ABBREVIATED STATISTICAL ANALYSIS PLAN

PHASE 1/2A OPEN-LABEL, MULTICENTER CLINICAL TRIAL OF A NOVEL SMALL MOLECULE EBNA1 INHIBITOR, VK-2019, IN PATIENTS WITH EPSTEIN-BARR VIRUS POSITIVE NASOPHARYNGEAL CANCER, WITH PHARMACOKINETIC AND PHARMACODYNAMIC CORRELATIVE STUDIES

SAP Version 1.0
FINAL
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for

Protocol No. VK-2019-001

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
BCAD	Biologically or Clinically Active Dose
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete Response
CTCAE	Common Toxicity Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose Limiting Toxicity
DOR	Duration of Response
EBNA1	Epstein-Barr Nuclear Antigen 1
EBV	Epstein-Barr Virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
h or hr	Hour
HR	Heart Rate
ICH	International Conference on Harmonisation
Mg	Milligram
MTD	Maximum tolerated dose
NPC	Nasopharyngeal Carcinoma
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PFS	Progression Free Survival
PD	Progressive Disease or Pharmacodynamics
PK	Pharmacokinetics
PR	Partial Response
QD	Once Daily
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
RR	Respiratory Rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
TEAEs	Treatment Emergent Adverse Events

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1 BACKGROUND

This is a phase 1/2a, open label, multicenter, multi dose, dose escalation trial of VK-2019, a potent and selective inhibitor of the EBV latency program through its specific binding to a viral target, EBNA1, in patients with Epstein Barr Virus positive nasopharyngeal cancer, with pharmacokinetic (PK), and pharmacodynamics (PD) correlative studies.

This statistical analysis plan (SAP) is for the abbreviated CSR of study VK-2019-001 and is based on the approved clinical study protocol, 15 October 2019, Version 9.0, Amendment 9.

The purpose of this document is to provide details about the statistical analysis methods for the VK-2019-001 protocol "Phase 1/2a open label, multicenter clinical trial of a novel small molecule EBNA1 inhibitor, VK-2019, in patients with Epstein Barr Virus positive nasopharyngeal cancer, with pharmacokinetic and pharmacodynamic correlative studies".

For background of study refer to Protocol Section 2 Background.

2 STUDY DESCRIPTION

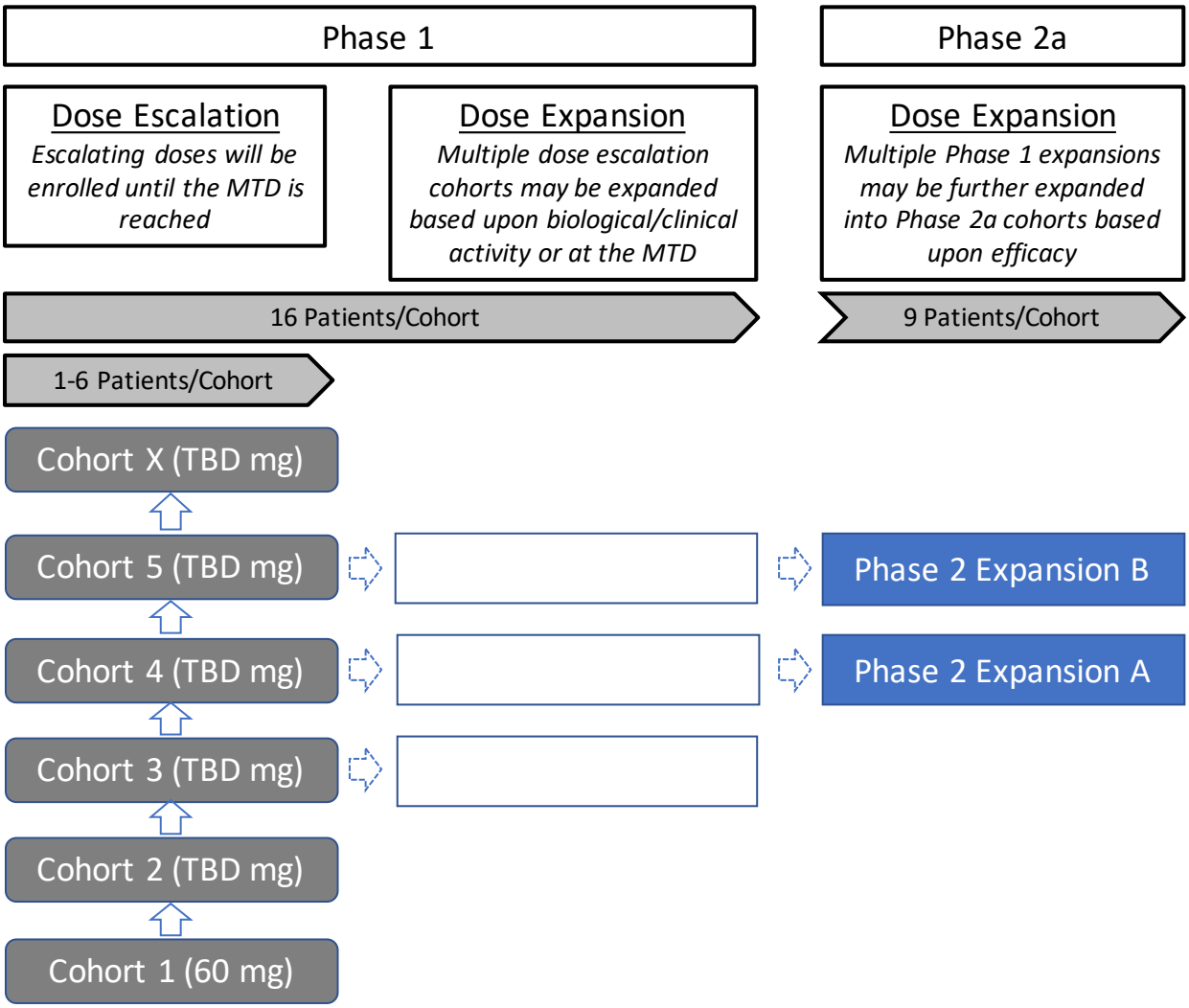
2.1 Study Design

This is a phase 1/2a, open label, multicenter, multi dose, dose escalation trial of VK-2019, a potent and selective inhibitor of the EBV latency program through its specific binding to a viral target, EBNA1.

For each patient enrolled, the study will consist of at least three periods: Screening (up to 28 days), Treatment (comprised of 28-day dosing cycles), and Follow up (comprised of a safety follow-up and long-term follow-up for survival status).

This trial is divided into three parts (Figure 1): Phase 1 Dose Escalation, Phase 1 Dose Expansion, and Phase 2a Dose Expansion. One sub-study, collecting tumor biopsies, will be conducted during the Phase 2 Expansion part of the trial.

Figure 1: Study Design Schema



Note: Three Phase 1 and two Phase 2 dose expansions are not specifically planned. The total number of expansions opened will depend upon biological and clinical activity observed in the trial

2.1.1 Phase 1 Dose Escalation

Dose escalation in this trial will be conducted utilizing both an accelerated titration, based in part upon a 3B design proposed by Simon et al (1), coupled with a "rolling six" design (2). Five dose escalation cohorts are planned, but additional dose escalation or intermediate de-escalation cohorts may be explored based upon emerging safety and/or PK data.

By utilizing these designs it is expected to maximize accrual at pharmacologically relevant doses, both by potentially minimizing accrual at subtherapeutic dose levels and more efficiently establishing an understanding of the safety profile of VK-2019 (3).

Dose escalation will initially proceed according to the accelerated titration design, enrolling one new patient per dose level. Upon any instance of a VK-2019 related Grade ≥ 2 AE during Cycle 1, dose escalation will convert to the Rolling Six design in which 3-6 patients per dose level will be enrolled.

2.1.2 Phase 1 Dose Expansion

During dose escalation, one or more cohorts may be selected for expansion, enrolling up to 16 patients (inclusive of the patients already enrolled at the same dose during escalation) at any dose level that is assessed to either be the MTD or have sufficient activity to meet criteria as a BCAD.

2.1.3 Phase 2a Dose Expansion

Further dose expansion in the Phase 2a part of the trial may be explored by utilizing the Simon 2 Stage design. Up to an additional nine patients may be enrolled at a particular dose if two or more objective responses (at least one must be confirmed) are observed out of 16 patients at that dose in the Phase 1 part of the trial (for a total accrual of up to 25 patients). See Protocol Section 6 for details on initiating a Phase 2a Dose Expansion.

2.2 Treatment Assignment

The starting dose for VK-2019 is 60 mg QD. Sample dose escalation tables are below in Table 1, detailing a sample dose escalation schema based upon when escalation converts from Accelerated Titration to a Rolling Six design.

2.2.1 Definition of a Completed Cohort and an Evaluable Patient

Each dose escalation cohort will consist of either:

- 1 evaluable patient (Accelerated Titration cohorts), or
- 3-6 evaluable patients (Rolling Six cohorts)

To be considered evaluable, a patient will have and one of the following:

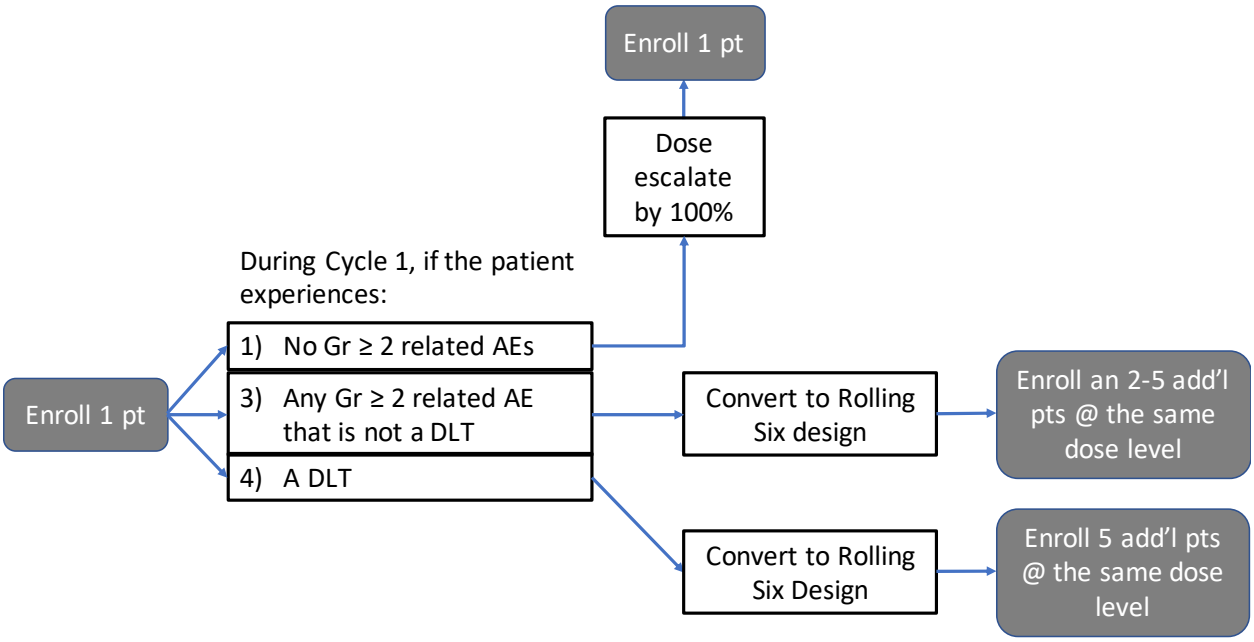
- Received 75% of doses during Cycle 1, or,
- Received at least one dose of VK-2019 and experienced a DLT during Cycle 1

2.2.2 Dose Escalation in Accelerated Titration Cohorts

Upon completion of an accelerated titration cohort (Figure 2):

- IF: No VK-2019 related Grade ≥ 2 AEs occur during Cycle 1; THEN: Dose escalation may proceed to the next accelerated titration cohort (no greater than a 100% dose increase).
- IF: The patient experiences any VK-2019 related Grade ≥ 2 AE during Cycle 1 (not meeting the definition of a DLT); THEN: Convert the current cohort to the Rolling Six design, and enroll an additional 2-5 patients (3-6 total).
- IF: The patient experiences a DLT;THEN: Convert to the Rolling Six design and enroll an additional five patients (six total).

Figure 2: Accelerated Titration Dose Escalation Schema



2.2.3 Dose Escalation in Rolling Six Cohorts

Upon completion of a Rolling Six cohort (a minimum of three, maximum of six evaluable patients), if:

- 0 of 3 patients experience a DLT; dose escalation may proceed to the next cohort (no greater than a 50% dose increase)
- 1 of 3 patients experience a DLT; an additional three evaluable patients will be enrolled into the cohort
- ≤1 of 6 patients experience a DLT; dose escalation may proceed to the next cohort (no greater than a 50% dose increase)

- ≥ 2 patients experience a DLT; the MTD has been exceeded and further enrollment into that cohort will cease. Lower-dose cohorts may then be explored until the MTD has been determined, including intermediate doses.

Table 1: Sample Dose Escalation Tables

Dose Escalation Schema	Target Dose / Actual Dose	Dose Increase
All cohorts enrolled using Accelerated Titration	60 mg / 60 mg	n/a
	120 mg / 120 mg	100%
	240 mg / 230 mg	100%
	460 mg / 460 mg	100%
	920 mg / 920 mg	100%
Rolling-six enrollment begins at the 60 mg cohort	60 mg / 60 mg	n/a
	90 mg / 90 mg	50%
	135 mg / 120 mg	50%
	180 mg / 180 mg	50%
	270 mg / 260 mg	50%
Rolling-six enrollment begins at the 120 mg cohort	60 mg / 60 mg	n/a
	120 mg / 120 mg	100%
	180 mg / 180 mg	50%
	270 mg / 260 mg	50%
	390 mg / 380 mg	50%
Rolling-six enrollment begins at the 230 mg cohort	60 mg / 60 mg	n/a
	120 mg / 120 mg	100%
	240 mg / 230 mg	100%
	345 mg / 320 mg	50%
	480 mg / 460 mg	50%
Rolling-six enrollment begins at the 460 mg cohort	60 mg / 60 mg	n/a
	120 mg / 120 mg	100%
	240 mg / 230 mg	100%
	460 mg / 460 mg	100%
	690 mg / 690 mg	50%

Note: Sample dose levels are based upon dose escalation (target dose) and available VK-2019 capsule strengths of 30 and 200 mg (actual dose).

2.2.4 Intra-Patient Dose Escalation in Accelerated Titration Cohorts

After an accelerated titration cohort has been declared safety by the SRC, patients at lower dose levels may be considered for intra-patient dose escalation if they meet the following criteria based in part on 3B design proposed by Simon et al:

- Have stable disease (SD) or better after Cycle 2 (or later)

- Experienced no VK-2019 related Grade 2 AEs during the previous cycle
- Have no other safety concerns as assessed by the inverstigator

The escalated dose must be agreed upon by the investigator and sponsor and may proceed beginning on Day 0 of the next cycle. Any patient that has their dose escalated will not be evaluated for DLT assessment at their new dose.

2.2.5 Intra-Patient Dose Escalation in Rolling Six Cohorts

After a Rolling Six cohort has enrolled a minimum of three patients and has been declared safe by the SRC, patients at lower dose levels may be considered for intra-patient dose escalation if the patient meets the following criteria:

- Have stable disease (SD) or better after Cycle 2 (or later)
- Have no other safety concerns as assessed by the investigator

The escalated dose must be agreed upon by the investigator and sponsor and may proceed beginning on Day 0 of the next cycle. Any patient that has their dose escalated will not be evaluated for DLT assessment at their new dose.

2.3 Blinding and Unblinding

This is an open-label study and there will be no blinding of subjects' treatment during this study.

2.4 Protocol Amendments

This analysis plan reflects revised protocol version 09, amendment 9, and dated 15-OCTOBER-2019.

3 OBJECTIVES

3.1 Primary

Phase 1:

- To define the MTD and the RP2D for orally administered VK-2019 monotherapy in patients with recurrent or metastatic NPC.
- To evaluate and characterize the safety profile of single agent VK-2019 in adult patients with recurrent or metastatic NPC.

Phase 2a:

- Evaluate preliminary efficacy (ORR, DOR, DCR, PFS, survival rate, and OS) of orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC.
- Confirm the safety and tolerability of orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC.

3.2 Secondary

Phase 1:

- To evaluate the anti tumor activity of single agent VK-2019 per RECIST v1.1.
- To characterize the single dose and steady state pharmacokinetic profile of single agent VK-2019 in adult patients with recurrent or metastatic NPC.
- To evaluate the anti-EBV activity by reduction of plasma EBV-DNA of single agent VK-2019 in adult patients with recurrent or metastatic NPC.

Phase 2a:

- To further characterize select PK parameters associated with orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC.
- Evaluate the anti EBV activity by reduction of plasma EBV DNA of orally administered VK 2019 monotherapy in adult patients with recurrent or metastatic NPC.

3.3 Exploratory

Phase 1:

- To explore blood PD markers.
- To explore PD markers such as alteration in EBV specific gene expression, both lytic and latent EBV genes.
- To explore exposure response relationships between VK 2019 exposure and the PD endpoints (safety, efficacy, and laboratory correlatives).

Phase 2a:

- To explore both blood and intratumoral PD markers.
- To explore PD markers such as alteration in EBV specific gene expression, both lytic and latent EBV genes.

- To explore exposure response relationships between VK 2019 exposure and the PD endpoints (safety, efficacy, and laboratory correlatives).

4 ENDPOINTS

4.1 Primary Endpoints

Phase 1:

- The frequency, severity, and duration of AEs and DLTs, AEs leading to discontinuation. and AEs leading to death.

Phase 2a:

- The durable ORR rate as well as ORR, DOR, DCR-6, DCR-12, PFS, rate of survival, and OS per RECIST v1.1.

4.2 Secondary Endpoints

Phase 1:

- The rate and severity of treatment emergent AEs at the MTD and BCAD.
- Single dose and steady state plasma pharmacokinetic parameters of VK 2019.
- Incidence of safety laboratory assessment abnormalities
- Incidence of abnormalities in vital signs or other clinical safety assessments
- ORR, DOR, and Disease control rate (DCR) per RECIST v1.1
- Rate of partial or complete plasma EBV DNA antiviral response during treatment (assessed as $3x\log^{10}$ reduction or a drop below the lower limit of detection of the assay [LLOD], respectively).

Phase 2a:

- The rate and severity of treatment emergent AEs at the MTD, BCAD, and RP2D.
- Rate of partial or complete plasma EBV DNA antiviral response during treatment (assessed as $3x\log^{10}$ reduction or a drop below the lower limit of detection of the assay [LLOD], respectively).
- Plasma PK parameters of VK-2019.

4.3 Exploratory Endpoints

Phase 1:

- Exploratory analysis of relationships among PK, PD and clinical activity in order to preliminarily define BCAD.

Phase 2a:

- Exploratory PD assay for EBER in situ hybridization levels in baseline and on treatment tumor biopsies in a limited number of patients at RP2D.

5 SAMPLE SIZE AND POWER

The number of patients in the dose escalation phase is estimated to be 30 patients (assuming six patients will be dosed in each of five cohorts). The number of patients in the Phase 1 Dose Expansion and Phase 2a Dose Expansion is based on a Simon 2-stage design as described below. The approximate sample size in the Phase 1 Dose Expansion is estimated to be 20 patients (assuming 10 additional patients in each of two expanded dose levels). During the Phase 2a portion of the trial, the approximate sample size in the Phase 2a Dose Expansions is estimated to be 18 (assuming 9 patients in each of two expansion cohorts). In total, it is estimated that up to approximately 68 patients will be dosed in this trial.

The number of patients for the Phase 1 and 2a expansions is based upon a Simon Two-Stage design at BCAD and MTD, respectively. The null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. In the first stage (i.e., a Phase 1 Dose Expansion cohort), a total of 16 patients will be accrued. If there is one or fewer responses in these 16 patients, accrual to this cohort will be stopped. Otherwise, 9 additional patients will be accrued (i.e., a Phase 2a Dose Expansion cohort) for a total of 25. The null hypothesis will be rejected if five or more responses are observed in 25 patients. This design yields a 1-sided type I error rate of 10% and power of 90% when the true response rate is 30%. This design yields a probability of 0.51 for a cohort stopping early if the true response rate for that cohort is 10%.The sample size in the dose escalation phase is not based on statistical considerations, but rather depends on the number of observed toxicities; up to 6 subjects are expected to be treated after the accelerated titration design has ended at each conventional escalation cohort dose prior to the expansion cohort at MTD.

6 STUDY PERIODS, DOSAGE AND ADMINISTRATION

6.1 Study Periods

For each patient enrolled, the study will consist of at least three periods: Screening (up to 28 days), Treatment (comprised of 28-day dosing cycles), and Follow up (comprised of a safety follow-up and long-term follow-up for survival status).

6.1.1 Safety Follow-Up

A safety follow up visit will be conducted at least 28 days (± 7 days) after the patient's last dose of study drug.

6.1.2 Long-Term Follow-Up

All patients that discontinue study treatment will be followed for:

- Survival: Via clinic visit (either at the study site or outside facility), telephone, or videotelephony until a) death, b) withdrawal of consent, c) they are lost to follow-up, d) the Sponsor notifies sites that survival follow-up is no longer required, or e) termination of study by the Sponsor, and
- Assessment of treatment-related SAEs until resolution to baseline or Grade ≤1.

Patients discontinuing treatment due to reasons other than radiographic disease progression will have their tumor assessed (using the same modality that was used during study treatment) every 12 weeks (± 14 days) for up to 2 years after the last treatment visit, or until a) they have progressive disease, b) they start a new therapy for their cancer, b) death, c) withdrawal of consent, d) they are lost to follow-up, e) the Sponsor notifies sites that tumor assessment is no longer required during long-term follow-up, or f) termination of study by the Sponsor.

6.2 Dosage and Administration

The number of patients in the dose escalation phase is estimated to be 30 patients (assuming six patients will be dosed in each of five cohorts). The starting dose for VK-2019 is 60 mg QD. Sample dose escalation tables are in Table 1, detailing a sample dose escalation schema based upon when escalation converts from Accelerated Titration to a Rolling Six design.

VK-2019 will be provided in HDPE bottles containing either 30 mg or 200 mg capsules with protection from moisture. Patients should be given sufficient supply to last until their next study visit or for an entire cycle, depending upon institutional policy and study team discretion.

Site personnel must ensure that patients clearly understand the directions for self medication. Patients should record daily administration of each study drug in their patient diaries. If a patient misses a dose, they must be instructed not to "make it up" or double the dose on the next day. Patient diaries and pill counts by research staff at least once each cycle will be used to determine actual dosing.

If a patient vomits any time after taking a dose, they must be instructed not to "make it up," but to resume subsequent doses the next day as prescribed.

7 STATISTICAL ANALYSES

7.1 General Methods

The statistical analysis will be conducted following the principles specified in the International Conference on Harmonisation (ICH) Topic E9 Statistical Principles for Clinical Trials (CPMP/ICH/363/96).

All statistical tabulations and analyses will be done using SAS®, Version 9.4 or higher.

Unless otherwise noted, continuous variables will be summarized using number of non-missing observations (n), arithmetic mean (mean), standard deviation (SD), median, minimum, and maximum; categorical variables will be summarized using the frequency count and the percentage of subjects in each category.

In the data listings, study day relative to first dose of study drug may be presented. Study day relative to first dose will be calculated as: event date – first dose date in the study (+ 1 if event date ≥ first dose date in the study).

When appropriate, baseline is defined as the last non-missing result with a collection date-time less than the date-time of the first dose of study medication. If time is missing, unless otherwise specified, baseline is the last non-missing result prior to or equal to the date of first dose of study drug.

7.2 Handling of Dropouts or Missing Data

7.2.1 Handling of Incomplete Dates for Adverse Events

Imputation rules for missing or partial AE start date are defined as follows.

If only day of AE start date is missing, - if the start date has month and year but day is missing, the first day of the month will be imputed. If this date is earlier than the first dose date, then the

first dose date will be used instead. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If day and month of AE start date are missing - if the start date has year but day and month are missing, the first of January will be imputed. If this date is earlier than the first dose date, then the first dose date will be used instead. If this date is later than the stop date (possibly imputed), then the stop date will be used instead.

If the year of AE start date is missing or AE start date is completely missing, then Data Management will query site with no imputation and compare the full (or partial) AE end date to the first dose date. If the AE end date is before the first dose date, then the AE should be considered a pre-treatment AE. Otherwise, the AE will be considered a TEAE.

7.2.2 Handling Missing or Partial Prior and Concomitant Medication Dates

For a missing or partial medication start date, if only Day is missing, the first day of the month will be assumed. If day and month are both missing, the first day of the year will be assumed. If day, month and year are all missing, the date before the first dose date will be assumed.

For a missing or partial medication stop date, if only day is missing, the last day of the month will be assumed. If day and month are both missing, the last day of the year will be assumed. If day, month and year are all missing, 'continuing' status to stop date will be assigned.

7.3 Study Population

- All Enrolled Population: All subjects who sign informed consent form and were confirmed eligible and assigned to a treatment cohort.
- All Treated Population (Safety Population): All subjects who receive at least one dose of VK-2019. All Treated Population will be used for the summaries of demographics, baseline characteristics, prior therapy, prior history, and safety.
- PK Population: All subjects who receive at least one dose of study medication and have available VK-2019 plasma concentration data.
- Response Evaluable Population: All treated subjects with measurable disease at baseline and one of the following: 1) at least one post-dose tumor assessment, 2) discontinuation prior to the first efficacy assessment due to clinical disease progression or toxicity or 3) death either on treatment or within 28 days of last VK-2019 dose.

- EBV DNA Population: All subjects who receive at least one dose of study medication and have available biomarker data.

7.4 Subject Accountability

Summaries of analysis populations and subject disposition will be presented by cohort and will contain the following information:

- Number of subjects enrolled
- Number and percent of subjects who were dosed
- Number and percent of subjects who discontinued early from the study and reason for early discontinuation
- Number and percent of subjects who discontinued treatment and reason for discontinuation
- Number and percent of subjects in the All Treated Population, Response Evaluable Population and EBV DNA Population
- Number and percent of subjects entered in safety and long term follow-up

This table will be based on All Enrolled Population.

Subject disposition listing will be provided for All Enrolled Population.

7.5 Protocol Deviation Reporting

No TLF's will be provided for abbreviated CSR.

7.6 Demographics Characteristics

A listing will be provided for demographics characteristics for All Treated Population, including patient age, sex, race, ethnicity, height and weight at baseline, etc.,

7.7 Medical and Surgical History

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.0 or later) and listed for All Treated Subjects by SOC and PT.

7.8 Prior and Concomitant Medications

Prior medications are defined as those medications that started and stopped prior to the first dose of study drug. Concomitant medications are defined as all medications received during the

treatment period, that is, those medications with a start date on or after the first dose of study drug (inclusive) and before last dose of study drug (inclusive), or started prior to the first dose of study drug and were continued after the first dose of study drug.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODDE – global March 20 B3 version) and classified according to anatomical therapeutic chemical code levels. Prior and concomitant medication data will be listed by ATC classifications level and preferred term for All Treated Population.

7.9 Extent of Exposure

The extent of exposure will be characterized according to the duration of exposure, the total number of cycles administered and the median (range) of cycles administered. Descriptive statistics of cumulative dose and dose intensity will also be presented for All Treated Population. A listing will also be provided.

7.10 Analysis of Pharmacokinetic Data

The PK concentration population is defined as all enrolled patients treated who have at least one concentration evaluation. The PK parameter analysis population is defined as all enrolled patients treated who have at least one of the PK parameters of interest.

Standard plasma pharmacokinetic parameters including the maximum plasma concentration (C_{max}) and area under the plasma concentration versus time curve (AUC) for VK-2019 will be estimated using non-compartmental analysis. If data permit or if considered appropriate, terminal elimination half-life ($t_{1/2}$) will be estimated. Descriptive statistics will be provided for these PK parameters in tabular form (N, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) by dose, cycle, and day.

Individual patient and median profiles of the concentration-time data will be plotted by dose, cycle, and day using nominal times. Median profiles will be presented on both linear-linear and log-linear scales.

Graphs of PK concentration over time and tables of PK parameters will be provided by Cullinan.

7.11 Pharmacodynamic EBV DNA

A line graph for mean +/- SD of change from baseline for EBV DNA will be provided by visit for all post baseline visits (C1D14, C2D0, C2D14, C3D0) for Phase 1 Dose Escalation. EBV DNA population will be used to generate this graph.

7.12 Pharmacodynamic EBNA1 inhibition

No TLF's will be provided for abbreviated CSR as no biopsies were collected.

7.13 Efficacy

The number and percentage of patients for best overall response (BOR) will be provided. The number and percentage of patients with ORR will also be summarized together with exact 95% confidence intervals (CI) using a binomial distribution for Response Evaluable Population.

The endpoint objective response rate (ORR) is defined as the number and percentage of patients whose best overall response is either a complete response (CR) or partial response (PR). To qualify as a responder, a patient must have a complete or partial visit response confirmed by a second scan performed at least 4 weeks after the criteria for response are first met. A by subject listing will also be provided for Overall Response.

7.14 Safety

Safety objectives in this study will be assessed using the following endpoints in the All Treated population:

- Incidence of adverse events, SAEs, adverse events meeting protocol-defined DLT criteria, severe adverse events, adverse events leading to study treatment or study discontinuation, and adverse events resulting in death.
- Incidence of clinical laboratory test abnormalities including hematology and serum chemistry abnormalities assessed at protocol designated time points
- Changes in vital signs relative to baseline include blood pressure and heart rate measured at protocol designated time points

7.14.1 Adverse Events

Adverse events will be listed, including the verbatim description and MedDRA preferred term and system organ class (SOC).

Treatment emergent adverse events (TEAEs) are defined as those starts or severity becomes worse after the first dose of study treatment.

TEAE leading to study treatment discontinuation and death will be summarized by SOC, by preferred term and by maximum CTCAE grade (according to NCI CTCAE Version 5.0). The incidence of TEAEs will be based on the numbers and percentages of patients with events and number of events. In addition summary of DLT will also be provided for first cycle.

TEAE data will be presented across all cycles and for each cycle. The denominator for each cycle will be the number of patients available at the start of the cycle who received at least 1 dose of study drug for that cycle.

Individual patient listings will be prepared for AE leading to study treatment discontinuation and death. Listing of the first cycle DLTs for each cohort will be provided.

7.14.2 Clinical Laboratory Assessments

Severity grading, using NCI CTCAE Version 5.0, will be assigned to laboratory safety values where applicable. Laboratory results in reported units and standard international units will be listed, including high and low flags, NCI CTCAE grades where applicable, the corresponding normal range and clinical significance.

Laboratory safety tests summaries will be based on results in SI units. Absolute and change from baseline results at each scheduled visit will be summarized using descriptive statistics.

7.14.3 Vital Signs

For vital sign parameters of heart rate, blood pressure (systolic and diastolic), temperature, height (baseline only), weight and BMI, the actual value and change from baseline for the maximum value, minimum value, and last available assessment will be summarized with descriptive statistics.

Vital signs data will be listed by subject at each scheduled visit.

7.14.4 Electrocardiograms

Absolute and change from baseline 12-lead ECG results will be summarized using descriptive statistics. QT analysis intervals will be corrected for heart rate using the Fridericia correction (QTcF). Study conclusions will be based on the most appropriate correction method for the

analysis. The effect of VK-2019 concentration on QTcF will be explored after dosing and will be baseline corrected for each patient.

Individual ECG data will be listed.

7.14.5 Physical Examinations

A by subject listing will be presented.

7.14.6 ECOG

No TLF's will be provided for abbreviated CSR.

7.14.7 Pregnancy Testing

No TLF's will be provided for abbreviated CSR.

7.15 Interim Analysis

No TLF's will be provided for abbreviated CSR.

7.16 General Conventions for Tables, Listings and Figures

Tables and listings will be presented in landscape mode with minimum of 3/4" bound edge margin and 3/8" other margins on 8.5" x 11" paper.

Times new roman font size of no less than 8 point will be used for tables and listings.

A source line will be included on the bottom of each page of all tables and listings. It will contain the SAS code program name and the run date and time.

Each variable is recorded to a specific number of decimal places. If the raw data is presented with varying precision, then the least precise value will be considered as the data precision.

For summary tables, unless otherwise specified, the number of decimal places provided in the SAS output will be based on the accuracy of the least accurate value in the raw data as follows:

- n integer
- Arithmetic mean 1 decimal place more than the least accurate number in the raw data
- SD 2 decimal places more than the least accurate number in the raw data
- Median 1 decimal place more than the least accurate number in the raw data
- Minimum same number of decimal places as raw data
- Maximum same number of decimal places as raw data

8 DOCUMENT HISTORY

Table 8-1: Document History

Version	Author	Summary of Changes
1.0	Wenjun Xin	Original version

9 REFERENCES

1. Simon R, Freidlin B, Rubinstein L, Arbuck SG, Collins J, Christian MC. Accelerated titration designs for phase I clinical trials in oncology. J Natl Cancer Inst. 1997; 89 (15): 1138-47. Epub 1997/08/06. PubMed PMID: 9262252.

2. Skolnik JM, Barrett JS, Javaraman B, Patel D, Adamson PC, Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol. 2008; 26 (2): 190-19. PubMed DOI: 10.1200/JCO.2007.12.7712. PMID: 18182661.

3. Horstmann E, McCabe MS, Grochow L, Yamamoto S, Rubinstein L, Budd T, Shoemaker D, Emanuel EJ, Grady C. Risks and benefits of phase 1 oncology trials, 1991 through 2002. The New England journal of medicine. 2005; 352 (9): 895-904. Epub 2005/03/05. doi: 10.1056/NEJMsa042220. PubMed PMID: 15745980.