STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2, Open-label, Randomized, Two-stage Clinical Study of Alvocidib in Patients with Relapsed/Refractory Acute Myeloid Leukemia Following Treatment with Venetoclax Combination Therapy
Sponsor	[redacted]
Protocol Number	TPI-ALV-202
IND Number	057729
Investigational Product	Alvocidib (formerly flavopiridol)
Phase of Development	Phase 2
Analysis Plan Version	Version 1.2
Analysis Plan Date	June 3, 2021

STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS AND DEFINITIONS

ADaM	analysis data model
AE	adverse event
ALDAC	Alvocidib + Low-dose cytarabine
ALV	Alvocidib
ATC	anatomical therapeutic chemical
BMI	body mass index
bpm	beats per minute
CR	complete response
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end-of-study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
ICH	International Committee for Harmonization
IP	Investigational Product
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NCS	not clinically significant
PD	progressive disease
PK	pharmacokinetic
PR	partial response
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SD	stable disease
SOC	system organ class
SDPO	Sumitomo Dainippon Pharma Oncology, Inc
TEAE	treatment-emergent adverse event

1. INTRODUCTION

The Statistical Analysis Plan (SAP) describes the data analysis specifications for Sumitomo Dainippon Pharma Oncology, Inc (SDPO) protocol TPI-ALV-202 titled: "*A Phase 2, Open-label, Randomized, Two-stage Clinical Study of Alvocidib in Patients with Relapsed/Refractory Acute Myeloid Leukemia Following Treatment with Venetoclax Combination Therapy*". It details the planned statistical methodologies to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses typically not provided in the clinical study protocol.

This version of the SAP was prepared in accordance with the protocol TPI-ALV-202 Amendment 2 dated August 11, 2020. Other related documents are the annotated patient case report forms (version 6 dated October 16, 2020) and the corresponding InForm electronic data capture (EDC) data dictionary.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described in a SAP Addendum and in the clinical study report. This SAP supersedes the statistical considerations identified in the protocol.

NOTE: On November 17, 2020, the investigative sites were notified of the decision by SDPO to close TPI-ALV-202 following a review of the company portfolio. This SAP will reflect the latest protocol (Amendment 2) along with the current study status where appropriate.

Enrollment status as of November 17, 2020:

- **Lead-In Safety Cohort: n=7 patients enrolled.**
  - **Arm 1: ALDAC (Alvocidib + Low-dose cytarabine): n=3**
  - **Arm 2: ALV (Alvocidib): n=4**
- **Stage 1: n=4 patients enrolled.**
  - **Arm 1: ALDAC (Alvocidib + Low-dose cytarabine): n=2**
  - **Arm 2: ALV (Alvocidib): n=2**

Efficacy endpoints will not be analyzed via inferential statistical methods due to low enrollment (sample size). Summary tables as described in this SAP and full patient listings will be provided to enable a synoptic clinical study report to be written for this study.

2. OVERVIEW OF STUDY DESIGN

Experimental Design:

This is an open-label, randomized, two-stage clinical study. During Stage 1, patients will be randomized in a 1:1 treatment allocation into one of two treatment arms:

- Arm 1: ALDAC (Alvocidib + Low-dose cytarabine
- Arm 2: ALV (Alvocidib)

stratified by prior response to venetoclax in combination with azacytidine or decitabine:

- Refractory (i.e., failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days. OR
- Relapsed (i.e., reoccurrence of disease following a CR/CRi with duration ≥90 days).

This study will be divided into three main parts:

1. **Lead-in Cohort**

   Current Status: Based on a review of data (n=7 patients) from the safety lead-in cohort, the Data Safety Monitoring Board (DSMB) granted unconditional approval to continue enrollment (reference DSMB Recommendation Form dated 11 Sep 2020) into the TPI-ALV-202 clinical trial.

   Planned: As an additional safety measure given the unique patient population and outpatient treatment administration, a separate lead-in cohort of approximately six patients (at least three patients in each treatment arm) will be enrolled, treated, and evaluated for dose-limiting toxicities (DLTs). If a DLT is observed, dose de-escalation will occur. Should no additional DLTs be observed during Cycle 1 and the Data Safety Monitoring Board (DSMB) confirm safety, randomization into Stage 1 will commence as outlined in the protocol. However, should an additional DLT be observed at Dose Level 1, a clinical meeting would be scheduled to discuss the utility/futility of continuing the study as currently designed.

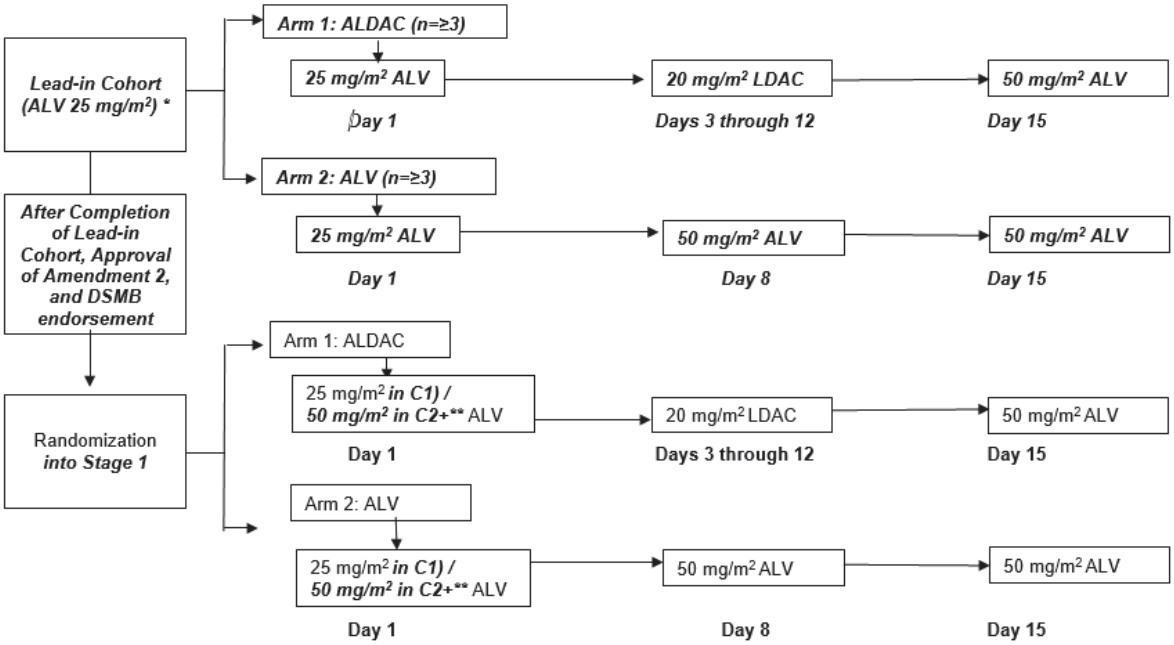
If the DSMB has confirmed safety, patients may be permitted to shift to the higher alvocidib (ALV) dose regimen, i.e., ALV 50 mg/m2 IV bolus, per investigator discretion.

Stage 1

Current Status: As of November 17, 2020, 4 patients were enrolled in Stage 1.

Planned: A futility analysis will be conducted at the end of Stage 1 to determine if the combined CR rate meets the threshold for continuing the study. Using an alpha spending function to control the overall level of significance, the threshold is that the one-sided p-value be <0.60525 in order to initiate Stage 2, which is achieved if there are more than 4 combined CRs among the 52 Stage 1 patients. No additional patients will be enrolled if the number of patients with combined CR at the end of Stage 1 fails to meet this criterion.

The sponsor may elect to close enrollment in Stage 1 once the minimum response threshold has been met in Stage 1 (as defined in the Study Design), and the sponsor has sufficient information to select the recommended alvocidib-based treatment arm for Stage 2. The recommended alvocidib-based treatment will be determined subjectively by comparing the response rates, relative safety, and the risk-benefit ratio of the two Stage 1 treatment arms.



2. Stage 2

Current Status: As of November 17, 2020, zero patients were enrolled in Stage 2.

Planned: Determination of the recommended alvocidib-based treatment arm for Stage 2 will be subjective, comparing the response rates, relative safety, and the risk-benefit ratio of the two Stage 1 treatment arms. An additional 76 patients will be enrolled into the treatment arm selected for Stage 2 for a total of 102 patients (26 and 76 from Stages 1 and 2, respectively). The combined CR rate (primary endpoint) will be tested at the end of Stage 2, with statistical significance declared if the one-sided p-value is <0.02407.

Any patient who withdraws from the study for treatment-related toxicity prior to being evaluated for response will be considered a non-responder. Patients who drop out of the study for other reasons prior to being assessed for response will be considered non-evaluable and may be replaced.

Study treatments:

Alvocidib + Low-dose cytarabine treatment will be given every 28 days.

Alvocidib treatment will be given every 28 days

Number of patients planned: It was planned that up to 6 evaluable patients will be enrolled into the Safety Lead-In Cohort, 52 evaluable patients in Stage 1, and 76 patients into Stage 2. Thus, up to 134 evaluable patients may be enrolled in the study.

Study Duration: The study was expected to take 18 months to enroll approximately 134 evaluable patients and an additional 2 years for follow up.

As of the study termination date of November 17, 2020; 11 patients have enrolled into this study.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Study Objectives

3.1.1 Primary Objective

To estimate the rate of combined complete remission (i.e., CR + CR with incomplete hematological recovery [CRi]) in patients with AML whose disease is either refractory to initial induction therapy with venetoclax in combination with azacytidine or decitabine (i.e., failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days) or who have relapsed (reoccurrence of disease following a CR/CRi duration ≥90 days).

3.1.2 Secondary Objectives

The secondary objectives are:

- Median Overall Survival (OS) = Time from treatment (Day 1) until death from any cause
- CR_{MRD-} = Percentage of patients achieving complete response (CR) whose bone marrow is determined to be negative for minimal residual disease (MRD) using standardized techniques (i.e., multiparametric flow cytometry [MPFC] and molecular testing including next generation sequencing [NGS])
- CR Rate = Percentage of patients achieving:
    - CR = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; hematologic recovery (absolute neutrophil count [ANC] ≥1000/µL and platelet count ≥100,000/µL)
- Composite CR rate = Combined percentage of patients achieving one of the following:
    - CR
    - CRi = Meets all CR criteria but with only full recovery of one peripheral blood cell type (i.e., ANC ≥1000/µL or platelet count ≥100,000/µL)
    - CRh = Meets all CR criteria but with only partial recovery of both peripheral blood cell types (i.e., ANC ≥500/µL and platelet count ≥50,000/µL
- Combined Response rate = Combined percentage of patients achieving one of the following:
    - CR
    - CRi
    - CRh
    - Morphologic leukemia-free state (MLFS) = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
    - Partial Response (PR) = Meets all hematologic values required for CR but with a decrease of at least 50% in the percentage of blasts to ≥5% to ≤25% in bone marrow
- Event-free Survival (EFS) = Time from first treatment (Day 1) until (a) treatment failure, (b) relapse after CR/CRi/CRh, or (c) death from any cause, whichever occurs first, censored at 2 years.

- Duration of Composite CR = Time from first documented response of CR, CRi, or CRh to relapse or death from any cause.
- Rates of 28- and 56-day Transfusion Independence (TI) = Percentages of patients who do not receive red blood cell (RBC) transfusions, platelet (PLT) transfusions, and neither RBC nor PLT transfusions for 28 and 56 days; comprised of 6 secondary endpoints:
    - 28-day RBC TI
    - 28-day PLT TI
    - 28-day TI (both RBC and PLT)
    - 56-day RBC TI
    - 56-day PLT TI
    - 56-day TI (both RBC and PLT)

3.1.3 Exploratory Objectives

- To evaluate potential biomarkers including but not limited to MCL-1 dependence, genetic mutations, and other biomarkers associated with AML.
- Additional exploratory analyses may be performed if useful in the interpretation of the data.

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoint is the rate of combined complete remission (CR+ CRi) as defined by the International Working Group Criteria and 2017 European LeukemiaNet.

3.2.2 Secondary Endpoints

- Median OS
- CR_{MRD}
- CR Rate
- Composite CR rate (CR + CRi + CRh)
- Combined Response Rate (CR + CRi + CRh + MLFS + PR)
- EFS

- Duration of composite CR = Time from first documented response of CR, CRi, CRh to relapse or death from any cause
- Rates of 28- and 56-day Transfusion Independence (TI) = Percentages of patients who do not receive red blood cell (RBC) transfusions, platelet (PLT) transfusions, and neither RBC nor PLT transfusions for 28 and 56 days (i.e., 6 secondary endpoints)

3.2.3 Safety Endpoints

Safety and tolerability of the regimen will be assessed by analyzing the incidence rates of treatment-emergent adverse events (TEAEs) summarized at the MedDRA preferred term and primary system organ class levels. Similar summaries will be made for subsets of adverse events (AEs) such as (1) those judged by the Investigator to be related to study treatment, and (2) serious adverse events (SAEs).

Other routine safety assessments (i.e., clinical laboratory parameters and vital signs) will be summarized by shift tables and treatment group using mean, standard deviation, median, minimum and maximum changes from baseline values.

Mortality (all causes) at 30 and 60 days following last treatment will also be calculated. Adverse events will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

A Data Safety Monitoring Board (DSMB) will monitor key outcomes from the study.

3.2.4 Pharmacodynamic (PD) Endpoints

- BH3 profiling, including determination of MCL-1 dependence, at Baseline and End of Treatment using bone marrow.
- Analysis of MRD to be performed at a central Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory on bone marrow samples collected at baseline and at time of response assessments using standardized techniques (i.e., MPFC and molecular testing including NGS).
- Peripheral blood and bone marrow samples will be collected at protocol-specific time points to evaluate other potential biomarkers including but not limited to MCL-1 dependence. These assessments may be explored in the context of AML or related conditions or drugs of similar class.

The samples may be retained for no longer than 20 years after study completion or per local requirements.

4. SAMPLE SIZE JUSTIFICATION

This study follows a 2-stage adaptive design that allows for continuing patient recruitment into the recommended alvocidib-based treatment arm used in Stage 1. It is designed to test the null hypothesis that the combined CR rate is 10% against the alternative that the combined CR rate is >10%. Up to 128 eligible patients from Stage 1 and Stage 2 will be evaluated for efficacy. Patients enrolled in the safety lead-in cohort will not be included in the efficacy analyses since they will receive a lower dose of alvocidib than the patients enrolled in Stage 1 and Stage 2. Assuming the actual combined CR rate is 20%, the study has 80% power at the one-sided 2.5% level of significance. The underlying statistical properties of this design are based on a 2-stage sequential design where the overall one-sided 2.5% level of significance is protected using error spending. Forty percent of total information will be accumulated prior to the interim analysis at the end of Stage 1, where 10% of the overall alpha will be used. All data from Stages 1 and 2 will be used for the statistical test of combined CR rate at the end of the study, hence the adaptive component of this design (dropping 1 of the 2 treatment arms at the end of Stage 1) does not affect the overall type-1 and type-2 error probabilities.

Note: As of the study termination date of November 17, 2020; 11 patients have enrolled into this study.

5. RANDOMIZATION, BLINDING, AND REPLACEMENT OF PATIENTS

This study follows a randomized, two-stage design. During the Lead-in Cohort and Stage 1, patients will be randomized 1:1 to receive either ALDAC or ALV:

- ALDAC – **Al**vocidib plus **L**ow **D**ose **A**ra-**C** (cytarabine)
- ALV – **ALV**ocidib

Randomization to treatment arm will be stratified by response to initial induction therapy with venetoclax in combination with azacytidine or decitabine:

- Refractory: failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days
- Relapsed: reoccurrence of disease following a CR/CRi with duration ≥90 days

Although this study is randomized, it is unblinded. IQVIA (data management vendor) was responsible for the randomization schedule and implementation into the EDC system.

Patients who are lost to follow-up or withdraw consent for study participation prior to administration of study drug may be replaced, at sponsor's discretion.

6. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

This study will have three analysis populations:

- Intent-to-Treat (ITT) analysis set includes all patients randomized/enrolled to receive study drug regardless of whether they actually received study drug and regardless of whether evidence is found indicating they failed to meet study inclusion/exclusion criteria or had other protocol violations. When the ITT patient population is analyzed, patients are grouped according to their randomized/assigned treatment regardless of actual treatment received.
- The safety patient population is the subset of ITT patients who received at least one dose of study drug. When the safety patient population is analyzed, patients are grouped according to actual treatment received.
- The per-protocol patient population is the subset of safety patients who either (a) have at least one response assessment on study, or (b) die prior to their first scheduled response assessment. However, patients are excluded from the per- protocol patient population if they have an important protocol deviation, such as when evidence is found indicating they failed to meet any study inclusion/exclusion criterion. When the per-protocol patient population is analyzed, patients are grouped according to actual treatment received.

NOTE: due to the study status, the safety population will be used for all summary tables.

7. PLANNED ANALYSES

7.1 Interim Analysis

There are no formal efficacy interim analyses planned for this study. The safety data was planned to be monitored every 3 months by the Data Safety Monitoring Board (DSMB).

The DSMB reviewed safety data from the safety lead-in cohort (n=7 patients). The DSMB granted unconditional approval to continue enrollment (reference DSMB Recommendation Form dated 11 Sep 2020) into the TPI-ALV-202 clinical trial. As noted earlier, this study was terminated November 17, 2020 prior to the next scheduled DSMB meeting.

7.2 Final Analysis

The final tables, listings, graphs, and data analysis will be conducted once all participants have completed the study and the clinical database has been locked.

NOTE: For this study, the database will be locked with 11 patients enrolled.

8. DATA PRESENTATION AND HANDLING

8.1 General Summary Table and Individual Patient Data Listing Considerations

Summary tables and listings will be prepared according to (ICH) Guideline E3 (as appropriate for a Phase I study).

In general, summary tables will be organized with respect to dose cohort and presented as:

Lead-In Cohort			Stage 1			
Arm 1: ALDAC (N=3)	Arm 2: ALV (N=4)	Total (N=7)	Arm 1: ALDAC (N=2)	Arm 2: ALV (N=2)	Total (N=4)	Overall (N=11)

- Lead-In Cohort: Arm 1 (ALDAC), Arm 2 (ALV), Total.
- Stage 1: Arm 1 (ALDAC), Arm 2 (ALV) , Total
- Overall study total.

Row entries in post text tables are made only if data exists for at least one patient (e.g., a row with all zeros will not appear). The only exception to this rule will apply to tables that summarize the study termination status of patients (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no patient satisfied. The summary tables will clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data.

Adverse event preferred terms and body/organ systems and medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 21.0 (or later).

Listings will also be sorted by lead-in cohort, Stage 1 (where applicable), and patient number. Listings will also include visit number, visit date/time.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual patient data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

8.2 General Summary Table and Patient Data Listing Format Considerations

The tables and listings will be numbered as closely as possible to the ALV-202 abbreviated clinical study report tables/listings. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g.,

Safety Population). Variables being summarized, and statistics reported will appear in the left most column(s) of a table. The next columns to the right should report the treatment arm data for the lead-in cohort and stage 1.

8.3 Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be patient to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Database build, AE coding, and data cleaning will be conducted according to the IQVIA Data Management Plan for this specific study.

Derived datasets will be created using SAS® software. Data analyses and summary tables will be generated using the currently supported version at the time of data analysis (currently version 9.4).

8.4 Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values and vital signs) will be listed to the same precision as the source data. Derived variables will be calculated and listed using the same precision as the value(s) from which they were derived.

For the tabular reporting of descriptive statistics:

- Continuous variables: the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- Categorical/discrete variables: the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100

will be reported as 100% and percentages will not be presented for zero frequencies. Unless otherwise specified, percentages will be calculated based on the number of patients specified by the appropriate population definition.

- Date variables: formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in patient listings. They will be used in summary tables which are not 'time specific', for example, summaries of maximum post dose values.

All tables, listings, figures will be produced in landscape orientation using Times New Roman 9-point font. Output files will be created in rich text file (RTF) format.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 9.5).

The table, figures and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

Minor modifications may be necessary to the planned design of tables, listings and figures to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will be documented (with justification) in the CSR.

8.5 Treatment Comparisons

The following labels for dose level will be used on all tabulations, in the following order:

Lead-In Cohort			Stage 1			
Arm 1: ALDAC (N=3)	Arm 2: ALV (N=4)	Total (N=7)	Arm 1: ALDAC (N=2)	Arm 2: ALV (N=2)	Total (N=4)	Overall (N=11)

8.6 Definitions, Computations, Derived Data

- Screening: Screening is defined as ≤ 14 days prior to Cycle 1 Day 1 prior to the first study drug administration.
- Baseline: Measurements taken at Screening or prior to receiving the first dose of study drug; whichever is latest.
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds.
- 1 inch = 2.54 cm and 1 cm = 0.3937 inches.
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703.
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: Age = ([Consent Date - Date of Birth] / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings, figures and summary tables for the disposition and safety, and efficacy data will be the responsibility of the study Biostatistician at Vantage Data Designs.

The currently supported version of SAS software (9.4 or later) will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by cohort (lead-in, stage 1), patient number and assessment date/time.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

9.1 Multicenter Studies

Data from all participating sites will be pooled for the analysis.

9.2 Other Strata and Covariates

Not applicable for this study.

9.3 Examination of Subgroups

Not applicable for this study.

9.4 Multiple Comparisons and Multiplicity

Not applicable for this study.

9.5 Missing Data and Dropouts

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in the statistical literature. As has been noted in the ICH-E9 guideline, "no universally applicable method of handling missing values can be recommended". The best approach is to minimize the chance of dropouts at the design stage of the clinical study and during study monitoring.

In general, data will be analyzed as received from the clinical database. Hence, missing values will not be replaced by imputed values.

9.5.1 Adverse Events

Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is classified as "treatment emergent".

9.5.2 Concomitant Medications

Medications with missing or partial dates will not have dates imputed and will presented as collected in the patient listings.

9.5.3 Other Situations

For patients who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

10. STUDY POPULATION

All disposition, baseline and demographic analyses will be conducted on the Safety population.

10.1 Patient Disposition

The patient disposition summary will include:

- The number of patients who were enrolled at each study center.
- Number of patients in Lead-In Cohort and Stage 1.
- A summary of primary reason for treatment discontinuation from study.
- A summary of primary reason for discontinuation from study.

A listing of patient enrollment and disposition will be provided. A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by patient, will also be presented.

10.2 Protocol Violations or Deviations

Protocol deviations were not collected per the eCRFs.

10.3 Demographics

Demographic characteristics will include age, age category (18-25, 26-35, 36-45, 46-55, 56-65, >65 years), sex, race, ethnicity, and ECOG Performance Status.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All demographic data will be listed by patient.

10.4 AML History

AML History variables include French-American-British (FAB) AML Type, MDS prior to AML, Primary or Secondary AML, Extramedullary Disease, central nervous system (CNS) involvement, FLT3 Mutations, CEBPA (C/EBP-Alpha) Mutations, NPM1 Mutations, ASXL1 Mutations, and RUNX1 Mutations.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All AML history data will be listed by patient.

10.5 Medical History

The incidence of Medical history will be summarized by system organ class (SOC) and preferred term (PT) using MedDRA version 21.1. In the summary tables, patients may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, patients will be counted only once. All medical history data will be presented in patient listings.

10.6 Concomitant Medications

All prior medication and concomitant medications will be presented in patient listings.

10.7 Study Drug Administration and Exposure

Study drug administration and exposure will be summarized by number of treatment cycles completed and the number of weeks on study. The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All study drug administration data will be listed by patient.

11. EFFICACY ANALYSIS

The response criteria for this study are from the 2017 European Leukemianet recommendations from an international expert panel (Blood 2017;129(4):424–447).

Response categories include CR, CRi, CRh, CR_{MRD}, MLFS, PR, SD, PD, Not Evaluated / Missing. The best objective response for each patient will be summarized by number and percentage.

In addition, response rates will be categorized and summarized by number and percentage of patients meeting these definitions:

- Combined Complete Remissions (CR, CRi).
- Composite Complete Remission Rate (CR, CRi, CR_h).
- Combined Response Rate (CR, CRi, CR_h, MLFS, and PR).

In addition to the summary tables, efficacy data will also be presented in the individual patient listings.

12. SAFETY ANALYSIS

The Safety Population is defined as all enrolled patients who received any amount of study treatment will be utilized for all safety analyses.

In addition to the summary tables, safety data will also be presented in the individual patient listings.

12.1 Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the date of the first administration of study drug. Related AEs are those reported as possibly related, probably related, or related to study drug (ALDAC or ALV). The verbatim terms of

the Treatment Emergent Adverse Events (TEAE) will be coded to preferred terms (PT) and system organ classes (SOC) per MedDRA® (Medical Dictionary for Regulatory Activities) Version 21.1 (or later).

All reported AEs (including non-TEAEs) will be listed, documenting all information collected on the eCRF including verbatim term, MedDRA preferred term, MedDRA system organ class, start date, stop date, severity and relationship to study drug action taken, and outcome.

The TEAEs will be graded by the Investigator in terms of:

- Severity graded 1-5 according to CTCAE v5.0:
    - 1=Mild, 2=Moderate, 3=Severe, 4= Life Threatening, 5=Fatal.
- Relation to study drug (ALDAC or ALV):
    - 'Related' includes events where the causality was reported as 'Possibly Related', or 'Probably Related', or 'Definitely Related', or where the relationship was not reported on the eCRF.
    - 'Not Related' includes events where the study drug causality was reported as 'Unrelated 'or 'Unlikely Related' on the eCRF.

All TEAE summary tables will be presented with the number and percentages of patients in the Safety population. An overall summary of TEAEs will be tabulated by treatment regimen, relation to study treatment, and grade. In addition, TEAEs will be summarized by system organ class (SOC) and preferred term (PT).

Planned TEAE summary tables include:

- Overall Summary of Treatment-Emergent Adverse Events (Safety Population)
- Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Severity Grade (Safety Population)
- Incidence of Treatment-Emergent Grade 3, Grade 4, and Grade 5 Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Treatment-Emergent Grade 3, Grade 4, and Grade 5 Adverse Events by MedDRA System Organ Class and Preferred Term and CTCAE Severity Grade (Safety Population)

- Incidence of Treatment-Emergent Adverse Events Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Treatment-Emergent Grade 3, Grade 4, and Grade 5 Adverse Events Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA System Organ Class and Preferred Term (Safety Population)

In the summary tables, patients may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, patients are only counted once. If a patient has the same AE on multiple occasions, the highest severity grade (fatal > life threatening > severe > moderate > mild) or drug relationship (related > possibly related > not related) recorded for the event will be summarized.

12.2 Serious Adverse Events

Planned Serious TEAE summary tables include:

- Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Serious Treatment-Emergent Adverse Events Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA System Organ Class and Preferred Term (Safety Population)
- Treatment-Emergent Adverse Events in the Standardized MedDRA Query for Tumor Lysis Syndrome Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA Preferred Term (Safety Population)

12.3 Clinical Laboratory Tests

Safety laboratory assessments will be presented in patient listings.

12.4 Vital Signs

Vital signs data will be presented in patient listings.

12.5 12-Lead Electrocardiogram (ECG)

ECG data will be presented in patient listings.

12.6 ECOG Performance Status

ECOG assessments will be presented in patient listings.

12.7 Physical Examination and Pregnancy Test

The physical examination data and pregnancy test results will be presented in patient listings.

13. PHARMACOKINETIC (PK) ANALYSIS

Not applicable.

14. PHARMACODYNAMIC (PD) ANALYSIS

Pharmacodynamic endpoints include:

- BH3 profiling, including determination of MCL-1 dependence, at Baseline and End of Treatment using bone marrow.
- Minimal residual disease (MRD) to be determined by central CLIA accredited laboratory evaluation of bone marrow samples collected at baseline and at time of response assessments using standardized techniques (i.e., MPFC and molecular testing including NGS).
- Peripheral blood and bone marrow samples will be collected at protocol- specific time points to evaluate other potential biomarkers including but not limited to MCL-1 dependence. These assessments may be explored in the context of AML or related conditions or drugs of similar class.

Any PD data analysis will be performed by SDPO R&D group and/or sponsor PD consultant.

15. COMMITMENT TO GOOD STATISTICAL PRACTICE

15.1 Definition of Good Statistical Practice

International Conference on Harmonization (ICH) Guidance on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and to maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and in a more detailed pre-specified statistical analysis plan such as this one.

Due to the early termination of this study and low sample size, efficacy and safety endpoints will not be analyzed via inferential statistical methods. Descriptive statistics will be presented in the summary tables as described in this SAP, and full patient listings will be provided to enable a synoptic clinical study report to be written for this study.

15.2 Data Management and Use of CDISC Standards

Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC).

SDPO used third party vendors for clinical data collection and data analysis. Clinical data will be managed by IQVIA (US based CRO). and will be captured in electronic case report form (eCRF) by the InForm EDC platform. The "raw" data contained in the eCRF clinical database will then be converted into Study Data Tabulation Model (SDTM) datasets per CDISC standards. The SDTM datasets will be utilized to create Analysis Data Model (ADaM) datasets. These CDISC data conversions will be conducted by Vantage Data Designs. These CDISC data conversions and data analysis will be conducted by Vantage Data Designs.

Other applicable standards include regulatory guidance's from the Food and Drug Administration (FDA), ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3), and ICH Guidance for Good Clinical Practice (ICH E6).

15.3 Testing/Validation Plan and Software System

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, patient data listings, and graphical representation of the data. All SAS computer programs will be validated using industry standard validation procedures including independent quality control programming.

16. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol TPI-ALV-202 Amendment Version 2.0 dated August 11, 2020. This SAP supersedes the statistical considerations identified in the protocol.

17. REFERENCES

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2. FDA Draft Guidance for Industry: Clinical Trial Imaging Endpoint Process Standards. March 2015.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.
4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice Integrated Addendum: ICH E6 (R2, March 2018.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
6. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 21.0. Reston, Virginia, USA; 2008.
7. Protocol TPI-ALV-202: "A Phase 2, Open-label, Randomized, Two-stage Clinical Study of Alvocidib in Patients with Relapsed/Refractory Acute Myeloid Leukemia Following Treatment with Venetoclax Combination Therapy". Amendment 2 dated August 11, 2020.
8. SAS Institute Inc. SAS Version 9.4. Cary, NC, USA; 2002-2003.

18. SCHEDULE OF ASSESSMENTS

Arm 1 (ALDAC)

	SCREENING		ALL TREATMENT CYCLES (CYCLE = 28 DAYS)															EOT	FU
TESTS/PROCEDURES	-14 days	-72 hours	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D15	D22	D28		
Visit window			±3d C2+												±2d	±3d	±3d		±5d
Obtain ICF	X																		
Medical history	X																		
Full PE	X		X C2+																
Abbreviated PE			X C1												X	X *C1*		X	
BSA			X																
Weight (kg)	X		X a															X	
Height (cm)	X																		
ECOG	X		X							X C1 only					X	X *C1*		X	
Vital signs	X		X							X					X	X		X	
Bone marrow & peripheral blood	X																X b	X c*	
Cytogenetic profiling	X																		
12-lead ECG	X																	X*	
Pregnancy test	X	X	X (**C1)																
Hematology	X	X	X C2	twice a week during the 10 day LDAC injections											X	X		X	
Full chemistry panel	X	X	X C2+	twice a week during the 10 day LDAC injections											X			X	
Pre-infusion TLS labs			X Only C1																
Post-infusion TLS labs			X Only C1	X Only C1	X Only C1	X REVIEW Only C1									X Only C1	X			
Coagulation			X C2+*													X*		X*	
Urinalysis		X																X	
Blood transfusions	Recorded from 56 days prior to first study treatment dose, through 56 days after last dose of study treatment																		
Lumbar puncture for CNS disease	X*																		
Review Inc/Exc Criteria		X																	
Daily oral allopurinol		Mandatory from 72 hours prior to D1 up to C1D28. As clinically indicated for subsequent cycles.																	

IV hydration pre & post infusion			X C2+***											X C2+***				
Oral phosphate binder			For C1, mandatory							As indicated based on TLS symptoms								
	SCREENING		**ALL TREATMENT CYCLES (CYCLE = 28 DAYS)**															
TESTS/PROCEDURES	**-14 days**	**-72 hours**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D15**	**D22**	**D28**	**EOT**	**FU**
Visit window			***±3d C2+***												±2d	±3d	±3d		±5d
Assess patient's hydration level			To be closely monitored throughout study treatment and replace excessive fluid losses unless not clinically indicated																
Prophylactic antibiotics, antifungals per site SOC			Should be administered to patients if ANC is <500/µL. These can be discontinued when the ANC ≥500/µL per institutional standards and physician discretion																
Antiviral per site SOC			To be administered daily to all patients throughout the study unless there are contraindications																
Alvocidib infusion			X												X				
LDAC injection					X	X	X	X	X	X	X	X	X	X					
Provide / review patient diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con meds	From 2 weeks prior to C1D1 through 14 days after the last dose of study treatment																		
Assessment of AEs			Recorded from first study treatment dose through 30 days after the last dose of study treatment																
Phone call to patient																			X d

a Dose is only adjusted at the beginning of each cycle after Cycle 1 if there has been a > 10% change in weight compared to the weight used to calculate the current dose.

b Required at C1 and then every even cycle thereafter (i.e. C2, C4, etc).

c Bone marrow and peripheral bloodare not collected if collected in the previous 30 days

d Year 1: Phone calls monthly (±5 days) beginning the month after the patient completes the end-of-study assessments to 12 months after End of Treatment visit regardless of how many cycles a patient receives (Year 1=Day of First Treatment plus 12 months).
Year 2: Phone calls every other month (±5 days) during Year 2 (Months 14 to 24 after End of Treatment visit).

* as clinically indicated

** only required if last pregnancy test was >72 hrs from C1D1 visit

*** optional for subsequent cycles for patients who have achieved a CR

Arm 2 (ALV)

Tests/Procedures	Screening		All Treatment Cycles (Cycle = 28 Days)									
	-14 days	-72 hours	D1	D2	D3	D4	D8	D15	D22	D28	EOT	FU
Visit window			±3d C2+				±1d	±2d	±3d	±3d		±5d
Obtain ICF	X											
Medical history	X											
Full PE	X		X C2+									
Abbreviated PE			X C1				X	X	X C1		X	
BSA			X									
Weight (kg)	X		X a								X	
Height (cm)	X											
ECOG	X		X				X	X	X C1		X	
Vital signs	X		X				X	X	X		X	
Bone marrow & peripheral blood	X									X b	X c*	
Cytogenetic profiling	X											
12-lead ECG	X										X*	
Pregnancy test	X	X	X (**C1)									
Hematology	X	X	X C2				X	X	X		X	
Full chemistry panel	X	X	X C2+				X	X			X	
Pre-infusion TLS labs			X Only C1									
Post-infusion TLS labs			X Only C1	X Only C1	X Only C1	X Only C1	X Only C1	X Only C1	X			
Coagulation			X C2+*				X*	X*	X*		X*	
Urinalysis		X									X	
Blood transfusions	Recorded from 56 days prior to first study treatment dose, through 56 days after last dose of study treatment											
Lumbar puncture for CNS disease	X*											
Review Inc/Exc Criteria		X										
Daily oral allopurinol		Mandatory from 72 hours prior to D1 up to C1D28. As clinically indicated for subsequent cycles.										
IV hydration pre & post infusion			X C2+***				X C2+***	X C2+***				
Oral phosphate binder			For C1, mandatory					As indicated based on TLS symptoms				
Assess patient's hydration level			To be closely monitored throughout study treatment and replace excessive fluid losses unless not clinically indicated									

Prophylactic antibiotics, antifungals per site SOC			Should be administered to patients if ANC is <500/μL. These can be discontinued when the ANC ≥500/μL per institutional standards and physician discretion									
	SCREENING		ALL TREATMENT CYCLES (CYCLE = 28 DAYS)									
TESTS/PROCEDURES	-14 days	-72 hours	D1	D2	D3	D4	D8	D15	D22	D28	EOT	FU
Visit window			±3d C2+				±1d	±2d	±3d	±3d		±5d
Antiviral per site SOC			To be administered daily to all patients throughout the study unless there are contraindications									
Alvocidib infusion			X				X	X				
Provide / review patient diary		X	X	X	X	X	X	X	X	X	X	
Con meds	From 2 weeks prior to C1D1 through 14 days after the last dose of study treatment											
Assessment of AEs			Recorded from first study treatment dose through 14 days after the last dose of study treatment									
Phone call to patient												X d

e Dose is only adjusted at the beginning of each cycle after Cycle 1 if there has been a > 10% change in weight compared to the weight used to calculate the current dose.

f Required at C1 and then every even cycle thereafter (i.e. C2, C4, etc).

g Bone marrow and peripheral bloodare not collected if collected in the previous 30 days

h Year 1: Phone calls monthly (±5 days) beginning the month after the patient completes the end-of-study assessments to 12 months after End of Treatment visit regardless of how many cycles a patient receives (Year 1=Day of First Treatment plus 12 months).
Year 2: Phone calls every other month (±5 days) during Year 2 (Months 14 to 24 after End of Treatment visit).

* as clinically indicated

** only required if last pregnancy test was >72 hrs from C1D1 visit

*** optional for subsequent cycles for patients who have achieved a CR