STATISTICAL ANALYSIS PLAN

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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SIGNATURE PAGE

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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TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABBREVIATION	DEFINITION
AE	Adverse event
AML	Acute myeloid leukemia
ATC	Anatomical Therapeutic Classification
CBC	Complete blood count
CI	Confidence interval
CDK9	Cyclin-dependent kinase 9
CLL	Chronic Lymphocytic Leukemia
CR	Complete response
CRF	Case report form
CRi	Complete remission with incomplete marrow recovery
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of response
DOT	Duration of treatment
DLBCL	Diffuse Large B-cell Lymphoma
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELN	European Leukemia Net
EOS	End of Study
FDG	Fluorodeoxyglucose
FL	Follicular Lymphoma
IgVH	Immunoglobulin g heavy chain variable region
IP	Investigational product
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
IWCLL	International workshop on CLL
mBED	Minimum biologically effective dose
MCL	Mantle Cell Lymphoma
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
MZL	Marginal Zone Lymphoma
NCI	National cancer institute
ORR	Overall response rate
PD	Progressive disease
PFS	Progression-free survival

ABBREVIATION	DEFINITION
PR	Partial response
PT	Preferred term
QTcF	QT corrected by Fridericia's formula
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SLL	Small Lymphocytic Lymphoma
SOC	System organ class
SPD	Sum of the product of the perpendicular diameters
SRC	Study Review Committee
TEAE	Treatment-emergent adverse event
TFLs	Tables, figures, and listings
TLS	Tumor Lysis Syndrome
WHO	World Health Organization

1. INTRODUCTION

This Statistical Analysis Plan (SAP) is created based on Protocol ME-522-001 (Original version, 05 December 2017, Amendment 1, 02 January 2018, Amendment 2, 15 August 2018, Amendment 3, 22 October 2018, Amendment 5, 28 January 2019, Amendment 7, 06 January 2020, and Amendment 11, 17 June 2022) and it describes in detail the statistical methodology and the statistical analyses to be conducted for the aforementioned protocol. The mockup shells of the Tables, Figures, and Listings (TFLs) for the statistical analysis will be described in a stand-alone programming specification document, which will be finalized before the database lock.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are as follows:

- 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 acute myeloid leukemia (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

The secondary objectives of the study are as follows:

- Evaluate the potential efficacy of voruciclib monotherapy based on:
  - International Workshop on Chronic Lymphocytic Leukemia (IWCLL) criteria for CLL/SLL or the Lugano classification of response assessment for lymphoma, as appropriate, for subjects with B-cell malignancies
  - The 2017 European LeukemiaNet (ELN) criteria for subjects with AML
- 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

2.3 Exploratory Objectives

The exploratory objectives of the study are as follows:

- 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. STUDY DESIGN

3.1 General Study Design and Plan

3.1.1 Overall Study Design

This is a Phase 1, open-label, 3 + 3 dose escalation study to determine the safety and preliminary efficacy of the cyclin-dependent kinase 9 (CDK9) selective inhibitor voruciclib in subjects with relapsed/refractory B cell malignancies and AML, and in combination with venetoclax in subjects with relapsed/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 dose limiting toxicities (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.

Voruciclib will be administered once daily in 28-day cycles, with the first day of treatment designated as Day 1. 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 DLT at 100 mg QD, intermittent dosing regimens are being studied at 100, 150, or 200 mg on an intermittent schedule (IS) of two weeks on therapy followed by two weeks off therapy ($IS_{2w,2w}$) or an IS of one week on therapy followed by three weeks off therapy ($IS_{1w,3w}$). The previously planned maximum daily dose of 250 mg was based on data from previous clinical studies which indicate that the dose is tolerated (less than the previously identified MTD of 350 mg daily).

Dose cohorts planned prior to Amendment 7 are defined in Table 3-1:

Table 3-1 Voruciclib Dose Escalation Levels Prior to Amendment 7

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

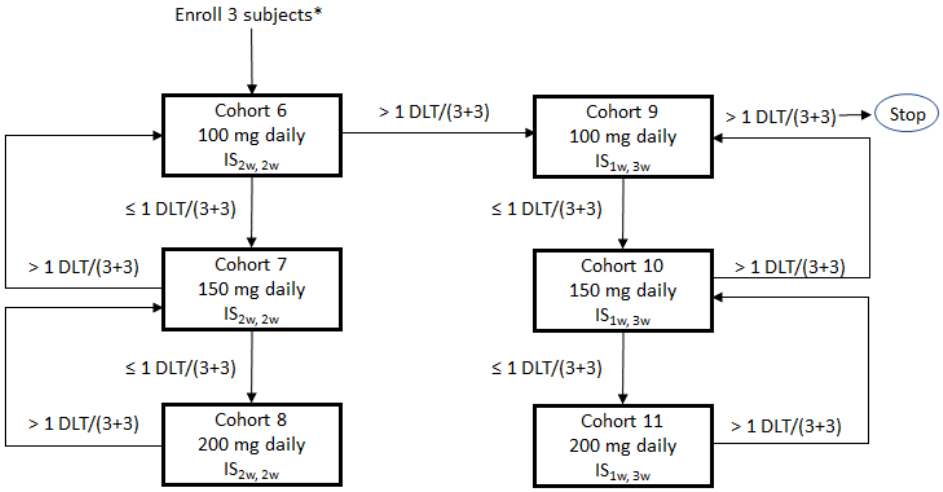
As of Amendment 7, dosing will be modified to test the safety and efficacy of voruciclib administered on an IS. Because the mBED and the recommended phase 2 dose (RP2D) will be assessed independently for subjects with AML and B-cell malignancies, dose and regimen evaluations will be conducted in each of these disease groups separately by opening the next cohort in each disease group as determined by the Study Review Committee (SRC). In order to differentiate disease-specific cohorts, subjects with AML will be designated as Cohorts 6**a**-11**a**, and subjects with B-cell malignancies will be designated as Cohorts 6**b**-11**b** (see Table 3-2).

Table 3-2 Voruciclib Dose Escalation Levels in Amendment 7

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

The dose escalation scheme for IS is detailed in Figure 3-2. The total number of cohorts will depend upon the incidence of DLTs.

Figure 3-1 Dose Escalation 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**.
Once the RP2D has been declared in AML group, an expansion cohort of 12 subjects will be enrolled to further characterize the Safety and efficacy of this dose and schedule in AML.

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 higher

dose level will depend on demonstrated safety, tolerability and DLT as defined in the study protocol (Section 4.4) and after approval by the SRC.

Subjects may continue to receive voruciclib while there is evidence of clinical benefit and acceptable toxicity as judged by the Investigator. 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.

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.

As of 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.

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 defined in Table 3-3:

Table 3-3 Cohorts with Combination Voruciclib + Venetoclax in Amendment 12

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
20	voruciclib 150 mg QD, administered $IS_{3w,1w}$ + venetoclax administered QD × 28 days

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, 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. The 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.

3.1.2 Maximum Tolerated Dose (MTD), Minimum Biologically Effective Dose (mBED) and Recommended Phase 2 Dose (RP2D)

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.

The study may not be sufficient to determine the RP2D and schedule of voruciclib therapy in hematologic malignancies. It will evaluate the safety, efficacy, and the safe and mBED of voruciclib therapy. 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 for monotherapy, and may be the same or lower than the MTD.

3.1.3 Dose Expansion Plan

Once the safe and mBED of voruciclib has been declared in the group of subjects with AML of voruciclib monotherapy and/or voruciclib + venetoclax combination therapy, an expansion cohort of 6 subjects with AML of voruciclib monotherapy, or an expansion cohort of 12 subjects with AML of voruciclib + venetoclax combination therapy, will be enrolled to further characterize the safety, efficacy, PK and effect on biomarkers of this dose level and schedule in AML.

To date, there is no plan to open a dose expansion cohort in B-cell malignancies.

3.1.4 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 a DLT, must receive at least 75% of the total planned dose in Cycle 1 to be assessed for a 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.

The data collected from subjects being replaced will be analyzed according to the analysis population(s) they belong to. Analysis population(s) are defined in Chapter 6.

3.1.5 Dose Modifications

Details are provided in the Dose Modification Schedule in the study protocol (Section 4.8), which is intended as a guideline since the final decision about a 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.

3.1.6 Discontinuation of Voruciclib Administration

Subjects may continue to receive voruciclib for up to 19 cycles (approximately 18 months). After this period, if there is continuing evidence of clinical benefit and acceptable toxicity as judged by the Investigator, following discussion with the Medical Monitor, the subject may be allowed to receive additional cycles. Subjects may discontinue voruciclib 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

3.2 Study Centers

This is a multi-center study and will include approximately 10-16 sites in the United States (US).

3.3 Study Population

The study population consists of subjects with relapsed/refractory B cell malignancies, including 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 acute myeloid leukemia (AML).

Specific inclusion and exclusion criteria are specified in Sections 3.1 and 3.2, respectively, of the study protocol.

3.4 Study Treatment

Voruciclib will be administered once daily either daily continuously or intermittently on dosing days of either $IS_{2w,2w}$ or $IS_{1w,3w}$, in 28-day cycles, with the first day of treatment designated as Day 1. For cohort 12 of voruciclib + venetoclax combination therapy, 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.

Voruciclib is provided as 50 and 100 mg capsules and 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. For 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. A missed dose may be taken up to 12 hours after the usual time. After 12 hours the dose will be omitted.

3.5 Study Duration

The study consists of a screening period, a treatment period, and an End-of-Study (EOS) visit. Screening assessments are to be performed within 28 days of the first dose of study drugMoreover, the treatment phase begins on the first day of study drug administration, continues through the last day of administration, and will be tracked by 28-day periods identified by a numerical cycle (e.g., Cycle 1, Cycle 2…). Response assessments will be performed according to the Schedule of Assessments (Appendices 1, 2and 3 of the protocol). Finally, the EOS visit will occur 30 days from the last day of study drug administration (or prior to starting a new treatment if urgent treatment is required).

3.6 Randomization and Blinding

Not applicable.

3.7 Study Assessments

For the detailed schedule of expected events and study procedures to be conducted at each visit, please refer to Appendices 1, 2, and 3 (Schedule of Assessments), 4 (AML Response Criteria), 5 (CLL/SLL Response Criteria)and 6 (FL Response Criteria) in the protocol.

4. SAMPLE SIZE DETERMINATION

The MTD will be determined employing a standard 3 + 3 design. For voruciclib monotherapy, because enrollment will be conducted independently in subjects with AML and B-cell malignancies, within each disease group, dose and regimen changes will follow the 3 + 3 design, summarized below. Initially, 3 subjects will be enrolled at the lowest dose level in $IS_{2w,2w}$ in each disease group:

- If 0 of 3 subjects experience a DLT during Cycle 1, another 3 subjects will be enrolled at the next higher dose level.
- If > 1 of 3 subjects have a DLT during Cycle 1, this dose level will be declared as not safe, further dose escalation on the $IS_{2w,2w}$ regimen will not proceed, and $IS_{1w,3w}$ evaluating a less intensive dose regimen will be studied.
- If 1 of 3 subjects experiences a DLT during Cycle 1, an additional 3 subjects will be enrolled at the same dose level, with dose escalation permitted only if there are no additional DLTs.
- If > 1 of 3 subjects experience a DLT (in all but the lowest dose level) during Cycle 1, the next lower dose level within the IS will enroll an additional 3 subjects (for a total of 6 subjects).*
    - If ≤ 1 of 6 subjects experience a DLT during Cycle 1, this dose level will be declared the MTD.
    - If > 1 of 6 subjects experience a DLT (in all but the lowest dose level) during Cycle 1, the next lower dose level within the IS will enroll an additional 3 subjects.*

*Within each disease group in a dose cohort, if the next lower dose regimen had previously enrolled 6 subjects, then the lower dose regimen will be declared the MTD.

For voruciclib + venetoclax combination therapy in AML, the same standard 3 + 3 design will be followed for voruciclib dose escalation on the $IS_{2w,2w}$ regimen.

At the start of Amendment 11, a total of 33 subjects have been enrolled in Cohorts 1, 2, 6a, 6b, 7a, 7b and 8a; the AML monotherapy expansion cohort enrolled 6 subjects. Assuming an average enrollment of 4 subjects per dose cohort for DLT evaluation, up to 12 subjects to be enrolled in the combination AML expansion cohort, and an additional 20% 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 initial dose/regimen escalation phase is estimated to be approximately 100 subjects for monotherapy (AML and B-cell malignancies), combination therapy (AML) and expansion cohorts.

5. STUDY ENDPOINTS

5.1 Efficacy Endpoints

5.1.1 Primary Efficacy Endpoint

Not applicable.

5.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints (within each tumor type: AML and B cell malignancies) are as follows:

- 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
- Estimates of the exposure and association with efficacy variables for voruciclib administered as monotherapy, and for voruciclib and venetoclax when administered in combination
- Duration of Response (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. DOR will be calculated as follows for subjects who have a best overall response of CR/CRi or PR:

  DOR (months) = (Progression/Censoring Date – Response Start Date + 1) / 30.4375

  Subjects meeting at least one of the following criteria will be right-censored for DOR:
  - death due to any cause prior to disease progression
  - subsequent anticancer therapy without documented disease progression
  - alive and without documented disease progression on or before the EOS visit

  If a subject meets more than one of these criteria, then the scenario that occurs first will be used for the analysis. The progression or censoring date will be determined based on the conventions listed in Table 5-1.

Table 5-1: Date of Progression or Censoring for DOR

Situation	Date of progression or censoring	Outcome
Disease progression or death	Date of death or date of disease assessment (planned or unplanned)	Event

	showing disease progression, whichever occurs first	
Subsequent anticancer treatment started before the first disease progression	Date of last disease assessment prior to the subsequent anticancer treatment	Censored
Alive and without disease progression on or before the EOS visit	Date of last disease assessment	Censored

- Progression-Free Survival (PFS) defined as time from first dose of study drug to date of documented disease progression or death due to any cause. PFS will be calculated as follows:

  PFS (months) = (Event/Censoring Date – Date of the First Dose + 1) / 30.4375

  PFS will be right-censored for subjects who met one or more of the following conditions:

  - subsequent anticancer therapy in the absence of documented disease progression
  - alive and without documented disease progression on or before the EOS visit

  If a subject meets more than one of these conditions, then the scenario that occurs first will be used to determine PFS. The event or censoring date will be determined based on the conventions listed in Table 5-2:

Table 5-2: Date of Progression or Censoring for PFS

Situation	Date of progression or censoring	Outcome
Death or disease progression	Date of death or first disease assessment (planned or unplanned) showing disease progression, whichever occurs first	Event
No evaluable disease assessments	Date of the first dose	Censored
Subsequent anticancer treatment started before the first documented disease progression or death	Date of last disease assessment prior to the subsequent anticancer treatment	Censored
Alive and without disease progression on or before EOS visit	Date of last disease assessment	Censored

5.2 Safety Endpoints

The protocol-defined safety endpoints are the incidence of AEs and the incidence of DLTs.The AEs will be coded using MedDRA version 24.1 and be graded by NCI CTCAE v5.0.

Standard safety assessments for oncology trials such as SAEs, clinical laboratory safety tests including hematology (complete blood count [CBC]), serum chemistry, physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, and 12-lead electrocardiogram (ECG) will be conducted and summarized.

5.3 Pharmacokinetics of Voruciclib in Monotherapy as well as Voruciclib and Venetoclax in Combination Therapy

In monotherapy, plasma concentration of voruciclib will be assayed pre- and post-dose of voruciclib as detailed in Section 9.14.1 in the protocol. In combination therapy, the pharmacokinetics of both voruciclib and venetoclax will be assayed as detailed in Section 9.14.2 in the protocol..

5.4 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, as detailed in Section 9.15 in the protocol.

5.5 Exploratory Endpoints

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

6. ANALYSIS POPULATION

6.1 Safety Evaluable Set

The Safety Evaluable Set will consist of all enrolled subjects who received any dose of study drug. Analyses pertinent to safety will be conducted on the Safety Evaluable Set.

6.2 DLT Evaluable Set

The DLT Evaluable Set will comprise all subjects in the Safety Evaluable Set who completed the first cycle of treatment (defined as taking at least 75% of the prescribed dose during Cycle 1; for Cohort 12, subjects must receive 100% of Cycle 1 doses (i.e., all 6 doses)) or experienced a DLT during the first cycle of treatment. Subjects who discontinue study therapy prior to completing Cycle 1 (Day 28) for reasons other than the development of a DLT will be replaced. Also, subjects with no DLT who fail to take at least 75% of the planned Cycle 1 voruciclib dose will be replaced; for Cohort 12, subjects with no DLT who fail to receive 100% of Cycle 1 voruciclib doses will be replaced.

The DLT rate will be computed based on subjects in the DLT Evaluable Set.

6.3 Efficacy Evaluable Set

The Efficacy Evaluable Set 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 Efficacy Evaluable Set will be utilized for the analyses of efficacy.

6.4 Pharmacokinetics (PK) Set

The PK Set 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.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1 Definition of Study Day

Study day will be calculated in reference to the first dose date of study drug as follows:

- Assessment/event date – first dose date of study drug + 1, if assessment/event date is on or after the first dose date;
- Assessment/event date – first dose date of study drug, if assessment/event date is before the first dose date.

Under the convention specified above, there will be no Study Day 0.

7.2 Baseline Definition

Baseline value for any given parameter is defined as the last assessment obtained prior to the first dose of study drug.

7.3 Unscheduled Visits

In general, by-visit summaries will be presented by the scheduled visits (visit number and corresponding visit name of planned clinical encounter). Visit windowing will not be used for handling unscheduled visits. Although unscheduled visits will not be included in by-visit summaries, they will be presented in data listings and will contribute to the derivation of best or worst-case values where required.

7.4 Handling of Missing Data

Missing/Partial Dates:

- In cases of incomplete dates (e.g., AE and concomitant medications), the missing components(s) will be assumed as the most conservative value possible. The detailed methods for handling conventions for treatment-emergent adverse events and concomitant medications derivations are specified below.

	Missing	Imputation	Exception
Start date (AE, concomitant medication)	Day	01	Default to Study Day 1 if an event starts the same year and month as Study Day 1 **(and end date is after first dose of IP or conmed/AE is ongoing/not resolved)**

	Day/Month	01JAN	Default to Study Day 1 if an event starts the same year as Day1 **(and end date is after first dose of IP or conmed/AE is ongoing/not resolved)**
Stop date (concomitant medication **only**)	Day	Last day of the month	Default to the End of Study Date or the primary analysis cut-off date for ongoing subjects if the concomitant medication stops the same year and month as the End of Study Date or primary analysis cut-off date for ongoing subjects respectively
	Day/Month	31DEC	Default to the End of Study Date or the primary analysis cut-off date (for ongoing subjects) if the concomitant medication stops the same year as the End of Study Date or primary analysis cut-off date for ongoing subjects respectively

- Time from initial diagnosis (months) is calculated as (date of first dose of study drug - date of initial diagnosis + 1)/ 30.4375. If the month and year of the diagnosis are provided but the day is missing, the missing day is imputed as 01. If only the year is provided, then the missing month and day are imputed as Jan 01 for the calculation.If year is missing, put the date to missing.
- Actual data values as they appear in the original case report forms (CRFs) will be presented in the data listings.

Other Missing Values: Missing values for other individual data points will remain as missing unless otherwise specified. Missing values will not be assumed/imputed and only observed values will be used in data analyses and presentations unless otherwise stated.

7.5 Handling of Data after Discontinuation of Treatment

If the subjects were not withdrawn from the study, the safety data collected after discontinuation of treatment will be reported unless specified otherwise, and AEs will be followed per protocol Section 6.

7.6 Handling of Data from Subjects Undergone Dose Modifications

Data from all enrolled subjects will be reported by the original cohort assignment at enrollment unless otherwise specified. For subjects who underwent dose modifications, results will be reported based on the initial dose level.

7.7 Presentation of Efficacy and Safety Results

Analytical results of efficacy will be reported overall and by tumor type (AML and B-cell malignancies) as well as by treatment regimen (monotherapy and combination therapy) as applicable, whereas safety results will be reported overall and by dose cohort, unless otherwise specified.

7.8 Multicenter Studies

Data will be pooled from all centers prior to analysis. Adjustments for different centers will not be performed.

7.9 Multiple Comparisons/Multiplicity

The study is considered exploratory. Thus, the issue of multiplicity will not be addressed for statistical inferences.

7.10 Data Monitoring

The Study Review Committee (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 accumulating safety data and advise if enrollment needs to be held at any time in a dose cohort for further safety evaluation.

8. STATISTICAL ANALYSIS

Descriptive statistics for continuous data will include the number of observations (n), mean, standard deviation, median, minimum, first and third quartiles, and maximum. For discrete variables, descriptive analyses will be based on estimates of the number of subjects and related percentages. Unless otherwise stated, confidence intervals, when presented, are 2-sided with 95% confidence level.

All analyses will be performed using SAS® Version 9.4 (SAS Institute Inc., Cary NC).

8.1 Subject Disposition

Subject disposition will be summarized for each dose cohort by tumor type, treatment regimen and in total for all enrolled subjects. In addition, subject disposition will be tabulated by tumor type and in total. The following categories of subject disposition will be included:

- Subjects who were enrolled
- Subjects who were treated
- Subjects who discontinued from the study
- Subjects who completed the study and were still alive at EOS visit

For subjects who discontinued from the study, the primary reason for ending the study will be summarized. Additionally, on-study deaths (defined as deaths during treatment period or within 30 days of treatment discontinuation) will be presented. The number and percentage of subjects in each defined analysis population will be tabulated as appropriate.

All deaths that occur on study will be reported in a subject listing, which will include the primary cause of death and the number of days between the date of the first (and last) dose of study drug and death.

All subject disposition data will be presented in a data listing.

8.2 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized descriptively by tumor type, treatment regimen and in total based on the Safety Evaluable Set and the Efficacy Evaluable Set as appropriate. Sex, race, ethnicity, age group (< 65 years and ≥ 65 years), and baseline ECOG performance status will be summarized with contingency tables. Age at informed consent (years) and baseline weight will be presented with descriptive statistics.

Time from initial diagnosis of primary disease presented at enrollment (months) and the number of prior anti-cancer therapies (regimens) will be summarized using descriptive statistics.

Moreover, for subjects of B-Cell malignancy, DLBCL type (subjects with DLBCL only), status from last treatment of the primary disease (relapsed or refractory), status of tumor FDG avidity, nodal site involvement, cancer type (unilateral or bilateral), extranodal site involvement, TLS risk category, IgVH mutation status (subjects with CLL or SLL only), and interphase cytogenetic abnormality (subjects with CLL or SLL only) will be summarized to show the number and percentage of subjects in each category; for subjects of AML, status from last treatment of the primary disease (relapsed, refractory having received 2 lines of therapy, induction and salvage, relapsed from hematopoietic stem cell transplant), WHO classification (2016) if applicable, and 2017 ELN genetic risk criteria, will be summarized to show the number and percentage of subjects in each category, by treatment regimen (monotherapy and combination therapy) and in total.

At the same time, the number and percentage of subjects who had undergone prior cancer surgery, prior radiation therapy, prior transplants (and type of transplants), prior anti-cancer therapy (and best response to therapy) will be tabulated by tumor type and in total.

Information of subject-level demographic and baseline disease characteristics will be presented as data listings.

8.3 Medical and Surgical History

Medical history will be coded using MedDRA Version 24.1

All data of medical history will be listed by subject.

8.4 Prior and Concomitant Medications

Prior and concomitant medications as well as prior anti-cancer therapies will be coded using WHO-DDE B3 (March 2018). Prior medications/therapies include those that were taken prior to and stopped before the first dose of the study drug. Concomitant medications include the ones taken on or after the first dose date of the study drug. Prior and concomitant medications will be tabulated by Anatomical Therapeutic Classification (ATC) and preferred term (PT) by tumor type, treatment regimen and in total for the Safety Evaluable Set.

The subject-level data listings for prior and concomitant medications as well as prior anti-cancer therapies will be presented.

8.5 Dosing Status and Duration of Treatment

The number and percentage of subjects who experienced dose adjustments (dose interruption, dose reduction, dose increase, or dose re-escalation), of subjects with missed doses, and of subjects who discontinued voruciclib will be tabulated for each dose cohort and in total by disease group. Reasons for dose modification will also be similarly tabulated.

Duration of treatment (DOT) will be summarized descriptively by dose cohort and in total. Additionally, the swimmer plot of DOT will be generated and grouped by dose cohort and tumor type. For subjects who either completed or discontinued the treatment by the EOS visit, DOT will be calculated as follows:

DOT (months) = (Last Dose Date – First Dose Date + 1) / 30.4375

All source data regarding study drug administration and study drug accountability log will be presented by subject-level data listings.

8.6 Efficacy Analyses

8.6.1 Primary Efficacy Analysis

Not applicable.

8.6.2 Secondary Efficacy Analysis

The secondary efficacy endpoints include the following:

- 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
- Estimates of the exposure and association with efficacy variables for voruciclib administered as monotherapy, and for voruciclib and venetoclax when administered in combination
- Duration of Response (DOR) defined as the time from first achieving a response to date of documented disease progression or death from any cause
- Progression-Free Survival (PFS) defined as time from first dose of study drug to date of documented disease progression or death due to any cause

The efficacy analyses will be conducted on the Efficacy Evaluable Set.

8.6.2.1 Overall Response Rate (ORR) and Rate of CR/CRi

ORR will be derived by calculating the proportion of subjects with best response of CR/CRi or PR by tumor type, treatment regimen and in total. Tumor responses will be determined by

the Investigator per International workshop on CLL guidelines (Hallek et al. 2008; see Appendix 4 in protocol) for CLL and SLL cancer type, by Lugano criteria (Cheson et al. 2014; see Appendix 5 in protocol) for the other Non-Hodgkin Lymphoma cancer types and by the 2017 ELN criteria for AML (Döhner 2017; see Appendix 4 in protocol). The procedure and requirement to confirm the CR/CRi or PR response will be followed per aforementioned guidelines and study protocol as well. The point estimate of ORR will be accompanied by 95% exact binomial confidence interval (CI) using the Clopper-Pearson method. Rate of CR/CRi will be summarized in the same manner as for ORR.

For subjects with measurable solid tumors, sum of the product of perpendicular diameters (SPD) will be computed by summing the products of the maximum diameter of a tumor and the largest diameter perpendicular to this maximum diameter (across all individual tumors). The baseline and the minimum post-baseline values of SPD as well as the best percentage change in the SPD from baseline will be calculated for subjects with measurable solid tumors. Waterfall plots will be used to depict graphically, grouped by tumor type, for individual subjects of their best percentage change from baseline with regards to SPD in target lesions.

All tumor assessment data (including liver/spleen assessment, target lesions, non-target lesions, and overall response assessment) will be listed by subject.

8.6.2.2 Duration of Response (DOR) and Progression-Free Survival (PFS)

Time-to-event endpoints including DOR and PFS will be summarized descriptively using the Kaplan-Meier method. The Kaplan-Meier estimates of the median DOR and PFS and the corresponding 2-sided 95% confidence intervals, calculated using the method of Brookmeyer and Crowley, will be presented by tumor type, treatment regimen and in total. Also, the Kaplan-Meier estimates of ongoing response rate and PFS rate along with the corresponding 2-sided 95% confidence intervals will also be provided by 3 months intervals (3, 6, 9 months, etc.), split by tumor type, treatment regimen and for overall. Plots of the Kaplan-Meier estimate of the survival function over time for ongoing response rate and PFS rate will be generated with number of subjects at risk noted by 3 months intervals, grouped by tumor type and treatment regimen. Similar analyses may be repeated for ongoing response rate but split by response type (CR/CRi versus PR) instead of tumor type for assessing difference in median relapsed time and/or ongoing response rate (by 3 months intervals) between complete and partial responders.

8.7 Safety Analyses

Safety will be assessed and relevant parameters will include AEs, serious adverse events (SAEs), laboratory safety tests including hematology (complete blood count [CBC]), serum chemistry; physical examination; vital signs; Eastern Cooperative Oncology Group (ECOG) performance status; and 12-lead electrocardiogram (ECG).

Safety analyses in general will be presented in tabular format with the appropriate summary statistics. Tabulations will be provided by dose cohort for the escalation part and the expansion part, by tumor type, and in total.

All safety analyses will be performed based on Safety Evaluable Set.

8.7.1 Dose Limiting Toxicities (DLT)

The number of DLTs identified among the DLT Evaluable Set will be listed and summarized for each dose cohort by the DLT criteria, and by the worst CTCAE grade v5.0, system organ class (SOC), and preferred term (PT).

8.7.2 Adverse Events (AE)

An AE is any untoward medical event that occurs to a subject following the start of study drug administration, 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 study drug administration. Adverse events will be captured from the first dose of study drug and continue until 30 days after the last dose, or until a subsequent anti-cancer therapy is initiated if this occurs earlier than 30 days after the last study drug dose.

Treatment-emergent adverse events (TEAEs) are defined identically as AEs in this study.

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 hospitalizations 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 study drug.

All deaths within 30 days of the last dose of study drug that are an outcome of an AE should be reported. Deaths due to disease progression should be reported as such and not as SAEs..

An overview of AEs will be provided by dose cohort, disease group and in total, summarizing subject incidence of the following information:

- Any TEAEs
- Drug-related TEAEs
- CTCAE grade ≥3 TEAEs
- Drug-related CTCAE grade ≥3 TEAEs
- Deaths due to AEs
- Treatment-emergent SAEs
- Drug-related treatment-emergent SAEs

- Dose interruption due to TEAEs
- Dose interruption due to drug-related TEAEs
- Dose reduction due to TEAEs
- Dose reduction due to drug-related TEAEs
- Discontinuation of study drug due to TEAEs
- Discontinuation of study drug due to drug-related TEAEs

The number and percentage of subjects with TEAEs and Grade 3/4/5 TEAEs will be summarized for each dose cohort, tumor type, and in total by SOC and PT. For these summaries, subjects with multiple adverse events will be counted only once per SOC and PT.

Additionally, the number and percentage of subjects with TEAEs will also be summarized by PT for each dose cohort, tumor type, and in total. Drug-related TEAEs, treatment-emergent SAEs, drug-related treatment-emergent SAEs, TEAEs leading to discontinuation of study drug, drug-related TEAEs leading to discontinuation of study drug, TEAEs leading to dose reduction/interruption of study drug, and drug-related TEAEs leading to dose reduction/interruption of study drug will be summarized in the same manner. For these summaries, subjects with multiple adverse events will be counted only once per PT.

Summaries will be provided by the worst CTCAE grade and PT for the number and percentage of subjects with TEAEs and drug-related TEAEs. Subjects with multiple adverse events will be counted only once by the highest CTCAE grade within a PT.

Furthermore, Tumor Lysis Syndrome (TLS) is considered AEs of special interest. The frequency and percentage of laboratory and clinical TLS (determined by Modified Cairo-Bishop criteria described in Appendix 10 of the protocol) will be tabulated by dose cohort, tumor type, and in total.

Listings will be provided for DLTs, SAEs, grade 3/4/5 AEs, AEs leading to dose reduction, AEs leading to dose interruption, AEs leading to discontinuation, and AEs leading to death. Additional listings may be provided for selected AEs of special interest. Moreover, a by-subject AE data listing including, but not limited to, verbatim, PT, SOC, CTCAE grade, action taken with voruciclib, and relationship to voruciclib will be provided.

8.7.3 Clinical Laboratory Tests

Descriptive statistics will be provided for selected clinical laboratory test results (hematology, chemistry) and changes from baseline for each scheduled measurement day, the minimum or maximum post-baseline value as appropriate. Both scheduled and unscheduled post-baseline values will be included for the derivation of minimum/maximum post-baseline values.

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. For analyses without a toxicity grading scale, the shift table will present directional shifts from baseline to above or below the

laboratory standard normal range using the maximum increase and/or decrease observed throughout the course of treatment/observation. Both scheduled and unscheduled post-baseline values will be considered for maximum increase and/or decrease observed.

In addition, the number and percentage of subjects with treatment-emergent laboratory abnormalities (any grade and grade ≥ 3) will be presented for hematology and chemistry laboratory parameters if applicable. Treatment-emergent laboratory abnormalities are defined as post baseline laboratory abnormalities with worsening CTCAE grade from baseline. Post-baseline laboratory abnormality with unknown baseline grade will be considered as treatment-emergent.

All clinical laboratory data will be listed by subject using the International System of units (SI units). Values outside the normal ranges will be flagged.

8.7.4 Vital Signs

Descriptive statistics will be provided for the vital signs measurements (systolic blood pressure, diastolic blood pressure, heart rate, body temperature, and body weight) and changes from baseline for each scheduled measurement day, the minimum post-baseline value, and the maximum post-baseline value. Both scheduled and unscheduled post-baseline values will be considered for the derivation of minimum/maximum post-baseline value.

For systolic blood pressure and diastolic blood pressure, the clinical findings (normal, abnormal but not clinically significant, abnormal and clinically significant) will be tabulated for each scheduled measurement day and for the worst post-baseline assessment, by dose cohort and in total.

All vital sign measurements will be listed by subject.

8.7.5 12-Lead Electrocardiogram (ECG)

Electrocardiogram parameters (PR, RR, QRS, QT, and QTcF) will be summarized using descriptive statistics by dose cohort and in total. The arithmetic average of the 3 ECG interval durations from the triplicate will be calculated and treated as a single observation for the descriptive summaries.

Descriptive statistics will be provided for actual values (averages of triplicate) and for change from baseline for each scheduled measurement day, the minimum post-baseline value, and the maximum post-baseline value. Both scheduled and unscheduled post-baseline values will be considered for the derivations of minimum/maximum post-baseline values.

Frederica's correction to the reported QT interval, QTcF, will be derived (in milliseconds) for all subjects and time points as follows:

$$\text{QTcF (msec)} = \frac{\text{QT(msec)}}{\sqrt[3]{\text{RR(msec)}/1000}}$$

All components for these calculations must be taken from the same assessment, which will be identified in the database by the date-time of the ECG recording.

The number and percentage of subjects with elevated QTcF over the post-baseline period will be presented for the following categories: QTcF worsening to >450 msec, >480 msec, and >500 msec from baseline, and increases in QTcF from baseline of >30 msec and >60 msec.

The overall interpretation of ECG assessments will be tabulated by dose cohort and in total at baseline and each evaluation time point. A shift table from baseline to the worst post-baseline assessment in terms of overall interpretation will also be provided for each dose cohort, disease group and in total. Both scheduled and unscheduled assessments will be considered for deriving the worst post-baseline evaluation.

All ECG measurements and overall interpretation will be listed by subject.

8.7.6 Physical Examination

Physical examination results will be listed by subject.

8.7.7 ECOG Performance Status

The ECOG performance status result at each scheduled visit will be tabulated by cohort, tumor type and in total. In addition, the worst ECOG performance status during the post-baseline period will be tabulated by cohort. Both scheduled and unscheduled post-baseline assessments will be considered when deriving the worst post-baseline ECOG performance status.

All ECOG performance status data will be listed by subject.

8.8 Analyses of Pharmacokinetics and Pharmacodynamics

Analyses of pharmacokinetics and pharmacodynamics data will be conducted separately. The respective analysis plans will be specified in separate documents.

9. ADDITIONAL ANALYSES ON THE IMPACT OF COVID-19

9.1 General Consideration

COVID-19 pandemic may impact the conduct of the study from different aspects including quarantines, site closures, travel limitations, interruptions to the supply chain for the investigational product, or other considerations if site personnel or trial subjects become infected with COVID-19.

Start date and end date of COVID-19 impact will be determined to assess the impact of the COVID-19 pandemic to the study. COVID-19 impact date is defined as the date at which the site and/or overall study was impacted by COVID-19, resulting in changes to how assessments were conducted at the site and/or for the study overall.

9.2 Subject Disposition

Subject disposition will be summarized for each dose cohort and in total for all enrolled subjects. In addition, subject disposition will be tabulated by tumor type and in total. The following categories of subject disposition will be included:

- Subjects who were screened
- Subjects who were screen failures
    - Subjects who were screen failures due to COVID-19
- Subjects who were enrolled
- Subjects who were treated
- Subjects who discontinued from the study
    - Subjects who discontinued from the study due to COVID-19
- Subjects who completed the study and were still alive at EOS visit

For subjects who discontinued from the study, the primary reason for ending the study will be summarized. Specifically, discontinued early from the study due to COVID-19 impact will be summarized. Additionally, on-study deaths (defined as deaths during treatment period or within 30 days of treatment discontinuation) will be presented. The number and percentage of subjects in each defined analysis population will be tabulated as well.

All deaths that occur on study will be reported in a subject listing, which will include the primary cause of death and the number of days between the date of the first (and last) dose of study drug and death.

All subject disposition data will be presented in a data listing.

9.3 Protocol Deviations

Subjects with CSR-reportable protocol deviations by deviation category will be summarized for tumor type, therapy regimen and in total for all enrolled subjects. Specifically, protocol deviations related to COVID-19 will be categorized and summarized separately.

CSR-reportable protocol deviations and COVID-19 related non-reportable protocol deviations will be presented in a data listing.

10. CHANGES FROM THE PROTOCOL SPECIFIED ANALYSES

No changes have been issued or planned.

11. REFERENCES

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