STATISTICAL ANALYSIS PLAN
Viracta Therapeutics, Inc.
Study VT3996-202 (NAVAL-1)
(NCT05011058)

Protocol Title:	An Open-Label, Phase 2 Trial of Nanatinostat in Combination with Valganciclovir in Patients with Epstein-Barr Virus-Positive (EBV+) Relapsed/Refractory Lymphomas (NAVAL-1)
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Sponsor:	Viracta Therapeutics, Inc. 2533 S. Coast Hwy 101 Suite 210 Cardiff, CA 92007
Prepared By:	Sarah Parisi Emanate Biostats, Inc. 5800 Armada Drive Suite 210 Carlsbad, CA 92008
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STATISTICAL ANALYSIS PLAN APPROVAL

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Approved By:

Signed by:
Darrel Cohen
Signer Name: Darrel Cohen
Signing Reason: I approve this document
Signing Time: 10/9/2024 | 3:30:34 PM PDT
2C842CB3918749DBBD8E4AFBFC0A2FBC

Darrel P. Cohen, MD, PhD
Chief Medical Officer
Viracta Therapeutics, Inc.

Signed by:
Sarah Parisi
Signer Name: Sarah Parisi
Signing Reason: I am the author of this document
Signing Time: 10/9/2024 | 3:43:39 PM PDT
A8C141FEDE374F26A2FD648E9BB91305

Sarah Parisi
Associate Director, Biostatistics
Emanate Biostats, Inc.

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ABBREVIATIONS

Table 1 List of Abbreviations

Abbreviation	Definition
AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALT	aminotransferase, alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	body mass index
CI	confidence interval
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CRR	complete response rate
CSR	Clinical Study Report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DILI	drug-induced liver injury
EBV^+	Epstein-Barr Virus-Positive
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ENKTL	extranodal NK/T-cell lymphoma
EOT	End of Treatment
FDG	fluorodeoxyglucose
FFPE	formalin-fixed paraffin-embedded
DLBCL	diffuse large B-cell lymphoma
DOR	duration of response
HDAC	histone deacetylase
HIV	human immunodeficiency virus
HL	Hodgkin lymphoma
ICH	International Council for Harmonisation
IPD	important protocol deviation
IRC	Independent Review Committee
IWG	International Working Group
KM	Kaplan-Meier
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NHL	non-Hodgkin lymphoma
OS	overall survival
PD-1	programmed cell death-1

Abbreviation	Definition
PD-L1	programmed cell death-ligand 1
PET	positron emission tomograph
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PTCL	peripheral T-cell lymphoma
PTLD	post-transplant lymphoproliferative disorder
NCI	National Cancer Institute
NOS	not otherwise specified
ORR	Objective Response Rate
Q1	1st quartile (25th percentile)
Q3	3rd quartile (75th percentile)
QTcF	corrected QT interval using Fridericia's method
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SI	Système International
TEAE	treatment-emergent adverse event
TIL	tumor-infiltrating lymphocyte
TTNLT	time to next anti-lymphoma treatment
TTP	time to progression
WHODDE	World Health Organization Drug Dictionary Enhanced
VGCV	valganciclovir

1. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide comprehensive and detailed descriptions of the methods and presentations of data analyses proposed for Viracta Therapeutics-sponsored Study VT3996-202 (An Open-Label, Phase 2 Trial of Nanatinostat in Combination with Valganciclovir in Patients with Epstein-Barr Virus-Positive [EBV^+] Relapsed/Refractory Lymphomas [NAVAL-1]). Descriptions of planned analyses are provided in order to avoid post hoc decisions that may affect the interpretation of the statistical analysis. The statistical methods applied in the design and planned analyses of this study are consistent with the International Council for Harmonisation (ICH) guideline *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1], Rev 1)* (2021).

This SAP will be finalized prior to any formal interim or final data analyses and before database lock to provide comprehensive details of the data analyses to be presented in the Clinical Study Report (CSR). For the purpose of the data analyses, this SAP will supersede the study protocol-specified analysis plan. Any changes or deviations from this SAP relative to the final analysis will be fully documented in the CSR. Minor changes or deviations from the templates for tables, figures, and listings need not be documented in the CSR.

2. STUDY OBJECTIVES

2.1 Primary Study Objective

The primary objective of this study is to evaluate the anti-tumor activity of the combination treatment of nanatinostat with valganciclovir (VGCV) based on objective tumor response rates.

2.2 Secondary Study Objectives

The secondary objectives of this study are to:

- Determine the duration of tumor control;
- Determine survival outcomes;
- Describe the safety profile of the combination treatment of nanatinostat and VGCV;
- Generate pharmacokinetic (PK) data with the intended commercial dose and administration of nanatinostat.

2.3 Exploratory Study Objectives

The exploratory objectives of this study are to:

- Explore correlation of baseline PD-L1 expression and other immune checkpoint molecules with outcome;
- Evaluate potential biomarkers of activity of combination therapy;
- Identify potential resistance markers to therapy.

3. INVESTIGATIONAL PLAN

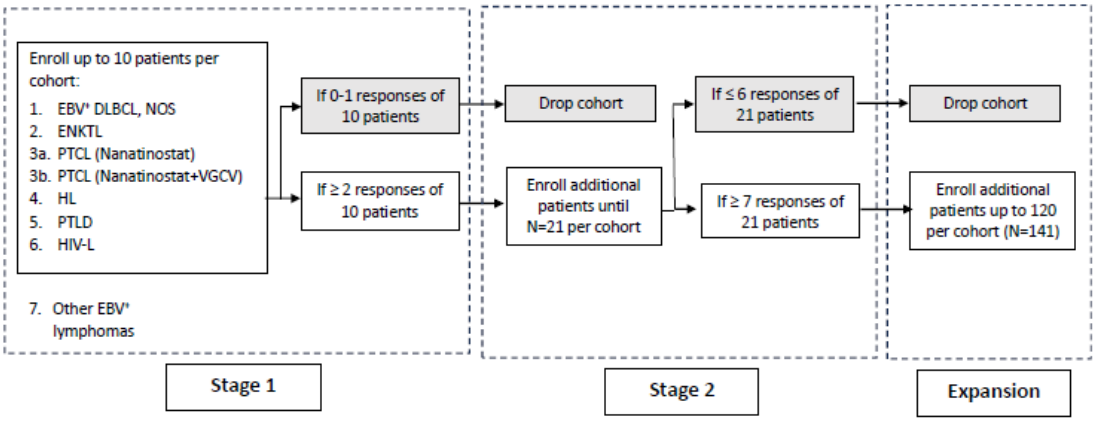
3.1 Overall Study Design

This is an open-label, multicenter, multinational single-arm, Phase 2 basket design study utilizing Simon's 2-stage design options for discontinuing enrollment into each cohort where treatment appears to be futile. The study will include 7 cohorts of patients with the following EBV^+ relapsed/refractory lymphomas:

- Cohort 1: EBV^+ diffuse large B-cell lymphoma, not otherwise specified (DLBCL, NOS)
- Cohort 2: Extranodal NK/T-cell lymphoma (ENKTL)
- Cohort 3: Peripheral T-cell lymphoma (PTCL), including PTCL-NOS and angioimmunoblastic T-cell lymphoma (AITL)
    - Cohort 3a: Nanatinostat monotherapy
    - Cohort 3b: Nanatinostat + valganciclovir
- Cohort 4: Hodgkin lymphoma (HL)
- Cohort 5: Post-transplant lymphoproliferative disorder (PTLD)
- Cohort 6: Lymphomas associated with human immunodeficiency virus (HIV) infection (HIV-L): Plasmablastic, Burkitt, Hodgkin, and DLBCL
- Cohort 7: EBV^+ lymphomas other than Cohorts 1, 3, 4, 5, and 6 above (Cohort 7 will not enroll patients in France).

A study schema is shown in the figure below:

Figure 1 Study Design



Note: Patients enrolled with PTCL will be randomized 1:1 to either nanatinostat monotherapy (in Cohort 3a) or nanatinostat plus valganciclovir (in Cohort 3b).

The purpose of this study is to determine the efficacy of the combination treatment of nanatinostat with valganciclovir in patients with relapsed/refractory EBV$^+$ lymphomas. At screening, the patient will provide a signed informed consent form prior to any study-related activities. A recent formalin-fixed paraffin-embedded (FFPE) specimen must be available for retrospective central review of diagnosis. FFPE tissue blocks are preferred; if a tissue block is not available, at least 15 unstained slides or freshly cut serial sections (3−5 µm in thickness), preferably with an accompanying block punch will be accepted. Collection and shipment of this formalin-fixed paraffin-embedded tumor sample to the central pathology lab should occur as early as possible, and no later than 8 weeks following Cycle 1 Day 1. The tumor sample will be used for central confirmation of EBV status and verification of lymphoma subtype. Additional screening evaluations must be performed within 28 days or 14 days before treatment start as defined in the Schedule of Events. Patient eligibility will be confirmed once all screening procedures are completed.

The method of assigning patients to individual cohorts is described in detail in Section 3.3.2. It is estimated that up to 486 patients in Cohorts 1 to 6 may be enrolled for combination therapy, of which approximately 60 would be enrolled in Stage 1 and 66 would be enrolled in Stage 2, and up to 360 would be enrolled into the post-Stage 2 expansion cohorts. Additional patients (n=10) with PTCL will be enrolled in Cohort 3a for nanatinostat monotherapy, and patients with lymphoma subtypes other than those assigned to Cohorts 1, 3, 4, 5, and 6 may be enrolled into Cohort 7 (with the exception of France).

If 10 patients of a given lymphoma subtype are enrolled into Cohort 7, then the Simon's decision criteria will be applied to determine whether or not to add patients in Stage 2 for that subtype. If none of the subtypes represented in Cohort 7 enrolls at least 10 patients, efficacy data collected on those patients will be listed but not summarized by group.

Enrolled patients will receive treatment until disease progression (per Investigator assessment), unacceptable toxicity, withdrawal of consent, Investigator's discretion, death, initiation of new antineoplastic therapy, discontinuation from the study for any

reason, or study termination by the Sponsor. All antineoplastic therapies given after the last dose of study drug (and time to next therapy) will be recorded in the electronic case report form (eCRF) (unless the patient withdraws consent or is lost to follow-up). Patients will be followed for survival regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up).

Study treatment will start on Cycle 1 Day 1. Patients enrolled in Cohorts 1 to 7 (with the exception of Cohort 3a), and patients crossed over from Cohort 3a will receive intermittent dosing of nanatinostat and continuous valganciclovir in 28-day cycles. Nanatinostat and valganciclovir will be taken at the same time following a light meal. During treatment Cycle 1, visits will occur on Days 1, 8, 15, and 22. Starting at Cycle 2, visits will occur on Days 1 and 15. Each scheduled clinic visit has an allowable ±3-day window.

For Cohort 3a, the PTCL patients randomized to monotherapy will begin with 6 weeks of nanatinostat monotherapy (20 mg orally once daily on Days 1 to 4 per week) with visits on Days 1, 15, 29, and 43. Each scheduled clinic visit has an allowable ±3-day window.

If a Cohort 3a patient has stable disease at the Day 43 visit (or progressive disease at any time), the patient will be offered the option to cross over to combination nanatinostat/valganciclovir therapy and follow the 28-day treatment cycles as described above. Patients must complete the End of Monotherapy Disease assessment and qualify (labs, no sign of central nervous system [CNS] disease progression, Eastern Cooperative Oncology Group [ECOG]) prior to beginning Cycle 1 Day 1 of the nanatinostat/valganciclovir combination therapy. If a patient has a response (complete or partial response) to nanatinostat monotherapy at the Day 43 visit, the patient will continue monotherapy treatment.

For patients enrolled in Cohorts 1 to 7 (with the exception of Cohort 3a prior to potential crossover to combination therapy), disease response assessments will be made every 8 weeks until 24 weeks, and then every 12 weeks for the remainder of the study, according to the revised response criteria for malignant lymphoma based on the International Working Group (IWG) guidelines (Cheson 2007). A scan to confirm an unconfirmed partial response (PR) or unconfirmed complete response (CR) ≥4 weeks later may also be performed. Responses will be assessed by both the Investigator and an Independent Review Committee (IRC).

The safety and tolerability of study drug treatments will be evaluated by means of adverse event (AE) reports (incidence, causality, and severity), ECOG performance status, physical examinations, 12-lead electrocardiograms (ECGs), and laboratory safety evaluations. Laboratory abnormalities and AE severity will be graded according to National Cancer Institute (NCI) *Common Terminology Criteria for Adverse Events* (CTCAE), version 5.0.

Upon discontinuation of the protocol-specified treatments, patients will enter the Follow-up period. All patients will be followed for AEs for 28 days after the last dose of study drug (permanent discontinuation) and complete the Safety Follow-up visit as described in Section 7.2.5 of the clinical study protocol, except if the patient is lost to follow-up or withdraws consent. The PK parameters of nanatinostat and its metabolites

and ganciclovir (primary active hydrolytic product of valganciclovir) will be evaluated for patients enrolled in Stage 1 and sparse sampling will be collected during the Stage 2 part of the study at selected sites.

In the Long-term Follow-up period, patients will be followed as described in Section 7.2.6 of the clinical study protocol (or more frequently if a survival update is required for safety or regulatory reasons) for disease progression, overall survival [OS], subsequent anti-lymphoma therapies, and response (best overall responses and disease progression date) to subsequent lymphoma therapies. Survival information can be obtained by phone calls, clinic visits, or public records, such as government census or death records, until the patient is lost to follow-up, death, or withdraws consent.

The end of the study occurs when all patients have either progressed, discontinued, died, become lost to follow-up, or have maintained a CR, PR, or stable disease (SD) for at least 3 years, or when the trial is terminated by the Sponsor. Patients continuing to derive benefit from study treatment in the opinion of the Investigator at the end of the study may be able to continue receiving study drugs on an individual basis (e.g., by separate protocol or post-trial access plan) with Sponsor approval.

Because of the open-label single-arm trial design elements, each cohort will be monitored individually for safety and efficacy. Therefore, each cohort may advance from Stage 1 to Stage 2 and complete Stage 2 at different rates. The decision to expand enrollment beyond Stage 2 will also occur independently for each cohort. However, a study-wide analysis of efficacy and safety over all cohorts will be performed once either all cohorts have completed assessments of response at the end of Stage 2 and those with responses have been followed for up to 3 years, or the study is prematurely terminated by the Sponsor.

3.2 Schedule of Assessments

For the complete schedule of assessments, refer to Section 6.1 of the clinical study protocol.

3.3 Treatments

3.3.1 Treatments Administered

Nanatinostat is a selective histone deacetylase (HDAC) Class I inhibitor with activity against HDAC1, HDAC2, and HDAC3. Valganciclovir (VALCYTE®) is an oral prodrug of ganciclovir. The antiviral activity of valganciclovir is based on the generation of ganciclovir-triphosphate, which is a competitive substrate for the cytomegalovirus (CMV) DNA polymerase.

Patients enrolled in Cohorts 1 to 7 (with the exception of Cohort 3a), and patients crossed over from Cohort 3a, will receive intermittent dosing of nanatinostat and continuous valganciclovir in 28-day cycles as follows:

- Nanatinostat 20 mg orally once daily on Days 1 to 4 per week (i.e., 4 days on, 3 days off)

- Valganciclovir 900 mg orally once daily, except patients with creatinine clearance 50-59 mL/min at study entry will receive valganciclovir 450 mg orally once daily as described in Table 2 below.

Table 2 Valganciclovir Dosing for Patients with Renal Impairment

Creatinine Clearance (mL/minute)	Valganciclovir Dose
≥60	900 mg once daily
40-59	450 mg once daily
25-39	450 mg every 2 days
10-24	450 mg twice weekly
<10 (on hemodialysis)	Not recommended (discuss with Medical Monitor)

If a scheduled dose of nanatinostat or valganciclovir is missed, the patient should take the missed dose(s) as soon as possible during the same day, but within 8 hours of the missed dose. If more than 8 hours or an entire day has passed, the normal dosing schedule will be resumed the following day without a change in the daily dose or schedule.

If a scheduled dose of nanatinostat or valganciclovir is vomited, the patient should contact the site for consideration of anti-nausea medication, and dosing should resume with the next scheduled dose. No replacement dose should be given. If the situation persists, the site should consult the Medical Monitor.

3.3.2 Method of Assigning Patients to Cohorts

Patients will be enrolled utilizing Simon's 2-stage design options for discontinuing enrollment into each cohort where treatment appears to be futile. In Stage 1, 6 cohorts (Cohorts 1, 2, 3b, 4, 5, and 6) will enroll up to 10 patients each. Patients will be enrolled into each cohort based on their primary lymphoma diagnosis to receive the combination nanatinostat plus valganciclovir with exception of Cohort 3a.

The first 20 patients enrolled with PTCL in Cohort 3 will be randomized 1:1 to either Cohort 3a (nanatinostat monotherapy) or Cohort 3b (nanatinostat plus valganciclovir). Randomization will occur at the time of drug dispensation for Cycle 1 Day 1. Following a disease response assessment at 6 weeks, patients in Cohort 3a with a CR or PR will continue nanatinostat monotherapy. Those in Cohort 3a with stable disease at 6 weeks or disease progression at any time will be offered the option to cross over to receive combination therapy for the remainder of the study, provided they qualify per hematology, chemistry, no sign of CNS disease progression, and ECOG performance status parameters.

All cohorts that have a response in 2 or more patients in Stage 1 will expand enrollment by 11 patients in Stage 2, for a total of 21 patients in each cohort (Figure 2). If ≥7 responses are observed in the initial 21 patients in any cohort, then enrollment will be expanded to include up to 120 additional patients in that cohort (N=141), with an interim analysis of efficacy and safety planned in the second-line EBV^+ lymphoma

subpopulation (see Section 4.7 for sample size details). Data from a total of 40 patients who have been followed for at least 6 months or permanently discontinued study treatment will be used for this interim analysis. If the interim efficacy analysis outcome is positive (see Section 4.5.6.3 for details of this interim efficacy analysis), then the final analysis would still be conducted for all second-line EBV^+ lymphoma patients and the entire cohort. Cohort 3a will not enroll beyond the initial 10 patients, regardless of the number of responders in Stage 1. See Section 4.7 for details.

Cohort 7 will be closed to enrollment when all other cohorts are closed, or sooner at the discretion of the Sponsor, regardless of the number of patients recruited at that time and will not be subject to the decision criteria of the Simon's 2-stage design.

3.4 Efficacy and Safety Variables

3.4.1 Efficacy Variables

3.4.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the objective response rate (ORR) as assessed by an IRC. The ORR is defined as the proportion of patients who achieve a complete response CR or PR using the 2007 International Working Group (IWG) NHL criteria (Cheson 2007). The investigator will also use the 2007 IWG for assessment of disease progression/relapse and for any clinical decisions requiring assessment of disease progression/relapse. The IRC review includes central radiology and clinical review. The radiologic assessments (fluorodeoxyglucose-positron emission tomograph [FDG-PET]/computed tomography [CT], CT with contrast, or magnetic resonance imaging [MRI]) are considered the primary method of response assessment. Any additional assessments (e.g., clinical assessments, bone marrow biopsy assessments, etc.) are considered confirmatory.

FDG-PET/CT scans in conjunction with diagnostic contrast-enhanced CT scans (or MRI if a CT with contrast is contraindicated) will be performed at baseline, and for the 8-week and 16-week tumor assessments. For Cohort 3a only, scans are performed at the 6-week tumor assessment instead of the 8-week tumor assessment to determine if patients may cross over to receive combination therapy. For patients who do cross over to receive combination therapy, subsequent scans will occur at the 8-week and 16-week visits, consistent with Cohort 3b. Patients continuing on nanatinostat monotherapy will have subsequent scans at the 14-week and 22-week tumor assessments. Diagnostic contrast-enhanced CT scans obtained as part of a PET/CT scan may be used in lieu of dedicated CT scans.

Subsequent evaluations will be performed by CT with contrast (without PET) or MRI only. Patients with FDG-avid lymphoma at baseline may have an FDG-PET/CT performed to evaluate a possible CR or PR after Week 16 (unless prohibited by local practice) and may use a diagnostic contrast-enhanced CT for follow-up once a complete metabolic response is obtained. FDG-PET/CT scans may also be obtained per investigator discretion (e.g., in instances where extranodal disease may be inadequately imaged by contrast-enhanced CT scan).

Responses will also be assessed by the investigator for management of the patient. Investigator-determined response assessments at each assessment time point will be recorded on the appropriate eCRF.

3.4.1.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the following:

- Complete response rate (CRR) – defined as the proportion of patients who achieve a CR using the 2007 IWG NHL criteria (Cheson 2007) per IRC review, as well as per Investigator assessment.

- Time to response (TTR) – defined as the interval from the start of study drug treatment to the date of first documented CR or PR per IWG criteria. TTR will be determined for response assessments per IRC review as well as by investigator.

- Duration of response (DOR) – defined as the interval from the date of first documented CR or PR per IWG criteria to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment. Dates of disease progression and censoring will be determined as described in Section 4.5.6.2. Duration of response will be determined for response assessments per IRC review as well as by investigator.

- Duration of complete response (DOCR) – defined as the interval from the date of first documented CR per IWG criteria to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment. Dates of disease progression and censoring will be determined as described in Section 4.5.6.2. Duration of complete response will be determined for response assessments per IRC review as well as by investigator.

- Time to next anti-lymphoma treatment (TTNLT) – defined as the interval from the start of study drug treatment to the date of next anti-lymphoma treatment (including chemotherapy, radiotherapy, radioimmunotherapy, or immunotherapy). Patients who do not receive subsequent anti-lymphoma treatment will be censored at the date of their last non-missing disease assessment prior to the start of therapy.

- Progression-free survival (PFS) – defined as the interval from the start of study drug treatment to the date of first documented disease progression, initiation of new antineoplastic therapy, or death from any cause, whichever occurs first. Dates of disease progression and censoring will be determined as described in Section 4.5.6.2.

- Time to progression (TTP) – defined as the interval from the start of study drug treatment to the date of disease progression. Patients whose disease does not progress will be censored at the date of their last tumor assessment.

- Overall survival (OS) – defined as the interval from the start of study drug treatment to the date of death, for any reason. Patients without documentation

of death at the time of analysis will be censored at the date the patient was last known to be alive.

3.4.1.3 Exploratory Efficacy Endpoints

The following will be used to explore the correlation of baseline programmed cell death-1 (PD-1) expression and other immune checkpoint molecules with outcome:

- Expression of programmed cell death-ligand 1 (PD-L1) and other immune checkpoint molecules in tumor
- Tumor-infiltrating lymphocyte (TIL) counts (e.g., CD3, CD4, CD8)
- EBV-associated genes/proteins (e.g., EBER, BZLF-1/ZTA, LMP-1, BGLF-4/PK, BXLF-1/TK, BRLF-1Rta)

In addition, the following potential biomarkers of activity will be evaluated for the combination therapy: histone H3 acetylation, plasma EBV DNA levels, ribonucleic acid (RNA) expression of selected immunological genes, and flow cytometry/IF/IHC for immune cell markers.

EBER, LMP-1, TIL counts, PD-L1, and other immune checkpoint molecules will be evaluated to identify potential resistance markers to therapy.

3.4.2 Safety Variables

Safety assessments consist of monitoring and recording all AEs, regular laboratory evaluation for hematology, blood chemistry, coagulation and urinalysis, periodic measurement of vital signs, ECGs, performance status, and physical examinations.

3.4.2.1 Adverse Events

An AE is any untoward medical event that occurs to a patient following the start of administration of the study drugs, whether or not considered study drug related. An AE can, therefore, be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom or disease temporally associated with the use of a drug, whether or not considered related to the drug. For example, it may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the patient's health, including laboratory test values (as specified by the criteria below), regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) will be considered an AE. A diagnosis or syndrome will be recorded on the Adverse Events eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

An overdose, accidental or intentional, associated with an AE, or abuse, withdrawal, sensitivity, or toxicity to an investigational product should be reported as an AE. Overdoses with or without an associated AE will be recorded on the dosing eCRF. All patients will be monitored for AEs during the study and continue until 28 days after the last dose of study drugs or until a new anticancer treatment is started, whichever occurs.

Pre-existing conditions are not considered AEs unless the condition worsens by at least one grade following the start of administration of the study drugs.

3.4.2.2 Laboratory Parameters

Clinical laboratory evaluations will follow those outlined in the clinical study protocol and will be performed using a central or local laboratory. Evaluations include hematology, chemistry, urinalysis, coagulation, and pregnancy tests (for women of childbearing-potential only). Specific parameters to be collected are listed below:

- Hematology (blood): Complete blood count with differential to include white blood cells and differential, red blood cells, hemoglobin, hematocrit, platelets, mean corpuscular hemoglobin, mean corpuscular volume

- Chemistry (blood): Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, aspartate aminotransferase (AST), aminotransferase, alanine aminotransferase (ALT), total bilirubin, alkaline phosphatase, total protein, albumin, uric acid, lactate dehydrogenase (LDH), and serum amylase

- Coagulation (blood): prothrombin time, partial thromboplastin time, and international normalized ratio

- Urinalysis (urine): color (appearance), glucose, bilirubin, ketones, specific gravity, blood pH, protein, urobilinogen, nitrite, leukocyte esterase

3.4.2.3 Other Safety Variables

Electrocardiograms

Electrocardiograms will be performed as outlined in the clinical study protocol. Triplicate ECGs should be obtained in close succession from the first ECG to the third ECG. For each sampling time point, 3 standard resting 12-lead ECGs will be obtained in close succession and no more than 2 minutes apart (4 minutes total for 3 ECGs). Average corrected QT interval using Fridericia's method (QTcF) will be calculated to confirm eligibility.

When performed on days that include PK sample collection (Stage 1), two triplicate ECGs will be performed post-dose (within 1 hour of dose, separated by at least 15 minutes). Post-dose ECGs will be performed prior to and as close as possible to each PK sample collection at C_{max} (1 and 2 hours) and 4 hours.

For days with no scheduled PK sample collections, the ECG may be performed at any time during the clinic visit, or when clinically indicated, irrespective of the time of study drug dosing. All ECGs will be independently reviewed by a central laboratory.

Clinically significant abnormalities present at screening should be reported on the Medical History eCRF page. New or worsened clinically significant findings occurring after informed consent must be recorded on the Adverse Events eCRF page. All eligibility and patient management decisions should be based on the local reading of the ECG.

Vital Signs

Vital signs (temperature, blood pressure, and heart rate) will be obtained at the Screening visit (Day -28 to Day -1), on Day 1 of each cycle (Day 4 of Cycles 2 and 6), and at the End of Treatment (EOT) visit. Vital signs will be collected just prior to the first dose of valganciclovir and nanatinostat, and in concert and just prior to PK blood draws. On other indicated visit days, collect vital signs once (prior to dosing of study drugs, if administered in clinic).

Height and weight will be measured at screening (Day -28 to Day -1), and weight will subsequently be measured on Day 1 of each cycle (Day 4 of Cycles 2 and 6) and at the EOT visit. Height should additionally be measured in patients 12 to 17 years of age on Day 1 of each cycle (Day 4 of Cycles 2 and 6).

Physical Examinations and Performance Scales

Physical examinations will be performed at the screening visit only; symptom-directed physical examinations will be conducted at each visit through Safety Follow-up as outlined in the clinical study protocol. Performance status will be measured by ECOG performance status assessments and will be regularly evaluated as outlined in the clinical study protocol.

3.4.3 Pharmacokinetic Variables

Pharmacokinetic endpoints include observed plasma concentrations and estimated PK parameters for nanatinostat and ganciclovir, and these will be described in a separate analysis plan.

3.5 Data Quality Assurance

Report summaries will be generated using validated Base SAS® software, version 9.4 or higher, on a PC or server-based platform. Additional validated software may be used to generate analyses, as needed.

All SAS programs that create outputs or supporting analysis datasets will be validated by a second statistical programmer or biostatistician. At a minimum, validation of programs will consist of a review of the program log, review of output or dataset format and structure, and independent confirmatory programming to verify output results or dataset content. Additionally, all outputs will undergo a review by a senior level team member before finalization.

The content of the source data will be reviewed on an ongoing basis by project statistical programmers and statisticians. Data will be checked for missing values, invalid records, and extreme outliers through defensive programming applications, analysis-based edit checks, and other programmatic testing procedures. All findings will be forwarded to the project data manager for appropriate action and resolution.

4. STATISTICAL METHODS

4.1 General Methodology

Data will be analyzed by Emanate biostatistics personnel. Statistical analyses will be reported in the form of tables, figures, and listings, presented in rich text format, and using recommended ICH numbering. Output specifications for all tables, figures, and listings will be in conformance with guidelines specified by the ICH in Appendix 7 of the *Electronic Common Technical Document Specification (Apr 2003)*.

4.1.1 Reporting Conventions

The Simon 2-stage and post-Stage 2 expansion parts of the study will be analyzed separately. For safety analyses only, all patients who receive combination therapy over the course of the study will also be analyzed separately.

Tables and figures will be summarized by cohort within each part. A more detailed description for how these data will be presented for each type of analysis (e.g., safety, efficacy, etc.) is provided in subsequent sections herein. In general, all data collected and any derived data will be presented in patient data listings for all enrolled patients. Listings will be ordered by phase, site, cohort, patient number, and assessment or event date. The cohort presented in listings will be based on the planned assignment, unless otherwise noted.

In general, continuous variables will be summarized to indicate the study population sample size (N), number of patients with available data (n), mean, SD, median, first (Q1) and third (Q3) quartiles, minimum, and maximum values. Categorical variables will be summarized by the population size (N), number of patients with available data (n), number of patients in each category, and the percentage of patients in each category. Unless otherwise noted, the denominator to determine the percentage of patients in each category will be based on the number of patients with available data. Select ordinal data may be summarized using both descriptive statistics and counts and percentages of patients in each category, as appropriate.

Non-zero percentages will be rounded to one decimal place. Rounding conventions for presentation of summary statistics will be based on the precision of the variable of summarization, as it is collected in its rawest form (i.e., on the electronic case report form [eCRF] or as provided within an external file) and are outlined as follows:

- The mean and median will be rounded to one more decimal place than the precision of the variable of summarization;
- Measures of variability (e.g., SD, SE) will be rounded to two more decimal places than the precision of the variable of summarization; and
- Minimum and maximum values will be presented using the same precision as the variable of summarization.

Other statistics (e.g., CIs) will be presented using the same general rules outlined above or assessed for the most appropriate presentation based on the underlying data.

No formal statistical analysis will be performed to compare cohorts. No formal type-1 error adjustment will be performed at the interim analysis or at the final analysis. Descriptive statistics will be tabulated by cohort and reviewed to evaluate all study endpoints.

4.1.2 Summarization by Visit

Data summarized by study visit will be based on the nominal, scheduled visit label as reported on the eCRF. Data collected for the last patient visit will be summarized separately and this summary will be labeled as "End of Treatment" in the analysis.

Data collected at unscheduled visits will not be included in by-visit summaries but will be considered when endpoint derivations potentially include multiple visits (e.g., determination of baseline value, determination of worst post-baseline value, etc.). All data will be included in patient listings.

4.1.3 Data Handling Rules

Unless otherwise noted, values reported as greater than or less than some quantifiable limit (e.g., "<1.0") will be summarized with the sign suppressed in summary tables and figures, using the numeric value reported. Data will display patient listings to include the sign.

4.1.4 Baseline Value

Unless otherwise noted, the baseline value will be defined as the last value reported prior to the first dose of study drug.

4.1.5 Standard Calculations

Where appropriate, the calculated study day of each assessment or event will be presented with the assessment or event date on patient data listings, where study day will be determined as:

- The assessment/event date minus the date of first dose of study drug, if the assessment/event date is prior to the date of first dose; and
- The assessment/event date minus the date of first dose of study drug, plus one, if the assessment/event date is on or after the date of first dose.

Other variables requiring calculations will be derived using the following formulas:

- **Days:** A duration between two dates expressed in days will be calculated using the following conventions:
    - Later date – earlier date + 1, if the earlier date is on or after the reference date of interest (e.g., date of first dose of study drug); or
    - Later date – earlier date, if the earlier date is prior to the reference date of interest.

- **Months:** A duration expressed in months will be calculated by dividing the duration in days by (365.25 / 12).

- **Years:** A duration expressed in years will be calculated by dividing the duration in days by 365.25.

- **Change from Baseline:** Change from baseline will be calculated as the post baseline value minus the baseline value.

- **Percentage Change from Baseline:** Percentage change from baseline will be calculated as the change from baseline divided by the baseline value, multiplied by 100.

- **Second-Line EBV$^+$ Lymphoma:** Relapsed or refractory disease following 1 prior systemic therapy (regimen). Inclusion in this subgroup will be determined using data collected for line of therapy on the Anti-Cancer Therapy Regimen eCRF.

4.2 Analysis Sets

The analysis sets are defined as follows:

- Intent-to-Treat Analysis Set: All patients who are enrolled into the trial, regardless of whether they received study treatment or not.

- Modified Intent-to-Treat Analysis Set: All enrolled patients who have received at least one dose of study medication with a confirmed diagnosis of lymphoma subtype by central pathology review. The primary efficacy analysis will be performed in the Modified Intent-to-Treat Analysis Set per FDA guidance and historical precedent.

- Efficacy-Evaluable Analysis Set: All enrolled patients who have received at least one dose of study medication, met all eligibility criteria, and have at least one adequate (radiographic) post-baseline tumor assessment.

- Safety Analysis Set: Patients who have received at least one dose of study medication will be summarized for safety by cohort and over all patients combined.

4.3 Study Patients

4.3.1 Disposition of Patients

Patient disposition will be summarized for all enrolled patients (i.e., the Intent-to-Treat Analysis Set) by cohort and over all patients combined within each part of the study (Simon 2-Stage, Expansion). Summaries will include the number and percentage of patients in each analysis set, completing the study, and discontinuing the study early by the primary reason for discontinuation.

For the post-Stage 2 expansion phase of the study, disposition will also be summarized for the subgroup of patients in the Intent-to-Treat Analysis Set with second-line EBV^+ lymphoma as defined in Section 4.1.5.

The number and percentage of screen failures within each part will be presented by screen failure reason, based on the total number of patients screened.

4.3.2 Protocol Deviations

Important Protocol Deviations (IPDs) will be summarized by cohort and over all patients combined for the Intent-to-Treat Analysis Set within each part of the study (Simon 2-Stage, Expansion). Important Protocol Deviations are identified by the Sponsor and are defined in the ICH guideline *Structure and Content of Clinical Study Reports – Questions and Answers (E3[R1], 2013)* as a subset of protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.

For the post-Stage 2 expansion phase of the study, disposition will also be summarized for the subgroup of patients in the Intent-to-Treat Analysis Set with second-line EBV^+ lymphoma as defined in Section 4.1.5. All IPDs will be determined and appropriately categorized prior to database lock. The number and percentage of patients with any IPDs as well as the number and percentage of patients with IPDs within each category will be presented.

4.4 Demographic and Other Baseline Characteristics

Demographic and baseline characteristic variables will be summarized by cohort and over all patients combined within each part of the study (Simon 2-Stage, Expansion) for the Modified Intent-to-Treat, Safety, and Efficacy Evaluable Analysis Sets. Demographic and baseline characteristic variable summaries may also be repeated for the Intent-to-Treat Analysis Set if meaningfully different than the Modified Intent-to-Treat Analysis Set.

For the post-Stage 2 expansion phase of the study, demographic and baseline characteristics will also be summarized in the Modified Intent-to-Treat Analysis Set for the subgroup of patients with second-line EBV^+ lymphoma as defined in Section 4.1, maintaining the option of repeating summaries of demographics and baseline characteristics for the Intent-to-Treat Analysis Set if meaningfully different than the Modified Intent-to-Treat Analysis Set. This subgroup will also be used for the primary interim analyses.

Demographic variables include age, sex, ethnicity, and race. Age as collected in the EDC will be summarized using descriptive statistics. Sex, ethnicity, and race will be summarized with the number and percentage of patients in each parameter category.

Baseline characteristics include medical history, ECOG performance status, height, weight, and body mass index (BMI), lymphoma subtype by central review, time from initial diagnosis, stage of disease at study entry, presence or absence of bone marrow involvement, number and types of prior systemic therapies (and prior local therapies) for lymphoma, and plasma EBV DNA level. Body mass index will be calculated as: weight (kg) / [height (cm) / 100]^2.

Height, weight, and BMI at baseline will be summarized using descriptive statistics. ECOG performance status will be summarized with the number and percentage of patients in each category.

Medical history conditions will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA, version 26.0). Frequency counts and percentages to summarize patients reporting abnormal medical history by system organ class will be presented.

For lymphoma medical history, pathological diagnosis, the number of prior systemic therapies, presence or absence of bone marrow involvement, best response achieved with the most recent treatment regimen, stage at study entry, whether or not patient is or refractory to last therapy received prior to entering the study, number of prior autologous or allogeneic stem cell transplants, and whether or not the patient has exhausted all available therapies in the opinion of the investigator will be summarized with the number and percentage of patients in each category. The time since the date of original lymphoma primary diagnosis will be summarized using descriptive statistics. All other lymphoma medical history will be included in patient data listings.

4.5 Efficacy Evaluation

For the Simon 2-stage part of the study, since Cohort 3 (PTCL) patients are initially randomized to monotherapy or combination therapy, their data will be summarized as follows: patients randomized to monotherapy, patients who start on monotherapy and then cross over to combination therapy, and patients randomized to combination therapy.

For the post-Stage 2 expansion part of the study, patients with second-line EBV^+ lymphoma will also be analyzed separately, and the primary efficacy analyses will be performed in this patient subgroup at the interim analysis (see Section 4.5.6.3 for details of this interim efficacy analysis) and at the final analysis.

4.5.1 Datasets Analyzed

Efficacy summaries will be produced as described in Section 4.2. Efficacy summaries will be repeated for the Efficacy Evaluable Analysis Set as supportive evidence and to assess the robustness of efficacy findings. Efficacy summaries may also be repeated for the Intent-to-Treat Analysis Set if meaningfully different than the Modified Intent-to-Treat Analysis Set. A data listing of patients excluded from the Intent-to-Treat, Modified Intent-to-Treat, and Efficacy Evaluable Analysis Sets, to include the reason for exclusion, will be presented.

4.5.2 Measurements of Treatment Compliance

Compliance with both nanatinostat and valganciclovir will be determined as the total number of tablets taken divided by the expected number of tablets dispensed, multiplied by 100.

The total number of tablets taken will be determined as the number of tablets dispensed minus the total number of tablets returned. The expected number of tablets received will be determined as the number of tablets dispensed.

Dosing compliance will be summarized using descriptive statistics, for each cohort based on the Safety Analysis Set. The number and percentages of patients who are <80% compliant and ≥80% compliant within each cohort will be summarized. Treatment compliance will also be included in a by-patient data listing.

4.5.3 Primary Efficacy Endpoint Analysis Methods

The primary efficacy endpoint is ORR assessed by an IRC.

Patients will be analyzed according to their cohort/lymphoma subtype. For Cohort 3a patients who cross over from monotherapy to receive combination therapy, the CT/PET scan immediately preceding their first dose of combination therapy will be used for their baseline tumor assessment (and not the scan performed at the screening visit).

The number and percentage of patients with a CR or PR after initiation of treatment will be summarized by cohort. Ninety-five percent (95%) confidence intervals (CIs) around the ORR (CR + PR) will be calculated using the Clopper-Pearson method. For patients with measurable disease, a swimmer plot of each patient's overall tumor response assessments during study participation and patient deaths (for those patients who have died) will be presented by cohort.

4.5.4 Secondary Endpoint Analysis Methods

The ORR per investigator assessment, CRR per IRC review, and CRR per investigator assessment will be summarized using the same methods as described for the primary efficacy endpoint.

Time to response, DOR, DOCR, TTNLT, TTP, PFS, and OS will be summarized in days using Kaplan-Meier (KM) methodology. The number of patients who experienced the event of interest and the number of patients censored will be presented; as will KM product limit estimates of the median with associated CIs (where estimable) using Greenwood's formula. The range for all patients, as well as those who experience the event of interest will also be summarized. Kaplan-Meier estimates of the survival distribution function for DOR, PFS, and OS over time will be generated and all derived efficacy measures will also be provided in a separate listing.

For Cohort 3a patients who crossover to receive combination therapy, DOR and DOCR will only be applicable after crossover given the requirement that patients only cross over from monotherapy to combination therapy after stable disease at the Day 43 visit (or progressive disease at any time).

4.5.5 Additional Efficacy Endpoint Analysis Methods

Each patient's EBV viral load will be plotted over time by cohort and displayed on logarithmic scales.

Additional exploratory endpoints will be described in a separate analysis plan.

4.5.6 Statistical/Analytical Issues

4.5.6.1 Adjustments for Covariates

There are no planned applications of covariate adjustments; all statistical results are descriptive in nature.

4.5.6.2 Handling of Dropouts or Missing Data

Overall response is based on those patients with available data (baseline and post-baseline response assessment). Non-evaluable patients are considered non-responders and will be included in the denominator. Progression-free survival and DOR will be right-censored for patients who meet one of the following conditions: 1) non-protocol systemic anti-cancer treatment started before documentation of disease progression or death, 2) death or disease progression after more than one missed disease assessment visit, or 3) alive and does not have documentation of disease progression before a data analysis cutoff date. These conventions are based on the FDA Guidance for Industry, *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics* (2018) and *Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics* (2015). The analyses of PFS and DOR will be right-censored according to the conventions described in the table below.

Table 3 Censoring Conventions for Progression-Free Survival, Time to Progression, and Duration of Response

Situation	Date of Progression for Censoring	Outcome
No baseline tumor assessments	Randomization (if applicable) or enrollment	Censored
New anti-cancer therapy started before documentation of PD or death	Date of last disease assessment prior to start of new anti-cancer therapy	Censored*
Death or PD immediately after more than one consecutively missed disease assessment visit	Date of last disease assessment visit without documentation of PD that is before the first missed visit	Censored
Alive and without PD documentation	Date of last disease assessment	Censored
Death or PD between planned disease assessments	Date of death or first disease assessment showing PD, whichever occurs first	Progressed

Situation	Date of Progression for Censoring	Outcome
Death before first disease assessment	Date of death	Progressed

*PFS, TTP, DOR will additionally be analyzed without censoring for hematopoietic stem cell transplant

4.5.6.3 Interim Analyses and Data Monitoring

In addition to the Stage 1 analysis specified by Simon's decision criteria for proceeding to Stage 2, a formal interim analysis will be performed for a post-Stage 2 expanded lymphoma subtype cohort overall and for patients with second-line EBV^+ lymphoma. A total of 40 second-line EBV^+ lymphoma patients who have been followed for at least 6 months or permanently discontinued study treatment, will be used for the interim analysis. For these interim analyses, the observed ORR by IRC will be evaluated along with the 95% confidence interval. Other secondary endpoints will be evaluated with descriptive statistics such as both point and interval estimates.

The final efficacy analysis will be performed as planned with a total 120 patients with relapsed or refractory EBV^+ lymphoma patients enrolled in the post-Stage 2 expansion phase of the study, which are anticipated to include approximately 50-60 patients with second-line EBV^+ lymphoma. The final analysis will be performed when all patients, including those with second-line EBV^+ lymphoma have been followed for at least 6 months or permanently discontinued study treatment. If at least 26 responses are observed for an ORR ≥65% (95% CI: 79%, 48%) at interim analysis of 40 patients with second-line EBV^+ lymphoma, then overwhelming efficacy would be declared to potentially support accelerated NDA submission after these patients are followed for at least 6 months for DOR and other secondary endpoints. This magnitude of treatment effect at the interim analysis would exclude an approximately 47% ORR with 95% confidence. Of note, enrollment into any post-Stage 2 expansion cohort would continue to complete the planned enrollment of 120 patients for the final analysis independent of the interim analysis outcome.

4.5.6.4 Multicenter Studies

This is a multicenter study, with approximately 80 sites expected to participate. Efficacy data collected from all study sites will be pooled for data analysis. The effect of study site on the efficacy analysis results may be explored post-hoc, as needed.

4.5.6.5 Multiple Comparisons/Multiplicity

There will be no adjustments for multiple comparisons in the efficacy analysis for this study. Results are descriptive in nature, and no statistical hypothesis testing is planned.

There will be no adjustments for multiple comparisons in the efficacy analysis for this study.

4.5.6.6 Use of an "Efficacy Subset" of Patients

The primary efficacy analysis will be performed in the Modified Intent-to-Treat Analysis Set; the Intent-to-Treat and Efficacy Evaluable Analysis Sets will be utilized as sensitivity analyses.

4.5.6.7 Active-Control Studies Intended to Show Equivalence

This study does not include an active-control product and is not intended to demonstrate equivalence between any two drug products.

4.5.6.8 Examination of Subgroups

The primary efficacy endpoint may be summarized by various subgroups of interest based on baseline and demographic categories including age (<65 years of age and ≥ 65 years of age), ECOG performance status at study entry (0, 1, and 2), number of prior systemic therapies (1 line and 2+ lines), stage of disease at study entry (Stages 1-2 and Stages 3-4), gender, and race. Summaries by subgroup will only be produced if there are at least 6 patients in the category of interest.

For the post-Stage 2 expansion part of the study, all efficacy analyses will also be summarized in the Modified Intent-to-Treat and Efficacy Evaluable Analysis Sets for the subgroup of patients with second-line EBV^+ lymphoma as defined in Section 4.1.

Additional subgroup analyses may be performed post-hoc, as appropriate.

4.5.7 Plasma Concentrations

Plasma concentration measurements will be summarized in a separate report and is outside the scope of this SAP.

4.5.8 Pharmacokinetic Analysis

Pharmacokinetic analysis will be summarized in a separate report and is outside the scope of this SAP.

4.6 Safety Evaluation

Safety analysis will be carried out for the Safety Analysis Set as defined in Section 4.2 to include all patients who receive at least one dose of study drug. Patients who do not complete the study, for whatever reason, will have all available data up until the time of study discontinuation included in the safety analysis.

For the Simon 2-stage part of the study, since Cohort 3 (PTCL) patients are initially randomized to monotherapy or combination therapy, their data will be summarized as follows for occurrence-based analyses: patients randomized to monotherapy, patients who start on monotherapy and then cross over to combination therapy, and patients randomized to combination therapy. For analyses presented by study visit, their data will be summarized as randomized.

In addition, all patients who receive combination therapy at any point on study (to include Cohort 3a patients who cross over from monotherapy to combination therapy

during the Simon 2-stage part of the study) will be summarized across both parts of the study separately by cohort and also overall.

4.6.1 Extent of Exposure

Extent of exposure to both study treatments will be summarized. The duration of exposure will be presented in days and calculated as the date of last dose of study drug minus the date of first dose of study drug, plus one. Duration of exposure and total dose received (mg) will be summarized using descriptive statistics.

4.6.2 Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as those AEs with onset after the first dose of study drug or existing events that worsened after the first dose during the study. Treatment-emergent AEs will be summarized by cohort and over all patients combined.

Specific to Cohort 3a, for patients who cross over to receive combination therapy, events that occur during the monotherapy period will be counted in the Cohort 3a monotherapy subcohort only. Events that occur after the end of monotherapy but prior to the first date of treatment within the combination period will also be counted in the Cohort 3a monotherapy subcohort only. Events occurring after the start of combination therapy will be counted in the Cohort 3a crossover subcohort only.

Events reported with a partial onset date (e.g., month and year are reported but the day is missing) will be considered to be treatment-emergent if it cannot be confirmed that the event onset was prior to the first dose of study drug based on the available date entries.

Verbatim terms on case report forms will be mapped to preferred terms and system organ classes using MedDRA, version 26.0.

Summaries that are displayed by system organ class and preferred terms will be ordered by descending incidence of system organ class and preferred term within each system organ class. Summaries displayed by preferred term only will be ordered by descending incidence of preferred term. Summaries of the following types will be presented:

- Overall summary of number of unique TEAEs and patient incidence of TEAEs meeting various criteria;
- Overall summary of number of unique treatment-emergent serious adverse events (SAEs) and patient incidence of treatment-emergent SAEs meeting various criteria;
- Patient incidence of TEAEs by MedDRA system organ class and preferred term;
- Patient incidence of the most frequently occurring TEAEs (i.e., TEAEs occurring in ≥ 10% of the Safety Analysis Set) by MedDRA preferred term;

- Patient incidence of TEAEs by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs by relationship to nanatinostat, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs by relationship to valganciclovir, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to nanatinostat by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to valganciclovir by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to nanatinostat or valganciclovir by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of the most frequently occurring TEAEs related to nanatinostat (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Set) by MedDRA preferred term;
- Patient incidence of the most frequently occurring TEAEs related to valganciclovir (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Set) by MedDRA preferred term;
- Patient incidence of the most frequently occurring TEAEs related to nanatinostat or valganciclovir (i.e., related TEAEs occurring in ≥ 10% of the Safety Analysis Set) by MedDRA preferred term;
- Patient incidence of TEAEs leading to dose interruption of nanatinostat by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to dose interruption of valganciclovir by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to dose interruption of nanatinostat or valganciclovir by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to dose reduction of nanatinostat by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to dose reduction of valganciclovir by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to dose reduction of nanatinostat or valganciclovir by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to nanatinostat leading to discontinuation of study drug by MedDRA system organ class and preferred term;

- Patient incidence of TEAEs related to valganciclovir leading to discontinuation of study drug by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs related to nanatinostat or valganciclovir leading to discontinuation of study drug by MedDRA system organ class and preferred term;
- Patient incidence of SAEs by MedDRA system organ class and preferred term;
- Patient incidence of SAEs by CTCAE grade, MedDRA system organ class and preferred term;
- Patient incidence of SARs (nanatinostat) by MedDRA system organ class and preferred term;
- Patient incidence of SARs (valganciclovir) by MedDRA system organ class and preferred term;
- Patient incidence of SARs (nanatinostat or valganciclovir) by MedDRA system organ class and preferred term;
- Patient incidence of TEAEs leading to death by MedDRA system organ class and preferred term.

Select AE summaries will also be repeated for different age subgroups (<65 years old, ≥65 years old). Separate AE summaries may also be repeated for adolescents 12-17 years old if there are at least 5 patients enrolled for this age group. Selected AE summaries may be repeated in terms of exposure-adjusted rates in 100 patient-years.

At each level of summarization (e.g., any AE, system organ class, and preferred term), patients experiencing more than one TEAE will be counted only once. In the summary of TEAEs by CTCAE grade, patients will be counted once at the highest severity reported at each level of summarization; in the summary of TEAEs by relationship, patients will be counted once at the closest relationship to study drug. Related events include those reported as "Possibly Related" or "Definitely Related" to study drug; events considered not related are those reported as "Unrelated" to study drug.

For summaries of treatment-related TEAEs by CTCAE grade, a column summarizing patients with at least one treatment-related Grade ≥3 TEAE will also be presented.

Adverse event data will be presented in data listings by patient, cohort, and event. Serious AEs and AEs leading to permanent discontinuation of the study drugs will also be presented in separate data listings.

4.6.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

All deaths during the study, including the post-treatment follow-up period, will also be listed by patient, to include the primary cause of death. Serious AEs and other significant AEs, including those that led to study withdrawal, dosing interruption, or dose reduction of either study drug, will be provided in separate patient data listings.

4.6.4 Clinical Laboratory Evaluation

All descriptive summaries of laboratory test results will be based on data analyzed by the central or local laboratories and presented in Système International (SI) units, as suggested by the Center for Biologics Evaluation and Research and the Center for Drug Evaluation and Research *Position on Use of SI Units for Lab Tests* (Oct 2013). All data will be included in by-patient data listings. Laboratory measurements identified as abnormal (i.e., outside the normal range) will also be listed separately by patient, laboratory test, and unit. By-patient data listings of laboratory test abnormalities Grade ≥3 will also be provided. In addition, normal ranges provided by the central or local laboratories will be presented in a separate listing.

Clinical laboratory measurements, including serum chemistry, hematology, and coagulation will be summarized by study phase and cohort. Descriptive statistics will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected per the clinical study protocol.

The cumulative number and percentage of patients with liver function test abnormalities meeting drug-induced liver injury (DILI) criteria will be summarized by cohort. Patients meeting DILI criteria will also be presented in a patient data listing.

In addition, creatinine clearance will be calculated by the Cockcroft-Gault formula. For males, the creatinine clearance in mL/min will be calculated as [(140 - age) × weight (kg)] / [72 ×serum creatinine (mg/dL)]. For females, the creatinine clearance in mL/min will be calculated as 0.85 × the male value. The mean change from baseline over time for creatinine and creatinine clearance will be presented graphically over time by cohort and over all patients combined.

Where applicable, laboratory results will be classified as “low,” “normal,” or “high” with respect to the parameter-specific reference ranges (i.e., below the lower limit of the normal range, within the normal range, or above the upper limit of the normal range). Three-by-three contingency tables will be presented for each laboratory parameter to summarize the shift from the baseline category to the worst post-baseline measurement, defined as the value numerically farthest outside of the normal range across all post-baseline visits through the end of the study.

Summary results will include the count and percentage of patients within each shift category and cohort.

Where applicable, hematology and chemistry results for selected parameters will be assigned a toxicity grade based on the U.S. Department of Health and Human Services *Common Terminology Criteria for Adverse Events (CTCAE)*, version 5.0 (27 Nov 2017). If criteria for a grade includes a quantitative component and a clinical intervention component, the clinical intervention component will be ignored where it cannot be programmatically addressed using available data and only the quantitative portion of the criteria will be considered. If the quantitative criteria for grading are equivalent for two grades and the differentiation is described by clinical interventions, the clinical intervention component will not be considered and the highest CTCAE grade will be assigned. Similarly, death related to AE (i.e., Grade 5) cannot be determined with available laboratory-based data collection and, thus, will not be

summarized as a category. Laboratory parameters that include multiple sets of criteria for each direction (e.g., separate criteria for potassium measures to assess hyperkalemia and hypokalemia) will be summarized separately to reflect each set of criteria.

Five-by-five contingency tables will be presented for laboratory tests where toxicity grading can be applied, to summarize the shift from the baseline grade to the worst post-baseline grade. Grades will be presented as none (Grade 0; i.e., measurements did not meet any CTCAE criteria for Grades 1 through 4), mild (Grade 1), moderate (Grade 2), severe (Grade 3), or life-threatening (Grade 4). Summary results will include the count and percentage of patients within each shift category.

4.6.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

4.6.5.1 Vital Signs

Descriptive statistics for vital sign parameter measurements will be presented for results and change from baseline at each visit where parameters were scheduled to be collected.

4.6.5.2 12-Lead Electrocardiogram

Descriptive statistics for 12-lead ECG interval parameters will be presented for observed values and changes from baseline at each visit where parameters were scheduled to be collected. All ECGs will be performed in triplicate, and the mean of these triplicate measurements at each time point will be used for summarization.

Twelve-lead ECGs will be classified by the investigator as “normal,” “abnormal,” “not clinically significant,” or “abnormal, clinically significant.” The worst classification for each set of triplicate 12-lead ECGs will be used for analysis. Three-by-three contingency tables will be presented to summarize the shift from the baseline category to the worst post-baseline value. Summary results will include the count and percentage of patients within each shift category and cohort.

Prolonged QTcF will be summarized as QTcF measurements (msec) that are >450, >480, and >500 msec averaged over each set of triplicate 12-lead ECGs at each visit where ECG is routinely collected per the clinical study protocol. Change from baseline categories will also be summarized for measurements that represent a change >30 or >60 msec relative to the baseline value. Summary results will include the percentage of patients within each category and cohort.

Clinically significant abnormalities occurring at any point in the study post-baseline will be presented in patient data listings.

4.6.5.3 Physical Examination

Results of physical examinations will be presented in patient data listings by patient, study visit, and body system. Any findings during symptom-directed exams will be reported as AEs.

4.6.5.4 ECOG Performance Status

Performance status will be assessed using the ECOG scale. Descriptive statistics will be presented for observed values and changes from baseline at each visit where assessments were scheduled to be collected per the clinical study protocol. Results will be presented in patient data listings.

4.6.5.5 Viral Levels

Viral levels [EBV, CMV, HHV-6, HHV-8, and HIV (for HIV+ patients only)] will be monitored for viral reactivation. Results will be presented in patient data listings only.

4.6.5.6 Prior and Concomitant Medications

Medications will be coded using the World Health Organization Drug Dictionary Enhanced (WHODDE), version March 1, 2023. Medications entered on the eCRF will be mapped to Anatomical Therapeutic Chemical (ATC) drug class (level 4) and drug name.

Prior and concomitant medications will be summarized separately, and the categorization of each medication will be determined programmatically based on medication start and end dates. A prior medication is defined as any medication administered prior to the date of the first dose of study drug with an end date prior to date of first dose of study drug. A concomitant medication is defined as any medication administered on or after the date of the first dose of study drug through 28 days after the last dose of study medication. Any medication whose start date/time cannot be determined due to partial or missing medication start and/or end dates will be considered a concomitant medication.

For both prior and concomitant medications summaries, the number and percentage of patients receiving any medication will be summarized by cohort, as will the number and percentage receiving any medication by ATC drug class and generic drug name. Prior medications will also be summarized over all patients combined. Patients reporting use of more than one medication at each level of summarization (any medication received, ATC class, and generic drug name) will be counted only once. ATC class terms will be displayed by descending order of incidence, as will generic drug names within each ATC class. The study phase during which each medication was received (e.g., prior, concomitant, or both) will be presented on the listing of prior and concomitant medications.

4.7 Determination of Sample Size

This multinational, multicenter study will employ a Simon's optimal 2-stage design to allow termination of enrollment into cohorts where treatment appears futile (Simon 1989). The decision to transition from Stage 1 to Stage 2 is dependent on the assumption of ORR: ORR ≤10% (poor response); ORR ≥35% (good response). The sample size estimation uses 1-sided alpha = 0.05 and targets statistical power = 85%.

Using the Simon's 2-stage design approach, the null hypothesis that the true response rate is 10% will be tested against a one-sided alternative. In the first stage, up to 10 patients will be accrued in each cohort. If there are 1 or fewer responses, the cohort will

be discontinued. If the cohort fails to enroll any patients within 1 year from the enrollment of the first patient, the cohort will be considered for termination of enrollment. Otherwise, if at least 2 patients in a cohort respond, additional patients will be accrued for a total of 21 in the cohort. The null hypothesis that the true response rate is 10% will be rejected in each cohort where 5 or more responses are observed in 21 patients. This design yields a type I error rate of 0.0440 and power of 86.2% within each cohort where the true response rate is 35%.

If 10 patients of a given lymphoma subtype are enrolled into Cohort 7, then the Simon's decision criteria will be applied to determine whether or not to add patients in Stage 2 for that subtype. If none of the subtypes represented in Cohort 7 enrolls at least 10 patients, efficacy data collected on those patients will be listed, but not summarized by group. All patients will be summarized for safety, regardless of the decision to discontinue enrollment into any cohort.

If at the end of Stage 2 there are at least 7 responders observed in the initial 21 patients in any cohort (ORR ≥33.3%), enrollment will be expanded to include up to 120 additional patients in that cohort (N=141), with an interim analysis in that cohort to be performed as described in Section 4.5.6.3. Simon's Stage 2 estimate was ORR=33.3% for the PTCL cohort. Using Clopper-Pearson Exact confidence interval approach, the sample size for a 95% CI that would exclude 25% if the ORR was 33.3% was N=120. Using ORR=35%, the minimum sample size is estimated to be N=85.

A formal interim analysis will be performed for each post-Stage 2 expanded lymphoma subtype cohort in patients with second-line EBV^+ lymphoma when a total of 40 second-line EBV^+ lymphoma patients have been followed for at least 6 months or permanently discontinued study treatment. The rationale for selecting 40 patients at the interim analysis is provided in Table 4 below using the Clopper-Pearson binomial confidence intervals of the proportion (Clopper 1934).

Table 4 Sample Sizes for the Interim and Final Analyses of Patients with Second-Line EBV^+ Lymphoma

Sample Size	Observed Rate	95% CI	Control Rate
40	42.5%	(59%, 27%)	25%
	52.5%	(68%, 36%)	35%
	65%	(79%, 48%)	45%
50	40%	(55%, 26%)	25%
	50%	(64%, 36%)	35%
	62%	(75%, 47%)	45%
60	38%	(52%, 26%)	25%
	48%	(61%, 35%)	35%

Sample Size	Observed Rate	95% CI	Control Rate
	60%	(72%, 46%)	45%

If the observed effect is 52.5% (i.e., 21 responders out of 40 patients) at the interim analysis, then the 95% CI will exclude an ORR effect size of 35%. For these interim analyses, the observed ORR by IRC will be evaluated along with 95% CI. Other secondary endpoints will be evaluated with descriptive statistics such as both point and interval estimates.

The final efficacy analysis will be performed as planned with total 120 patients in the expansion stage of the study. Approximately 50-60 patients with second-line EBV^+ lymphoma are anticipated to be enrolled at the time of the final analyses. The final analyses will be performed when all patients, including second-line EBV^+ lymphoma patients, have been followed for at least 6 months or permanently discontinued study treatment.

4.8 Changes in the Conduct of the Study or Planned Analyses

The following changes were made to planned analyses identified during the development of this SAP, relative to the descriptions provided within the clinical study protocol amendment 5, dated 19 October 2023:

The protocol states that the Intent-to-Treat population will be used for the primary efficacy analysis. This SAP substitutes the following analysis sets as defined in Section 4.2 above for efficacy analyses, preserving the opportunity to repeat efficacy summaries for the Intent-to-Treat Analysis Set if meaningfully different than the Modified Intent-to-Treat Analysis Set:

- Modified Intent-to-Treat Analysis Set
- Efficacy-Evaluable Analysis Set

Addition of the following secondary efficacy endpoints as defined in Section 3.4.1.2 above:

- Complete response rate
- Duration of complete response
- Time to response

5. REFERENCE LIST

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007;25(5):579-86

CJ Clopper and ES Pearson. The use of confidence or fiducial limits illustrated in the case of the binomial. *Biometrika.* 1934; **26**:404-413.

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) (US). Guidance for industry: *Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.* December 2018. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-cancer-drugs-and-biologics

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (CBER) (US). Guidance for industry: *Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics*. April 2015. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-trial-endpoints-approval-non-small-cell-lung-cancer-drugs-and-biologics

ICH guideline *Statistical Principles for Clinical Trials (E9)* (1998) and *Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials (E9[R1], Rev 1)* (2021).

ICH in Appendix 7 of the *Electronic Common Technical Document Specification (Apr 2003)*

ICH guideline *Structure and Content of Clinical Study Reports – Questions and Answers (E3[R1], 2013)*

Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10(1):1-10.

Younes A, Hilden P, Coiffier B, et al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). *Ann Oncol Off J Eur Soc Med Oncol*. 2017; 28(7): 1436-1447.