CLINICAL STUDY PROTOCOL

Protocol Number: ME-522-001

A Phase 1, Open-Label, Study of Voruciclib in Subjects with Relapsed and/or Refractory B-Cell Malignancies or Acute Myeloid Leukemia After Failure of Prior Standard Therapies and Voruciclib in Combination with Venetoclax in Subjects with Relapsed and/or Refractory Acute Myeloid Leukemia

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Investigational Drug:	Voruciclib (ME-522, formerly P1446A-05)
IND Number:	121938, 159178
Amendment 12:	29 January 2024

SPONSOR'S PROTOCOL SIGNATURE PAGE

By signing below, the Sponsor declares that this study will be conducted in accordance with current United States (US) Food and Drug Administration Code of Federal Regulations, Good Clinical Practice (GCP) standards, the Declaration of Helsinki (Scotland 2000, as clarified 2002), the Medical Research council's "Code of Ethics for Research Involving Humans – May 1997," and local ethical and legal requirements.

DocuSigned by:

Richard Ghalie

Signer Name: Richard Ghalie
Signing Reason: I approve this document
Signing Time: 30-Jan-2024 | 14:09 PST

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30-Jan-2024 | 14:09 PST

Richard Ghalie, M.D.
Chief Medical Officer

Date

INVESTIGATOR'S SIGNATURE PAGE

By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any changes to the protocol must be approved by MEI Pharma, Inc., before seeking approval from the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

The study will be conducted in accordance with the current International Council on Harmonisation (ICH) Guidelines, the Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, the Medical Research council's "Code of Ethics for Research Involving Humans – May 1997," and local ethical and regulatory requirements.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from MEI Pharma, Inc., except to the extent necessary for the conduct of the study at this study site.

Principal Investigator:

Signature	Date
Printed Name	
Institution	

PROTOCOL SYNOPSIS

TITLE

A Phase 1, Open-label, Study of Voruciclib in Subjects with Relapsed and/or Refractory B-Cell Malignancies or Acute Myeloid Leukemia After Failure of Prior Standard Therapies and Voruciclib in Combination with Venetoclax in Subjects with Relapsed and/or Refractory Acute Myeloid Leukemia

PROTOCOL NUMBER

ME-522-001

SUBJECT POPULATION

Subjects with relapsed and/or refractory B-cell malignancies (Follicular lymphoma [FL], mantle cell lymphoma [MCL], marginal zone lymphoma [MZL], small lymphocytic lymphoma [SLL], chronic lymphocytic leukemia [CLL], and diffuse large B-cell lymphoma [DLBCL]) or relapsed and/or refractory acute myeloid leukemia (AML)

INVESTIGATIONAL PRODUCT

The active pharmaceutical ingredient, voruciclib, is (+)-trans-3-[2[(2-Chloro-4-trifluoromethyl-phenyl)-5,7-dihydroxy-8-(2-hydroxymethyl-1-methyl-pyrrolidin-3-yl)-chromen-4-one, and is available in 2 salt forms, hydrochloride and malonate.

Voruciclib is a potent oral cyclin-dependent kinase (CDK) inhibitor that indirectly suppresses the function of the pro-survival Myeloid cell leukemia protein (Mcl-1).

Voruciclib is provided as 50 and 100 mg capsules (hydrochloride salt) or tablets (malonate salt) for oral administration. The malonate salt tablet is the only formulation that will be used in the voruciclib and venetoclax (Venclexta®) combination portion of this study.

Other co-administered drug (combination study cohorts in AML subjects only, per this amendment [Amendment 11]):

Voruciclib will be administered, in some cohorts, in combination with the Bcl-2 inhibitor venetoclax. Venetoclax is approved by the US Food and Drug Administration for the treatment of adults with CLL or SLL, and in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults aged 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy.

Venetoclax is available commercially as 10 mg, 50 mg, and 100 mg tablets for oral administration.

STUDY OBJECTIVES

Primary Objectives

- Determine the safety and tolerability of voruciclib and identify a safe and minimum biologically effective dose (mBED) of voruciclib monotherapy in subjects with relapsed or refractory B-cell malignancies and relapsed or refractory AML
- Determine the safety and tolerability, and identify the safe and mBED of voruciclib in combination with venetoclax in subjects with relapsed or refractory AML

Secondary Objectives

- Evaluate the potential efficacy of voruciclib monotherapy based on:
  - International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for CLL/SLL (Appendix 5) or the Lugano classification of response assessment for lymphoma (Appendix 6), as appropriate, for subjects with B-cell malignancies
  - The 2017 European LeukemiaNet (ELN) criteria for subjects with AML (Appendix 4)
- Evaluate the potential efficacy of voruciclib in combination with venetoclax in subjects with AML based on the 2017 ELN criteria
- Evaluate the pharmacokinetics (PK) of voruciclib administered as monotherapy, and the PK of voruciclib and venetoclax when administered in combination

Exploratory Objectives

- Determine the effect of voruciclib monotherapy and voruciclib in combination with venetoclax (AML only) on biomarkers and functional activities of proteins in the apoptotic pathway
- Correlate anti-tumor activity with baseline tumor characteristics

STUDY DESIGN

This is a Phase 1, open-label, 3 + 3 dose escalation study to determine the safety and preliminary efficacy of voruciclib as monotherapy in subjects with relapsed or refractory B-cell malignancies or AML, and in combination with venetoclax in subjects with relapsed or refractory AML after treatment with standard therapy.

Dose-Escalation Cohorts

Voruciclib Monotherapy: Dose escalation with voruciclib monotherapy will be conducted separately for subjects with AML and B-cell malignancies, as tolerability, dose limiting toxicity (DLT), and safe and mBED may be different for these 2 disease groups.

As of Amendment 7 (rationale provided below), voruciclib monotherapy is evaluated using an intermittent (IS) dosing schedule of 2 weeks on therapy and 2 weeks off therapy (IS $IS_{2w,2w}$). If $IS_{2w,2w}$ is not tolerated, an intermittent schedule of 1 week on therapy followed by 3 weeks off therapy in a 28-day cycle ($IS_{1w,3w}$) may be evaluated.

Subjects will be enrolled into separate but parallel dose cohorts, designated as ‘a’ for AML subjects and ‘b’ for B-cell malignancy subjects. The following voruciclib monotherapy dose/schedule cohorts will potentially be enrolled:

- Cohort 6 a,b: 100 mg QD, administered $IS_{2w,2w}$
- Cohort 7 a,b: 150 mg QD, administered $IS_{2w,2w}$
- Cohort 8 a,b: 200 mg QD, administered $IS_{2w,2w}$
- Cohort 9 a,b: 100 mg QD, administered $IS_{1w,3w}$
- Cohort 10 a,b: 150 mg QD, administered $IS_{1w,3w}$
- Cohort 11 a,b: 200 mg QD, administered $IS_{1w,3w}$

Enrollment will proceed first on the $IS_{2w,2w}$ from Cohorts 6a to 8a (AML) and 6b to 8b (B-cell malignancies), with dose escalation based on DLT assessment in each disease group separately. If voruciclib monotherapy is deemed not tolerated in a Cohort 6 group (i.e., 6a or 6b), then dose escalation on the $IS_{2w,2w}$ schedule for that group will be closed and the $IS_{1w,3w}$ schedule for the same

disease group will be evaluated, with enrollment proceeding from Cohorts 9 to 11 (a, and/or b, as appropriate).

Dose escalation to the next 'a' or 'b' cohort will be allowed after 3 subjects have completed Cycle 1 with no reported DLTs or after 6 subjects have completed Cycle 1 with no more than 1 DLT in the respective 'a' or 'b' cohort (DLT criteria defined below). Escalation to the next dose level or moving to the less intensive dosing schedule will depend on demonstrated safety and tolerability within a cohort and with the approval of the Study Review Committee (SRC), composed of clinical investigators and sponsor representatives (including the Medical Monitor).

If the next dose level in the AML or B-cell malignancies monotherapy cohorts has been declared safe by the SRC, subjects with the same disease type (AML or B-cell malignancies) enrolled in the monotherapy cohorts at a lower dose level may have their dose escalated to the next dose level after completing Cycle 1 without a DLT (intra-subject dose escalation). For example, a subject with B-cell malignancies enrolled in Cohort 6b (100 mg $IS_{2w,2w}$) may have the dose increased to 150 mg $IS_{2w,2w}$ in Cycle 2 if the dose of 150 mg $IS_{2w,2w}$ was deemed safe in the B-cell malignancies cohort by the SRC.

Voruciclib + Venetoclax Combination Therapy (AML Only)

In Amendment 11, subsequent to determination of the safe and mBED of voruciclib monotherapy in AML subjects, the combination of voruciclib with venetoclax will be evaluated in subjects with relapsed and/or refractory AML (see rationale provided below).

The combination cohorts, beginning at Cohort 12 dose level of voruciclib in combination with venetoclax on an $IS_{2w,2w}$ dosing schedule, will be enrolled as follows:

- Cohort 12: 50 mg once every other day (QOD), administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 13: 50 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 14: 100 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 15: 150 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 16: 200 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 17: 250 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 18: 300 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
- Cohort 19: 350 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days

Dose escalation to the next cohort will be reviewed by the SRC after 3 subjects have completed 1 cycle with no reported DLTs, or after 6 subjects have completed 1 cycle with no more than 1 DLT. (DLT criteria defined below.) Escalation to a subsequent cohort will depend on demonstrated safety and tolerability within a cohort and with the approval of the SRC.

If the next dose level in the AML combination cohort has been declared safe by the SRC, subjects enrolled at a lower dose level may have their dose escalated to the next dose level after completing Cycle 1 without a DLT (intra-subject dose escalation). For example, a subject with AML enrolled in Cohort 13 (50 mg $IS_{2w,2w}$) may have the dose increased to 100 mg in Cycle 2 if the dose of 100 mg $IS_{2w,2w}$ was deemed safe in Cohort 14 by the SRC.

Dose escalation proceeds until a real-time assessment of clinical and PK parameters by the SRC establishes the safe and mBED for voruciclib in combination with venetoclax. More specifically, a voruciclib dose in combination with venetoclax that meets the following criteria:

- DLT not to exceed 1 in 6 subjects, overall response rate (ORR) ≥30%, as compared to historical ORR of 19% with 400-800 mg venetoclax alone in relapsed/refractory AML (Konopleva 2016), and

- Trough plasma concentration of 1 to 1.5 µM, concentrations shown to be synergistic in combination with venetoclax in preclinical models.

In Amendment 12, the combination of voruciclib with venetoclax will be evaluated in subjects with relapsed and/or refractory AML using a voruciclib intermittent schedule of daily dosing on Days 1–21 in a 28-day cycle, with no voruciclib dosing on Days 22–28 of the cycle, designated as $IS_{3w,1w}$. (see rationale below). In Cycle 1, voruciclib dosing begins on Day 3 after completion of venetoclax dose ramp-up. The starting voruciclib dose level on $IS_{3w,1w}$ will be 150 mg (i.e., 2 dose levels lower than the dose of 250 mg that was shown to have no DLTs in the $IS_{2w,2w}$ schedule). The venetoclax dose will be 200 mg on Days 1–21 and 400 mg on Days 22–28 in a 28-day cycle. In Cycle 1, venetoclax dose ramp-up will consist of venetoclax 100 mg on Day 1, then 200 mg on Days 2–21, then 400 mg on Days 22–28, with voruciclib beginning on Day 3. Dose escalation will follow the same 3+3 design as in the $IS_{2w,2w}$ cohorts, and uses the same definition for DLT, MTD, and mBED.

In the $IS_{2w,2w}$ dose escalation cohorts, no DLTs have been reported at doses ranging from 50 mg QOD to 250 mg QD, and enrollment was ongoing at the 300 mg dose level at the time of issuance of protocol Amendment 12.

The combination cohorts on $IS_{3w,1w}$ will be numbered as listed below:

- Cohort 21: 150 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
- Cohort 22: 200 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
- Cohort 23: 250 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
- Cohort 24: 300 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
- Cohort 25: 350 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days

Expansion Cohorts

For AML subjects only, after review of safety and clinical activity data, the SRC may select a recommended dose level for expansion cohorts of voruciclib monotherapy (6 subjects) and/or voruciclib + venetoclax combination therapy (up to an additional 12 subjects each for $IS_{2w,2w}$ and $IS_{3w,1w}$) in order to obtain additional safety, efficacy, PK, and pharmacodynamic/biomarker data. Formal stopping rules for excess toxicity in the AML combination therapy expansion cohort are provided in the protocol (Section 4.5).

Rationale for Dose Schedule Changes in Amendment 7

In the earlier dose-escalation phase of this study, in which voruciclib was administered QD for 28 days per 28-day cycle, there were no DLTs in the 50 mg QD dose cohorts in either B-cell or AML subjects. However, at 100 mg QD dose level, 2 subjects with AML had DLTs of pneumonitis (n = 1) and interstitial lung disease (n = 1), prompting a Sponsor decision to no longer pursue a QD dosing schedule in either disease group. Because there were no objective responses reported at the dose of 50 mg QD, intermittent dosing schedules ($IS_{2w,2w}$ and $IS_{1w,3w}$) were started with voruciclib 100 mg to determine whether doses of 100 mg or greater can be administered safely. These doses are projected to achieve plasma concentrations consistent with concentrations shown to demonstrate anti-proliferative effects in in vitro models.

(Note: Amendments 8, 9, and 10 were not implemented)

Rationale for the Addition of Voruciclib + Venetoclax Combination Therapy in Amendment 11

For the treatment of AML subjects, it is hypothesized that use of a CDK9 inhibitor (such as voruciclib) with its corollary effect on Mcl-1 inhibition when given in combination with a Bcl-2 inhibitor (such as venetoclax) could synergistically bring about disruption of the cell cycle and inhibition of pro-survival cell cycle pathways. Based on preliminary safety and tolerability data with voruciclib monotherapy, the $IS_{2w,2w}$ dosing schedule will be used for the combination of voruciclib and venetoclax in AML patients.

Rationale for an Additional Voruciclib Schedule in Amendment 12

The rationale for the $IS_{3w,1w}$ is to decrease the number of days without voruciclib from 14 to 7 days in a treatment cycle, thereby reducing the potential risk of AML regrowth during the 2-week treatment break in the $IS_{2w,2w}$ schedule.

STUDY TREATMENT

Study Drug Administration

For monotherapy cohorts, voruciclib will be administered once daily on dosing days of $IS_{2w,2w}$ or $IS_{1w,3w}$ cohorts in 28-day cycles, with the first day of treatment designated as Day 1.

For combination cohorts, see Administration Schedule of Voruciclib $IS_{2w,2w}$ and Venetoclax per 28-day Cycle, below.

Administration Schedule of Voruciclib $IS_{2w,2w}$ and Venetoclax per 28-day Cycle

Cycle 1	Day 1	Day 2	Days 3 to 14	Days 15 to 21	Days 22 to 28
Venetoclax	100 mg	200 mg	200 mg	200 mg	400 mg
Voruciclib QD	-	-	Cohort dose	None	None
Voruciclib QOD[a]	-	-	50 mg[a]	None	None

Cycle 2 and beyond	Days 1 to 14	Days 15 to 21	Days 22 to 28
Venetoclax	200 mg	200 mg	400 mg
Voruciclib QD	Cohort dose	None	None
Voruciclib QOD[a]	50 mg[a]	None	None

Abbreviation: QOD = once every other day

[a] For Cohort 12, the dose of voruciclib will be 50 mg once every other day (QOD) on Days 3, 5, 7, 9, 11, and 13 of Cycle 1, and on Days 1, 3, 5, 7, 9, 11, and 13 of Cycle 2 and beyond

For combination cohorts, see Administration Schedule of Voruciclib $IS_{3w,1w}$, and Venetoclax per 28-day Cycle below.

Administration Schedule of Voruciclib $IS_{3w,1w}$ and Venetoclax per 28-day Cycle

Cycle 1	Day 1	Day 2	Days 3 to 21	Days 22 to 28
Venetoclax	100 mg	200 mg	200 mg	400 mg
Voruciclib QD	-	-	Cohort dose	None

Cycle 2 and beyond	Days 1 to 21	Days 22 to 28
Venetoclax	200 mg	400 mg
Voruciclib QD	Cohort dose	None

Abbreviation: QD = once per day.

Dosing Instructions

For subjects in the monotherapy cohorts, voruciclib is to be taken orally on an empty stomach, at least 1 hour prior to food or 2 hours after food, at approximately the same time each day on dosing days. It is recommended that voruciclib be taken in the morning. A missed dose may be taken up to 12 hours after the usual time; after 12 hours the dose should be omitted.

For subjects in the combination voruciclib + venetoclax cohorts, venetoclax is to be taken first (with a meal) followed by voruciclib taken at least 2 hours later (e.g., meal completed at 8 a.m. with venetoclax, dose voruciclib after 10:00 a.m.), with the exception of C2D1 when voruciclib is to be dosed 6 hours after venetoclax administration, after completion of the 6-hour PK sample collection.

Voruciclib tablets must not be chewed, crushed, or broken.

Dose Modifications

For subjects enrolled on voruciclib monotherapy cohorts, criteria for interrupting study drug treatment and requirements for re-treatment or discontinuation of study drug are provided in Table 10 of the protocol.

For subjects enrolled on voruciclib + venetoclax combination cohorts, dose modifications for toxicities attributed to venetoclax or for the combined effect of voruciclib and venetoclax will be based on the Venclexta US Prescribing Information and are provided in protocol Table 11.

Duration of Therapy

Subjects may continue to receive voruciclib monotherapy or voruciclib + venetoclax while there is evidence of clinical benefit (partial remission [PR] or better) in subjects with B-cell malignancies or AML by the end of Cycle 6 and acceptable toxicity as judged by the Investigator.

SAFETY PLAN

Dose-Limiting Toxicity (DLT)

A DLT will be defined as any of the following treatment-emergent adverse events (TEAEs) occurring in Cycle 1 (first 28 days) of voruciclib monotherapy or voruciclib + venetoclax combination therapy that are clearly unrelated to the underlying disease or extraneous causes:

- Symptomatic nonhematological Grade ≥3 laboratory abnormalities or asymptomatic nonhematological Grade ≥3 laboratory abnormalities that fail to improve to Grade ≤2 within 72 hours
- Grade 3 vomiting lasting >48 hours despite recommended antiemetic support or any occurrence of Grade ≥4 vomiting
- Grade 3 diarrhea lasting >48 hours despite recommended antidiarrheal support or any occurrence of Grade ≥4 diarrhea
- All other Grade ≥3 nonhematological adverse event (AE) not listed above
- Grade 3 or higher tumor lysis syndrome (TLS) regardless of prophylaxis
- Hy's law cases
- Febrile neutropenia of any duration (not applicable to AML subjects)
- Grade 4 neutropenia lasting ≥7 days; or in AML subjects only lasting ≥42 days and not due to progressive disease
- Grade ≥3 thrombocytopenia with Grade ≥2 bleeding or Grade 4 thrombocytopenia of any duration (not applicable to AML subjects)
- Grade 4 thrombocytopenia lasting ≥42 days (AML subjects only)
- Grade 4 anemia unexplained by underlying disease

Additionally, discontinuation of study drug in Cycle 1 due to an AE that is clearly unrelated to the underlying disease, or an extraneous cause will be considered a DLT.

For subjects receiving combination voruciclib + venetoclax, the DLT assessment period will begin with the initial dose of venetoclax in Cycle 1.

STUDY ASSESSMENTS

Assessments for safety, efficacy/antitumor activity, PK, and biological/correlative activity will be performed according to the schedules outlined in Appendix 1, Appendix 2 or Appendix 3, as appropriate for disease type and cohort enrollment.

Safety Assessments

Safety will be assessed by AEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0, laboratory safety tests including hematology (complete blood count [CBC]), serum chemistry, physical examination, vital signs, and 12-lead electrocardiogram (ECG).

ESTIMATED NUMBER OF SUBJECTS

At the start of Amendment 12, a total of 40 subjects have been enrolled in the now completed monotherapy dose escalation/expansion cohorts. Assuming an average enrollment of 4 subjects per dose level for DLT evaluation, up to 12 subjects to be enrolled in the 2 combination AML expansion cohorts, and an additional 10% for early drop-outs due to non-evaluability after failure to complete Cycle 1 treatment for reasons other than AEs related to voruciclib, the total enrollment for the voruciclib plus venetoclax combination group is estimated to be approximately 68 subjects, for a total of approximately 108 subjects to be enrolled in the study.

ESTIMATED NUMBER OF SITES

Approximately 10 to 16 sites in the United States (US)

SUBJECT ELIGIBILITY

Inclusion Criteria

To be eligible for study participation, subjects must meet all of the following inclusion criteria:

1. Signed, informed consent
2. Age ≥18 years
3. Histologically confirmed diagnosis of FL, MCL, marginal zone lymphoma (MZL), SLL, CLL, or DLBCL, and:
    a. Subjects must have disease that has relapsed or is refractory to 2 or more prior regimens and in need of treatment due to progressive disease (PD)
    b. Subjects must have received appropriate standard therapy for the subject's malignancy and have developed disease progression or are intolerant to appropriate standard therapy
    c. The clinical investigator must have discussed all alternative treatment options with the potential study subject prior to study enrollment
4. Histologically confirmed diagnosis of primary AML or secondary AML (e.g., following myelodysplastic syndrome or myeloproliferative disease) as defined by World Health Organization (WHO) criteria (Arber 2016)
    a. Relapsed or primary refractory disease having received 2 or more lines of therapy (voruciclib monotherapy cohorts) or 1 or more lines of therapy (voruciclib plus venetoclax combination cohorts)

b. Subjects must not be eligible for, or have failed, other therapies known to be effective for treatment of their AML

NOTE: a subject must meet inclusion criterion 3 or 4, but not both

5. Presence of measurable disease defined per the 2008 International Workshop on CLL guidelines (see Appendix 5) or by 2014 Lugano criteria for non-Hodgkin lymphoma (see Appendix 6); these criteria do not apply to subjects with AML
6. Life expectancy of ≥3 months
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
8. For subjects with B-cell malignancies, adequate hematologic parameters unless clearly due to the disease under study:
   a. Absolute neutrophil count (ANC) ≥0.5 × 109/L
   b. Platelet count >50 × 109/L
   c. Hemoglobin ≥8.0 g/dL
9. Adequate coagulation parameters:
   a. Prothrombin time (PT) ≤1.5 × ULN (i.e., Grade ≤1)
   b. Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (i.e., Grade ≤1)
10. Adequate renal and hepatic function, per laboratory reference range at screening:
    a. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/ serum glutamate-pyruvate transaminase (SGPT) ≤2.5 × ULN
    b. Total bilirubin ≤1.5 × ULN (if secondary to Gilbert's syndrome, ≤3 × ULN is permitted)
    c. Creatinine clearance ≥60 mL/minute
11. Subjects with B-cell malignancies must have completed:
    a. Previous anti-cancer medication a minimum of 5 elimination half-lives (t½) or 2 weeks (whichever is less) prior to Day 1 (a course of corticosteroids ≤7 days in duration prior to Day 1 is allowed)
    b. Radiation therapy or surgery ≥2 weeks before Day 1
12. Subjects with AML must have completed:
    a. Previous anti-cancer medication for a minimum of 5 elimination half-lives (t½) or 2 weeks (whichever is less) prior to start of voruciclib (monotherapy) or venetoclax (combination therapy) administration
    b. Radiation therapy ≥2 weeks or major surgery ≥4 weeks before start of voruciclib (monotherapy) or venetoclax (combination therapy) administration

    Note: Hydroxyurea and other therapy to control leukocytosis is allowed up to the end of Cycle 1
13. All clinically significant treatment-related toxicity from prior therapy (other than alopecia) must have resolved to Grade ≤1, or to a new stable baseline at time of enrollment
14. Females of childbearing potential must have a negative serum pregnancy test within 14 days prior to Day 1
15. For subjects capable of procreation, agree to use medically effective contraception during the study (which must, at the minimum, include a barrier method), and for 90 days after

discontinuation of study drug. Females of childbearing potential should use 2 forms of contraception, one of which should be a barrier contraceptive

16. Agree to not donate sperm or oocytes during the entire study treatment period and for 90 days after study drug discontinuation

Exclusion Criteria

Subjects meeting *any* of the following criteria will be excluded from the study:

1. History of pneumonitis due to any cause
2. For AML subjects only
   a. Acute promyelocytic leukemia (APL with promyelocytic leukemia/retinoic acid receptor alpha [PML-RARA])
   b. Peripheral blast count >25 × 109/L (hydroxyurea or other treatment to lower white blood cell [WBC] count to avoid this exclusion is allowed)
3. Known central nervous system involvement
4. History of another malignancy, except for the following:
   a. Adequately treated local basal cell or squamous cell carcinoma of the skin
   b. Adequately treated carcinoma in situ without evidence of disease
   c. Adequately treated papillary, noninvasive bladder cancer
   d. Other cancer that has been in complete remission for ≥ 2 years (subjects with low-grade prostate cancer on active surveillance and not expected to clinically progress over 2 years are allowed)
5. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥ 3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥ 160 mmHg) despite antihypertensive therapy
6. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥ 2 bradycardia, or corrected QT by Fridericia formula (QTcF average of triplicate ECG) >450 msec
7. Subjects who are receiving:
   a. Warfarin
   b. Other anti-cancer therapy (treatment to reduce leukocyte count in AML subjects is allowed)
   c. Strong or moderate CYP3A inhibitors (including grapefruit, Seville oranges, and star fruit) are to be avoided. Other CYP inhibitors (see Appendix 7) should be avoided and used only if essential for patient care. Strong or moderate CYP3A inhibitors and P-gp inhibitors must be discontinued 3 or more days before initiating venetoclax (subjects enrolled on combination voruciclib + venetoclax cohorts)
   d. Strong or moderate CYP3A inducers should be discontinued at least 7 days prior to venetoclax administration (subjects enrolled on combination voruciclib + venetoclax cohorts)
   e. Calcineurin inhibitors within 28 days prior to start of study drug

f. Any other investigational agent

8. Gastrointestinal (GI) diseases that may interfere with drug absorption or that will affect interpretation of GI AEs (including but not limited to gastric or intestinal bypass surgery, pancreatic enzyme insufficiency, malabsorption syndrome, symptomatic inflammatory bowel disease, chronic diarrheal illness, bowel obstruction). The Medical Monitor should be contacted if there is any question of eligibility in this regard
9. Ongoing risk for bleeding due to active peptic ulcer disease, bleeding diathesis, or other condition
10. Evidence of an ongoing systemic bacterial, fungal, or viral infection (including upper respiratory tract infections) at the time of start of voruciclib therapy, including:
    a. Positive hepatitis B surface antigen and/or hepatitis B core antibody test plus a positive hepatitis B polymerase chain reaction (PCR) assay (subjects with a negative PCR assay are permitted with appropriate anti-viral prophylaxis)
    b. Positive hepatitis C virus antibody (HCV Ab) test; subjects with positive HCV Ab test are eligible if they are negative for hepatitis C virus by PCR
    c. Symptomatic/uncontrolled HIV infection/AIDS, or currently taking contraindicated medications for HIV control
11. Receipt of an allogeneic transplant at any time prior to enrollment or an autologous transplant within the preceding 3 months at time of enrollment in the monotherapy cohorts

    Note: Prior allogenic transplant is permitted for AML subjects enrolled in voruciclib + venetoclax combination cohorts
12. Pregnant or breastfeeding or planning to become pregnant
13. Prior solid organ transplantation
14. Prior therapy with a CDK9 inhibitor
15. Ongoing immunosuppressive treatment (including calcineurin inhibitors as noted in Exclusion 7) at the time of the start of study treatment (Cycle 1, Day 1), including systemic or enteric corticosteroids except as follows:
    a. Prior to the start of study treatment, subjects may be using systemic corticosteroids (≤20 mg/day of prednisone or equivalent), topical, or inhaled corticosteroids
    b. During study treatment, subjects may use systemic, topical, or enteric corticosteroids, if needed
16. Concurrent participation in another therapeutic clinical trial
17. Any illness, medical condition, organ system dysfunction, medication use, or social situation (including mental illness or substance abuse) deemed by the Investigator to be likely to interfere with a subject's ability to sign informed consent, adversely affect the subject's ability to cooperate and participate in the study, or otherwise compromise the interpretation of study results

STUDY TREATMENT CONSIDERATIONS

In vitro studies have shown that voruciclib has the potential to inhibit CYP2C9, CYP2C19, CYP2D6, and CYP3A4, therefore, drugs with a narrow therapeutic window that are metabolized by these enzymes should be avoided or used with caution (see Appendix 7).

Subjects receiving warfarin treatment are excluded, since voruciclib is highly protein bound and a competitive inhibitor of CYP2C9 at higher concentrations, and may, therefore, potentiate the action of warfarin.

Tumor lysis syndrome (TLS) includes electrolyte abnormalities (hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia), cardiac dysrhythmias, and renal failure. Guidance on categorizing AML and CLL subjects for risk of TLS (Appendix 9), as well as a monitoring plan based on the Venclexta [US Prescribing Information] Rev 2022, is provided in Table 24.

Differentiation syndrome (DS) was considered a contributing factor in the pneumonitis cases and was reported as a DLT in 2 subjects with AML enrolled in Cohort 2. Therefore, tumor cytoreduction with hydroxyurea should be considered in subjects with AML and high peripheral counts, and corticosteroids administered per institutional standards if DS is suspected.

STATISTICAL ANALYSIS

Subjects completing the first cycle of treatment or experiencing a DLT during the first cycle (28 days) of treatment, will be considered evaluable for the occurrence of DLTs. The 3 + 3 design targets a DLT rate for the MTD of approximately 20 to 25%.

Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages.

Response to treatment will be tabulated with 95% exact binominal confidence intervals (CI)s, analyzing all subjects who complete the first scheduled post-baseline efficacy evaluation (scheduled on C3D1 for B-cell lymphoma subjects and C2D1 for AML subjects) or who experienced disease progression prior to completing the first scheduled post baseline disease assessment. The Kaplan-Meier method will be used to estimate PFS within subjects of the same tumor type. For PFS, subjects without documented progression will be censored at the date of last disease assessment.

Associations between PK findings, efficacy findings, and biomarker results will be explored by tests of association for binary endpoints (e.g., Fisher's exact test) and by T-tests (or appropriate non-parametric alternatives) for continuous variables.

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ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALT	alanine aminotransferase
ALP	Alkaline phosphatase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
APL	acute promyelocytic leukemia
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	area under the concentration versus time curve
BUN	blood urea nitrogen
CBC	complete blood count
CDK	cyclin-dependent kinase
CI	confidence interval
CLL	chronic lymphocytic leukemia
CR	complete response/remission
CRi	complete remission with incomplete marrow recovery
CRh	complete remission with partial hematologic recovery
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome
DDI	drug-drug interaction
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DOR	duration of response
DS	differentiation syndrome
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELN	European LeukemiaNet
FDA	Food and Drug Administration

Abbreviation	Definition
FDG	fluorodeoxyglucose
FDG-PET	fluorodeoxyglucose positron emission tomography
FL	follicular lymphoma
GI	gastrointestinal
h	hour
HCV Ab	Hepatitis C virus antibody
ICF	informed consent form
IDH	isocitrate dehydrogenase
IEC	Independent Ethics Committee
IgHV	immunoglobulin g heavy chain variable region
ILD	interstitial lung disease
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
IS	intermittent dosing schedule
$IS_{1w,3w}$	intermittent dosing schedule of 1 week on therapy and 3 weeks off therapy
$IS_{2w,2w}$	intermittent dosing schedule of 2 weeks on therapy and 2 weeks off therapy
$IS_{3w,1w}$	intermittent dosing schedule of 3 weeks on therapy and 1 week off therapy
IVIG	intravenous immune globulin
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
LDH	lactate dehydrogenase
LDi	longest diameter
mBED	minimum Biologically Effective Dose
MCL	mantle cell lymphoma
Mcl-1	myeloid cell leukemia protein 1
MRD	minimal residual disease
MTD	maximum tolerated dose
MZL	marginal zone lymphoma
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
OTC	over-the-counter
PCR	polymerase chain reaction

Abbreviation	Definition
PFS	progression-free survival
PI	prescribing information
PK	pharmacokinetic(s)
PML-RARA	promyelocytic leukemia/retinoic acid receptor alpha
PPI	proton pump inhibitor
PR	partial response
PT	prothrombin time
QD	quaque die (once per day)
QOD	once every other day
QTc	QT corrected (corrected QT interval)
QTcF	QT-interval corrected according to Fridericia's formula
RBC	red blood cell
RP2D	recommended Phase 2 dose
RU	ramp-up
SAE	serious adverse event
SD	stable disease
SDi	shortest diameter
SLL	small lymphocytic lymphoma
SRC	Study Review Committee
TEAE	treatment-emergent adverse event
TLS	tumor lysis syndrome
ULN	upper limit of normal
uMRD	undetectable minimal residual disease
US	United States
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

B-cell lymphoid malignancies arise from the accumulation of monoclonal, neoplastic B lymphocytes in lymph nodes and often in organs such as blood, bone marrow, spleen, and liver. Among the variants of B-cell lymphoid cancers is chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). As it progresses, this disorder is characterized by disabling constitutional symptoms: lymphadenopathy and organomegaly that can induce life-threatening organ dysfunction, as well as myelosuppression and immunocompromise that can result in susceptibility to infection and bleeding. Front-line use of multiagent chemoimmunotherapy or a Bruton tyrosine kinase inhibitor (e.g., ibrutinib) is commonly successful in suppressing disease manifestations for prolonged periods. However, CLL/SLL is incurable, and patients require further therapy to maintain disease control.

Acute myeloid leukemia (AML) has a similar pathogenesis. Most adult patients will achieve a complete remission with initial chemotherapy and more than 45% of patients in complete response/remission (CR) will survive more than 3 years. The proportion of patients achieving a CR and the duration of remission is inversely related to age with a markedly worse prognosis for older patients. Patients who have failed to respond to initial treatment or relapsed after remission also have a poor prognosis, and allogeneic stem cell transplantation after achieving a remission to salvage chemotherapy offers the best option for long-term survival.

Among the agents that have been approved for the therapy of CLL/SLL and AML is the oral drug, venetoclax, which is an inhibitor of the antiapoptotic protein B-cell leukemia/lymphoma-2 (Bcl-2). Venetoclax is approved by the Food and Drug Administration (FDA) for the treatment of adults with CLL or SLL and in combination with azacytidine, or decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (Venclexta® [US Prescribing Information] Rev 2022).

Venetoclax has also been studied in other B-cell malignancies. A Phase 1 study which enrolled patients with follicular lymphoma (FL), diffuse large B-cell lymphoma (DLBCL), mantle cell lymphoma (MCL), Waldenström macroglobulinemia, and marginal zone lymphoma, showed evidence of efficacy with a 44% ORR. Adverse events (AEs) observed were similar to those reported in CLL except for a lower incidence of tumor lysis syndrome (TLS) with no clinical cases and laboratory findings only (Davids 2017).

Approval of venetoclax in AML was based on data from a randomized, double-blind, placebo-controlled multicenter trial (VIALE-A) and 2 open-label studies. (Venclexta [US Prescribing Information] Rev 2022). In VIALE-A, patients were randomized to either venetoclax + azacitidine (n = 286) or placebo + azacitidine (n = 145). Median overall survival with venetoclax + azacitidine was 14.7 months versus 9.6 months with placebo + azacitidine (Hazard ratio = 0.66 [95% CI 0.52, 0.85]; $p < 0.001$). The CR rate was 37% with venetoclax + azacitidine versus 18% for placebo + azacitidine ($p < 0.001$), while the combined CR + CR with partial hematologic recovery (CRh) rate was 65% with venetoclax + azacitidine versus 23% for placebo + azacitidine ($p < 0.001$).

In one of the open-label studies, venetoclax was evaluated in combination with azacitidine (n = 67) or decitabine (n = 13) and achieved CR and CRh rates of 43% and 18%, respectively, when administered with azacitidine and CR and CRh rates of 54% and 7.7%, respectively, when

administered with decitabine. In the other open-label study, venetoclax was evaluated in combination with low dose cytarabine (n = 61) and achieved a CR and CRh rate of 21% and 21%, respectively.

A Phase 2 study of venetoclax monotherapy in 32 patients with AML (30 with relapsed and/or refractory; 2 newly diagnosed), demonstrated a 19% response rate (2 CR and 4 complete remissions with incomplete hematologic recovery [CRi]) with a median duration of response (DOR) of 48 days. Venetoclax was generally tolerated up to doses of 1200 mg daily (Konopleva 2016). In another study, venetoclax in combination with azacitidine or decitabine in 57 previously untreated elderly AML patients was administered at doses up to 1200 mg. No dose-limiting toxicities (DLTs) were observed, but subjects at the 1200 mg dose had frequent dose reductions due to gastrointestinal (GI) events. Overall, a 61% remission rate was obtained with 14/57 CR and 21/57 CRi (DiNardo 2018).

These data demonstrate that targeted therapy specific for the apoptotic pathway can have significant clinical benefit for patients with both B-cell malignancies and AML. However, despite high response rates, patients are not cured by currently approved therapy and will generally experience disease progression, indicating the need for development of new agents with a complementary mechanism of action that either alone or in combination with venetoclax or other agents enhance disease clearance and circumvent disease resistance.

Myeloid cell leukemia protein 1 (Mcl-1) is a member of the Bcl-2 anti-apoptotic, pro-survival family of molecules that are commonly over-expressed in B-cell malignancies and AML. Overexpression of Mcl-1 is associated with poor prognosis and resistance to therapy. Mcl-1 is not inhibited by venetoclax, which is specific for Bcl-2, and increased expression of Mcl-1 can be a mechanism of resistance for venetoclax therapy. Acquired resistance of lymphoma cell lines to Bcl-2 inhibition in vitro has been shown to involve transcriptional upregulation of Mcl-1 (Yecies 2010). Additionally, non-clinical studies have also demonstrated the ability of Mcl-1 to render AML cells resistant to Bcl-2 targeted agents, and have demonstrated synergy in AML models between agents targeting Bcl-2 with those targeting Mcl-1 expression including cyclin-dependent kinase 9 (CDK9) inhibitors (Pan 2015, Bogenberger 2017, Luedtke 2017).

Voruciclib is a potent oral cyclin-dependent kinase (CDK) inhibitor that indirectly suppresses the function of the pro-survival Mcl-1. Voruciclib inhibits Mcl-1 activity via 2 primary mechanisms: transcriptional repression through CDK9 inhibition and upregulation of the endogenous Mcl-1 antagonist, NOXA. Exposure to voruciclib at concentrations of 1.5 µM and above leads to near complete apoptosis of CLL cells in vitro. This effect was independent of prognostic characteristics of the CLL cells (such as immunoglobulin heavy-chain variable-region [IgHV] mutation status, ZAP-70, or expression of CD38), although CLL cells with P53 mutations showed slightly decreased susceptibility. This effect was specific for CLL cells and not donor B cells (Paiva 2015). Voruciclib has also been demonstrated to induce apoptosis in AML cell lines in vitro and shows synergy with venetoclax (Luedtke 2018).

The safety profile of voruciclib has been established in two Phase 1 single-agent studies in subjects with solid tumors (India study Protocol P1446A-05/19/08 and Canada study Protocol P1446A-05/20/08, total subjects n = 77) and in one Phase 1 study in advanced or inoperable malignant melanoma in combination with the BRAF inhibitor, vemurafenib, (Protocol P1446A-05/72/12); this study was terminated early by Piramal, the original voruciclib Sponsor, due to business reasons after 9 subjects were enrolled. In the first single-agent study

(Protocol P1446A-05/19/08), conducted in India, voruciclib was administered for 14 days in 21-day cycles. Dose levels of 75 to 850 mg/day were evaluated, and a total of 29 subjects were enrolled. Common AEs (occurring in ≥25% subjects) were vomiting, nausea, diarrhea, decreased appetite, pyrexia, asthenia, constipation, abdominal pain, headache, and back pain. One subject in the 600 mg cohort experienced DLTs of Grade 3 diarrhea and Grade 3 intestinal obstruction. Two DLTs (Grade 3 abdominal pain and Grade 2 acute renal failure) leading to discontinuation from the study were reported in the 850 mg/day cohort. The dose level of 600 mg/day was declared the maximum tolerated dose (MTD). Six serious adverse events (SAEs) related to voruciclib were reported during this study, including gastroenteritis, hematuria, diarrhea, elevated creatinine, death not otherwise specified, and acute renal failure. Stable disease (SD) was reported in 8 subjects for at least 2 cycles, with 4 of 6 subjects achieving SD for 4 cycles, and 1 of the 6 achieving SD for 6 cycles.

The second single-agent study (Protocol P1446A-05/20/08), conducted in Canada, evaluated dose levels of 75 to 500 mg/day administered daily continuously, with a total of 39 subjects enrolled. Common AEs (occurring in ≥25% subjects) were diarrhea, nausea, fatigue, decreased appetite, vomiting and dyspnea. Three DLTs (including an increase in International Normalized Ratio [INR], hypokalemia, and diarrhea) were reported at 500 mg/day cohort. One DLT of diarrhea was reported in the expanded MTD cohort of 350 mg/day. Three SAEs related to voruciclib were reported in this study, including increased INR (500 mg dose cohort), sudden death (500 mg dose cohort), and diarrhea leading to death (350 mg dose cohort). Overall, SD lasting for at least 2 cycles was reported in 12 subjects. One subject with small cell lung cancer remained on treatment with SD for 6 cycles, while another with alveolar soft tissue sarcoma, whose disease was progressing at the time of enrollment, achieved SD as a best response and remained on treatment for 12 cycles.

Based on PK data from Phase 1 studies P1446A-05/19/08 and P1446A-05/20/08 the average accumulation ratios of 2.06 and 2.77, voruciclib effective half-life value was estimated to be 24 hours to 36 hours (for further justifications of voruciclib dosing rationale in combination with venetoclax see Section 4.2.2.1). There was modest accumulation with steady state being reached by 14 days. Doses of ≥200 mg daily achieved through levels above 1.5 µM at 14 days. Further details on the PK are presented in the current Investigator's Brochure.

Prior to this ongoing study, voruciclib has not been studied in patients with B-cell malignancies or AML, although the intravenous CDK inhibitors (flavopiridol and dinaciclib) have been studied in both. In CLL activity has been seen with partial remission rates in the 25–40% range. Tumor lysis syndrome (TLS) was observed with these agents and was the DLT for flavopiridol (Lanasa 2015, Ghia 2017). The safety and efficacy of flavopiridol has also been examined in a Phase 1 study in non-Hodgkin lymphoma, with a 14% partial response (PR) rate observed with responses in MCL, FL, DLBCL, and SLL. The rate of TLS was lower in lymphoma patients compared to CLL, with 2 of 46 enrolled subjects showing biochemical evidence of TLS (Jones 2014). In AML, both have shown limited activity as single agents with transient reduction in peripheral leukocyte counts but no true complete remissions (Blum 2010, Gojo 2013). This level of activity may be due to the intravenous (IV) route of administration, the intermittent administration schedule and/or the short half-life of less than 4 hours for each compound. Voruciclib is administered orally, once daily and has a half-life of 24 to 48 hours, and therefore has the potential for continuous inhibition of CDK9. The ability to continuously suppress the

target has the potential for significantly greater efficacy than that seen with other CDK9 inhibitors.

Collectively, these data provide context for the clinical development of voruciclib for the treatment of B-cell malignancies and AML. This clinical protocol will further characterize the safety, pharmacology, and activity of voruciclib in these hematologic malignancies. In addition, the combination of voruciclib and venetoclax will be investigated since these agents target distinct proteins (Mcl-1 and Bcl-2) involved in regulating apoptosis. It is hypothesized that co-administration of venetoclax and voruciclib will result in a higher proportion of patients achieving CR and improved progression-free survival (PFS).

2. STUDY OBJECTIVES

2.1. Primary Objectives

- Determine the safety and tolerability of voruciclib and identify a safe and minimum biologically effective dose (mBED) of voruciclib monotherapy in subjects with relapsed or refractory B-cell malignancies and relapsed or refractory AML
- Determine the safety and tolerability and identify the safe and mBED of voruciclib in combination with venetoclax in subjects with relapsed or refractory AML

2.2. Secondary Objectives

- Evaluate the potential efficacy of voruciclib monotherapy based on:
    a. International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for CLL/SLL (Appendix 5) or the Lugano classification of response assessment for lymphoma (Appendix 6), as appropriate, for subjects with B-cell malignancies
    b. The 2017 European LeukemiaNet (ELN) criteria for subjects with AML (Appendix 4)
- Evaluate the potential efficacy of voruciclib in combination with venetoclax in subjects with AML based on the 2017 ELN criteria
- Evaluate the PK of voruciclib administered as monotherapy, and the PK of voruciclib and venetoclax when administered in combination

2.3. Exploratory Objectives

- Determine the effect of voruciclib monotherapy and voruciclib in combination with venetoclax (AML only) on biomarkers and functional activities of proteins in the apoptotic pathway
- Correlate anti-tumor activity with baseline tumor characteristics

3. SUBJECT ELIGIBILITY

3.1. Inclusion Criteria

To be eligible for study participation, subjects must meet all of the following inclusion criteria:

1. Signed, informed consent
2. Age ≥18 years
3. Histologically confirmed diagnosis of FL, MCL, marginal zone lymphoma (MZL), SLL, CLL, or DLBCL, and:
   a. Subjects must have disease that has relapsed or is refractory to 2 or more prior regimens and in need of treatment due to progressive disease (PD)
   b. Subjects must have received appropriate standard therapy for the subject's malignancy and have developed disease progression or are intolerant to appropriate standard therapy
   c. The clinical investigator must have discussed all alternate treatment options with the potential study subject prior to study enrollment
4. Histologically confirmed diagnosis of primary AML or secondary AML (e.g., following myelodysplastic syndrome or myeloproliferative disease) as defined by World Health Organization (WHO) criteria (Arber 2016)
   a. Relapsed or primary refractory disease having received 2 or more lines of therapy (voruciclib monotherapy cohorts) or 1 or more lines of therapy (voruciclib plus venetoclax combination cohorts)
   b. Subjects must not be eligible for, or have failed, other therapies known to be effective for treatment of their AML

   NOTE: A subject must meet inclusion criterion 3 or 4, but not both
5. Presence of measurable disease defined per the 2008 International Workshop on CLL guidelines (see Appendix 5) or by 2014 Lugano criteria for non-Hodgkin lymphoma (see Appendix 6); these criteria do not apply to subjects with AML
6. Life expectancy of ≥3 months
7. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
8. For subjects with B-cell malignancies, adequate hematologic parameters unless clearly due to the disease under study:
   a. Absolute neutrophil count (ANC) ≥0.5 × 109/L
   b. Platelet count >50 × 109/L
   c. Hemoglobin ≥8.0 g/dL
9. Adequate coagulation parameters:
   a. Prothrombin time (PT) ≤1.5 × ULN (i.e., Grade ≤1)
   b. Activated partial thromboplastin time (aPTT) ≤1.5 × ULN (i.e., Grade ≤1)

10. Adequate renal and hepatic function, per laboratory reference range at screening:
    a. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamate-pyruvate transaminase (SGPT) ≤2.5 × ULN
    b. Total bilirubin ≤1.5 × ULN (if secondary to Gilbert's syndrome, ≤3 × ULN is permitted)
    c. Creatinine clearance ≥60 mL/minute
11. Subjects with B-cell malignancies must have completed:
    a. Previous anti-cancer medication a minimum of 5 elimination half-lives (t½) or 2 weeks (whichever is less) prior to Day 1 (a course of corticosteroids ≤7 days in duration prior to Day 1 is allowed)
    b. Radiation therapy or surgery ≥2 weeks before Day 1
12. Subjects with AML must have completed:
    a. Previous anti-cancer medication for a minimum of 5 elimination half-lives (t½) or 2 weeks (whichever is less) prior to start of voruciclib (monotherapy) or venetoclax (combination therapy) administration
    b. Radiation therapy ≥2 weeks or major surgery ≥4 weeks before start of voruciclib (monotherapy) or venetoclax (combination therapy) administration

    Note: Hydroxyurea and other therapy to control leukocytosis is allowed up to the end of Cycle 1
13. All clinically significant treatment-related toxicity from prior therapy (other than alopecia) must have resolved to Grade ≤1, or to a new stable baseline at time of enrollment
14. Females of childbearing potential must have a negative serum pregnancy test within 14 days prior to Day 1
15. For subjects capable of procreation, agree to use medically effective contraception during the study (which must, at the minimum, include a barrier method), and for 90 days after discontinuation of study drug. Females of childbearing potential should use 2 forms of contraception, one of which should be a barrier contraceptive
16. Agree to not donate sperm or oocytes during the entire study treatment period, and for 90 days after study drug discontinuation

3.2. Exclusion Criteria

Subjects meeting *any* of the following criteria will be excluded from the study:

1. History of pneumonitis due to any cause
2. For AML subjects only
    a. Acute promyelocytic leukemia (APL with promyelocytic leukemia/retinoic acid receptor alpha [PML-RARA])
    b. Peripheral blast count >25 × 10^9/L (hydroxyurea or other treatment to lower WBC count to avoid this exclusion is allowed)

3. Known central nervous system involvement
4. History of another malignancy, except for the following:
   a. Adequately treated local basal cell or squamous cell carcinoma of the skin
   b. Adequately treated carcinoma in situ without evidence of disease
   c. Adequately treated papillary, noninvasive bladder cancer
   d. Other cancer that has been in complete remission for ≥2 years (subjects with low-grade prostate cancer on active surveillance and not expected to clinically progress over 2 years are allowed)
5. Significant cardiovascular disease (e.g., myocardial infarction, arterial thromboembolism, cerebrovascular thromboembolism) within 3 months prior to start of study therapy; angina requiring therapy; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; or uncontrolled Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg) despite antihypertensive therapy
6. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, atrial fibrillation/flutter, left bundle branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or corrected QT by Fridericia formula (QTcF average of triplicate ECG) >450 msec
7. Subjects who are receiving:
   a. Warfarin
   b. Other anti-cancer therapy (treatment to reduce leukocyte count in AML subjects is allowed)
   c. Strong or moderate CYP3A inhibitors (including grapefruit, Seville oranges, and star fruit) are to be avoided. Other CYP inhibitors (see Appendix 7) should be avoided and used only if essential for patient care. Strong or moderate CYP3A inhibitors and P-gp inhibitors must be discontinued 3 or more days before initiating venetoclax (subjects enrolled on combination voruciclib + venetoclax cohorts)
   d. Strong or moderate CYP3A inducers should be discontinued at least 7 days prior to venetoclax administration (subjects enrolled on combination voruciclib + venetoclax cohorts)
   e. Calcineurin inhibitors within 28 days prior to start of study drug
   f. Any other investigational agent
8. GI diseases that may interfere with drug absorption or that will affect interpretation of GI AEs (including but not limited to gastric or intestinal bypass surgery, pancreatic enzyme insufficiency, malabsorption syndrome, symptomatic inflammatory bowel disease, chronic diarrheal illness, bowel obstruction). The Medical Monitor should be contacted if there is any question of eligibility in this regard
9. Ongoing risk for bleeding due to active peptic ulcer disease, bleeding diathesis, or other condition

10. Evidence of an ongoing systemic bacterial, fungal, or viral infection (including upper respiratory tract infections) at the time of start of voruciclib therapy, including:
    a. Positive hepatitis B surface antigen and/or hepatitis B core antibody test plus a positive hepatitis B polymerase chain reaction (PCR) assay (subjects with a negative PCR assay are permitted with appropriate anti-viral prophylaxis)
    b. Positive hepatitis C virus antibody (HCV Ab) test; subjects with positive HCV Ab test are eligible if they are negative for hepatitis C virus by PCR
    c. Symptomatic/uncontrolled HIV infection/AIDS, or currently taking contraindicated medications for HIV control
11. Receipt of an allogeneic transplant at any time prior to enrollment or an autologous transplant within the preceding 3 months at time of enrollment in the monotherapy cohorts

    Note: Prior allogenic transplant is permitted for AML subjects enrolled in voruciclib + venetoclax combination cohorts
12. Pregnant or breastfeeding or planning to become pregnant
13. Prior solid organ transplantation
14. Prior therapy with a CDK9 inhibitor
15. Ongoing immunosuppressive treatment (including calcineurin inhibitors as noted in Exclusion 7) at the time of the start of study treatment (Cycle 1, Day 1), including systemic or enteric corticosteroids except as follows:
    a. Prior to the start of study treatment, subjects may be using systemic corticosteroids (≤20 mg/day of prednisone or equivalent), topical, or inhaled corticosteroids
    b. During study treatment, subjects may use systemic, topical, or enteric corticosteroids, if needed
16. Concurrent participation in another therapeutic clinical trial
17. Any illness, medical condition, organ system dysfunction, medication use, or social situation (including mental illness or substance abuse) deemed by the Investigator to be likely to interfere with a subject's ability to sign informed consent, adversely affect the subject's ability to cooperate and participate in the study, or otherwise compromise the interpretation of study results

4. STUDY DESIGN

4.1. Overall Study Design

This is a Phase 1, open-label, 3 + 3 dose escalation study to determine the safety and preliminary efficacy of voruciclib as monotherapy in subjects with relapsed and/or refractory B-cell malignancies or AML and in combination with venetoclax in subjects with relapsed and/or refractory AML after treatment with standard therapy.

Initially 3 subjects will be enrolled into a dose cohort and followed for 28 days. Due to the likelihood of subjects with advanced malignancy discontinuing between the start of the informed

consent process and before completion of the first 28-day cycle for reasons unrelated to voruciclib toxicity, a fourth subject may be enrolled. This will mitigate the risk of delay in assessing each dose level. If a fourth subject is enrolled, the DLT period will close when 3 subjects have completed 28 days without DLT. If one DLT occurs in any of the four subjects during the DLT assessment period, an additional 2 subjects will be enrolled to a total of 6 subjects.

As of Amendment 7, intermittent schedule (IS) dosing regimens were implemented in order to mitigate toxicities observed with continuous voruciclib dosing (see rationale provided in Section 4.2.1.1).

Amendments 8, 9 and 10 were not implemented.

Starting with Amendment 11, the safety and tolerability of voruciclib administered in combination with venetoclax will be evaluated in subjects with relapsed and/or refractory AML (see rationale provided in Section 4.2.2.1).

In Amendment 12, an additional intermittent dosing schedule of 3 weeks on/1 week off ($IS_{3w,1w}$) of voruciclib administered in combination with venetoclax will be evaluated in subjects with relapsed and/or refractory AML (see rationale provided in Section 4.2.2.2).

4.2. Starting Dose and Dose Levels

4.2.1. Voruciclib Monotherapy

Voruciclib has been studied in two previous single-agent Phase 1 studies in advanced refractory malignancies (India study Protocol P1446A-05/19/08 and Canada study Protocol P1446A-05/20/08). The MTD in these previous studies was identified as 600 mg when given daily for 14 days in a 21-day cycle, and 350 mg when given daily as a continuous administration. The initial dose level was 75 mg in both studies.

The initial dose level in this current study was 50 mg voruciclib daily in Cohort 1, followed by additional dose cohorts increasing stepwise up to 250 mg (i.e., 50, 100, 150, 200, and 250 mg). Due to dose limiting toxicities at 100 mg QD, intermittent dosing regimens are being studied at 100, 150, or 200 mg either on an $IS_{2w,2w}$ or an $IS_{1w,3w}$. The previously planned maximum daily dose of 250 mg was based on data from previous clinical studies which indicate the dose is tolerated (less than the previously identified MTD of 350 mg daily). Additionally, data from the prior Phase 1 studies show that doses of 150-250 mg are associated with trough serum levels of voruciclib that exceed the level required for maximum in vitro activity against CLL and AML cells.

4.2.1.1. Rationale for Dose and Schedule Changes in Amendment 7 – Voruciclib Monotherapy

Prior to Amendment 7, a total of 16 subjects had been administered voruciclib; 8 in Cohort 1 and 8 in Cohort 2, including 12 subjects with B-cell malignancies and 4 subjects with AML; with all 4 AML subjects enrolled in Cohort 2 following the implementation of Amendment 5. During the continuous daily dosing cohorts, there were no DLTs in the 50 mg QD dose cohort. At the 100 mg QD dose cohort, 2 subjects with AML had a DLT of pneumonitis, pre-empting further dose escalation on the continuous daily dosing schedule. In addition, one subject with DLBCL

enrolled at the 50 mg QD dose cohort experienced hypoxemic respiratory failure with pulmonary infiltrates in Cycle 4. There was no identified cause for this event, which was considered related to study drug and led to voruciclib discontinuation.

The mechanism of this pulmonary toxicity is not understood. PK data from the Phase 1 studies in solid tumors indicated that voruciclib has a very high volume of distribution (>100 L), suggesting higher exposure in tissues than in plasma. Interstitial pneumonitis has been reported post-marketing with the CDK4/6 inhibitors, which are approved in the US for the treatment of patients with breast cancer (FDA Drug Safety Communications, September 2019).

Because there were no objective responses reported at the dose of 50 mg QD, an IS was implemented to determine whether doses of 100 mg or greater could be administered safely. These doses were projected to achieve plasma concentrations needed for antitumor activity based on non-clinical models (data on file). The planned intermittent schedule allowed for complete clearance of the drug from the plasma and tissues during the 2-3 weeks off therapy and may mitigate the risk of toxicity. In the Phase 1 study P1446A-05/19/08 in various solid tumors, voruciclib was administered on a 2 weeks on/1 week off schedule with doses escalated up to 850 mg and the MTD was established at 600 mg. The intermittent schedule to be evaluated in Amendment 7 will further expand the treatment-free interval to 2 weeks (Cohorts 6-8) or 3 weeks (Cohorts 9-11) and evaluate voruciclib doses levels up to 200 mg.

Beginning with Amendment 7, subjects with AML and B-cell malignancies were to be evaluated in up to 6 new potential IS dose regimens separately.

4.2.2. Voruciclib + Venetoclax Combination Therapy in Subjects with AML

Note: Amendments 8, 9 and 10 were not implemented.

Upon determination of the safe and mBED of voruciclib monotherapy in AML subjects, the combination of voruciclib with venetoclax will be evaluated in subjects with relapsed or refractory AML. Based on preliminary safety and tolerability data with voruciclib monotherapy, the $IS_{2w,2w}$ dosing schedule was selected for use in the combination cohorts of voruciclib and venetoclax.

4.2.2.1. Rationale for Voruciclib + Venetoclax Combination Therapy in Amendment 11

For the treatment of AML subjects, the sponsor hypothesized that use of a CDK9 inhibitor (such as voruciclib) with its corollary effect on Mcl-1 inhibition when given in combination with a Bcl-2 inhibitor (such as venetoclax) could synergistically bring about disruption of the cell cycle and inhibition of pro-survival cell cycle pathways. Support for this hypothesis was provided by preclinical in vitro and murine xenograft studies. In vitro studies using selected AML cell lines, exposure to the combination of voruciclib + venetoclax produced significantly greater apoptosis compared to either agent alone; a finding that was observed in both venetoclax resistant and sensitive cell lines (Luedtke 2020). In a murine xenograft model using MV4-11 AML cells, the combination of voruciclib + venetoclax was associated with a significantly longer median overall survival time compared to either agent alone (Luedtke 2020).

4.2.2.2. Rationale for an Additional Voruciclib Schedule in Amendment 12

The rationale for $IS_{3w,1w}$ is to decrease the number of days without voruciclib from 14 to 7 days in a treatment cycle, thereby reducing the potential risk of AML regrowth during the 2-week treatment break in the $IS_{2w,2w}$ schedule.

4.3. Dose Escalation Scheme

4.3.1. Voruciclib Monotherapy

Dose cohorts are defined in Table 1 (prior to Amendment 7) and Table 2 (per Amendment 7), with the dose escalation scheme is detailed in Figure 1. The total number of cohorts will depend upon the incidence of DLTs.

4.3.1.1. Dose Cohort Escalation Prior to Amendment 7

Dose escalation will be allowed after 3 subjects have completed 1 cycle with no reported DLT, or 6 subjects have completed 1 cycle with no more than 1 DLT. Escalation to the next dose level will depend on demonstrated safety, tolerability, and DLT as defined in Section 4.4, and after approval by the Study Review Committee (SRC), which is composed of clinical investigators and sponsor representatives (including the Medical Monitor). The SRC will review ongoing safety data and any potential safety signals. Escalation to a new dose level may proceed only after the SRC conducts a review of safety data from all preceding subjects who are evaluable for DLTs.

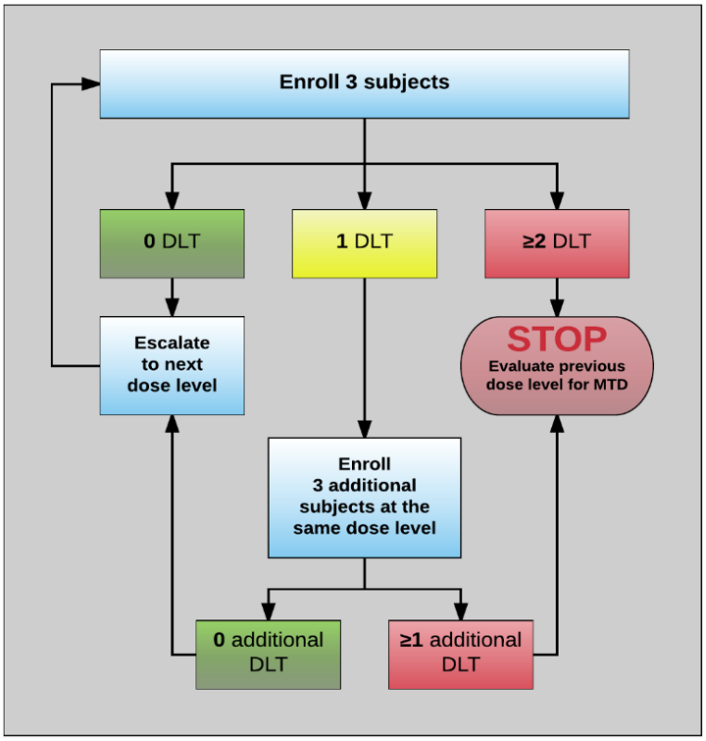
The SRC will evaluate the accumulated safety data and advise if enrollment needs to be held at any time in a dose cohort for further safety evaluation.

The Investigator may increase the voruciclib dose level above the initial dose assigned at enrollment after the SRC has authorized opening enrollment at a new dose level, and after consultation with the Medical Monitor. Subjects whose voruciclib dose is increased to the next dose level will not count toward the assessment of DLTs at the higher dose level.

Table 1: Voruciclib Dose Escalation (Prior to Amendment 7)

Cohort/Dose Level	Daily Dose
1	50 mg
2	100 mg
3	150 mg
4	200 mg
5	250 mg

Figure 1: Dose Escalation Scheme



Abbreviations: DLT = dose-limiting toxicity; MTD = maximum tolerated dose.
Note: a fourth subject may be enrolled in each dose cohort to mitigate the risk of one of the initial 3 subjects not being evaluable for DLT due to disease progression or other reason unrelated to voruciclib.

4.3.1.2. Dose Cohort Escalation as of Amendment 7

As of Amendment 7, dosing was modified to administer voruciclib monotherapy on an IS. The safety and tolerability, identification of a safe and mBED will be assessed independently for subjects with AML and B-cell malignancies, dose and regimen evaluations will be conducted in each of these disease groups separately by opening the next cohort in each disease group as determined by the SRC. In order to differentiate disease-specific cohorts, subjects with AML will be designated as Cohorts 6a-11a, and subjects with B-cell malignancies will be designated as Cohorts 6b-11b.

Initially, IS of 2 weeks on therapy followed by 2 weeks off therapy ($IS_{2w,2w}$) will be evaluated for up to 3 dose levels for AML and B-cell malignancies separately (Cohorts 6a - 8a and 6b - 8b, respectively). If the $IS_{2w,2w}$ in Cohort 6a or 6b (i.e., the lowest dose on $IS_{2w,2w}$) for either disease group is not tolerated in that group then further evaluation of the $IS_{2w,2w}$ will be stopped in that disease group and the IS with 1 week on therapy followed by 3 weeks off ($IS_{1w,3w}$), in a 28-day cycle will be evaluated in that disease group. The dose cohorts that will potentially be enrolled are defined in Table 2.

Table 2: Voruciclib Dose Levels in Amendment 7

Cohort Dose Level	Dose/Schedule
6a, b	100 mg $IS_{2w,2w}$
7a, b	150 mg $IS_{2w,2w}$
8a, b	200 mg $IS_{2w,2w}$
9a, b	100 mg $IS_{1w,3w}$
10a, b	150 mg $IS_{1w,3w}$
11a, b	200 mg $IS_{1w,3w}$

Cohorts comprising subjects with AML are designated "a" and cohorts of subjects with B-cell malignancies are designated "b"

Because enrollment will be conducted independently in subjects with AML and B-cell malignancies, it is possible the voruciclib dose and/or schedule under evaluation at any time point may be different in the 2 groups.

Within each disease group, dose escalation will follow the 3+3 design described in Figure 2, and summarized below:

- Cohort 6: 100 mg QD, administered $IS_{2w,2w}$
  - If 0 of 3 subjects have a DLT, the study will continue to enroll in Cohort 7.
  - If >1 of 3 subjects have a DLT, this dose level will be declared as not safe, further dose escalation on the $IS_{2w,2w}$ regimen will not proceed, and Cohort 9 evaluating a less intensive dosing schedule ($IS_{1w,3w}$) will be studied.
  - If 1 of 3 subjects have a DLT, 3 more subjects will be enrolled in Cohort 6.
  - If >1 of 6 subjects have a DLT, this dose level will be declared as not safe, further dose escalation on $IS_{2w,2w}$ will not proceed, and Cohort 9 will be studied.
  - If ≤1 of 6 subjects have a DLT, the study will continue to enroll in Cohort 7.
- Cohort 7: 150 mg QD, administered $IS_{2w,2w}$
  - If 0 of 3 subjects have a DLT, this dose and schedule will be declared safe for either dose escalation to Cohort 8 or evaluation of 3 additional subjects in Cohort 7; this will be determined by the SRC based on PK and clinical results.
  - If >1 of 3 subjects have a DLT, this dose will be considered as not safe, further dose escalation will not proceed, and 3 subjects will be enrolled in Cohort 6 (for up to 6 evaluable subjects in Cohort 6) to confirm it is the MTD.
  - If 1 of 3 subjects have a DLT, 3 more subjects will be enrolled in Cohort 7.
  - If >1 of 6 subjects have a DLT, this dose level will be considered as not safe for further evaluation and 3 additional subjects will be enrolled in Cohort 6 to confirm it is the MTD. However, if Cohort 6 has previously enrolled 6 subjects with ≤1 DLTs, then the Cohort 6 dose level will be declared the MTD.

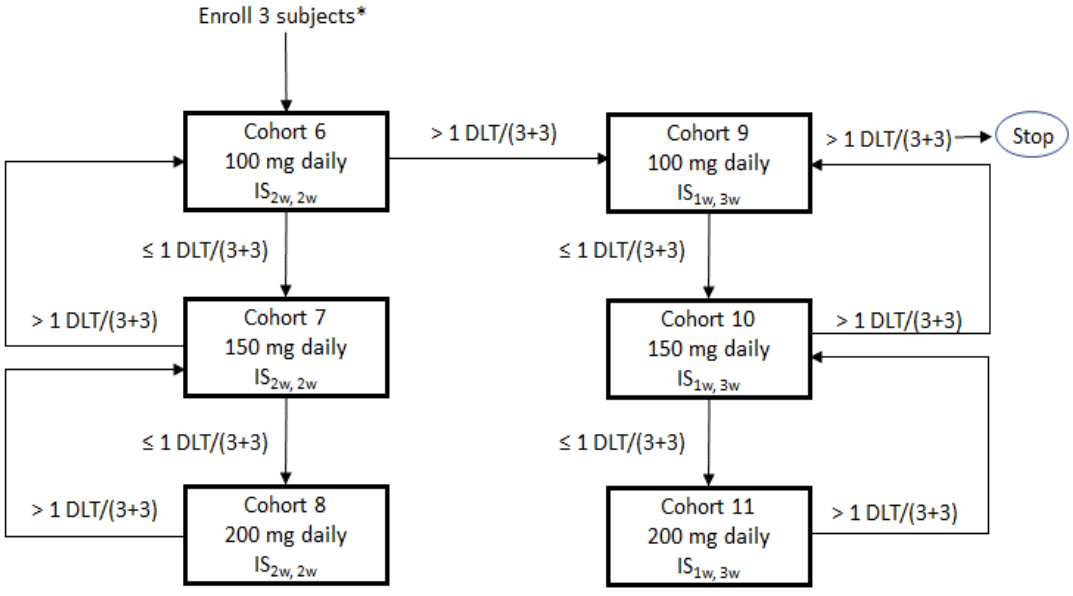
  - If ≤1 of 6 subjects have a DLT, this dose and schedule will be declared safe for either dose escalation to Cohort 8 or evaluation of that dose in an expansion cohort; this will be determined by the SRC based on PK and clinical results.

- Cohort 8: 200 mg QD, administered $IS_{2w,2w}$
  - If 0 of 3 subjects have a DLT, this dose and schedule will be declared safe, and 3 additional subjects will be enrolled in Cohort 8 to confirm it is the MTD.
  - If >1 of 3 subjects have a DLT, this dose will be considered as not safe, and 3 subjects will be enrolled in Cohort 7 (for up to 6 evaluable subjects enrolled in Cohort 7) to confirm it is the MTD.
  - If 1 of 3 subjects have a DLT, 3 more subjects will be enrolled in Cohort 8.
  - If >1 of 6 subjects have a DLT, this dose level will be considered as not safe for further evaluation and 3 additional subjects will be enrolled in Cohort 7 to confirm it is the MTD. However, if Cohort 7 has previously enrolled 6 subjects with ≤1 DLTs then Cohort 7 dose level will be declared the MTD.
  - If ≤1 of 6 subjects have a DLT, this dose and schedule will be declared safe for cohort expansion.

Cohorts 9 to 11, using $IS_{1w,3w}$, will open to enrollment only if the $IS_{2w,2w}$ in Cohort 6 is deemed not tolerable. Enrollment in Cohorts 9 to 11 will follow the same dose escalation scheme described for Cohort 6 to 8.

The potential cohorts and dose/schedule changes to evaluate the safety of dose levels with IS dosing is presented in Figure 2.

Figure 2: Dose Level/Schedule Scheme for IS



* Patients with AML and B-Cell malignancies will be enrolled separately into this scheme.
Subjects with AML will be designated as Cohorts X**a**, and subjects with B-cell malignancies will be designated as Cohorts X**b**.

If the next dose level in the AML or B-cell malignancies monotherapy cohorts has been declared safe by the SRC, subjects with the same disease type (AML or B-cell malignancies) enrolled in the monotherapy cohorts at a lower dose level may have their dose escalated to the next dose level after completing Cycle 1 without a DLT (intra-subject dose escalation). For example, a subject with B-cell malignancies enrolled in Cohort 6b (100 mg $IS_{2w,2w}$) may have the dose increased to 150 mg $IS_{2w,2w}$ in Cycle 2 if the dose of 150 mg $IS_{2w,2w}$ was deemed safe in the B-cell malignancies cohort by the SRC.

Once safe and mBED has been identified, the SRC may select a dose for an expansion cohort that may enroll up to 6 additional AML subjects in order to obtain additional safety and biomarker data. Formal stopping rules for excess toxicity in expansion cohorts are provided Section 4.5.

Subjects may continue to receive voruciclib monotherapy while there is evidence of clinical benefit (partial remission [PR] or better) in subjects with B-cell malignancies or AML by the end of Cycle 6 and acceptable toxicity as judged by the Investigator.

4.3.2. Dose Cohort Evaluation of Voruciclib + Venetoclax Combination Therapy in AML

Combination therapy with voruciclib and venetoclax will be evaluated in AML subjects only, and only subsequent to the determination of the safety, tolerability, and minimum biologically effective dose of voruciclib monotherapy in AML subjects. Dose escalation of voruciclib in the combination cohorts will be informed by the safety, tolerability, and PK results and require the approval of the SRC.

The voruciclib monotherapy results in AML subjects as of 21 September 2021 demonstrated the dose level voruciclib 200 mg $IS_{2w,2w}$ (Cohort 8a) as safe, had antitumor activity in some patients, and achieved steady state (Day 8) pre-dose plasma concentrations of 0.9 µM and C_{max} of 1.5 µM (concentrations shown to be active in non-clinical models in AML and CLL). The Sponsor determined that 200 mg is a safe and minimum biologically effective dose, and in consultation with the SRC, the decision was made to stop voruciclib dose escalation because continued dose escalation solely to determine the MTD of single agent voruciclib in AML may expose subjects to potential toxicity, and single-agent CDK9 inhibitors are unlikely to induce durable responses in AML. A more clinically meaningful approach would be to evaluate voruciclib in combination with venetoclax, and to conduct the evaluation of additional dose levels with the combination therapy.

Amendment 11 – $IS_{2w,2w}$ Dosing Schedule

Voruciclib dosing in combination with venetoclax will utilize the $IS_{2w,2w}$ dosing schedule, starting with the dose level of voruciclib 50 mg QOD (Cohort 12) and escalating as per Table 3. The voruciclib starting dose of 50 mg QOD was selected because it is 4 dose levels lower than 200 mg QD, the dose established to be safe as a monotherapy on $IS_{2w,2w}$ in AML. The dose of 50 mg is 25% of the highest dose studied in AML, and for which no DLTs were reported, to take into account potential drug interaction with venetoclax and the first introduction in clinical studies of the voruciclib malonate salt tablets (see Section 4.3.2.2 for details).

The dose levels of voruciclib to be evaluated range from 50 mg to 350 mg administered $IS_{2w,2w}$. For reference, the MTD of voruciclib in Phase 1 studies in solid tumors was 600 mg when

administered daily for 14 days in a 21-day cycle and 350 mg daily when administered continuously.

Only the tablet formulation containing the voruciclib malonate salt will be used in the voruciclib plus venetoclax combination group.

Table 3: Dose Cohorts with Combination Voruciclib + Venetoclax (Amendment 11)

Cohort Dose Level	Doses and Schedule
12	voruciclib 50 mg QOD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
13	voruciclib 50 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
14	voruciclib 100 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
15	voruciclib 150 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
16	voruciclib 200 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
17	voruciclib 250 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
18	voruciclib 300 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days
19	voruciclib 350 mg QD, administered $IS_{2w,2w}$ + venetoclax administered QD × 28 days

Abbreviation: QOD = once every other day
At the completion of the DLT period for each cohort, decisions to escalate in subsequent cohorts will be guided by SRC review of all available safety data, PK and PD data.
For Cohort 12, the dosing of voruciclib will be Days 3, 5, 7, 9, 11, and 13 of Cycle 1, and Days 1, 3, 5, 7, 9, 11, and 13 of Cycle 2 and beyond.

Dose escalation to the next cohort will be initiated after 3 subjects have completed 1 cycle with no reported DLTs, or after 6 subjects have completed 1 cycle with no more than 1 DLT (as defined in Section 4.4) and with the approval of the SRC after review of safety from the cohort under review.

Intra-patient dose escalation to the next dose in Cycle 2 or later cycle is allowed at the discretion of the investigator and after consultation with the Sponsor if the next dose level has been declared safe by the SRC. More specifically, a subject enrolled at a dose level X may have their dose escalated to the next dose level X + 1 after completing Cycle 1 without a DLT.

Dose escalation proceeds until assessment of clinical and PK parameters by the SRC establishes the safe BED for voruciclib in combination with venetoclax. More specifically, a voruciclib dose in combination with venetoclax that meets the following criteria:

- DLT not to exceed 1 in 6 patients, overall response rate (ORR) ≥30%, as compared to historical ORR of 19% with 400-800 mg venetoclax alone in relapsed/refractory AML (Konopleva 2016), and
- Trough plasma concentration of 1 to 1.5 µM, concentrations shown to be synergistic in combination with venetoclax in preclinical models.

Once the safe and mBED of voruciclib in combination with venetoclax is identified by the SRC, which could be a dose less than 350 mg, dose escalation will stop and the SRC may recommend opening the dose expansion for the combination therapy (up to 12 subjects). At that time, subjects still actively dosing in the prior cohort may have their dose escalated to the next dose level after completing Cycle 1 (intra-subject dose escalation). Subjects may continue to receive

voruciclib plus venetoclax while there is evidence of clinical benefit (partial remission [PR] or better) by the end of Cycle 6 and acceptable toxicity as judged by the Investigator.

Amendment 12 – $IS_{3w,1w}$ Dosing Schedule

In Amendment 12, the combination of voruciclib with venetoclax will be evaluated in subjects with relapsed and/or refractory AML using a voruciclib intermittent schedule of daily dosing on Days 1–21 in a 28-day cycle, with no voruciclib dosing on Days 22–28 of the cycle, designated as $IS_{3w,1w}$ with the exception of Cycle 1 where voruciclib dosing begins on Day 3. In Cycle 1, venetoclax dose ramp-up will consist of venetoclax 100 mg on Day 1, then 200 mg on Days 2–21, then 400 mg on Days 22–28, with voruciclib beginning on Day 3.

The starting voruciclib dose level will be 150 mg in combination with venetoclax (i.e., 2 dose levels lower than the dose of 250 mg that has been shown to have no DLTs on $IS_{2w,2w}$). Dose escalation will follow the same 3+3 design as in the $IS_{2w,2w}$ cohorts, and uses the same definition for DLT, MTD, and mBED.

In the $IS_{2w,2w}$ dose escalation cohorts, no DLTs have been reported at doses ranging from 50 mg QOD to 250 mg QD, and enrollment was ongoing at the 300 mg dose level at the time of issuance of protocol Amendment 12.

The combination cohorts on $IS_{3w,1w}$ will be numbered as listed below in Table 4.

Table 4: Dose Cohorts with Combination Voruciclib + Venetoclax (Amendment 12)

Cohort Dose Level	Doses and Schedule
21	voruciclib 150 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
22	voruciclib 200 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
23	voruciclib 250 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
24	voruciclib 300 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days
25	voruciclib 350 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days

Abbreviation: QD = once per day.

4.3.2.1. Administration Schedules and Doses of Voruciclib + Venetoclax

Amendment 11 – $IS_{2w,2w}$ Dosing Schedule

For Cycle 1 in combination cohorts 12–19, the dosing will be as follows (Table 5):

- Venetoclax will be ramped up starting with 100 mg on Day 1, 200 mg on Days 2–21, then 400 mg administered as a single agent on Days 22–28.
- Voruciclib dosing will be administered on Days 3–14 at the appropriate Cohort Dose (Table 3).

For Cycle 2 and beyond, the dosing will be as follows:

- Venetoclax 200 mg will be administered on Days 1–21, and 400 mg administered as a single agent on Days 22–28.
- Voruciclib at the cohort dose (Table 3) on Days 1–14.

Venetoclax should be taken with a meal and water. When both venetoclax and voruciclib are to be taken, venetoclax should be taken first with a meal followed by voruciclib at least 2 hours later (e.g., meal completed at 8 a.m. with venetoclax, dose of voruciclib taken after 10:00 a.m.). Voruciclib tablets must not be chewed, crushed, or broken.

Table 5: Administration Schedules of Voruciclib given in Combination with Venetoclax ($IS_{2w,2w}$)

Administration Schedule of Voruciclib $IS_{2w,2w}$ and Venetoclax per 28-day Cycle					
Cycle 1	**Day 1**	**Day 2**	**Days 3 to 14**	**Days 15 to 21**	**Days 22 to 28**
Venetoclax	100 mg	200 mg	200 mg	200 mg	400 mg
Voruciclib QD	-	-	Cohort dose	None	None
Voruciclib QOD[a]	-	-	50 mg[a]	None	None
Cycle 2 and beyond	**Days 1 to 14**		**Days 15 to 21**		**Days 22 to 28**
Venetoclax	200 mg		200 mg		400 mg
Voruciclib QD	Cohort dose		None		None
Voruciclib QOD[a]	50 mg[a]		None		None

Abbreviation: QOD = once every other day

[a] For cohort 12, the dose of voruciclib will be 50 mg once every other day (QOD) on Days 3, 5, 7, 9, 11, and 13 of Cycle 1, and on Days 1, 3, 5, 7, 9, 11, and 13 of Cycle 2 and beyond.

Amendment 12 – $IS_{3w,1w}$ Dosing Schedule

For Cycle 1 in combination cohorts 21–25, the dosing will be as follows (Table 6):

- Venetoclax dose will be ramped up starting with 100 mg on Day 1, 200 mg on Days 2–21, then 400 mg administered as a single agent on Days 22–28.
- Voruciclib dosing will be administered on Days 3–21 at the appropriate Cohort Dose (Table 4).

For Cycle 2 and beyond, the dosing will be as follows:

- Venetoclax 200 mg will be administered on Days 1–21, and 400 mg administered as a single agent on Days 22–28.
- Voruciclib at the cohort dose (Table 4) will be administered on Days 1–21.

Venetoclax should be taken with a meal and water. When both venetoclax and voruciclib are to be taken, venetoclax should be taken first with a meal followed by voruciclib at least 2 hours later (e.g., meal completed at 8 a.m. with venetoclax, dose of voruciclib taken after 10:00 a.m.). Voruciclib tablets must not be chewed, crushed, or broken.

Table 6: Administration Schedules of Voruciclib given in Combination with Venetoclax ($IS_{3w,1w}$)

Administration Schedule of Voruciclib $IS_{3w,1w}$ and Venetoclax per 28-day Cycle				
Cycle 1	**Day 1**	**Day 2**	**Days 3 to 21**	**Days 22 to 28**
Venetoclax	100 mg	200 mg	200 mg	400 mg
Voruciclib QD	-	-	Cohort dose	None
Cycle 2 and beyond	**Days 1 to 21**			**Days 22 to 28**
Venetoclax	200 mg			400 mg
Voruciclib QD	Cohort dose			None

Abbreviation: QD = once per day.

In both $IS_{2w,2w}$, and $IS_{3w,1w}$, venetoclax dosing on Day 1 of Cycle 1 may proceed when any non-hematologic toxicity from prior antileukemic therapy has resolved to Grade ≤1 or is considered stable.

4.3.2.2. Justification of Dose and Administration Sequence of Voruciclib + Venetoclax

In vitro studies indicate that voruciclib has the potential to inhibit CYP3A4 and P-gp (Section 4.15). At the proposed starting dose of voruciclib of 50 mg, an increase of venetoclax exposure may be observed based on the following assessment of time dependent inhibition of CYP3A4 by voruciclib.

CYP3A4 time-dependent inhibition potential of voruciclib

The CYP3A4 time-dependent inhibition potential of voruciclib was evaluated according to FDA guidance (In Vitro Drug Interaction Studies - Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions) using the following input parameters.

Parameter	Value (source)
Voruciclib dose	50 mg
Voruciclib C_{max} after 50 mg multiple dose	225 ng/mL or 0.225 mg/L (extrapolated; IB Section 5.2.1.1)
Fraction unbound in plasma	0.05 (IB Section 4.3.2)
Fraction absorbed after oral administration	80% (preclinical data; IB Section 4.3.1)
Fraction available after intestinal metabolism	100% (unknown; assumed per FDA guidance)
K_a	0.67 h^{-1} (assumed based on slow absorption as evidenced by median T_{max} 4 to 6 hours; IB Section 5.2.1.1)
Blood: Plasma ratio of concentration	1 (unknown; assumed)
k_{inact}	0.021 min^{-1} (estimated from raw data; Study No. P1446APK16)
K_I	5.0478 mg/L (estimated from raw data; Study No. P1446APK16)
$K_{deg,CYP3A4,\ liver}$	0.00032 min^{-1} (literature)
$K_{deg,CYP3A4,\ interstine}$	0.00048 min^{-1} (literature)
Hepatic blood flow	97 L/h (according to FDA guidance)
Blood flow in enterocytes	18 L/h (according to FDA guidance)

Based on the input parameter values listed in the table above, the effect of voruciclib on the PK of midazolam (a sensitive CYP3A4 substrate) was assessed. For these calculations, midazolam fm_{CYP3A4} and Fg values of 0.93 and 0.6, respectively were used and an AUCR value of 2.03 was determined indicating an approximately 2-fold increase in midazolam exposure when co-administered with voruciclib 50 mg once daily.

Therefore, during the period of coadministration with voruciclib, the dose of venetoclax was reduced by 50% to 200 mg once daily.

Effective half-life of voruciclib

In Study P1446A-05/19/08 and Study P1446A-05/20/08, voruciclib PK samples were collected for 24 hours post-dose after single and multiple administrations. Sample collection only during the 24-hour dosing interval precluded reliable estimation of terminal phase half-life. However, effective half-life may be calculated based on accumulation ratio (multiple dose $AUC_{(0-24)}$ divided by single dose $AUC_{(0-24)}$) using the following formula:
Accumulation Ratio = $1 / (1 - \exp(-k_{el} \times tau))$.

Based on accumulation ratio, voruciclib effective half-life was estimated at the 600 mg and 350 mg dose levels in Study P1446A-05/19/08 and Study P1446A-05/20/08, respectively. These dose levels were chosen because of the large sample size of 16 and 24, respectively, thus permitting a robust estimation. Based on average accumulation ratios of 2.06 and 2.77, voruciclib effective half-life value was estimated to be 24 to 36 hours.

Preliminary PK results for voruciclib and venetoclax for Cohorts 12 (voruciclib 50 mg QOD) to 15 (voruciclib 150 mg QD) indicate that administration of multiple doses of voruciclib does not have an effect on venetoclax PK. In these cohorts, on Cycle 1 Day 21 (i.e., 7 days after the last voruciclib dose on Cycle 1 Day 14), plasma voruciclib concentrations were either below the lower limit of quantitation or very low. At the highest voruciclib dose level evaluated for PK (150 mg QD, Cohort 15), average plasma voruciclib concentration on Cycle 1 Day 21 was 8 ng/mL (less than 2% of maximum plasma concentration) indicating nearly complete elimination of voruciclib from the systemic circulation one week after the last dose. Lack of pharmacokinetic interaction at steady-state and very low voruciclib concentrations observed one week after the end of treatment justifies administration of the labeled dose of venetoclax on voruciclib treatment-free days. Therefore, in Cohorts 21–25 (voruciclib $IS_{3w,1w}$) the labeled dose of venetoclax (400 mg QD) may be administered on Days 22 to 28 of each cycle when voruciclib is not administered.

Sequence of administration

Per the Venclexta [US Prescribing Information] Rev 2022, it is noted that P-gp substrates (such as voruciclib) should be administered at least 6 hours before venetoclax administration. However, this timing and sequence presents logistical considerations related to the collection of serial blood samples for PK analysis over the course of a treatment/PK sampling day. As venetoclax requires administration with food, it is administered first followed by voruciclib at least 2 hours after the meal, allowing for PK sampling through 8 hours post the venetoclax dose and pre-dose sampling on the subsequent day to be completed in the morning (see Section 9.14.2).

4.4. Dose-Limiting Toxicity (DLT)

A DLT will be defined as any of the following treatment-emergent adverse events (TEAEs) occurring in Cycle 1 of voruciclib monotherapy or voruciclib + venetoclax combination therapy that are clearly unrelated to the underlying disease or extraneous causes:

- Symptomatic nonhematological Grade ≥3 laboratory abnormalities or asymptomatic nonhematological Grade ≥3 laboratory abnormalities that fail to improve to Grade ≤2 within 72 hours
- Grade 3 vomiting lasting >48 hours despite recommended antiemetic support or any occurrence of Grade ≥4 vomiting
- Grade 3 diarrhea lasting >48 hours despite recommended antidiarrheal support or any occurrence of Grade ≥4 diarrhea
- All other Grade ≥3 nonhematological adverse event (AE) not listed above
- Grade 3 or higher TLS regardless of prophylaxis
- Hy's law cases
- Febrile neutropenia of any duration (not applicable to AML subjects)
- Grade 4 neutropenia lasting ≥7 days; or lasting ≥42 days and not due to progressive disease in AML subjects
- Grade ≥3 thrombocytopenia with Grade ≥2 bleeding or Grade 4 thrombocytopenia of any duration (not applicable to AML subjects)
- Grade 4 thrombocytopenia lasting ≥42 days (AML subjects only)
- Grade 4 anemia unexplained by underlying disease

Hy's law cases of drug-related hepatocellular injury are defined as elevated ALT or AST ≥3 × ULN, elevated total bilirubin >2 × ULN without findings of cholestasis, and no other reason can be found to explain the combination of increased aminotransferase and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, pre-existing liver disease, or another drug capable of causing the observed injury.

Additionally, discontinuation of study drug in Cycle 1 due to an AE that is clearly unrelated to the underlying disease, or an extraneous cause will be considered a DLT.

Safety will be assessed by AEs graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0; laboratory safety tests including hematology (complete blood count [CBC]), serum chemistry; physical examination; vital signs; ECOG performance status; and 12-lead electrocardiogram (ECG).

4.5. Expansion Cohort and Early Stopping Boundaries for Toxicity

Once the safe and mBED of voruciclib in combination with venetoclax on $IS_{2w,2w}$ and $IS_{3w,1w}$ has been declared in subjects with AML, an expansion cohort of up to 12 additional subjects for each of the 2 voruciclib dose schedules will be enrolled to further characterize the safety, efficacy, PK, and pharmacodynamics of the mBED on $IS_{2w,2w}$ and $IS_{3w,1w}$.

Sequential boundaries will be used to monitor the rate of unacceptable toxicities in AML subjects enrolled on expansion cohorts, using criteria consistent with those used to define DLTs in escalation cohort subjects, with focus on potential cumulative toxicities over time. If an excessive number of unacceptable toxicities are observed, the SRC will have the option of either halting study accrual or reducing the dose to reduce the level of toxicity. The boundaries at which enrollment into an expansion cohort will be halted or safe and mBED reduced are listed in Table 7. This is a Pocock-type boundary that yields 0.2 or greater probability of crossing the boundary when the rate of DLT/unacceptable toxicity is equal to the acceptable rate of 20% (Ivanova 2005).

Since these boundaries are very conservative, to avoid a high false positive rate in the early stage of the enrollment period due to a small sample size, the Pocock boundary described below will be implemented after 4 subjects have been enrolled; for subjects 1-3 the decision to halt study accrual or reduce the dose will be based on clinical judgment, SRC, and Sponsor.

Table 7: Early Stopping Boundaries for Toxicity – Expansion Cohort

# Subjects	1	2	3	4	5	6	7	8	9	10	11	12
Boundary	-	*	*	3	3	3	4	4	4	5	5	5

*Subjects 1 – 3 will be based on clinical judgement.

4.6. Maximum Tolerated Dose (MTD)

With respect to voruciclib monotherapy, for each disease group and schedule (continuous, $IS_{2w,2w}$, $IS_{1w,3w}$,), an MTD of voruciclib will be defined as the highest dose at which <2 of 6 subjects experience a DLT.

With respect to voruciclib +venetoclax combination therapy, an MTD will be defined as the highest dose cohort level at which <2 of 6 subjects experience a DLT.

4.7. Recommended Phase 2 Dose (RP2D) for Voruciclib Monotherapy

The study may not be sufficient to determine the RP2D and schedule of voruciclib monotherapy in hematologic malignancies. It will evaluate the safety, efficacy, and the safe and mBED of voruciclib monotherapy. The safe and mBED and schedule will be determined based on safety and tolerability over two or more cycles, achievement of voruciclib blood levels that have demonstrable activity in non-clinical studies, and/or additional evidence of biologic or clinical activity. The safe and mBED may be different in AML and B-cell malignancies and may be the same or lower than the MTD.

4.8. Dose Modifications

4.8.1. Dose Modifications for Cohorts 1 to 5 - Voruciclib Monotherapy Continuous Dosing

Details are provided in the Dose Modification Schedule (Table 8), which is intended as a guideline as the final decision of dose reduction or whether to restart study medication is to be made by the Investigator. Variations from these recommendations may be warranted based on an Investigator's individual judgment in considering potential risks, benefits, and therapeutic

alternatives available to each subject, and after discussion with the Medical Monitor. In addition, Investigators should always consider and eliminate other potential causes for AEs (e.g., underlying malignancy, intercurrent illness, comorbid conditions, or concomitant medications).

During the first cycle, subjects experiencing a DLT should be considered for permanent discontinuation.

Such subjects may, however, continue to receive additional voruciclib:

- If additional treatment with voruciclib is clinically appropriate, and
- At the discretion of the Investigator, after consultation with and approval by the Medical Monitor

Continued treatment with voruciclib will follow the Dose Modification Schedule (Table 8).

Table 8 Dose Modification Schedule Cohorts 1 to 5

Cohort/Dose Level	Voruciclib Dose	Reduced Dose
-1	Intermittent Schedule (QOD)	Discontinue
1	50 mg	Intermittent Schedule (QOD)
2	100 mg	50 mg
3	150 mg	100 mg
4	200 mg	150 mg
5	250 mg	200 mg

Abbreviation: QOD = every other day.

Table 9: Dose Modification Cohorts 1 to 5

Toxicity[1]	Requirement for Holding Dose or Discontinuing Study Drug	Amount of Dose Reduction
Grade 4 non-hematologic	Discontinue study drug	Not allowed
Grade 3 non-hematologic	Hold dose until recovery to Grade ≤1	Dose may remain unchanged or be reduced by one dose level (see Table 8) based on overall assessment of the subject
Grade 3 vomiting or diarrhea	Dose interruption required if not controlled within 48 hours by supportive therapy	
Grade 4 thrombocytopenia, or neutropenia[2] with associated symptoms (e.g., fever)*	Hold dose until recovery to Grade ≤3	Reduce by one dose level (see Table 8) if recovery within 7 days; if longer than 7 days, discontinue study drug
Grade 3 hematologic (ANC ≤500 to 1000/mm^3 or platelets ≤25,000 to 50,000/mm^3)*	May continue on treatment, but requires weekly CBC until toxicity resolves to Grade ≤2 (unless myelosuppression is due to disease)	Dose may remain unchanged or be reduced by one dose level (see Table 8) based on overall assessment of the subject Consider use of G-CSF in subsequent cycles

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count; G-CSF = granulocyte colony-stimulating factor.

[1] Toxicity graded per CTCAE v5.0.

[2] Hematopoietic growth factor (see Section 4.14 regarding acceptable and prohibited types) may be administered to subjects with neutropenia per the institutional standard of care.

* Not applicable to AML subjects.

For an AE that is attributed to voruciclib, and which requires a dose modification, the dose should be reduced by 1 dose level. Successive single level adjustments to progressively lower dose levels can be made. After a dose reduction, the dose may be maintained at that reduced dose level. However, if the subject tolerates the drug at a reduced dose for ≥4 weeks, the dose may be re-escalated to the next higher dose level at the discretion of the Investigator (particularly if the AE-associated TLS; or if further evaluation reveals that the AE that led to the dose reduction was primarily related to the underlying malignancy, an intercurrent illness, a comorbid condition, or a concomitant medication). Successive single-level dose adjustments to progressively higher dose levels may be made at intervals of ≥4 weeks and will not exceed dose levels the SRC has not yet determined to be safe.

The dose level for a subject may be escalated above the assigned enrollment dose once the SRC has determined that the higher dose is safe and after consultation with the Medical Monitor.

Voruciclib re-challenge is prohibited in subjects experiencing Grade 4 non-hematologic toxicity and must be permanently discontinued.

4.8.2. Re-treatment Following Adverse Events in Cohorts 6 to 11 with Intermittent Schedules of Voruciclib Monotherapy

Subjects enrolled in Cohorts 6a and b to 11a and b, i.e., receiving voruciclib on an IS, who experience Grade 3-4 AEs will be managed as follows:

During the first cycle, subjects experiencing a DLT should be considered for permanent discontinuation. Such subjects may, however, continue to receive voruciclib on the same dosing schedule upon resolution of the DLT to Grade ≤1:

- If additional treatment with voruciclib is clinically appropriate, and
- At the discretion of the Investigator, after consultation with and approval by the Medical Monitor

In later cycles, subjects experiencing a Grade 3-4 AE in Cohorts 6 to 11, may continue to receive voruciclib at the same dose but using the $IS_{1w,3w}$ schedule upon resolution of the AE to Grade ≤1 as outlined in Table 10.

Table 10: Re-treatment Following a Grade 3-4 Adverse Event in Cycles ≥2 in the Intermittent Schedules

Toxicity[1]	Requirement for Holding Dose or Discontinuing Study Drug	Retreatment with Voruciclib
Grade 4 non-hematologic	Discontinue study drug	Not allowed
Grade 3 non-hematologic	Hold dose until recovery to Grade ≤1	Allowed based on overall assessment of the subject
Grade 3 vomiting or diarrhea	Dose interruption required if not controlled within 48 hours by supportive therapy	
Grade 4 thrombocytopenia, or neutropenia[2] with associated symptoms (e.g., fever)*	Hold dose until recovery to Grade ≤3	Allowed if recovery within 7 days; if longer than 7 days, discontinue study drug
Grade 3 hematologic (ANC ≤500 to 1000/mm^3 or platelets ≤25,000 to 50,000/mm^3)*	May continue on treatment, but requires weekly CBC until toxicity resolves to Grade ≤2 (unless myelosuppression is due to disease)	Allowed based on overall assessment of the subject Consider use of G-CSF in subsequent cycles

Abbreviations: ANC = absolute neutrophil count; CBC = complete blood count; G-CSF = granulocyte colony-stimulating factor.

[1] Toxicity graded per CTCAE v5.0.

[2] Hematopoietic growth factor (see Section 4.14 regarding acceptable and prohibited types) may be administered to subjects with neutropenia per the institutional standard of care.

* Not applicable to AML subjects.

4.8.3. Dose Modifications for Cohorts 12–19 and 21–25 - Voruciclib + Venetoclax Combination Dosing in AML

Dose reductions for toxicities attributed to venetoclax or for the combined effect of voruciclib and venetoclax will be managed according to the Venclexta [US Prescribing Information] Rev 2022.

The safety profile of venetoclax in AML has been characterized in several studies, including Phase 3 trials in combination with azacitidine or low dose cytarabine. The safety profile of

voruciclib has not been well defined due to the small number of subjects (~100) studied to date. However, the emerging voruciclib safety profile suggests potential overlapping toxicities with venetoclax, including gastrointestinal (nausea, diarrhea, vomiting, abdominal pain), hematologic (myelosuppression and febrile neutropenia), fatigue, infections, and dyspnea.

Venetoclax and voruciclib dose modifications for drug-related adverse reactions are shown in Table 11. For more details on voruciclib dose interruption and re-treatment during the DLT window and after the DLT window see Table 10.

Study drug dose reduction will proceed stepwise upon recovery to Grade ≤2 in subjects in CR, CRh, or CRi who experience Grade 4 neutropenia, with or without fever or infection, or Grade 4 thrombocytopenia. Upon recovery, voruciclib will be restarted at one dose level lower and venetoclax will resume at the same dose. If there is a recurrence of Grade 4 neutropenia or thrombocytopenia, then venetoclax will be resumed at the lower dose level upon recovery to Grade ≤2.

Table 11: Venetoclax Schedule Modification and Voruciclib Dose Modification for Toxicity

Adverse Reaction	Venetoclax	Voruciclib
Hematologic Adverse Reactions		
Grade 3-4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Prior to achieving a remission: • Continue venetoclax unless treatment interruption is deemed necessary by the Investigator • A bone marrow evaluation is recommended For subjects who achieve CR, CRh, or CRi, at the end of Cycle 1 (or later cycle): • Hold venetoclax until recovery to Grade ≤2 • Monitor blood counts • Upon resolution to Grade 1 or 2, resume at the same dose Cycle 2 and beyond: For subsequent occurrences in cycles after achieving remission and lasting ≥7 days, the following stepwise schedule duration reductions are allowed for persistent cytopenia: • Hold venetoclax until recovery to Grade ≤2 • Monitor blood counts. Retreat at same dose level and same schedule (no reduction)	Prior to achieving a remission: • Continue voruciclib unless treatment interruption is deemed necessary by the Investigator • A bone marrow evaluation is recommended For subjects who achieve CR, CRh, or CRi, at the end of Cycle 1 (or later cycle) • Hold voruciclib until recovery to Grade ≤2 • Monitor blood counts • Re-treatment at the same dose and schedule is allowed • If no recovery by Day 42 after start of Grade 4 neutropenia, retreat at one dose level lower and same schedule Cycle 2 and beyond: • Hold voruciclib until recovery to Grade ≤2 • Monitor blood counts. • Retreat at one dose level lower and same schedule.

Adverse Reaction	Venetoclax	Voruciclib
	Reduction level 1: venetoclax duration may be reduced to administration on Days 1 through 21 of the 28-day cycle Reduction level 2: venetoclax duration may be reduced to administration Days 1 through 14 of the 28-day cycle	
Nonhematologic Adverse Reactions		
Grade 3 or 4 nonhematologic toxicities	Interrupt venetoclax if not resolved with supportive care. Upon resolution to Grade 1 or baseline level, resume venetoclax at the same dose.	See Requirement for Holding Dose or Discontinuing Study Drug and Retreatment with Voruciclib rules for non-hematologic toxicities in Table 10

4.9. Tumor Lysis Syndrome (TLS)

TLS includes electrolyte abnormalities (hyperkalemia, hypocalcemia, hyperuricemia, and hyperphosphatemia), cardiac dysrhythmias, and renal failure. TLS is a known risk in subjects treated with CDK9 inhibitors. The risk of TLS depends on tumor type, tumor burden, and subject factors such as pre-existing renal impairment and splenomegaly. Therefore, risk assessment for TLS, prophylaxis, and monitoring, including assessment of need for hospitalization, is required for all subjects. Investigators must institute appropriate prophylactic measures, including for low-risk subjects, during screening and prior to Cycle 1 Day 1.

Risk assessment for subjects with B-cell tumors and AML are provided in Appendix 9 in Table 24 and Figure 3, respectively. All AML subjects should have white blood cell count less than 25×10^9/L prior to initiation of venetoclax; cytoreduction prior to treatment may be required.

Recommended TLS prophylaxis and monitoring in Table 24 are per those indicated for CLL/SLL patients in the Venclexta [US Prescribing Information] Rev 2022. Additional guidance for subjects with AML is provided in Appendix 9. Guidance on the diagnosis of TLS is provided in Appendix 10.

4.10. Differentiation Syndrome

Differentiation syndrome (DS) is a relatively common and potentially severe complication seen in patients with acute promyelocytic leukemia treated with all-trans retinoic acid and/or arsenic trioxide. The syndrome includes, but may not be limited to, unexplained fever, weight gain, dyspnea with pulmonary infiltrates, pleuro-pericardial effusion, hypotension, and/or renal failure. Cases of DS have been recently reported in patients with various types of AML administered FMS-like tyrosine kinase 3 (Flt3) inhibitors and isocitrate dehydrogenase (IDH) inhibitors.

Although the pathogenesis of DS has not been entirely clarified, it has been speculated it is due to a cascade of pathophysiologic mechanisms, leading to a systemic inflammatory response syndrome, endothelium damage with capillary leak syndrome, occlusion of microcirculation, and tissue infiltration with leukocytes. In this study, a diagnosis of DS should be suspected in subjects with AML in the presence of any of the above-mentioned signs and symptoms, and preemptive treatment with dexamethasone should be started immediately, particularly in patients with leukocyte counts greater than 10,000/µL. Other supportive measures can also be crucial for

the correct management of DS, especially in patients with life-threatening complications (Sanz 2014). Temporary interruption of voruciclib is indicated for patients in poor clinical condition. Treatment with hydroxyurea (or an anthracycline if appropriate) to control rising leukocyte counts is also recommended.

Two subjects with AML enrolled in Cohort 2 (monotherapy) of this study experienced symptoms consistent with DS in Cycle 1 of voruciclib administration, including fever, hypoxemia, pulmonary infiltrate, and pleural effusion. The mechanism by which voruciclib may induce DS is unclear. Investigators should be aware of DS as differential diagnosis in patients with AML experiencing fever, pulmonary or hemodynamic complications in the first weeks of voruciclib administration. After ruling out an infection or other causes, treatment with dexamethasone and supportive care measures is recommended. Hydroxyurea (1-2 g/day) or an anthracycline (if appropriate) can be used to control rising leukocyte counts.

4.11. Interstitial Lung Disease/Pneumonitis

Interstitial lung disease (ILD)/pneumonitis has been reported post-marketing with the CDK4/6 inhibitors, which are approved in the US for the treatment of patients with breast cancer (FDA Drug Safety Communications, September 2019). With the continuous dosing schedule of voruciclib, 2 subjects with AML had DLTs of pneumonitis (n = 1) or ILD (n = 1) at the 100 mg QD dose level. Of note, the 2 subjects had confounding factors that may have contributed to this toxicity, including a history of secondary AML following a myelodysplastic syndrome, heavily pretreated disease, allogeneic stem cell transplantation in the preceding 12 months, and evidence of differentiation syndrome occurring 1 to 2 weeks after voruciclib initiation. These DLTs prompted the Sponsor decision to no longer pursue a QD dosing schedule in either disease group. In addition, one subject with DLBCL enrolled at the 50 mg QD dose cohort experienced hypoxemic respiratory failure with pulmonary infiltrates in Cycle 4. There was no identified cause for this event, which was considered related to study drug and led to voruciclib discontinuation.

The mechanism of this pulmonary toxicity is not understood. PK data from the Phase 1 studies in solid tumors indicated that voruciclib has a very high volume of distribution (>100 L), suggesting higher exposure in tissues than in plasma.

Subjects should be monitored for symptoms indicative of ILD/pneumonitis (e.g., hypoxia. cough, dyspnea), with management as indicated in Table 12. In subjects with new or worsening respiratory symptoms and in whom pneumonitis is suspected, voruciclib administration is to be suspended and permanently discontinued if pneumonitis is confirmed.

Table 12: Monitoring and Management of Interstitial Lung Disease/Pneumonitis

Grade 1	Monitor patients weekly with history and physical examination, pulse oximetry and imaging
Grade 2	Hold voruciclib until at least ≤ Grade 1 Consider prednisone 1-2 mg/kg/day with taper by 5-10 mg/week over 4-6 weeks Consider bronchoscopy with bronchoalveolar lavage (BAL) Consider empiric antibiotics Monitor Q3 days with history and physical examination, pulse oximetry and imaging

Grade 3 or 4	Permanently discontinue voruciclib Consider empiric antibiotics Consider methylprednisolone IV 1-2 mg/kg/day Consider infliximab 5 mg/kg or mycophenolate mofetil IV 1 gm twice daily or IVIG X 5 days or cyclophosphamide if no improvement Consider pulmonary and infectious disease consults Patients should be hospitalized for further management

Adapted from Brahmer 2018.

4.12. Subject Replacement

Subjects who discontinue study therapy prior to completing Cycle 1 (Day 28) for reasons other than the development of a DLT will be replaced. Subjects who miss one or more doses for reasons other than DLT, must receive at least 75% of the total planned voruciclib dose in Cycle 1 to be assessed for DLT. Subjects with no DLT who fail to receive at least 75% of the planned Cycle 1 voruciclib dose will be replaced.

For Cohort 12, subjects must receive 100% of Cycle 1 doses (i.e., all 6 doses) to be DLT evaluable; subjects with no DLT who fail to receive 100% of Cycle 1 voruciclib doses will be replaced.

4.13. Discontinuation of Voruciclib Administration

Subjects may continue to receive voruciclib monotherapy or voruciclib + venetoclax combination therapy provided there is evidence of clinical response (PR or better) by the end of Cycle 6. Subjects may discontinue voruciclib monotherapy or voruciclib + venetoclax combination therapy for reasons including the following:

- Documented progression of disease while receiving therapy
- Unacceptable AE(s) considered secondary to voruciclib despite appropriate therapy and/or dose modification
- Intercurrent illness that precludes continued study therapy
- Withdrawal of consent by the subject
- Changes in the subject's medical condition that render further administration of voruciclib unacceptable in the judgment of the Principal Investigator or sponsor
- Treatment of the disease with another therapeutic regimen
- Pregnancy or breastfeeding
- Substantial noncompliance with study procedures
- Termination of study by the sponsor

4.14. Prohibited Treatments and Concomitant Medications – Cautions and Prohibitions

4.14.1. Concomitant Medications with Voruciclib – Cautions and Prohibitions

In vitro studies have shown that voruciclib has the potential to inhibit cytochrome (CYP) CYP2C9, CYP2C19, CYP2D6, and CYP3A4, therefore, drugs with a narrow therapeutic

window that are metabolized by these enzymes should be avoided or used with caution (see Appendix 7).

Subjects receiving warfarin treatment are excluded, since voruciclib is highly protein bound and is a competitive inhibitor of CYP2C9 at higher concentrations and increased INR was a DLT in the previous Phase 1 studies. Subjects on study who initiate warfarin therapy must discontinue voruciclib.

Consistent with subject safety and comfort, administration of any prescription or over-the-counter (OTC) drug products other than study medication will be minimized during the study period. Subjects should be discouraged from use of herbal remedies, self-prescribed drugs, tobacco products, or street drugs during their participation in the clinical study and should be counseled to minimize use of alcohol or nonmedical marijuana.

If considered necessary for the subject's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the Investigator. The Investigator's decision to authorize the use of any drug other than study drug will take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Subjects will be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, OTC, or illicit) before and during the course of the study.

No other anti-cancer therapeutics or investigational agents are permitted during the study treatment period, except for hydroxyurea or anthracycline for the treatment of DS and to manage rapidly rising white blood cell counts in Cycles 1 and 2 only in patients with AML. Palliative radiotherapy is permitted after Cycle 1 but should be minimized and used for control of local tumor-related symptoms only.

If a subject experiences an AE, appropriate supportive care (e.g., antiemetics, antidiarrheals, antibiotics, granulocyte colony-stimulating factor [G-CSF] hydration) should be instituted consistent with the nature of the event. If the AE requires a dosing modification, the treatment regimen should be interrupted, as necessary. A decision should be made as to whether the subject can reasonably continue with the study drug based upon the nature and severity of the AE.

Recommendations regarding specific types of concomitant therapies, supportive care, diet, and other interventions are provided below. To minimize variations in supportive care, the recommended supportive care agents (e.g., loperamide, granisetron) should be used unless there is a medical rationale in a specific subject for use of an alternative product.

Antibiotics, Antifungals, Antivirals

Care should be taken to avoid or minimize concomitant administration of prophylactic or therapeutic antibacterial, antifungal, or antiviral agents that are moderate or strong CYP3A4 inhibitors or inducers. For subjects with CLL/SLL and a history of recurrent infections, prophylaxis with intravenous immunoglobulin may be offered and consideration may be given to initiation of antibiotic prophylaxis against pneumocystis infection (e.g., with trimethoprim-sulfamethoxazole, dapsone, aerosolized pentamidine, or atovaquone) beginning prior to study drug administration. Such support also offers the benefit of reducing the risk for other bacterial infections. Local practices or guidelines regarding infection prophylaxis may be followed.

Subjects developing an intercurrent infection during study drug treatment may receive therapeutic antibacterial, antiviral, or antifungal drugs for intercurrent infections as needed. Continuation of study therapy during treatment for an intercurrent infection is at the discretion of the Investigator. Given that voruciclib is a CYP3A4 substrate and the critical role of azole antifungals (commonly strong CYP3A4 inhibitors) in the treatment of fungal infections in patients with AML, voruciclib must be held during treatment with an azole and restarted when the azole therapy is completed. Antifungals other than azoles may be used if considered by the investigator as a clinically appropriate alternative to azoles.

In the voruciclib and venetoclax combination groups, antifungal prophylaxis (excluding azoles) may be provided according to institutional guidelines and in accordance with guidance for management of potential venetoclax interactions per the venetoclax PI (Venclexta [US Prescribing Information] Rev 2022) provided in Table 13.

Of note, hepatitis B virus reactivation can occur in subjects previously treated with anti-CD20 therapeutic antibodies. The median time to diagnosis of hepatitis among subjects with hematologic malignancies is 4 months after the initiation of therapy, but such events can occur months after completion of anti-CD20 antibody therapy.

Anticoagulants

Use of systemic anticoagulants should be avoided unless necessary for a serious intercurrent thrombotic or embolic condition. Because voruciclib appears to increase exposure to warfarin, subjects receiving warfarin are ineligible for enrollment and subjects on study who start warfarin must discontinue voruciclib.

Antidiarrheals

Subjects experiencing diarrhea (and/or abdominal cramping) may take loperamide at the earliest sign of a loose stool, an increase in bowel movements by 1 to 2 episodes compared to baseline, or an increase in stool volume or liquidity. The recommended regimen is 4 mg at the first onset of diarrhea, and then 2 mg with each succeeding diarrheal stool until the subject is diarrhea-free for at least 12 hours.

Additional antidiarrheal measures may be implemented at the discretion of the Investigator. Subjects should also be instructed to maintain oral fluid intake to help sustain fluid and electrolyte balance during episodes of diarrhea.

Antiemetics

While prophylactic antiemetics can be considered, antiemetics should not be given prophylactically before initial study drug administration on Cycle 1 Day 1. Choice of antiemetic therapy should be based on standard practice and/or institutional guidelines.

Antihistamine, Anti-inflammatory, and Antipyretic Drugs

Antihistamines (e.g., cetirizine, diphenhydramine), and anti-inflammatory/antipyretic drugs (e.g., acetaminophen [paracetamol], nonsteroidal anti-inflammatory drugs [NSAIDs]), may be used during the study, as medically warranted.

Corticosteroids

At study entry, subjects may not be using enteric corticosteroids but may be receiving systemic corticosteroids (at doses of ≤20 mg/day of prednisone or equivalent) or topical or inhaled corticosteroids. During study therapy, subjects may use systemic, enteric, topical, or inhaled corticosteroids as required for treatment-emergent conditions.

Calcineurin inhibitors are prohibited during study treatment.

CYP3A4 Inhibitors and Inducers

Whenever possible moderate or strong inhibitors or inducers of CYP3A4 should be avoided and only administered if essential for patient care (Appendix 7).

Drugs Affecting Gastric pH

A potential effect of altering gastric pH on the absorption of voruciclib cannot be excluded. Proton pump inhibitors should be avoided if possible. Antacids and H2-receptor antagonists should be taken at least 4 hours before or after voruciclib.

Drugs with a Narrow Therapeutic Range that are P-gp substrates

Based on in vitro studies, voruciclib may be a P-gp inhibitor; however, the clinical relevance of this finding is not known. Drugs with a narrow therapeutic range that are P-gp substrates should be avoided or used with caution (e.g., digoxin, colchicine).

Hematopoietic Support

Granulocyte colony-stimulating factor (G-CSF) (e.g., filgrastim, filgrastim-snd, peg-filgrastim, lenograstim) may be administered in response to Grade ≥3 neutropenia or neutropenic complications.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) should not be administered, given the potential for GM-CSF-related inflammatory symptoms.

Erythropoietic agents (e.g., erythropoietin or darbepoetin) may be administered for Grade ≥ 3 anemia, at the discretion of the treating physician.

Red blood cell or platelet transfusions may be administered as medically indicated.

Drugs Known to Prolong QT Interval

The effect of voruciclib on the QT interval has not been determined, therefore, drugs known to prolong QT interval should be avoided, if possible (ondansetron use is acceptable). See Appendix 8 for a list of medications known to prolong the QT/QTc interval.

Immunization

For subjects who are at risk of an infection (e.g., influenza, herpes zoster) that might be prevented by immunization, consideration should be given to providing the vaccine prior to initiation of study therapy.

Immunization for the SARS-CoV-2 virus, responsible for COVID-19 infection, may be performed according to institutional guidelines.

Whether voruciclib would increase the risk of live viral vaccines during study therapy is unknown. Pending the acquisition of additional information, live viral vaccination should be avoided 10 days prior to first dose and during study therapy.

Do not administer live attenuated vaccines prior to, during, or after treatment with venetoclax until B-cell recovery occurs. The safety and efficacy of immunization with live attenuated vaccines during or following venetoclax therapy have not been studied. Advise patients that vaccinations may be less effective (Venclexta [US Prescribing Information] Rev 2022).

Cytoreductive Therapy in AML patients

Cytoreduction with hydroxyurea (or another cytoreductive therapy) must be implemented prior to initiating voruciclib, or venetoclax in Cohorts 12–25, if the subject has white blood cell counts ≥25 × 10^9/L.

In subjects with rapidly rising white blood cell counts in Cycles 1 and 2, a short course of hydroxyurea (or another cytoreductive therapy) may be administered at the discretion of the Investigator to control rising cell counts while continuing study drug(s) administration.

4.14.2. Procedures and Surgery

The extent to which voruciclib may affect wound healing, enhance the risk of infection, or increase the risk of bleeding is unknown. Considering parameters such as ANC, platelet count, and PT/aPTT, Investigators may use clinical discretion in deciding whether to interrupt study therapy before and after surgery or other invasive procedures.

4.14.3. Concomitant Medications with Venetoclax – Cautions and Prohibitions

Drugs prohibited according to the Venclexta [US Prescribing Information] Rev 2022 (PI) are not permitted in patients enrolled in venetoclax combination cohorts. Per the Venclexta US PI, concomitant use of venetoclax with strong CYP3A inhibitors (e.g., posaconazole) at initiation and during the ramp-up period is contraindicated but allowed for AML with dose reduction (Table 13). Subjects administered prohibited drugs (e.g., azoles) during the screening period must undergo a wash out period (at least 4 half-lives of the prohibited drug) prior to starting Day 1 dosing. For subjects who complete the ramp-up phase and are on a steady daily dose of venetoclax, the venetoclax dose should be reduced by at least 75% when used concomitantly with strong CYP3A inhibitors (e.g., posaconazole). Moderate CYP3A and P-gp inhibitors can be used with venetoclax dose reduction of 50%.

Table 13: Management of Potential Venetoclax Interactions with CYP3A and P-gp Inhibitors

Coadministered Drug	Venetoclax Initiation and Ramp-Up Phase		Steady Daily Dose (After Ramp-Up Phase)
Posaconazole	CLL/SLL	Contraindicated	Reduce venetoclax dose to 70mg
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 70 mg	
Other strong CYP3A inhibitor	CLL/SLL	Contraindicated	Reduce venetoclax dose to 100mg
	AML	Day 1 – 10 mg Day 2 – 20 mg Day 3 – 50 mg Day 4 – 100 mg	

Coadministered Drug	Venetoclax Initiation and Ramp-Up Phase	Steady Daily Dose (After Ramp-Up Phase)
Moderate CYP3A inhibitor	Reduce venetoclax dose by at least 50%	
P-gp inhibitor		

Avoid concomitant use of venetoclax with a P-gp substrate. If a concomitant use is unavoidable, separate dosing of the P-gp substrate by at least 6 hours before venetoclax.

4.15. CYP3A4 and P-gp Inhibition Potential of Voruciclib

In in vitro studies, voruciclib was found to inhibit CYP3A4 (testosterone 6β-hydroxylase activity but not midazolam 1'-hydroxylase activity). Nevertheless, an assessment of voruciclib CYP3A4 inhibition potential was performed using preliminary estimates of enzyme inhibition parameters in a static mechanistic model, and it was estimated that concomitant administration of voruciclib (100 mg dose) and midazolam, a sensitive and specific CYP3A4 substrate widely used in clinical drug-drug interaction studies, may result in approximately 2.5-fold increase in midazolam exposure.

Based on in vitro studies, voruciclib may be a P-gp inhibitor with an IC_{50} value of 50 μM; however, the clinical relevance of this finding is not known. The P-gp inhibition potential of voruciclib was assessed according to FDA guidance. At the 100 mg dose level, the ratio of gut concentration to IC_{50} ($Igut/IC_{50}$) was estimated to be 17 (0.4 mg/mL divided by 0.024 mg/mL) which is only slightly greater than the threshold value of 10, indicating that the potential for intestinal P-gp inhibition after a voruciclib oral dose of 100 mg is low. Additionally, venetoclax and voruciclib administration will be separated by at least 2 hours (venetoclax will be administered before voruciclib) to further minimize the effect of intestinal P-gp inhibition by voruciclib on venetoclax exposure.

Thus, for the combined therapy portion of the study, at the proposed starting dose of 50 mg of voruciclib, based on in vitro CYP3A4 and P-gp inhibition data presented above, an increase in venetoclax exposure may be observed. [Note that a daily dose of venetoclax above 800 mg has been used in AML without DLTs (Konopleva 2016).] Therefore, during the period of coadministration with voruciclib, the dose of venetoclax is limited to 200 mg. When administered as a single agent (i.e., on Day 22 through Day 28 with no voruciclib co-administered) the venetoclax dose is 400 mg, consistent with the Venclexta [US Prescribing Information] Rev 2022. The summary of the sensitive cytochrome P450 substrates can be found in Appendix 7.

For the combination cohorts on $IS_{2w,2w}$ (Amendment 11), the starting dose of voruciclib in Cohort 12 is 50 mg QOD, which will further reduce voruciclib exposure to account for potential increases (if any) in bioavailability of the new malonate tablet formulation during the exposure cycles. Dosing in Cohort 13 (50 mg QD) will commence only after the safety of QOD dosing of voruciclib with venetoclax in Cohort 12 is established.

For the first two dose levels (50 mg QOD and 50 mg QD), for which voruciclib dose reduction is not possible, voruciclib will be temporarily stopped if the subject requires treatment with an azole antifungal due to the potential of drug-drug interactions and increase exposure to voruciclib. Subjects who recover from the infection can restart voruciclib after the last dose of the azole antifungal (after at least 5 times the half-life of the agent). For subjects receiving

voruciclib at or above 100 mg, a dose reduction by 1 dose level will be required for concomitant treatment with an azole or other strong CYP3A4 inhibitor.

4.16. Impact of COVID-19 on Study Procedures/Visits

MEI Pharma requires the subject to attend the Cycle 1 Day 1 visit on-site; however, if subsequent on-site visits are not possible, study visits during the treatment period may be conducted remotely if a subject is unable to visit a study site due to COVID-19. In this situation, study drug may be shipped directly to a subject if this is deemed appropriate by the Investigator and is acceptable per institutional guidelines and local regulations. If any study visits during the treatment period are conducted via telephone or a tele-health platform, this will be documented in the source file and any missed visit procedures will be recorded as protocol deviations.

4.17. Removal of Subjects from Study

Subjects will be removed from the study for any of the following reasons:

- Withdrawal of consent
- Investigator deems removal to be in the subject's best interest
- Subject is lost to follow-up
- Termination of study by sponsor

5. VORUCICLIB ADMINISTRATION

5.1. Preparation and Administration of Voruciclib

Voruciclib is provided as 50 mg and 100 mg capsules or tablets (requiring no preparation prior to administration) and is dosed on a milligram (mg) basis with no adjustment in dosing based on subject weight. It is recommended that voruciclib be taken in the morning. Voruciclib is to be administered orally once a day on dosing days.

- Monotherapy cohorts: voruciclib is to be taken on an empty stomach at least 1 hour prior to food or 2 hours after food at the same time each day.
- Combination voruciclib + venetoclax cohorts: subjects should take venetoclax with a meal and water, and then take voruciclib (malonate salt tablets) at least 2 hours later (e.g., meal completed at 8 a.m. with venetoclax, dose of voruciclib taken after 10:00 a.m.).

Note that voruciclib is only to be taken on dosing days in the monotherapy IS regimens (i.e., on Days 1 through 14 of the 28-day cycle on the $IS_{2w,2w}$, and on Days 1 through 7 only in the 28-day cycle on the $IS_{1w,3w}$). Dosing days for voruciclib when given in combination with venetoclax are defined in Table 5 for $IS_{2w,2w}$, and in Table 6 for $IS_{3w,1w}$.

If a dose is missed it may be taken up to 12 hours after the specified time. After 12 hours the dose should be omitted. If a subject vomits after taking voruciclib, no replacement dose will be given.

5.2. Voruciclib Accountability and Compliance

The Principal Investigator or their representative will maintain detailed drug accountability records for all voruciclib provided by the sponsor. All voruciclib will be stored in a temperature-controlled (see Section 5.3), secure, locked location, and away from direct sunlight. The Principal Investigator shall maintain adequate records of the disposition of voruciclib, including dates, quantity, and use by subjects. Upon completion of the study, all remaining voruciclib will be accounted for and unused material will be returned to the Sponsor (or designee) using a traceable method (UPS, FedEx, etc.) or disposed of as otherwise instructed by the sponsor.

5.3. Storage of Voruciclib

The capsules and tablets should be protected from direct sunlight and stored in a cool place or at controlled room temperature, 15-25°C (59-77°F). Some US sites will store between 20-25°C (68-77°F) per investigational product label.

5.4. Storage of Venetoclax

Venetoclax will not be provided by the Sponsor. Venetoclax should be stored at or below 86°F (30°C) according to the US Prescribing Information (Venclexta [US Prescribing Information] Rev 2022).

6. ADVERSE EVENTS

6.1. Adverse Event (AE) Definition Using CTCAE V5.0

An AE is any untoward medical event that occurs to a subject following the start of voruciclib administration in monotherapy cohorts or the start of venetoclax in combination cohorts, whether or not the event is considered drug related. Pre-existing conditions are not considered an AE unless the condition worsens by at least one grade following the start of voruciclib administration in monotherapy cohorts or the start of venetoclax in combination cohorts.

Any drug-related AE of Grade 2 or higher should be followed for resolution until:

- The start of subsequent anti-cancer therapy or
- Subject discontinuation from the study or
- A new stable baseline or
- Death

Disease-related out-of-range laboratory values will not be considered AEs/SAEs if there is no change from the screening laboratory values, or if they are not deemed clinically significant by the Investigator.

6.2. Assessment of AEs

The Investigator will assess AEs for severity and relationship to voruciclib and to venetoclax and determine if an AE meets the criteria for an SAE. Each AE will be graded in the source documents using CTCAE v5.0.

6.3. Serious Adverse Event (SAE) Definition

An SAE is an AE that results in any of the following outcomes:

- Death
- A life-threatening condition
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above

Elective hospitalization not in response to an AE is not considered an SAE. Adverse events constituting an SAE will be reported beginning from the first dose of voruciclib, or venetoclax in the combination therapy group.

Disease progression, including death due to disease progression, is not considered an SAE.

6.4. Serious Adverse Event (SAE) Reporting

Serious adverse events will be captured from the first dose of voruciclib monotherapy or venetoclax in the combination regimen and continue to be captured until 30 days after the last dose of study drug(s), or until a subsequent anti-cancer therapy is initiated. SAEs occurring after 30 days will be captured if believed to be related to study drug.

All SAEs, regardless of drug attribution, must be reported to the Sponsor or designee within 24 hours of the Investigator becoming aware of the SAE. The SAEs must be reported in EDC; however, if EDC is not accessible, a paper SAE form must be submitted to the Medpace Safety email or fax number within 24 hours of being aware of the event. When the EDC system becomes available, all applicable SAE information must be entered in EDC. The designee, as listed below, will also be specified in the Study Manual.

To report an SAE, contact Medpace Clinical Safety as listed below:

Email: medpace-safetynotification@medpace.com

Phone: (800) 730-5779, Option 3 OR (513) 579-9911, Option 3

Fax: 866) 336-5320 OR (513) 570-5196

Sites must follow-up to confirm receipt of the SAE Report.

The Investigator must report new significant follow-up information for these events to the sponsor or designee immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information

- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

SAEs must be reported by each site to the appropriate Institutional Review Board (IRB)/Independent Ethics Committee (IEC) in accordance with local reporting requirements.

Reporting requirements will also be based on the Investigator's assessment of causality and seriousness, with allowance for upgrading by the sponsor as needed.

Deaths within 30 days of the administration of voruciclib or the administration of combination therapy must be reported as an SAE unless the death is due to disease progression. Deaths occurring >30 days after the last dose of voruciclib or the last dose of combination therapy must be reported as an SAE if considered by the investigator as related to study drug(s).

The Investigator should make every effort to obtain and send death certificates and autopsy reports for all deaths to the sponsor.

In the event of a medical emergency (requiring immediate attention regarding operation of the clinical study and/or the use of study drug), study site staff will apply appropriate medical intervention according to current standards of care and contact the Medical Monitor or other designated sponsor representative.

6.5. Pregnancies

To ensure subject safety, each pregnancy in a subject on study treatment must be reported within 24 hours of learning of its occurrence; refer to Section 6.4 and the study reference manual for reporting contact information. Study drug must be discontinued in a subject who becomes pregnant. The pregnancy must be followed for at least 3 months after term or spontaneous or voluntary termination to determine outcome including details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy is not an AE but should be recorded and reported by the Investigator to the Sponsor or Designee. Pregnancy follow-up should be recorded and should include an assessment of the possible relationship to the study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

Fertile male subjects, defined as all males physiologically capable of conceiving offspring, with female partners of childbearing potential must use condoms plus spermicidal agent during the study treatment period and for 90 days after the last dose of study drug, and should not father a child during this period.

Male subjects must also refrain from donating sperm during their participation in the study.

6.6. Relationship of Adverse Events to Study Treatment

The Investigator is obligated to assess the relationship between voruciclib or venetoclax and the occurrence of each AE. The Investigator is to use his/her best medical judgment in determining

the likely relationship of the AE to voruciclib or venetoclax. The relationship of an AE or SAE to voruciclib or venetoclax is to be classified as either 'Related' or 'Not Related.'

7. RESPONSE ASSESSMENT

7.1. Response Assessment for Subjects with CLL/SLL

For subjects with CLL/SLL, efficacy assessments will be based on International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria (Halleck 2008). Lymphocytosis may feature prominently during early treatment and can persist over time and should not be confused with disease progression in subjects with otherwise persistent disease control. Absent other objective evidence of disease progression, the occurrence of lymphocytosis will not preclude subjects from meeting the criteria for PR (if other criteria for PR are met) and will not be considered evidence of CLL/SLL progression if occurring in isolation. Response criteria are summarized in Appendix 5.

7.2. Response Assessment for Subjects with FL and Other B-Cell Lymphomas

For subjects with FL, MCL, MZL, DLBCL, and high-grade B-cell lymphomas, efficacy assessments will be based on the Lugano Classification response criteria (Cheson 2014). Response criteria are summarized in Appendix 6.

7.3. Response Assessment for Subjects with AML

Response assessments will be based on the European LeukemiaNet (ELN) recommendations (Döhner 2017). Response criteria are summarized in Appendix 4.

8. STUDY PROCEDURES

See the Schedule of Assessments (Appendix 1) for a detailed list of study procedures and assessments for subjects with CLL/SLL, FL, MCL, MZL, DLBCL, and high-grade B-cell lymphomas. See the Schedule of Assessments (Appendix 2 and Appendix 3) for a detailed list of study procedures and assessments for subjects with AML receiving voruciclib monotherapy or voruciclib + venetoclax combination therapy, respectively. Instructional details (where applicable) for procedures are contained in Section 9.

8.1. Informed Consent

Each subject's signature must be obtained on a written Inform Consent Form (ICF), which has been approved by an IRB or IEC, prior to any study-related procedures being performed. The ICF must incorporate a Release of Medical Information that authorizes release of medical records to the trial investigators, monitors, sponsor and its designees, the FDA or other regulatory authority. The ICF must be in a language fully comprehensible to the prospective subject. The consenting process must be documented in the medical chart, and a signed copy of the ICF provided to the subject.

8.2. Subject Enrollment

Prior to Amendment 11, sites submitted a Subject Enrollment Form to the sponsor or designee (e.g., contract research organization [CRO]) for approval prior to enrolling each subject in the study. The Subject Enrollment Form is no longer implemented as of Amendment 11.

8.3. Screening Period

During the screening period, the Investigator should carefully review each subject's past medical history to ensure eligibility. All inclusion and exclusion criteria should be supported by corresponding documentation in the medical records.

Screening assessments are to be performed within 28 days of first dose of voruciclib or the first dose of venetoclax in combination cohorts. Laboratory assessments need not be repeated on Day 1 if performed within the prior 72 hours. Physical examinations need not be repeated on Day 1 if performed within the prior 7 days. Some tests performed as part of routine care prior to obtaining ICF (e.g., computed tomography [CT] scan, bone marrow biopsy) may not need to be repeated for the study as long as they were performed within the allowed screening window. This avoids unnecessary repeat tests and undue burden on subjects.

The risk for TLS must be assessed and the Investigator must make sure appropriate prophylaxis has been provided (see guidelines in Table 24 and Figure 3, Appendix 9).

8.4. Enrollment and Randomization

There is no randomization in this study. Once the subject has been deemed eligible, approved, and registered, the subject may enroll on study.

8.5. Cycle 1 Day 1 Tests and Administration of Voruciclib or Venetoclax

The Investigator should assess any changes in the subject's medical condition or history since the Screening visit. Any significant changes since screening should be discussed with the Medical Monitor to confirm that the subject can start study drug administration. All Cycle 1 Day 1 tests and procedures outlined in the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) must be performed prior to study drug administration. Cycle 1 Day 1 should be on Monday, if possible, so that specimens for correlative and biomarker assays can be shipped for receipt no later than a Friday.

The risk for TLS must be assessed and the Investigator must make sure appropriate prophylaxis has been followed (see guidelines in Table 24, Appendix 9).

A record of the administration of the first dose of voruciclib or venetoclax (AML only) will be documented in the source documents.

Any safety laboratory tests at Cycle 1 Day 1 should be performed at the local institutional laboratory as specified on the Schedule of Assessments.

PK samples will be shipped to a central laboratory for analysis.

8.6. Treatment

The treatment phase begins on the day voruciclib or venetoclax is first administered and continues through the last day of administration. Treatment will be tracked by 28-day periods identified by a numerical cycle (e.g., Cycle 1, Cycle 2…). Response assessments for subjects with CLL/SLL, FL, MCL, MZL, DLBCL, and high-grade B-cell lymphomas, as defined in Section 7, will be performed according to the Schedule of Assessments (Appendix 1) and detailed in Appendix 5 and Appendix 6. Response assessments for subjects with AML will be performed according to the Schedule of Assessments (Appendix 2 and Appendix 3) and detailed in Appendix 4.

8.7. End of Study Visit

The End of Study (EOS) visit will occur 30 days (± 3 days) from the last day of treatment drug(s) administration (or prior to starting a new treatment if urgent treatment is required). The end of treatment date and reason for discontinuation study drugs will be entered in the End of Treatment form in the EDC.

8.8. End of Study

The study will be closed when all subjects who received study drug have competed their EOS visit and all study data have been collected for analysis.

9. STUDY ASSESSMENTS

The following sections describe the methods for assessments of clinical and functional outcomes included in the trial. Refer to the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) for frequency and specific timing of assessments.

9.1. Medical History and Prior Anti-Cancer Treatment

A complete medical history will be collected during screening. Data associated with any interventional procedure, surgical operation (for any reason), and all prior cancer therapies will be collected.

9.2. Demographics

Subject demographic data including date of birth (year of birth required at a minimum), sex, race, and ethnicity will be recorded in the electronic case report forms (eCRFs).

9.3. Concomitant Medication

Data on concomitant prescription and OTC medications will be collected. This data will be recorded from 28 days prior to Day 1 of any study drug administration through 30 days after the last dose of voruciclib or venetoclax (combination cohorts), or until a subsequent anti-cancer therapy is initiated. See Section 4.14 for further details regarding prohibited treatments and concomitant medications.

9.4. Physical Examination and Vital Signs

The physical examination will include the examination of all organ systems (at the Investigator's discretion, genitourinary system may be excluded). Vital sign measurements will include systolic and diastolic blood pressure, heart rate (HR), body temperature, height (Screening visit only), and weight.

A symptom-directed exam will be performed as indicated in Schedule of Assessments, and additional exams may be performed as clinically indicated.

9.5. Adverse Events

Adverse events will be collected at each visit as described in Section 6.

A treatment-emergent AE (TEAE) is defined as an adverse event starting or worsening in CTCAE grade after the first dose until 30 days after the last dose of study drug(s), or start of new anti-cancer therapy, whichever is earlier. An adverse event reported ≥30 days after the last dose of study drug(s) will be reported and counted as TEAE if considered related to study drug and resulted in study drug discontinuation or an SAE.

9.6. Electrocardiograms

12-lead ECGs will be performed in triplicate, approximately 2–5 minutes apart while the subject is resting (See Schedule of Assessments for timing of ECGs (Appendix 1, Appendix 2, and Appendix 3)

9.7. Laboratory Tests

Laboratory tests listed on the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3) will be analyzed at a local laboratory and used in all safety analyses and or response assessments (see Appendix 4, Appendix 5, and Appendix 6). PK samples discussed in Section 9.14 will be shipped to a central laboratory for analysis.

The following are descriptions of the tests to be performed. For timing and frequency of the below listed tests, refer to the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3):

- CBC with differential – WBCs, ANC, red blood cells (RBCs), hemoglobin (Hgb), hematocrit (Hct), platelets, mean corpuscular hemoglobin (MCH), and differential
- Serum chemistry – glucose, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, calcium, phosphate, uric acid, phosphorus, carbon dioxide, alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, total protein, albumin, and lactate dehydrogenase (LDH). (Additional chemistry will be performed as indicated in the TLS management plan and as clinically indicated.)
- Coagulation – activated partial thromboplastin time (aPTT), PT, and INR
- Urinalysis (Dipstick)
- Pharmacokinetic sampling – see Section 9.14

- Pharmacodynamic and biomarker studies – see Section 9.12, Site Laboratory Manual and Schedule of Assessments
- Pregnancy test – serum/urine pregnancy test in females of childbearing potential
- HIV testing
- Hepatitis B core antibody, surface antibody and surface antigen, and hepatitis C virus antibody (HCV Ab) tests are required. Hepatitis B polymerase chain reaction (PCR) is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if HCV Ab test is positive.
- Cytogenetics
    - Classical cytogenetics for subjects with AML only. At least 20 bone marrow metaphases are needed to define a normal karyotype and recommended to describe an abnormal karyotype. Abnormal karyotypes may be diagnosed from blood specimens. If abnormal cytogenetics at screening, repeat cytogenetics in a subject with CR/CRi to confirm a cytogenetic remission.
    - Fluorescence in situ hybridization [FISH] for subjects with SLL or CLL only – FISH for del(13q), del(11q), del(17), trisomy 12, del(6q) performed on blood or biopsy specimen. Result is not required prior to enrollment
- IgHV mutational testing (subjects with SLL or CLL only) – IgHV mutational testing performed in the peripheral blood lymphocytes or biopsy specimen. Result is not required prior to enrollment
- Quantitative serum immunoglobulin levels (IgA, IgG, IgM) will be performed for subjects with SLL and CLL
- Screening for gene mutations and gene rearrangements for subjects with AML only. Screening is not required for enrollment in the study but will be collected if performed as part of the standard of care, including genes defined in the 2017 ELN response criteria. If obtained as screening, repeat the test for the genetic marker by RT-qPCR or flow cytometry in a subject with CR/CRi to confirm CR with minimal residual disease per the 2017 ELN response criteria.
- Bone marrow aspiration/biopsy are required for assessment of response and as clinically indicated. For subjects with CLL/SLL, FL, MCL, MZL, DLBCL, and high-grade B-cell lymphomas refer to Appendix 5, Table 19 and Appendix 6, Table 21. For subjects with AML refer to Appendix 4, Table 18. Additionally, for monotherapy cohorts, optional biopsy/aspirates pre-first dose, at the end of Cycle 6 and at end of treatment may be conducted for correlative studies. See Laboratory Manual. For AML combination therapy cohorts, bone marrow aspirate/biopsy and laboratory evaluation should be completed at screening (up to 28 days prior to starting venetoclax), Cycle 2 Day 1, and Day 1 of every subsequent cycle until a CR or CRi is achieved. Thereafter, response assessments should be performed when bone marrow examinations are obtained as clinically indicated and at EOS. Both biopsy and aspirate are recommended for disease assessment, but biopsy may be omitted if aspirate is considered to be sufficient. Bone marrow aspirate sample collected at the time of disease assessment may be used for exploratory biomarker analysis in bone

marrow/bone marrow aspirate. If any remaining sample is available after evaluation for disease assessment, it should be submitted to the central laboratory for pharmacodynamic biomarker/correlative study (refer to the Lab Manual).

- Tumor biopsy – Formalin fixed material is acceptable although fresh tissue is preferred.
- Chest X-ray, unless recent CT scan shows no pulmonary abnormalities (for patients treated with voruciclib/venetoclax combination therapy).

9.8. Disease Assessment

Computed tomography (CT) scans, positron emission tomography (PET)-CT scans, bone marrow aspirate/biopsy, and laboratory evaluation will be completed as appropriate for individual subjects. For subjects with CLL/SLL, efficacy assessments will be based on criteria of the IWCLL guidelines per Appendix 5. For subjects with FL, MCL, MZL, DLBCL, and high grade- B-cell lymphomas, efficacy assessments will be based on the Lugano Classification response criteria per Appendix 6. For subjects with AML, efficacy assessments will be based on European LeukemiaNet (ELN) Response Criteria per Appendix 4.

9.9. ECOG

Eastern Cooperative Oncology Group (ECOG) performance status to be evaluated at Screening, Day 1 of each cycle, and EOS.

9.10. Pregnancy Test

Serum pregnancy test in females of childbearing potential at screening, urine pregnancy test Day 1 of each cycle and at EOS.

9.11. Virology

HIV antibody testing is required to determine eligibility.

Hepatitis B core antibody, surface antibody and surface antigen, and hepatitis C virus antibody (HCV Ab) tests are required to determine eligibility. Hepatitis B polymerase chain reaction (PCR) is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if HCV Ab test is positive.

9.12. Compliance Diary

A compliance diary will be provided to the subject at each study drug dispensing timepoint, according to the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3).

9.13. Dispensation, Administration, and Accountability of Voruciclib and Venetoclax

Voruciclib is administered orally once daily on dosing days, on an empty stomach at least 1 hour prior to food, or 2 hours after food at approximately the same time each day. On days of PK sampling, subjects should be instructed not to take voruciclib until after the pre-dose PK sample is collected.

Venetoclax is commercially available as 10 mg, 50 mg, and 100 mg tablets. Venetoclax is to be taken once daily with a meal and water.

In order to minimize intestinal P-gp interaction, venetoclax must be taken with a meal, followed by voruciclib administration 2 hours later.

A compliance diary assessment and returned drug accountability will be performed at each visit which includes voruciclib dispensing. Refer to Section 5 for additional information on the storage and management of voruciclib and venetoclax.

9.14. Pharmacokinetics

Pharmacokinetic (PK) samples are to be obtained as noted below:

9.14.1. Voruciclib Monotherapy

In monotherapy IS Cohorts 1-5:

Pre-dose specimens should be drawn within 2 hours prior to dosing and post-dose within ±30 minutes of designated post-dose sampling times.

Samples for voruciclib plasma concentration analysis will be collected as follows:

- Cycle 1 Day 1: Pre-dose, 4-, and 6-hours post-dose
- Cycle 1 Day 2: Pre-dose (24 hours after the preceding last dose)
- Cycle 1 Day 8: Pre-dose (24 hours after the preceding last dose)
- Cycle 1 Day 15: Pre-dose (24 hours after the preceding last dose), 4- and 6-hours post-dose

In monotherapy IS Cohorts 6-11:

- Cycle 1 Day 1: Pre-dose, 4-, and 6-hours post-dose
- Cycle 1 Day 2: Pre-dose (24 hours after the preceding last dose)
- Cycle 1 on Day 8 (24 hours after the preceding last dose)
- Cycle 1 Day 15 (24 hours after the preceding last dose, if applicable [Day 15 samples only to be collected for IS2w2w schedule])
- Cycle 2 Day 1: Pre-dose

9.14.2. Voruciclib + Venetoclax Combination Therapy

Pre-dose specimens should be drawn within 2 hours prior to dosing and post-dose within +30 minutes of designated post-dose sampling times.

Blood samples for characterization of **voruciclib PK** will be collected in Cohorts 12–19 and 21–25 as shown in Table 14 and Table 15, relative to dosing of voruciclib.

Table 14: PK Sample Collection for Voruciclib, Cohort 12 (QOD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	Post-dose
1	3	X	2, 4, 6 hours
	4*	-	approximately 24 hours after **Day 3 dose**
	8	-	approximately 24 hours after **Day 7 dose**
	13	X	2, 4, 6 hours
	14	-	approximately 24 hours after **Day 13 dose**
	21	anytime during clinic visit	
2	1	X	-
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

* Day 4 sample to be collected only if the subject is able to visit the clinic.

Table 15: PK Sample Collection for Voruciclib, Cohorts 13–19 and 21–25 (QD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	Post-dose
1	3	X	2, 4, 6 hours
	4*	X (approximately 24 hours after **Day 3 dose**)	-
	8	X (approximately 24 hours after **Day 7 dose)**	-
	14	X	2, 4, 6 hours
	15	-	approximately 24 hours after **Day 14 dose**
	21	anytime during clinic visit	
2	1	X	-
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

* Day 4 sample to be collected only if the subject is able to visit the clinic.

Drug-Drug Interaction (DDI) Assessment: Voruciclib exposures (when co-administered with venetoclax) will be compared to historical single agent data to assess DDI and the effect of venetoclax on voruciclib PK.

Blood samples for characterization of **venetoclax PK** will be collected in Cohorts 12–19 and 21–25 as shown in Table 16 and Table 17, relative to dosing of venetoclax.

Table 16: PK Sample Collection for Venetoclax, Cohort 12 (QOD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	**Post-dose**
1	13	X	2, 4, 6, 8 hours
	14	X (approximately 24 hours after **Day 13 dose**)	-
	21	anytime during clinic visit	
2	1	X	2, 4, and 6-hours post-dose of venetoclax (voruciclib to be dosed 6 hours after venetoclax administration, after completion of the 6- hour sample collection)
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

Table 17: PK Sample Collection for Venetoclax, Cohorts 13–19 and 21–25 (QD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	**Post-dose**
1	14	X	2, 4, 6 and 8-hours
	15	X (approximately 24 hours after **Day 14 dose**)	-
	21	anytime during clinic visit	
2	1	X	2, 4 and 6-hours post-dose of venetoclax (voruciclib to be dosed 6 hours after venetoclax administration, after completion of the 6- hour sample collection)
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

DDI Assessment: Venetoclax exposure (when co-administered with voruciclib) will be compared to historical single agent data to assess DDI and the effect of voruciclib on venetoclax pharmacokinetics. Venetoclax concentrations on Cycle 2 Day 1 and Cycle 1 Day 14 will also be compared assuming limited effect, if any, on voruciclib on Cycle 2 Day 1.

Voruciclib PK and other relevant data from all clinical trials (including late phase clinical trials) will be pooled and analyzed using population PK methods. Additionally, voruciclib exposure-response and exposure-safety assessments will be performed and the results will be presented in a separate report.

PK of voruciclib in subjects receiving co-administered azole antifungals versus those without azole antifungals will be compared.

Detailed instructions on collection of plasma for determination of voruciclib and venetoclax will be provided in the Site Laboratory Manual.

9.15. Pharmacodynamics of Voruciclib and Voruciclib + Venetoclax

Blood will be collected for determination of the effect of voruciclib monotherapy and the combination of voruciclib + venetoclax on biomarkers, e.g., apoptotic pathway proteins, and to correlate antitumor activity with baseline tumor characteristics, according to the following schedules, as follows:

Monotherapy Cohorts 6a,b – 8a,b

- Cycle 1 Day 1: Pre-dose, and approximately 6-hours post-dose
- Cycle 1 Day 2: Pre-dose (approximately 24 hours after preceding dose)
- Cycle 1 Day 15: Pre-dose (approximately 24 hours after preceding dose)

Combination therapy Cohorts 12–19 and 21–25:

- Cycle 1 Day 1: Pre-dose of venetoclax and approximately 6-hours post-dose of venetoclax for Cohorts 12–16 or 4–6 hours post-dose for Cohorts 17–25
- Cycle 1 Day 3: Pre-dose of voruciclib and approximately 6-hours post-dose of voruciclib for Cohorts 12–16 or 4–6 hours post-dose for Cohorts 17–25
- Cycle 1 Day 14*: Pre-dose of venetoclax and approximately 6-hours post-dose of voruciclib for Cohorts 12–16 or 4–6 hours post-dose for Cohorts 17–25

*For Cohort 12, since there is no voruciclib dosing on Cycle 1 Day 14, blood will be collected on Cycle 1 Day 13 pre-dose of venetoclax and approximately 6-hours post-dose of voruciclib during clinic visit for PK sample collection.

For PK and PD collection visits that fall on weekends or holidays, please contact the Sponsor to discuss sampling schedule.

10. STATISTICS

10.1. Number of Subjects

At the start of Amendment 12, a total of 40 subjects have been enrolled in the now-completed monotherapy dose escalation/expansion cohorts. Assuming an average enrollment of 4 subjects per dose level for DLT evaluation, up to 12 subjects to be enrolled in the 2 combination AML expansion cohorts, and an additional 10% for early drop-outs due to non-evaluability after failure to complete Cycle 1 treatment for reasons other than AEs related to voruciclib, the total enrollment for the voruciclib plus venetoclax combination group is estimated to be approximately 68 subjects, for a total of approximately 108 subjects to be enrolled in the study.

10.2. Study Endpoints

The primary study objectives are to determine the safety and tolerability and safe and mBED of voruciclib monotherapy in subjects with relapsed and/or refractory B-cell malignancies and AML and to determine the safety, tolerability and safe and mBED of voruciclib in combination with venetoclax in subjects with relapsed and/or refractory AML.

Safety will be assessed by AEs graded according to NCI CTCAE v5.0; laboratory safety tests including hematology (CBC), serum chemistry; physical examination; vital signs; ECOG performance status; and triplicate 12-lead ECG. If 2 or more of 6 subjects experience a DLT in a dose cohort, then the next lower dose will be the MTD.

The primary endpoint is:

- The incidence of AEs, including DLTs.

Secondary endpoints are:

- Efficacy endpoints within each tumor type:
    a. Overall Response Rate (ORR), defined as the proportion of subjects who achieve a best overall response of
        - CR, CRi, or PR, with responses defined per 2008 International Workshop on CLL (IWCLL) guidelines,
        - CR or PR by 2014 Lugano criteria for non-Hodgkin lymphoma,
        - CR, CRi, CR_{MRD}, MLFS by the 2017 ELN criteria for AML
    b. DOR defined as the time from first achieving a response to date of documented disease progression or death from any cause. Subjects who die due to any cause prior to progression will be censored
    c. PFS defined as time from first dose of study drug to date of documented disease progression or death from any cause
    d. Estimates of the exposure and association with efficacy and safety variables for voruciclib administered as monotherapy, and the PK of voruciclib and venetoclax when administered in combination

The exploratory endpoints are:

a. Effects on biomarkers and functional activities of proteins in the apoptotic pathway
b. Correlations of anti-tumor activity and baseline tumor characteristics

10.3. Analysis Methods

Subjects completing the first cycle of treatment with at least 75% of study drug compliance or experiencing a DLT during the first cycle (28 days) of treatment, will be considered evaluable for the occurrence of DLTs. The 3 + 3 design targets a DLT rate for the MTD of approximately 20–25%.

Summary statistics for continuous variables will include the mean, standard deviation, median and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages.

See Section 10.6 for efficacy analysis methods**.**

10.3.1. Handling of Missing Data

For summary statistics, missing data will not be imputed; results will be reported based upon observed data.

10.3.2. Analysis Populations

The Safety population is defined as subjects who receive at least one dose of study drug(s).

The DLT evaluable population includes subjects in dose escalation cohorts who complete the first cycle of treatment with at least 75% of study drug compliance or experience a DLT during the first cycle (28 days) of treatment.

The Efficacy evaluable population is defined as subjects who complete the first scheduled post-baseline efficacy evaluation (scheduled on C3D1 for B-cell lymphoma subjects and C2D1 for AML subjects) or develop progression of disease or death prior to the first scheduled post-baseline efficacy.

The PK population will include all subjects who receive at least 1 dose of voruciclib or venetoclax and have at least 1 non-missing post-dose concentration value.

10.4. Safety Analyses

10.4.1. Adverse Events

The incidence of all TEAEs will be tabulated by cohort. These TEAEs will be classified by system organ class and preferred term or by preferred term in descending order of frequency using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject will be counted only once for that specific system organ class or preferred term. An overview of AEs, which includes subject incidence of TEAEs, TEAEs by severity, related TEAEs, related TEAEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

10.4.2. Clinical Safety Laboratory Results

The observed data and change from baseline for each measurement day will be summarized with descriptive statistics.

Where criteria are available, laboratory values will be assigned toxicity grades, using NCI CTCAE v5.0. Directional shifts in laboratory toxicity grades (comparing baseline grade with worst post-baseline grade) will be analyzed using standard shift tables, presenting number and proportion of subjects and their maximum grade shift.

10.4.3. Vital Signs

The observed data and change from baseline for each measurement day will be summarized with descriptive statistics.

10.4.4. Electrocardiogram

The observed QTc data and change from baseline for each measurement day will be summarized with descriptive statistics.

10.5. Pharmacokinetic Analyses

For all monotherapy cohorts, the PK of voruciclib will be summarized by descriptive statistics. Pharmacokinetic parameters will be estimated, where appropriate, by non-compartmental analysis using statistical computer packages as specified in the statistical analysis plan. Graphic evaluation will be used for data analysis where appropriate. Pharmacokinetics and fit will be evaluated graphically; modeling will also be used if sufficient data are available.

For the combination treatment cohorts, the PK of voruciclib and venetoclax will be summarized separately, as above and compared to historical data.

10.6. Efficacy Analyses

For the Efficacy population, response to treatment will be tabulated with 95% exact binominal CIs.

The Kaplan-Meier method will be used to estimate PFS and DOR within subjects of the same tumor type. For PFS, subjects without documented progression will be censored at the date of last disease assessment.

11. REGULATORY AND REPORTING REQUIREMENTS

The study will be conducted according to the principles of the Declaration of Helsinki (World Medical Association 2013), the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), Guideline E6(R2): Good Clinical Practice (ICH 2016), and the requirements of all local regulatory authorities regarding the conduct of clinical trials and the protection of human subjects. The study will be conducted by scientifically and medically qualified persons and the rights and welfare of the subjects will be respected.

Each subject will provide written informed consent before any study-related tests or evaluations are performed.

11.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Approval of this study will be obtained from an IRB/IEC prior to enrolling subjects and will be reviewed and approved on an annual basis by the IRBs/IECs representing the participating institutions. Such IRBs/IECs must be appropriately constituted and meet all requirements as described in Title 21, Part 56 of the Code of Federal Regulations. The review must include the

protocol, subject recruitment materials, the Investigator's Brochure, the ICF, any other study-related material that will be provided to subjects (including study drug compliance diaries). A copy of the Letter or Notice of Approval from the IRB/IEC must be received by the sponsor prior to shipment of drug supplies to the Investigator. The IRB/IEC membership list or Federal Wide Assurance (FWA) number must be submitted to the Sponsor with the written IRB approval, and lists must be updated, if applicable.

11.2. Public Clinical Trial Registry

This study will be listed on a public clinical trial registry such as www.clinicaltrials.gov, per applicable regulations.

11.3. Confidentiality

The Principal Investigator and designees, employees, and agents involved with this study will comply with relevant state and federal laws relating to the confidentiality, privacy, and security of subjects' health information. Data generated during this study or disclosed by the sponsor to the Investigator will only be used as appropriate for the execution, analysis, review, and reporting of this study. Such information shall not be used for any other purposes and will remain confidential.

In order to verify subject eligibility criteria and ensure ongoing subject safety during the study and preserve the integrity of study data, notwithstanding source data verification at the study site, the Sponsor/CRO may request to review subject source medical data. Should the Sponsor request copies of subject medical data, the rationale for such request will be ethically and scientifically justified. Such records will promptly be destroyed by the Sponsor/CRO when the purpose of the review has been met.

In order to ensure subject safety and in adherence with regulatory guidelines, personal medical information may be reviewed by the IRB/IEC, or regulatory authorities. Every reasonable effort will be made to maintain strict confidentiality.

Though the results of the study may be presented in reports, published in scientific journals, or presented at medical meetings; subject names or identifiers will never be used.

11.4. Financial Disclosure

Investigators must maintain compliance with the current FDA guidelines and regulations concerning financial disclosure.

11.5. Data Quality Assurance

Good Clinical Practice (GCP) guidelines regarding clinical data management practices and procedures are to be utilized to ensure accurate, consistent, and reliable data. The sponsor or designee will establish a Data Management Plan for this study.

12. DATA MANAGEMENT

12.1. Use of Electronic Case Report Forms

Study data will be stored and transmitted using eCRFs, with a system determined by the sponsor. The sponsor will provide secure access and eCRF completion guidelines, as well as study-specific training, as needed, to each site.

Data recorded in the eCRFs must be supported by information captured in source documents, which must be available at all times for inspection by authorized representatives of the sponsor, the FDA, or other regulatory agencies. The eCRFs must be completed as soon as possible after each study visit or contact.

12.2. Study Site Monitoring

A sponsor-designated study monitor will conduct a site initiation visit prior to study enrollment, a visit shortly after enrollment of the first subject, and periodic interim monitoring visits during the study, as per the study-specific monitoring plan.

The primary purposes of the site visits are to:

- Ensure the accuracy and completeness of eCRF entries, as verified against the source documentation
- Verify that the conduct of the study adheres to the written protocol approved by the IRB/IEC, as well as regulatory requirements
- Verify that regulatory and other study-related documentation is maintained and current
- Perform voruciclib study drug accountability (reconcile study drug receipt, storage, dispensing, and return records)

12.3. Record Retention

The Investigator will retain the records of the study for 2 years following the last date that a marketing application for voruciclib is approved in any ICH region, or if marketing approval is not obtained, for 2 years after the Investigational New Drug (IND) for voruciclib has been closed. The sponsor will notify the Investigators when study records retention is no longer required.

For studies conducted outside the US under a US IND, the Principal Investigator must comply with the record-retention requirements set forth in the US FDA IND regulations and the relevant national and local health authorities, whichever is longer.

The site will retain copies of all versions of the protocol, Investigator's Brochure, correspondence with the IRB/IEC (including submission and approval letters, approved ICFs), curricula vitae and medical licenses of the Investigator and sub-Investigator(s), Forms FDA-1572, correspondence, laboratory documentation (including accreditation documents, reference ranges, and manuals), Delegation of Authority Log (documenting procedures delegated by the Investigator to be performed by study staff), voruciclib study drug records (including receipt, storage, dispensing, and return records), source documents (including clinic charts,

medical records, laboratory results, radiographic reports), training records, screening/enrollment logs, monitoring visit logs, and study procedure manuals.

Should the Investigator leave the institution or otherwise withdraw from the investigation or should there be any changes in the archival arrangements for the study records, the sponsor will be notified. The sponsor will be notified of the identity of any individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the investigational site is willing to assume this responsibility, the sponsor will assume responsibility for maintaining the study records.

13. AMENDMENTS TO THE PROTOCOL

Amendments will be originated and documented by the sponsor. Individual study sites should communicate requests for protocol amendments directly to the sponsor. The sponsor may be required to discuss potential protocol amendments with the appropriate regulatory agencies. Amendments shall only be implemented following the required regulatory and ethical review and approval. Protocol amendments also may require changes to the ICF.

14. PUBLICATION POLICY

The sponsor intends to publish the results of this trial as soon as possible following completion of data analysis. Data derived from the trial are the exclusive property of the sponsor. Authorship (both inclusion and sequence) will be determined by mutual agreement. In the event of a disagreement on authorship, the sponsor will serve as adjudicator.

15. REFERENCES

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APPENDIX 1. SCHEDULE OF ASSESSMENTS – CLL/SLL, FL, MCL, MZL, DLBCL, AND HIGH-GRADE B-CELL LYMPHOMAS

	Screening [b]	Cycle 1				Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7[c]	End of Study[d]
Day(s) [a]	**-28 to -1**	**1 [a]**	**2**	**8**	**15**	**1**	**15**	**1**	**1**	**1**	**1**	**1**	**30 days (± 3 days) post last dose**
Informed consent	X												
Medical history	X												
Physical examination	X	X				X						X	X
Symptom-directed exam [e]				X	X		X	X	X	X	X		
Vital signs [f]	X	X		X	X	X		X	X	X	X	X	X
Height [f]	X												
Weight [f]	X	X				X		X	X	X	X	X	X
ECOG performance status	X	X				X		X	X	X	X	X	X
Pregnancy test [g]	X	X				X		X	X	X	X	X	X
HIV testing [h]	X												
Hepatitis B and C testing [i]	X												
Blood for PD/biomarker assays		X***	X			X							
Bone marrow biopsy/aspiration*	X											X	X
Tumor biopsy** (optional)	X			X									
Cytogenetics (FISH) [j]	X												X
IgHV mutational testing [k]	X												
Adverse events [l]		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medication [m]	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG [n]	X	X		X	X	X							X
CBC with differential [o]	X	X		X	X	X	X	X	X	X	X	X	X
Serum chemistry [p]	X	X	X	X	X	X	X	X	X	X	X	X	X
TLS risk assessment and monitoring [p]	X	X	X										
Immunoglobulin tests [q]	X	X										X	
Coagulation [r]	X		X		X	X		X	X	X	X	X	X
Urinalysis (Dipstick) [s]	X					X		X				X	X
Issue and assess compliance diary [t]		X				X		X	X	X	X	X	
Dispense voruciclib [u]		X				X		X	X	X	X	X	
PK Sampling (all subjects) [v]		X	X	X	X	X							
Disease assessment [w]	X							X				X	X

APPENDIX 1. SCHEDULE OF ASSESSMENTS – CLL/SLL, FL, MCL, MZL, DLBCL, AND HIGH-GRADE B-CELL LYMPHOMAS (CONTINUED)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CLL = chronic lymphocytic leukemia; CR = complete response; CT = Computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; FISH = fluorescence in situ hybridization; FL = follicular lymphoma; Hct = hematocrit; HCV Ab = hepatitis C virus antibody; Hgb = hemoglobin; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; IgHV = immunoglobulin heavy-chain variable-region gene; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; SLL = small lymphocytic lymphoma; TLS = tumor lysis syndrome; WBC = white blood cell.

a. Cycle 1 Day 1 and Study Assessment Day(s) – C1D1 and visits when blood for pharmacodynamic/biomarker studies are collected should be conducted Monday through Wednesday if possible so that specimens can be shipped for receipt no later than a Friday. There is ± 3day window allowable for each clinic visit during Cycle 1. Following Cycle 1, the allowable window is up to 7 days prior and 2 days after the scheduled clinic visit and its associated assessments.

b. Screening – Screening assessments are to be performed within 28 days of first dose of voruciclib. Laboratory assessments need not be repeated on Day 1 if performed within the prior 72 hours. Physical examination need not be repeated on Day 1 if performed within the prior 7 days. Some tests performed prior to obtaining ICF (e.g., CT scan, bone marrow biopsy) may not need to be repeated for the study as long as they were performed within the allowed screening window.

c. Cycle 7+ – Subjects who remain on study after 7 cycles should follow the following study visit procedures:

- For Cycles 8-12, and Cycles 14-18, study visit procedures from Cycle 6 should be performed
- For Cycles 13 and 19, study visit procedures from Cycle 7 should be performed
- Cycles after 19 should follow the same schedule as Cycle 7 assessments every 6 cycles

d. EOS – The EOS visit will occur 30 days ± 3 days from the last day of voruciclib administration (or prior to starting a new treatment if urgent treatment is required).

e. Symptom-directed exam – Performed only as needed/indicated, based on interim history.

f. Vital signs, Height, Weight – includes systolic and diastolic blood pressure (BP), heart rate (HR) and body temperature. Height collected at Screening only.

g. Pregnancy test – Serum pregnancy test in females of childbearing potential at screening, urine pregnancy test Day 1 of each cycle and at EOS.

h. HIV testing – HIV antibody testing is required.

i. Hepatitis B and Hepatitis C testing – Hepatitis B core antibody, surface antibody and surface antigen, and hepatitis C virus antibody (HCV Ab) tests are required. Hepatitis B polymerase chain reaction (PCR) is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if HCV Ab test is positive.

j. Cytogenetics (FISH) – For subjects with SLL, CLL only; perform cytogenetics (FISH) for del(13q), del(11q), del(17), trisomy 12, del(6q) performed on blood or biopsy specimen of histologically-confirmed CLL/SLL. To be repeated when subject achieves a CR. The result does not need to be available for enrollment or initiation of study treatment.

k. IgHV mutational testing – For subjects with SLL, CLL only; perform IgHV mutational testing in the peripheral blood lymphocytes or biopsy specimen at any time prior to initiation of therapy (may be collected prior to study screening). The result does not need to be available prior to enrollment or initiation of study treatment.

l. Adverse events – Recorded from the first dose of voruciclib and continue until 30 days after the last dose, or until a subsequent anti-cancer therapy is initiated.

m. Concomitant medications – Recorded from 28 days prior to Cycle 1 Day 1 through 30 days after the last dose of voruciclib, or until a subsequent anti-cancer therapy is initiated.

n. ECG – 12 lead ECGs performed in triplicate (approximately 2–5 minutes apart while the subject is resting) at screening, Day 1 (Pre-dose and 4 hours post-dose), Day 8 (24 ± 3 hours after the preceding last dose in Cohorts 9-11), Day 15 (Pre-dose and 4 hours post-dose in Cohorts 1-5, and 24 ± 3 hours after the preceding last dose in Cohorts 6-8), and a single triplicate ECG at Day 1 of Cycle 2, pre-dose, if possible, and EOS. Additional ECG's as clinically indicated. For Cycle 1, pre-dose ECG should be within the 2 hours prior to dosing and post-dose within a 30-minute window either side of the nominal time. When a PK blood draw is scheduled at the same time as ECG, the ECG should be performed first and as close as possible immediately followed by the PK draw.

o. CBC with differential – WBC, ANC, RBC, Hgb, Hct, platelets, MCH, and differential.

APPENDIX 1. SCHEDULE OF ASSESSMENTS – CLL/SLL, FL, MCL, MZL, DLBCL, AND HIGH-GRADE B-CELL LYMPHOMAS (CONTINUED)

p. **TLS monitoring/ Serum chemistry** –Chemistry for monitoring of TLS risk (including potassium, uric acid, phosphorus, calcium and creatinine) will be performed as indicated in the TLS management plan (see Appendix 9 and as clinically indicated. Subjects must be assessed for TLS risk during screening and before first dose of voruciclib (monotherapy) on cycle 1 Day 1. Standard chemistry panel to include glucose, BUN, creatinine, sodium, potassium, chloride, calcium, phosphate, uric acid, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, LDH.

q. **Immunoglobulin tests** – Quantitative serum immunoglobulin levels (IgA, IgG, IgM) will be performed for subjects with SLL and CLL at screening, at Day 1 of Cycle 1, and then every 6 months.

r. **Coagulation** – aPTT, PT, and INR.

s. **Urinalysis** – Dipstick.

t. **Issue and Assess Compliance Diary** – Compliance diary to record voruciclib administration. Returned diaries assessed for study drug compliance. New compliance diary dispensed with each dispensing of voruciclib.

u. **Dispense study drug** – Voruciclib is administered orally once a day on an empty stomach at least 1 hour prior to food or 2 hours after food at approximately the same time each day. On days of PK sampling, subjects should be instructed not to take voruciclib until after the PK sample is collected (note that in Amendment 7, there is no dosing on Day 8 for the IS_{1w3w} and Day 15 for the $IS_{2w,2w}$). A compliance diary assessment and returned voruciclib drug accountability should be performed at each visit which includes voruciclib dispensing.

As of Amendment 7, voruciclib will be administered on an intermittent dosing schedule of 2 weeks on/2 week off ($IS_{2w,2w}$) or 1 week on/3 weeks off ($IS_{1w,3w}$), in the 28-day cycle. Note that voruciclib is taken daily on dosing days only, i.e., Days 1 through 14 for $IS_{2w,2w}$, and on Days 1 through 7 only on the $IS_{1w,3w}$ regimen.

v. **PK sampling** – Pre-dose specimens should be within 2 hours of dosing and for post-dose within ± 30 minutes) after dosing.
Cohorts 1-5:

- Cycle 1 Day 1: pre-dose (before voruciclib dose is taken); and at 4- and at 6- hours post-dose
- Cycle 1 Day 2: pre-dose (i.e., 24 hours after the Cycle 1 Day 1 voruciclib dose)
- Cycle 1 Day 8: pre-dose (24 hours after the preceding last dose, before voruciclib is taken)
- Cycle 1 Day 15: pre-dose (before voruciclib dose is taken); at 4- and at 6- hours post dose

Cohorts 6b-11b (IS dosing):

- Cycle 1 Day 1: pre-dose and at 4- and at 6- hours post-dose
- Cycle 1 Day 2: pre-dose (24 hours after the preceding last dose)
- Cycle 1 Day 8: pre-dose (24 hours after the preceding last dose)
- Cycle 1 Day 15: (24 hours after the preceding last dose), if applicable [Day 15 samples only collected for the $IS_{2w,2w}$ schedule]
- Cycle 2 Day 1: pre-dose

w. **Disease assessment** – Scans, bone marrow aspirate/biopsy and laboratory evaluation as appropriate for individual subjects. Scans to be performed at baseline within 3 months of Cycle 1 Day 1 and after termination of prior therapy, Cycle 3 Day 1, Cycle 7 Day 1, every 6 cycles thereafter, and upon permanently stopping study treatment. Response assessments for CLL/SLL and FL and other B-cell lymphomas, refer to Appendix 5 and Appendix 6, respectively.

* Bone marrow – Biopsy/aspirate are required for assessment of response (as described in Appendix 5, Table 19, and Appendix 6, Table 21) and as clinically indicated. Bone marrow biopsies may not need to be repeated for the study as long as they were performed within the allowed 28-day screening window. Additionally, optional biopsy/aspirates pre-first dose, at the end of cycle 6 and at end of treatment may be conducted for correlative studies. See Laboratory Manual.

** Tumor biopsy – tissue can be collected after completion of prior therapy and within 3 months of Cycle 1 Day 1 per Site Laboratory Manual. Formalin fixed material acceptable although fresh tissue preferred. Both the initial and repeat biopsy at Cycle 1 Day 8 are **optional**.

*** For Cohorts 6b-8b, the first blood specimen for Pharmacodynamic /Correlative studies must be taken prior to first dose on Cycle 1 Day 1, a second specimen approximately 6 hours post dose on Day 1, and a third specimen pre-dose on Day 2. The specimen obtained prior to starting study drug may be taken up to 7 days prior to Cycle 1 Day 1. On Cycle 1 Day 15, a specimen will be taken prior to administration of study drug.

APPENDIX 2. SCHEDULE OF ASSESSMENTS - AML SUBJECTS ONLY - MONOTHERAPY

	Screening[b]	Cycle 1				Cycle 2		Cycle 3 and Subsequent Cycles[c]	End of Study[d]
Day(s) [a]	-28 to -1	1[a]	2	8	15	1	15	1	30 days (± 3 days) post last dose
Informed consent	X								
Medical history	X								
Physical examination	X	X							X
Symptom-directed exam [e]				X	X	X		X	
Vital signs [f]	X	X		X	X	X		X	X
Height	X								
Weight	X					X		X	X
ECOG performance status	X	X				X		X	X
Pregnancy test [g]	X	X				X		X	X
HIV testing [h]	X								
Hepatitis B and C testing [i]	X								
Adverse events [j]		X	X	X	X	X	X	X	X
Concomitant medication [k]	X	X	X	X	X	X	X	X	X
ECG [l]	X	X		X	X	X			X
CBC with differential [m]	X	X		X	X	X	X	X	X
Serum chemistry [n]	X	X	X	X	X	X	X	X	X
TLS risk assessment and monitoring [n]	X	X	X						
Coagulation [o]	X		X		X	X		X	X
Urinalysis (dipstick) [p]	X					X			X
Issue and assess compliance diary [q]		X				X		X	
Dispense study drug [r]		X				X		X	
PK Sampling (all subjects) [s]		X	X	X	X	X			
Disease assessment / Bone marrow [t]	X					X		X	X
Cytogenetics [u]	X								
Molecular mutations [v]	optional								
Blood for PD/biomarker assays [w]		X	X	X	X				X

APPENDIX 2. SCHEDULE OF ASSESSMENTS - AML SUBJECTS ONLY - MONOTHERAPY (CONTINUED)

Abbreviations: AML = acute myeloid leukemia; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; Hct = hematocrit; HCV Ab = hepatitis C virus antibody; Hgb = hemoglobin; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; TLS = tumor lysis syndrome; WBC = white blood cell.

a. **Study Assessment Day(s)** – C1D1 and visits when blood for pharmacodynamic/biomarker studies are collected should be conducted Monday through Wednesday if possible so that specimens can be shipped for receipt no later than a Friday. There is ± 3-day window allowable for each clinic visit during Cycle 1. Following Cycle 1, the allowable window is up to 7 days prior and 2 days after the scheduled clinic visit and its associated assessments.

b. **Screening** – Screening assessments are to be performed within 28 days of first dose of voruciclib. Laboratory assessments need not be repeated on Day 1 if performed within the prior 72 hours. Physical examination need not be repeated on Day 1 if performed within the prior 7 days. Some tests performed prior to obtaining ICF (e.g., CT scan, bone marrow biopsy) may not need to be repeated for the study as long as they were performed within the allowed screening window.

c. **Cycle 3 and subsequent cycles, and EOS** – All cycles after Cycle 3 should follow the same schedule of activities as Cycle 3.

d. **EOS** - The End of Study (EOS) visit will occur 30 days (±3 days) from the last day of voruciclib administration (or prior to starting a new treatment if urgent treatment is required).

e. **Symptom-directed exam** – performed only as needed/indicated, based on interim history

f. **Vital signs, Height and Weight** – includes systolic and diastolic blood pressure (BP), heart rate (HR), and body temperature. Height collected at Screening visit only.

g. **Pregnancy test** – Serum pregnancy test in females of childbearing potential at screening, urine pregnancy test Day 1 of each cycle and at EOS.

h. **HIV testing** – HIV antibody testing is required.

i. **Hepatitis B and Hepatitis C testing** – Hepatitis B core antibody, surface antibody and surface antigen, and hepatitis C virus antibody (HCV Ab) tests are required. Hepatitis B polymerase chain reaction (PCR) is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if HCV Ab test is positive.

j. **Adverse events** – Recorded from the first dose of voruciclib and continue until 30 days after the last dose, or until a subsequent anti-cancer therapy is initiated.

k. **Concomitant medications** – Recorded from 28 days prior to Cycle 1 Day 1 through 30 days after the last dose of voruciclib, or until a subsequent anti-cancer therapy is initiated.

l. **ECG** – 12 lead ECGs performed in triplicate (approximately 2–5 minutes apart while the subject is resting) at screening, Cycle 1 Day 1, Day 8 (24 ± 3 hours after the preceding last dose in Cohorts 9-11), and Cycle 1 Day 15 (pre-dose and 4 hours post-dose voruciclib in Cohorts 1-5, and 24 ± 3 hours after the preceding last dose in Cohorts 6-8), and at Cycle 2 Day 1 (pre-dose voruciclib) and EOS (single triplicate post-dose).

m. **CBC with differential** – WBC, ANC, RBC, Hgb, Hct, platelets, MCH, and differential.

n. **TLS monitoring/ Serum chemistry** – Chemistry for monitoring of TLS risk (including potassium, uric acid, phosphorus, calcium and creatinine) will be performed as indicated in the TLS management plan (see Appendix 9) and as clinically indicated. Subjects must be assessed for TLS risk during screening and before first dose of voruciclib (monotherapy) on Cycle 1 Day 1. Standard chemistry panel to include glucose, BUN, creatinine, sodium, potassium, chloride, calcium, phosphate, uric acid, CO2, ALP, AST, ALT, total bilirubin, total protein, albumin, LDH.

o. **Coagulation** – aPTT, PT, and INR.

APPENDIX 2. SCHEDULE OF ASSESSMENTS - AML SUBJECTS ONLY - MONOTHERAPY (CONTINUED)

p. Urinalysis – Dipstick.

q. Issue and Assess Compliance Diary – Compliance diary to record voruciclib administration. Returned diaries are to be assessed for study drug compliance. New compliance diary to be dispensed with each dispensing of voruciclib.

r. Dispense study drug – Voruciclib is administered orally once a day on dosing days, on an empty stomach at least 1 hour prior to food or 2 hours after food at approximately the same time each day. On days of PK sampling, subjects should be instructed to not take voruciclib until after the pre-dose PK sample is collected.

As of Amendment 7, voruciclib will be administered on an intermittent dosing schedule of 2 week on/2 week off (IS2w,2w) or 1 week on/3 weeks off (IS1w,3w), in the 28-day cycle. Note that voruciclib is taken daily on dosing days only, i.e., days 1 through 14 on IS2w,2w , and on days 1 through 7 only on the IS1w,3w regimen. Therefore, there is no dosing on Day 8 on IS1w,3w and on Day 15 of the IS2w,2w cycle.

s. PK sampling – Unless stated otherwise, pre-dose specimens should be within 2 hours prior to dosing, post-dose samples within ±30 minutes of the sampling time
For monotherapy for Cohorts 1-5:

- Cycle 1 Day 1: pre-dose (before voruciclib dose is taken); and at 4- and at 6- hours post-dose
- Cycle 1 Day 2: pre-dose (i.e., 24 hours after the Cycle 1 Day 1 voruciclib dose)
- Cycle 1 Day 8: pre-dose (24 hours after the preceding last dose, before voruciclib is taken)
- Cycle 1 Day 15: pre-dose (before voruciclib dose is taken); at 4- and at 6- hours post dose

For monotherapy Cohorts 6a-11a (IS dosing):

- Cycle 1 Day 1: pre-dose and at 4- and at 6- hours post-dose
- Cycle 1 Day 2: pre-dose (24 hours after the preceding last dose)
- Cycle 1 Day 8: pre-dose (24 hours after the preceding last dose)
- Cycle 1 Day 15: 24 hours after the preceding last dose), if applicable [Day 15 samples only collected for the $IS_{2w,2w}$ schedule]
- Cycle 2 Day 1: pre-dose

t. Disease assessment / Bone marrow – Bone marrow aspirate/biopsy and laboratory evaluation at screening, Cycle 2 Day 1, Cycle 3 Day 1, and Day 1 of every subsequent cycle until a CR or CRi is achieved after which bone marrow examinations are obtained if clinically indicated, and at EOS. Both biopsy and aspirate are recommended for disease assessment, but biopsy may be omitted if aspirate is considered to be sufficient. A fresh specimen of aspirate is to be obtained at each timepoint as described in the Study Manual and submitted to the central laboratory for pharmacodynamic/correlative study. The first blood specimen for pharmacodynamic/correlative studies must be taken prior to first dose on Cycle 1 Day 1 and a second specimen approximately 6 hours after the first dose on Day 1. Specimen may be taken up to 7 days prior to C1D1.

u. Cytogenetics – If abnormal cytogenetics at screening, repeat cytogenetics in a subject with CR/CRi to confirm a cytogenetic remission.

v. Molecular mutations/rearrangements analysis – Not required for the study. Collect if obtained as standard of care for a subject. If abnormalities identified at screening, repeat the test for the genetic marker by RT-qPCR or flowcytometry in a subject with CR/CRi to confirm CR with minimal residual disease.

w. Pharmacodynamic biomarker – The first blood specimen for Pharmacodynamic/biomarker assay must be taken prior to first dose on Cycle 1 Day 1, a second specimen approximately 6 hours post-dose on Day 1, and a third specimen pre dose on Day 2. The specimen obtained prior to starting study drug may be taken up to 7 days prior to C1D1. On Days 8 and 15 specimen will be taken prior to administration of study drug (Cohorts 1-5).

APPENDIX 3. SCHEDULE OF ASSESSMENTS - AML SUBJECTS ONLY – COMBINATION THERAPY

	Screening[b]	Cycle 1- Inclusive of Venetoclax Ramp-up[c]					Cycle 2		Cycle 3 and Subsequent Cycles[d]	End of Study[e]
	-28 to -1	1[a]	2	3	8	14	1	14	1	30 days (± 3 days) Post Last Dose Study Drug
Informed consent	X									
Medical history/Prior Treatment/Demographics	X									
Physical examination	X	X								X
Symptom-directed exam [f]				X	X	X	X		X	
Vital signs [g]	X	X		X	X	X	X		X	X
Height	X									
Weight	X						X		X	X
ECOG performance status	X	X					X		X	X
Pregnancy test [h]	X	X					X		X	X
HIV testing [i]	X									
Hepatitis B and C testing [j]	X									
Adverse events [k]		X	X	X	X	X	X	X	X	X
Concomitant medication [l]	X	X	X	X	X	X	X	X	X	X
ECG [m]	X	X		X	X	X	X			X
CBC with differential [n]	X	X		X	X	X	X	X	X	X
Serum chemistry [o]	X	X	X	X	X	X	X	X	X	X
TLS risk assessment and monitoring [o]	X	X	X	X						
Coagulation [p]	X		X			X	X		X	X
Urinalysis (dipstick) [q]	X						X			X
Baseline chest x-ray [r]	X									
Issue and assess compliance diary [s]		X					X		X	
Dispense study drug(s) [t]		X					X		X	
Disease assessment, bone marrow aspirate [u]	X						X		X	X
Cytogenetics [v]	X									
Molecular mutations [w]	optional									
Blood for PD/biomarker assays [x]		X		X		X				
Blood for PK analysis	See specific PK collection timepoints in table below									

APPENDIX 3. SCHEDULE OF ASSESSMENTS - AML SUBJECTS ONLY – COMBINATION THERAPY (CONTINUED)

Abbreviations: AML = acute myeloid leukemia; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ANC = absolute neutrophil count; aPTT = activated partial thromboplastin time; AST = aspartate aminotransferase; BP = blood pressure; BUN = blood urea nitrogen; CBC = complete blood count; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOS = End of Study; Hct = hematocrit; HCV Ab = hepatitis C virus antibody; Hgb = hemoglobin; HIV = human immunodeficiency virus; HR = heart rate; ICF = informed consent form; INR = international normalized ratio; LDH = lactate dehydrogenase; MCH = mean corpuscular hemoglobin; PCR = polymerase chain reaction; PD = pharmacodynamic; PK = pharmacokinetic; PT = prothrombin time; RBC = red blood cell; RU = ramp-up; TLS = tumor lysis syndrome; WBC = white blood cell.

a. **Study Assessment Day(s) –** C1D1 and visits when blood for pharmacodynamic/biomarker studies are collected should be conducted Monday through Wednesday if possible so that specimens can be shipped for receipt no later than a Friday. There is ± 3-day window allowable for each clinic visit during Cycle 1. Following Cycle 1, the allowable window is up to 7 days prior and 2 days after the scheduled clinic visit and its associated assessments.

b. **Screening –** Screening assessments are to be performed within 28 days before the first dose of venetoclax. Laboratory assessments need not be repeated on Day 1 if performed within the prior 72 hours. Physical examination need not be repeated on Day 1 if performed within the prior 7 days. Some tests performed prior to obtaining ICF (e.g., CT scan, bone marrow biopsy) may not need to be repeated for the study as long as they were performed within the allowed screening window.

c. **Venetoclax Ramp-up** – applies to **combination Cohorts 12–19 and 21–25**. Venetoclax ramp-up dosing begins on Cycle 1 Day 1 at 100 mg and 200 mg on Day 2. Dosing continues at 200 mg on Days 3–21, then 400 mg on Days 22–28. Increasing venetoclax dose from 200 mg to 400 mg on Day 22 is not considered dose ramp-up.

d. **Cycle 3 and subsequent cycles** – all cycles after Cycle 3 should follow the same schedule of activities as Cycle 3.

e. **EOS -** The End of Study (EOS) visit will occur 30 days (±3 days) from the last day of study drug (voruciclib or venetoclax) administration or prior to starting a new treatment if urgent treatment is required.

f. **Symptom-directed exam** – performed as indicated, and additional exams may be performed based on interim history

g. **Vital signs** – includes systolic and diastolic blood pressure (BP), heart rate (HR), and body temperature.

h. **Pregnancy test** – Serum pregnancy test in females of childbearing potential at screening, urine pregnancy test Day 1 of each cycle and at EOS.

i. **HIV testing** – HIV antibody testing is required.

j. **Hepatitis B and Hepatitis C testing** – Hepatitis B core antibody, surface antibody and surface antigen, and hepatitis C virus antibody (HCV Ab) tests are required. Hepatitis B polymerase chain reaction (PCR) is required if hepatitis B core antibody and/or surface antigen is positive. Hepatitis C PCR is required if HCV Ab test is positive.

k. **Adverse events** – Recorded from the first dose of venetoclax and continues until 30 days after the last dose of any study drug, or until a subsequent anti-cancer therapy is initiated, whichever is earlier.

l. **Concomitant medications** – Recorded from 28 days prior to Cycle 1 Day 1 through 30 days after the last dose of any study drug, or until a subsequent anti-cancer therapy is initiated.

m. **ECG** – 12 lead ECGs performed in triplicate (approximately 2–5 minutes apart while the subject is resting). ECGs will be performed at screening and pre venetoclax dose on Cycle 1 Day 1. On Cycle 1 Day 3, pre voruciclib dose and 4 hours post voruciclib dose, on Cycle 1 Day 8 pre voruciclib dose, on Cycle 1 Day 14* pre voruciclib dose and 4 hours post voruciclib dose, at Cycle 2 Day 1 pre-dose voruciclib, and EOS. Additional ECGs as clinically indicated. For Cycle 1, pre-dose ECG should be within the 2 hours prior to dosing and post-dose within a 30-minute window either side of the nominal time. When a PK blood draw is scheduled at the same time as ECG, the ECG should be performed first and as close as possible immediately followed by the PK draw.

*For Cohort 12 (QOD dosing), since there is no dosing on Cycle 1 Day 14, ECGs will be performed on Cycle 1 Day 13 pre voruciclib dose and 4 hours post voruciclib dose.

n. **CBC with differential** – WBC, ANC, RBC, Hgb, Hct, platelets, MCH, and differential.

o. **TLS monitoring/ Serum chemistry** – Chemistry for monitoring of TLS risk (including potassium, uric acid, phosphorus, calcium and creatinine) will be performed as indicated in the TLS management plan (see Appendix 9) and as clinically indicated. Subjects must be assessed for TLS risk during screening and before first dose of venetoclax. Standard chemistry panel to include glucose, BUN, creatinine, sodium, potassium, chloride, calcium, phosphate, phosphorus, uric acid, CO_2, ALP, AST, ALT, total bilirubin, total protein, albumin, LDH.

APPENDIX 3. SCHEDULE OF ASSESSMENTS - AML SUBJECTS ONLY – COMBINATION THERAPY (CONTINUED)

p. Coagulation – aPTT, PT, and INR.

q. Urinalysis – Dipstick.

r. Baseline chest x-ray – recommended if the subject has not had recent chest imaging.

s. Issue and Assess Compliance Diary – Assess returned diaries for study drug dosing compliance. New compliance diary to be dispensed with each dispensing of study drug.

t. Dispense study drug –Venetoclax is administered orally once daily to be taken with food and water. Voruciclib is administered orally once a day on dosing days, at least 2 hours after venetoclax. On days of PK sampling (for PK sampling schedules refer to Section 9.14.2), subjects should be instructed to not to take venetoclax or voruciclib until after the pre-dose PK sample is collected.

As of Amendment 11, voruciclib will be administered on an intermittent dosing schedule of 2 week on/2 week off ($IS_{2w,2w}$) in the 28-day cycle. Note that voruciclib is taken once daily on dosing days only (i.e., Days 1 through 14 on $IS_{2w,2w}$), with the exception of Cohort 12 which is taken every other day (i.e., Days 3, 5, 7, 9, 11, and 13 of Cycle 1 and Days 1, 3, 5, 7, 9, 11, and 13 of Cycle 2 and beyond).

As of Amendment 12, voruciclib will be administered on an intermittent dosing schedule of 3 weeks on/1 week off ($IS_{3w,1w}$) in the 28-day cycle for Cohorts 21–25. Voruciclib is taken once daily on dosing days only (i.e., Days 1 through 21 on $IS_{3w,1w}$).

u. Disease assessment / Bone marrow – Bone marrow aspirate/biopsy and laboratory evaluation at screening (up to 28 days prior to starting venetoclax), Cycle 2 Day 1, and Day 1 of every subsequent cycle until a CR or CRi is achieved. Thereafter when bone marrow examinations are obtained as clinically indicated, and at EOS. Both biopsy and aspirate are recommended for disease assessment, but biopsy may be omitted if aspirate is considered to be sufficient. Bone marrow assessment may be omitted if the subject has clear evidence of disease progression based of peripheral blood count/blasts analysis. Bone marrow aspirate sample collected at the time of disease assessment may be used for exploratory biomarker analysis in bone marrow/bone marrow aspirate. If any remaining sample is available after evaluation for disease assessment. it should be submitted to the central laboratory for pharmacodynamic biomarker/correlative study (refer to the Lab Manual).

v. Cytogenetics – If abnormal cytogenetics at screening, repeat cytogenetics in a subject with CR/CRi to confirm a cytogenetic remission

w. Molecular mutations/rearrangements analysis – Not required for the study. Collect if obtained as standard of care for a subject. If abnormalities identified at screening, repeat the test for the genetic marker by RT-qPCR or flow cytometry in a subject with CR/CRi to confirm CR with minimal residual disease

x. Blood Pharmacodynamic biomarker assays– Blood for pharmacodynamic/biomarker assays for Cohorts 12–19 and 21–25 will be collected as follows:

- Cycle 1 Day 1*: Pre-dose of venetoclax and approximately 6 hours post-dose of venetoclax for Cohorts 12–16, or 4–6 hours post-dose for Cohorts 17–25.
- Cycle 1 Day 3: Pre-dose of voruciclib and at approximately 6 hours post-dose of voruciclib for Cohorts 12–16, or 4–6 hours post-dose for Cohorts 17–25.
- Cycle 1 Day 14**: Pre-dose of venetoclax and approximately 6 hours post-dose of voruciclib for Cohorts 12–16, or 4–6 hours post-dose for Cohorts 17–25.

* The specimen obtained prior to starting study drug may be taken up to 7 days prior to C1D1.

** For Cohort 12, since there is no dosing on Cycle 1 Day 14, blood will be collected at the Cycle 1 Day 13 pre-dose of venetoclax and approximately 6 hours post-dose of voruciclib during the clinic visit for PK sample collection.

APPENDIX 3. BLOOD SAMPLING SCHEDULE FOR PHARMACOKINETC ANALYSES, COMBINATION THERAPY

Unless stated otherwise, pre-dose specimens should be obtained 2 hours prior to dosing and for post-dose within ±30 minutes after dosing) for Cohorts 12–19 and 21–25.

Blood Sampling Schedule for Voruciclib, Cohort 12 (QOD Dosing),

Cycle	Day	Time of Collection	
		Pre-dose	**Post-dose**
1	3	X	2, 4, 6 hours
	4*	-	approximately 24 hours after **Day 3 dose**
	8	-	approximately 24 hours after **Day 7 dose**
	13	X	2, 4, 6 hours
	14	-	approximately 24 hours after **Day 13 dose**
	21	anytime during clinic visit	
2	1	X	-
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

*Day 4 sample to be collected only if the subject is able to visit the clinic.

Blood Sampling Schedule for Voruciclib, Cohorts 13–19 and Cohorts 19–25 (QD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	**Post-dose**
1	3	X	2, 4, 6 hours
	4*	X (approximately 24 hours after **Day 3 dose**)	-
	8	X (approximately 24 hours after **Day 7 dose)**	-
	14	X	2, 4, 6 hours
	15	-	approximately 24 hours after **Day 14 dose**
	21	anytime during clinic visit	
2	1	X	-

Blood Sampling Schedule for Voruciclib, Cohorts 13–19 (QD Dosing, Continued)

Cycle	Day	Time of Collection	
		Pre-dose	Post-dose
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

*Day 4 sample to be collected only if the subject is able to visit the clinic.

Blood Sampling Schedule for Venetoclax, Cohort 12 (QOD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	Post-dose
1	13	X	2, 4, 6, 8 hours
	14	X (approximately 24 hours after **Day 13 dose**)	-
	21	anytime during clinic visit	
2	1	X	2, 4, and 6-hours post-dose of venetoclax (voruciclib to be dosed 6 hours after venetoclax administration, after completion of the 6- hour sample collection)
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

Blood Sampling Schedule for Venetoclax, Cohorts 13–19 and Cohorts 21–25 (QD Dosing)

Cycle	Day	Time of Collection	
		Pre-dose	Post-dose
1	14	X	2, 4, 6, and 8-hours
	15	X (approximately 24 hours after **Day 14 dose**)	-
	21	anytime during clinic visit	
2	1	X	2, 4, and 6-hours post-dose of venetoclax (voruciclib to be dosed 6 hours after venetoclax administration, after completion of the 6- hour sample collection)
4, 6	1, 14 (±3 days)	anytime during clinic visit	
Every 3 cycles thereafter	1, 14 (±3 days)	anytime during clinic visit	

APPENDIX 4. AML RESPONSE CRITERIA

Table 18: European LeukemiaNet (ELN) Response Criteria in AML

Category	Definition	Comment
Response		
CR without minimal residual disease (CR_{MRD-})	If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by MFC	Sensitivities vary by marker tested, and by method used; therefore, test used, and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
Complete remission (CR)	Bone marrow blasts < 5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0×10^9/L (1000/μL); platelet count ≥100×10^9/L (100,000/μL)	MRD^+ or unknown
CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia (<1.0×10^9/L [1000/μL]) or thrombocytopenia (<100×10^9/L [100,000/μL])	
Morphologic leukemia-free state (MLFS)	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Marrow should not merely be "aplastic"; at least 200 cells should be enumerated, or cellularity should be at least 10%
Partial remission (PR)	All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%	Especially important in the context of phase 1-2 clinical trials
Treatment Failure		
Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding subjects with death in aplasia or death due to indeterminate cause‡	Regimens containing higher doses of cytarabine are generally considered as the best option for subjects not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
Death in aplasia	Deaths occurring ≥ 7 days following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia‡	
Death from indeterminate cause	Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available‡	
Response criteria for clinical trials only		
Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 months

Table 18: European LeukemiaNet (ELN) Response Criteria in AML (Continued)

Category	Definition	Comment
Progressive disease (PD)*,†	Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood:	Category mainly applies for older subject given low-intensity or single-agent "targeted therapies" in clinical trials
	• >50% increase in marrow blasts over baseline (a minimum 15%-point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level (>0.5 × 10^9/L [500/µL], and/or platelet count to >50 × 10^9/L [50,000/µL] non-transfused); or	In general, at least 2 cycles of a novel agent should be administered
	• >50% increase in peripheral blasts (WBC × % blasts) to >25 × 10^9/L (>25,000/µL) (in the absence of differentiation syndrome)†; or	Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date
	• New extramedullary disease	Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
Molecular relapse (after CR_{MRD-})	If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by MFC	Test applied, sensitivity of the assay, and cutoff values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Abbreviations: ANC = absolute neutrophil count; IDH = isocitrate dehydrogenase; MFC = multiparameter flow cytometry; MLFS = morphologic leukemia-free state; MRD = minimal residual disease; RT-qPCR = quantitative reverse transcription polymerase chain reaction (assay); WBC = white blood cell.

‡ For this study, "intensive induction treatment" and "completion of initial therapy" are not applicable, and "completion of therapy" is defined as the last day of voruciclib administration followed by treatment discontinuation.

* The authors acknowledge that this new provisional category is arbitrarily defined; the category aims at harmonizing the various definitions used in different clinical trials.

† Certain targeted therapies, for example, those inhibiting mutant IDH proteins, may cause a differentiation syndrome, that is, a transient increase in the percentage of bone marrow blasts and an absolute increase in blood blasts; in the setting of therapy with such compounds, an increase in blasts may not necessarily indicate PD.

Reference: Döhner 2017.

APPENDIX 5. CLL/SLL RESPONSE CRITERIA: IWCLL

Table 19: Schedule of Response Assessments for Subjects with CLL/SLL

Response Assessment	Screening	Cycle 3, Cycle 7	Every 6 Cycles Thereafter and EOS
Day(s)	-28 to -1	1	1
History, physical examination	X	X	X
CBC and differential count	X	X	X
CT chest/abdomen/pelvis [a]	X	X	X[a]
Bone marrow biopsy/aspirate [b]	X	X	X

Abbreviations: CBC = complete blood count; CLL = chronic lymphocytic leukemia; CR = complete response; CT = computed tomography; EOS = end of study; SLL = small lymphocytic lymphoma.

NOTE: Subjects who meet diagnostic criteria for SLL (i.e., absolute lymphocyte count <5,000) will have formal response assessment per Lugano criteria (Cheson 2014).

[a] CT of the chest, abdomen and pelvis must be obtained at screening; at Cycles 3 and 7; and every 6 months thereafter.

[b] Bone marrow biopsy/aspirate is obtained at screening only as clinically indicated (at the discretion of the Investigator). Bone marrow biopsy/aspirate must be performed at least 2 months after other criteria for CR are met. Bone marrow biopsy is otherwise optional unless clinically indicated or to confirm CR.

Table 20: Response Criteria for CLL/SLL per IWCLL (Hallek et al)

Parameter	Complete Remission (CR) All Criteria Must be Met[a]	Partial Remission (PR) At Least 2 Criteria from Group A AND At Least 1 Criterion from Group B Must be Met	Progressive Disease (PD) at Least 1 Criterion from Group A OR 1 Criterion from Group B Must be Met[b]	Stable Disease (SD) All Criteria Must be Met
Group A				
Lymphadenopathy[i]	None >1.5 cm	Decrease ≥50%[c]	Increase ≥50%[d] or any new LN >1.5 cm	Change[e] of -49% to +49%
Blood Lymphocytes	<4000/µL	Decrease ≥50% from baseline	Increase ≥50% over nadir (≥5000/µL)	Change of –49% to +49%
Hepatomegaly[f]	None	Decrease ≥50%	Increase ≥50%[g]	Change of –49% to +49%
Splenomegaly[f]	None	Decrease ≥50%	Increase ≥50%[g]	Change of –49% to +49%
Marrow	Normocellular, <30% lymphocytes, no B-lymphoid nodules; hypocellular marrow defines CRi	N/A	N/A	N/A
Group B				
Platelet Count	>100,000/µL[h]	>100,000/µL or increase ≥50% over baseline[h]	Decrease of ≥50% from baseline secondary to CLL	Change of –49% to +49%
Hemoglobin	>11.0 g/dL[h]	>11.0 g/dL or increase ≥50% over baseline[h]	Decrease of >2 g/dL from baseline secondary to CLL	Increase to ≤11.0 g/dL over baseline, or decrease <2 g/dL
Neutrophils	>1500/µL[h]	>1500/µL or increase ≥50% over baseline[h]	Decrease ≥50% from baseline secondary to CLL	N/A
Other Considerations				
New Lesions	None	None	Appearance of new palpable lymph nodes (>1.5 cm in longest diameter) or any new extranodal lesion (regardless of size) or transformation to a more aggressive histology, e.g., Richter syndrome[d]	None
Non-Target Lesions	Nodes must be normal size as visually estimated; extranodal and other assessable disease should be absent	No change/decreased	Unequivocal progression	No change or decrease or non-substantial increase
Target Extranodal Disease	Absence of any extranodal disease by physical examination (palpable, visualized extranodal) and CT scan	≥50% decrease in SPD	≥50% increase in the longest diameter of any extranodal lesion	Not CR, CRi, PR, or PD

Table 18: Response Criteria for CLL/SLL per IWCLL (Hallek et al) (Continued)

Abbreviations: CLL = chronic lymphocytic leukemia; CRi = complete remission with incomplete marrow recovery; CT = Computed tomography; LN = lymph nodes; N/A = Not applicable; PD = SPD = sum of the products of diameter.

[a] CR also requires the lack of disease-related constitutional symptoms.

[b] Transformation to a more aggressive histology (e.g., Richter syndrome) would also qualify as a PD.

[c] Sum of the products of multiple LNs (as evaluated by CT scans).

[d] Increase in SPD of multiple nodes, or in greatest diameter of any previous site, or appearance of any new lymphadenopathy or organomegaly. Degree of change in LN or lymphocyte counts should be measured from nadir (lowest post-treatment) values.

[e] Sum products of up to 6 LNs or LN masses (target lesions), with no increase in an LN or new enlarged LN. Increase of <25% in small LNs (<2 cm) not significant. Decreases should be measured compared to baseline (pre-treatment) values.

[f] If enlarged before therapy.

[g] An increase in the previously noted enlargement of the liver or spleen by 50% or more or the de novo appearance of hepatomegaly or splenomegaly.

[h] Without the need for exogenous growth factors or transfusions.

[i] Lymphocytosis can be prominent early during treatment and can persist over time, and should not be confused with disease progression in subjects who otherwise have persistent disease control. In the absence of other objective evidence of disease progression, the occurrence of lymphocytosis will not preclude subjects from meeting the criteria for PR if other criteria for PR are met, and will not be considered evidence of CLL progression if occurring in isolation.

The goal of confirmation of objective response is to avoid overestimating responses. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome that the response(s) is (are) not confirmed.

For subjects experiencing disease progression due to Richter's Syndrome while on study, supplemental data may be collected.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed at least 2 months after the criteria for response is first met. Bone marrow biopsy and aspirate to confirm CR must be obtained at least 2 months after other criteria for CR are first met.

APPENDIX 6. FOLLICULAR LYMPHOMA RESPONSE CRITERIA: LUGANO CLASSIFICATION

Table 21: Schedule of Response Assessments for Subjects with Follicular Lymphoma and Other B-Cell Lymphomas

Response Assessment	Screening	Cycle 3, Cycle 7	Every 6 Cycles Thereafter and EOS
Day(s)	-28 to -1	1	1
History, physical examination	X	X	X
CBC and differential count	X	X	X
CT chest/abdomen/pelvis [a]	X	X	X[a]
FDG-PET scan [a]	X	X[a]	X[a]
Bone marrow biopsy/aspirate [b]	X	X	X

Abbreviations: CBC = complete blood count; CR = complete response; CT = computed tomography; EOS = End of Study visit; FDG-PET = fluorodeoxyglucose positron emission tomography.

[a] CT of the chest, abdomen and pelvis must be obtained at screening; at Cycles 3, 5, 7, 13, 27; and every 6 months thereafter. FDG-PET scan must be obtained at screening (within 6 weeks prior to Cycle 1 Day 1) and subsequently for subjects who achieve a CR by CT criteria.

[b] Bone marrow biopsy/aspirate is obtained at screening only as clinically indicated (at the discretion of the Investigator). Bone marrow biopsy/aspirate must be performed at least 2 months after other criteria for CR are met. Bone marrow biopsy is otherwise optional unless clinically indicated or to confirm CR.

SELECTION OF TARGET LESIONS

Up to 6 of the largest dominant nodes or tumor masses selected according to all of the following:

1. Clearly measurable in 2 diameters (longest diameter [LDi] and shortest diameter [SDi]) at baseline
    a. All nodal lesions must measure >1.5 cm in longest diameter regardless of short axis measurement
    b. All measurable extranodal lesions should have a longest tumor diameter ≥1.0 cm
2. All other lesions (including nodal, extranodal, and assessable disease) should be followed as non-target lesions
3. If possible, the lesions should be from disparate regions of the body
4. Should include mediastinal and retroperitoneal areas of disease whenever these sites are involved

SELECTION OF NON-TARGET LESIONS

Non-target lesions will be qualitatively assessed at each subsequent time point. All of the sites of disease present at baseline and not classified as target lesions will be classified as non-target lesions, including any measurable lesions that were not chosen as target lesions.

Examples of non-target lesions include:

1. All bone lesions, irrespective of the modality used to assess them
2. Lymphangitis of the skin or lung
3. Cystic lesions

4. Splenomegaly and hepatomegaly (all lymphomas)
    a. Cutoff for splenomegaly of more than 13 cm
    b. Diffusely increased or focal uptake, with or without focal or disseminated nodules, supports spleen or liver involvement
5. Irradiated lesions
6. Measurable lesions beyond the maximum number of 6
7. Groups of lesions that are small and numerous
8. Pleural/pericardial effusions and/or ascites
    a. Effusions, ascites, or other fluid collections will be followed as non-target lesions
    b. At each assessment point, radiologists will check for the presence or absence of effusions/ascites. If there is a significant volume increase in the absence of a benign etiology, progression can be assessed
    c. Significant new effusions, ascites or other fluid collections, which are radiographically suggestive of malignancy should be recorded as new lesions and should be assessed

Response should be determined on the basis of radiographic and clinical evidence of disease. For subjects who achieve a CR by CT criteria, an FDG-PET will be performed. Assessment by PET should follow the criteria described by Cheson et al (Cheson 2014) which is summarized in the table below (Table 22).

Table 22: Revised Criteria for Response Assessment from Cheson et al 2014

Response and Site	PET-CT–Based Response	CT-Based Response
Complete Response	**Complete Metabolic Response**	**Complete Radiologic Response (all of the following)**
Lymph nodes and extralymphatic sites	• Score 1, 2, or 3 [a] with or without a residual mass on 5PS [b] • It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	• Target nodes/nodal masses must regress to ≤1.5 cm in LDi • No extralymphatic sites of disease
Nonmeasured lesion	• Not applicable	• Absent
Organ enlargement	• Not applicable	• Regress to normal
New lesions	• None	• None
Bone marrow	• No evidence of FDG-avid disease in marrow	• Normal by morphology; if indeterminate, IHCnegative
Partial Response	**Partial Metabolic Response**	**Partial Remission (all of the following):**
Lymph nodes and extralymphatic sites	• Score 4 or 5b with reduced uptake compared with baseline and residual mass(es) of any size • At interim, these findings suggest responding disease • At end of treatment, these findings indicate residual disease	• ≥50% decrease in SPD of up to 6 target measurable nodes and extranodal sites • When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value • When no longer visible, 0 × 0 mm • For a node >5 mm × 5 mm, but smaller than normal; use actual measurement for calculation
Nonmeasured lesions	• Not applicable	• Absent/normal, regressed, but no increase
Organ enlargement	• Not applicable	• Spleen must have regressed by >50% in length beyond normal
New lesions	• None	• None
Bone marrow	• Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan.	• Not applicable

No Response or Stable Disease	No Metabolic Response	Stable Disease
Target nodes/nodal masses, extranodal lesions	• Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	• <50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	• Not applicable	• No increase consistent with progression
Organ enlargement	• Not applicable	• No increase consistent with progression
New lesions	• None	• None
Bone marrow	• No change from baseline	• Not applicable
Progressive Disease	**Progressive Metabolic Disease**	**Progressive Disease Requires at least one of the following**
Individual target nodes/nodal masses	• Score 4 or 5 with an increase in intensity of uptake from baseline and/or	• PPD progression: any new nodal mass or increase in an existing nodal mass
Extranodal lesions	• New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	• An individual node/lesion must be abnormal with • LDi >1.5 cm and • Increase by ≥50% from PPD nadir and • An increase in LDi or SDi from nadir ○ 0.5 cm for lesions ≤2 cm ○ 1.0 cm for lesions >2 cm • In the setting of splenomegaly, the splenic length must increase by >50% of the extent of its prior increase beyond baseline (e.g., a 15 cm spleen must increase to >16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline. New or recurrent splenomegaly
Nonmeasured lesions	• None	• New or clear progression of pre-existing nonmeasured lesions

New Lesions	• New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	• Regrowth of previously resolved lesions • A new node >1.5 cm in any axis • A new extranodal site >1.0 cm in any axis; if <1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma • Assessable disease of any size unequivocally attributable to lymphoma
Bone Marrow	• New or recurrent FDG-avid foci	• New or recurrent involvement

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

a. Measured dominant lesions: up to 6 of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in 2 diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (e.g., liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (e.g., GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (e.g., with marrow activation as a result of chemotherapy or myeloid growth factors).

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

APPENDIX 7. LIST OF SENSITIVE CYTOCHROME P450 SUBSTRATES: CYP2C9, CYP2C19, CYP2D6, AND CYP3A4

Substrates can be classified by their sensitivity as:

- sensitive substrates (≥5-fold increase in AUC with a strong inhibitor of the cytochrome P450 [CYP] specified)
- moderately sensitive substrates (≥2 to <5-fold increase in AUC with a strong inhibitor of the CYP specified)

Following is a table of sensitive substrates of CYP2C9, CYP2C19, CYP2D6, and CYP3A4.

Table 23: Sensitive Substrates of CYP2C9, CYP2C19, CYP2D6, and CYP3A4

	Sensitive substrates	Moderate sensitive substrates
CYP2C9	celecoxib(c)	glimepiride, phenytoin, tolbutamide, warfarin
CYP2C19	S-mephenytoin, omeprazole	diazepam, lansoprazole(d), rabeprazole, voriconazole
CYP2D6	atomoxetine, desipramine, dextromethorphan , eliglustat(e), nebivolol, nortriptyline, perphenazine, tolterodine, venlafaxine	amitriptyline, encainide, imipramine, metoprolol, propafenone, propranolol, tramadol, trimipramine,
CYP3A4	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir(f), ebastine, everolimus, ibrutinib, lomitapide, lovastatin(g), midazolam, naloxegol, nisoldipine, saquinavir(f), simvastatin(g), sirolimus, tacrolimus, tipranavir(f), triazolam, vardenafil	alprazolam, aprepitant, atorvastatin(c), colchicine, eliglustat(e), pimozide, rilpivirine, rivaroxaban, tadalafil
	budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir(f), lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan	

Please note the following: Additional drug-drug interaction data can be obtained from the University of Washington Metabolism and Transport Drug Interaction Database [Hachad et al. (2010), Hum Genomics, 5(1):61-72].

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL

The table below includes a list of drugs known to prolong QT/QTc interval from http://medicine.iupui.edu/clinpharm/ddis/main-table/

Note: Medicines on this list must be reviewed by Principal Investigators on an ongoing basis to assure updates.

LIST OF DRUGS KNOWN TO PROLONG QT/QTc INTERVAL	
Generic Name	**Brand Names (Partial List)**
Alfuzosin	Uroxatral®
Amantadine	Symmetrel®, Symadine®
Amiodarone	Cordarone®, Pacerone®, Nexterone®
Amisulpride (Only on Non-US Market)	Solian®, Supitac®, Soltus®, Amitrex®, Amazeo®
Amitriptyline	Elavil® (Discontinued 6/13), Tryptomer®, Tryptizol®, Laroxyl®, Saroten®, Sarotex® Lentizol®, Endep®
Anagrelide	Agrylin®, Xagrid®
Apomorphine	Apokyn®, Ixense®, Spontane®, Uprima®
Aripiprazole	Abilify®, Aripiprex®
Arsenic trioxide	Trisenox®
Artenimol+piperaquine	Eurartesim®
Asenapine	Saphris®, Sycrest®
Astemizole (Removed from Market)	Hismanal®
Atazanavir	Reyataz®
Atomoxetine	Strattera®
Azithromycin	Zithromax®, Zmax®
Bedaquiline	Sirturo®
Bepridil (Removed from Market)	Vascor®
Bortezomib	Velcade®, Bortecad®
Bosutinib	Bosulif®
Ceritinib	Zykadia®
Chloral hydrate	Aquachloral®, Novo-Chlorhydrate®, Somnos®, Noctec®, Somnote®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®, Largactil®, Megaphen®
Cilostazol	Pletal®
Ciprofloxacin	Cipro®, Cipro-XR®, Neofloxin®
Cisapride (Removed from Market)	Propulsid®
Citalopram	Celexa®, Cipramil®
Clarithromycin	Biaxin®, Prevpac®
Clomipramine	Anafranil®
Clozapine	Clozaril®, Fazaclo®, Versacloz®
Cocaine	Cocaine
Crizotinib	Xalkori®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

LIST OF DRUGS KNOWN TO PROLONG QT/QTc INTERVAL	
Generic Name	**Brand Names (Partial List)**
Cyamemazine (cyamepromazine) (Only on Non-US Market)	Tercian®
Dabrafenib	Tafinlar®
Dasatinib	Sprycel®
Degarelix	Firmagon®
Delamanid (Only on Non-US Market)	Deltyba®
Desipramine	Pertofrane®, Norpramine®
Dexmedetomidine	Precedex®, Dexdor®, Dexdomitor®
Diphenhydramine	Benadryl®, Nytol®, Unisom®, Sominex®, Dimedrol®, Daedalon®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Dolasetron	Anzemet®
Domperidone (Only on Non-US Market)	Motilium®, Motillium®, Motinorm Costi®, Nomit®
Donepezil	Aricept®
Doxepin	Sinequan®, Silenor®, Aponal®, Adapine®, Doxal®, Deptran®, Sinquan®
Dronedarone	Multaq®
Droperidol	Inapsine®, Droleptan®, Dridol®, Xomolix®
Eribulin mesylate	Halaven®
Erythromycin	E.E.S.®, Robimycin®, EMycin®, Erymax®, Ery-Tab®, Eryc Ranbaxy®, Erypar®, Eryped®, Erythrocin Stearate Filmtab®, Erythrocot®, E-Base®, Erythroped®, Ilosone®, MY-E®, Pediamycin®, Zineryt®, Abboticin®, Abboticin-ES®, Erycin®, PCE Dispertab®, Stiemycine®, Acnasol®, Tiloryth®
Escitalopram	Cipralex®, Lexapro®, Nexito®, Anxiset-E® (India), Exodus® (Brazil), Esto® (Israel), Seroplex®, Elicea®, Lexamil®, Lexam®, Entact® (Greece), Losita® (Bangladesh), Reposil® (Chile), Animaxen® (Colombia), Esitalo® (Australia), Lexamil® (South Africa)
Famotidine	Pepcid®, Fluxid®, Quamatel®
Felbamate	Felbatol®
Fingolimod	Gilenya®
Flecainide	Tambocor®, Almarytm®, Apocard®, Ecrinal®, Flécaine®
Fluconazole	Diflucan®, Trican®
Fluoxetine	Prozac®, Sarafem®, Fontex®
Foscarnet	Foscavir®
Furosemide (frusemide)	Lasix®, Fusid®, Frumex®
Galantamine	Reminyl®, Nivalin®, Razadyne-ER®,
Gatifloxacin (Removed from Market)	Tequin®
Gemifloxacin	Factive®
Granisetron	Kytril®, Sancuso®, Granisol®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

LIST OF DRUGS KNOWN TO PROLONG QT/QTc INTERVAL	
Generic Name	**Brand Names (Partial List)**
Grepafloxacin	Raxar®
Halofantrine	Halfan®
Haloperidol	Haldol® (US & UK), Aloperidin®, Bioperidolo®, Brotopon®, Dozic®, Duraperidol® (Germany), Einalon S®, Eukystol®, Halosten®, Keselan®, Linton®, Peluces®, Serenace®, Serenase®, Sigaperidol®
Hydrochlorothiazide	Apo-Hydro®, Aquazide H®, BP Zide®, Dichlotride®, Hydrodiuril®, HydroSaluric®, Hydrochlorot®, Microzide®, Esidrex®, Oretic®
Hydrocodone - ER	Hysingla™ ER, Zohydro ER
Hydroxychloroquine	Plaquenil®, Quineprox®
Hydroxyzine	Atarax®, Vistaril®, Aterax®, Alamon®, Durrax®, Equipose®, Masmoran®, Orgatrax®, Paxistil® Quiess®, Tran-Q®, Tranquizine®
Ibutilide	Corvert®
Iloperidone	Fanapt®, Fanapta®, Zomaril®
Imipramine (melipramine)	Tofranil®
Indapamide	Lozol®, Natrilix®, Insig®
Isradipine	Dynacirc®
Itraconazole	Sporanox®, Onmel®
Ivabradine	Procoralan®, Coralan®, Corlentor®, Coraxan®, Ivabid®, Bradia®
Ketoconazole	Nizoral®, Sebizole®, Ketomed®, Keton®
Lapatinib	Tykerb®, Tyverb®
Lenvatinib	Lenvima®
Leuprolide	Lupron®, Eligard®, Viadur®, Carcinil®, Enanton®, Leuplin®, Lucrin®, Procren®, Prostap® and others
Levofloxacin	Levaquin®, Tavanic®
Levomepromazine (Only on Non-US Market)	Nosinan®, Nozinan®, Levoprome®
Levomethadyl (Removed from Market)	Orlaam®
Lithium	Eskalith®, Lithobid®
Mesoridazine (Removed from Market)	Serentil®
Methadone	Dolophine®, Symoron®, Amidone®, Methadose®, Physeptone®, Heptadon®
Metoclopramide	Reglan®, Afipran®, Maxolon®, Cerucal®, Clopamon®, Clopra®, Maxeran®, Maxolon®, Metozolv®, Plasil®, Pramin®, Primperan®, Perinorm®
Metronidazole	Flagyl® and many others
Mifepristone	Korlym®, Mifeprex®
Mirabegron	Myrbetriq®
Mirtazapine	Remeron
Moexipril/HCTZ	Uniretic®, Univasc®
Moxifloxacin	Avelox®, Avalox®, Avelon®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

LIST OF DRUGS KNOWN TO PROLONG QT/QTc INTERVAL	
Generic Name	**Brand Names (Partial List)**
Nelfinavir	Viracept®
Nicardipine	Cardene®
Nilotinib	Tasigna®
Norfloxacin	Noroxin®, Ambigram®
Nortriptyline	Pamelor®, Sensoval®, Aventyl®, Norpress®, Allegron®, Noritren®, Nortrilen®
Ofloxacin	Floxin®
Olanzapine	Zyprexa®, Zydis®, Relprevv®
Ondansetron	Zofran®, Anset®, Ondemet®, Zuplenz®, Emetron®, Ondavell®, Emeset®, Ondisolv®, Setronax®
Osimertinib	Tagrisso®
Oxaliplatin	Eloxatin®
Oxytocin	Pitocin®, Syntocinon®
Paliperidone	Invega®, Xepilon®
Panobinostat	Farydak®
Pantoprazole	Protonix® and others
Papaverine HCl	none
Paroxetine	Paxil®, Aropax®, Pexeva®, Seroxat®, Sereupin®
Pasireotide	Signifor®
Pazopanib	Votrient®
Pentamidine	Pentam®
Perflutren lipid microspheres	Definity®
Pimozide	Orap®
Pipamperone (Only on Non-US Market)	Dipiperon (E.U), Propitan (Japan)
Posaconazole	Noxafil®, Posamol®
Probucol (Removed from Market)	Lorelco®
Procainamide	Pronestyl®, Procan®
Promethazine	Phenergan®
Propofol	Diprivan®, Propoven®
Quetiapine	Seroquel®
Quinidine	Quinaglute®, Duraquin®, Quinact®, Quinidex®, Cin-Quin®, Quinora®
Quinine sulfate	Qualaquin®
Ranolazine	Ranexa®, Ranozex®
Rilpivirine	Edurant®, Complera®, Eviplera®
Risperidone	Risperdal®
Ritonavir	Norvir®
Roxithromycin (Only on Non-US Market)	Rulide®, Xthrocin®, Roxl-150®, Roxo®, Surlid®, Rulide®, Biaxsig®, Roxar®, Roximycinv®, Roxomycin®, Rulid®, Tirabicin®, Coroxin®

APPENDIX 8. LIST OF DRUGS KNOWN TO PROLONG QT/QTC INTERVAL (CONTINUED)

LIST OF DRUGS KNOWN TO PROLONG QT/QTc INTERVAL	
Generic Name	**Brand Names (Partial List)**
Saquinavir	Invirase®(combo)
Sertindole (Only on Non-US Market)	Serdolect®, Serlect®
Sertraline	Zoloft®, Lustral®, Daxid®, Altruline®, Besitran®, Deprax®, Elrval®, Emergen®, Gladem®, Implicane®, Sedoran®, Sealdin®, SerivoLowfin®, Stimuloton®, Tresleen®, Sertralin Bluefish®
Sevoflurane	Ulane®, Sojourn®
Solifenacin	VESIcare®
Sorafenib	Nexavar®
Sotalol	Betapace®, Sotalex®, Sotacor®
Sparfloxacin (Removed from Market)	Zagam®
Sulpiride (Only on Non-US Market)	Dogmatil®, Dolmatil®, Eglonyl®, Espiride®, Modal®, Sulpor®
Sunitinib	Sutent®
Tacrolimus	Prograf®, Prograf®, Advagraf®, Protopic®
Tamoxifen	Nolvadex®(discontinued 6/13), Istubal®, Valodex®
Telaprevir	Incivo®
Telavancin	Vibativ®
Telithromycin	Ketek®
Terfenadine (Removed from Market)	Seldane®
Tetrabenazine	Nitoman®, Xenazine®
Thioridazine	Mellaril®, Novoridazine®, Thioril®
Tizanidine	Zanaflex®, Sirdalud®
Tolterodine	Detrol®, Detrusitol®
Toremifene	Fareston®
Torsemide	Demadex®, Diuver®, Examide®
Trazodone	Desyrel® (discontinued 6/13), Oleptro®, Beneficat®, Deprax®, Desirel®, Molipaxin®, Thombran®, Trazorel®, Trialodine®, Trittico®, Mesyrel®
Trimipramine	Surmontil®, Rhotrimine®, Stangyl®
Tropisetron (Only on Non-US Market)	Navoban®, Setrovel®
Vandetanib	Caprelsa®
Vardenafil	Levitra®
Vemurafenib	Zelboraf®
Venlafaxine	Effexor®, Efexor®
Voriconazole	VFend®
Vorinostat	Zolinza®
Ziprasidone	Geodon®, Zeldox®

APPENDIX 9. MANAGEMENT OF TUMOR LYSIS SYNDROME

Prior studies with the CDK inhibitors, flavopiridol and dinaciclib have shown that these drugs can cause severe and potentially life-threatening TLS in patients with CLL. The Investigator must assess the risk of TLS for each patient based on the tumor type, extent of disease and patient factors such as comorbidities, in particular renal function, and age.

All subjects enrolled in this study, even those considered at low risk for TLS, must take prophylaxis.

Guidance for TLS risk assessment, prophylaxis, and monitoring, based on the recommendations for CLL/SLL patients in the Venclexta [US Prescribing Information] Rev 2022, are provided in Table 24. Patients with B-cell malignancies should be assessed for low, medium, or high risk for TLS, with prophylaxis and monitoring guidance as per Table 24.

Patients with AML should be assessed for low, intermediate, or high risk of TLS, as defined in Figure 3. Additional considerations, prophylaxis, and monitoring of TLS in AML patients are as follows:

- All AML subjects should have white blood cell count less than 25×10^9/L prior to initiation of venetoclax; cytoreduction (e.g., with hydroxyurea) prior to venetoclax treatment may be required if white blood cell counts greater than 25×10^9/L or lower than this cutoff but rapidly rising counts.
- Prior to first dose of venetoclax, provide all patients with prophylactic measures including adequate hydration and anti-hyperuricemic agents (see Table 24) and continue during ramp-up phase.
- Blood chemistry (potassium, uric acid, phosphorus, calcium, and creatinine) should be assessed prior to initiation of treatment with venetoclax, and pre-existing abnormalities corrected.
- Monitor blood chemistries for TLS at pre-dose, 6 to 8 hours after each new venetoclax dose during ramp-up, and 24 hours after reaching final ramp-up dose (i.e., pre-dose on Day 3 in Cohorts 12–25).
- For patients with risk factors for TLS (e.g., circulating blasts, high burden of leukemia involvement in bone marrow, elevated pretreatment lactate dehydrogenase [LDH] levels, or reduced renal function), consider additional measures, including increased laboratory monitoring.

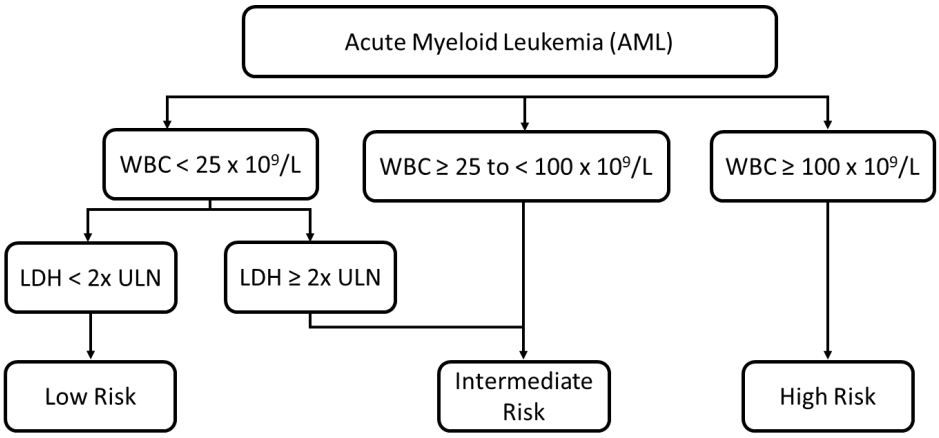
Table 24: Guidelines for Prophylaxis and Monitoring for Patients with CLL/SLL and other B-cell Malignancies at Risk of TLS

RISK	Tumor/CLL Leukemic Burden	Prophylaxis		Hospital setting and biochemical monitoring
		Hydration	Anti-hyperuricemic therapy	
LOW	All LN <5cm **AND** ALC <25 × 10^9/L	Oral 1.5 – 2.0 L	Allopurinol starting ≥2 days before treatment	Outpatient • TLS blood panel monitoring* For each new dose: o pre-first dose; 6 to 8 hr, and 24 hr After reaching final ramp up dose: o pre-dose only
MEDIUM	ANY LN 5 to <10 cm **OR** ALC ≥25 × 10^9/L	Oral 1.5 – 2.0 L and consider intravenous (150 to 200 mL/hr)	Allopurinol starting ≥2 days before treatment	Outpatient, but consider hospitalization based on age or renal function (creatinine clearance <80 ml/min) • TLS blood panel monitoring* o pre-first dose; 6 to 8 hr, and 24 hr o for subsequent ramp-up doses: pre-dose
HIGH	ANY LN ≥10 cm **OR** ALC ≥25 × 10^9/L **AND** any LN ≥10 cm	Oral 1.5 – 2.0 L and intravenous (150 to 200 ml/hr)	Allopurinol starting ≥2 days before treatment or consider rasburicase if baseline uric acid above ULN	Inpatient for 24 hours post first dose • TLS blood panel monitoring* o pre-first dose; 6 to 8 hr, and 24 hr Outpatient o for subsequent ramp-up doses: pre-dose; 6 to 8 hr, and 24 hr

Abbreviations: ALC = absolute lymphocyte count; LN = lymph node; TLS = tumor lysis syndrome; ULN = upper limit of normal.
*Sampling timepoints ±30 minute window permitted.

TLS blood chemistry panel must include potassium, uric acid, phosphorus, calcium, and creatinine.

Figure 3: TLS Risk Assessment for AML



TLS risk assessment for acute leukemia. Classification of acute myeloid leukemia depends on white blood cell (WBC) counts and relative lactate dehydrogenase (LDH) levels to upper limit of normal (ULN) (adapted from Cairo 2010).

APPENDIX 10. CAIRO-BISHOP CRITERIA FOR DIAGNOSIS OF TUMOR LYSIS SYNDROME

For a diagnosis of laboratory tumor lysis syndrome (TLS), 2 or more of the metabolic abnormalities shown in Table 25 must be present during the same 24-hour period within 3 days before the start of therapy, or up to 7 days after. Clinical TLS requires the presence of laboratory TLS plus an increased creatinine, seizures, cardiac dysrhythmia, or death.

Table 25: Definitions of Laboratory and Clinical Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Laboratory TLS	Criteria for Classification of Clinical TLS
Hyperuricemia	Uric acid >8.0 mg/dL (475.8 µmol/L) in adults or above the ULN for age in children	
Hyperphosphatemia	Adults: phosphorus >4.5 mg/dL (1.5 µmol/L) Children: phosphorus >6.5 mg/dL (2.1 µmol/L)	
Hyperkalemia	Potassium >6.0 mmol/L	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 (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 serum creatinine level of 0.3 mg/dL (26.5 µmol/L) (or single value >1.5 times the ULN of the age-appropriate range if no baseline creatinine measure is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hr

Abbreviations: hr = hour; TLS = tumor lysis syndrome; ULN = upper limit of normal.

[a] The corrected calcium level in mg/dL = measured calcium level in mg/dL + 0.8 × (4 – albumin 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 hr or more. By definition, if acute kidney injury is present, the patient has clinical TLS. See Levin et al for data about acute kidney injury.

Reference: Howard 2011.

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Signature Page for VV-CLIN-000078 v14.0