   a. Myocardial infarction within six months prior to enrollment
   b. New York Heart Association Class III or IV heart failure (Appendix IV) or known left ventricular ejection fraction <40%
   c. A history of familial long QT syndrome
   d. Symptomatic atrial or ventricular arrhythmias not controlled by medications
   e. QTcF ≥470 msec, unless due to underlying BBB and/or pacemaker and with the approval of the Medical Monitor.
14. Concomitant malignancies or previous malignancies with less than a 1-year disease-free interval at the time of signing consent. Patients with adequately treated basal or squamous cell carcinoma of the skin, or adequately treated carcinoma *in situ* (e.g., cervix) may enroll irrespective of the time of diagnosis. Patients with controlled, advanced prostate cancer are permitted.
15. Female patients who are pregnant or breast-feeding.
16. Active uncontrolled systemic infection.
17. Received an investigational agent within 30 days or within 5 $T_{1/2}$, whichever is shorter prior to the first dose of study treatment.
18. Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption of any of the study drugs.
19. Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp or breast cancer resistance protein inhibitors (see Appendix VI).

4.9 Inclusion of Women, Minorities and Children

Both men and women ≥18 years of age and members of all races and ethnic groups are eligible for this study. Children are not eligible for this study because the safety and tolerability of the proposed dosing schedule have not been determined in adults.

4.10 Withdrawal Criteria

Protocol therapy can continue for patients receiving clinical benefit, unless one or more study treatment discontinuation criteria are met, or at the patient's discretion, or if the study is terminated. Patients are free to discontinue treatment or withdraw from the study at any time and for any reason, without penalty to their continuing medical care. Any discontinuation of treatment or withdrawal from

the study must be fully documented in the eCRF and should be followed up by the Investigator. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.

4.10.1 Study Treatment Discontinuation

Study treatment must be discontinued if:

- Evidence of disease progression is observed. Note that patients who have disease progression but are continuing to derive clinical benefit in the opinion of the Investigator may continue to receive study treatment.
- A female patient becomes pregnant.
- A patient is non-compliant with the requirements of the protocol.
- A patient has an adverse experience that would, in the Investigator's judgment, make continued participation in the study an unacceptable risk.
- The patient starts new treatment for their disease under study.

4.10.2 Study Completion

A patient must be taken off the study if:

- The patient dies during the study.
- The patient is lost to follow-up.
- The patient withdraws consent.

4.10.3 Withdrawn Patients

When a patient is removed from the study treatment, the Investigator will clearly document the reason in the medical record and complete the appropriate eCRF page describing the reason for discontinuation. In addition, every effort should be made to complete the appropriate assessments listed in Section 6.9.

Patients who miss >25% of APR-246 doses for a nonmedical reason (patient's preference) or noncompliance will be replaced.

4.11 Noncompliance

All instances of protocol deviations will be recorded according to guidelines per Sponsor's Representative.

5.0 TREATMENT OF PATIENTS

5.1 Drug Preparation and Administration

Study treatment may be administered on an outpatient basis or on an inpatient basis if the patient is hospitalized. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's disease under study.

[redacted]

[redacted]

5.1.2 Venetoclax

In Cycle 1, treatment with venetoclax should be administered over a 5-week ramp up period per the USPI (refer to Table 4 below). The 5-week ramp-up dosing schedule is designed to gradually reduce tumor burden (debulk) and decrease the risk of TLS[53]. After the ramp-up phase is completed, venetoclax at a dose of 400 mg should be taken PO once daily with a meal and water, at approximately the same time every day. Note that on Day 1 of Cycle 1, venetoclax will be taken 1 hour prior to administration of the APR-246 infusion.

Table 4. Dosing Schedule for Ramp-Up Period in Cycle 1

Week Number	Venetoclax Daily Dose
Week 1	20 mg
Week 2	50 mg
Week 3	100 mg
Week 4	200 mg
Week 5 and beyond	400 mg

If required, any dosage modifications of venetoclax are presented in Section 5.3.3.

Detailed instructions on administration of venetoclax can be found in the Pharmacy Binder and current USPI[47].

5.1.3 Rituximab

Rituximab will be given on Day 2 of each cycle for a maximum of 6 cycles starting in Cycle 2. Rituximab will be given at a dose of 375 mg/m^2 in Cycle 2 and 500 mg/m^2 for Cycles 3 through 7.

The first infusion of rituximab should be initiated at a rate of 50 mg/hour. In the absence of infusion toxicity, increase infusion rate by 50 mg/hour increments every 30 minutes, to a maximum of 400 mg/hour.

For subsequent infusions, initiate infusion at a rate of 100 mg/hour. In the absence of infusion toxicity, increase rate by 100 mg/hour increments at 30-minute intervals, to a maximum of 400 mg/hour.

Interrupt the infusion or slow the infusion rate for IRRs. Continue the infusion at one-half the previous rate upon improvement of symptoms.

5.1.4 Dose-Limiting Toxicity

All TEAEs are relevant to the determination of DLTs unless they are clearly and solely due to the disease under study. The DLT evaluation period will be up to 91 days (7 days of APR-246 monotherapy plus 84 days for Cycle 1-3 with combination therapy) after the first dose of APR-246 is administered. A DLT is defined as any of the following TEAEs using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), as follows:

- Any neurologic toxicity of grade 4
- Any grade ≥3 non-hematologic toxicity except for:
    - First occurrence of grade 3 electrolyte abnormalities and/or creatinine CL decrease resolving to grade 2 (or baseline if baseline is grade ≥2) within 48 hours with supportive treatment.
    - Grade 3 fatigue, nausea, vomiting, diarrhea or other manageable constitutional symptom(s) that is/are responsive to supportive therapy.
    - Grade 3 infection responding to appropriate antimicrobial therapy.
    - Any neurologic toxicity of grade 3 that does not return to grade ≤1 or baseline within 7 days.
- Any grade ≥3 hematologic toxicity will be considered a DLT except for:
    - Grade 3 neutropenia without fever
    - Grade 4 neutropenia without fever lasting 8 days or less
    - Grade 3 thrombocytopenia that does not result in bleeding or transfusion
    - Grade 3/4 lymphopenia/lymphocytosis
    - Grade 3/4 WBC decreased
    - Grade 3/4 WBC increased

Any toxicity, regardless of the NCI-CTCAE v5.0 grade, resulting in discontinuation, dose reduction or treatment with less than 75% of planned doses of APR-246 study drug, will be reviewed by the DRT, and will be considered a DLT unless clearly and solely related to the disease under study. The DRT will consist of the Medical Monitor, Site Principal Investigators, and other clinical research personnel that the Sponsor may deem appropriate.

G-CSF support for the management of neutropenia and prophylactic antimicrobial therapy are allowed, including during the DLT period.

TEAEs that meet the above criteria but that occur after the DLT evaluation period will not be defined as DLTs and will be reported as AEs/SAEs and will be reviewed across all cohorts during the study to help determine the AE profile for the respective treatment regimens under study. A patient that discontinues APR-246 therapy before completion of Cycle 3 without DLT is considered evaluable for the purpose of safety review by the DRT only if at least 75% of the scheduled doses of APR-246 were administered in Cycles 1 through 3.

5.1.5 Recommended Dose of APR-246

The recommended dose of APR-246 in combination with venetoclax and rituximab represents the dose of APR-246 at or below the maximum intended dose, or the MTD, that results in the greatest apoptosis of circulating malignant cells in the monotherapy cycle.

The MTD of APR-246 will be defined as the dose at which <2 out of 6 patients experience DLT during the defined safety assessment period after administration of APR-246 in combination with venetoclax and rituximab. Up to 10 additional patients may be enrolled at the MTD, and at prior dose levels, to confirm the confidence at that dose level.

A DRT consisting of the Medical Monitor, Site Principal Investigators, and other clinical research personnel that the Sponsor may deem appropriate, will hold Data Review Meetings (DRMs) on an

interim basis at a frequency dependent on study accrual. At these meetings, the DRT will review any AEs, DLTs, and any available PK and PD data and make recommendations regarding the optimal dose of APR-246. All accumulated safety data will be discussed during DRMs. The optimal dose of APR-246 will be based upon the MTD and upon all accumulated safety data, PK/PD data, and preliminary efficacy data.

5.2 Dose Interruptions/Withholding

Study treatment, including APR-246, venetoclax, and/or rituximab, may be withheld from a patient based on the Investigator's decision in the event of intercurrent illness, AE, administrative reasons, or other reasons. If the patient's condition subsequently improves, or the situation that resulted in withholding study drug rectifies itself, the Investigator may resume dosing as soon as possible, unless the delay is more than 4 weeks. For study treatments held longer than 4 weeks, the Investigator should consult with the Medical Monitor before study treatments are resumed.

Dose management guidelines in Table 5 should be followed for each occurrence of a grade ≥3 hematologic toxicity or those in Table 6 for non-hematologic toxicity.

Table 5. Dose management guidelines for new onset hematologic toxicities

Toxicity	Occurrence	APR-246	Venetoclax	Rituximab
Grade 3 hematologic toxicity with fever and/or infection; or grade 4 hematologic toxicity	1st occurrence • Hold all study treatments until blood count(s) return to baseline or grade ≤1 and fever and/or infection resolve if present. Treat promptly.	• Consider reducing APR-246 by one dose level from starting dose for all future cycles of treatment if toxicity does not resolve to grade ≤1 within 7 days from onset date despite maximal medical intervention(s). • If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing treatment. • Initiate or reassess prophylaxis measures. Refer to Section 5.3.2.2 for supportive management guidelines specific to infection prophylaxis and neutropenia.	• Refer to Section 5.3.3.1 for venetoclax dose modification guidelines.	• Resume rituximab at same dose level once event resolves to baseline or grade ≤1, except in case of serious infection. For patients diagnosed with a serious grade ≥3 infection, rituximab should be permanently discontinued.
	2nd occurrence • Hold all study treatments until blood count(s) return to baseline or Grade ≤1 and fever and/or infection resolve if present. Treat promptly.	• Consider reducing APR-246 by one dose level from current dose for all future cycles of treatment if the toxicity does not resolve to grade ≤1 within 7 days from onset despite maximal medical intervention(s). • If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing treatment. • Initiate or reassess prophylaxis measures. Refer to Section 5.3.2.2 for supportive management guidelines specific to infection prophylaxis and neutropenia.	• Refer to Section 5.3.3.1 for venetoclax dose modification guidelines.	• Reduce rituximab dose from 500 mg/m^2 to 375 mg/m^2. If unable to reduce dose of rituximab, discuss with study Medical Monitor before resuming treatment. For patients diagnosed with a serious grade ≥3 infection, rituximab should be permanently discontinued.
	3rd occurrence • Hold all study treatments until blood	• Consult with study medical monitor to determine if further dose modifications of study treatment(s) are medically necessary or if study treatment(s) should be discontinued.		

	count(s) return to baseline or grade ≤1 and fever and/or infection resolve if present. Treat promptly.	• Assess current prophylaxis measures being administered and adjust treatment plan as clinically indicated. Refer to Section 5.3.2.2 for supportive management guidelines specific to infection prophylaxis and neutropenia.

Administration of supportive measures such as G-CSF, platelet or blood transfusions, and/or antimicrobial therapy should be considered as clinically indicated.

Actions noted in table above for rituximab are specific to toxicities occurring during Cycles 2 through 7. Rituximab may be reduced by one dose level, from 500 mg/m^2 to 375 mg/m^2, when clinically indicated. Please consult with study Medical Monitor to discuss dose modification(s) for rituximab.

Patients experiencing 3 occurrences of the same toxicity should be discussed with the study Medical Monitor before study treatments are resumed.

Dose management guidelines for non-hematologic toxicities are provided below in Table 6.

Table 6. Dose management guidelines for Grade 3 or 4 non-hematologic toxicities

Occurrence	APR-246	Venetoclax	Rituximab
1st occurrence • Hold all study treatments until toxicity returns to baseline or grade ≤1. Treat promptly.	• Consider reducing APR-246 by one dose level from current dose for all future cycles of treatment if toxicity does not resolve to grade ≤1 within 7 days from onset date despite maximal medical intervention(s). • If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing treatment.	Refer to Section 5.3.3.1 for venetoclax dose modification guidelines.	Resume rituximab at same dose level once event resolves to baseline or grade ≤1, except in case of serious infection. For patients diagnosed with a serious grade ≥3 infection, rituximab should be permanently discontinued.
2nd occurrence • Hold all study treatments until toxicity returns to baseline or grade ≤1	• Consider reducing APR-246 by one dose level from starting dose for all future cycles of treatment.	Refer to Section 5.3.3.1 for venetoclax dose modification guidelines.	Reduce rituximab dose from 500 mg/m^2 to 375 mg/m^2. If unable to reduce rituximab, discuss with study Medical Monitor before resuming or discontinuing rituximab. For patients diagnosed with serious grade ≥3 infection, rituximab should be permanently discontinued.
3rd occurrence • Hold all study treatments until toxicity returns to baseline or grade ≤1. Treat promptly.	• Consult with study medical monitor to determine if further dose modifications of study treatment(s) are medically necessary or if study treatment(s) should be discontinued.		

Actions noted in table above for rituximab are specific to toxicities occurring during Cycles 2 through 7. Rituximab may be reduced by one dose level, from 500 mg/m^2 to 375 mg/m^2, when clinically indicated. Please consult with study Medical Monitor to discuss dose modification(s) for rituximab.

Treatment may be discontinued if a TEAE has not improved (to an acceptable grade) or resolved after ≥4 weeks, at the discretion of the Investigator. Please consult study Medical Monitor if this situation occurs.

Patients experiencing 3 occurrences of the same toxicity should be discussed with the study Medical Monitor before study treatments are resumed.

5.3 Supportive Management

5.3.1 Neutropenia with or without Fever

Monitor complete blood counts throughout the treatment period. Consider supportive measures including antimicrobials for prophylaxis, in the setting of prolonged myelosuppression, and/or at the first signs of infection and use of growth factors (e.g., G-CSF). Myeloid growth factors may be used in the setting of neutropenia with or without fever as clinically indicated. Refer to Section 5.2 for guidelines on dose modifications.

5.3.2 APR-246

This section outlines the requirements for proceeding with treatment with APR-246, and the protocol rules for APR-246 dose modification due to management of QTc prolongation, CNS related AEs, nausea and vomiting, and infections.

5.3.2.1 APR-246 Dose Modification in the Setting of Moderate Renal Impairment

APR-246 is partially eliminated via the kidney and moderate renal impairment, defined by a creatinine CL or estimated glomerular filtration rate value of >30 to <60 mL/min, can lead to increases in plasma levels of approximately 30%. Therefore, for patients with moderate renal impairment, the dose of APR-246 should be reduced by 33% from the current dose (Table 7).

Table 7. APR-246 Dose Modification in the Setting of Moderate Renal Impairment

APR-246 Dose	33% Reduced Dose	Reduced Loading Dose (45mins)	Reduced Maintenance Dose (5h 15mins)
1.5 g	1.0 g	0.33 g	0.67 g
3.0 g	2.0 g	0.66 g	1.33 g
4.0 g	2.7 g	0.9 g	1.8 g

Monitoring renal function by assessment of serum creatinine prior to infusion of APR-246 is recommended in all patients.

5.3.2.2 Bone Marrow Suppression Management Guidelines

Complete blood counts should be monitored throughout the course of treatment with APR-246. Supportive measures such as antimicrobials administered for prophylaxis or in the setting of

prolonged myelosuppression, and/or at the first signs of infection are recommended to reduce the risk of a serious or severe infection that may lead to a fatal outcome in the setting of neutropenia with or without fever. Antimicrobial prophylaxis should be implemented, including appropriate prophylaxis for bacterial, viral, fungal or other types of infections or infestations (Table 8). Treatment should be individualized based on level of myelosuppression at the time of study enrollment and throughout the course of study treatment, with consideration for the patient's medical history, inclusive of prior infections.

The following recommendations were taken from National Comprehensive Cancer Network Guidelines for Prevention and Treatment of Cancer-Related Infections (Version 1.2021).

Table 8. Recommendations for Prevention and Treatment of Cancer-Related Infections

Organism	Recommendations
Bacterial	Consider fluoroquinolone or other suitable anti-bacterial prophylaxis during neutropenia
Fungal	Consider prophylaxis during neutropenia and for anticipated mucositis. Assess risk for Pneumocystis jirovecii pneumonia and select agent(s) as clinically indicated.
Viral	Start treatment with anti-viral medication in the setting of neutropenia and continually assess the risk for viral infection during treatment with anti-cancer therapy.

Myeloid growth factor may be used in the setting of severe or prolonged neutropenia. The use of blood products, including packed red blood cells (PRBCs) and platelet transfusions, are permitted and to be given at the discretion of the treating physician. Recommended guidelines for transfusion include a platelet threshold of 10×10^9/L for platelet transfusion and a hemoglobin threshold of 8.0 g/dL for PRBC transfusion or as clinically indicated at the discretion of the treating physician.

5.3.2.3 Management Guidelines for QTc Prolongation

At screening, 12-lead ECGs should be collected in triplicate to confirm QTcF interval does not exceed 470 msec. The mean QT interval must be calculated from three ECG readings using Fridericia's correction ($QTcF = QT/RR^{0.33}$).

During APR-246 monotherapy lead-in period, and first cycle of combination therapy (venetoclax ramp-up), ECG should be collected in triplicate within 30 minutes prior to the infusion of APR-246 and within ±30 min of end of the 6-hour infusion on all days APR-246 is administered (Days 1 and 2 of the APR-246 monotherapy lead-in, and Day 1, 8, 15 of Cycle 1). QTcF must be calculated from a mean of all three ECG readings.

On Day 2 of the APR-246 monotherapy lead-in period, ECG will be obtained prior to PO administration of APR-246, and then 6 hours after APR-246 administration.

If a pre-dose ECG shows QTcF ≥470 msec, the QTc reading should be confirmed by manual assessment using Fridericia's correction ($QTcF=QT/RR^{0.33}$), unless due to BBB and/or pacemaker. Serum concentrations of electrolytes should be monitored and corrected, if necessary. Additionally, concomitant medication should be reviewed and adjusted, if necessary. ECG may be repeated at any time, including the same day. APR-246 may only be administered when QTcF has returned to <470 msec, unless due to BBB and/or pacemaker. If APR-246 is given on the same day, procedures

outlined in the Schedule of Study Evaluations must be followed. If APR-246 cannot be administered on the same day, that dose must be omitted from the cycle.

If there is a significant change in QTcF, defined as either: a) increase >60 msec from baseline (or pre-dose), or b) increase to an absolute value ≥501 msec, i.e., consistent with NCI-CTCAE grade 3 QTc prolongation, QTc prolongation must be confirmed by a manual assessment of the ECG, and using Fridericia's correction ($QTcF = QT/RR^{0.33}$). If confirmed, APR-246 should be interrupted until a cause (electrolyte disorders or an effect of a concomitant medication) has been identified and addressed, and QTcF has returned to <470 msec, or baseline in patients with BBB and/or pacemaker. If all other causes for clinically significant QT interval prolongation are excluded, APR-246 may be permanently discontinued. Please consult with study Medical Monitor for discussion when clinically significant QT interval prolongation is identified in a patient receiving APR-246.

During subsequent cycles, ECG should be collected in triplicate prior to infusion of APR-246 and at end of infusion (EOI) on Day 1 of each cycle. QTcF must be calculated from the mean of all three ECG readings to confirm it does not exceed 469 msec for the cycle to be initiated. If post-dose ECG shows a significant change in QTcF, defined as either: a) increase >60 msec from baseline (or pre-dose), or b) increase to an absolute value ≥501 msec, i.e., consistent with NCI-CTCAE grade 3 QTc prolongation, QTc prolongation must be confirmed by a manual assessment of the ECG, and using Fridericia's correction ($QTcF = QT/RR^{0.33}$). If confirmed, the therapy should be interrupted until a cause (electrolyte disorders or an effect of a concomitant medication) has been identified and addressed, and QTcF has returned to <470 msec, unless due to BBB and/or pacemaker. If all other causes for clinically significant QT interval prolongation are excluded, APR-246 may be permanently discontinued. Please consult with study Medical Monitor for discussion when clinically significant QT interval prolongation is identified in a patient receiving APR-246. If QTcF is unchanged or there is no significant change, additional ECG is not required during that cycle.

Table 9. Management Guidelines for QTc Prolongation

ECG	QTcF <450 msec	QTcF = 450-469 msec	QTcF = 470-500 msec	QTcF ≥501 or absolute increase >60 msec
Pre-dose [a]	No action required. APR-246 may be administered.	APR-246 may be administered, and additional triplicate ECG should be collected at the EOI (6 hours after start of infusion, ±30 min)	QTc reading should be confirmed by manual assessment, unless due to BBB and/or pacemaker. Review serum concentrations of electrolytes and concomitant medications and adjust if necessary. ECG may be repeated at any time, including the same day. APR-246 may be administered when QTcF has returned to <470 msec, unless due to BBB and/or pacemaker. If APR-246 cannot be administered on the same day, that dose should be omitted from the cycle.	
Post-dose	No action required			If QT prolongation confirmed by manual assessment, APR-246 should be interrupted until a cause has been identified and addressed, and QTcF has returned to <470 msec or baseline value for patient with BBB or pacemaker. If all other causes for clinically significant QT interval prolongation are excluded, APR-246 may be permanently discontinued. Please consult study Medical Monitor to discuss patient's condition.

[a] During APR-246 monotherapy lead-in, ECG should be collected in triplicate within 30 minutes prior to the infusion of APR-246 and within ±30 min of end of the 6-hour infusion (EOI) of APR-246 on Days 1 – 2. QTcF must be calculated from a mean of all three ECG readings.

If a patient starts treatment with a medication associated with QT interval prolongation, such as triazole antifungals, fluoroquinolones, and anti-emetics, while receiving study treatment, an additional pre- and post-dose (within 30 minutes prior to the infusion of APR-246 and within ±30 min of 6 hours after start of infusion) ECG should be performed on the next APR-246 treatment day.

5.3.2.4 Management Guidelines for APR-246 Dose Modifications and Criteria for Treatment Interruption and Re-Initiation with Treatment-Related Adverse Events

Table 10. Recommendations for APR-246 Dose Modifications and Criteria for Treatment Interruption and Re-Initiation with Treatment-Related Adverse Events

Renal Toxicities

Parameter	Worst toxicity [1]	Dose Modifications for APR-246
Serum Creatinine	Grade 1 (<1.5 × baseline)	Maintain dose level
	Grade 2 (>1.5–3.0 × baseline)	Omit dose until resolved to grade ≤1, then: If first occurrence, then maintain dose level If second or more consecutive occurrence, then ↓ 1 dose level
	Grade 3 (>3.0–6.0 × baseline)	Omit dose until resolved to grade ≤1, then: ↓ 1 dose level If not resolved or resolved in >7 days, evaluate if other contributing factors are present. If none, or after consideration of best interest of the patient, discontinue patient from APR-246. If other factors present, consider continuing after ↓ 1 dose level
	Grade 4 (>6.0 × baseline)	Permanently discontinue patient from APR-246

[1] Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Hepatic Toxicities [1]

Parameter	Worst toxicity [2]	Dose Modifications for APR-246
Bilirubin [3]	Grade 1 (>ULN-1.5×ULN)	Maintain dose level with LFTs [4] monitored as per protocol
	Grade 2 (>1.5-3.0×ULN) with ALT or AST ≤3.0×ULN	Omit dose until resolved to grade ≤1, then: If resolved in ≤7 days, if first occurrence, then maintain dose level If second or more consecutive occurrence or if resolved in >7 days, then ↓ 1 dose level
	Grade 3 (>3.0-10.0×ULN) with ALT or AST ≤3.0×ULN	Omit dose until resolved to grade ≤1, then: If resolved in ≤7 days, ↓ 1 dose level. If no subsequent event, consider re-escalation to original dose level. Omit dose until resolved to grade ≤1, then: ↓ 1 dose level. If second or more consecutive occurrence or if not resolved or resolved in >7 days, evaluate if other contributing factors are present. If none, or after consideration of best interest of the patient, discontinue patient from APR-246. If other factors present, consider continuing after ↓ 1 dose level.
	Grade 4 (>10.0×ULN)	Permanently discontinue patient from APR-246

Parameter	Worst toxicity [2]	Dose Modifications for APR-246
AST or ALT	Grade 1 (>ULN-3.0×ULN if baseline was normal; 1.5-3.0 × baseline if baseline was abnormal)	Maintain dose level with LFTs [4] monitored per protocol
	Grade 2 (>3.0-5.0×ULN if baseline was normal; >3.0-5.0 × baseline if baseline was abnormal) in the absence of total bilirubin elevation to > 2.0×ULN	Omit dose until resolved to grade ≤1, then If resolved in ≤7 days, if first consecutive occurrence, then maintain dose level If second or more consecutive occurrence or if resolved in >7 days, then ↓ 1 dose level
	Grade 3 (>5.0-20.0×ULN if baseline was normal; >5.0–20.0 x baseline if baseline was abnormal) in the absence of total bilirubin elevation to >2.0×ULN	Omit dose until resolved to grade ≤1, then If resolved in ≤7 days, if first consecutive occurrence, then maintain dose level. If second or more consecutive occurrence or if not resolved or resolved in >7 days, evaluate if other contributing factors are present. If none, or after consideration of best interest of the patient, discontinue patient from APR-246. If other factors present, consider continuing after ↓ 1 dose level
	Grade 4 (>20.0×ULN if baseline was normal; >20.0 × baseline if baseline was abnormal)	Permanently discontinue patient from APR-246

[1] Please note that the Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study. Hy's law identifies patients at risk for severe drug-induced liver injury and is defined as AST or ALT ≥3× ULN together with Total Bilirubin Level ≥2×ULN, where no other reason, other than the suspected drug, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, or another drug.
[2] Common Terminology Criteria for Adverse Events (CTCAE) version 5.
[3] For patients with Gilbert's syndrome, these dose modifications apply to changes in direct bilirubin only.
[4] LFTs include albumin, ALT, AST, total bilirubin (fractionated if total bilirubin >2.0×ULN), alkaline phosphatase.

Other Non-Hematological Toxicities

Toxicity	Worst toxicity [1]	Dose Modifications for APR-246
Infusion-Related Reaction	Grade 1	Maintain dose level.
	Grade 2	Maintain dose level; Symptomatic management (e.g., antihistamines, corticosteroids, narcotics, IV fluids)
	Grade 3	If resolved (to grade ≤1) in <4 hours with treatment interruption and medical therapy (e.g., antihistamines, corticosteroids, narcotics, IV fluids), continue same dose level and rate. If not resolved in < 4 hours despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose
	Grade 4	Permanently discontinue patient from APR-246.
Nausea, Vomiting, and/or Diarrhea	Grade 1	Maintain dose level. Monitor subject and provide supportive care measures as clinically indicated.
	Grade 2	Interrupt APR-246 dosing and monitor subject; treat promptly. Resume at current dose level if toxicity resolves to grade ≤1 or baseline, with or without use of supportive care measures, within 72 hours of onset. If toxicity does not resolve to grade ≤1 within 72 hours despite maximal medical intervention(s), then reduce APR-246 by 1 dose level once the

Toxicity	Worst toxicity [1]	Dose Modifications for APR-246
		toxicity resolves to grade ≤1 or baseline. If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing treatment. For subsequent doses of APR-246, premedication with prophylactic supportive therapy should be given if clinically indicated.
	Grade 3	**1st occurrence:** Interrupt APR-246 dosing and monitor subject; treat promptly. Resume at current dose level if toxicity resolves to grade ≤1 or baseline, with supportive care measures, within 72 hours of onset. If toxicity does not resolve to grade ≤1 within 72 hours despite maximal medical intervention(s), then reduce APR-246 by 1 dose level once the toxicity resolves to grade ≤1 or baseline. If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing APR-246. For subsequent doses of APR-246, pre-medication with prophylactic supportive therapy should be given. **2nd occurrence:** Interrupt APR-246 dosing and monitor subject; treat promptly. Reduce APR-246 by 1 dose level if the toxicity resolves to grade ≤1 or baseline within 72 hours of onset. If toxicity does not resolve to grade ≤1 despite maximal medical intervention(s) within 72 hours of onset, then consult with study Medical Monitor before resuming or discontinuing APR-246. If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing treatment. Prior to subsequent doses of APR-246, reassess prophylactic supportive therapy regimen and adjust as clinically indicated. **3rd occurrence:** Interrupt APR-246 dosing and monitor subject; treat promptly. Consult with study Medical Monitor before resuming or discontinuing APR-246.
	Grade 4	Interrupt APR-246 dosing and monitor subject; treat promptly. Consult with study Medical Monitor to discuss dose modification or permanent discontinuation of APR-246.
Any Other Toxicity	Grade 3 or 4	Delay dose until resolution to grade ≤1 or baseline, then ↓ 1 dose level. If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing APR-246.

[1] Common Terminology Criteria for Adverse Events (CTCAE) version 5.

Treating physicians should use clinical judgment and may consult the Medical Monitor for additional guidance with APR-246 dose modifications.

5.3.2.5 Management of CNS Adverse Events

If a patient reports any clinical AE of any grade during the administration period of APR-246 that could be considered to originate from the CNS (e.g., dizziness, tremor, vertigo, nausea), then the patient will be given a rescue medication as per the institutional standard of care.

Dose modifications have been successfully used to manage potential CNS effects occurring during the infusion (Table 11). For any clinical AE grade ≥3, the infusion should be interrupted and if the AE resolves to CTCAE grade ≤1 within 2 hours, the infusion may be resumed at the same infusion rate. If

the same symptoms recur or increase in severity during re-challenge, the infusion should be interrupted.

If the event lasts longer than 2 hours, then the APR-246 infusion should be discontinued for that day and the remaining drug should be discarded.

Table 11. Management of CNS Adverse Events (e.g., Dizziness, Tremor, Confusion, and Ataxia)

Worst toxicity	Dose Modifications for APR-246
Grade 1	Maintain dose level
Grade 2	If resolved to grade ≤1 with medical therapy, continue same dose level If not resolved despite treatment interruption and maximal medical therapy, stop infusion and ↓ 1 dose level for subsequent dose. If unable to reduce APR-246, discuss with study Medical Monitor before resuming or discontinuing APR-246.
Grade ≥3	Stop infusion and give medical therapy. If resolved (to grade ≤1) with medical therapy in ≤2 hours from onset, infusion may resume at the Investigator's discretion. If not resolved despite treatment interruption and maximal medical therapy, infusion should be discontinued for that day. ↓ 1 dose level for subsequent dose. If unable to reduce APR-246 dose, discuss with study Medical Monitor before resuming or discontinuing APR-246.
Grade 4	Permanently discontinue patient from APR-246.

In prior APR-246 studies, prochlorperazine 10 mg PO three times daily, anti-emetics (e.g., ondansetron), or medication(s) to treat motion sickness (e.g., meclizine) have been used for prophylaxis and/or to treat CNS-related AEs that have occurred during treatment with APR-246. Prochlorperazine, anti-emetic, or motion sickness medication(s) should be administered as clinically indicated to prevent or treat CNS-related AEs while subjects are receiving treatment with APR-246. When prophylaxis is clinically indicated, it is recommended to start prochlorperazine, anti-emetic, or motion sickness medication(s) at least one day prior to the scheduled dose of APR-246. Please follow dose administration guidelines in the current USPI for prochlorperazine, anti-emetic, or motion sickness medication(s). The US label for prochlorperazine does not list QT interval prolongation as a known risk associated with use of this drug.

5.3.2.6 Management of Nausea, Vomiting, and Diarrhea

Prior to starting study treatment, patients should be evaluated to determine risk for nausea, vomiting, and/or diarrhea based on medical history and concomitant medications. Anti-nausea, anti-emetic, and/or anti-diarrheal medications should be initiated in patients with intermediate or high risk for nausea, vomiting, or diarrhea. Patients who experience nausea, vomiting, and/or diarrhea in association with APR-246 administration should be prescribed appropriate rescue treatment and prophylaxis (e.g., anti-nausea, anti-emetics, or anti-diarrheal medication).

A list of suggested rescue medications for nausea and vomiting is provided below in Table 12.

Table 12. Medications for Management of Nausea and Vomiting

Drug	Dosage	QT Interval Prolongation [a]
Ondansetron	8 mg PO administered 30 minutes before the start of infusion or per label	Yes
Dolasetron	100 mg PO administered within one hour before start of infusion or per label	Yes
Palonosetron	0.5 mg PO administered approximately one hour prior to the start of infusion or per label	No
Prochlorperazine	10 mg PO three times daily. Continue until the end of Day 4 of the cycle. When used prophylactically in subsequent cycles, start the day prior to Day 1 administration of APR-246	No

[a] Please refer to Section 5.3.2.3 for details on concurrent administration of medications known to cause QTc interval prolongation.

Monitor electrolyte levels and renal function during the course of study treatment and institute appropriate supportive care measures, such as electrolyte and/or fluid repletion, in the setting of vomiting and/or diarrhea.

5.3.2.7 Management of Infusion Reactions Associated with APR-246 Administration

If a patient experiences an infusion reaction during the study, the infusion may be stopped and appropriate medical care (e.g., epinephrine, oxygen, H1 and H2 antagonists, and/or corticosteroids) administered[54]. Consultation with the Medical Monitor before additional administration of APR-246 is encouraged.

If the patient develops an acute infusion reaction (grade ≥2), the infusion should be interrupted until the reaction has resolved to grade ≤1. Premedication (e.g., systemic corticosteroids) may be used as required.

5.3.3 Venetoclax

5.3.3.1 Dosage Modifications Based on Toxicities

Interrupt dosing or reduce dose for toxicities. See tables below for recommended dose modifications for toxicities related to venetoclax. For patients who have had a dosing interruption greater than 1 week during the first 5 weeks of ramp-up phase or greater than 2 weeks after completing the ramp-up phase, reassess for risk of TLS to determine if re-initiation with a reduced dose is necessary. Please consult full prescribing information in USPI[47], as clinically warranted, and Section 5.2 for management of overlapping toxicities.

Table 13. Recommended Venetoclax Dose Modifications for Toxicities

Event	Occurrence	Action
Tumor Lysis Syndrome		
Blood chemistry changes or symptoms suggestive of TLS	Any	Withhold the next day's dose. If resolved within 24 to 48 hours of last dose, resume at the same dose.
		For any blood chemistry changes requiring more than 48 hours to resolve, resume at a reduced dose.
		For any events of clinical TLS resume at a reduced dose following resolution.
Non-Hematologic Toxicities		
Grade 3 or 4 nonhematologic toxicities	1st occurrence	Interrupt venetoclax. Once the toxicity has resolved to grade 1 or baseline level, venetoclax therapy may be resumed at the same dose. No dose modification is required.
	2nd and subsequent occurrences	Interrupt venetoclax. Follow dose reduction guidelines in the table below when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.
Hematologic Toxicities		
Grade 3 neutropenia with infection or fever, or grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, granulocyte-colony stimulating factor (G-CSF) may be administered with venetoclax if clinically indicated. Once the toxicity has resolved to grade 1 or baseline level, venetoclax therapy may be resumed at the same dose.
	2nd and subsequent occurrences	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in the table below when resuming treatment with venetoclax after resolution. A larger dose reduction may occur at the discretion of the physician.

Consider discontinuing venetoclax for patients who require dose reductions to less than 100 mg for more than 2 weeks.

Table 14. Dose Reduction for Toxicity During Venetoclax Treatment

Dose Interruption, mg	Restart Dose, mg [a]
400	300
300	200
200	100
100	50
50	20
20	10

[a] During the ramp-up phase, continue the reduced dose for 1 week before increasing the dose.

5.3.3.2 Management of Potential Venetoclax Interactions with CYP3A and P-gp Inhibitors

Table 15. Venetoclax Dose Modifications for Use with CYP3A Inhibitors

Co-administered Drug	Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase) [a]
Posaconazole	Contraindicated	Reduce venetoclax dose to 70 mg
Other strong CYP3A inhibitor	Contraindicated	Reduce venetoclax dose to 100 mg
Moderate CYP3A inhibitor	Reduce venetoclax dose by at least 50%	
P-gp inhibitor		

[a] Consider alternative medications or reduce the venetoclax dose as described in table.

5.3.3.3 Tumor Lysis Syndrome

TLS, including fatal events and renal failure requiring dialysis, has occurred in patients with high tumor burden when treated with venetoclax.

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS at initiation and during the ramp-up phase. Changes in blood chemistries consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax and at each dose increase.

The risk of TLS is a continuum based on multiple factors, including tumor burden and comorbidities. Reduced renal function further increases the risk. Patients should be assessed for risk and should receive appropriate prophylaxis for TLS, including hydration and antihyperuricemics. Monitor blood chemistries and manage abnormalities promptly. Interrupt dosing if needed. Employ more intensive measures (IV hydration, frequent monitoring, hospitalization) as overall risk increases.

Concomitant use of venetoclax with P-gp inhibitors or strong or moderate CYP3A inhibitors increases venetoclax exposure, may increase the risk of TLS at initiation and during ramp-up phase and requires venetoclax dose adjustment.

Table 16. Recommended TLS Prophylaxis Based on Tumor Burden in Patients

Tumor Burden	Prophylaxis		Blood Chemistry Monitoring [c,d]
	Hydration [a]	Anti-hyperuricemics	Setting and Frequency of

				Assessments
Low	All LN <5 cm AND ALC <25×10^9/L	Oral (1.5-2 L)	Allopurinol [b]	Outpatient • For first dose of 20 mg and 50 mg: Pre-dose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Pre-dose
Medium	Any LN 5 cm to <10 cm OR ALC ≥25×10^9/L	Oral (1.5-2 L) and consider additional IV	Allopurinol	Outpatient: • For first dose of 20 mg and 50 mg: Predose, 6 to 8 hours, 24 hours • For subsequent ramp-up doses: Predose • For first dose of 20 mg and 50 mg: Consider hospitalization for patients with creatinine CL <80 mL/min; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 x10^9/L AND any LN ≥5 cm	Oral (1.5-2L) and IV (150-200 mL/h as tolerated)	Allopurinol; consider rasburicase if baseline uric acid is elevated	In hospital • For first dose of 20 mg and 50 mg: Pre-dose, 4, 8, 12 and 24 hours Outpatient • For subsequent ramp-up doses: Pre-dose, 6 to 8 hours, 24 hours

ALC = absolute lymphocyte count; LN = lymph node.
[a] Administer IV hydration for any patient who cannot tolerate oral hydration.
[b] Start allopurinol or xanthine oxidase inhibitor 2 to 3 days prior to initiation of Venetoclax.
[c] Evaluate blood chemistries (potassium, uric acid, phosphorus, calcium, and creatinine); review in real time.
[d] For patients at risk of TLS, monitor blood chemistries at 6 to 8 hours and at 24 hours at each subsequent ramp-up dose.

5.3.3.4 Missed Dose

If the patient misses a dose of venetoclax within 8 hours of the time it is usually taken, the patient should take the missed dose as soon as possible and resume the normal daily dosing schedule. If a patient misses a dose by more than 8 hours, the patient should not take the missed dose and should resume the usual dosing schedule the next day.

If the patient vomits following dosing, no additional dose should be taken that day. The next prescribed dose should be taken at the usual time.

5.3.4 Rituximab

5.3.4.1 Infusion-Related Reactions

Rituximab can cause severe, including fatal, IRRs. Severe reactions typically occurred during the first infusion with time to onset of 30−120 minutes. Rituximab induced IRRs and sequelae include urticaria, hypotension, angioedema, hypoxia, bronchospasm, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, cardiogenic shock, anaphylactoid events, or death. Please consult full prescribing information in USPI[48], as clinically warranted.

Premedicate patients with an antihistamine and acetaminophen prior to dosing. Institute medical management (e.g., glucocorticoids, epinephrine, bronchodilators, or oxygen) for IRRs as needed. Depending on the severity of the IRR and the required interventions, temporarily or permanently discontinue rituximab. Resume infusion at a minimum 50% reduction in rate after symptoms have resolved. Closely monitor the following patients: those with pre-existing cardiac or pulmonary conditions, those who experienced prior cardiopulmonary adverse reactions, and those with high numbers of circulating malignant cells (≥25,000/mm^3).

5.3.4.2 Severe Mucocutaneous Reactions

Mucocutaneous reactions, some with fatal outcome, can occur in patients treated with rituximab. These reactions include paraneoplastic pemphigus, Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of these reactions has been variable and includes reports with onset on the first day of rituximab exposure. Discontinue rituximab in patients who experience a severe mucocutaneous reaction. The safety of re-administration of rituximab to patients with severe mucocutaneous reactions has not been determined.

5.3.4.3 Hepatitis B Virus Reactivation

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, can occur in patients treated with drugs classified as CD20-directed cytolytic antibodies, including rituximab.

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA levels or detection of hepatitis B surface antigen (HBsAg) in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels. In severe cases increase in bilirubin levels, liver failure, and death can occur.

Monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following rituximab therapy. HBV reactivation has been reported up to 24 months following completion of rituximab therapy.

In patients who develop reactivation of HBV while on rituximab, immediately discontinue rituximab and any concomitant chemotherapy, and institute appropriate treatment. Insufficient data exist regarding the safety of resuming rituximab treatment in patients who develop HBV reactivation.

5.3.4.4 Progressive Multifocal Leukoencephalopathy

John Cunningham virus infection resulting in progressive multifocal leukoencephalopathy (PML) and death can occur in rituximab-treated patients with hematologic malignancies or with autoimmune diseases.

Consider the diagnosis of PML in any patient presenting with new-onset neurologic manifestations. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain magnetic resonance imaging (MRI), and lumbar puncture.

Discontinue rituximab and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.

5.3.4.5 Cardiovascular Adverse Reactions

Discontinue infusions for serious or life-threatening cardiac arrhythmias. Perform cardiac monitoring during and after all infusions of rituximab for patients who develop clinically significant arrhythmias, or who have a history of arrhythmia or angina.

5.4 Concomitant Treatment

Patients must not receive any other concurrent anti-cancer therapy, including investigational agents while on study treatment. Please also see Section 2.5, regarding known drug-drug interactions for venetoclax, and the importance of avoiding certain food such as grapefruits and Seville oranges. This is important both for patient safety and for enabling a correct assessment of an unlikely drug-drug interaction between the study drug APR-246 and the combination treatments.

For patients taking blood thinners, such as warfarin, and anti-platelet agents, international normalization ratio should be monitored closely due to increased risk of bleeding.

As the mechanism of action for APR-246 is associated with enhanced oxidative stress in tumor cells, use of the following medications that may antagonize therapeutic effects of APR-246 is discouraged, but not prohibited during study treatment administration:

- Antioxidants (including but not limited to coenzyme Q10)
- Supplementation with vitamin C, vitamin E, zinc and/or selenium outside of a daily multi-vitamin
- Iron chelators (e.g., deferoxamine or deferasirox)
- Melatonin

Patients may continue their baseline medication(s) as long as they are not prohibited. Palliative and supportive care (e.g., anti-emetics, bisphosphonates) for disease-related symptoms may be utilized according to institutional practices. AEs will be treated as clinically indicated. All concomitant medications should be recorded in the eCRF.

5.5 Monitoring Patient Compliance

This study will be monitored by Aprea Therapeutics, Inc. or its Contract Research Organization (CRO) according to ICH E6 guidelines of GCP. The study site monitor will regularly visit the study sites to ensure that the study is conducted according to the protocol and GCP principles. All instances of protocol deviations will be entered and reviewed by the Investigator, Sponsor and appropriate [redacted] designee.

6.0 STUDY EVALUATIONS

6.1 Schedule of Study Evaluations

Study evaluations are summarized in Table 17 and described in Sections 6.2 through 6.10.

Table 17: Schedule of Assessments

Protocol activities	Screening [a]	APR-246 Lead-In [b]			Cycle 1				Cycles 2 -7				Cycles 8 and Beyond			Cycles 4, 7, 10, 13, 16, 19, 22 and 25[i]	End of Treatment [p]	Follow-up (28 Days after End of Treatment) [q]
		D1	D2	D3	D1	D2	D8 [b]	D15[b]	D1[c]	D2	D8 [b]	D15[b]	D1[c]	D8 [b]	D15[b]	D1		
Informed consent	×																	
Medical history [d]	×																	
Physical examination [e]	×	×			×				×				×				×	
Height [s]	×																	
Weight	×	×			×				×				×				×	
Vital signs [e]	×	×	×		×		×	×	×	×	×	×	×	×	×		×	
ECOG PS	×	×			×				×				×				×	
APR-246 (IV) [f]		×			×		×	×	×		×	×	×	×	×			
APR-246 (PO) [f]			×															
Venetoclax [g]					Ramp-up Week 1-5				Given PO at a dose of 400 mg daily through Cycle 24									
Rituximab [h]										×								
Disease assessment [i]	×															×	×	
Hematology [j]	×	×[j]	×[j]	×[j]	×			×	×		×	×	×	×	×		×	
Serum chemistry [k]	×	×			×			×	×		×	×	×	×	×		×	
Creatinine CL [l]	×																	
PD assessments [u]		×	×	×	×													
Blood sample for GSH assay (Local Lab) [v]		×	×	×	×													
HCV/HBV test [t]	×																	
Pregnancy test [m]	×																	
ECG [n]	×	×	×		×		×	×	×				×				×	
APR-246 PK sample [o]		×	×	×					×		× [o]	× [o]	×					
Clinical toxicity assessment		Starting at the time of informed consent through 30 days after last dose [r]																
Concomitant medications	Reviewed throughout study																	
Survival																		×

Footnotes to Schedule of Assessments

a. All screening/baseline evaluations are performed within 28 days prior to the start of study treatment. In the event that a visit or test cannot be scheduled on the exact visit day, a window of ±3 days is allowable. Cycle 1 is 5 weeks (35 days) in duration. Subsequent cycles are 28 days in duration.

b. A window of ±3 days applies to this study visit.

c. After the first cycle, Day 1 evaluations of subsequent cycles are to be done within 3 days prior to next cycle drug administration.

d. Full medical history is obtained at screening for safety and eligibility purposes; this will include any clinically significant findings from 28 days prior to screening date.

e. Physical exam and vital signs (including blood pressure, heart rate, respiration rate and temperature) are completed for safety purposes and clinically significant items are recorded as AEs where appropriate. Vital signs are collected prior to APR-246 infusion, 2 hours into infusion and at EOI (±30 minutes at all time points). On Day 2 of the APR-246 monotherapy lead-in period, vital signs are collected prior to PO administration of APR-246, and then 2 hours and 6 hours after APR-246 administration. For patients with palpable lymphadenopathy and/or organomegaly, 2 dimensional measurements of lymph nodes and measurements of liver/spleen size (below costal margin) may be included as part of each physical examination as clinically indicated.

f. Study treatment will consist of APR-246 at assigned dose level administered once weekly, on Days 1, 8 and 15 of each 28-day cycle. On Day 2 of the monotherapy lead-in period, a single dose of APR-246 will be administered PO.

g. Venetoclax is given PO at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5 and thereafter. Each dose should be given once daily at approximately the same time every day, with a meal and water. At the discretion of the treating Investigator, patient may be hospitalized prior to administration of the first dose of venetoclax (20 and 50 mg) and continuing for 24 hours after.

h. Rituximab will be initiated IV, following the 5-week venetoclax dose ramp-up, at 375 mg/m^2 on Cycle 2, Day 2 (+3 days) and 500 mg/m^2 on Day 2 (+3 days) of Cycles 3-7. After 6 cycles of treatment with APR-246 + venetoclax + rituximab, APR-246 and venetoclax will continue to be administered in Cycle 8 and beyond for up to 24 cycles.

i. Responses will be assessed every 3 cycles starting at Cycle 4 on Day 1 (±7 days) according to Lugano response criteria via PET/CT imaging, blood, and BM. For patients who achieve CR, imaging may be omitted, and MRD assessment will be completed using flow cytometry and/or molecular techniques.

j. Hematology must include complete blood count with differential. Hematology test should be completed before and after APR-246 administration on Days 1and 2 of the APR-246 monotherapy lead-in period, Day 3 of the lead-in period, and on Day 1 of Cycle 1 before and approximately 4 hours after APR-246 administration.

k. Serum chemistry must include sodium, potassium, magnesium, phosphorus, chloride, CO_2, blood urea nitrogen (BUN), creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid, and lactate dehydrogenase (LDH).

l. Cockcroft-Gault method (see Appendix I).

m. Serum or urine beta-human chorionic gonadotrophin (βhCG) must be performed within 7 days prior to study treatment initiation in female patients of childbearing potential.

n. Standard 12-lead ECGs in triplicate at screening, Days 1-2 of APR-246 Lead-In, Days 1, 8 and 15 of Cycle 1 and on Days 1 of each subsequent cycle with patient in a semi-recumbent position prior to APR-246 administration. Please consult Table 19 for ECG collection schedule.

o. Please consult Section 7.4 for PK sample collection schedule.

p. Patients discontinuing treatment should complete their end of treatment visit within approximately 28 days of their last dose of APR-246. Physical exam, weight, vital signs, ECOG PS, clinical toxicity assessment, concomitant medications, hematology, serum chemistry, ECG and disease assessment should be performed, if feasible.

q. Long-term follow up can be done remotely (e.g., via telephone, via local practitioner or via review of medical records). Assuming there is no withdrawal of consent, patients who stop study treatment for any reason (e.g., toxicity, transition to stem cell transplant, disease progression) will continue long term follow-up (see Section 6.9). If a patient is removed from the study due to unacceptable AEs, the event(s) will be followed until resolution or stabilization.

r. AE description, grade and start date and resolution date should be documented.

s. Historical record can be used from up to 1 year in the past.

t. Testing mandatory. Patients with prior exposure to hepatitis B (i.e., positive anti-hepatitis B core antibody) must demonstrate hepatitis B PCR to be negative during screening period and undergo prophylaxis and monitoring for hepatitis B according to institutional guidelines. Reflex PCR testing is required if serology is positive.

u. PD analyses as described in Table 18 and Section 8.8.

v. Blood sample collected for glutathione assay to measure reduced glutathione (GSH) levels in blood during APR-246 monotherapy lead-in period (prior to and approximately 4 hours after APR-246 IV infusion on Day 1, prior to and approximately 10 hours after APR-246 administration PO on Day 2, and approximately 24 hours after Day 2 APR-246 PO administration on Day 3) and during Cycle 1 (prior to and approximately 4 hours after APR-246 IV infusion on Day 1). *GSH sample is collected and sent to LabCorp following sites standard practice.

6.2 Pre-Study Assessments

Prior to performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all patient candidates and written informed consent will be obtained. Patients who choose to participate will have to consent to collection and storage of blood for correlative studies. Evaluations obtained as part of routine medical care and performed during the screening period may be used in place of the study specific evaluations. Patients will acknowledge and agree to the possible use of this information for the study by giving informed consent.

6.3 Screening

All screening evaluations are to be performed within approximately 28 days of study treatment initiation, unless otherwise noted.

- Signed written informed consent
- Medical history
- Physical examination
- Height: historical record can be used from up to 1 year in the past.
- Weight
- ECOG performance status (Appendix II)
- Vital signs, including blood pressure, heart rate, respiration rate and temperature
- Hematology, including complete blood count with WBC differential.
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, blood urea nitrogen (BUN), creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and lactate dehydrogenase (LDH).
- Creatinine CL (Cockcroft-Gault method; Appendix I)
- Serum or urine beta-human chorionic gonadotrophin (βhCG) must be performed within 7 days prior to study treatment initiation for female patients of childbearing potential.
- HBV/HCV test: Patients with prior exposure to hepatitis B (i.e., positive anti-hepatitis B core antibody) must demonstrate hepatitis B PCR to be negative during screening period and undergo prophylaxis and monitoring for hepatitis B according to institutional guidelines. Reflex PCR testing is required if serology is positive.
- ECG: standard 12-lead ECGs with patient in a semi-recumbent position in triplicate.
- Clinical toxicity assessment
- Concomitant medication review
- Baseline tumor assessment. Responses will be assessed according to disease specific response criteria via blood, BM, and imaging (PET/CT), as appropriate, on Day 1 (±14 days) of Cycles 4, 7, 13, 19, 22 and 25. If IV contrast is contraindicated, CT without contrast can be used. For patients with BM disease, BM assessments will be done at Day 1 (±14 days) of Cycles 7, 13 and 25 and if required to confirm CR.

6.4 APR-246 Monotherapy Lead-in

6.4.1 Day 1

- Clinical toxicity assessment
- Concomitant medications review
- Physical examination

- Weight
- ECOG performance status (Appendix II)
- Vital signs, including blood pressure, heart rate, respiration rate and temperature, collected 2 hours into APR-246 infusion (±30 min) and at EOI (±30 min)
- Hematology, including complete blood count with WBC differential. Hematology test should be completed before and approximately 4 hours after APR-246 administration
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- APR-246 IV administration
- ECG: standard 12-lead ECGs with patient in semi-recumbent position before and after APR-246 infusion, per Table 19
- Blood samples for APR-246 PK, per Table 18
- Blood samples for PD, per Table 18
- Blood sample for GSH assay (prior to and approximately 4 hours after APR-246 IV infusion). Sample is collected and sent to LabCorp following sites standard practice.

6.4.2 Day 2

- Clinical toxicity assessment
- Concomitant medications review
- Vital signs, including blood pressure, heart rate, respiration rate and temperature, collected 2 hours (±30 min) and 6 hours (±30 min) after APR-246 PO administration
- Hematology, including complete blood count with WBC differential. Hematology test should be completed before and approximately 10 hours after APR-246 PO administration
- APR-246 PO administration
- ECG: standard 12-lead ECGs with patient in semi-recumbent position before and after APR-246 infusion, per Table 19
- Blood samples for APR-246 PK, per Table 18
- Blood samples for PD approximately 10 hours after APR-246 administration PO), per Table 18Blood sample for GSH assay (prior to and approximately 10 hours after APR-246 administration PO). Sample is collected and sent to LabCorp following sites standard practice.

6.4.3 Day 3

- Hematology, including complete blood count with WBC differential (approximately 24 hours after APR-246 PO administration).
- Blood samples for APR-246 PK, per Table 18
- Blood samples for PD (approximately 24 hours after APR-246 PO administration), per Table 18
- Blood sample for GSH assay (approximately 24 hours after APR-246 PO administration). Sample is collected and sent to LabCorp following sites standard practice.

6.5 Cycle 1 (Venetoclax Ramp-up, Weeks 1-5)

6.5.1 Day 1

- Physical examination: Day 1
- Weight: Day 1
- ECOG performance status (Appendix II): Day 1
- Vital signs, including blood pressure, heart rate, respiration rate and temperature
- Hematology, including complete blood count with WBC differential. Hematology test should be completed before and after APR-246 administration on Day 1
- Serum chemistry including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase (for TLS assessment), uric acid and LDH: Day 1
- Concomitant medications review
- Clinical toxicity assessment
- APR-246 IV administration: Day 1
- ECG before and after APR-246 administration, see Table 19 (Day 1)
- Venetoclax is given PO at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5. Each dose should be given once daily at approximately the same time every day, with a meal and water. Please see current prescribing information for venetoclax.
- *Optional* hospitalization for the first dose of 20 and 50 mg of venetoclax beginning the evening prior to the dose of venetoclax and continuing for 24 hours after, at the discretion of the treating Investigator.
- Blood samples for PD, per Table 18 (Day 1)
- Blood sample for GSH assay (prior to and approximately 4 hours after APR-246 IV infusion on Day 1). Sample is collected and sent to LabCorp following sites standard practice.

6.5.2 Day 8

- Vital signs
- APR-246 IV administration
- ECG before and after APR-246 administration, see Table 19
- Venetoclax is given PO at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5. Each dose should be given once daily at approximately the same time every day, with a meal and water. Please see current prescribing information for venetoclax.
- Clinical toxicity assessment
- Concomitant medications review

6.5.3 Day 15

- Vital signs
- APR-246 IV administration
- ECG before and after APR-246 administration, see Table 19
- Venetoclax is given PO at the dose of 20 mg during Week 1, 50 mg during Week 2, 100 mg during Week 3, 200 mg during Week 4, and 400 mg during Week 5. Each dose should be given

once daily at approximately the same time every day, with a meal and water. current prescribing information for venetoclax.
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase (for TLS assessment), uric acid and LDH
- Clinical toxicity assessment
- Concomitant medications review

6.6 Cycles 2-7

6.6.1 Day 1

- Clinical toxicity assessment
- Concomitant medications review
- Physical examination
- Weight
- ECOG performance status (Appendix II)
- Vital signs
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- ECG, per Table 19
- APR-246 IV administration
- Blood sample for APR-246 PK, per Table 18
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp-up) once daily at approximately the same time every day, with a meal and water.

6.6.2 Day 2

- Clinical toxicity assessment
- Concomitant medications review
- Vital signs
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp up) once daily at approximately the same time every day, with a meal and water.
- Rituximab administered intravenously at 500 mg/m^2

6.6.3 Day 8 (±3 Days)

- Clinical toxicity assessment
- Concomitant medications review
- Vital signs, including blood pressure, heart rate, respiration rate and temperature, collected 2 hours into APR-246 infusion (±30 min) and at EOI (±30 min)
- Hematology, including complete blood count with WBC differential

- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- APR-246 IV administration
- Blood sample for APR-246 PK, per Table 18
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp up) once daily at approximately the same time every day, with a meal and water

6.6.4 Day 15 (±3 Days)

- Clinical toxicity assessment
- Concomitant medications review
- Vital signs, including blood pressure, heart rate, respiration rate and temperature, collected 2 hours into APR-246 infusion (±30 min) and at EOI (±30 min)
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- APR-246 IV administration
- Blood sample for APR-246 PK, per Table 18
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp up) once daily at approximately the same time every day, with a meal and water

6.7 Tumor Assessment (Cycles 4, 7, 10, 13, 19, 22 and 25)

- Tumor assessment is performed on Day 1 (±14 days) of Cycles 4, 7, 10, 13, 19, 22 and 25. Response to study treatment will be assessed via blood, BM, and imaging (PET/CT), as appropriate. If IV contrast is contraindicated, CT without contrast can be used. For patients with BM disease, BM assessments will be done at Day 1 (±14 days) of Cycles 7, 13 and 25 and if required to confirm CR. For patients who achieve CR, imaging may be omitted and MRD assessment will be completed using flow cytometry and/or molecular techniques.

6.8 Cycle 8 and Beyond

6.8.1 Day 1

- Clinical toxicity assessment
- Concomitant medications review
- Physical examination
- Weight
- ECOG performance status (Appendix II)
- Vital signs
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- APR-246 IV administration

- ECG before and after APR-246 administration, see Table 19
- Blood sample for APR-246 PK, per Table 18
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp up) once daily at approximately the same time every day, with a meal and water

6.8.2 Day 8 (±3 Days)

- Clinical toxicity assessment
- Concomitant medications review
- Vital signs, including blood pressure, heart rate, respiration rate and temperature, collected 2 hours into APR-246 infusion (±30 min) and at EOI (±30 min)
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- APR-246 IV administration
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp up) once daily at approximately the same time every day, with a meal and water

6.8.3 Day 15 (±3 Days)

- Clinical toxicity assessment
- Concomitant medications review
- Vital signs, including blood pressure, heart rate, respiration rate and temperature, collected 2 hours into APR-246 infusion (±30 min) and at EOI (±30 min)
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH
- APR-246 IV administration
- Venetoclax is given PO at the dose of 400 mg (or tolerable dose following 5-week ramp up) once daily at approximately the same time every day, with a meal and water

6.9 End of Treatment Visit

This visit should take place within 28 days of the last dose of study treatment, if treatment is stopped early for any reasons.

- Physical examination
- Weight
- Vital signs
- ECOG performance status (Appendix II)
- Hematology, including complete blood count with WBC differential
- Serum chemistry, including sodium, potassium, magnesium, phosphorus, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase, uric acid and LDH

- Clinical toxicity assessment up to 30 days after the last dose
- ECG, per Table 19
- Disease assessment
- Concomitant medications review

6.10 Long-Term Follow-Up

Long-term follow-up can be done remotely (e.g., via telephone, via local practitioner or via review of medical records). After a patient is removed from the study, the patient will be followed until death. If a patient has withdrawn consent from study, then follow-up has to cease on the date when consent for study was withdrawn. Off-treatment data on OS will be updated every 3 months or until death or withdrawal of consent for study participation, whichever occurs first. If a patient is removed from the study due to unacceptable AEs, the event(s) will be followed until resolution or stabilization of the AE. Patients who respond and discontinue study treatment for reasons other than disease progression should have response assessments and survival should be collected every 2 months until disease progression or death, whichever occurs first. After disease progression, data for survival should be collected every 3 months until death or withdrawal of consent for study participation.

7.0 STUDY ASSESSMENTS

7.1 Safety Assessments

7.1.1 Safety Analysis

Safety data will be tabulated for all patients and include vital signs, laboratory parameters, and AEs.

7.1.2 Reporting of Adverse Events

7.1.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An AE can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The AE reporting period starts at the time of study treatment initiation. For the time period from signing of informed consent up to receipt of the first dose of APR-246, non-serious events should be recorded as medical history on the appropriate eCRF page within the clinical database. SAEs that occur during the screening period are required to be reported and should include an assessment on whether the SAE was related to a protocol-defined procedure or activity. AEs will be collected for up to 30 days after the last dose of study treatment, unless the patient has withdrawn consent for study participation or started a new anti-cancer treatment for the disease under study, whichever occurs first. Hospitalization to start new anti-cancer treatment for primary disease after confirmed progression/relapse does not meet criteria for AE or SAE.

Progression of primary disease and events unequivocally related only to progression of primary

disease do not need to be reported on the AE CRF page. Progression of primary disease should be reported on a response assessment eCRF.

At each evaluation, patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an AE will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms.

All AEs (except laboratory abnormalities that are assessed as not clinically significant by the Investigator), regardless of causal relationship, are to be recorded in the eCRF and source documentation. The Investigator must determine the intensity of any AEs according to the NCI CTCAE version 5.0 and their causal relationship to each study medication administered that has been administered to the patient at the time of event onset. Those AEs not covered by these criteria will be graded as follows:

1. Mild: Discomfort noticed, but no disruption of normal daily activity. Prescription drug not ordinarily needed for relief of symptom but may be given because of personality of patient.
2. Moderate: Discomfort sufficient to reduce or affect normal daily activity. Patient is able to continue in study; treatment for symptom may be needed.
3. Severe: Incapacitating, severe discomfort with inability to work or to perform normal daily activity. Severity may cause cessation of treatment with test drug; treatment for symptom may be given and/or patient hospitalized.
4. Life-Threatening: Symptom(s) place the patient at immediate risk of death from the reaction as it occurred; it does not include a reaction that, had it occurred in a more serious from, might have caused death.
5. Fatal: Event caused the death of the patient.

AEs will be followed until resolution or stabilization while the patient remains on-study. Once the patient is removed from study treatment, events thought to be related to the study medication will be followed until resolution or stabilization, unless, in the Investigator's opinion the event is unlikely to resolve due to the patient's underlying disease, or until the patient starts a new treatment regimen or the patient is lost to follow-up.

7.1.2.2 AE Relationship Attribution Definitions

An AE is considered to be associated with the use of the study treatment if the attribution is determined as possible or definite.

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

- Definitely related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to the medication administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug should be clinically plausible.
- Possibly related: A clinical event, including laboratory test abnormality, with a reasonable time sequence to the medication administration, but which could also be explained by concurrent disease or other drugs or chemicals. Information on the drug withdrawal may be lacking or unclear.

- Unlikely related: A clinical event, including laboratory test abnormality, with little or no temporal relationship to medication administration, and which other drugs, chemicals, or underlying disease provide plausible explanations.
- Not related: A clinical event, including laboratory test abnormality that has no temporal relationship to the medication or has more likely alternative etiology.

7.1.2.3 Definition of an Unexpected Adverse Event

An unexpected AE is defined as any adverse drug experience, the specificity or severity of which is not consistent with the reference safety information in the current Investigator Brochure for a study product or products administered to a patient; or, if an Investigator Brochure is not available, the specificity or severity of which is not consistent with the risk information described in this protocol or in the regulatory agency study authorization application.

For study treatments used in this protocol that have been approved for use in the US by the FDA (i.e., venetoclax, and rituximab), the reference safety information that will be used for making expectedness decisions is the most current version of the product USPI that can be found on the FDA website.

Unexpected, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the IB[40] or other product reference safety information such as the USPI) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

7.1.2.4 Serious Adverse Event

An SAE is defined as any untoward medical occurrence that at any dose:

1. Results in death,
2. Is life-threatening (i.e., the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe),
3. Requires inpatient hospitalization or prolongation of existing hospitalization excluding that for pain management, disease staging/re-staging procedures, or catheter placement, for administration of study treatments, or for pre-existing condition or elective surgery that was planned prior to study enrollment, unless associated with other serious events,
4. Results in persistent or significant disability/incapacity, or
5. Is a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

SAEs during the screening period that are assessed as related to a study procedure or activity should be reported to the Sponsor.

7.1.2.5 Pregnancy

Any pregnancy detected during the study, or that occurs within 30 days after stopping study medication, must be reported immediately to the Investigator. Pregnancy, in and of itself, is not regarded as an AE, unless there is suspicion that study medication may have interfered with the effectiveness of a contraceptive medication. If the patient becomes pregnant while on-study, the study drug should be immediately discontinued. Pregnancy information about a female patient or a female partner of a male patient should be reported immediately from the time the Investigator first becomes aware of a pregnancy or its outcome. This will be performed by the Investigator per instructions from the Sponsor's monitoring CRO.

Any pregnancy complication, spontaneous abortion, elective termination of a pregnancy for medical reasons, outcome of stillbirth, congenital anomaly/birth defect, or SAE in the mother will be recorded as an SAE and will be reported as described in Section 7.1.2.6.

7.1.2.6 Reporting of Serious Adverse Events

AEs classified as serious require expeditious handling and reporting to Sponsor's monitoring CRO to comply with regulatory requirements.

For any SAE that occurs while a patient is on-study; within 30 days of the last study treatment administration, regardless of any opinion as to the relationship of the SAE to the study treatment; or if any SAE that the Investigator feels is related to the study treatment occurs later than 30 days after the last study treatment administration, the Sponsor's monitoring CRO must be notified immediately (within 24 hours of becoming aware of the event). The primary mechanism for reporting an SAE to the Sponsor will be the electronic data collection tool. An SAE eCRF should be completed in the electronic data capture (EDC) system within 24 hours of site becoming aware of the event. EDC Alerts will be sent to Safety desk for all SAEs.

If the EDC system is inaccessible/unavailable, then the site will use the paper SAE form in order to report the SAE within 24 hours. Emailing the paper SAE forms is the preferred method of notification.

SAEs will be reported to the following email address: [redacted]

7.1.2.7 Safety Monitoring Plan

The Medical Monitor is responsible for ongoing safety monitoring for the study per the detailed safety plan. This monitoring will include a review of all SAEs as they are reported by the study site. The Medical Monitor will also be in contact with site monitors and will be available to discuss any issues concerning safety with site staff. Safety data will be reviewed periodically by [redacted] and the Sponsor Medical Officer.

The DRT consisting of the Medical Monitor, Site Principal Investigators, and other clinical research personnel that the Sponsor may deem appropriate will hold DRMs on an interim basis at a frequency dependent on study accrual. At these meetings, the DRT will review AEs and DLTs and any available PK and/or PD data and make recommendations regarding the recommended dose of APR-246. All accumulated safety data will be discussed during DRMs.

The DRT will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human patients and the integrity of data.

7.2 Efficacy Assessments

7.2.1 Complete Remission Rate

CR rate will be defined as the proportion of patients who achieve CR. The rate of MRD-negative CR is defined as the proportion of patients who achieve MRD-negative CR.

7.2.2 Duration of Response

Duration of response (DOR) will be measured from the time of initial response to disease progression or death.

7.2.3 Objective Response Rate

ORR, defined as the proportion of patients achieving CR or partial response, measured per Lugano criteria (see Appendix V).

7.2.4 Overall Survival

OS is defined for all enrolled patients, as measured from the date of enrollment until the date of death.

7.3 Progression-Free Survival

PFS is defined for each patient as the time from start of treatment to the date of the first documented progression or death due to any cause. Patients who die without a reported prior progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumor assessment. Patients who started any subsequent therapy without a prior reported progression will be censored at the last evaluable tumor assessment prior to the initiation of the subsequent anticancer therapy.

7.4 Pharmacokinetic and Pharmacodynamic Evaluation

APR-246 will be administered in a 7-day monotherapy cycle on Days 1 and 2, via IV and PO route, respectively. PK samples for APR-246 measurements will be taken on Day 1 pre-dose, at the end of the infusion and 1, 2 and 4 hours after the end of the infusion, and 24 hours after the end of the infusion prior to APR-246 PO administration on Day 2, as well as 0.5, 1, 1.5, 2, 3, 4, 6, 10 and 24 hours after the oral administration on Day 2. Following review of the initial PK profiles after oral administration, the PK sampling scheme will be reviewed and optimized. Unnecessary samples will be removed from the schedule and sampling times changed (the total number of samples specified below will not be exceeded).

Blood samples for PD markers and GSH will be collected as follows: on Day 1 pre-dose and 4 hours after the end of the infusion; on Day 2 prior to oral administration as well as 10 and 24 hours after the oral administration.

In addition, blood samples for PD and GSH markers will be collected on Cycle 1 Day 1 pre-dose and 4 hours after the end of the infusion.

Table 18: PK, PD, and Glutathione Blood Sampling Timepoints for APR-246

PK and PD Blood Sampling Timepoints	APR-246 PK and PD Sample Collection										
	APR-246 Monotherapy Lead-In Period						Cycle 1	Cycle 2			Cycles 3+
	D1[a]		D2[b]		D3		D1	D 1	D 8	D 15	D1
	PK	PD	PK	PD	PK	PD	PD	PK	PK	PK	PK
Prior to APR-246 administration [b,c]	×	×[d]	×[b]	×[d]	×[c]	×[d]	×[d]	×	×	×	
After APR-246 administration (<5 min after end of IV infusion [EOI])	×							×	×	×	×
0.5 h after APR-246 administration			×								
1 h (±5 min) after APR-246 administration	×		×					×	×	×	
1.5 h (±5 min) after APR-246 administration			×								
2 h (±5 min) after APR-246 administration	×		×								
3 h (±15 min) after APR-246 administration			×								
4 h (±15 min) after APR-246 administration	×	×[d]	×				×[d]				
6 h (±15 min) after APR-246 administration			×								
10 h (±1 h) after APR-246 administration			×	×[d]							

[a] PK samples are collected at time points related to IV administration of APR-246 on Day 1 of monotherapy lead-in period
[b] PK samples are collected at time points related to PO administration of APR-246 on Day 2 of monotherapy lead-in period with the exception of the pre-dose sample collected 24 h after IV administration of APR-246 on Day 1 (prior to PO administration of APR-246 on Day 2)
[c] Sample collected 24 h (±1 h) after PO administration of APR-246 on Day 2 of monotherapy lead-in period
[d] Blood sample for glutathione assay and hematology

On Day 1, 8 and 15 of Cycle 2, venetoclax will be taken 1 hour prior to administration of the APR-246 infusion. Please refer to Sections 2.5 and 5.4, regarding the risk of certain drugs and foods influencing the PK of venetoclax such as grapefruits (see Appendix VII). The time of venetoclax administration on the PK sampling day will be recorded to allow popPK evaluation of venetoclax, if deemed necessary.

7.5 Electrocardiographic Assessment

Table 19 describes the routine ECG requirements.

Table 19. ECG Assessment Requirements

Time Point	ECG, number	Timing
Baseline/Screening	Triplicate	Within 28 days of study treatment [1]
APR-246 Monotherapy Lead-In	Triplicate	Pre-dose; at the end of the infusion (±30 min) [2]
Cycle 1, Day 1, 8 and 15	Triplicate	Pre-dose; at the end of the infusion (±30 min)
Cycles 2+, Day 1	Triplicate	Pre-dose; at the end of the infusion (±30 min)
End of Treatment	Triplicate	Within 28 days of the last dose of APR-246

[1] Baseline/Screening registration is for eligibility purpose and should be performed before the patient is approved and registered in IWRS to start any treatment on study, i.e., 28 days prior to the first dose of venetoclax in ramp-up.

[2] On Day 2 of the APR-246 monotherapy lead-in period, ECG is obtained prior to PO administration of APR-246, and then 6 hours after APR-246 administration.

If repeated QTcF measurements show a stable QTcF <470 msec, unless due to BBB and/or pacemaker, with no significant change at the EOI during several cycles of treatment, reducing the number of ECGs performed in the study may be discussed with the Medical Monitor.

If a patient starts treatment with another medication known to prolong QT interval at any time during the study therapy, an additional pre- and post-dose (6 hours after start of infusion, ±30 min) ECG should be performed on the next treatment day.

Please consult Section 5.3.1 for additional requirements for proceeding with treatment with APR-246.

8.0 STATISTICS

Continuous variables will be presented by *n*, mean, median, standard deviation and range (minimum and maximum), and categorical variables will be presented by count and percentage of patients as appropriate. Data will be presented by dose escalation cohort. All patient data, efficacy and safety data will be summarized and listed.

8.1 Sample Size

A total of up to 48 evaluable patients will be included in the study.

Patients with RT will be enrolled and receive APR-246 at the assigned dose cohort level. Dose escalation will proceed in a 3 + 3 design. Cohorts will consist of 3-6 patients and 10 additional patients may be enrolled at the MTD. Approximately 6 + 6 + 6 (18) DLT evaluable patients will be enrolled. In the event Dose Level 3 is declared the MTD, up to 10 additional patients may be enrolled at Dose Levels 1 and 2 to gain additional safety, PK, and/or PD data to help define the recommended dose of APR-246 in this combination.

8.2 Analysis Populations

Safety population: Patients will be evaluable for safety if they receive at least one dose of APR-246. The safety population will be the primary analysis population used for all analyses such as patient disposition, patient demographics, exposure, safety parameters and efficacy parameters. The safety population will be the primary analysis population for efficacy.

Efficacy evaluable (EE) population: All patients who complete at least one treatment cycle of APR-246 and venetoclax and rituximab and who have at least one post-treatment clinical response assessment. The EE population will be the secondary analysis population for efficacy.

PD population: Patients will be evaluable for PD if at least one sample for PD evaluation has been obtained after administration of APR-246.

PK population: Patients will be evaluable for PK if at least one sample for PK evaluation has been obtained.

8.3 Endpoints

8.3.1 Primary

1. PD analysis of circulating peripheral blood cells to determine effects of APR-246 on cellular viability and apoptosis.
2. Frequency of TEAEs and SAEs related to APR-246 in combination with venetoclax and rituximab therapy.
3. The highest tested dose of APR-246 with acceptable toxicity (the dose producing <33% of DLT).

8.3.2 Secondary

1. PK parameters: C_{max}, AUC, V_d and CL of APR-246, and C_{max}, time to maximum concentration (T_{max}), and AUC of venetoclax.
2. PD analysis of circulating peripheral blood cells to determine effects of APR-246 on cellular viability and apoptosis *(PK/PD Substudy of APR-246 Monotherapy*).
3. PK parameters after oral dosing: C_{max}, T_{max}, AUC, relative bioavailability (F), apparent volume of distribution (V_d/F) and apparent clearance (CL/F) of APR-246, *(PK/PD Substudy of APR-246 Monotherapy*).
4. CR rate, defined as the proportion of patients who achieve CR as per response criteria.
5. ORR, defined as the proportion of patients achieving a response, as per response criteria.
6. DOR, defined as the time from documentation of tumor response to disease progression or death as a result of any cause.
7. PFS, defined as the time from the first study dose date to the date of first documentation of confirmed disease progression or death (whichever occurs first).

8.3.3 Exploratory

The exposure response relationship for safety and efficacy of APR-246 when combined with venetoclax and rituximab therapy.

8.4 Safety Stopping Criteria

The study will implement the following stopping criteria:

- Any death occurring between receipt of the first dose of APR-246 through 30 days of last dose of study treatment which is not clearly and solely due to underlying disease.
- A medically equivalent SAE experienced by >1 patient, which is not clearly and solely due to underlying disease.
- A severe AE (NCI-CTCAE toxicity grade >3) experienced by >2 patients that does not return to grade ≤1 or baseline within 7 days.
- A grade ≥3 neurologic AE that does not return to grade ≤1 or baseline within 7 days.

If a stopping criterion is met, enrollment will be temporarily suspended. The DRT will perform a prompt cumulative review of safety data and the circumstances of the event(s) in question to determine whether dosing and/or the protocol should be modified.

8.5 Futility Criteria

As this is a phase 1 study intended to determine the recommended dose of APR-246 in combination with venetoclax and rituximab in a limited number of patients with RT, futility criteria based on efficacy are not included.

8.6 Safety

Safety data will be summarized for the safety population. These data will include AEs, laboratory parameters, electrocardiogram, and physical exam findings. AE terms will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA)®, version 22.0 or higher. AEs will be summarized by SOC, preferred term, severity, and relationship to treatment. SAEs, deaths, and AEs leading to early discontinuation of study treatment will be summarized. Laboratory parameters will be summarized by maximum NCI-CTCAE version 5.0 severity grade and also by change from pre-treatment to scheduled time points using descriptive statistics. Laboratory parameter listings will include the normal ranges for each parameter. Each value will be classified as falling above, below, or within the normal range.

Only SAEs related to study screening procedures from the time of signing informed consent and AEs from the time of first dose of APR-246, throughout study enrollment, and up to 30 days after last dose of study treatment are to be collected. Data summaries will include only TEAEs, defined as events occurring at the start of APR-246 infusion in the monotherapy lead-in or Cycle 1, Day 1 up to and including 30 days after last dose of study treatment.

8.7 Efficacy

CR rate will be summarized for the safety and EE patients as the proportion (%) of patients with CR. In addition to presenting the CR rate, its associated exact 95% CI will also be presented.

DOR is defined as the time from the date when criteria for response are met to the date of disease

progression or death due to any cause, whichever occurs first. Patients alive with no disease progression will have their DOR censored at the date of the last clinical assessment. The duration of CR will be summarized by providing the median DOR together with associated 95% CI, using Kaplan-Meier methodology.

ORR will be summarized in number (%) of patients in each category of responses and ORR will be analyzed by using a similar method to the one used for the CR rate. ORR is defined as the number of patients who achieve CR and partial remission (PR) measure per Lugano criteria (see Appendix V).

Survival data are collected at treatment and follow-up periods. Patients will be followed until death or withdrawal of consent from the study, whichever occurs first.

OS is defined as the number of days from the first day of treatment to the date of death due to any cause. Kaplan-Meier methodology will be utilized.

PFS is defined as the time from the first day of treatment to disease progression or death due to any cause, whichever occurs first. If neither event occurs, PFS will be censored at the date of the last clinical assessment. Kaplan-Meier methodology will be utilized.

8.8 Pharmacodynamic Analysis

PD analysis will be conducted using flow cytometry of circulating CLL/RT cells before and after treatment with APR-246 during monotherapy and the first day of combination treatment ramp-up to assess viability and apoptosis. Descriptive statistics (mean, standard deviation, CV% mean, geometric mean, CV% geometric mean) will be utilized to compare the post- and pre-treatment samples and the differences at each dose cohort level will be tested for relationship to dose.

8.9 Pharmacokinetic Analysis

Concentrations of APR-246 will be determined using validated bioanalytical methods.

During the APR-246 monotherapy cycle, PK sampling for APR-246 will be performed on Day 1 and 2. Noncompartmental PK analysis will be used to determine C_{max}, T_{max}, AUC and bioavailability after oral dosing for decision making on dose escalation of the oral dose.

PK sampling for APR-246 will be performed during Cycle 2, on Day 1, 8 and 15 and on Day 1 from Cycle 3 onwards.

PK sampling for venetoclax and rituximab will not be performed for this study.

The PK of APR-246 will be summarized using descriptive statistics (mean, standard deviation, CV% mean, geometric mean, CV% geometric mean). The concentration data for APR-246 will be evaluated using (popPK analysis in combination with data from other studies.

APR-246 AUC and C_{max} will then be tested for association with signs of efficacy and safety. If an observable trend exists, a PK/PD model will be developed to evaluate the exposure-response relationship between APR-246 plasma exposure and outcome measures. Demographic and clinical

data (ethnicity, current age, body weight, sex, disease status, etc.) will be utilized to assess interpatient variability in the PK and PK/PD relationships.

9.0 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

9.1 Monitoring of the Study and Regulatory Compliance

The project manager, or designee, will make an initiation site visit to each institution to review the protocol and its requirements with the Investigator(s), inspect the drug storage area, fully inform the Investigator of his/her responsibilities and the procedures for assuring adequate and correct documentation. During the initiation site visit the eCRFs will be reviewed. Other pertinent study materials will also be reviewed with the Investigator's research staff. During the course of the study, the monitor will make regular site visits in order to review protocol compliance, examine eCRFs and individual patient's medical records and assure that the study is being conducted according to pertinent regulatory requirements. All eCRF entries will be verified with source documentation. The review of medical records will be done in a manner to assure that patient's confidentiality is maintained.

9.2 Curricula Vitae and Financial Disclosure of Investigators

All Principal Investigators will be required to provide a current signed and dated curriculum vitae, a completed FDA Form 1572 and a financial disclosure statement to Sponsor's monitoring CRO. All Sub-Investigators will be required to provide a current curriculum vitae and a financial disclosure statement to Sponsor's monitoring CRO.

9.3 Protocol Modifications

No modification of the protocol should be implemented without the prior written approval of the Sponsor or the Sponsor's representative. Any such changes which may affect a patient's treatment or informed consent, especially those increasing potential risks, must receive prior approval by the IRB/IEC. The exception to this is where modifications are necessary to eliminate an immediate hazard to trial patients, or when the change involves only logistical or administrative aspects of the trial (e.g., change in monitor, change in telephone number). Other administrative revisions which may impact the clinical portion of a study will be duly reported to the IRB/IEC by the Principal Investigator.

9.4 Publication Policy

The publication of the results of the study will be subject to the terms and conditions of the clinical trial agreement between the Sponsor and Investigators. Sponsor approval is required for publication of any data from this trial.

10.0 ETHICAL CONSIDERATIONS

10.1 Informed Consent

The Investigator will obtain written informed consent from each patient, or their authorized representative, participating in the study. The form must be signed, witnessed and dated. The

informed consent form will contain all the Essential Elements of Informed Consent set forth in 21 CFR, Part 50, the European Union Directive 2001/20/EC and its associated Detailed Guidances, European Union GCP Directive 2005/28/EC, the ICH Guideline for GCP, Section 4.8, and the terms of the Declaration of Helsinki (2013). Copies of the signed document should be given to the patient and filed in the Investigator's study file, as well as the patient's medical record if in conformance with the institution's Standard Operating Procedures.

10.2 Institutional Review Board/Independent Ethics Committee

The study will not be initiated without approval of the appropriate IRB/IEC and compliance with all administrative requirements of the governing body of the institution. This protocol, consent procedures, and any amendments must be approved by the IRB/IEC in compliance with current regulations of the FDA and the European Union as applicable and in accordance with ICH/GCPs. A letter of approval will be sent to the Sponsor prior to initiation of the study and when any subsequent modifications are made. The IRB/IEC will be kept informed by the Investigator, Sponsor's monitoring CRO or the Sponsor, as required by national regulations, as to the progress of the study as well as to any serious and unexpected AEs.

10.3 Patient Privacy

In order to maintain patient confidentiality, all eCRFs, study reports and communications relating to the study will identify patients by initials and assigned patient numbers; patients should not be identified by name. In accordance with local, national or federal regulations, the Investigator will allow the Sponsor or designee personnel access to all pertinent medical records in order to verify the data gathered on the eCRFs and to audit the data collection process. Regulatory agencies such as the US FDA may also request access to all study records, including source documentation for inspection. Clinical information will not be released without the written permission of the patient as outlined in the patient consent form.

11.0 DATA HANDLING AND RECORD KEEPING

11.1 Data to be Entered Directly in the Case Report Form

The eCRF will be the source record.

11.2 Recording of Data

Data collected during the study will be entered in the patient's eCRF by the investigational site staff. The staff will keep records of the patient's visit in the files considered as source documents for the site, e.g., hospital chart, research chart. The Investigator will be responsible for the recording of all data on the eCRF and for submitting the data to the Sponsor or their designee in a timely manner. Should any value be significantly different from normal, the Investigator will comment in the appropriate sections provided in the eCRF.

The Investigator will provide access to his/her original records to permit a representative from the Sponsor to verify the proper transcription of data.

11.3 Study Records

U.S. Federal laws require that an Investigator maintain all study records for the indication under investigation for two years following the date a Product Licensing Application is approved or, if no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

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APPENDIX I - Cockcroft-Gault Equation

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

APPENDIX II - ECOG Performance Status

Grade	
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

APPENDIX III - Acceptable Contraceptive Methods

- Male or female condom with or without spermicide
- Cervical cap, diaphragm or sponge with spermicide

Highly Effective Contraceptive Methods That Are User Dependent [a]
Failure rate of <1% per year when used consistently and correctly.

- Combined (estrogen- and progesterone-containing) hormonal contraception [b]
  - Oral
  - Intravaginal
  - Transdermal
  - Injectable
- Progestogen-only hormonal contraception [b]
  - Oral
  - Injectable

Highly Effective Methods That Have Low User Dependency
Failure rate of <1% per year when used consistently and correctly.

- Progesterone-only contraceptive implant [b, c]
- Intrauterine hormone-releasing system (IUS) [b]
- Intrauterine device (IUD)
- Bilateral tubal occlusion
- **Vasectomized partner**

A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.

- **Sexual abstinence**

Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.)

Notes:
Use should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies.
a) Typical use failure rates are lower than perfect-use failure rates (i.e., when used consistently and correctly).
b) If hormonal contraception efficacy is potentially decreased due to interaction with study treatment, condoms must be used in addition to the hormonal contraception during the treatment period and for at least 120 days, (corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential) after the last dose of the study treatment.
c) If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable hormonal contraceptives are limited to those which inhibit ovulation.

APPENDIX IV - New York Heart Association (NYHA) Classification

NYHA Grading		MET*
Class I	No limitations. Ordinary physical activity does not cause undue fatigue, dyspnea or palpitations (asymptomatic LV dysfunction)	>7
Class II	Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, dyspnea or angina pectoris (mild Congestive Heart Failure (CHF)).	5
Class III	Marked limitation of physical activity. Less than ordinary physical activity leads to symptoms (moderate CHF)	2 – 3
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of CHF present at rest (severe CHF).	1.6

*MET (metabolic equivalent) is defined as the resting VO_2 for a 40-year-old 70kg man.
1 MET = 3.5 mL O_2/min/kg body weight.

APPENDIX V - Lugano Criteria for RT Patients [55]

Response and Site	PET-CT-Based Response	CT-Based Response
Complete	*Complete metabolic response*	*Complete radiologic response (all of the following)*
Lymph nodes and extra-lymphatic sites	Score 1, 2, or 3* with or without a residual mass 5 PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be interred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	*Partial metabolic response*	*Partial remission (all of the following)*
Lymph nodes and extra-lymphatic sites	Score of 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings indicate responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value When no longer visible, 0 x 0 mm For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by >50% in length beyond normal
New lesions	None	None

Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared w/ baseline (diffuse uptake compatible w. reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation w/ MRI or biopsy or an interval scan	Not applicable
No response or stable disease	*No metabolic response*	*Stable disease*
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	<50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non measure lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	*Progressive metabolic disease*	*Progressive disease requires at least 1 of the following*
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi >1.5 cm and Increase by ≥50% from PPD nadir and an increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions >2 cm In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly

Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node >1.5 cm in any axis A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Revised Response Criteria (Table Key)

Abbreviations: 5PS, 5-point scale, CT computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

[*] A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measureable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasure lesions: Any disease not selected as measure, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

[†] PET 5 PS: 1, no uptake above background; 2 uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

APPENDIX VI - Dose Modifications of Venetoclax with Use of CYP3A or P-gp Inhibitors

Concomitant use of venetoclax with *strong* CYP3A inhibitors at initiation and during ramp-up phase is contraindicated. Concomitant use of venetoclax with strong CYP3A inhibitors increases venetoclax exposure (i.e., C_{max} and AUC) and may increase the risk for TLS at initiation and during ramp-up phase. For patients who have completed the ramp-up phase and are on a steady daily dose of venetoclax, reduce the venetoclax dose by at least 75% when *strong* CYP3A inhibitors must be used concomitantly.

Avoid concomitant use of venetoclax with *moderate* CYP3A inhibitors or P-gp inhibitors. Consider alternative treatments. If a moderate CYP3A inhibitor or a P-gp inhibitor must be used, reduce the venetoclax dose by at least 50%. Monitor these patients more closely for signs of toxicities.

Resume the venetoclax dose that was used prior to initiating the CYP3A inhibitor or P-gp inhibitor 2 to 3 days after discontinuation of the inhibitor.

The recommendations for managing drug-drug interactions are summarized in the table below.

Co-administered drug	**Initiation and Ramp-Up Phase**	**Steady Daily Dose (After Ramp-Up Phase)**
Posaconazole	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	Reduce venetoclax dose to 70 mg.
Other strong CYP3A inhibitor	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	Reduce venetoclax dose to 100 mg.
Moderate CYP3A inhibitor	Reduce the venetoclax dose by at least 50%	
P-gp inhibitor		

Warfarin
Concomitant use of venetoclax increases warfarin C_{max} and AUC_{inf}, which may increase the risk of bleeding. Closely monitor international normalized ratio (INR) in patients using warfarin concomitantly with venetoclax.

P-gp Substrates
Concomitant use of venetoclax increases C_{max} and AUCinf of P-gp substrates, which may increase toxicities of these substrates. Avoid concomitant use of venetoclax with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate at least 6 hours before venetoclax.

Please refer to the venetoclax USPI[56] for additional details on drug-drug interactions.

Below (Table 20) are examples of CYP3A inhibitors and inducers (strong and moderate); however,

this is not an exhaustive list.

Table 20. CYP3A Inhibitors and Inducers

CYP3A Inhibitors	
Strong CYP3A Inhibitors	**Moderate CYP3A Inhibitors**
boceprevir, cobicistat, danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, itraconazole, ketoconazole, lopinavir and ritonavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), posaconazole, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, telithromycin, troleandomycin, voriconazole	aprepitant, ciprofloxacin, conivaptan, crizotinib, cyclosporine, diltiazem, dronedarone, erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, verapamil
CYP3A Inducers	
Strong CYP3A Inducers	**Moderate CYP3A Inducers**
apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort	bosentan, efavirenz, etravirine, phenobarbital, primidone

Note: In addition to the medications listed above, patients taking venetoclax should not consume grapefruit, grapefruit products, Seville oranges, (including marmalade containing Seville oranges), or star fruit.

VENETOCLAX DRUG DIARY

Instructions:
You will use this diary to record each dose of venetoclax that you take. You should also use this diary to record any side effects that you experience and medications that you take other than the venetoclax. Please be sure to bring this diary with you to your next clinic visit.

Venetoclax:

- Venetoclax is taken once a day every day, approximately 24 hours apart.
- Venetoclax should be taken with food. Venetoclax can be taken before or after start of APR-246 infusion (±2 hours).
- If you forget to take a dose of venetoclax and it is within 8 hours of when it should have been taken, you should take the dose. If it has been more than 8 hours, you should skip that dose and take the next dose at the next regular time.
- If you vomit after taking a dose of venetoclax, you should not make up the dose or take additional pills, you should take the next dose at the next regular time.
- Always bring your pill bottles (including those that are empty) and your diary with you to each clinic visit.

Your study doctor will make sure you reach the required dose of venetoclax slowly, over the period of 5 weeks called ramp-up, as shown in the table below.

Week Number	Venetoclax Daily Dose
Week 1	20 mg
Week 2	50 mg
Week 3	100 mg
Week 4	200 mg
Week 5 and beyond	400 mg

If you have any questions, please ask a study team member or your doctor.

Patient Number: _____

Patient Initials: _____

Cycle Number: _____

Start Date: _____

STUDY STAFF USE ONLY

Staff member reviewing diary at end of study cycle:

Venetoclax tablets to take at each dose: 20 mg = _____
50 mg = _____
100 mg = _____

Other information/Comments:

_____

_____

VENETOCLAX DRUG DIARY (continued)

Patient Number/Initials: _____ Cycle: _____

Cycle Day	**Date Taken**	**Time Taken**	**Number of venetoclax tablets taken**	**Dose taken**	**Comments** (Side effects, complaints, other medications)
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

* NOTE: Add additional days in case needed due to scheduling delay or dose modifications.

APPENDIX VII - Patient Handout: Prohibited Medications

PROHIBITED MEDICATIONS

One of the medications you are receiving during this clinical trial, venetoclax, interacts with some drugs that are processed by your liver. Because of this, it is very important to tell your study doctors about all of your medicine before you start this study. It is also very important to tell them if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the-counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement). Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial.

Bring this paper with you.

- Venetoclax is processed by a certain enzyme in the liver called CYP3A4. Drugs that increase the activity of this enzyme are called "inducers", and drugs that decrease the activity of this enzyme are called "inhibitors". Venetoclax must be used very carefully with other medicines that are inducers or inhibitors of CYP3A4. Venetoclax may also interact with other drugs that are processed by the liver.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category.

Before you start the study, your study doctor will work with your regular prescriber to switch the following medications if you are taking them:

Avoid strong CYP3A inhibitors, i.e., clarithromycin, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole. Avoid grapefruits and grapefruit juice. If a strong CYP3A inhibitor must be co-administered, the dose of venetoclax should be reduced. If the strong inhibitor is discontinued, the dose of venetoclax should be increased (after 3 to 5 half-lives of the inhibitor) to the dose used prior to initiation of the strong inhibitor.

Avoid strong CYP3A inducers, i.e., phenytoin, rifampin, enzalutamide, and St John's wort.

Avoid P-gp inhibitors, i.e., amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil.

Avoid P-gp substrates with narrow therapeutic index, i.e., amitriptyline, carbamazepine, clonidine, ciclosporin, digitoxin, digoxin, imipramine, phenobarbital, phenytoin, quinidine.

Your regular prescribers should look at these websites: https://www.crediblemeds.org http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.

Eating grapefruit, grapefruit containing products, Seville oranges (including marmalade made with Seville oranges), and starfruit is prohibited while you are taking venetoclax as these may increase the amount of venetoclax in your blood. Please discuss any questions about prohibited foods with your study doctor.

Other medicines can be a problem with your study drugs.

- You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.
- Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

Phase 1 Study of APR-246 in Combination with Venetoclax and Rituximab Therapy in Patients with Richter's Transformed Non-Hodgkin's Lymphomas

Protocol No.:	A20-11197
IND No.:	147956
Sponsor:	Aprea Therapeutics, Inc. [redacted]
Responsible Medical Officer:	Eyal C. Attar, M.D.
Medical Monitor:	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]