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Protocol for Study M18-803

T-Cell Prolymphocytic Leukemia: Venetoclax and Ibrutinib

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1 SYNOPSIS

Title: A Prospective, Open-Label, Single-Arm, Phase 2, Multicenter Study Evaluating the Efficacy of Venetoclax Plus Ibrutinib in Subjects with T-cell Prolymphocytic Leukemia	
Background and Rationale:	T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive T-lymphoid malignancy characterized by proliferation of post-thymic prolymphocytes, usually refractory to current treatment strategies or complicated by relapse and associated with short overall survival. In 2 recent ex vivo drug screening studies, consistent activities of B-cell lymphoma (BCL)-2 inhibition in T-PLL were observed. Venetoclax is a potent, selective, and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity for BCL-2 (inhibition rate constant [Ki] < 0.010 nM) than for B cell lymphoma – extra large (BCL-X_L; Ki = 48 nm) or myeloid cell leukemia (MCL)-1 (Ki > 444 nM). As proof of principle, the first-in-human treatment using venetoclax in 2 late-stage subjects with T PLL was reported. Responses were positive; however, potential mechanisms of resistance may develop through BCL-2 and BCL-X_L induction. Therefore, studies testing venetoclax with appropriate combination partners in subjects with T-PLL are warranted. Ex vivo drug combination studies in primary T-PLL subject samples demonstrated that T-PLL cell-specific synergism of venetoclax was highest with ibrutinib. Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) which was co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of patients with B-cell malignancies.
Objectives and Endpoints:	The primary objective is to demonstrate the efficacy in subjects with relapsed or refractory (R/R) T-PLL treated with venetoclax plus ibrutinib. The secondary objectives of this study are: • To assess safety and tolerability in subjects with T-PLL treated with venetoclax plus ibrutinib. • To assess the ability of the subset of transplant-naïve subjects to proceed to further autologous/allogeneic stem cell transplantation (assessed by number of eligible subjects reaching transplant). • To evaluate the progression-free survival, duration of response, time-to-progression, event-free survival, disease control rate, and overall survival. The exploratory objective is to identify biomarker/genetically-defined subgroups regarding response and survival. The primary endpoint is the overall response rate (ORR) in R/R T-PLL subjects. Secondary endpoints include: progression-free survival, duration of response, time-to-progression, event-free survival, disease control rate, overall survival, and number of eligible subjects reaching autologous or allogeneic transplantation. Safety endpoints include evaluation of adverse event (AE) monitoring,

	physical examinations, vital sign measurements, electrocardiogram variables (if clinically indicated), and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability for the entire study duration. Plasma samples for venetoclax and ibrutinib will be collected to determine trough concentrations. A nonlinear mixed-effects modeling approach may be used to estimate the population central values and the individual values of venetoclax parameters such as clearance. Biospecimens (blood and bone marrow aspirates and/or biopsy) may be collected at specified time points throughout the study for exploratory analyses of known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, or metabolites. These biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. The analyses may include but are not limited to: molecular profiling of T-PLL cells, ex-vivo sensitivity, and minimal residual disease assessments.
Investigators:	Investigator information is on file at AbbVie.
Study Sites:	Approximately 20 sites in 9 countries: Australia, Austria, Finland, France, Germany, Italy, The Netherlands, United Kingdom, and United States.
Study Population and Number of Subjects to be Enrolled:	The patient population consists of subjects with R/R T-PLL. The study will enroll 14 subjects with R/R T-PLL in Stage 1 and up to 23 subjects in Stage 2 with a maximal total of 37 subjects (Stage 1 plus Stage 2). Subjects who are treatment-naïve may be enrolled during Stage 2 of the study. The number of treatment-naïve subjects to be enrolled will depend on the required sample size for the R/R subjects in Stage 2 which is based on the number of responders from Stage 1 and considering the maximum of 37 subjects in total to be enrolled in the study.
Investigational Plan:	This study is an open-label, single-arm, Phase 2, multicenter study evaluating the efficacy of venetoclax plus ibrutinib with an optimal adaptive 2-stage design as follows: • Stage 1: Enroll 14 subjects with R/R T-PLL and move to Stage 2 if 4 or more responders as follows: • response assessment for Stage 1 will be performed on a continued basis until all 14 subjects have enrolled into Stage 1 and have completed the Week 24 disease assessment • Stage 2: Enroll up to an additional 23 subjects Safety will be continuously assessed and dose adjustments will be considered for both venetoclax and ibrutinib. Interim analysis will occur after Stage 1. The study will stop for futility if the number of responders at Stage 1 is ≤ 3. If 4 or more subjects respond prior to enrolling all 14 subjects in Stage 1, enrollment will not pause between stages. The maximal sample size will be 37 subjects. If there are 7 or more responders out of 14 subjects in Stage 1, 17 subjects with R/R T-PLL will be enrolled in Stage 2.
Key Eligibility Criteria:	Male or female subjects, at least 18 years old, with a diagnosis of T-PLL that

	requires treatment and suitable for oral administration of study drugs. Subjects should meet the following disease activity criteria: an Eastern Cooperative Oncology Group performance status ≤ 2. Subjects should have laboratory values meeting the following criteria: • alanine aminotransferase/aspartate aminotransferase ≤ 3 × the upper limit of normal (ULN); • adequate liver function as indicated by a total bilirubin ≤ 1.5 x ULN (subjects with documented Gilbert's syndrome may have bilirubin > 1.5 × ULN); • absolute neutrophil count > 1000/µL; • platelet count > 50,000/µL; • creatinine clearance ≥ 50 mL/minute; and • hemoglobin > 8 g/dL.
Study Drug and Duration of Treatment:	**Ibrutinib** 420 mg will be dosed orally (PO), once daily (QD) starting on Day –1. **Venetoclax** will be initiated on Week 1, Day 1 with an initial 5-day dose ramp-up for venetoclax. Venetoclax 400 mg (target dose) will be dosed PO, QD; an option to increase the dose of venetoclax to 600 mg QD will be available at Week 8 or thereafter if there is evidence of incomplete response and/or if the dose of ibrutinib has been decreased to 280 mg/day or 140 mg/day due to toxicity management. The dose of venetoclax should not be increased to 600 mg/day in subjects with significant venetoclax toxicity. The maximum dose allowed for venetoclax is 600 mg/day. Treatment duration of combination treatment will be as follows: • eligible subjects will proceed to stem cell transplantation after reaching complete remission (CR) (combination therapy will be discontinued but subjects will be followed for disease progression) • 2 years, will be given to subjects who are ineligible for stem cell transplantation unless treatment is intolerable or the subject develops progressive disease For subjects who continue to derive clinical benefit after 2 years of treatment, AbbVie will work with the investigator to consider the potential continuation of therapy, as per local regulations.
Date of Protocol Synopsis:	11 November 2020

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

T-cell prolymphocytic leukemia (T-PLL) is a rare and aggressive T-lymphoid malignancy characterized by proliferation of post-thymic prolymphocytes, usually refractory to current treatment strategies or complicated by relapse and associated with short overall survival. Patients with T-PLL typically experience elevated and exponentially rising lymphocyte counts along with splenomegaly, hepatomegaly, lymphadenopathy, and effusions. Responses to alkylating agents, purine analogs, and polychemotherapy are poor, ranging from 20% to 53% in mostly previously untreated patients with short survival durations. There is very scarce clinical data for the overall response rate (ORR) in the relapsed or refractory (R/R) patient population and the ORR is not expected to be greater than 20%. Therefore, in pretreated patients, responses to non-alemtuzumab therapy are estimated to achieve an ORR of 20%.[1,2,3]

The use of the monoclonal anti-CD52 antibody alemtuzumab has improved response rates of 50% to 75% or even higher (up to 90%) when applied in the first-line setting.[4,5] Based on data available, benefit (if any) from a combination of alemtuzumab with purine analogs or polychemotherapy compared to alemtuzumab alone is unclear. Thus far, alemtuzumab remains the most effective treatment option in patients with T-PLL; however, despite relatively high response rates (50% to 90%), all patients eventually relapse with a median progression-free survival (PFS) of less than 12 months. Allogeneic stem cell transplantation is considered a treatment goal for eligible patients since long survival durations have been observed.

In 2 recent ex vivo drug screening studies, consistent activities of B-cell lymphoma (BCL)-2 inhibition in T-PLL were observed.[6,7] Venetoclax is a potent, selective, and orally bioavailable small molecule inhibitor of BCL-2 that binds with > 1,000-fold higher affinity for BCL-2 (inhibition rate constant [Ki] < 0.010 nM) than for B-cell lymphoma – extra large (BCL-X_L; Ki = 48 nm) or myeloid cell leukemia (MCL)-1 (Ki > 444 nM). Venetoclax (also referred to as ABT-199, A-1195425.0, GDC-0199, RO5537382, Venclexta®, and Venclyxto®) is currently being evaluated for the treatment of patients with chronic lymphocytic leukemia (CLL), small lymphocytic lymphoma (SLL), acute myeloid leukemia (AML), multiple myeloma, and non-Hodgkin's lymphoma (NHL).

Venetoclax is currently approved in the United States (US) for the treatment of patients with CLL or SLL with or without 17p deletion and who have received at least 1 prior therapy. In addition, venetoclax was granted a conditional marketing authorization from the European commission for the following indication: Venclyxto monotherapy is indicated for the treatment of CLL in the presence of 17p deletion or tumor protein p53 (TP53) mutation in adult patients who are unsuitable for or have failed a B-cell receptor inhibitor (BCRi) or in the absence of 17p deletion or TP53 mutation in adult patients who have failed both chemoimmunotherapy and a BCRi. As of July 2018, marketing authorizations have been granted in the US, European Union, Canada, and more than 20 additional countries worldwide.

As proof of principle, the first-in-human treatment using venetoclax in 2 late-stage subjects with T-PLL was reported.[7] Responses were positive; however, potential mechanisms of resistance may develop

through BCL-2 and BCL-X_L induction. Therefore, studies testing venetoclax with appropriate combination partners in subjects with T-PLL are warranted. Ex vivo drug combination studies in primary T-PLL subject samples demonstrated that T-PLL cell-specific synergism of venetoclax was highest with ibrutinib.[8] Ibrutinib (IMBRUVICA®) is a first-in-class, potent, orally administered, covalently binding inhibitor of Bruton's tyrosine kinase (BTK) which was co-developed by Pharmacyclics LLC and Janssen Research & Development LLC for the treatment of patients with B-cell malignancies. Ibrutinib has been approved in many regions globally including the US and European Union for adult patients in one or more of the following indications: CLL/SLL including CLL/SLL with a 17p deletion; mantle cell lymphoma in patients who have received at least 1 prior therapy; Waldenström's macroglobulinemia; marginal zone lymphoma who require systemic therapy and who have received at least 1 prior anti-CD20-based therapy; and chronic graft versus host disease following the failure of 1 or more lines of systemic therapy. For further details, please refer to the IMBRUVICA® (ibrutinib) Investigator's Brochure.[9]

Preliminary clinical response from 1 subject treated with venetoclax in combination with ibrutinib was recently reported at the 23rd Congress of the European Hematology Association;[8] clinical response was demonstrated by significant clinical improvement, significant decrease in spleen size, and improvement in disease-related laboratory values such as leukocytosis, lactate dehydrogenase, and β2 microglobulin (B2M).

Clinical Hypothesis

The combination of venetoclax with ibrutinib can be safely administered and will result in a greater percentage of subjects who achieve a best ORR (complete remission [CR]/CR with incomplete bone marrow recovery [CRi] + partial response [PR]).

In subjects with R/R T-PLL, the treatment with venetoclax plus ibrutinib will be considered promising if the combination yields a best ORR of 40% or greater. A poor rate is defined a best ORR of 20% or less based on the previously available data.

2.2 Benefits and Risks to Subjects

Effective treatment options remain dismal for patients with R/R T-PLL as well as for treatment-naïve patients who have no access or are ineligible to treatment with alemtuzumab. While clinical trials are the recommended treatment option for both treatment-naïve and R/R patients by treatment guidelines (e.g., National Comprehensive Cancer Network [NCCN] guidelines), as of August 2018 there are currently no ongoing interventional clinical studies specific to this rare disease.

The recently reported ex vivo data and very limited subject data provide rationale for a clinical study with the combination of venetoclax and ibrutinib. Clinical data from this same combination target dose regimen has also recently been presented for a different indication (i.e., CLL [CAPTIVATE study]). Early data from 163 subjects show a spectrum of adverse events (AEs) consistent with the historic safety profile of single-agent ibrutinib and single-agent venetoclax with no new safety signals and promising activity (77% undetectable minimal residual disease [MRD] in peripheral blood after 6 months of therapy).[8]

For further details, please see findings from completed studies including safety data in the venetoclax Investigator's Brochure[10] and the ibrutinib Investigator's Brochure.[9]

Considering the coronavirus disease – 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study has been re-evaluated. Based on the limited information to date, no additional risk to study participants is anticipated with the use of venetoclax plus ibrutinib.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

Primary

- To demonstrate the efficacy in subjects with R/R T-PLL treated with venetoclax plus ibrutinib.

Secondary

- To assess safety and tolerability in subjects with T-PLL treated with venetoclax plus ibrutinib.
- To assess the ability of the subset of transplant-naïve subjects to proceed to further autologous/allogeneic stem cell transplantation (assessed by number of eligible subjects reaching transplant).
- To evaluate the PFS, duration of response, time-to-progression, event-free survival, disease control rate, and overall survival.

Exploratory

- To identify biomarker/genetically-defined subgroups regarding response and survival.

3.2 Primary Endpoint

The primary endpoint is the ORR which is defined as the proportion of subjects achieving CR, CRi, or PR as their best overall response (per investigator assessment) in R/R T-PLL subjects based on the T-PLL consensus criteria 2019 (refer to the Operations Manual Section 3.14).[1,11]

3.3 Secondary Endpoints

Key secondary endpoints are as follows:

- PFS, defined as the time from the date of first dose of any study drug to the date of earliest disease progression or death
- duration of response, defined for subjects who achieve a best overall response of CR, CRi, or PR, as the time from the date of first response (CR, CRi, or PR) to the earliest date of disease progression or death
- time-to-progression, defined as the time from the date of first dose of any study drug to the date of earliest disease progression

- event-free survival, defined as the time from the date of first dose of any study drug to the date of earliest disease progression, death, or start of a new anti-T-PLL therapy
- disease control rate, defined as the proportion of subjects achieving CR, CRi, PR, or stable disease as best overall response
- overall survival, defined as the time from the date of first dose of any study drug to death from any cause
- number of eligible subjects reaching autologous or allogeneic transplantation; eligible subjects are the transplant-naïve subjects who have achieved CR

All secondary endpoints will be assessed per investigator assessment in R/R T-PLL subjects based on the T-PLL consensus criteria 2019.[11]

3.4 Safety Endpoints

Safety evaluations include AE monitoring, physical examinations, vital sign measurements, electrocardiogram (ECG) variables (if clinically indicated), and clinical laboratory testing (hematology and chemistry) as measures of safety and tolerability for the entire study duration.

3.5 Pharmacokinetic Endpoints

Plasma samples for venetoclax and ibrutinib will be collected to determine trough concentrations (C_{trough}). A nonlinear mixed-effects modeling approach may be used to estimate the population central values and the individual values of venetoclax parameters such as clearance.

Additional parameters may be estimated if useful in the interpretation of the data.

3.6 Biomarker and Exploratory Research Endpoints

Biospecimens (blood and bone marrow aspirates and/or biopsy) may be collected at specified time points throughout the study for a side study for exploratory analyses of known and/or novel disease-related or drug-related biomarkers. Types of biomarkers may include nucleic acids, proteins, lipids, or metabolites. These biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. The analyses may include but are not limited to: molecular profiling of T-PLL cells, ex-vivo sensitivity, and MRD assessments.

The analyses are exploratory in nature, may be conducted in non-Good Laboratory Practice (GLP) laboratories, and the results from these correlative studies may not be included with the clinical study report. The collection of these biospecimens will be optional and subjects will be asked to sign a separate informed consent form. Further details regarding the biomarker research rationale and collection times are located in the Operations Manual Section 3.17.

The samples may also be used to develop new therapies, research methods, or technologies. In addition, samples from this study may be stored for future use. Samples may then be used to validate

putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This study is an open-label, single-arm, Phase 2, multicenter study evaluating the efficacy of venetoclax plus ibrutinib with an optimal adaptive 2-stage design as follows:

- Stage 1: Enroll 14 subjects with R/R T-PLL and move to Stage 2 if 4 or more responders as follows:
  - response assessment for Stage 1 will be performed on a continued basis until all 14 subjects have enrolled into Stage 1 and have completed the Week 24 disease assessment
- Stage 2: Enroll up to an additional 23 subjects in Stage 2 (up to a total of 37 subjects for Stage 1 and Stage 2).

If a pretreatment bone marrow assessment was performed per standard-of-care prior to the first dose of study drug, the results should be recorded in the electronic case report form (eCRF).

Safety will be continuously assessed and dose adjustments will be considered for both venetoclax and ibrutinib, in accordance with product-specific guidelines (refer to Section 6.2).

Interim analysis will occur after Stage 1. The study will stop for futility if the number of responders at Stage 1 is ≤ 3. If 4 or more subjects respond prior to enrolling all 14 subjects in Stage 1, enrollment will not pause between stages. The maximal sample size will be 37 subjects. If there are 7 or more responders out of 14 subjects in Stage 1, 17 subjects with R/R T-PLL will be enrolled in Stage 2. Details of the adaptive 2-stage design will be provided in the Statistical Analysis Plan (SAP) and Table 6.

Subjects who are treatment-naïve (i.e., unsuitable for alemtuzumab or alemtuzumab treatment is unavailable) may be enrolled during Stage 2 of the study. The number of treatment-naïve subjects to be enrolled will depend on the required sample size for the R/R subjects in Stage 2 which is based on the number of responders from Stage 1 and considering the maximum of 37 subjects in total to be enrolled in the study.

Ibrutinib 420 mg will be dosed orally (PO), once daily (QD) starting on Day –1. Venetoclax will be initiated on Week 1, Day 1 with an initial 5-day dose ramp-up for venetoclax (Figure 1). Venetoclax 400 mg (target dose) will be dosed PO, QD; an option to increase the dose of venetoclax to 600 mg QD will be available at Week 8 or thereafter if there is evidence of incomplete response and/or if the dose of ibrutinib has been decreased to 280 mg/day or 140 mg/day due to toxicity management. The dose of venetoclax should not be increased to 600 mg/day in subjects with significant venetoclax toxicity. The maximum dose allowed for venetoclax is 600 mg/day.

Treatment duration of combination treatment will be as follows:

- eligible subjects will proceed to stem cell transplantation after reaching CR (combination therapy will be discontinued but subjects will be followed for disease progression)
- up to 2 years, will be given to subjects who are ineligible for stem cell transplantation unless treatment is intolerable or the subject develops progressive disease

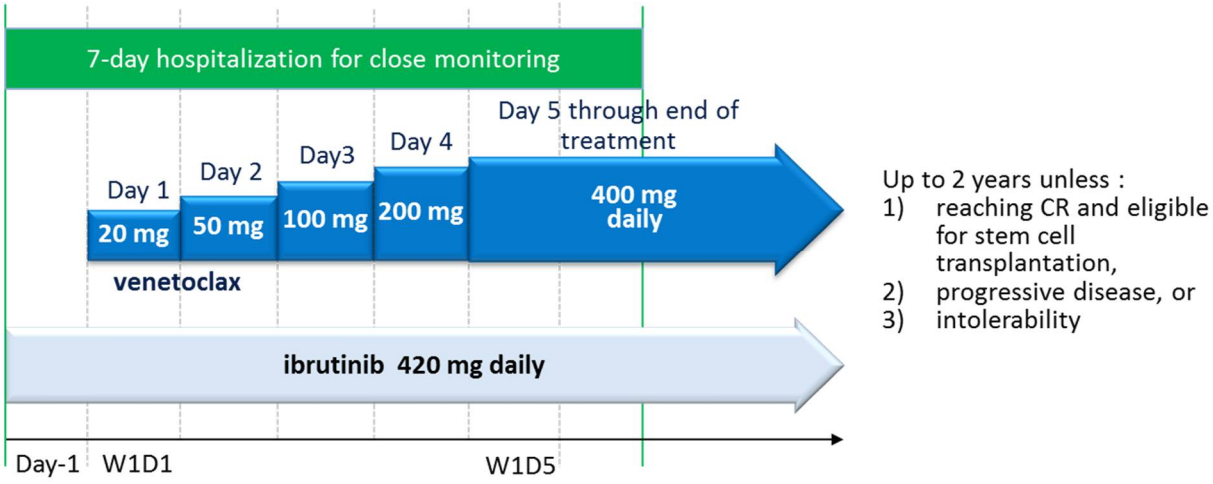
For subjects who continue to derive clinical benefit after 2 years of treatment, AbbVie will work with the investigator to consider the potential continuation of therapy, as per local regulations.

See Section 5 for information regarding eligibility criteria.

The dosing schematic is shown in Figure 1. To mitigate the risk of tumor lysis syndrome (TLS) (see Section 6.2) with venetoclax, a 5-step dose ramp-up with hospitalization for close monitoring and prophylaxis has been developed. Due to the aggressive nature of T-PLL, the venetoclax ramp-up will be administered in a daily manner, starting with 20 mg on Week 1, Day 1 and reaching the target dose of 400 mg on Week 1, Day 5. Refer to Section 6.2 for details for TLS management.

Further information regarding study procedures is located in the Operations Manual Section 3.

Figure 1. Dosing Schematic



CR = complete remission; D = day; W = week

Note: Venetoclax 5-step dose ramp-up in 5 days to target dose of 400 mg daily with an option to increase the dose to 600 mg QD at Week 8 or thereafter if there is evidence of incomplete response and/or if the dose of ibrutinib has been decreased to 280 mg/day or 140 mg/day due to toxicity management.

4.2 Discussion of Study Design

Choice of Control Group

Not applicable.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. All efficacy measurements in this study are standard for assessing disease activity in subjects with T-PLL. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

Subjects with T-PLL have poor survival rates with currently available therapy. Venetoclax (ABT-199) is a potent, selective, and orally bioavailable small molecule inhibitor of BCL-2 and can be safely combined with ibrutinib, a BTK inhibitor. Treatment with this combination may result in potentially meaningful clinical efficacy in this patient population.

Selection of Doses in the Study

The maximum-tolerated dose for venetoclax monotherapy has not been reached, but daily doses up to 800 mg were well tolerated in CLL/SLL and doses up to 1200 mg were tolerated in NHL (Study M12-175). A 400-mg dose of venetoclax was selected as the target dose since this is the approved dose in CLL as monotherapy and was the dose evaluated in combination with ibrutinib at 420 mg in CLL (i.e., CAPTIVATE) and MCL (i.e., AIM) clinical studies which there are supportive efficacy and safety data for this combination. Additionally, a 420-mg dose of ibrutinib was selected as the evaluated dose since this is the approved dose for CLL/SLL, Waldenström's macroglobulinemia, and chronic graft versus host disease. Venetoclax dosing will be introduced at an initial dose of 20 mg and escalated (if no TLS occurs) to the 400-mg target dose over a 5-day dose ramp-up period that occurs during the initial hospitalization.

Ongoing combination trials of venetoclax with either low-dose cytarabine (Studies M14-387 and M16-043) or azacitidine (Studies M14-358 and M15-656) initiated venetoclax at a 100-mg dose and ramp-up over 3 to 4 days to the target dose level. To date, this strategy has been effective at minimizing the risk of clinical TLS with a rate across the AML program of < 1%. The proposed ramp-up period for T-PLL is a more conservative approach to minimize the TLS risk in this indication. If the effective dose is not established in T-PLL at 400 mg, additional escalation of venetoclax dose to 600 mg may be investigated to establish whether escalating doses and exposures improve the subject's clinical response.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study. Anything other than a positive response to the questions below will result in exclusion from study participation.

Consent

- 1. Subjects or their legally authorized representative(if permitted per local regulations) must voluntarily sign and date an informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Adult male or female, at least 18 years old, suitable for oral administration of study drugs.
- 3. Laboratory values meeting the following criteria within the screening period prior to the first dose of study drug:
  - alanine aminotransferase (ALT)/aspartate aminotransferase (AST) ≤ 3 × the upper limit of normal (ULN);
  - adequate liver function as indicated by a total bilirubin ≤ 1.5 × ULN (subjects with documented Gilbert's syndrome may have bilirubin > 1.5 × ULN)
  - absolute neutrophil count (ANC) > 1000/µL (growth factor support is allowed to achieve eligibility criteria);
  - platelet count > 50,000/µL (platelet transfusion is allowed if the cytopenia is due to infiltration of the leukemia in the bone marrow);
  - creatinine clearance (CrCL) ≥ 50 mL/minute (calculated according to the modified formula of Cockcroft and Gault [Men: ([140 – age (years)] × bodyweight [kg])/(72 × creatinine [mg/dL]); Women: (modified Cockcroft and Gault formula) for men × 0.85] or directly measured with a 24-hour urine collection);
  - hemoglobin > 8 g/dL (red blood cell transfusion is allowed if the cytopenia is due to infiltration of the leukemia in the bone marrow).
- 4. Willingness or ability to comply with procedures required in this protocol.

Disease Activity

- 5. Diagnosis of T-PLL that requires treatment because of disease-related constitutional symptoms, symptomatic bone marrow failure, rapidly enlarging lymph nodes, spleen, and liver, increasing lymphocytosis, or extra-nodal involvement.
- 6. Subject meets an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.

Subject History

- 7. No history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.
- 8. No history of or current decompensated cirrhosis including Child-Pugh class B or C, ascites, hepatic encephalopathy, or variceal bleeding.

- 9. No malignancies other than T-PLL that:
  - currently requires systemic therapies;
  - was not previously treated with curative intention (unless the malignant disease is in a stable remission due to the discretion of the treating physician); or
  - has developed signs of progression after curative treatment.
- 10. Negative for human T-cell lymphotropic virus, type 1 (testing only required in endemic countries).
- 11. No prior allogeneic stem cell transplant within 6 months of study drug administration and no requirement for graft versus host therapy.
- 12. No life-threatening illness, medical condition, or organ system dysfunction which, in the investigator's opinion, could compromise the subject's safety, interfere with the absorption or metabolism of ibrutinib capsules, or put the study outcomes at undue risk.
- 13. No history of stroke or intracranial hemorrhage within 6 months prior to enrollment.
- 14. No major surgery within 4 weeks of first dose of study drug.
- 15. No known bleeding disorders (e.g., von Willebrand's disease or hemophilia).
- 16. No currently active, clinically significant cardiovascular disease such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to enrollment.
- 17. No active infection with human immunodeficiency virus (HIV) (i.e., positive for anti-HIV antibody).
- 18. No active infection with hepatitis B virus. Subjects testing positive for hepatitis B surface antigen or hepatitis B core antibody but having undetected viral load (i.e., hepatitis B virus DNA testing negative) at screening may be enrolled.
- 19. No active infection with hepatitis C virus. Subjects testing positive for hepatitis C antibody may only be enrolled if completed curative therapy and polymerase chain reaction are negative for hepatitis C virus RNA at screening.
- 20. No uncontrolled or active infection including severe acute respiratory syndrome (SARS)-coronavirus (CoV)-2 which is confirmed by a local, medically acceptable testing method.
- 21. No history of clinically significant medical conditions or any other reason that the investigator determines would interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug.
- 22. No history of an allergic reaction or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 23. No clinically relevant or significant ECG abnormalities.

Contraception

- 24. A negative serum pregnancy test for all women of childbearing potential at the screening visit and a negative urine pregnancy test at baseline prior to the first dose of study drug.
- 25. If female, subject must be either postmenopausal OR permanently surgically sterile OR, for women of childbearing potential, practicing at least 1 protocol-specified method of birth control that is effective from study Day 1 through at least 30 days after the last dose of venetoclax or 3 months after the last dose of ibrutinib, whichever is later.
- 26. Female who is not pregnant, breastfeeding, or considering becoming pregnant during the study or for approximately 30 days after the last dose of venetoclax or 3 months after the last dose of ibrutinib, whichever is later.
- 27. If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of venetoclax and 90 days after the last dose of ibrutinib, to practice the protocol-specified contraception.
- 28. Male who is not considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of venetoclax and 90 days after the last dose of ibrutinib.

Concomitant Medications

- 29. Subject must have received prior alemtuzumab (unless unsuitable or unavailable).
- 30. Subject must not have been previously treated with a BCL-2 inhibitor.
- 31. Subject must not have been treated with any of the following within 14 days or 5 half-lives of the drug (whichever is shortest) prior to the first dose of ibrutinib or venetoclax and through the last dose of study drug, or has not recovered to < Grade 2 clinically significant adverse effect(s)/toxicity(s) of the previous therapy:
  - any anticancer therapy including chemotherapy or radiotherapy
  - investigational therapy, including targeted small molecule agents
- 32. Subject must not have received the following within 7 days prior to the first dose of ibrutinib or venetoclax through the last dose of any study drug:
  - steroid therapy for antineoplastic treatment
  - other chronic immunosuppressants (e.g., for immune thrombocytopenia or autoimmune hemolytic anemia)
  - warfarin or other vitamin K antagonists
- 33. Subject must not have received biologic agents (e.g., monoclonal antibodies) for antineoplastic treatment within 30 days prior to first dose of ibrutinib or venetoclax and through the last dose of study drug.
- 34. Subject must not have systemically used known moderate or strong cytochrome P450 (CYP)3A inhibitors or inducers within 7 days prior to the first dose of ibrutinib or venetoclax.

- 35. Subject must not have received any live or attenuated live vaccine within 28 days prior to the first dose of ibrutinib or venetoclax. Seasonal flu vaccines that do not contain a live virus are permitted.
- 36. Subject must not have consumed grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges), or starfruit within 3 days before the first dose of study drug administration and through the last dose of study drug.
- 37. Subject must not anticipate the use of prohibited medications or foods during study participation (see Section 5.3 for additional prohibited medications or foods).

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Nonchildbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of nonchildbearing potential due to meeting any of the following criteria:

  - postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause;
  - postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone level > 40 IU/L; or
  - permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy).

- Females, Childbearing Potential

  Females of childbearing potential must avoid pregnancy while taking study drugs and for at least 30 days after the last dose of venetoclax or 3 months after the last dose of ibrutinib, whichever is later. Females must commit to one of the following methods of birth control:

  - combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline (Day 1). Also, a barrier method must be used during this study from initial study drug administration to 30 days after the last dose of venetoclax or 3 months after the last dose of ibrutinib, whichever is later, as drug-drug interaction with venetoclax or ibrutinib upon the hormonal contraception is unknown;
  - progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 30 days prior to study baseline (Day 1). Also, a barrier method must be used during this study from initial study drug administration to 30 days after the last dose of venetoclax or 3 months after the last dose of ibrutinib, whichever is later, as drug-drug interaction with venetoclax or ibrutinib upon the hormonal contraception is unknown;

- bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure);
- intrauterine device;
- intrauterine hormone-releasing system;
- vasectomized partner (provided the partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject); or
- true abstinence, defined as refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] and withdrawal are not acceptable).

Contraception recommendations related to use of concomitant therapies prescribed should be based on the local label. If required per local practices, one of the following should be used in addition to one of the birth control methods listed above (excluding true abstinence):

- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action, initiated at least 30 days prior to Study Day 1;
- male or female condom with or without spermicide;
- cap, diaphragm, or sponge with spermicide; or
- a combination of male condom with either cap, diaphragm, or sponge with spermicide (double-barrier method).

Contraception Requirements for Males

Male subjects who are sexually active with a woman of childbearing potential must agree **to use condoms**, even if the male subject has undergone a successful vasectomy, from Study Day 1 through at least 30 days after the last dose of venetoclax and at least 90 days after the last dose of ibrutinib. His female partner(s) must also use at least one of the following methods of birth control:

- combined (estrogen- and progestogen-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 30 days prior to study Day 1
- progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month prior to study Day 1
- bilateral tubal occlusion/ligation (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure)
- intrauterine device
- intrauterine hormone-releasing system

5.3 Prohibited Medications and Therapy

In addition to the medications and therapy listed in the eligibility criteria (concomitant medications section), the following medications are prohibited throughout the study:

- warfarin and coumarin derivatives

The following are prohibited during ibrutinib initiation and venetoclax dose ramp-up (refer to the Operations Manual Section 3.6):

- strong CYP3A inhibitors

Live vaccination is prohibited during study participation. Live vaccination can only be administered at least 4 weeks after the last dose of study drug and only after B-cell or absolute lymphocyte count (ALC) recovery.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject is receiving at the time of enrollment or receives during the study must be recorded through the post-treatment visit (30-day follow-up visit) (refer to the Operations Manual Section 3.6).

Short courses (≤ 14 days) of steroid treatment for noncancer-related medical reasons (e.g., joint inflammation, asthma exacerbation, rash, antiemetic use, and infusion reactions) at doses that are clinically indicated are permitted.

Any questions regarding concomitant or prior therapy should be raised to the AbbVie emergency contact.

The following medications are allowed to use with caution **after** completion of the venetoclax dose ramp-up if no appropriate therapeutic alternative exists (additional guidance noted):

- strong CYP3A inhibitors (dose reductions for both venetoclax and ibrutinib)

The following **cautionary** medications include (if necessary, additional guidance noted):

- moderate CYP3A inhibitors (requires venetoclax and ibrutinib dose reductions)
- strong and moderate CYP3A inducers (avoid)
- P-glycoprotein (P-gp) substrates
- breast cancer resistance protein substrates/inhibitors
- organic anion-transporting polypeptide (OATP)1B1/1B3 substrates
- P-gp inhibitors

- supplements such as fish oil and vitamin E
- other anticoagulants or medications that inhibit platelet function (warfarin and coumarin derivatives prohibited)

Co-administration of a strong or moderate CYP3A inhibitor requires a specified venetoclax and ibrutinib dose adjustment as presented in Table 1. After discussion with the investigator and AbbVie Therapeutic Area Medical Director (TA MD), co-administration of a strong CYP3A inhibitor with ibrutinib may be allowed.

Table 1. Dose Modifications for Venetoclax and Ibrutinib: Moderate and Strong CYP3A Inhibitor Use

Drug	Dose if No Moderate or Strong CYP3A Inhibitor	Dose if Co-Administered with a Moderate CYP3A Inhibitor	Dose if Co-Administered with a Strong CYP3A Inhibitor[a]
Venetoclax	20 mg	10 mg	--[b]
	50 mg	20 mg	--[b]
	100 mg	50 mg	--[b]
	200 mg	100 mg	--[b]
	400 mg	200 mg	100 mg
	600 mg	300 mg	150 mg
Ibrutinib	420 mg	140 mg	Withhold for duration of inhibitor use or reduce to 140 mg

CYP = cytochrome P450

a. Further dose reductions may be required.

b. Strong CYP3A inhibitors are prohibited during initial ramp-up.

Note: Refer to Section 4.1 for venetoclax ramp-up and target doses.

Moderate and strong CYP3A inhibitors and inducers should only be used when no appropriate therapeutic alternative exists.

Consult the Operations Manual Appendix B for specific examples of prohibited and cautionary medications that fall into these categories. Additional information regarding prohibited and cautionary medications is summarized in the Operations Manual Section 3.6.

5.5 Withdrawal of Subjects and Discontinuation of Study

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

- clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie TA MD;
- investigator's opinion that discontinuation is in the best interest of the subject;

- subject requests withdrawal from the study;
- eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk;
- introduction of prohibited medications or dosages and continuation of the study drug would place the subject at risk;
- subject becomes pregnant while on study drug;
- subject's response to therapy is unsatisfactory as evidenced by progression of disease while on study drug;
- subject requires radiotherapy, cancer-related surgery as a result of tumor progression, or alternate antineoplastic agents during the study period;
- subject is significantly noncompliant with study procedures which would put the subject at risk for continued participation in the trial.

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

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

COVID-19 Pandemic-Related Acceptable Protocol Modification

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix I.

The investigator should contact the sponsor TA MD before discontinuing a subject from the study for a reason other than "planned per protocol" to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix I for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the study drug dosing period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie TA MD along with the possibility of premature discontinuation from the study drug dosing period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

5.6 Follow-Up for Subject Withdrawal from Study

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

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the final visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure all treatment-emergent AEs/serious adverse events (SAEs) have been resolved.

5.7 Study Drug

Venetoclax manufactured by AbbVie will be administered PO, QD beginning on Week 1, Day 1 and should be taken at approximately the same time each day. Subjects will be trained to self-administer venetoclax (refer to Operations Manual Section 6.1).

Ibrutinib 420 mg will be administered PO, QD starting on Day –1 and should be taken around the same time each day. Subjects will be trained to self-administer ibrutinib (refer to Operations Manual Section 6.1).

Venetoclax and ibrutinib should be taken approximately at the same time with a meal and water, within 30 minutes after the completion of breakfast or the subject's first meal of the day.

If vomiting occurs after taking venetoclax or ibrutinib, no additional dose should be taken that day. In cases where a dose of venetoclax or ibrutinib is missed or forgotten, the subject should take the forgotten dose as soon as possible, provided that the dose is taken within 8 hours of the missed dose and is taken with 240 mL of water and food. Otherwise, the missed dose should not be taken and the subject should take the next dose at the next scheduled dosing time.

Subject dosing will be recorded in a subject dosing diary. The subject will be instructed to return all drug containers (even if empty) to the study site personnel at each study visit. The study site personnel will document compliance.

AbbVie will supply drug for venetoclax and ibrutinib. Study drug provided by AbbVie should not be substituted or alternately sourced unless otherwise directed by AbbVie. Noninvestigational medicinal product (standard-of-care) must be obtained commercially. If a subject is unable to come to the study

site to pick up their study drug due to COVID-19, a direct-to-patient (DTP) study drug shipment can be made from the study site to the subject if allowed by local regulations. AbbVie will submit any required notifications to the regulatory authority as applicable. Refer to the Operations Manual in Appendix I for details on DTP shipment of study drug.

Study drug information is presented in Table 2.

Table 2. Study Drug Information

Investigational Product	Mode of Administration	Dosage Form	Strength
Venetoclax	Oral	Film-coated tablet	100, 50, and 10 mg
Ibrutinib	Oral	Hard capsule	140 mg

Venetoclax will be packaged in blisters or bottles with quantities sufficient to accommodate study design. Ibrutinib will be packaged in bottles with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects. Study drug will only be used for the conduct of this study.

5.8 Randomization/Drug Assignment

This is an open-label, single-arm study. There is no randomization for this study. All subjects will be assigned a unique identification number by the IRT at the screening visit (refer to the Operations Manual Section 6.3).

5.9 Protocol Deviations

The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. Protocol deviations are prohibited except when necessary to eliminate an immediate hazard to study subjects. If a protocol deviation occurs (or is identified including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB regulatory authorities (as applicable) and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or

performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

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

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

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

Medical Complaints/Adverse Events and Serious Adverse Events

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

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations," such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all which must be reported whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE should be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study, necessitate therapeutic medical intervention, meets protocol-specific criteria (see Section 6.2 regarding toxicity management), and/or if the investigator considers them to be AEs.

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

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

If an AE, whether associated with study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (as appropriate) as an SAE within 24 hours of the site being made aware of the SAE (refer to the Operations Manual Section 4.3 for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, protocol-related SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for a Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in an SAE as defined above.
SUSAR	A suspected SAR: refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is not listed in the applicable Reference Safety Information, and meets one of the above serious criteria. All individually reported SARs are considered suspected.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

AEs will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

The following AEs of special interest will be monitored during the study:

- TLS
- major hemorrhage
- neutropenia

Adverse Event Severity and Relationship to Study Drug

The investigators will rate the severity of each AE according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. If a reported AE increases in severity, the initial AE should be given an outcome date and a new AE must be reported on a different onset date than the end date of the previous AE to reflect the change in severity. The dates on the AEs cannot overlap. For all reported SAEs that increase in severity, the supplemental eCRFs also need to be updated to reflect any changes due to the increase in severity.

For AEs not captured by the NCI CTCAE, the following should be used:

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

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

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

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

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 1 working day after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject or in the partner of a study subject, information regarding the pregnancy and the outcome will be collected.

In the event of pregnancy occurring in a subject's partner during the study, written informed consent from the partner must be obtained prior to collection of any such information. AbbVie will provide a separate consent form for this purpose. Pregnancy in a subject's partners will be collected from the date of the first dose through 30 days following the last dose of study drug.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered an SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

6.2 Toxicity Management

The management of specific AEs and laboratory parameters is described below. This includes AEs of TLS, major hemorrhage, and neutropenia for venetoclax and known potential risks associated with ibrutinib.

Tumor lysis syndrome: There is a potential for TLS in subjects affected by hematologic malignancies. Depending on the specific tumor type, risk factors may include one or more of the following: bulky disease or high tumor burden, renal insufficiency, splenomegaly, elevated pretreatment lactate dehydrogenase levels, elevated leukocyte count, and dehydration.

Venetoclax can cause rapid reduction in tumor and thus poses a risk for TLS. Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6 to 8 hours following the first dose of venetoclax (Appendix E). Potassium increases can be life-threatening and should be treated as an emergency. Definitions of laboratory TLS and clinical TLS are provided in the Appendix D (Howard grading classification). Due to the short dose ramp-up used in this study, all subjects will be managed as high risk for TLS. If a subject experiences blood chemistry changes suggestive of TLS, the dose of venetoclax should be withheld and reductions may be required (Appendix F).

Major hemorrhage: Fatal bleeding events have occurred in patients treated with ibrutinib. A major hemorrhage is any hemorrhagic AE of Grade 3 or higher; any SAE of bleeding of any grade; or any

central nervous system hemorrhage/hematoma of any grade. All hemorrhagic AEs requiring a transfusion of red blood cells should be reported as a Grade 3 or higher per NCI-CTCAE. Ibrutinib may be withheld and/or reductions may be required.

Neutropenia: Venetoclax may cause neutropenia. Subjects with a history of neutropenia who have received multiple prior therapies and/or have significant bone marrow involvement may be at a particularly high risk. Grade 3 or 4 neutropenia has been reported in subjects treated with venetoclax. Subjects will be managed for neutropenia as detailed below.

Known potential risks associated with ibrutinib are listed below, and treatment may be discontinued or adjusted in response to occurrence of these events, as appropriate. Please refer to the ibrutinib Investigator's Brochure[9] for additional information on potential risks for ibrutinib.

- hemorrhage, infections, cytopenias, cardiac arrhythmias, hypertension, second primary malignancies, and TLS

Subjects will be monitored for these events throughout the study and treatment may be discontinued or adjusted as appropriate.

Prophylaxis and Management of Tumor Lysis Syndrome

The risk of TLS is a continuum based on multiple factors including tumor burden, CrCL, and other comorbidities. Subjects with high tumor burden (e.g., any lymph node with a diameter > 5 cm or ALC > 25×10^9/L) are at greater risk of TLS when initiating venetoclax. Reduced renal function (CrCL < 80 mL/min) further increases the risk. The risk may decrease as tumor burden decreases with venetoclax treatment. Tumor burden categories are provided in Table 3.

Prior to initiating venetoclax, tumor burden assessment, including radiographic evaluation (e.g., CT scan), should be performed for all subjects during screening. In addition, blood chemistry (potassium, calcium, phosphorus, uric acid, and creatinine) assessments should be performed in all subjects at screening with correction of pre-existing abnormalities.

Table 3. Tumor Burden Categories

Tumor Burden Category	Criteria
Low	• All measurable lymph nodes with the largest diameter < 5 cm AND ALC < 25×10^9/L
Medium	• Any measurable lymph node with the largest diameter ≥ 5 cm and < 10 cm OR ALC ≥ 25×10^9/L
High	• Any measurable lymph node with the largest diameter ≥ 10 cm OR ALC ≥ 25×10^9/L AND any measurable lymph node with the largest diameter ≥ 5 cm but < 10 cm

ALC = absolute lymphocyte count

All subjects will be hospitalized for close monitoring and prophylaxis during the venetoclax dose ramp-up, starting 1 day prior to venetoclax initiation until 1 day after reaching target dose of venetoclax (400 mg QD).

All TLS prophylaxis measures should be appropriately recorded in the eCRF.

Hydration: All subjects, regardless of risk for TLS, should be adequately hydrated before starting treatment with venetoclax and during the dose ramp-up phase. The recommended volume is 1.5 to 2.0 L (approximately 6 to 8 glasses) of water each day. Subjects should be instructed to drink water at least 48 hours before and on the day of the first dose. Intravenous (IV) fluids should be administered (i.e., 150 – 200 mL/hour) daily, as tolerated, during the hospitalization period.

Antihyperuricemic agents: Oral uric acid-reducing agent (allopurinol except if contraindicated) should be administered 72 hours before first venetoclax dose to all subjects; rasburicase should be considered prophylactically if the subject's baseline uric acid is elevated, unless contraindicated.

Blood chemistry monitoring: Chemistry and hematology laboratory tests are to be performed upon admission the night before the first dose of venetoclax. The investigator's decision to proceed with venetoclax treatment initiation will be based on these laboratory values. Laboratory monitoring for TLS is to occur at time 0 (predose, within 4 hours before venetoclax administration) and 4, 8, 12, and 24 hours after each dose escalation (including the optional increase to 600 mg at Week 8 or thereafter) on real time (turnaround < 2 hours). A dose increase must not be allowed until the subject's 24-hour laboratory test results have been reviewed by investigator. Results from time 0 (predose) laboratory values will be collected and used as baseline to assess potential electrolyte abnormalities occurring after venetoclax administration. Results from time 0 (predose) on Day 1 are not required to be available prior to initiating venetoclax treatment.

Nephrology consultation: Nephrology (or other acute dialysis service) consultation should be considered upon admission per institutional standards at the investigators' discretion to ensure emergency dialysis is available and the appropriate staff is aware and prepared to handle any necessary intervention for TLS. Telemetry should also be considered.

In case of evidence of TLS, dosing with venetoclax should be interrupted and/or reduced (refer to Appendix F). Drug interruption for up to 72 hours following transient (i.e., lasting < 48 hours) chemical changes and laboratory TLS will not require a dose reduction. If the TLS has not resolved within 72 hours, then a dose reduction should be considered. The subject may be allowed to re-escalate to the final dose based on a risk assessment (including tumor burden status) after discussion between the investigator and the TA MD. If active correction of electrolytes was performed, the first dose of venetoclax should only be given when electrolytes have been stable without additional treatment for at least 24 hours. For subjects who have had a dosing interruption lasting more than 1 week during the ramp-up or more than 2 weeks when subjects are receiving the daily dose of 400/600 mg, TLS risk should be reassessed to determine if restarting at a reduced dose is necessary (e.g., all or some levels of the dose titration).

Management of Treatment-Related Neutropenia

Complete blood counts should be monitored throughout the treatment period. Dose interruptions are required and dose reductions might be needed for subjects with severe neutropenia. Supportive measures including antimicrobials for any signs of infection and prophylactic use of growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) should be considered (refer to Appendix F).

Prophylaxis for Infection

Anti-infective prophylaxis for viral (e.g., acyclovir, zelitrex, or similar agent) and/or bacterial (e.g., trimethoprim-sulfamethoxazole and either levofloxacin or amoxicillin-clavulanate or similar agents

and pneumococcal vaccination) infections is required for all subjects with ANC of < 500/µL at any time point. Institutional infectious organisms and their drug resistance patterns should primarily be considered and the choice of these agents should be based on regional guidelines or institutional standards. The investigator should confirm that the prophylaxis agent(s) can be safely administered with study drugs. Some medications may require dose adjustments due to the potential for drug-drug interactions. Refer to Table 4 and Table 5 for implementing dose modifications for venetoclax + ibrutinib as necessary.

Management of Infection

Management of treatment-emergent infections is the responsibility of the investigator. Institutional infectious organisms and their drug resistance patterns should primarily be considered and the choice of agents to treat these infections should be based on regional guidelines or institutional standards. The investigator should confirm that a concomitant medication/supplement can be safely administered with study drugs. Some medications may require dose adjustments due to the potential for drug-drug interactions. Refer to Table 4 and Table 5 for implementing dose modifications for venetoclax + ibrutinib as necessary.

Management of Major Hemorrhage

Fatal bleeding events have occurred in subjects treated with ibrutinib. For all hemorrhagic AEs, a transfusion of red blood cells may be required and ibrutinib may be withheld and/or reductions may be required.

Guidelines for Management with Antiplatelet Agents and Anticoagulants

Warfarin or vitamin K antagonists should not be administered concomitantly with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided. Use ibrutinib with caution in subjects requiring other anticoagulants or medications that inhibit platelet function. Subjects with congenital bleeding diathesis have not been studied. Subjects requiring the initiation of therapeutic anticoagulation therapy (e.g., atrial fibrillation) should consider the risks and benefits of continuing ibrutinib treatment. If therapeutic anticoagulation is clinically indicated, treatment with ibrutinib should be held and not be restarted until the subject is clinically stable and has no signs of bleeding. Subjects should be observed closely for signs and symptoms of bleeding. No dose reduction is required when study drug is restarted.

In a drug-drug interaction study in healthy subjects, administration of a single dose of venetoclax with warfarin resulted in an 18% to 28% increase in observed maximum concentration (C_{max}) and area under the concentration versus time curve from time 0 to infinite time ($AUC_{0\text{-}inf}$) of R-warfarin and S-warfarin. Because venetoclax was not dosed to steady state, the international normalized ratio is recommended to be monitored closely in subjects receiving warfarin.

Guidelines for Ibrutinib Management with Surgeries or Procedures

Ibrutinib may increase risk of bleeding with invasive procedures or surgery. The following guidance should be applied to the use of ibrutinib in the perioperative period for subjects who require surgical intervention or an invasive procedure while receiving ibrutinib:

- Minor Surgical Procedures: For minor procedures (such as a central line placement, needle biopsy, lumbar puncture [other than shunt reservoir access], thoracentesis, or paracentesis) ibrutinib should be held for at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to hold ibrutinib.
- Major Surgical Procedures: For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be held at least 7 days prior to the intervention and should be held at least 7 days after the procedure and restarted at the discretion of the investigator when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes.
- Emergency Procedures: For emergency procedures, ibrutinib should be held as soon as possible and until the surgical site is reasonably healed or for at least 7 days after the urgent surgical procedure, whichever is longer.

Management of Treatment-Related Hematologic Toxicities Other Than Neutropenia or Lymphopenia

Treatment should be withheld for any Grade 4 hematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), treatment may be restarted (Appendix F). If the toxicity recurs, the dose reduction guidelines outlined in Table 4 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the investigator.

Management of Treatment-Related Nonhematologic Toxicity

Treatment should be withheld for any clinically relevant ≥ Grade 3 nonhematologic toxicity. Once the toxicity has resolved to Grade 1 or baseline level (recovery), treatment may be restarted (Appendix F). If the toxicity recurs, the dose reduction guidelines outlined in Table 4 should be followed when resuming study treatment following resolution. Additional dose reductions may occur at the discretion of the investigator.

Management of Decrease in Spermatogenesis

Venetoclax may cause a decrease in spermatogenesis. Male subjects considering preservation of fertility should bank sperm before initiating treatment with venetoclax.

Dose Modifications Based on Toxicities

Subjects who discontinue 1 study drug because of study drug-related toxicities may continue to receive the other study drug per the discretion of the investigator.

Dose Interruptions and Modifications for Venetoclax

See Appendix F for dose modifications for toxicities related to venetoclax and Table 4 for recommendations for re-initiating venetoclax treatment after interruption. If venetoclax dose interruption is > 4 weeks, the TA MD should be consulted.

Dose modifications for possible drug-drug interactions are provided in Section 5.4.

Table 4. Dose Modification for Toxicity During Venetoclax Treatment

Dose at Interruption (mg/day)	Restart Dose (mg/day)[a]
600	400
400	300
300	200
200	100
100	50
50	20
20	10

a. If patient is not hospitalized for close monitoring, continue the reduced dose for 1 week before increasing the dose.

Dose Interruptions and Modifications for Ibrutinib

Treatment with ibrutinib should be temporarily stopped for unmanageable, potentially ibrutinib-related toxicity that is Grade ≥ 3 in severity. Ibrutinib may be temporarily stopped for a maximum of 28 consecutive days. Ibrutinib should be discontinued permanently in the event of a toxicity lasting more than 28 days unless continued treatment is approved by the sponsor.

The dose of ibrutinib must be modified according to the dose modification guidance in Table 5 and Appendix F if any of the following potentially drug-related toxicities occur:

- Grade 3 or higher neutropenia with infection or fever
- ANC < 500/µL
- platelets < 50,000/µL in the presence of clinically significant bleeding (Grade ≥ 2)
- platelets < 25,000/µL
- Grade 3 nausea or Grade 3 or 4 vomiting or diarrhea if persistent despite optimal antiemetic or antidiarrheal therapy
- any other Grade 4 or unmanageable Grade 3 toxicity

If the dose of ibrutinib is reduced, the dose of ibrutinib may be re-escalated at the investigator's discretion in the absence of a recurrence of the toxicity that led to the reduction. No dose escalation of ibrutinib above 420 mg is allowed in this study. Dose changes must be recorded in the dose administration eCRF.

Table 5. Ibrutinib Dose Reduction Levels

Starting Dose Level	420 mg
Dose reduction Level 1	280 mg
Dose reduction Level 2	140 mg
Dose reduction Level 3	Discontinue

For dose modification during concomitant treatment with CYP3A inhibitors, refer to Table 1.

During combination dosing with venetoclax, the decision to dose modify a study drug due to a toxicity will be based on the investigator attribution of relatedness to a given drug. For example, if an AE occurs and is considered related to venetoclax but not ibrutinib, the dose of venetoclax should be modified while ibrutinib should remain the same. If the AE is considered potentially related to both drugs, adjusting the dose of venetoclax before ibrutinib is the recommended first action, taking into consideration the possibility of higher systemic exposure of venetoclax when administered in combination with ibrutinib. For cases where the investigator is uncertain of what action to take, the TA MD may be contacted for further discussion.

If ibrutinib is discontinued for toxicity, then treatment with venetoclax may be continued.

Please consult the ibrutinib Investigator's Brochure[9] for more details regarding management of known risks of the drug and/or discontinuation (permanent or temporary).

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the SAP. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA) under the UNIX operation system.

An interim efficacy analysis will be performed when Stage 1 subjects have completed the Week 24 disease assessments in R/R T-PLL subjects.

The primary efficacy analysis will be performed for Stage 1 and Stage 2 subjects after their completion of the Week 24 disease assessments in R/R T-PLL subjects.

The final analysis will be performed when all subjects have discontinued the study or have completed protocol defined follow-up time, whichever is later.

7.2 Determination of Sample Size

Approximately 37 subjects will be enrolled based on the optimal adaptive 2-stage design.[12] The adaptive 2-stage design is presented in the Table 6 below and details will be provided in the SAP.

Table 6. Sample Size Using Optimal Adaptive 2-Stage Design

H_0: $p \leq 20\%$ versus H_1: $p \geq 40\%$ $1-\beta = 80\%$, 1-sided test, significance level = 0.05				Comments
$n_1 = 14$				
S	**$n_2(S)$**	**n(S)**	**r(S)**	
≤ 3	0	14	0	Stop for futility after Stage 1
4	23	37	11	R/R versus treatment-naïve Stage 2 sample size distribution will vary depending on the number of responses from Stage 1
5	20	34	10	
6	20	34	10	
≥ 7[a]	17	31	9	

CR = complete remission; CRi = CR with incomplete bone marrow recovery; PR = partial response; R/R = relapsed or refractory

p: probability of achieving a response (CR, CRi, or PR).

Power: $1-\beta = 80\%$.

Significance level: 10% (2-sided).

n_1: Sample size for Stage 1.

S: Number of responses from Stage 1.

$n_2(S)$: R/R sample size for Stage 2.

n(S): Total R/R sample size of Stage 1 and Stage2.

r(S): Critical value of total number of responses from Stage 1 and Stage 2 to demonstrate efficacy. "Critical value" is the threshold beyond which the null hypothesis is rejected (i.e., claiming efficacy). For example, the test is statistically significant if the number of responders is at least 12 with a sample size of 37 subjects.

a. The Stage 2 portion will still be conducted to evaluate efficacy in additional subjects even if the Stage 1 portion shows significant efficacy.

7.3 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all R/R T-PLL subjects who received at least 1 dose of study drug. The FAS will be used for all safety, pharmacokinetic, efficacy and baseline analyses. The analyses for the treatment-naïve subjects will be included in the SAP.

7.4 Statistical Analyses for Efficacy

The primary efficacy endpoint will be the ORR, defined as the proportion of subjects achieving CR, CRi, or PR as their best overall response in R/R T-PLL subjects as per investigator based on the T-PLL consensus criteria 2019.[11] The best overall response of CR/CRi/PR will be defined as achieving CR, CRi, and PR at any point during the study (CR/CRi will need confirmation assessment based on the T-PLL consensus criteria 2019).[11] The estimate and 90% confidence interval for ORR based on binomial distribution will be constructed. Subjects who have not achieved any component of ORR will be considered as nonresponders in the calculation of ORR at the time of analysis.

The secondary efficacy analysis will be based on the following endpoints: PFS, duration of response, time-to-progression, event-free survival, disease control rate, overall survival, and number of eligible subjects reaching autologous or allogeneic transplantation. All secondary endpoints will be assessed per investigator assessment in R/R T-PLL subjects based on the T-PLL consensus criteria 2019.[11]

Time-to-event endpoints will be analyzed using Kaplan-Meier methodology. Median time-to-event and the corresponding 95% CI will be provided. Binary endpoints will be analyzed using binomial distribution and estimate of proportion along with 95% confidence interval will be provided.

Details on the primary and other efficacy analyses are provided in the SAP.

7.5 Statistical Analyses for Safety

The safety and tolerability will be assessed by evaluation of study drug exposure, AEs, SAEs, and deaths as well as changes in laboratory measurements, physical examinations, and vital sign parameters.

Statistical analyses for safety are described and fully documented in the SAP.

7.6 Interim Analysis

An interim analysis for efficacy and safety will be conducted after all subjects enrolled in Stage 1 have completed the Week 24 disease assessment for the purpose of submission. The study will stop for futility if the numbers of responses at Stage 1 is ≤ 3.

Details pertaining to the interim analyses can be found in the SAP.

A Steering Committee composed of a group of investigators who are participating in this study and who are experts in the management of T-PLL and an internal specialist in infectious diseases who is not currently involved in the conduct or oversight of Study M18-803 will review efficacy, safety, and exploratory research throughout the study.

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

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

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation (ICH) guidelines, applicable regulations, and guidelines governing clinical study

conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts or virtual site visits), alternative locations for data collection (e.g., use of a local laboratory instead of a central laboratory), and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

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

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

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

12 REFERENCES

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2. Jain P, Aoki E, Keating M, et al. Characteristics, outcomes, prognostic factors and treatment of patients with T-cell prolymphocytic leukemia (T-PLL). Annals Oncol. 2017;28(7):1554-9.
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7. Boidol B, Kornauth C, van der Kouwe E, et al. First-in-human response of BCL-2 inhibitor venetoclax in T-cell prolymphocytic leukemia. Blood. 2017;130(23):2499-503.
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9. Pharmacyclics. Imbruvica (ibrutinib) Investigator's Brochure. Current version.
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11. Staber PB, Herling M, Bellido M, et al. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. Blood. 2019;134(14):1132-43.
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APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
$AUC_{0\text{-}inf}$	area under the concentration versus time curve from time 0 to infinite time
B2M	β2 microglobulin
BCL	B-cell lymphoma
BCL-X_L	B-cell lymphoma – extra large
BCRi	B-cell receptor inhibitor
BTK	Bruton's tyrosine kinase
CLL	chronic lymphocytic leukemia
C_{max}	observed maximum concentration
CoV	coronavirus
COVID-19	coronavirus disease – 2019
CR	complete remission
CrCL	creatinine clearance
CRi	complete remission with incomplete bone marrow recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	trough concentrations
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DTP	direct-to-patient
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FAS	Full Analysis Set
GCP	Good Clinical Practice

G-CSF	granulocyte-colony stimulating factor
GLP	Good Laboratory Practice
HIV	human immunodeficiency virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
IV	intravenous
K_i	inhibition rate constant
MCL	myeloid cell leukemia
MRD	minimal residual disease
NCI	National Cancer Institute
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
OATP	organic anion-transporting polypeptide
ORR	overall response rate
PFS	progression-free survival
P-gp	P-glycoprotein
PO	oral
PR	partial response
QD	once daily
RNA	ribonucleic acid
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SARS	severe acute respiratory syndrome
SLL	small lymphocytic lymphoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TLS	tumor lysis syndrome
TP53	tumor protein p53
T-PLL	T-cell prolymphocytic leukemia
ULN	upper limit of normal
US	United States

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M18-803: A Prospective, Open-Label, Single-Arm, Phase 2, Multicenter Study Evaluating the Efficacy of Venetoclax Plus Ibrutinib in Subjects with T-Cell Prolymphocytic Leukemia

Protocol Date: 11 November 2020

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

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and operations manual, and making changes to a protocol only after notifying AbbVie and the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC), except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]	Study Project Manager	Clinical Program Development
[redacted]	Senior Manager	Medical Writing
[redacted]	Assistant Medical Director	Global Medical Affairs
[redacted]	Head of Statistics, Oncology	Statistical Science
[redacted]	Director	Clinical Pharmacology and Pharmacometrics

APPENDIX D. DEFINITIONS OF LABORATORY AND CLINICAL TUMOR LYSIS SYNDROME

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid > 8.0 mg/dL (475.8 µmol/L) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L) in adults or > 6.5 mg/dL (2.1 mmol/L) in children	
Hyperkalemia	Potassium > 6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium < 7.0 mg/dL (1.75 mmol/L) or ionized calcium < 1.12 mg/dL (0.3 mmol/L)[a]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury[b]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or a single value > 1.5 × the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output < 0.5 mL/kg/hr for 6 hrs

a. The corrected calcium level in mg/dL = measured calcium level in mg/dL + 0.8 × (4-albumin in g/dL).

b. Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg/dL (26.5 µmol/L) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the subject has clinical tumor lysis syndrome.

Note: In laboratory tumor lysis syndrome, 2 or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

Source: Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. N Engl J Med. 2011;364(19):1844-54.

APPENDIX E. RECOMMENDATIONS FOR INITIAL MANAGEMENT OF ELECTROLYTE ABNORMALITIES AND PREVENTION OF TUMOR LYSIS SYNDROME

Abnormality	Management Recommendations
Hyperkalemia (Including Rapidly Rising Potassium)	
Potassium ≥ 0.5 mmol/L increase from prior value (even if potassium within normal limits [WNL])	• Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. If further ≥ 0.2 mmol/L increase in potassium, but still < upper limit of normal (ULN), manage as per potassium ≥ ULN. Otherwise recheck in 1 hour. • Resume per protocol testing if change in potassium is < 0.2 mmol/L, and potassium < ULN, and no other evidence of tumor lysis. • At the discretion of the investigator, may recheck prior to hospitalization. If stable or decreased, and still WNL, hospitalization is at the discretion of the investigator. Potassium, phosphorus, uric acid, calcium and creatinine must be rechecked within 24 hours.
Potassium > upper limit of normal	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) notification with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If potassium < ULN 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 1, 2 and 4 hours, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Potassium ≥ 6.0 mmol/L (6.0 mEq/L) and/or symptomatic (e.g., muscle cramps, weakness, paresthesias, nausea, vomiting, diarrhea)	• Perform STAT ECG and commence telemetry. • Nephrology (or other acute dialysis service) assessment with consideration of initiating dialysis. • Administer Kayexalate 60 g (or Resonium A 60 g). • Administer furosemide 20 mg IV × 1. • Administer insulin 0.1 U/kg IV + D25 2 mL/kg IV. • Administer sodium bicarbonate 1 to 2 mEq IV push. • If sodium bicarbonate is used, rasburicase should not be used as this may exacerbate calcium phosphate precipitation. • Administer calcium gluconate 100 to 200 mg/kg IV slowly if there is ECG/telemetry evidence of life-threatening arrhythmias. Do not administer in same IV line as sodium bicarbonate. • Recheck potassium, phosphorus, uric acid, calcium and creatinine every hour STAT.
Hyperuricemia	
Uric acid ≥ 8.0 mg/dL (476 µmol/L)	• Consider rasburicase (dose based on local guidelines and/or institutional standards). • If rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour STAT.
Uric acid ≥ 10 mg/dL (595 µmol/L) OR Uric acid ≥ 8.0 mg/dL (476 µmol/L) with 25% increase and creatinine increase ≥ 0.3 mg/dL (≥ 0.027 mmol/L) from predose level	• Administer rasburicase (dose based on local guidelines and/or institutional standards). ◦ When rasburicase is used, sodium bicarbonate should not be used as this may exacerbate calcium phosphate precipitation. • Notify nephrology (or other acute dialysis service). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 hour STAT. • If uric acid < 8.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.

Abnormality	Management Recommendations
Calcium ≤ 7.0 mg/dL (1.75 mmol/L) AND Subject symptomatic (e.g., muscle cramps, hypotension, tetany, cardiac arrhythmias)	• Administer calcium gluconate 50 to 100 mg/kg IV slowly with ECG monitoring. • Telemetry. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour STAT. • If calcium normalized 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis. • Calculate corrected calcium and check ionized calcium if albumin low.
Hyperphosphatemia	
Phosphorus ≥ 5.0 mg/dL (1.615 mmol/L) with ≥ 0.5 mg/dL (0.16 mmol/L) increase	• Administer a phosphate binder (e.g., aluminum hydroxide, calcium carbonate, sevelamer hydroxide, or lanthanum carbonate). • Nephrology (or other acute dialysis service) notification (dialysis required for phosphorus ≥ 10 mg/dL). • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1-hour STAT. • If phosphorus < 5.0 mg/dL 1 hour later, repeat potassium, phosphorus, uric acid, calcium and creatinine 2 and 4 hours, later, if no other evidence of tumor lysis.
Creatinine	
Increase ≥ 25% from baseline	• Start or increase rate of IV fluids. • Recheck potassium, phosphorus, uric acid, calcium and creatinine in 1 to 2 hours STAT.

ECG = electrocardiogram; IV = intravenous

APPENDIX F. RECOMMENDED DOSE REDUCTIONS RELATED TO DRUG TOXICITIES

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 (see Table 4).
		For any events of clinical TLS, resume at a reduced dose following resolution (see Table 4).
		Dose reduction or interruption of companion study drug may occur at the discretion of the investigator.
Non-Hematologic Toxicities		
Grade 3 or 4 non-hematologic 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 Table 4 when resuming treatment with venetoclax after resolution. A greater dose reduction may occur at the discretion of the investigator.
Hematologic Toxicities		
Grade 3 or 4 neutropenia with infection or fever; or Grade 4 hematologic toxicities (except lymphopenia)	1st occurrence	Interrupt venetoclax. To reduce the infection risks associated with neutropenia, 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 occurrence	Interrupt venetoclax. Consider using G-CSF as clinically indicated. Follow dose reduction guidelines in Table 4 when resuming treatment with venetoclax after resolution. Additional dose reductions may occur at the discretion of the physician.
Consider discontinuing venetoclax for subjects who require dose reductions to less than 100 mg for more than 2 weeks.		

G-CSF = granulocyte-colony stimulating factor; TLS = tumor lysis syndrome

Recommended Ibrutinib Dose Modifications for Toxicities

Event	Occurrence	Action
Any of the following potentially drug-related toxicities (refer to Section 6.2): • Grade 3 or higher neutropenia with infection or fever • ANC < 500/µL • platelets < 50,000/µL in the presence of clinically significant bleeding (Grade ≥ 2) • platelets < 25,000/µL • Grade 3 nausea or Grade 3 or 4 vomiting or diarrhea if persistent despite optimal antiemetic or antidiarrheal therapy • any other Grade 4 or unmanageable Grade 3 toxicity	1st occurrence	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level.
	2nd occurrence	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower (i.e., dose reduction Level 1). Follow dose reduction guidelines in Table 5.
	3rd occurrence	Withhold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at 1 dose level lower (i.e., dose reduction Level 2). Follow dose reduction guidelines in Table 5.
	4th occurrence	Discontinue study drug (i.e., dose reduction Level 3). Follow dose reduction guidelines in Table 5.
Note: For hematologic toxicities, restart of ibrutinib may be considered once the toxicity has resolved to study entry criteria level or better.		

ANC = absolute neutrophil count

APPENDIX G. ACTIVITY SCHEDULE

The following table shows the required activities. The individual activities are described in detail in the Operations Manual Section 3. Allowed modifications due to COVID-19 are detailed within the Operations Manual.

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Study Activities Table

Activity	Screen	Week 1									Week 4	Week 8	Week 12	Week 16	Week 24	≥ Week 36	Final Visit	Follow-Up	PTFU	Survival
	Day –28 to Day –4	Day –3	Day –2	Day –1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 1	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Every 12 weeks Day 1 (± 3 days)		30-Day	Same as visit schedule	Every 6 months
INTERVIEWS & QUESTIONNAIRES																				
Informed consent	✓																			
Eligibility criteria	✓																			
Medical/oncology history	✓																			
Drug and alcohol screen	✓																			
Eastern Cooperative Oncology Group	✓														✓		✓			
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Prior/concomitant therapy	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Dispense/collect subject calendars/diaries and dosing instructions										✓	✓	✓	✓	✓	✓	✓	✓			
Survival assessment																				✓
Any new anticancer therapy																				✓
LABORATORY ASSESSMENTS & EXAMINATIONS																				
Physical examination	✓	✓									✓	✓	✓	✓	✓	✓	✓	✓	✓	
Height (screening only) and weight	✓	✓								✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination (or ultrasound) for the clinical response assessment of lymph nodes and spleen	✓										✓	✓	✓	✓	✓	✓			✓	

Activity	Screen	Week 1									Week 4	Week 8	Week 12	Week 16	Week 24	≥ Week 36	Final Visit	Follow-Up	PTFU	Survival
	Day −28 to Day −4	Day −3	Day −2	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 1	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Every 12 weeks Day 1 (± 3 days)		30-Day	Same as visit schedule	Every 6 months
Electrocardiogram	✓																			
Serum pregnancy test	✓																			
Urine pregnancy test				✓							✓	✓	✓	✓ Every 4 weeks			✓	✓		
Vital signs	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Hematology/chemistry samples	✓			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Coagulation panel	✓																			
Tumor lysis syndrome risk assessment	✓																			
Tumor lysis syndrome laboratory samples					✓	✓	✓	✓	✓	✓		TLS monitoring if escalation of venetoclax to 600 mg occurs								
Computed tomography (±7 days)	✓										Week 24 and any time during the study to confirm CR/CRi based on laboratory test results and physical examination.								✓	
Bone marrow sample (±7 days)	✓ (optional)										If a CT scan indicates a CR/CRi, then a bone marrow aspirate and biopsy will be required as soon as possible to confirm the clinical response.								✓	
Clinical response assessment											✓	✓	✓	✓	✓	✓	✓		✓	
Pharmacokinetic blood samples (predose)											✓	✓								
Cheek swab for biomarker assessment	✓																			
Blood sample for biomarker assessment	✓			✓	✓					✓	✓	✓	✓	✓	✓	✓	✓		✓	

Activity	Screen	Week 1									Week 4	Week 8	Week 12	Week 16	Week 24	≥ Week 36	Final Visit	Follow-Up	PTFU	Survival
	Day –28 to Day –4	Day –3	Day –2	Day –1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 1	Day 1	Day 1 (± 3 days)	Day 1 (± 3 days)	Day 1 (± 3 days)	Every 12 weeks Day 1 (± 3 days)		30-Day	Same as visit schedule	Every 6 months
℞ TREATMENT																				
Dispense venetoclax and ibrutinib		✓								✓	✓	✓	✓	✓	✓	✓				
Hospitalization				✓	✓	✓	✓	✓	✓	✓										
Oral hydration		✓	✓																	
Oral antihyperuricemic agent		✓	✓																	
Intravenous hydration				✓	✓	✓	✓	✓	✓	✓										
Venetoclax dosing					Once daily until end of treatment															
Ibrutinib dosing				Once daily until end of treatment																

CR = complete remission; CRi = complete remission with incomplete blood count recovery; CT = computed tomography; PTFU = post-treatment follow-up

APPENDIX H. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	01 October 2018
Version 2.0	02 May 2019
Version 2.1 (United Kingdom Only)	10 September 2019
Version 2.2 (Italy Only)	02 October 2019
Version 2.3 (France Only)	08 November 2019
Version 2.4 (Germany Only)	17 January 2020
Version 2.4.1 (Germany Only)	15 July 2020

The purpose of this version is to correct minor clerical errors for consistency throughout the protocol, incorporate necessary protocol modifications due to the COVID-19 pandemic, and the following:

- **Rationale:** To list only 1 TA MD for this protocol and update the address for [redacted].
  - Updated [redacted] address on the Protocol cover page and in the Operations Manual, Appendix I (Section 1 and Section 4.3).
  - Removed [redacted] as an additional TA MD for this protocol on the Protocol cover page and in the Operations Manual, Appendix I (Section 1).
- **Rationale:** To refer to the T-PLL consensus criteria 2019 for the primary endpoint.
  - Added a reference to the T-PLL consensus criteria 2019 for clarification of the primary endpoint in the Protocol, Section 3.2.
- **Rationale:** To align secondary objectives with secondary endpoints.
  - Added a secondary objective in the Protocol, Section 1 and Section 3.1 as follows: To evaluate the PFS, duration of response, time-to-progression, event-free survival, disease control rate, and overall survival.
  - Added disease control rate to the secondary endpoints in the Protocol, Section 1 and Section 3.3.
  - Added brief definitions for the secondary endpoints in Section 3.3.
  - Added a reference to the T-PLL consensus criteria 2019 for clarification of assessment of the secondary endpoints in Section 3.3.
- **Rationale:** To add instruction for recording bone marrow assessment data if a pretreatment bone marrow sample was provided.
  - Added the following statement in the Protocol, Section 4.1 and the Operations Manual, Appendix I (Section 2): " If a pretreatment bone marrow assessment was performed per

standard-of-care prior to the first dose of study drug, the results should be recorded in the electronic case report form (eCRF)."

- **Rationale:** To clarify that once the clinical trial treatment has been completed, the potential continuation of therapy will be as per local regulations and to extend the post-treatment follow-up visits period in the Protocol, Section 1 and Section 4.1.
  - Added that AbbVie will work with the investigator to consider the potential continuation of therapy as per local regulations.
  - Removed requirement for subjects to be followed for disease progression for "up to 2 years" after eligible subjects proceed to stem cell transplantation.
- **Rationale:** To update eligibility criteria (Section 5.1) for signing the informed consent because a legally authorized representative is not allowed to sign according to German Drug Act.
  - Added that subjects or their legally authorized representative (if permitted per local regulations) must voluntarily sign and date an informed consent to Criterion #1.
- **Rationale:** To update eligibility criteria (Section 1 and Section 5.1) for creatinine clearance because limited safety data exists for venetoclax administered among subjects with renal function between 30 and 50 mL/minute.
  - Changed the creatinine clearance requirement from ≥ 30 mL/minute to ≥ 50 mL/minute in Criterion #3.
- **Rationale:** To clarify that subjects should not receive any live or attenuated live vaccine during study participation from 28 days prior to the first dose of study drug, to include only those criteria applicable for entry into the study, and to allow seasonal flu vaccines.
  - Modified eligibility Criterion #35 in the Protocol, Section 5.1 to state "Subjects must not have received any live or attenuated live vaccine within 28 days prior to the first dose of ibrutinib or venetoclax. Seasonal flu vaccines that do not contain a live virus are permitted."
- **Rationale:** To clarify the contraception recommendations for male subjects relative to the first dose of venetoclax or ibrutinib to match the package insert.
  - Updated eligibility Criterion #27 (Section 5.1) to include the following: "If male, and subject is sexually active with female partner(s) of childbearing potential, he must agree, from Study Day 1 through 30 days after the last dose of venetoclax and 90 days after the last dose of ibrutinib, to practice the protocol-specified contraception."
  - Updated eligibility Criterion #28 (Section 5.1) to include the following: "Male who is not considering fathering a child or donating sperm during the study or for approximately 30 days after the last dose of venetoclax and 90 days after the last dose of ibrutinib."
  - Updated male contraception recommendation (Section 5.2) to include the following: "Male subjects who are sexually active with a woman of childbearing potential must agree **to use condoms**, even if the male subject has undergone a successful vasectomy, from Study Day 1 through at least 30 days after the last dose of venetoclax and at least 90 days after the last dose of ibrutinib."
- **Rationale:** To add live vaccines to the list prohibited medications and therapy in Section 5.3.

- Updated the list of prohibited medications and therapy to include live vaccinations during study participation and until at least 4 weeks after the last dose of study drug and only after B-cell or absolute lymphocyte count (ALC) recovery.

- **Rationale:** To update the required safety text in the Protocol Section 6.1.
  - Updated the guidance on the "special situations" that may cause an AE.
  - Added additional guidance to define an AE for the following situations: worsening of a pre-existing condition, worsening in severity of a reported AE, or laboratory abnormalities and changes in vital signs.
  - Added definitions for a Serious Adverse Reaction (SAR) and Suspected Unexpected Serious Adverse Reaction (SUSAR).
- **Rationale:** To fix a discrepancy in the timing of recording adverse events (AEs) as stated in the Protocol, Section 6.1 versus the Operations Manual, Appendix I (Section 4.1).
  - Added language in Section 6.1 to clarify that all AEs reported from the time of study drug administration until 30 days after discontinuation of study drug administration will be collected.
- **Rationale:** To remove reporting guidance for AEs associated with the underlying disease under investigation in the Protocol, Section 6.1 because this is no longer valid protocol language.
  - Deleted all language related to the following: disease progression and the underlying disease under investigation including symptoms that the investigator assesses as specific to disease progression should not be reported as an AE unless it results in a serious outcome.
- **Rationale:** To include laboratory monitoring for TLS for any increase in venetoclax dose.
  - Updated Section 6.2 to include TLS laboratory monitoring for the optional increase of venetoclax to 600 mg at Week 8 or thereafter.
- **Rationale:** To clarify and standardize the recommendations for the management of treatment-emergent infections and anti-infective prophylaxis requirements.
  - Updated Section 6.2 to include guidelines for the management of infections and to require anti-infective prophylaxis for all subjects with absolute neutrophil count (ANC) of < 500/µL.
- **Rationale:** To clarify the dose interruption and modification language for venetoclax and ibrutinib in Section 6.2.
  - Updated Section 6.2 to include that the TA MD should be consulted if venetoclax dose interruption is > 4 weeks.
  - Updated Section 6.2 to align ibrutinib dose modification guidelines with Appendix F.
- **Rationale:** To add when the interim, primary, and final analyses will take place in the Protocol, Section 7.1.
  - Added an interim efficacy analysis that will be performed when Stage 1 subjects have completed the Week 24 disease assessments.
  - Added a primary efficacy analysis that will be performed for Stage 1 and Stage 2 subjects after their completion of the Week 24 disease assessments.

- Added a final analysis will be performed when all subjects have discontinued the study or have completed protocol defined follow-up time.

- **Rationale:** To define terms used in Table 6, Section 7.2.
  - Added the following definition to the footnotes for critical value: "Critical value" is the threshold beyond which the null hypothesis is rejected (i.e., claiming efficacy).
  - Added the following definition to the footnotes for p: probability of achieving a response (CR, CRi, or PR).
  - Added the following definition to the footnotes for power: 1-β = 80%.
  - Added the following definition to the footnotes for significance level: 10% (2-sided).
- **Rationale:** To add further description of the statistical analyses for efficacy and safety in Section 7.4 and Section 7.5.
  - Added clarification to the primary efficacy endpoint (Section 7.4).
  - Added the endpoints to be analyzed for the secondary efficacy analysis (Section 7.4) and the safety analysis (Section 7.5).
  - Added a description of the time-to-event endpoints that will be analyzed using Kaplan-Meier methodology (Section 7.4).
  - Removed the interim and final efficacy analyses which is now presented in the Protocol, Section 7.1.
- **Rationale:** To update the steering committee membership to include an internal specialist in infectious diseases and remove "optional" from the heading in Section 7.6.
  - Updated to include an internal specialist in infectious diseases who is not currently involved in the conduct or oversight of Study M18-803 as a member of the Steering Committee.
- **Rationale:** To update the required text for the ethical conduct of the study in the Protocol Section 8.2.
  - Updated the guidance for study procedures in the event a significant disaster/crisis occurs.
- **Rationale:** To update the protocol signatory list in Appendix C.
  - Changed the statistical sciences signatory from [redacted] (Director) to [redacted] (Head of Statistics).
- **Rationale:** To update Appendix F to include any Grade 3 non-hematologic toxicities for venetoclax dose modifications and to include additional criteria for ibrutinib dose modifications.
  - Updated Appendix F to include Grade 3 or 4 non-hematologic toxicities for recommended venetoclax dose modifications.
  - Added "Grade 3 or higher neutropenia with infection or fever" to the list of potentially drug-related toxicities that would result in a recommended dose modification of ibrutinib.
  - Removed the time criteria of "after 7 days" for the potentially drug-related toxicity of ANC < 500/µL that would result in a recommended dose modification of ibrutinib.

- **Rationale:** To add monthly pregnancy testing during the treatment period and until the end of the relevant systemic exposure.
  - Updated the Protocol, Appendix G (Schedule of Activities) to include monthly urine pregnancy tests during the treatment period until the 30-day follow-up visit.
  - Updated the Operation Manual, Appendix I (Section 2) to reflect the changes made in the Protocol, Schedule of Activities.
  - Updated the Operation Manual, Appendix I (Section 3.12) to update the urine pregnancy language as follows: "A urine pregnancy test will be performed for all female subjects of childbearing potential on Day –1 and every 4 weeks until 30 days after the last dose of venetoclax or 90 days after the last dose of ibrutinib, whichever the latest, as indicated in Section 2.1."
  - Updated the Operations Manual, Appendix I (Section 3.12, Table 1, footnote [b]) to align with the additional pregnancy tests required post-screening: "Performed at screening and as indicated in Section 2.1."
- **Rationale:** To add lymph node and spleen measurements during the physical examination and an optional pretreatment bone marrow assessment.
  - Updated the Protocol, Appendix G (Schedule of Activities) to include physical examination (or ultrasound) procedure for lymph node and spleen measurements.
  - Updated the Protocol, Appendix G (Schedule of Activities) to include an optional pretreatment bone marrow assessment per standard-of-care prior to the first dose of study drug.
  - Updated the Operation Manual, Appendix I (Section 2) to reflect the changes made in the Protocol, Schedule of Activities.
  - Updated the Operation Manual, Appendix I (Section 3.7) to include that spleen and lymph node measurements will be performed during the physical examination or via ultrasound as part of the clinical response assessment.
- **Rationale:** To add TLS monitoring for all venetoclax dose-escalation.
  - Updated the Protocol, Appendix G (Schedule of Activities) to include TLS monitoring if escalation of venetoclax to 600 mg at Week 8 or thereafter occurs.
  - Updated the Operation Manual, Appendix I (Section 2) to reflect the changes made in the Protocol, Schedule of Activities.
- **Rationale:** To add post-treatment follow-up visits for any subject who has not experienced PD at the time of permanent discontinuation of venetoclax and ibrutinib and to add and unlimited survival calls.
  - Updated the Protocol, Appendix G (Schedule of Activities) to include post-treatment follow-up visits.
  - Updated the Protocol, Appendix G (Schedule of Activities) to remove the time restriction of 2 years for survival follow-up calls.

- Updated the Operation Manual, Appendix I (Section 2) to reflect the changes made in the Protocol, Schedule of Activities.
- Updated the Operation Manual, Appendix I (Section 2) to clarify the criteria for subjects who may be contacted for survival every 6 months by telephone.
- Updated the Operation Manual, Appendix I (Section 3.11) to include a description and timing of the post-treatment follow-up visits and removed the 2-year time limit for survival follow-up telephone calls.
- Updated the Operation Manual, Appendix I (Section 3.17 [Table 5]) to include post-treatment follow-up visits.

- **Rationale:** To clarify the visit days in the Schedule of Activities and to modify the visit windows.
  - Added Day 1 to the Weeks ≥ 4 visits in the Protocol, Appendix G (Schedule of Activities).
  - Removed the visit windows on Weeks 4 and 8, Day 1.
  - Changed the visit window from –7 days to ± 3 days for Weeks ≥ 12, Day 1.
  - Added a ± 7-day window for the CT scan and bone marrow biopsy sample.
  - Updated the Operation Manual, Appendix I (Section 2) to reflect the changes made in the Protocol, Schedule of Activities.
- **Rationale:** To delete any mention of end-of-study at the Final visit to avoid confusion.
  - Updated the Protocol, Appendix G (Schedule of Activities) to remove end-of-study from the Final visit.
  - Updated the Operation Manual, Appendix I (Section 2 and Section 3.17 [Table 5]) to clarify that the final visit will occur at the end of study treatment.
- **Rationale:** To delete the blood sample for clinical response because clinical response laboratory tests are already included in the standard hematology tests.
  - Deleted the row for "blood sample for clinical response" in the Protocol, Appendix G (Schedule of Activities).
  - Updated the Operation Manual, Appendix I (Section 2) to reflect the changes made in the Protocol, Schedule of Activities.
- **Rationale:** To update the timing of the dispensing of study drug in the Operations Manual, Appendix I (Section 2).
  - Changed the timing of the dispensing of venetoclax and ibrutinib from "Day –3, Day –2, or Day –1" to "within 3 days of the first dose of study drug (Day –1)."
- **Rationale:** To clarify the timing of the TLS laboratory samples in the Operations Manual, Appendix I (Section 2 and Section 3.12).
  - Updated the timing of the of the TLS laboratory samples during ramp-up of venetoclax as follows: "TLS monitoring will occur predose (full chemistry panel is required) and at 4, 8, 12, and 24 hours postdose (TLS chemistry panel is required) after each dose escalation of venetoclax (including escalation to 600 mg at Week 8 or thereafter). For the 24-hour sample, a window of –1 hour is allowed. If the predose sample coincides with the 24-hour

postdose sample, then the predose sample may be used for both the predose and 24-hour analyses."

- **Rationale:** To update the criteria for signing the informed consent in the Operations Manual (Appendix I) because a legally authorized representative is not allowed to sign according to German Drug Act.
  - Updated Section 3.1 to add that the informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative (if permitted per local regulations).
- **Rationale:** To update the Operations Manual (Appendix I) to include SARS-CoV-2 testing.
  - Updated Section 3.12, Table 1 to add SARS-CoV-2 testing at screening to the list of clinical laboratory tests (other tests).
- **Rationale:** To clarify that subjects who have a positive hepatitis B serology should be monitored and managed following local medical standards to reduce risk of hepatitis B reactivation.
  - Added the following text to the Operation Manual, Appendix I (Section 3.12): "All subjects enrolled will be followed with clinical laboratory testing at scheduled time points throughout the study. If a subject experiences a sign or symptom that may be suggestive of hepatitis B reactivation and/or a laboratory abnormality suggestive of potential hepatitis B reactivation (e.g., elevated aminotransferases), the investigator should pursue further work-up per clinical practice guidelines/standards. If a subject has positive hepatitis B serology, the subject should be monitored and managed following local medical standard to reduce risk of hepatitis B reactivation."
- **Rationale:** To delete baseline criteria for subjects who receive intravenous hydration prior to first dose of study drug and to clarify that tumor burden is only defined by 2 factors in the Operations Manual (Appendix I).
  - Deleted the following criteria from Section 3.12: "The baseline value will be the last laboratory value before the subject receives intravenous hydration for TLS prophylaxis within 72 hours."
  - Updated Section 3.12 to clarify that tumor burden will be determined by CT scans and ALC levels.
- **Rationale:** To update the disease assessment criteria using the response evaluation criteria in lymphoma (RECIL)-based T-PLL consensus criteria and to clarify that disease assessment will continue after last dose of study drug in Appendix I.
  - Updated Section 3.13 to indicate that disease assessment will be performed using the RECIL-based T-PLL consensus criteria assessment schedule.
  - Updated Table 2 and Table 3 to add additional information and criteria for the clinical response and the confirmatory response, respectively, using the RECIL-based T-PLL consensus criteria (Section 3.14).
  - Updated Section 3.14 to clarify that "clinical response will be assessed by laboratory tests and physical examination (or ultrasound) using the T-PLL consensus criteria."

- Updated Section 3.14 the instruction for any subject who has not experienced PD at time of discontinuation of study drug as follows: "Disease assessment will continue to be performed after the last dose of study drug until disease progression for any subject who has not experienced progressive disease (PD) at the time of permanent discontinuation of venetoclax and ibrutinib."
- Updated Reference 1 with RECIL-based T-PLL consensus criteria for disease assessment.

- **Rationale:** To clarify the method for taking blood draws for pharmacokinetic (PK) samples in the Operations Manual, Appendix I (Section 3.16).
  - Added that PK blood draws will be collected "by venipuncture."
- Rationale: To include information on COVID-19-related re-evaluation of the benefit and risk to subjects participating in the study.
  - Added information on the re-evaluation of the benefit and risk to subjects in Section 2.2.
- Rationale: To add eligibility criteria to exclude subjects who tested positive for SARS-CoV-2 infection from participating in the study.
  - Updated eligibility criteria (Criterion #20) in Section 5.1 to exclude subjects positive for SARS-CoV-2 infection.
- Rationale: To add instructions for necessary protocol modifications in the event of a COVID-19-related temporary study drug interruption.
  - Added instructions to refer to the Operations Manual for acceptable protocol deviations in Section 5.5.
- Rationale: To include instructions on COVID-19-related study drug pickup and DTP shipment.
  - Added instructions to refer to the Operations Manual for DTP shipment in the event that subjects are unable to pick up study drug onsite due to COVID-19 in Section 5.7.
- Rationale: To include a statement that AbbVie will modify the study protocol as needed due to a COVID-19-related state of emergency.
  - Added a statement in Section 8.2 noting that AbbVie will modify the study protocol as necessary due to the pandemic, referring to the Operations Manual in Appendix I for additional details.
- Rationale: To note that remote monitoring of subjects may be employed as needed during a COVID-19-related state of emergency.
  - Added a statement in Section 9 that remote monitoring may be employed as needed.
- Rationale: To include information on COVID-19-related allowed protocol modifications.
  - Added a reference to the Operations Manual for allowed modifications in Appendix I.
- Rationale: To provide details on completing study activities/procedures in a COVID-19-related state of emergency.
  - Updated Appendix I – Operations Manual updated to include details on how to perform specific activities/procedures that may be impacted by a COVID-19 state-of-emergency.

APPENDIX I. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M18-803

T-Cell Prolymphocytic Leukemia: Venetoclax and Ibrutinib

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	Venetoclax (ABT-199) and Ibrutinib

FULL TITLE: A Prospective, Open-Label, Single-Arm, Phase 2, Multicenter Study Evaluating the Efficacy of Venetoclax Plus Ibrutinib in Subjects with T-Cell Prolymphocytic Leukemia

1 CONTACTS

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2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the coronavirus disease – 2019 (COVID-19) pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall treatment period activity schedule.

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

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed for the Weeks ≥ 4 visits:

- The Weeks ≥ 4 visits and/or activities may be performed by phone/virtually.
    - During a virtual visit, if the clinical response assessment is suggestive of a CR/CRi, the computed tomography (CT) scan and/or bone marrow biopsy will need to be done onsite as soon as possible to confirm the clinical response.
    - If an activity is missed during a virtual visit, perform the activity at the earliest feasible opportunity.
    - Laboratory draws must be obtained within 24 hours or as soon as possible from the scheduled visit and may be performed by a local clinic/hospital/laboratory. All procedures performed at local facilities must be performed by appropriately qualified personnel.

Screening, Days –28 to –4:

INTERVIEW	Informed consent Eligibility criteria Medical/oncology history	Drug and alcohol screen Eastern Cooperative Oncology Group performance assessment Adverse event assessment Prior/concomitant therapy
EXAMINATION	Physical examination Height and weight Physical examination (or ultrasound) of lymph nodes and spleen	Vital signs Electrocardiogram
LABORATORY	Serum pregnancy test Hematology/chemistry sample Coagulation panel TLS risk assessment Cheek swab (Day –28 to Day –2)	Computed tomography (Day –28 to Day –2) Blood sample for optional biomarker assessment (Day –28 to Day –2) Bone marrow sample for optional biomarker assessment (Day –28 to Day –2)

NOTES:
- All screening procedures must be performed onsite.
- If a pretreatment bone marrow assessment was performed per standard-of-care prior to the first dose of study drug, the results should be recorded in the electronic case report form (eCRF).
- A complete physical examination will be performed at screening only.
- Spleen and lymph node measurements will be performed during the physical examination or via ultrasound in addition to CT scan to have baseline data for the upcoming clinical disease assessments.
- CT scan will be accepted for screening purposes if previously performed within 35 days before the first dose of study drug.
- Cheek swab and blood sample for optional biomarker assessments (if consent was given for the correlative studies) may be performed once any time from Day –28 to Day –2.

Days –3 and –2:

INTERVIEW	Adverse event assessment	
EXAMINATION	Physical examination (Day –3 to Day –1)	Weight (Day –3 to Day –1)
LABORATORY	Computed tomography (Day –28 through Day –2) Cheek swab (Day –28 to Day –2)	Blood sample for optional biomarker assessment (Day –28 to Day –2)
TREATMENT	Dispense venetoclax and ibrutinib	Oral hydration Oral antihyperuricemic agent

NOTES: All Days -3 and -2 procedures must be performed onsite.

A sign- and symptom-directed physical examination and weight may be performed any time from Day –3 to Day –1.

CT scan will be accepted for screening purposes if previously performed within 35 days before the first dose of study drug.

Cheek swab and blood sample for optional biomarker assessments (if consent was given for the correlative studies) may be performed once any time from Day –28 to Day –2.

Electronic transaction for dispensation of venetoclax and ibrutinib can be performed within 3 days of the first dose of study drug (Day –1).

Day –1:

INTERVIEW	Adverse event assessment	Prior/concomitant therapy
EXAMINATION	Physical examination (Day –3 to Day –1)	Weight (Day –3 to Day –1) Vital signs
LABORATORY	Urine pregnancy test Hematology/chemistry sample (predose)	Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib Hospitalization	Intravenous hydration Ibrutinib dosing

NOTES: All Day –1 procedures must be performed onsite.

A sign- and symptom-directed physical examination and weight may be performed any time from Day –3 to Day –1.

Ibrutinib dosing occurs once daily until end of treatment.

Electronic transaction for dispensation of venetoclax and ibrutinib can be performed within 3 days of the first dose of study drug (Day –1).

Blood sample for biomarker optional assessments will be collected at predose and 6 hours postdose for subjects who provided consent for the correlative studies.

Week 1, Days 1 through 5:

INTERVIEW	Adverse event assessment Concomitant therapy	
EXAMINATION	Vital signs	
LABORATORY	Hematology/chemistry sample (predose) TLS laboratory sample	Blood sample for optional biomarker assessments (Days 1 only)
TREATMENT	Hospitalization	Intravenous hydration Venetoclax dosing Ibrutinib dosing

NOTES: All Week 1 procedures must be performed onsite.
The full chemistry panel will be obtained predose daily. Laboratory monitoring for tumor lysis syndrome (TLS) will occur at 4, 8, 12, and 24 hours postdose after each dose escalation of venetoclax. For the 24-hour sample, a window of –1 hour is allowed.
Blood samples for optional biomarker assessments will be collected at predose and 6 hours postdose for subjects who provided consent for the correlative studies.
Venetoclax and ibrutinib dosing occurs once daily until end of treatment.

Week 1, Day 6:

INTERVIEW	Adverse event assessment Concomitant therapy	Dispense subject calendars/diaries and dosing instructions
EXAMINATION	Vital signs	Weight
LABORATORY	Hematology/chemistry sample (predose) TLS laboratory sample	Blood sample for optional biomarker assessments
TREATMENT	Dispense ibrutinib Dispense venetoclax End of Hospitalization	End of intravenous hydration Venetoclax dosing Ibrutinib dosing

NOTES: All Week 1 procedures must be performed onsite.
The full chemistry panel will be obtained predose. Laboratory monitoring for TLS will occur 24 hours postdose after Week 1 Day 5 dose escalation of venetoclax; a window of –1 hour is allowed.
Blood samples for optional biomarker assessments will be collected at predose and 6 hours postdose for subjects who provided consent for the correlative studies.
Venetoclax and ibrutinib dosing occurs once daily until end of treatment.

Week 4, Day 1:

INTERVIEW	Adverse event assessment Concomitant therapy	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs Physical examination (or ultrasound) of lymph nodes and spleen	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi) Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test Pharmacokinetic sample (predose) Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib Venetoclax dosing	Ibrutinib dosings

NOTES: Clinical response assessment is based on physical examination and blood sample.

Spleen and lymph node measurements will be performed during the physical examination or via ultrasound for clinical response assessment.

If clinical response assessment is suggestive of a CR/CRi, a computed tomography (CT) will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments). The CT scan and bone marrow biopsy will have a ± 7-day window.

Venetoclax and ibrutinib dosing occurs once daily until end of treatment.

Blood sample for optional biomarker assessments will be collected for subjects who provided consent for the correlative studies.

Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.

Week 8, Day 1:

INTERVIEW	Adverse event assessment Concomitant therapy	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs Physical examination (or ultrasound) of lymph nodes and spleen	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi) Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test Pharmacokinetic sample (predose) Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib	Venetoclax dosing (TLS monitoring needed if dose escalated to 600 mg) Ibrutinib dosing

NOTES: Clinical response assessment is based on physical examination and blood sample.

Spleen and lymph node measurements will be performed during the physical examination or via ultrasound for clinical response assessment.

If clinical response assessment is suggestive of a CR/CRi, a CT will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments). The CT scan and bone marrow biopsy will have a ± 7-day window.

Venetoclax and ibrutinib dosing occurs once daily until end of treatment.

Blood sample for optional biomarker assessments will be collected for subjects who provided consent for the correlative studies.

Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.

Week 12, Day 1:

INTERVIEW	Adverse event assessment Concomitant therapy	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs Physical examination (or ultrasound) of lymph nodes and spleen	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi) Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib	Venetoclax dosing (TLS monitoring needed if dose escalated to 600 mg) Ibrutinib dosing

NOTES:
- Actual study visit procedures can be done ± 3 days of the targeted visit date.
- Clinical response assessment is based on physical examination and blood sample.
- Spleen and lymph node measurements will be performed during the physical examination or via ultrasound for clinical response assessment.
- If clinical response assessment is suggestive of a CR/CRi, a CT will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments). The CT scan and bone marrow biopsy will have a ± 7-day window.
- Venetoclax and ibrutinib dosing occurs once daily until end of treatment.
- Blood samples for optional biomarker assessments will be collected for subjects who provided consent for the correlative studies.
- Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.

Week 16, Day 1:

INTERVIEW	Adverse event assessment Concomitant therapy	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs Physical examination (or ultrasound) of lymph nodes and spleen	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi) Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test (every 4 weeks) Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib	Venetoclax dosing (TLS monitoring needed if dose escalated to 600 mg) Ibrutinib dosing

NOTES:
- Actual study visit procedures can be done ± 3 days of the targeted visit date.
- Clinical response assessment is based on physical examination and blood sample.
- Spleen and lymph node measurements will be performed during the physical examination or via ultrasound for clinical response assessment.
- If clinical response assessment is suggestive of a CR/CRi, a CT will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments). The CT scan and bone marrow biopsy will have a ± 7-day window.
- Venetoclax and ibrutinib dosing occurs once daily until end of treatment.
- Blood samples for optional biomarker assessments will be collected for subjects who provided consent for the correlative studies.
- Urine pregnancy test will be performed every 4 weeks for women of childbearing potential (Weeks 16 and 20); testing will be performed at home in between site visits.
- Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.

Week 24, Day 1

INTERVIEW	Adverse event assessment Concomitant therapy Eastern Cooperative Oncology Group performance assessment	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs Physical examination (or ultrasound) of lymph nodes and spleen	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test (every 4 weeks) Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib	Venetoclax dosing (TLS monitoring needed if dose escalated to 600 mg) Ibrutinib dosing

NOTES:
- Actual study visit procedures can be done ± 3 days of the targeted visit date.
- Clinical response assessment is based on physical examination and blood sample.
- Spleen and lymph node measurements will be performed during the physical examination or via ultrasound for clinical response assessment.
- CT is not optional for the Week 24 visit. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments). The CT scan and bone marrow biopsy will have a ± 7-day window.
- Blood samples for optional biomarker assessments will be collected for subjects who provided consent for the correlative studies.
- Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.
- Venetoclax and ibrutinib dosing occurs once daily until end of treatment.
- Urine pregnancy test will be performed every 4 weeks for women of childbearing potential (Weeks 24, 28, and 32); testing will be performed at home in between site visits.

Week 36 and every 12 weeks thereafter, Day 1: 

INTERVIEW	Adverse event assessment Concomitant therapy	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs Physical examination (or ultrasound) of lymph nodes and spleen	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi) Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test (every 4 weeks) Blood sample for optional biomarker assessments
TREATMENT	Dispense venetoclax and ibrutinib	Venetoclax dosing (TLS monitoring needed if dose escalated to 600 mg) Ibrutinib dosing

NOTES:
- Actual study visit procedures can be done ± 3 days of the targeted visit date.
- Clinical response assessment is based on physical examination and blood sample.
- Spleen and lymph node measurements will be performed during the physical examination or via ultrasound for clinical response assessment.
- If clinical response assessment is suggestive of a CR/CRi, a CT will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments). The CT scan and bone marrow biopsy will have a ± 7-day window.
- Venetoclax and ibrutinib dosing occurs once daily until end of treatment.
- Blood samples for optional biomarker assessments will be collected for subjects who provided consent for the correlative studies.
- Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.
- Urine pregnancy test will be performed every 4 weeks for women of childbearing potential; testing will be performed at home in between site visits.

Final Visit:

INTERVIEW	Adverse event assessment Concomitant therapy Eastern Cooperative Oncology Group performance assessment	Dispense/collect subject calendars/diaries and dosing instructions
EXAMINATION	Physical examination Vital signs	Weight Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi) Bone marrow sample (if needed for confirmation of CR/CRi)	Urine pregnancy test Blood sample for optional biomarker assessments

NOTES:
- The final visit will occur at the end of study treatment.
- Actual study visit procedures can be done within 7 days before the targeted visit date.
- Clinical response assessment is based on physical examination and blood sample.
- If clinical response assessment is suggestive of a CR/CRi, a CT will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments).
- Blood samples will be collected for optional biomarker assessments for subjects who provided consent for the correlative studies.
- Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit. The dot pattern on the upper right indicates the place of the visit in the overall post-treatment period activity schedule.

Activities are grouped by category (interview, examination, etc.). Further information about the activities is presented in Section 3.

30-Day Follow-Up Visit:

INTERVIEW	Adverse event assessment	Concomitant therapy
EXAMINATION	Physical examination Weight	Vital signs
LABORATORY	Hematology/chemistry sample	Urine pregnancy test

NOTES: Follow-up visit to be conducted no earlier than 30 days after the last dose of study drug (venetoclax or ibrutinib) but prior to any new anticancer therapy.

A symptom-directed physical examination will be performed at the follow-up visit.

Urine pregnancy testing to be performed every 4 weeks up to 30 days after the last dose of venetoclax and 90 days after the last dose of ibrutinib, whichever the latest.

Post-Treatment Follow-Up Visits:

INTERVIEW	Adverse event assessment	Concomitant therapy
EXAMINATION	Physical examination Weight Physical examination (or ultrasound) of lymph nodes and spleen	Vital signs Clinical response assessment
LABORATORY	Hematology/chemistry sample Computed tomography (if needed for confirmation of CR/CRi)	Bone marrow sample (if needed for confirmation of CR/CRi) Blood sample for optional biomarker assessments

NOTES:
- Post-treatment follow-up visits will be conducted until documented progressive disease (PD) or other post-treatment therapies (including stem cell transplantation) are received. The post-treatment follow-up visits will follow the same schedule as the visit schedule (i.e., Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, and every 12 weeks thereafter).
- Clinical response assessment is based on physical examination (or ultrasound) and blood sample.
- Spleen and lymph node measurements will be performed during the physical examination or via ultrasound.
- If clinical response assessment is suggestive of a CR/CRi, a CT will be taken for confirmation of the clinical response. If a CT scan indicates a CR/CRi, a bone marrow biopsy will be required as soon as possible to confirm the clinical response (the sample will be split for analyses of disease and biomarker assessments).
- Blood samples will be collected for optional biomarker assessments for subjects who provided consent for the correlative studies.
- Bone marrow sample for optional biomarker assessments to be collected for subjects who provided consent for the relative studies AND if a bone marrow sample is collected to confirm CR/CRi or collected per standard-of-care.

Survival Follow-Up:

INTERVIEW	Survival assessment	Any new anticancer therapy

NOTES:
- Subjects who discontinue the study drug and are no longer in post-treatment follow-up should be contacted every 6 months by telephone for survival assessment and for information on new anticancer therapies.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

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

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

Samples for optional biomarker analyses will only be collected if the subject has voluntarily signed and dated a separate written consent form for biomarker testing that has been approved by an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) after the nature of the testing has been explained and the subject has had an opportunity to ask questions. The separate written consent may be part of the main consent form. If the subject does not consent to the biomarker testing, the subject's participation in the study will not be impacted.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained prior to these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Medical History

A complete medical history including demographics, history of tobacco, alcohol, and drug use will be taken at screening. The subject's medical history will be updated before the first dose of study drug (Day –1). This updated medical history will serve as the baseline for clinical assessment. A detailed oncology history will also be collected including: histology, date of diagnosis of T-cell prolymphocytic leukemia (T-PLL), any surgical procedures, and treatments administered (including dates and type of modality).

On Day –1, any additional medical history observed after signing of the informed consent but before initial study drug administration and not considered related to study-required procedures will be recorded in the subject's medical history.

3.3 Drug and Alcohol Screen

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 6 months.

3.4 Eastern Cooperative Oncology Group Performance Status

For all subjects, the Eastern Cooperative Oncology Group (ECOG) performance status will be performed as outlined in Section 2.

ECOG performance status will be assessed as follows:

Grade	Description
0	Fully active, able to carry on all predisease 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

3.5 Adverse Event Assessment

Please refer to Section 4.

3.6 Concomitant Medication

If a subject reports taking any over-the-counter or prescription medications, vitamins, and/or herbal supplements or if administration of any medication becomes necessary beginning with the screening visit through 30 days after last dose of study drug, the name of the medication, dosage information including dose, route, and frequency, dates of administration including start and end dates, and reason for use must be recorded on the appropriate electronic Case Report Form (eCRF).

Subjects should receive full supportive care during study participation, including transfusion of blood products, fluid and electrolyte replacement, and antibiotics when appropriate. Subjects who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

General guidelines regarding prohibited and cautionary concomitant medications and dietary restrictions are provided in Protocol Section 5.1, Section 5.3, and Section 5.4. Co-administration of venetoclax and ibrutinib with a strong cytochrome P450 (CYP)3A inhibitor is prohibited during ibrutinib initiation and venetoclax dose ramp-up (refer to the Protocol Section 5.3). Although cautionary, use of a

strong CYP3A inhibitor (after dose ramp-up), moderate CYP3A inhibitors, and strong or moderate CYP3A inducers are allowed if no appropriate therapeutic alternative exists (refer to the Protocol Section 5.4). Dose reductions of venetoclax and ibrutinib are required with concomitant administration of a strong or moderate CYP3A inhibitor (refer to the Protocol Section 5.4). Alternative treatments with less CYP3A induction or inhibition should be considered.

A sample list of prohibited medications and cautionary medications that may interact with study drug is provided in Appendix B. It is not possible to produce a complete list of medications that fall into these categories; if in question, please refer to the appropriate product label.

For guidance regarding medications for management of TLS and neutropenia, refer to the Protocol Section 6.2.

The AbbVie Therapeutic Area Medical Director (TA MD) identified in Section 1 should be contacted if there are any questions regarding concomitant or prior therapy(ies).

3.7 Physical Examination and Ultrasound

A complete physical examination will be performed at screening and a sign- and symptom-directed physical examination for all other scheduled visits as specified in Section 2. The physical examination performed at screening will serve as the baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as adverse events (AEs). All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

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

Additionally, spleen and lymph node measurements will be performed during the physical examination or via ultrasound as part of the clinical response assessment at screening and for the scheduled visits as specified in Section 2.

3.8 Height and Weight

Height will be measured at the screening visit only. Body weight will be measured at scheduled visits as specified in Section 2.1. The subject should wear lightweight clothing and no shoes during weighing.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, height and weight measurements may be performed by the subject or caregiver as needed.

3.9 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in Section 2.1. In addition, vital signs will be measured as clinically

indicated. Blood pressure and pulse rate should be measured after the subject has been sitting for at least 3 minutes.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone or video conference. In these situations, vital signs may be obtained by the subject or caregiver as needed.

3.10 12-Lead Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at screening and if clinically indicated. The ECG should be performed prior to blood collection.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source folder. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit or arrange to have an alternative acceptable local facility perform the ECG for the subject.

3.11 Post-Treatment Follow-Up and Survival Visits

Subjects who discontinue study drug but have not experienced progressive disease (PD) will return for post-treatment follow-up visits. The post-treatment follow-up visits will follow the same schedule as the visit schedule (i.e., Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, and every 12 weeks thereafter). Subjects will return for post-treatment follow-up visits until study completion starting from study drug discontinuation until documented PD or other post-treatment therapies (including stem cell transplantation) are received. Follow-up hematology and disease response assessment data will be collected.

Survival information (i.e., the date and cause of death) will be collected via telephone calls at 6-month intervals or as needed to allow for more frequent survival analyses.

All subjects will be followed for survival information (i.e., date and cause of death, all poststudy anticancer treatment including stem cell transplantation, reasons for poststudy anticancer treatment, regimens, dates of initiation and completion, etc.) unless the subject requests to be withdrawn from the

study survival follow-up; this request must be documented in the subject's medical record and signed by the investigator. If the subject withdraws from study follow-up, the study staff may use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

3.12 Clinical Laboratory Tests

The blood samples for serum chemistry tests will be collected as specified in Section 2. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified laboratory will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained prior to the initiation of the study. Required tests are listed in Table 1.

Local laboratories will be utilized to process and provide results for clinical laboratory tests allowing for immediate subject medical management. The principal investigator or subinvestigator will review, initial, and date all laboratory results after receipt from the local laboratory. Local laboratory values will be entered by the site directly onto the appropriate eCRF and laboratory normal ranges and certification for the laboratory that is used will be provided to the AbbVie clinical team if the result is clinically significant (i.e., necessitating an immediate treatment or treatment modification).

For chemistry laboratory tests performed for TLS prophylaxis and monitoring, refer to Table 1.

The baseline laboratory tests will be reviewed for eligibility before study drug administration as specified in Section 2.1.

If a laboratory test value is outside the reference range and the investigator considers the laboratory result to be clinically significant, the investigator will:

- repeat the test to verify the out-of-range value;
- follow the out-of-range value to a satisfactory clinical resolution; or
- discontinue the subject from the study or require the subject to receive treatment.

Table 1. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Other Tests
Hematocrit Hemoglobin Red blood cell count White blood cell count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable)	Blood urea nitrogen Creatinine Total bilirubin Albumin Alanine aminotransferase Aspartate aminotransferase Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid[a] Total protein Glucose Bicarbonate Creatinine clearance (Cockcroft-Gault calculation) Lactate dehydrogenase Serum β2 microglobulin	Urine and serum[b] qualitative pregnancy testing human chorionic gonadotropin[c,d] Follicle-stimulating hormone[b,c,e] Anti-HIV antibody[b] Viral serologies[b,f] hepatitis B surface antigen or hepatitis B core antibody HCV antibody (and RNA if HCV antibody is positive) T-cell lymphotropic virus, type 1[g] SARS-CoV-2[b]
Coagulation Panel[b]		**TLS Chemistry Panel**
Prothrombin time (PT) AND/OR International normalized ratio (INR) AND/OR Activated partial thromboplastin time (aPTT)		Creatinine Potassium Calcium Inorganic phosphorus Lactate dehydrogenase Uric acid[a]

CoV = coronavirus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; RNA = ribonucleic acid; SARS = severe acute respiratory syndrome; TLS = tumor lysis syndrome

a. At room temperature, rasburicase causes enzymatic degradation of the uric acid in blood/plasma/serum samples potentially resulting in spuriously low plasma uric acid assay readings. The following special sample handling procedure must be followed to avoid ex vivo uric acid degradation. Uric acid must be analyzed in plasma. Blood must be collected into prechilled tubes containing heparin anticoagulant. Immediately immerse plasma samples for uric acid measurement in an ice water bath. Plasma samples must be prepared by centrifugation in a precooled centrifuge (4°C). Finally, the plasma must be maintained in an ice water bath and analyzed for uric acid within 4 hours of collection.

b. Performed at screening and as clinically indicated in Section 2.1.

c. Females only.

d. Pregnancy testing is not required for females of nonchildbearing potential.

e. If needed to determine postmenopausal status.

f. Monitoring for hepatitis reactivation should be performed per local clinical standards.

g. Performed at screening in endemic countries only.

Serum Pregnancy Test

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Pregnancy testing should not be performed for postmenopausal women. Determination of postmenopausal status will be made during the screening period based on the subject's history.

A qualitative serum pregnancy test will be performed at screening for all women of childbearing potential.

The serum pregnancy test will be sent to and performed by the local laboratory. If the serum pregnancy test is positive the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine eligibility.

If the repeat serum pregnancy test is:

- positive, the subject is considered a screen failure;
- negative, the subject can be enrolled into the trial;
- still borderline will be considered documentation of continued lack of a positive result, the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Urine Pregnancy Test

A urine pregnancy test will be performed for all female subjects of childbearing potential on Day –1 and every 4 weeks until 30 days after the last dose of venetoclax or 90 days after the last dose of ibrutinib, whichever the latest, as indicated in Section 2.1. Unless a woman is suspected to have become pregnant, additional pregnancy testing during the clinical trial is not necessary; however, additional urine pregnancy tests can be done at any visit, as needed.

If the urine pregnancy test (which is performed at the site) is negative, begin or continue dosing. If urine pregnancy test is positive, withhold dosing and perform a serum pregnancy test. Pregnant subjects must discontinue from the study.

Viral Serology

Samples will be collected to identify hepatitis B virus (hepatitis B surface antigen or hepatitis B core antibody) and hepatitis C virus (HCV) (HCV antibody and ribonucleic acid [RNA] if HCV antibody is positive) as listed in Table 1.

All subjects enrolled will be followed with clinical laboratory testing at scheduled time points throughout the study. If a subject experiences a sign or symptom that may be suggestive of hepatitis B reactivation and/or a laboratory abnormality suggestive of potential hepatitis B reactivation (e.g., elevated aminotransferases), the investigator should pursue further work-up per clinical practice guidelines/standards. If a subject has positive hepatitis B serology, the subject should be monitored and managed following local medical standard to reduce risk of hepatitis B reactivation.

Viral serology samples are to be collected and sent to the local laboratory for testing.

Human Immunodeficiency Virus

Samples will be collected to identify human immunodeficiency virus (HIV) (anti-HIV antibody) at screening, unless prohibited by local regulations, as listed in Table 1. The investigator must discuss any local reporting requirements to local health agencies with the subject. The site will report confirmed positive results to their health agency per local regulations, if necessary.

Coagulation

Prothrombin time (PT) and activated partial thromboplastin time (aPTT)/international normalized ratio (INR) samples will be collected at screening and on study when clinically indicated.

TLS Risk Assessment and Monitoring

TLS risk assessment will occur at screening as indicated in Section 2.1.

TLS risk assessment will be defined by tumor burden, renal function, and other factors (refer to the Protocol Section 6.2). Tumor burden will be determined by computed tomography (CT) scans and absolute lymphocyte count (ALC) levels.

Laboratory monitoring for TLS will occur during the ramp-up period and once reaching the designated dose during Week 1 as indicated in Section 2.1; TLS monitoring will occur predose (full chemistry panel is required) and at 4, 8, 12, and 24 hours postdose (TLS chemistry panel is required) after each dose escalation of venetoclax (including escalation to 600 mg at Week 8 or thereafter). For the 24-hour sample, a window of –1 hour is allowed. If the predose sample coincides with the 24-hour postdose sample, then the predose sample may be used for both the predose and 24-hour analyses.

Laboratory monitoring for TLS will occur during the ramp-up period and once reaching the designated dose during Week 1 as indicated in Section 2.1; TLS monitoring will occur 4, 8, 12, and 24 hours after each dose escalation. For chemistry laboratory tests performed for TLS monitoring, refer to Table 1.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. Local laboratory results should be reviewed by the investigator as soon as possible.

If laboratory samples cannot be obtained, study drug administration may be continued provided the investigator has reviewed all prior laboratory results and confirms and discusses with the subject that there is no safety concern for the subject to continue use of the study drug in the absence of current laboratory results. The subject should be scheduled for laboratory draws as soon as feasible within 3 days from the scheduled visit.

3.13 Computed Tomography Scan

A CT scan with contrast (or magnetic resonance imaging [MRI]) will be performed at screening, at Week 24 visit, and at any time during the study as listed in Section 2.1 to confirm a clinical response (complete remission [CR]/complete remission with incomplete blood count recovery [CRi]). A CT scan will be accepted for screening purposes if previously performed within 35 days before the first dose of study drug. Otherwise, a CT scan must be performed within the screening window (28 days) for all subjects.

Contrast-enhanced CT scans including neck, chest, abdomen, and pelvis will be performed for disease assessment using the response evaluation criteria in lymphoma (RECIL)-based T-PLL consensus criteria

assessment schedule[1] (as outlined in Table 3) as reported by a local radiologist. A contrast-enhanced MRI of the neck, chest, abdomen and pelvis with a noncontrast CT scan of the chest may be used for subjects with whom a contrast CT is medically contraindicated (i.e., subjects with a severe allergy to CT contrast agents or subjects with impaired renal clearance). Whichever method is used at screening, this method should be consistently used throughout the duration of the study.

Any CT scan (or MRI) done throughout the study should be captured on the appropriate eCRF.

3.14 Disease Assessment

All measurable disease must be documented at screening (baseline) before the first dose of study drug for all subjects based on the analysis of clinical laboratory tests (hematology), physical examination, and contrast-enhanced CT scan of involved neck, chest, abdomen, and pelvis (or MRI, if CT scan is medically contraindicated).

For all subjects, clinical response (laboratory and physical examination assessments) will be assessed by the investigator during Weeks 4, 8, 12, 16, 24, 36 and every 12 weeks thereafter, and at the final visit. Note: disease assessments may be performed approximately 7 days before the scheduled visit. The clinical response will be assessed by laboratory tests and physical examination (or ultrasound) using the T-PLL consensus criteria[1] (as outlined in Table 2).

If clinical response is suggestive of a CR/CRi, a CT scan with contrast (or MRI) should be done for a confirmatory assessment as outlined in Section 3.13.

If a CT scan indicates a CR/CRi, a bone marrow aspirate and biopsy will be required as soon as possible to confirm the clinical response. For subjects who opt-in for correlative biomarker analyses, a portion of the bone marrow aspirate should be split for the optional biomarker collections listed in Section 3.17.

To meet the CR criteria, the CT scan and bone marrow are both required to be negative. Some subjects fulfill all the criteria for a CR but have a persistent anemia, thrombocytopenia, or neutropenia apparently unrelated to T-PLL, but related to drug toxicity. These subjects will be assessed with a response of CRi.

Disease assessment will continue to be performed after the last dose of study drug until disease progression for any subject who has not experienced PD at the time of permanent discontinuation of venetoclax and ibrutinib.

Table 2. Clinical Response Criteria (Based on Physical Examination/Ultrasound and Laboratory Tests)

Group	Parameter	Complete Remission (all met)	Partial Remission (≥ 2 in Group A and ≥ 1 in B met)	Stable Disease (all met)	Progressive Disease (≥ 1 in Group A or B met)
A	Lymph nodes **by physical examination/ ultrasound**	All long-axis diameters to < 1.0 cm	Decrease ≥ 30% in SLD	Change of –29% to +20% in SLD	Increase in > 20% in SLD from Nadir[a]
	Spleen **by physical examination/ ultrasound**	Spleen < 13 cm	Decrease ≥ 50% in vertical length beyond normal from baseline	Change of –49% to +49% beyond normal from baseline	Increase ≥ 50% in vertical length beyond normal from baseline
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	< 4×10^9/L	≤ 30×10^9/L **and** decrease ≥ 50% from baseline	> 30×10^9/L or change of –49% to +49%	Increase ≥ 50% from baseline[b]
	Bone marrow **only to assess if CT/MRI confirms CR/CRi**	T-PLL cells < 5% of mononuclear cells	Any	Any	Any
	Any other specific site involvement[c]	None	Any	Any	Any
B	Platelet count	≥ 100×10^9/L (untransfused)	≥ 100×10^9/L or increase ≥ 50% from baseline	Change of –49% to +49%	Decrease of ≥ 50% from baseline
	Hemoglobin	≥ 11.0 g/dL (untransfused, independent of erythropoietin)	≥ 11 g/dL or increase ≥ 50% from baseline	< 11.0 g/dL or increase < 50% from baseline or decrease < 2 g/dL	Decrease of ≥ 2 g/dL from baseline
	Neutrophils	≥ 1.5×10^9/L (independent of growth factor)	≥ 1.5×10^9/L or increase ≥ 50% from baseline	Change of –49% to +49%	Decrease of ≥ 50% from baseline

CR = complete remission; CRi = complete remission with incomplete blood count recovery; CT = computed tomography; MRI = magnetic resonance imaging; **SLD = sum of long-axis diameters of up to 3 target lesions**; T-PLL = T-cell prolymphocytic leukemia

a. Lymphadenopathy: > 20% increase in the SLD; for small lymph nodes measuring < 1.5 cm after therapy, a minimum increase of 5 mm and a long-axis diameter of ≥ 1.5 cm; or appearance of a new lesion.

b. Although no compartment shift is expected under ibrutinib in T-PLL, due to the theoretical possibility of ibrutinib-related redistribution of lymphocytes, increase ≥ 50% from baseline alone may not define progressive disease if it is associated

with lymph node or spleen size decrease or if the isolated increase occurs along the improvement of other disease parameters.

c. Pleural or peritoneal effusion, skin infiltration, central nervous system involvement.

Note: Clinical response assessments are based on physical examination/ultrasound and laboratory test values.

Source: Adapted from the response assessment of the T-PLL consensus criteria.[1]

Response definitions for disease assessments are summarized below:[1]

Complete Remission (CR): all of the response criteria have to be met.

Complete Remission with Incomplete Marrow Recovery (CRi): all of the CR response criteria in Group A have to be met and at least 1 parameter in Group B is not achieved.

Partial Remission (PR): at least 2 of the parameters in Group A and 1 parameter in Group B need to improve if previously abnormal. If only one parameter of both Groups A and B is abnormal prior to therapy, only 1 parameter needs to improve.

Stable Disease (SD): all of the above criteria have to be met. This state needs to be sustained for at least 3 months.

Progressive Disease (PD): at least one of the above criteria of Group A or Group B has to be met. Constitutional symptoms alone do not define PD.

Table 3. Confirmatory Response Criteria (Based on CT and Bone Marrow Assessments)

Group	Parameter	Complete Remission (all met)	Partial Remission (≥ 2 in Group A and ≥ 1 in B met)	Stable Disease (all met)	Progressive Disease (≥ 1 in Group A or B met)
A	Lymph nodes **by CT/MRI**	All long-axis diameters to < 1.0 cm	Decrease ≥ 30% in SLD	Change of –29% to +20% in SLD	Increase in > 20% in SLD from Nadir[a]
	Spleen **by CT/MRI**	Spleen < 13 cm	Decrease ≥ 50% in vertical length beyond normal from baseline	Change of –49% to +49% beyond normal from baseline	Increase ≥ 50% in vertical length beyond normal from baseline
	Constitutional symptoms	None	Any	Any	Any
	Circulating lymphocyte count	< 4×10^9/L	≤ 30×10^9/L **and** decrease ≥ 50% from baseline	> 30×10^9/L or change of –49% to +49%	Increase ≥ 50% from baseline[b]
	Bone marrow **only to assess if CT/MRI confirms CR/CRi**	T-PLL cells < 5% of mononuclear cells	Any	Any	Any
	Any other specific site involvement[c] **by CT/MRI**	None	Any	Any	Any

Group	Parameter	Complete Remission (all met)	Partial Remission (≥ 2 in Group A and ≥ 1 in B met)	Stable Disease (all met)	Progressive Disease (≥ 1 in Group A or B met)
B	Platelet count	≥ 100 × 10^9/L (untransfused)	≥ 100 × 10^9/L or increase ≥ 50% from baseline	Change of –49% to +49%	Decrease of ≥ 50% from baseline
	Hemoglobin	≥ 11.0 g/dL (untransfused, independent of erythropoietin)	≥ 11 g/dL or increase ≥ 50% from baseline	< 11.0 g/dL or increase < 50% from baseline or decrease < 2 g/dL	Decrease of ≥ 2 g/dL from baseline
	Neutrophils	≥ 1.5 × 10^9/L (independent of growth factor)	≥ 1.5 × 10^9/L or increase ≥ 50% from baseline	Change of –49% to +49%	Decrease of ≥ 50% from baseline

CR = complete remission; CRi = complete remission with incomplete blood count recovery; CT = computed tomography; MRI = magnetic resonance imaging; **SLD = sum of long-axis diameters of up to 3 target lesions**; T-PLL = T-cell prolymphocytic leukemia

a. Lymphadenopathy: > 20% increase in the SLD; for small lymph nodes measuring < 1.5 cm after therapy, a minimum increase of 5 mm and a long-axis diameter of ≥ 1.5 cm; or appearance of a new lesion.

b. Although no compartment shift is expected under ibrutinib in T-PLL, due to the theoretical possibility of ibrutinib-related redistribution of lymphocytes, increase ≥ 50% from baseline alone may not define progressive disease if it is associated with lymph node or spleen size decrease or if the isolated increase occurs along the improvement of other disease parameters.

c. Pleural or peritoneal effusion, skin infiltration, central nervous system involvement.

Note: Confirmatory response assessments based on CT scan and bone marrow aspirate and biopsy.

Source: Adapted from the response assessment of the T-PLL consensus criteria.[1]

3.15 Bone Marrow Aspirate and Biopsy

Bone marrow aspirate and biopsy samples will be performed as soon as possible after a CT scan indicates a CR/CRi, to confirm the clinical response. Each time a bone marrow aspirate or biopsy is performed, the sample will be split for analyses of disease (see Section 3.14) provided informed consent was given for correlative studies for biomarker (Section 3.17) assessments.

Local laboratory results to confirm response will be captured on the appropriate eCRF. Results from bone marrow aspirates and biopsies performed throughout the study should be captured on an appropriate eCRF, including those performed to confirm or rule out disease progression.

3.16 Pharmacokinetic Sampling

Venetoclax and Ibrutinib Samples

Blood samples (3 mL each) will be collected by venipuncture for analysis of venetoclax and ibrutinib plasma concentrations. In preparation for visits that include collection of a pharmacokinetic (PK) blood sample, site personnel will contact the subject approximately 2 days before the scheduled visit date to

review the importance of properly documenting dosing information. Blood samples will be collected at the time points presented in Table 4.

Table 4. Pharmacokinetic Sampling Times

Pharmacokinetic Blood Samples[a,b]	
Week 4	**Week 8**
Predose	Predose

a. Predose samples will be collected within 1 hour prior to dosing.

b. Pharmacokinetic samples will be collected to measure venetoclax and Ibrutinib plasma concentrations.

Subjects should take venetoclax and ibrutinib doses at the site after PK blood sample collection.

For all PK samples, the date and accurate time of the PK sample collection will be recorded on the laboratory requisition form. Date and time of the 3 study drug doses taken prior to PK sample collection will also be documented (see Section 3.18).

Additionally, the date and time (to the nearest minute) of each venetoclax dose and whether or not the prior venetoclax dose was taken within 30 minutes after the completion of meal will be recorded for each scheduled PK sampling day. Sites will ensure all information is captured through source documents (site or subject calendar/diary provided by AbbVie).

Disposition of Samples

Whole blood will be collected into appropriately labeled tubes and processed as outlined in the most current version of Study M18-803 laboratory manual.

The frozen PK samples will be packed in dry ice sufficient to last during transport and shipped from the study site to a central laboratory designated by AbbVie. An inventory of the samples included will accompany the package. Please refer to current study-specific M18-803 laboratory specifications for complete sample processing and shipping instructions.

Measurement Method

Plasma concentrations of venetoclax will be determined by the bioanalysis department at AbbVie using a validated method. Plasma concentrations of ibrutinib will be determined by a vendor under the supervision of the bioanalysis department at AbbVie. Plasma concentration of possible venetoclax metabolite(s) may be determined with validated or nonvalidated methods.

3.17 Optional Biomarker and Exploratory Research Sampling

Participation in these correlative studies is optional. If informed consent is provided, then peripheral blood and/or bone marrow biospecimens will be collected to conduct exploratory analyses to identify potential prognostic, predictive, or surrogate biomarker signatures. The types of biomarkers may include nucleic acids, proteins, lipids, or metabolites. These assessments may include biomarkers related to the pathway targeted by the study drug or those believed to be related to the disease or to drug response. The information learned from analyzing these samples may be used to investigate

factors influencing response to treatment, scientific questions related to T-PLL, and/or in the development of new therapies and diagnostic tests. The analyses are exploratory in nature, may be conducted in non-Good Laboratory Practice (GLP) laboratories, and the results from correlative studies may not be included with the clinical study report.

Cells isolated from the peripheral blood/bone marrow may be analyzed to assess specific genetic mutations and/or to track the tumor cells to determine the presence of minimal residual disease (MRD). Additionally, the expression levels (RNA or protein) of molecules may be assessed (e.g., molecules involved in the apoptosis machinery) and evaluated for correlations with efficacy.

All biomarker samples should be labeled and shipped as outlined in the study-specific laboratory manual. AbbVie (or people or companies working with AbbVie) will store these samples in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on venetoclax or drugs of this class, or this disease and related conditions continues, but for no longer than 20 years after study completion or per local requirement.

Biomarker Collections

Peripheral blood samples will be collected at screening (Day –28 through Day –2), Week 1 (Days –1, 1, and 6), Weeks 4, 8, 12, 16, 24, 36, and every 12 weeks thereafter, and at the final visit (see Table 5).

A cheek swab will be collected at screening (refer to Table 5).

Specific instructions for preparation and storage of biomarker specimens will be provided by AbbVie or its designee.

Biomarker sampling times are listed in Table 5.

Table 5. Sampling Times for Optional Biomarkers

Parameter	Sample[a,b] (volume)	Day –28 through Day –2	Week 1 (Day –1, Day 1, Day 6)	Weeks 4, 8, 12, 16, and 24	Week 36 and Every 12 Weeks Thereafter	Final Visit[c] and PTFU[d]
MRD (molecular)	Peripheral blood (6 mL)	X		X	X	X
Tumor profiling	Peripheral blood (8 mL)	X				
Tumor ex vivo sensitivity	Peripheral blood (8 mL)	X	X[e]			
MRD (molecular)	Bone marrow (2 mL)			Any time during the study (i.e., confirmation of a clinical response).		
Tumor profiling	Bone marrow (1 mL)			Any time during the study (i.e., confirmation of a clinical response).		
Tumor ex vivo sensitivity	Bone marrow (3 mL)			Any time during the study (i.e., confirmation of a clinical response).		
Germline control for tumor profiling	Cheek swab	X				

MRD = minimal residual disease; PTFU = post-treatment follow-up

a. Peripheral blood for biomarker assessment will be taken at indicated time points and any other time during the study with a bone marrow sample for confirmation of a clinical response.

b. If a computed tomography scan indicates a CR/CRi, a bone marrow sample will be taken during the study to confirm the clinical response; the sample will be split for analyses of disease and biomarker assessments provided informed consent was given for correlative studies.

c. The final visit will occur at the end of the study or the end of study treatment.

d. Post-treatment follow-up visits will be conducted until documented progressive disease or other post-treatment therapies (including stem cell transplantation) are received. The post-treatment follow-up visits will follow the same schedule as the visit schedule (i.e., Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, and every 12 weeks thereafter).

e. Predose and 6 hours post-venetoclax dose.

Note: Participation in the biomarker/correlative studies is optional. If informed consent is provided, then peripheral blood and/or bone marrow biospecimens will be collected at the indicated time points.

3.18 Dispense Study Drug

Study drug will be dispensed to subjects as specified in Section 2.1. The first dose of study drug will be administered after all other baseline (Day –1) procedures are completed. At the visits specified in Section 2.1, the site personnel will review and retain a copy of the dosing diary, review returned study drug kits, and empty study drug packaging to verify compliance.

Dosing Instructions and Dosing Card

Subjects will be provided with self-administration dosing instructions and a study drug dosing diary at visits noted in Section 2.1. Subjects will be instructed to record the exact date, time (to the nearest minute), and number of tablets and capsules of the last 2 doses of venetoclax and ibrutinib, respectively, taken prior to each scheduled PK sample collection as noted in Section 2.1. Subjects should be instructed to complete the dosing diary at the time the doses are taken. Site personnel will collect the completed dosing diaries from all subjects at the visits indicated in Section 2.1. The information from the study drug dosing diary will be recorded in the eCRF. In the event that the dosing diary is not available, the site may obtain dosing information via subject interview and record this information in the eCRF and the subject's source documents.

To facilitate proper dosing of study drug before PK blood samples are taken, the following procedures should be performed:

- Site personnel will contact the subject approximately 2 days prior to the scheduled visit date to review the importance of properly documenting dosing information (specifically, the date and time of the last 2 doses prior to the visit where the PK sample is drawn) onto the dosing diary and remind the subject to bring the completed dosing diary to the scheduled study visit. The date and time of the contact will be recorded in the subject's source documents.
- The completed dosing diary will be collected by site personnel on the day of the visit and kept as a source record of dosage administration times documented in the eCRF.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Study drug may be shipped from the study site directly to the study subject's home if all the following criteria are met:

- Direct-to-patient (DTP) shipment of study drug is allowed by local regulations and the relevant ethics committee
- Study drug can be administered by the subject (or subject's caregiver) at home
- Subject agrees to have the study drug shipped directly to their home
    - Shipments may also include other study supplies (e.g., drug dosing diaries). Instructions will be provided by AbbVie as to how a study site can initiate a DTP shipment using Marken, a global vendor selected by AbbVie to provide this service when necessary. Shipments of study drugs from the study site to a subject's home will be appropriately temperature controlled (qualified shipper or temperature monitoring) within the labeled storage conditions. Signature is required upon delivery; due to COVID-19 related social distancing, this may be provided by the courier after delivery. Documentation of the shipment is to be retained by the clinical site.
    - AbbVie will not receive subject identifying information related to these shipments, as the site will work directly with the courier.

The study site is responsible for meeting IRB/IEC reporting requirements related to DTP shipments of study drug, and for obtaining consent to provide delivery information to the courier and documenting this consent in source documents.

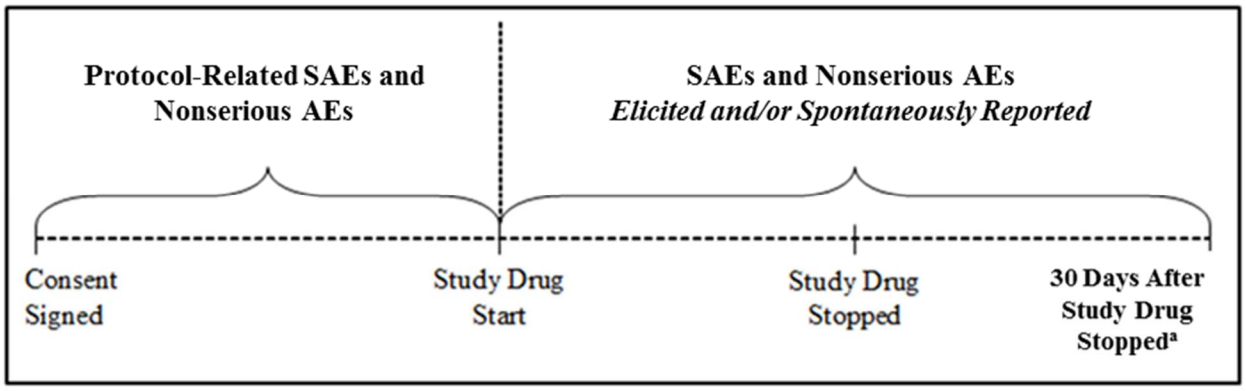
3.19 Subject Withdrawal from Study

All attempts must be made to determine the date of the last study drug dose and the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment, irrespective of whether or not the subject decides to continue participation in the study.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All protocol-related serious adverse events (SAEs) as well as protocol-related nonserious AEs (e.g., infection at liver biopsy site done during screening) will be collected from the time the subject signed the study-specific informed consent until study drug administration. From the time of study drug administration until 30 days after discontinuation of study treatment, all AEs and SAEs will be collected whether solicited or spontaneously reported by the subject. After 30 days following completion of study treatment and throughout the post-treatment period, all spontaneously reported SAEs will be collected (nonserious AEs will not be collected). All AEs should be followed until resolution, return to baseline, or determined to be stable per the investigator.



AE = adverse event; SAE = serious adverse event

a. 30 Days after the last dose of venetoclax or ibrutinib.

4.2 Recording Data and Analyses of Safety Findings

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent AEs (i.e., any event that begins or worsens in severity after initiation of study drug through 30 days poststudy drug dosing) will be tabulated by primary MedDRA system organ class (SOC) and preferred term. The tabulation of the number of subjects with treatment-emergent AEs by severity grade and relationship to study drug also will be provided. Subjects reporting more than 1 AE for a given MedDRA preferred term will be counted only once for that term using the most severe grade according to the severity grade table and the most related according to the relationship to study drug tables. Subjects reporting more than 1 type of event within an SOC will be counted only once for that SOC.

4.3 Reporting Adverse Events and Intercurrent Illnesses

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

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the oncology safety team at:

Oncology Safety Team
Dept. R48S, Bldg. AP30
1 North Waukegan Road
North Chicago, Illinois 60064
Office: +1 (847) 935-2609
Email: SafetyManagement_Oncology@abbvie.com

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

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted], **MD**
AbbVie
Alte Steinhausenstrasse 14
CH-6330 Cham, Switzerland

Contact Information:

Mobile: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation hotline where your call will be redirected to a designated backup AbbVie TA MD:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the investigational medicinal product in accordance with Directive 2001/20/EC.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study CRFs should be completed in the event of COVID-19-related missed/virtual visits, study drug interruptions or discontinuations, or AEs (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as AEs. If the event meets the criteria for an SAE, then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 supplemental signs/symptoms
- COVID-19 status form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact (TA MD) listed above before reintroducing study drug.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 SUSAR Reporting

AbbVie will be responsible for SUSAR reporting for the investigational medicinal product in accordance with global and local guidelines. Appendix A of the venetoclax Investigator Brochure[2] and Section 6 of the ibrutinib Investigator Brochure[3] will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' serious adverse reaction will be used to assess expectedness.

6 STUDY DRUG

6.1 Treatments Administered

Venetoclax will be dispensed in the form of 10-, 50- and 100-mg film-coated tablets (refer to the Protocol Section 5.7) at the visits listed in Section 2.1. Each dose of venetoclax will be taken with approximately 240 mL of water. Subjects will be trained to self-administer venetoclax orally once daily (QD) **within 30 minutes after the completion of breakfast or the subject's first meal of the day**. On days the subject is given ibrutinib, venetoclax and ibrutinib should be administered approximately at the same time.

Ibrutinib will be self-administered orally QD in the form of 140-mg hard capsules (refer to the Protocol Section 5.7) at the visits listed in Section 2.1. The capsules should be swallowed whole with water and should not be opened, broken, or chewed. On Day -1, ibrutinib should be taken with 240 mL of water and within 30 minutes after the completion of breakfast or the subject's first meal of the day.

Study drug must not be dispensed without contacting the interactive response technology (IRT) system. Study drug may only be dispensed to subjects enrolled in the study through the IRT system. At the end of the treatment period or at the final visit, the site will contact the IRT system to provide visit date information and study drug return information for each kit.

For additional details on dispensing study drug, especially in the event DTP is necessary, see Section 3.18.

6.2 Packaging and Labeling

Ibrutinib will be supplied in bottles and venetoclax will be supplied in bottles or blister cards to accommodate the study design. Each kit will be labeled as required per country requirements. The

labels must remain affixed to the kits. All blank spaces should be completed by site staff prior to dispensing to subject.

Storage and Disposition of Study Drug

Venetoclax and ibrutinib must be stored at controlled room temperature (15° to 25°C/59° to 77°F). The investigational products are for investigational use only and are to be used only within the context of this study. The study drugs supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use, destroyed on site, or returned to AbbVie, as appropriate.

6.3 Method of Assigning Subjects to Treatment Groups

This is a nonrandomized, open-label, single arm study. All eligible subjects will receive the venetoclax 400 mg (target dose) QD and ibrutinib 420 mg QD for up to 2 years.

At the screening visit, all subjects will be assigned a unique subject number through the use of the IRT. For subjects who do not meet the study selection criteria, the site personnel must contact the IRT system and identify the subject as a screen failure. For subjects who rescreen, the screening number assigned by the IRT at the initial screening visit should be used.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Upon receipt of study drug, the site will acknowledge receipt in the IRT system (refer to the Protocol Section 5.8).

Contact information and user guidelines for IRT use will be provided to each site.

6.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in the study protocol, Section 4.2.

All tablets of venetoclax will be dosed together QD. All capsules of ibrutinib will be dosed together QD. All subjects should take all doses of study drugs as detailed in Section 6.1.

Venetoclax and ibrutinib will be administered at the designated study visits as specified in Section 2.1.

7 REFERENCES

1. Staber PB, Herling M, Bellido M, et al. Consensus criteria for diagnosis, staging, and treatment response assessment of T-cell prolymphocytic leukemia. Blood. 2019;134(14):1132-43.
2. AbbVie. Venetoclax (ABT-199) Investigator's Brochure. Current version.
3. Amgen. Imbruvica (ibrutinib) Investigator's Brochure. Current version.

APPENDIX A. STUDY SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
AE	adverse event
ALC	absolute lymphocyte count
aPTT	activated partial thromboplastin time
CLL	chronic lymphocytic leukemia
COVID-19	coronavirus disease – 2019
CR	complete remission
CRi	complete remission with incomplete bone marrow recovery
CT	computed tomography
CYP	cytochrome P450
DTP	direct-to-patient
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
GLP	Good Laboratory Practice
HCV	hepatitis C virus
HIV	human immunodeficiency virus
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
MedDRA	Medical Dictionary for Regulatory Activities
MRD	minimal residual disease
MRI	magnetic resonance imaging
OATP	organic anion-transporting polypeptide
PD	progressive disease
PK	pharmacokinetic(s)
P-gp	P-glycoprotein
PT	prothrombin time
QD	once daily
RECIST	response evaluation criteria in solid tumors

RNA	ribonucleic acid
SAE	serious adverse event
SOC	system organ class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TLS	tumor lysis syndrome
T-PLL	T-cell prolymphocytic leukemia

APPENDIX B. SAMPLE LIST OF PROHIBITED AND CAUTIONARY MEDICATIONS

Prohibited
Warfarin and coumarin derivatives[a] **Corticosteroids for the treatment of the underlying malignancy**
Prohibited during Ramp-Up and Cautionary Afterwards
Strong CYP3A inhibitors – boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, elvitegravir/ritonavir, idelalisib,* indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, paritaprevir/ritonavir combinations, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole
Cautionary
Strong CYP3A inducers – avasimibe, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St John's wort **Moderate CYP3A inducers** – bosentan, efavirenz, etravirine, modafinil, nafcillin **Moderate CYP3A inhibitors** – amprenavir, aprepitant, atazanavir, cimetidine, ciprofloxacin, clotrimazole, crizotinib,* cyclosporine,* darunavir/ritonavir, diltiazem,[b] dronedarone, erythromycin, fluconazole, fluvoxamine, fosamprenavir, imatinib,* isavuconazole, tofisopam, verapamil **P-gp substrates** – aliskiren, ambrisentan, colchicine, dabigatran etexilate, digoxin, everolimus,* fexofenadine, lapatinib,* loperamide, maraviroc, nilotinib,* ranolazine, saxagliptin, sirolimus,* sitagliptin, talinolol, tolvaptan, topotecan* **BCRP substrates** – methotrexate,* mitoxantrone,* irinotecan,* lapatinib,* rosuvastatin, sulfasalazine, topotecan* **OATP1B1/1B3 substrates** – asunaprevir, atrasentan, atorvastatin, cerivastatin, docetaxel, ezetimibe, fluvastatin, glyburide, nateglinide, paclitaxel, rosuvastatin, pitavastatin, pravastatin, repaglinide, simvastatin acid, telmisartan, valsartan, olmesartan **P-gp inhibitors** – amiodarone, captopril, carvedilol, felodipine, propafenone, quercetin, quinidine, ronalzine, ticagrelor **BCRP inhibitors** – geftinib,* curcumin **Other anticoagulants** or medications that inhibit platelet function (warfarin and coumarin derivatives prohibited)

BCRP = breast cancer resistance protein; CYP = cytochrome P450; FDA = Food and Drug Administration; OATP = organic anion-transporting polypeptide; P-gp = P-glycoprotein; USPI = United States package insert

a. Closely monitor the international normalized ratio.

b. Moderate CYP3A inhibitor per venetoclax FDA USPI.

* These are anticancer agents; consult contact the AbbVie Therapeutic Area Medical Director before use.

Note: This is not an exhaustive list. For an updated list, see the following link:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm

In addition to the medications listed in this table, subjects receiving venetoclax should not consume grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or star fruits.