# CLINICAL STUDY PROTOCOL

| | |
|---|---|
| **Protocol Title:** | 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 |
| **Product:** | VK-2019 |
| **Protocol Number:** | VK-2019-001 |
| **Protocol Versions:** | 9.0, Amendment 9 (15 October 2019) |
| **IND Number:** | 137265 |
| **EudraCT Number:** | 2019-001791-11 |
| **Sponsor:** | Cullinan Apollo Corp. (Cullinan-Apollo)<br>1 Main Street, Suite 520<br>Cambridge, MA 02142<br>USA<br>+1 617-425-9200 |
| **Protocol Chair** | A. Dimitrios Colevas, MD<br>Professor of Medicine (Oncology) and, By Courtesy, of Otolaryngology Head and Neck Surgery<br>Stanford Cancer Institute (SCI)<br>Phone: +1 650-720-9707<br>Fax: +1 650-498-5800<br>E mail: colevas@stanford.edu |
| **Medical Monitor** | 24/7 Medical Emergency Phone Number<br>+1 (919) 674-5468 |
| **Pharmacovigilance** | Fax: +44 (0) 208 100 5005<br>Email: ICON-Safety-CentralReceipt@iconplc.com |

## Confidentiality Statement

***This document is confidential and is to be distributed for review only to investigators, potential investigators, consultants, trial staff, and applicable independent ethics committees or institutional review boards. The contents of this document shall not be disclosed to others without written authorization from Cullinan-Apollo (or its representatives).***

## SPONSOR PROTOCOL APPROVAL PAGE

Sponsor's Responsible Medical Officer:

Briggs Morrison, MD
Acting Chief Medical Officer

Date

## PROTOCOL SIGNATURE PAGE

The signature of the Principal Investigator below constitutes his/her agreement to comply with the contents of this Protocol and to conduct this study according to Good Clinical Practices (GCP) and applicable requirements.

_____ _____

Principal Investigator's Signature Date

Principal Investigator's Name:

Name of Institution:

## LIST OF TERMS, ACRONYMS, AND ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Transaminase (SGPT) |
| ALP | Alkaline Phosphatase |
| ANC | Absolute Neutrophil Count |
| AST | Aspartate Transaminase (SGOT) |
| AUC | Area Under the Drug Concentration-Time Curve |
| BCAD | Biologically or Clinically Active Dose |
| BLQ | Below the Limit of Quantitation |
| BP | Blood Pressure |
| BUN | Blood Urea Nitrogen |
| °C | Degrees Celsius |
| Ca | Calcium |
| CBC w/ Diff | Complete Blood Count with Differential |
| CFR | Code of Federal Regulations |
| CI | Confidence Interval |
| Cl | Chloride |
| CL | Clearance |
| $C_{max}$ | Maximum Drug Concentration |
| $C_{min}$ | Minimum Drug Concentration |
| $CO_2$ | Carbon Dioxide |
| Cr | Creatinine |
| CR | Complete Response |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CT | Computed tomorgraphy |
| CTCAE | Common Toxicity Criteria for Adverse Events |
| DLT | Dose Limiting Toxicity |
| DOR | Duration of Response |
| EBNA1 | Epstein-Barr Nuclear Antigen 1 |
| EBV | Epstein-Barr Virus |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| EMR | Electronic Medical Record |
| EU | European Union |
| °F | Degrees Fahrenheit |
| FDA | Food and Drug Administration (U.S.) |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practice |
| h or hr | Hour |
| HR | Heart Rate |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonisation |
| IEC | Independent Ethics Committee |
| IND | Investigational New Drug (Application) |
| INR | International Normalised Ratio |
| IRB | Institutional Review Board |

| | |
|---|---|
| K | Potassium |
| kg | Kilogram |
| L | Liter |
| m or min | Minute |
| $m^2$ | Meter squared |
| mg | Milligram |
| Mg | Magnesium Sulfate |
| mL | Milliliter |
| ms or msec | Millisecond |
| MTD | Maximum tolerated dose |
| Na | Sodium |
| NCI | National Cancer Institute |
| NPC | Nasopharyngeal Carcinoma |
| ORR | Overall Response Rate |
| OS | Overall Survival |
| PCR | Polymerase Chain Reaction |
| PFS | Progression Free Survival |
| PD | Progressive Disease or Pharmacodynamics |
| PI | Principal Investigator |
| PK | Pharmacokinetics |
| PR | Partial Response |
| PT | Prothrombin Time |
| PTT | Partial Thromboplastin Time |
| QD | Once Daily |
| RBC | Red Blood Cells |
| 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 |
| SOC | System Organ Class |
| $t_{1/2}$ | Half-Life |
| $t_{max}$ | Time to Cmax |
| T | Temperature |
| TEAEs | Treatment Emergent Adverse Events |
| ULN | Upper Limit of Normal |
| VS | Vital Signs |
| WBC | White Blood Cells |
| WOCBP | Women of Child-Bearing Potential |

**TABLE OF CONTENTS**

# 1 SYNOPSIS

| | |
|---|---|
| **Study Title:** | 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 |
| **Protocol Number:** | VK-2019-001 |
| **Study Drug:** | VK-2019 |
| **Sponsor:** | Cullinan Apollo Corp |
| **Hypothesis for Phase 1** | Plasma exposures of single agent VK-2019 associated with pre-clinical efficacy can be achieved in patients with NPC with less than 18% of patients experiencing a dose limiting toxicity (DLT). |
| **Hypothesis for Phase 2a:** | Oral administration of single agent VK-2019 at one or more doses will be associated with a durable overall response rate (CR+PR maintained for at least 6 months) of 30%. |
| **Objectives for Phase 1:** | Primary Objectives<br>• To define the maximum tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for orally administered VK-2019 monotherapy in patients with recurrent or metastatic NPC.<br>• To evaluate and characterize the safety profile of orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC. |
| | Secondary Objectives<br>• To evaluate the anti-tumor activity of orally administered VK-2019 monotherapy per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.<br>• To characterize the PK of orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC.<br>• To 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. |
| | Exploratory Objectives<br>• To explore blood PD markers.<br>• To explore PD markers such as alteration in EBV specific gene expression, both lytic and latent EBV genes.<br>• To explore exposure-response relationships between VK-2019 exposure and the PD endpoints (safety, efficacy, and laboratory correlatives). |
| **Objectives for Phase 2a:** | Primary Objectives<br>• Evaluate preliminary efficacy (overall response rate [ORR], duration of response [DOR], disease control rate [DCR], progression free survival [PFS], survival rate, and overall survival [OS]) of orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC.<br>• Confirm the safety and tolerability of orally administered VK-2019 monotherapy in adult patients with recurrent or metastatic NPC. |
| | Secondary Objectives<br>• 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. |
| | Exploratory Objectives<br>• To explore both blood and intratumoral PD markers.<br>• To explore PD markers such as alteration in EBV specific gene expression, both lytic and latent EBV genes.<br>• To explore exposure-response relationships between VK-2019 exposure and the PD endpoints (safety, efficacy, and laboratory correlatives). |
| **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.<br><br>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).<br><br>This trial is divided into three parts: 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.<br><br><u>Phase 1 Dose Escalation</u><br>Dose escalation in this trial will be conducted utilizing both an accelerated titration coupled with a "rolling six" design.<br>• Dose escalation will initially proceed according to the accelerated titration design, enrolling one new patient per dose level.<br>• Upon any instance of a VK-2019 related Grade ≥ 2 toxicity during Cycle 1, dose escalation will convert to the Rolling Six design in which a total of 3-6 patients per dose level will be enrolled.<br>• 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.<br><br><u>Phase 1 Dose Expansion</u><br>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 Biologically or Clinically Active Dose (BCAD).<br><br><u>Phase 2a Dose Expansion</u><br>Further dose expansion in the Phase 2a part of the trial may be explored by utilizing a 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 at that dose in the Phase 1 part of the trial (for a total accrual of up to 25 patients). |

| | |
|---|---|
| **Safety Review Committee:** | During the trial, a Safety Review Committee (SRC) comprised of two external, independent oncologists, the Medical Monitor, Chief Medical Officer, Protocol Chairperson, Principal Investigators from each site, plus additional delegates (as needed), will review available safety, tolerability, PK, PD, efficacy, and other clinical data for the purposes of trial oversight and decision making as it relates to dose escalation and de-escalation, dose selection and expansion, study termination, etc. |
| **Dose Escalation Procedures:** | The starting dose for VK-2019 is 60 mg.<br><br>Each dose escalation cohort will consist of either:<br>• 1 evaluable patient (Accelerated Titration cohorts), or<br>• 3-6 evaluable patients (Rolling Six cohorts)<br><br>To be considered evaluable, a patient will have one of the following:<br>• Received 75% of doses during Cycle 1, or,<br>• Received at least one dose of VK-2019 and experienced a DLT during Cycle 1<br><br><u>For Accelerated Titration Cohorts</u><br>Upon completion of an accelerated titration cohort, :<br>• 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)<br>• IF: The patient experiences a 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 evaluable patients (3-6 total) at the same dose level<br>• IF: The patient experiences a DLT; THEN: Convert to the Rolling Six design and enroll an additional five evaluable patients (six total) at the same dose level<br><br><u>For Rolling Six Cohorts</u><br>Upon completion of a Rolling Six cohort (a minimum of three, maximum of six evaluable patients),<br>• IF: 0 of 3 patients experience a DLT; THEN: Dose escalation may proceed to the next cohort (no greater than a 50% dose increase)<br>• IF: 1 of 3 patients experience a DLT; THEN: An additional three evaluable patients will be enrolled into the cohort at the same dose level<br>• IF: ≤ 1 of 6 patients experience a DLT; THEN: Dose escalation may proceed to the next cohort (no greater than a 50% dose increase)<br>• IF: ≥ 2 patients experience a DLT; THEN: 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<br><br><u>Intra-patient Dose Escalation in Accelerated Titration Cohorts</u><br>After an accelerated titration cohort has been declared safe 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:<br>• Have stable disease (SD) or better after Cycle 2 (or later)<br>• Experienced no VK-2019 related Grade 2 AEs during the previous cycle<br>• Have no other safety concerns as assessed by the investigator<br>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.<br><br><u>Intra-patient Dose Escalation in Rolling Six Cohorts</u><br>After a Rolling Six cohort has enrolled a minimum of three patients and has been declared safe by the SRC, patients at lower dose level may be considered for intra-patient dose escalation if the patient meets the following criteria:<br>• Have stable disease (SD) or better after Cycle 2 (or later)<br>• Have no safety concerns as assessed by the investigator<br><br>In either situation, the escalated dose must be agreed upon by the investigator and sponsor and may proceed beginning on Day 0 of the next cycle. |
| **Definition of DLT:** | DLTs will be determined based on the incidence and intensity of AEs assessed as being at least possibly related to VK-2019 and occurring up to 28 days after initiation of QD VK-2019 dosing. Toxicity will be graded by the CTCAE v5.0.<br><br><u>Dose-limiting Hematologic Toxicity</u><br>• Grade 4 neutropenia > 7 days<br>• Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding or requiring platelet transfusion<br>• Grade 3 febrile neutropenia<br>• Grade 4 anemia or anemia that requires blood transfusion<br><br><u>Dose-limiting Non-hematologic Toxicities</u><br>• Any Grade 3 or higher non-hematology toxicity, excluding the following:<br>  o Toxicities assessed by Investigator as clearly related only to disease progression or intercurrent illness<br>  o Elevations of AST, ALT, and bilirubin, that correct to Grade 1 within one week and do not meet any of the definitions of acute liver injury as listed below<br>  o Other asymptomatic laboratory abnormalities<br>  o Grade 3 fever without neutropenia that returns to Grade 1 or less within three days, and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)<br>  o Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within three days with medical intervention |

| | |
|---|---|
| | ○ Grade 3 pruritis or rash that returns to Grade 1 or baseline within seven days or baseline with medical intervention<br>○ Grade 3 fatigue<br>○ Grade 3 tumor flare (defined as pain, irritation or rash that localizes to sites of known or suspected tumor)<br><br>A DLT will also include:<br>• A laboratory finding of acute liver injury defined as:<br>○ Sustained (> 1 week) doubling of AST or ALT levels to no less than 4 x ULN, or sign of increasing functional liver impairment with > 2x baseline increase in total bilirubin<br>○ Increased AST or ALT levels above 8 x ULN<br>○ Suspected acute liver injury (per Hy's law) ALT/AST > 3 x ULN in combination with Total Bilirubin > 2 x ULN in the absence of cholestatic injury (ALP < 2 x ULN).<br>• Any AE resulting in a patient missing > 7 days of dosing with VK-2019<br>• Any AE not otherwise meeting the criteria or timing of a DLT as defined above, but is declared a DLT by the SRC |
| **Definition of the MTD:** | The MTD is defined as the highest dose level of VK-2019 at which fewer than two DLTs are observed in six evaluable patients treated at that dose. |
| **Definition of a BCAD:** | A BCAD is defined as a dose level that appears to have preliminary clinical or biological activity based upon the following criteria:<br>○ There are no safety concerns in that cohort based upon the SRC's analysis of safety data.<br>○ The following criteria for either clinical or biological activity:<br><u>Clinical:</u><br>○ At least one patient has experienced an objective response per RECIST v1.1 (i.e., a PR or CR) at that dose level.<br><u>Biological:</u><br>○ Post-baseline plasma EBV DNA levels have declined by three log from baseline, or are below the lower limit of detection of the assay, AND<br>○ Plasma AUC level VK-2019 at the end of Cycle 1 is above the biologically active dose as defined in preclinical models (10,000 ng*h/mL) |
| **Definition of the RP2D** | The dose of orally administered VK-2019 monotherapy that, in the opinion of the SRC, can be safely administered for three or more cycles, factoring in cumulative adverse experiences and adverse experiences that lead to study drug discontinuation. |
| **Initiation of Phase 1 Expansion Cohorts:** | The SRC may elect to initiate a Phase 1 Dose Expansion Cohort and enroll additional patients at any dose level that:<br>• Meets the definition of the MTD.<br>• Meets the definition of a BCAD.<br>The total number of patients enrolled at any one dose level during Phase 1 (dose escalation and expansion) will not exceed 16 patients. |

| | |
|---|---|
| | Based upon the above criteria, the SRC may elect to explore multiple dose levels as Phase 1 Expansion Cohorts (either staggered or concurrently). |
| **Initiation of Phase 2a Expansion Cohorts:** | Upon completion of any Phase 1 Expansion Cohort, the SRC may elect to expand the cohort further, initiating a Phase 2a Dose Expansion and enrolling additional nine patients if the dose level meets the following:<br>• Two or more patients have experienced an objective response per RECIST v1.1 (i.e., a PR or CR), of which at least one is a confirmed response.<br>• There are no additional safety concerns in the cohort of existing patients based upon the SRC's analysis of emerging safety data.<br>The total number of patients enrolled at any one dose level during all phases of the study will not exceed 25 patients.<br><br>Based upon the above criteria, the SRC may elect to explore multiple dose levels as Phase 2a Expansion Cohorts (either staggered or concurrently). |
| **Study Population:** | Inclusion Criteria:<br>A patient who meets all of the following inclusion criteria will be eligible to participate in this study:<br>1. Informed consent obtained prior to any protocol mandated assessment.<br>2. Age ≥ 18.<br>3. Either loco-regionally recurrent or metastatic EBV-positive nasopharyngeal carcinoma not amenable to curative treatment.<br>a. EBV positivity is defined as high EBV viral load in plasma (> 4000 genomes per µg plasma DNA) and/or biopsy tissue positive for EBV.<br>4. Prior palliative radiation must have been completed at least 2 weeks prior to study Cycle 1 - Day 0.<br>5. Prior anti-cancer systemic treatment must have been completed greater than 4 weeks prior to study Cycle 1 - Day 0.<br>6. Toxicities related to prior anti-cancer therapy must have returned to Grade 1 or less. Peripheral neuropathy must be Grade 2 or less. Chronic but stable toxicities Grade > 1 (e.g., dysphasia, G tube dependence, etc.) may be allowed after agreement between the Investigator and Sponsor.<br>7. For the dose expansion in Phase 1 and Phase 2a, patients must have RECIST v1.1 measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 10 mM with spiral CT scan, MRI, or calipers by clinical exam.<br>8. ECOG performance status score of ≤ 2 at study entry.<br>9. Absolute neutrophil count > 1500/µL (stable off any growth factor for at least 1 week prior to study drug administration).<br>10. Hemoglobin > 9g/dL (transfusion to achieve this level is permitted).<br>11. Platelet count > 75 x 103/ µL (transfusion to achieve this level is NOT permitted).<br>12. Serum aspartate transaminase (AST) and serum alanine transaminase |

| | |
|---|---|
| | (ALT) ≤ 2.5 x upper limit of normal (ULN).<br>13. Total serum bilirubin ≤ 1.5 x ULN.<br>14. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min as calculated per Cockcroft-Gault equation.<br>15. Urinary protein < 2+ by dipstick. If dipstick ≥ 2+, then a 24-hour urine collection can be done and the patient may enter only if urinary protein is < 1 g/24 hour.<br>16. Sexually active patients must agree to utilize birth control method during treatment and for 18 weeks after the last dose of VK-2019. Using effective birth control methods as defined in https://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf. See Appendix 3 and Section 17.3.<br>17. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures. |
| | Exclusion Criteria<br>1. Severe or active symptomatic cardiopulmonary diseases, including unstable angina, congestive heart failure, or peripheral vascular disease within 12 months prior to study drug administration; and/or chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization within 4 weeks prior to study drug administration.; Patients with effectively treated conditions (e.g., stenting for coronary artery disease) are eligible if stable for at least 4 weeks prior to study drug administration.<br>2. Metastatic disease with active central nervous system (CNS) involvement, defined as parenchymal brain involvement. Patients with cranial nerve or base of skull involvement without the above are eligible. Patients with CNS metastases that are stable on imaging at least 1 month following focal treatment with radiation are eligible.<br>3. Concurrent treatment with systemic cancer directed therapy including complementary, alternative, herbal or nutritional supplement-based treatments whose purpose is for anti-cancer effect.<br>4. Known history of human immunodeficiency virus (HIV) unless the HIV-positive patient has:<br>• A stable regimen of highly active anti-retroviral therapy (HAART)<br>• No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections<br>• A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test<br>5. Serious uncontrolled medical disorder or active infection which would, in the opinion of the Investigator, impair the ability of the subject to receive protocol therapy or whose control may be jeopardized by the complications of this therapy.<br>6. Currently taking drugs that inhibit or induce OATP1B1 or OATP1B3 within five half-lives of that agent. Examples are included in Appendix 2.<br>7. Have received a prior organ allograft or allogeneic bone marrow transplant.<br>8. Current non-prescription drug or alcohol dependence.<br>9. For all female patients, pregnancy or breastfeeding. |

| | |
|---|---|
| | 10. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment.<br>11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study.<br>12. Corrected QT by Fridericia's formula (QTcF) of > 470 ms average (mean) on triplicate ECG performed during Screening. |
| **Safety Evaluation** | Safety parameters will include AEs, serious adverse events (SAEs), physical examinations, ECGs, vital signs, and clinical laboratory evaluations. Safety and tolerability will be assessed by the incidence and severity of adverse events as determined by CTCAE v5. |
| **Efficacy Evaluation** | The antitumor activity of study treatment will be assessed according to RECIST v1.1 guideline. |
| **Pharmacokinetic Assessments** | PK (blood and urine) samples will be collected during this study. |
| **Pharmacodynamic Assessments** | Plasma EBV DNA samples will be collected on all patients during this study. Samples will be analyzed to inform changes in EBV DNA and the mechanism of EBNA1 inhibition.<br><br>Optional tumor biopsies will be collected in the Phase 2a part of the study. |
| **Sample Size Determination and Statistical Analysis** | The number of patients to be enrolled in this trial will depend upon the observed safety profile and the number of dose escalations and expansions. However, it is estimated that up to approximately 68 patients will be enrolled in this trial.<br><br>During the Phase 1 portion of the trial, the approximate sample size in the dose escalation is estimated to be 30 patients (assuming six patients in each of five cohorts). The approximate sample size in the Phase 1 Dose Expansion is estimated to be 20 patients (assuming 10 additional patients enrolled 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 additional patients in each of two expansion cohorts).<br><br>The estimate 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), 16 patients will be accrued. If there is one or fewer responses in these 16 patients, accrual to this cohort will be stopped. Otherwise, nine 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%. |

| | |
|---|---|
| | Detailed statistical analyses will be specified in the Statistical Analysis Plan (SAP). |

**Table 1: Schedule of Events in Phase 1 Dose Escalation**

| Assessment[16] | Screening | Cycle 1 | | Cycle 2 | | Cycle 3 and Odd Cycles[15] | Cycle 4 and Even Cycles[15] | EOT | Safety FU | LTFU |
|---|---|---|---|---|---|---|---|---|---|---|
| | Within 28 days of C1D0 | Day 0 | Day 14 (± 1 d) | Day 0 (+3 d) | Day 14 (± 3 d) | Day 0 (± 3 d) | Day 0 (± 3 d) | 7 d (± 3 d) post-last dose | 28 d (± 7 d) post-last dose | q12 w (± 1 w) post-last dose |
| Informed consent | X | | | | | | | | | |
| Medical/Oncology History | X | | | | | | | | | |
| ECOG Performance Status[1] | X | X[10] | | | | | | X | | |
| Vital Signs[2] | X | X | X | X | X | X | X | X | X | |
| Height & Weight[3] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Physical Examination[4] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Hematology Labs[5] | X | X[10] | X | X[10] | X | X[10] | X[10] | X | X | |
| Chemistry Labs[5] | X | X[10] | X | X[10] | X | X[10] | X[10] | X | X | |
| Urinalysis[5] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Coagulation Panel[5] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Pregnancy Test[5] | X | X[6,10] | | X[6,10] | | X[6,10] | X[6,10] | X | X[6,10] | |
| Triplicate ECG[7] | X | X | X | X | | | | X | X | |
| Adverse Events | X | X | X | X | X | X | X | X | X | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | |
| VK-2019[8] | | X | | | | | | | | |
| PK Plasma[9] | | X | X | X | | X (C3 only) | | | | |
| Plasma EBV DNA[5] | X | | X | X | X | X (C3 only) | | X | | |
| Tumor Assessments[11] | X | | | | | X[11] | | X[12] | | X[13] |
| Survival | | | | | | | | | | X[14] |

Phase 1 Dose Escalation Footnotes

1 ECOG performance scale is available in Appendix 1.
2 Vital signs (VS) include blood pressure (BP), temperature (T), and heart rate (HR). See Table 4 for collection time points.
3 Height is required at screening only.
4 A full physical exam is required at screening only. All other physical exams may be symptom directed.
5 Lab Assessments should include:
- Hematology labs: CBC with Differential
- Chemistry labs: Na, K, Cl, $CO_2$, BUN, Cr, glucose, Ca, total bili, AST, ALT, ALP, albumin, total protein, Mg
- Urinalysis: pH, specific gravity, glucose, ketones, blood, protein, nitrates, leukocytes
- Coagulation: PT, PTT, INR
- Pregnancy labs can be performed via blood or urine
- Plasma EBV DNA

6 Pregnancy tests on D1 of each cycle and at the Safety FU visit are only required at sites in the European Union (EU). For sites in other regions, pregnancy tests at these visits are only required if clinically indicated.
7 All ECGs must be performed in triplicate. See Table 4 for specific collection time points.
8 VK-2019 must be taken in the morning on an empty stomach. Patients must fast for one hour before and two hours after each dose. Study drug accountability will be performed at each visit.
9 See Table 4 for PK collection time points. PK samples will only be collected through C3D0, not beyond.
10 Assessments need not be repeated if performed within three days prior to the visit.
11 Tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). Assessments should include evaluation of the neck, chest, abdomen, and pelvis, Post-baseline assessments will be performed within seven days of D0 of odd numbered cycles (i.e., C3D0, C5D0, etc).
12 Tumor assessments performed within four weeks of the EOT visit need not be repeated.
13 Tumor assessments in LTFU are only required for patients that have discontinued for reasons other than radiographic progression of disease, and may be performed ± 2 weeks of the scheduled LTFU date.
14 Survival status may be assessed via clinic visit (either at the study site or outside facility), telephone, or videotelephony.
15 After completing 13 cycles of treatment (i.e., > 12 months), the Investigator and Sponsor may agree that a patient will require study visits on an every odd cycle basis only (i.e., C15D0, C17D0, C19D0, etc.), until more frequent visits become clinically indicated.
16 Visits performed out of window due to holidays, natural disasters, and similar circumstances will not be a protocol deviation.

**Table 2: Schedule of Events in Phase 1 Dose Expansion**

| Assessment[16] | Screening | Cycle 1 | | Cycle 2 | | Cycle 3 and Odd Cycles[15] | Cycle 4 and Even Cycles[15] | EOT | Safety FU | LTFU |
|---|---|---|---|---|---|---|---|---|---|---|
| | Within 28 days of C1D0 | Day 0 | Day 14 (± 1 d) | Day 0 (+3 d) | Day 14 (± 3 d) | Day 0 (± 3 d) | Day 0 (± 3 d) | 7 d (± 3 d) post-last dose | 28 d (± 7 d) post-last dose | q12 w (± 1 w) post-last dose |
| Informed consent | X | | | | | | | | | |
| Medical/Oncology History | X | | | | | | | | | |
| ECOG Performance Status[1] | X | | | | | | | X | | |
| Vital Signs[2] | X | X | X | X | X | X | X | X | X | |
| Height & Weight[3] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Physical Examination[4] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Hematology Labs[5] | X | X[10] | X | X[10] | X | X[10] | X[10] | X | X | |
| Chemistry Labs[5] | X | X[10] | X | X[10] | X | X[10] | X[10] | X | X | |
| Urinalysis[5] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Coagulation Panel[5] | X | X[10] | | X[10] | | X[10] | X[10] | X | X | |
| Pregnancy Test[5] | X | X[6,10] | | X[6,10] | | X[6,10] | X[6,10] | X | X[6,10] | |
| Triplicate ECG[7] | X | X | X | X | | | | X | X | |
| Adverse Events | X | X | X | X | X | X | X | X | X | |
| Concomitant Medications | X | X | X | X | X | X | X | X | X | |
| VK-2019[8] | | X | | | | | | | | |
| PK Plasma[9] | | X | X | X | | X (C3 only) | | | | |
| PK Urine[9] | | X | X | | | | | | | |
| Plasma EBV DNA[5] | X | | X | X | X | X (C3 only) | | X | | |
| Tumor Assessments[11] | X | | | | | X[11] | | X[12] | | X[13] |
| Survival | | | | | | | | | | X[14] |

Phase 1 Dose Expansion Footnotes

1 ECOG performance scale is available in Appendix 1.
2 Vital signs (VS) include blood pressure (BP), temperature (T), and heart rate (HR). See Table 5 for collection time points.
3 Height is required at screening only.
4 A full physical exam is required at screening only. All other physical exams may be symptom directed.
5 Lab Assessments should include:
- Hematology labs: CBC with Differential
- Chemistry labs: Na, K, Cl, $CO_2$, BUN, Cr, glucose, Ca, total bili, AST, ALT, ALP, albumin, total protein, Mg
- Urinalysis: pH, specific gravity, glucose, ketones, blood, protein, nitrates, leukocytes
- Coagulation: PT, PTT, INR
- Pregnancy labs can be performed via blood or urine
- Plasma EBV DNA

6 Pregnancy tests on D1 of each cycle and at the Safety FU visit are only required at sites in the EU. For sites in other regions, pregnancy tests at these visits are only required if clinically indicated.
7 All ECGs must be performed in triplicate. See Table 5 for specific collection time points.
8 VK-2019 must be taken in the morning on an empty stomach. Patients must fast for one hour before and two hours after each dose. Study drug accountability will be performed at each visit.
9 See Table 5 for PK collection time points. PK samples will only be collected through C3D0, not beyond.
10 Assessments need not be repeated if performed within three days prior to the visit.
11 Tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). Assessments should include evaluation of the neck, chest, abdomen, and pelvis, Post-baseline assessments will be performed within seven days of D0 of odd numbered cycles (i.e., C3D0, C5D0, etc).
12 Tumor assessments performed within four weeks of the EOT visit need not be repeated.
13 Tumor assessments in LTFU are only required for patients that have discontinued for reasons other than radiographic progression of disease, and may be performed ± 2 weeks of the scheduled LTFU date.
14 Survival status may be assessed via clinic visit (either at the study site or outside facility), telephone, or videotelephony.
15 After completing 13 cycles of treatment (i.e., > 12 months), the Investigator and Sponsor may agree that a patient will require study visits on an every odd cycle basis only (i.e., C15D0, C17D0, C19D0, etc.), until more frequent visits become clinically indicated.
16 Visits performed out of window due to holidays, natural disasters, and similar circumstances will not be a protocol deviation.

**Table 3: Schedule of Events in Phase 2a Dose Expansion**

| Assessment[16] | Screen | Cycle 1 | | Cycle 2 | Cycle 3 and Odd Cycles[15] | Cycle 4 and Even Cycles[15] | EOT | Safety FU | LTFU |
|---|---|---|---|---|---|---|---|---|---|
| | Within 28 days of C1D0 | Day 0 | Day 14 (± 3 d) | Day 0 (±3 d) | Day 0 (± 3 d) | Day 0 (± 3 d) | 7 d (± 3 d) post-last dose | 28 d (± 7 d) post-last dose | q12 w (± 1 w) post-last dose |
| Informed consent | X | | | | | | | | |
| Medical/Oncology History | X | | | | | | | | |
| ECOG Performance Status[1] | X | | | | | | X | | |
| Vital Signs[2] | X | X | X | X | X | X | X | X | |
| Height & Weight[3] | X | X[10] | | X[10] | X[10] | X[10] | X | X | |
| Physical Examination[4] | X | X[10] | | X[10] | X[10] | X[10] | X | X | |
| Hematology Labs[5] | X | X[10] | X | X[10] | X[10] | X[10] | X | X | |
| Chemistry Labs[5] | X | X[10] | X | X[10] | X[10] | X[10] | X | X | |
| Urinalysis[5] | X | X[10] | | X[10] | X[10] | X[10] | X | X | |
| Coagulation Panel[5] | X | X[10] | | X[10] | X[10] | X[10] | X | X | |
| Pregnancy Test[5] | X | X[6,10] | | X[6,10] | X[6,10] | X[6,10] | X | X[6,10] | |
| ECG[7] | X | X | | X | | | X | X | |
| Adverse Events | X | X | X | X | X | X | X | X | |
| Concomitant Medications | X | X | X | X | X | X | X | X | |
| VK-2019[8] | | X | X | X | X | X | | | |
| PK Plasma[9] | | X | | X | X (C3 only) | | | | |
| Plasma EBV DNA[5] | X | | | X | X (C3 only) | | X | | |
| Optional Tumor Biopsy[9] | X | | | X | | | | | |
| Tumor Assessments[11] | X | | | | X[11] | | X[12] | | X[13] |
| Survival | | | | | | | | | X[14] |

Phase 2a Dose Expansion Footnotes

1 ECOG performance scale is available in Appendix 1.
2 Vital signs (VS) include blood pressure (BP), temperature (T), and heart rate (HR). See Table 6 for collection time points.
3 Height is required at screening only.
4 A full physical exam is required at screening only. All other physical exams may be symptom directed.
5 Lab Assessments should include:
- Hematology labs: CBC with Differential
- Chemistry labs: Na, K, Cl, $CO_2$, BUN, Cr, glucose, Ca, total bili, AST, ALT, ALP, albumin, total protein, Mg
- Urinalysis: pH, specific gravity, glucose, ketones, blood, protein, nitrates, leukocytes
- Coagulation: PT, PTT, INR
- Pregnancy labs can be performed via blood or urine
- Plasma EBV-DNA

6 Pregnancy tests on D1 of each cycle and at the Safety FU visit are only required at sites in the EU. For sites in other regions, pregnancy tests at these visits are only required if clinically indicated.
7 All ECGs must be performed in triplicate. See Table 6 for specific collection time points. PK samples will only be collected through C3D0, not beyond. PD samples will be collected through C3D0 and at the end of treatment visit.
8 VK-2019 must be taken in the morning on an empty stomach. Patients must fast for one hour before and two hours after each dose. Study drug accountability will be performed at each visit.
9 See Table 6 for PK collection time points. PK samples will only be collected through C3D0, not beyond.
10 Assessments need not be repeated if performed within three days prior to the visit date.
11 Tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). Assessments should include evaluation of the neck, chest, abdomen, and pelvis, Post-baseline tumor assessments may be performed within seven days of D0 of odd numbered cycles (i.e., C3D0, C5D0, etc).
12 Tumor assessments performed within four weeks of the EOT visit need not be repeated.
13 Tumor assessments in LTFU are only required for patients that have discontinued for reasons other than radiographic progression of disease, and may be performed ± 2 weeks of the scheduled LTFU date.
14 Survival status may be assessed via clinic visit (either at the study site or outside facility), telephone, or videotelephony.
15 After completing 13 cycles of treatment (i.e., > 12 months), the Investigator and Sponsor may agree that a patient will require study visits on an every odd cycle basis only (i.e., C15D0, C17D0, C19D0, etc.), until more frequent visits become clinically indicated.
16 Visits performed out of window due to holidays, natural disasters, and similar circumstances will not be a protocol deviation.

**Table 4: Phase 1 Dose Escalation PK and ECG Schema**

| Visit | Timepoint | Assessments | |
|---|---|---|---|
| | | PK Plasma | ECG |
| Screening | n/a | | X |
| C1D0 | Pre-dose (-1 hour) | X | X |
| | 30 mins post-dose (± 5 m) | X | |
| | 1 h post (± 10 m)[1] | X | X |
| | 2 h post (± 10 m) | X | |
| | 3 h post (± 10 m) | X | |
| | 4 h post (± 10 m) | X | |
| | 6 h post (± 10 m) | X | |
| | 8 h post (± 30 m) | X | |
| | 24 h post (± 2 h) | X | |
| C1D14 | Pre-dose (-1 h) | X | X |
| | 1 h post (± 10 m)[1] | X | X |
| C2D0 | Pre-dose (-1 h) | X | X |
| | 1 h post (± 10 m)[1] | X | X |
| C2D14 | Pre-dose (-1 h) | | |
| | 1 h post (± 10 m) | | |
| C3D0 | Pre-dose (-1 h) | X | |
| | 1 h post (± 10 m)[1] | X | |
| EOT | n/a | | X |

Footnotes

1 For post-dose timepoints in which PK and ECGs are both collected, the ECGs should be collected first within the timepoint window. PK can then be drawn up to 10 minutes after the ECG collection time.

**Table 5: Phase 1 Dose Expansion PK and ECG Schema**

| Visit | Timepoint | Assessments | | |
|---|---|---|---|---|
| | | PK Plasma | PK Urine | ECG |
| Screening | n/a | | | X |
| C1D0 | Pre-dose (-1 hour) | X | | X |
| | 30 mins post-dose (± 5 m) | X | | |
| | 1 h post (± 10 m)[1] | X | | X |
| | 2 h post (± 10 m) | X | X[2] | |
| | 3 h post (± 10 m) | X | | |
| | 4 h post (± 10 m) | X | | |
| | 6 h post (± 10 m) | X | | |
| | 8 h post (± 30 m) | X | | |
| | 24 h post (± 2 h) | X | X[3] | |
| C1D14 | Pre-dose (-1 h) | X | | X |
| | 30 mins post-dose (± 5 m) | X | | |
| | 1 h post (± 10 m)[1] | X | | X |
| | 2 h post (± 10 m) | X | X[2] | |
| | 3 h post (± 10 m) | X | | |
| | 4 h post (± 10 m) | X | | |
| | 6 h post (± 10 m) | X | | |
| | 8 h post (± 30 m) | X | | |

| Visit | Timepoint | Assessments | | |
|---|---|---|---|---|
| | | PK Plasma | PK Urine | ECG |
| | 24 h post (± 2 h) | X | X[3] | |
| C2D0 | Pre-dose (-1 hour) | X | | X |
| | 1 h (± 10 m)[1] | X | | X |
| C2D14 | Pre-dose (-1 hour) | | | |
| | 1 h (± 10 m) | | | |
| C3D0 | Pre-dose (-1 hour) | X | | |
| | 1 h (± 10 m)[1] | X | | |
| EOT | n/a | | | X |

Footnotes
1 For post-dose timepoints in which PK and ECGs are both collected, ECGs should be collected first within the timepoint window. PK can then be drawn up to 10 minutes after the ECG collection time.
2 Patients should empty their bladders as close to dosing as possible. Urine will then be collected until 8 hours post-dose, with a specimen collected as close to the 8 hour time point as possible.
3 Urine for PK will then be collected 8 to 24 hours post-dose with a specimen collected as close to the 24 hour time point as possible.

**Table 6: Phase 2a Dose Expansion PK, PD, and ECG Schema**

| Visit | Timepoint | Assessments | | |
|---|---|---|---|---|
| | | PK Plasma | Optional Tumor Biopsy | ECG |
| Screening | n/a | | X | X |
| C1D0 | Pre-dose (-1 hour) | X | | X |
| | 1 h post-dose (± 10 mins)[1] | X | | X |
| C2D0 | Pre-dose (-1 hour) | X | X[2] | X |
| | 1 h post (± 10 m)[1] | X | | X |
| C3D0 | Pre-dose (-1 hour) | X | | |
| | 1 h post (± 10 m)[1] | X | | |
| EOT | n/a | | | X |

Footnotes
1 For post-dose timepoints in which PK and ECGs are both collected, ECGs should be collected first within the timepoint window. PK can then be drawn up to 10 minutes after the ECG collection time.
2 The post-dose tumor biopsy may be collected ± 7 days of C2D0.

# 2 BACKGROUND

Nasopharyngeal carcinoma (NPC) arises from the epithelium of the nasopharynx. The incidence and death rates from NPC worldwide are approximately 86,000 and 50,000 respectively, with an approximately 2 to 3-fold higher incidence in males.(1) The incidence in Southern China is about 35/100,000 while in the US overall rates are approximately 1-2/100,000. Risk seems to migrate with populations, so in ethnic Asians in the US, the incidence is intermediate between these two rates and seems to fall in subsequent generations following migration away from regions of high endemic incidence. Peak incidence is in the sixth decade of life and most patients present with locoregional advanced disease.

While early stage local disease is highly curable (> 90%) with radiation therapy, advanced locoregional disease is fatal in approximately 1/3 of all patients despite intensive chemotherapy and radiation treatments.(2) There are no reliable cures for patients with metastatic disease. The present standard systemic treatments for metastatic or locoregional recurrent disease is combination chemotherapy with agents such as gemcitabine and cisplatin. Such combinations typically are associated with response rates of 40-60% and median survivals of 20-30 months.(3)

Evidence strongly implicates Epstein-Barr virus (EBV) as the primary etiologic agent in the development of NPC.(4) While most humans have evidence of EBV exposure by adolescence, the reason a small subset of these develop NPC is unknown. The association between EBV infection and NPC development is extremely strong. Increased immunoglobulin titers against EBV, specifically against viral capsid antigen (VCA) of the EBV and IgA antibodies against EBV are highly associated with the development and presence of NPC.(5) Latent EBV infection is evident in virtually all cases of NPC without regard to geography or ethnicity. Copy numbers per cancer cell of latent EBV are highest in the undifferentiated WHO 3 type of NPC, the form of NPC seen most often in Asian populations. EBV in NPC tumor cells are monoclonal, indicating that EBV infection likely precedes tumorigenesis.

EBV, also known as HHV-4, is a member of the gamma human herpesvirus family. The viral genome is encapsulated in an infectious particle as linear double stranded DNA approximately 170 kb long. During latent infection, EBV DNA circularizes and replicates. It is latent infection that has oncogenic potential and thought to be the causative agent in NPC. Other lymphoid and epithelial malignancies associated with EBV include Burkitt's lymphoma, Hodgkin's lymphoma, gastric carcinoma, angiocentric T/NK lymphoma, lymphoproliferative disorders of the immunosuppressed, and oral hairy leukoplakia. During latency, EBV expresses a limited set of viral genes that stimulate cellular proliferation and promote survival.

Chief among the latency genes is the Epstein-Barr Nuclear Antigen 1 (EBNA1), which is consistently expressed in all EBV positive tumors. EBNA1 is required for the stable maintenance of the EBV genome in latently infected cells and provides a survival function to host-cells.(6)(7) EBNA1 localizes to the nucleus, binds to circularized EBV episomal DNA at a specific region known as the latent origin of replication (*OriP*). In addition to its roles in replication, EBNA1 also binds to a viral region called the Family of Repeats (FR) while simultaneously binding to cellular genomic DNA. Thus, EBNA1 acts as a tether to promote the distribution of viral DNA to each of the daughter cells. EBNA1 also acts as a transcription factor for other latent EBV genes including EBNA2, and LMP1.

Thus, EBNA1 plays a critical role in several processes thought to promote and maintain transformation and an ideal target for pharmacological inhibition. siRNA knockdown of EBNA1

in EBV–driven models and a dominant negative version of EBNA1 causes substantial cell death and inhibition of cellular growth.(8)(9)(10)(11)(12) This EBNA1 knockout strategy appears to be selective for EBV transformed cells, suggesting possible selectivity to a EBNA1 targeted anti-cancer strategy.(13) For all of the aforementioned activities of EBNA1, the site-specific DNA binding function of EBNA1 is required.

Small molecule inhibitors of the DNA binding activity of EBNA1 have been developed. The X-ray crystal structure of EBNA1 bound to the inhibitor VK-2019 shows that this inhibitor binds to a concave surface of EBNA1 critical for DNA binding. VK-2019 has nanomolar activity in *in vitro* competition assays and low micromolar activity in several cell-based assays. EBNA1 inhibitors disrupt the interaction with viral DNA in Chromatin Immunoprecipitation (ChIP) assays and interfere with replication and maintenance in episomal maintenance assays.

To assess the efficacy of EBNA1 inhibitors *in vivo*, a set of four unique EBV-dependent xenograft models were developed: One lymphoma model and three NPC models, including 2 patient-derived xenograft (PDX) models. The models include tumors that express varying EBV latency programs, all of which express EBNA1, and different mouse strains. For the PDX models, a primary nasopharyngeal tumor (C15) as well as a metastatic tumor line (C17) were included.

Luciferase-positive Mutu LCL (Burkitt's lymphoma line) were engrafted into the flanks of NSG-SCID mice and monitored by IVIS imaging and caliper measurements. Treatment with VK-2019 provided significant tumor growth inhibition (> 90%) compared to vehicle control with a P value < 0.0001, the null hypothesis being no effect of treatment. VK-2019 treated mice had significant tumor growth inhibition. VK-2019 was well tolerated with no weight loss observed.

For the NPC models, two patient-derived tumor lines were engrafted, C15-PDX and C17-PDX into six to eight week old athymic nude mice, weighing 18 to 25 grams. C15-PDX was derived from a treatment naïve primary tumor from a patient of Moroccan decent and has been classified as latency program II. C17-PDX was derived from a cutaneous metastatic tumor sample that had previously been treated with cisplatin, bleomycin and 5-fluorouracil and is in latency program I. Tumor fragments of approximately 3 mM were engrafted subcutaneously. Treatment with 10 mg/kg VK-2019 resulted in significant (> 75%) tumor growth inhibition in both the C15-PDX and C17-PDX. In a dose escalation experiment, significant dose response was observed with tumor growth inhibition of ~90% at 100 mg/kg dosed orally. VK-2019 is well-tolerated. Twice daily oral administration of 100 mg/kg for > 50 days results in no weight loss, behavioral symptoms nor adverse findings during gross necropsy.

To verify target engagement, i.e., that treatment with VK-2019 had an effect on latent virus—RNA was isolated from the xenograft tumor material and performed gene expression analysis using the Nanostring hybridization system. Treatment with VK-2019 caused a significant decrease in the expression of all EBV-encoded genes—both lytic and latent genes. This result provides further validation and is consistent with the hypothesis that VK-2019 treatment inhibits EBV replication and maintenance in latently infected cells and, thus, reduces the tumor burden of EBV-positive tumors. To assess selectivity, mice engrafted with EBV-positive and EBV-negative cell lines were treated. Treatment with 10 mg/kg VK-2019 resulted in ~70% tumor grown inhibition in the C666-1 (an EBV positive cell line) xenograft, whereas the same treatment resulted in < 10% tumor growth inhibition in A549 xenograft.

Extensive PK analysis of VK-2019 has been performed. In rat and dog PK experiments, significant systemic exposure was seen with $C_{max}$ in the 25 to 50 µM range when dosed at 30 and

10 mg/kg, respectively. The half-life in rat (~4 hrs) and in dog (7 to 8 hrs) suggest a reasonable exposure may be expected in humans. In addition, significant oral bioavailability of > 50% was observed in both species. PK data demonstrate significant exposures at 10, 30, and 100 mg/kg/day in rat and dog. Using the exposures from the mouse xenograft studies (AUC = ~8600 ng*hr/mL) at the efficacious dose (10 mg/kg), the exposure levels from toxicity studies to ask whether a safe, efficacious is achievable. As will be described below, no serious adverse events were observed at the high dose (100 mg/kg/day) in both rats and dogs over the 28 days. At this high dose, exposure multiples of 80-fold and 160-fold over the efficacious exposure were calculated in rat and dog, respectively. This gives confidence that significant exposure in humans is achievable.

To assess preclinical safety non-GLP Dose-limiting Toxicity (DLT), Dose Range Finding (DRF) studies, and GLP 28-day repeat dose toxicity studies were performed. In single dose MTD studies, rats were dosed at 50, 100, 200, and 400 mg/kg and observed for clinical signs, body weight, and food consumption. A slight decrease in body weight gain was observed in the 400 mg/kg group, and in 7-day repeat dose DRF study at 30 and 300 mg/kg/day. PK sampling on Day 1 and Day 7 were similar. At the 300 mg/kg dose level, morbidity was observed in about half of the rats after 3-5 days. Bioanalytical data showed that the surviving rats had > 400 μM plasma concentrations with a few having concentrations of ~1 mM. Averaged across all surviving rats, the exposure multiple was 327-fold greater than the anticipated clinical efficacious exposure. Clinical pathology data indicated that the target organs were kidney and liver. For the IND-enabling, 28-day GLP repeat dose toxicity study in rat, 0 (control), 10, 30, and 100 mg/kg/day were dosed, which included toxicokinetics (TK) and 28-day recovery groups for the control and high dose animals. Bioanalytical evaluations of animal groups at each of the dose levels were performed. At all dose levels, no morbidity/mortality, no effects on body weight or food consumption, and no adverse clinical signs were observed. Gross necropsy uncovered a slight increase in liver weight, which was reversed in the recovery animals. Clinical chemistry data indicated slight, but significant changes in alkaline phosphatase, bilirubin, BUN, creatinine, cholesterol and total protein. These effects were reversible 28-days after the treatment period. Other clinical chemistry or hematology effects were not observed. There were no drug-related neurobehavioral findings. Histopathology assessments indicated that at the high dose, mild centrilobular liver vacuolation, mild periportal vacuolation, minimal tubular basophilia, and mononuclear infiltration were seen. Bioanalytical results indicated that the exposure multiple was > 87-fold higher than the efficacious exposure. In dog, single dose MTD studies were carried out at concentrations of 25, 50, 75, and 100 mg/kg. No adverse clinical signs, effects on body weight or food consumption with a single dose were observed. In dog 7-day repeat dose DRF studies, we dosed 10, 50, 100, and 150 mg/kg/day. At all dose levels, no adverse clinical signs, body weight or food consumption changes were observed. PK data on Day 1 and Day 7 were similar. In 28-day repeat dose toxicity study in dog, animals were dosed with 0 (control), 10, 30, and 100 mg/kg/day and included recovery groups. Morbidity/Mortality, adverse clinical signs, effects on body weight and food consumption were not observed at any dose levels. Clinical chemistry was normal at all dose levels. A slight, but significant decrease in the reticulocyte count was observed in the 100 mg/kg/day group on Day 27 compared to the controls. In sum, preclinical safety studies suggest that VK-2019 will be safe at efficacious doses.

Results from *in vitro* ADME experiments are not an obstacle to further development and suggest that VK-2019 will be safe. Aqueous solubility of > 500 μM at pH 7.4 and 9.2 was observed. CYP450 inhibition assays with Cyp1A2, 2D6 and 3A4 showed IC50 values of > 50 μM, the highest concentration that VK-2019 was tested. No hERG binding (0%) was observed up to

50 μM. Metabolic stability in human, rat and mouse liver microsomes was measured, both with and without cofactors. The stability was ~100% at 60 minutes when incubated with human, rat or mouse liver microsomes, with and without cofactors. In the hemolysis assay, we observed no hemolysis (0%) up to 500 μM. We have run the Cerep 44 Safety Screen with 10 μM VK-2019. VK-2019 had no activity in all 44 receptors and enzymes ≤ 30% of positive controls at 10 μM. The effect of VK-2019 on OATP1B3 and PGP transporters has been characterized. VK-2019 did not interact with PGP transporters, but did interact with OATP1B3, comparable to atorvastatin. VK-2019 did not inhibit transport of atorvastatin by OATP1B3. In accordance with the 2012 FDA DDI draft guidance and the decision tree, it was determined that VK-2019 falls well outside the parameters that would require a drug-drug interaction study.

A specific and sensitive method to measure the progression of NPC uses real-time quantitative PCR to quantify cell-free circulating EBV DNA. (14) EBV DNA in plasma is thought to originate from apoptotic or necrotic tumor cells. (15) EBV DNA levels have been shown to correlate with tumor staging, tumor burden before treatment and likelihood of tumor recurrence. (16), (17), (18) EBV DNA concentrations have been shown to be sensitive (> 96%) and specific (93%) in predicting overall survival and are possibly more accurate than the TNM staging system. (19) Serum EBV DNA levels have been shown to remain consistently low or undetectable in patients in complete clinical remission. Interestingly, NPC patients who had an increase in plasma EBV DNA concentrations after achieving an undetectable level post treatment typically relapse up to six months after the detected rise in plasma EBV DNA levels. These findings suggest that EBV DNA levels may be a reliable relapse predictor before any clinical evidence of recurrence is found. (20) This protocol outlines the use of EBV plasma levels as an early surrogate biomarker for efficacy. Tumor cell EBV copy number and viral expression will also be evaluated to potentially elucidate the direct mechanism of action of the EBNA inhibitor VK-2019 as EBNA1 inhibition preclinically has been shown to cause a decrease in EBV viral gene expression.

# 3 OBJECTIVES OF THE STUDY

## [redacted] Phase 1 Objectives

### 3.1.1 Primary

- 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.

### 3.1.2 Secondary

- 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.

### 3.1.3 Exploratory

- 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).

## [redacted] Phase 2a Objectives

### 3.2.1 Primary

- 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.

### 3.2.2 Secondary

- 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.

### 3.2.3 Exploratory

- 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).

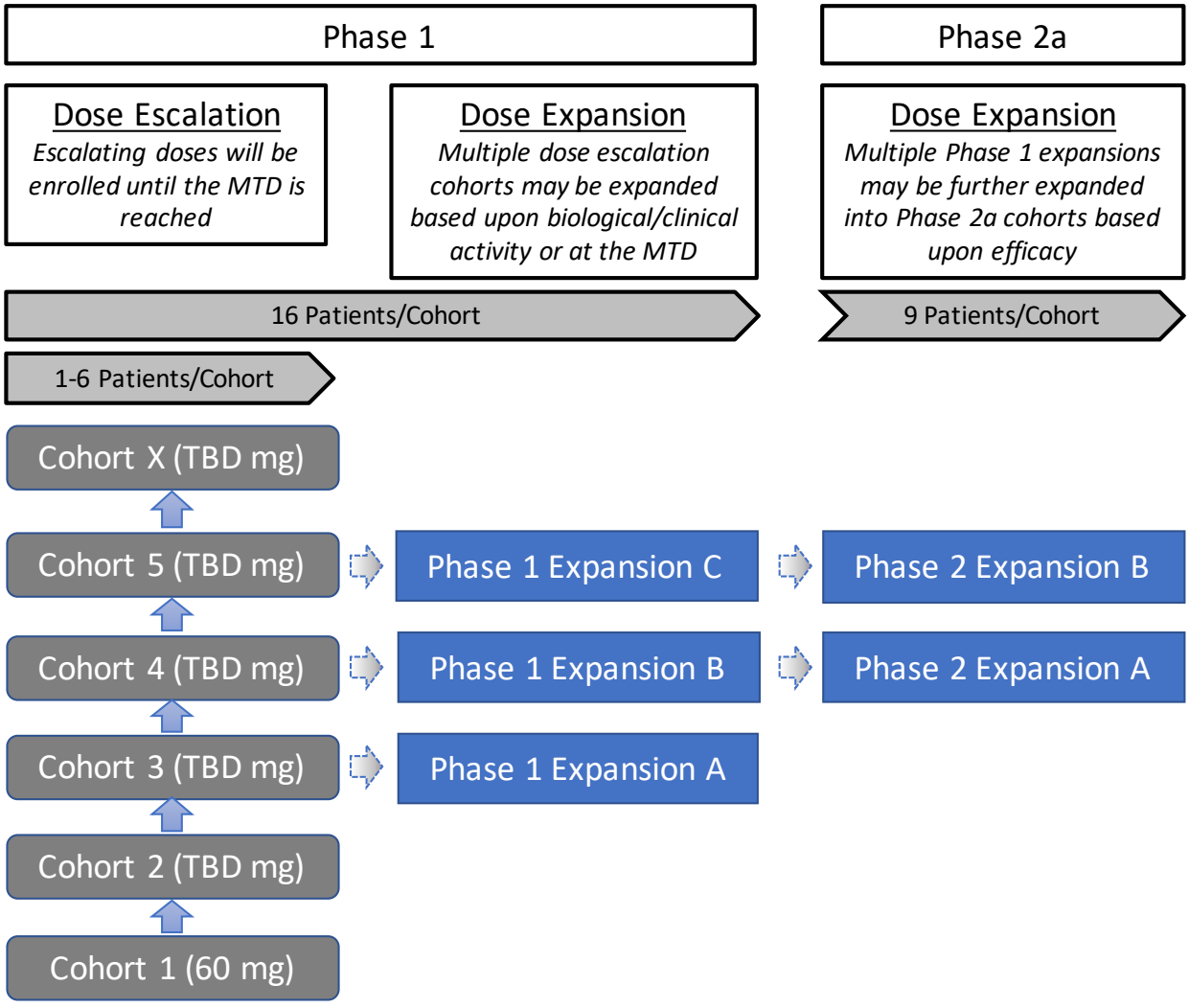
# 4 STUDY DESIGN

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*

**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 (21), coupled with a "rolling six" design (22). 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 (23).

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.

See Section 6.2 for dose escalation procedures.

**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. See Section 6.7 for details on initiating a Phase 1 Dose Expansion.

**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 Section 6 for details on initiating a Phase 2a Dose Expansion.

# 5 ELIGIBILITY CRITERIA

The inclusion and exclusion criteria for this study are provided on the Eligibility Checklist below.

A patient must meet all of the inclusion criteria and must not meet any of the exclusion criteria to be eligible to participate in this study.

The checklist may be utilized to review and confirm each patient's eligibility prior to registration (unless a separate checklist is required by the institution). If used for confirmation of eligibility, the completed, signed, and dated checklist will be retained in the patient's study file and the study's regulatory binder.

**Patient Eligibility Checklist**

## I. Protocol Information

| | |
|---|---|
| Protocol Title: | 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 |
| Protocol number (Sponsor/Institution): | **VK-2019-001/** |
| Principal Investigator: | |

## II. Patient Information

| | | |
|---|---|---|
| **Patient Identifier (i.e., Subject Number, etc.):** | | |
| **Gender** | ☐ Male | ☐ Female |

## III. Study Information

**Inclusion Criteria**

| Prospective Study Patient Must MATCH ALL these Inclusion Criteria to be Eligible | Yes | No | Supporting Documentation * |
|---|---|---|---|
| 1. Informed consent obtained prior to any protocol mandated assessment | ☐ | ☐ | |
| 2. Age ≥ 18 | ☐ | ☐ | |
| 3. Either loco-regionally recurrent or metastatic EBV-positive nasopharyngeal carcinoma not amenable to curative treatment. EBV positivity is defined as high EBV viral load in plasma (> 4000 genomes per µg plasma DNA) and/or biopsy tissue positive for EBV | ☐ | ☐ | |
| 4. Prior palliative radiation must have been completed at least 2 weeks prior to study Cycle 1 – Day 0 | ☐ | ☐ | |
| 5. Prior anti-cancer systemic treatment must have been completed greater than 4 weeks prior to the first dose of VK-2019 | ☐ | ☐ | |

| Prospective Study Patient Must MATCH ALL these Inclusion Criteria to be Eligible | Yes | No | Supporting Documentation * |
|---|---|---|---|
| 6. Toxicities related to prior anti-cancer therapy must have returned to Grade 1 or less. Peripheral neuropathy must be Grade 2 or less. Chronic but stable toxicities Grade > 1 (e.g., dysphasia, G tube dependence, etc.) may be allowed after agreement between the Investigator and Sponsor. | ☐ | ☐ | |
| 7. **For the dose expansion phase in Phase 1 and Phase 2a**: Patients must have RECIST v1.1 measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥ 10 mM with spiral CT scan, MRI, or calipers by clinical exam | ☐ | ☐ | |
| 8. ECOG performance status score of ≤ 2 at study entry. | ☐ | ☐ | |
| 9. Absolute neutrophil count > 1500/μL (stable off any growth factor for at least 1 week of study drug administration) | ☐ | ☐ | |
| 10. Hemoglobin > 9g/dL (transfusion to achieve this level **is permitted**) | ☐ | ☐ | |
| 11. Platelet count > 75 x 103/ μL (transfusion to achieve this level **is NOT permitted**) | ☐ | ☐ | |
| 12. Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) ≤ 2.5 x upper limit of normal (ULN) | ☐ | ☐ | |
| 13. Total serum bilirubin ≤ 1.5 x ULN | ☐ | ☐ | |
| 14. Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 mL/min as calculated per Cockcroft-Gault equation | ☐ | ☐ | |
| 15. Urinary protein < 2+ by dipstick. If dipstick ≥ 2+, then a 24-hour urine collection can be done and the patient may enter only if urinary protein is < 1 g/24 hour | ☐ | ☐ | |

| Prospective Study Patient Must MATCH ALL these Inclusion Criteria to be Eligible | Yes | No | Supporting Documentation * |
|---|---|---|---|
| 16. Sexually active patients must agree to utilize birth control method during treatment and for 18 weeks after the last dose of VK-2019. Using effective birth control methods as defined in https://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf. See Appendix 3 and Section 17.3 | ☐ | ☐ | |
| 17. Willingness and ability to comply with the study scheduled visits, treatment plans, laboratory tests and other procedures | ☐ | ☐ | |

**Exclusion Criteria**

| Prospective Study Patient Must NOT Match ANY of These Exclusion Criteria | Yes | No | Supporting Documentation * |
|---|---|---|---|
| 1. Severe or active symptomatic cardiopulmonary diseases, including unstable angina, congestive heart failure, or peripheral vascular disease within 12 months prior to study drug administration; and/or chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization within 4 weeks prior to study drug administration. Patients with effectively treated conditions (eg, stenting for coronary artery disease) are eligible if stable for at least 4 weeks prior to study drug administration. | ☐ | ☐ | |
| 2. Metastatic disease with active central nervous system (CNS) involvement, defined as parenchymal brain involvement. Patients with cranial nerve or base of skull involvement without the above are eligible. Patients with CNS metastases that are stable on imaging at least 1 month following focal treatment with radiation are eligible | ☐ | ☐ | |
| 3. Concurrent treatment with systemic cancer directed therapy including complementary, alternative, herbal or nutritional supplement-based treatments whose purpose is for anti-cancer effect | ☐ | ☐ | |

| Prospective Study Patient Must NOT Match ANY of These Exclusion Criteria | Yes | No | Supporting Documentation * |
|---|---|---|---|
| 4. Known history of human immunodeficiency virus (HIV) unless the HIV-positive patients has:<br>• A stable regimen of highly active anti-retroviral therapy (HAART)<br>• No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections<br>• A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based test | ☐ | ☐ | |
| 5. Serious uncontrolled medical disorder or active infection which would, in the opinion of the Investigator, impair the ability of the subject to receive protocol therapy or whose control may be jeopardized by the complications of this therapy | ☐ | ☐ | |
| 6. Currently taking drugs that inhibit or induce OATP1B1 or OATP1B3 within 5 half-lives of that agent. Examples are included in Appendix 2. | ☐ | ☐ | |
| 7. Have received a prior organ allograft or allogeneic bone marrow transplant. | ☐ | ☐ | |
| 8. Current non-prescription drug or alcohol dependence | ☐ | ☐ | |
| 9. For all female patients, pregnancy or breastfeeding | ☐ | ☐ | |
| 10. All female patients with reproductive potential must have a negative pregnancy test (serum or urine) prior to enrollment | ☐ | ☐ | |
| 11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration, or may interfere with the interpretation of study results, or in the judgment of the investigator would make the patient inappropriate for entry into the study | ☐ | ☐ | |

| Prospective Study Patient Must NOT Match ANY of These Exclusion Criteria | Yes | No | Supporting Documentation * |
|---|---|---|---|
| 12. Corrected QT by Fridericia's formula (QTcF) of > 470 ms average (mean) on triplicate ECG performed during screening | ☐ | ☐ | |

* All patient files must include supporting documentation to confirm eligibility. The method of confirmation can include, but is not limited to, laboratory test results, radiology test results, subject self-report, and medical record review.

## V. Statement of Eligibility

By signing this form of this study, I verify that this subject is: ☐ eligible / ☐ ineligible for participation in the study.

| Study Coordinator Printed Name: | Date: |
|---|---|
| Signature: | |

| Investigator Printed Name: | Date: |
|---|---|
| Signature: | |

| Additional Reviewer Printed Name (if required): | Date: |
|---|---|
| Signature: | |

**Age and Reproductive Status**

Sexually active patients (excluding women who are not of childbearing potential) must use effective methods of birth control during treatment and for up to 18 weeks after the last dose of VK-2019. See Appendix 3.

Acceptable methods of highly effective birth control include:

- Condom with spermicide
- Diaphragm and spermicide
- Cervical cap and spermicide
- Hormonal implant
- Intrauterine device
- Male or female surgical sterilization
- Oral contraceptive pills

Women must not be breastfeeding.

Women of child-bearing potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), and who is not postmenopausal.

# 6 STUDY TREATMENT AND CONDUCT

## [redacted] Safety Review Committee

During the Dose Escalation and Dose Expansion parts of this study, an SRC will review safety, tolerability, PK, and, if available, PD data for the purposes of oversight and decision making.

The SRC's membership will consist of:

- Two external, independent oncologists (one of which will serve as SRC Co-Chair)
- The Protocol Chairperson (who will also serve as SRC Co-Chair)
- The sponsor Medical Monitor and/or Chief Medical Officer
- Principal Investigators from each site

Additional attendees including (but not limited to) the study statistician, pharmacologist, pharmacovigilance representatives, site staff, or sponsor representatives may be invited to participate on an ad hoc basis.

More information about SRC membership and roles and responsibilities is contained in the SRC Charter.

### 6.1.1 During Phase 1 Dose Escalation

After completion of a dose escalation cohort, the SRC will convene to evaluate the safety, tolerability, PK, and, if available, PD data of VK-2019 from that cohort with the purpose of deciding upon the next dose level.

Upon reviewing data from that cohort, the SRC may decide to:

- Escalate to the next dose level
- Convert to the rolling-six dose escalation schema
- Enroll up to a maximum of 6 evaluable patients
- De-escalate to either a previously explored lower dose level (up to a maximum of 6 evaluable patients) or to an intermediate lower dose level
- Discontinue dose escalation in the trial
- Initiate a Phase 1 Dose Expansion Cohort
- Consider alternative dosing frequencies or intermittent dosing schedules
- Terminate the trial
- Defer their decision until additional data from patients in that cohort and/or other cohorts becomes available

Additionally, PK profiles for patients treated two dose levels below a dose level under consideration for escalation will be required by the SRC prior to starting a given dose level, e.g., Cohort 3 will begin only after PK information on Cohort 1 is available for review. If super-proportional PK is observed following the single-dose PK on C1D0, the dose of VK-2019 may be modified to account for the increase in exposure. If significantly less than dose proportional exposure is observed, dose escalation may be stopped and one of the doses with the highest exposure may be selected for expansion.

Any patient started on treatment in error, i.e., he/she failed to comply with all of the selection criteria, but still meets the criteria of an evaluable patient will be reviewed on a case by case basis by the SRC to determine if the patient should be included or excluded in the decision for dose escalation.

During the dose escalation, decisions made by the SRC will be documented and provided to the investigators prior to dosing any new patients.

#### 6.1.2 During Phase 1 Dose Expansion

Upon completion of any Phase 1 Dose Expansion Cohort in the trial, the SRC will convene to review accumulating safety, tolerability, pharmacokinetics, and, if available, pharmacodynamic data. Additionally, SRC reviews will be required at various intervals during a given expansion cohort. The timing and criteria for convening these reviews are described in the SRC Charter.

Upon review of this data, the SRC may decide to:

- Continue the trial as planned
- Stop enrollment into a particular expansion cohort or all cohorts in the Phase 1 Dose Expansion part of the trial
- De-escalate one or more of the doses being explored in the expansion
- Initiate a Phase 2a Dose Expansion Cohort
- Consider alternative dosing frequencies or intermittent dosing schedules
- Terminate the trial
- Defer their decision until additional data becomes available

#### 6.1.3 During Phase 2a Dose Expansion

Upon completion of any Phase 2a Dose Expansion Cohort in the trial, the SRC will convene to review accumulating safety, tolerability, pharmacokinetics, and, if available, pharmacodynamic data. Additionally, SRC reviews will be required at various intervals during a given expansion cohort. The timing and criteria for convening these reviews are described in the SRC Charter.

Upon review of this data, the SRC may decide to:

- Continue the trial as planned
- Stop enrollment into a particular expansion cohort or all cohorts in the Phase 2a Dose Expansion part of the trial
- De-escalate one or more of the doses being explored in the expansions
- Consider alternative dosing frequencies or intermittent dosing schedules
- Terminate the trial
- Defer their decision until additional data becomes available

**[redacted] Dose Escalation Procedures**

The starting dose for VK-2019 is 60 mg QD. Sample dose escalation tables are below in Table 7, detailing a sample dose escalation schema based upon when escalation converts from Accelerated Titration to a Rolling Six design.

### 6.2.1 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:

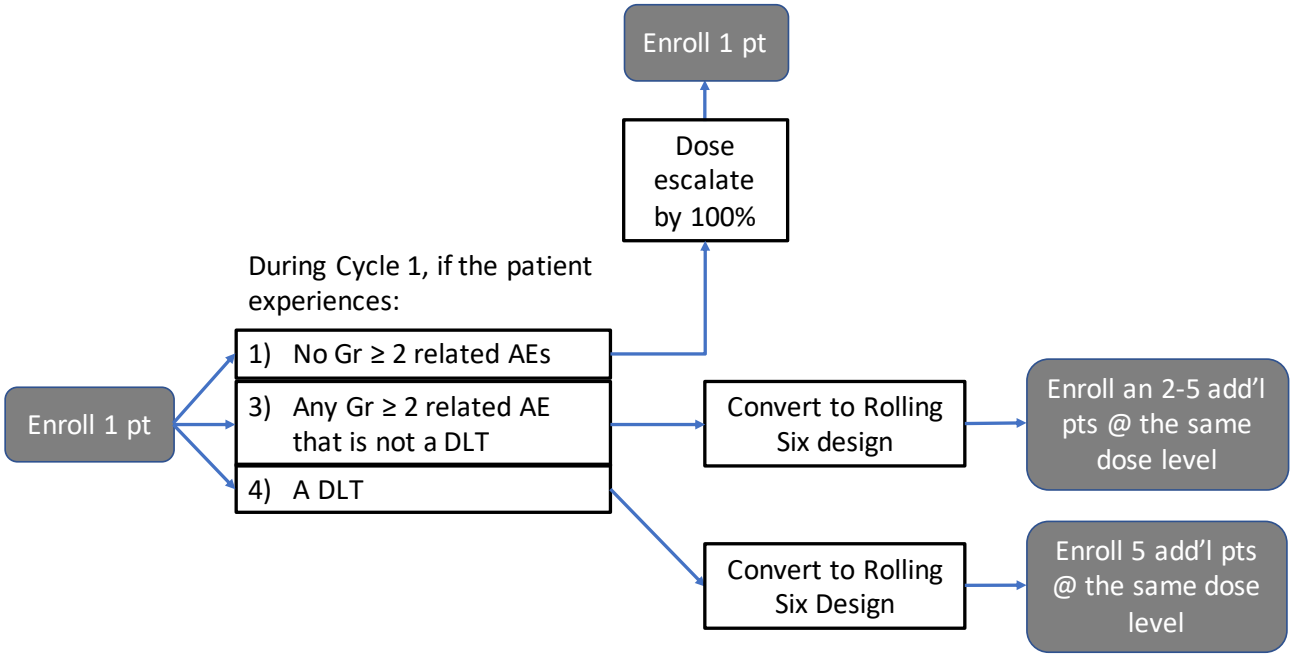
- Received 75% of doses during Cycle 1, or,
- Received at least one dose of VK-2019 and experienced a DLT during Cycle 1

### 6.2.2 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**




### 6.2.3 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 7: 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).

#### 6.2.4 Intra-Patient Dose Escalation in Accelerated Titration Cohorts

After an accelerated titration cohort has been declared safe 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 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.

6.2.5 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.

**[redacted] Dose-limiting Toxicity**

DLTs will be determined based on the incidence and intensity of AEs assessed as being at least possibly related to VK-2019 and occurring up to 28 days after initiation of QD VK-2019 dosing on C1D0.

6.3.1 Dose-limiting Hematologic Toxicity

- Grade 4 neutropenia > 7 days
- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia associated with bleeding or requiring platelet transfusion
- Grade 3 febrile neutropenia
- Grade 4 anemia or anemia that requires blood transfusion

6.3.2 Dose-limiting Non-hematologic Toxicities

- Any Grade 3 or higher non-hematology toxicity, excluding the following:
    - Toxicities assessed by Investigator as clearly related only to disease progression or intercurrent illness
    - Elevations of AST, ALT, and bilirubin, that correct to Grade 1 within one week and do not meet any of the definitions of acute liver injury as listed below
    - Other asymptomatic laboratory abnormalities
    - Grade 3 fever without neutropenia that returns to Grade 1 or less within 3 days, and is not associated with hemodynamic compromise (including hypotension, or clinical or laboratory evidence of end organ perfusion impairment)
    - Grade 3 diarrhea, nausea, vomiting, or abdominal pain that returns to Grade 1 or baseline within 3 days and with medical intervention
    - Grade 3 pruritis or rash that returns to Grade 1 or baseline within 7 days or baseline with medical intervention
    - Grade 3 fatigue
    - Grade 3 tumor flare (defined as pain, irritation or rash that localizes to sites of known or suspected tumor)

A DLT will also include:

- A laboratory finding of acute liver injury defined as:
    - Sustained (> 1 week) doubling of AST or ALT levels to no less than 4 x ULN, or sign of increasing functional liver impairment with > 2x baseline increase in total bilirubin
    - Increased AST or ALT levels above 8xULN
    - Suspected acute liver injury (per Hy's law) ALT/AST > 3 x ULN in combination with Total Bilirubin > 2 x ULN in the absence of cholestatic injury (ALP < 2 x ULN) and no other cause identified.
- Any AE resulting in a patient missing < 7 days of dosing with VK-2019
- Any AE not otherwise meeting the criteria or timing of a DLT as defined above, but is declared a DLT by the SRC

### [redacted] Definition of the MTD

The MTD is defined as the highest dose level of VK-2019 at which fewer than two DLTs are observed in six evaluable dose escalation patients at that dose level.

### [redacted] Definition of a BCAD

A BCAD is defined as any dose level that appears to have preliminary clinical or biological activity based upon the following criteria:

- There are no safety concerns in that cohort based upon the SRC's analysis of safety data.
- The following criteria for either clinical or biological activity:

Clinical:

- At least one dose escalation patient has experienced an objective response per RECIST v1.1 (i.e., a PR or CR) at that dose level.

Biological:

- Post-baseline plasma EBV DNA levels have declined by three log from baseline, or are below the lower limit of detection of the assay, AND,
- Plasma AUC level VK-2019 at the end of Cycle 1 is above the biologically active dose as defined in preclinical models (10,000 ng*h/mL).

**[redacted] Definition of the RP2D**

The dose of orally administered VK-2019 monotherapy that, in the opinion of the SRC, can be safely administered for three or more cycles, factoring in cumulative adverse experiences and adverse experiences that lead to study drug discontinuation.

**[redacted] Initiation of Phase 1 Expansion Cohorts**

The SRC may elect to initiate a Phase 1 Dose Expansion Cohort and enroll additional patients at any dose level that:

- Meets the definition of the MTD.
- Meets the definition of a BCAD.

The total number of patients enrolled at any one dose level during Phase 1 (dose escalation and expansion) will not exceed 16 patients.

Based upon the above criteria, the SRC may elect to explore multiple dose levels as Phase 1 Expansion Cohorts (either staggered or concurrently).

**[redacted] Initiation of Phase 2a Expansion Cohorts**

Upon completion of any Phase 1 Expansion Cohort, the SRC may elect to expand the cohort further, initiating a Phase 2a Dose Expansion and enrolling an additional nine patients if the dose level meets the following:

- Two or more patients have experienced an objective response per RECIST v1.1 (i.e., a PR or CR), of which at least one is a confirmed response.
- There are no additional safety concerns in the cohort of existing patients based upon the SRC's analysis of emerging safety data.

The total number of patients enrolled at any one dose level during all phases of the study will not exceed 25 patients.

Based upon the above criteria, the SRC may elect to explore multiple dose levels as Phase 2a Expansion Cohorts (either staggered or concurrently).

**[redacted] Duration of Therapy**

Patients may continue to receive treatment until meeting criteria for discontinuation/withdrawal, e.g., adverse events, disease progression, etc. as outlined in Section 6.11.

**[redacted] Re-initiation of Therapy for Patients in Long-Term Follow-Up**

Patients having discontinued treatment after achieving a confirmed CR may reinitiate study therapy at the time of confirmed disease progression if there is agreement between the Investigator and the Sponsor.

Patients will be required to meet eligibility criteria at the time of reinitiating study drug and will receive the same dose level of VK-2019 that they received prior to discontinuation. However, if higher dose levels of VK-2019 have been explored and deemed tolerable by the SRC, the Investigator and Sponsor may agree that the patient may reinitiate VK-2019 at a higher dose level. Patients reinitiating VK-2019 at a higher dose level will not be evaluable for a DLT.

Patients resuming therapy in this setting will do so at the next cycle after they completed therapy and will be followed as specified for all patients in the study. For example, patients that discontinued therapy after Cycle 14 will reinitiate therapy at the beginning of Cycle 15.

Patients that achieved a CR will not be eligible to reinitiate treatment if they:

- Discontinued study drug due to a treatment related adverse event(s), or
- Have completed one year of follow-up (from date of last dose of study drug) without evidence of disease progression.

Additional safety and efficacy summaries will be presented for patients that reinitiated study therapy under these conditions.

### [redacted] Patient Withdrawal

Patients may withdraw from the trial at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. Patients that withdraw from treatment should be encouraged to return for the end-of-treatment visit, complete all safety assessments, and enter long-term follow-up. If the patient withdraws from both treatment and follow-up, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

The primary reason for withdrawal must be recorded in the subject's medical record and in the appropriate eCRF pages. If a subject is withdrawn for more than one reason, each reason should be documented in the source document and the most medically significant reason should be entered on the eCRF. For example, in order to best characterize the safety profile of VK-2019, patients that withdraw consent from treatment due to tolerability issues with VK-2019 should be captured in the eCRFs as having discontinued due to AE or toxicity instead of having withdrawn consent from treatment.

Patients will be discontinued from treatment and begin long-term follow-up in the case of:

- Disease progression or requirement for anticancer therapy not specified in the protocol.
- Inter-current illness, general, or specific changes in the patient's condition where, in the opinion of the Investigator, further treatment is not in the best interest of the patient.
- DLT or unmanageable AE related to therapy.
- Withdraw of consent from treatment.
- Significant protocol violation or non-compliance with protocol.
- Termination of the study by Sponsor. Note: Any patients still receiving investigational product at the time of study termination by the sponsor will be able to continue to receive VK-2019 if they are deriving clinical benefit and after agreement between the Investigator and sponsor. Such patients will continue to be monitored for SAEs as

described in Section 13. Drug Accountability information must still be collected until all patients have completed treatment.

Patients will be withdrawn from study (long-term follow-up) in the case of:

- Withdrawal of consent from follow-up.
- Patient lost to follow-up.
- Death.
- Termination of study by Sponsor.

# 7 STUDY DRUG: VK-2019

## [redacted] Description, Supply and Storage of Investigational Drugs

### 7.1.1 Classification

VK-2019 is an anti-viral compound being tested for its effect on cancer.

### 7.1.2 Mechanism of Action

VK-2019 binds to EBNA1 and inhibits EBNA1 DNA binding activity.

### 7.1.3 Metabolism

Two VK-2019 metabolites were observed when incubated with liver microsomes: A hydroxylated form and a glucouronidation form. These forms are likely the major routes of clearance of VK-2019.

### 7.1.4 Drug interactions

Drug interaction studies with VK-2019 have not been conducted. The following information is based on results from *in vitro* studies with VK-2019. All concomitant medications must be recorded and approved by the sponsor at study entry and up to the end of Cycle 2.

VK-2019 did not inhibit CYP450 1A2, 2D6 or 3A4 *in vitro*. $IC_{50}$ values were greater than 50 μM, the highest concentration that was tested. In addition, VK-2019 did not induce the mRNA expression of drug-metabolizing CYP450 1A2, 2B6 and 3A4 in primary human hepatocytes from 3 different donors. Therefore, the interaction of VK-2019 with metabolism of drugs through these P450 subtypes appears unlikely at clinical concentrations. In cell assay, VK-2019 was classified as a substrate of OATP1B3 transporter at low concentration, but not at high concentrations. The influx rate of atorvastatin was increased in the presence of VK-2019, suggesting that OATP1B3 mRNA expression was induced. It is not known how the administration of VK-2019 will affect the absorption of drugs that are transported by OATP1B3, for example, atorvastatin. See Appendix 2 for details regarding disallowed medications.

### 7.1.5 VK-2019 capsules

VK-2019 will be provided in capsules containing either 30 mg or 200 mg VK-2019.

### 7.1.6 Storage and handling

VK-2019 is formulated in capsules, in 30 mg and 200 mg per capsule formulations. The capsules are packaged in High-Density Polyethylene (HDPE) bottles, with protection from moisture and should be handled with care.

The site Investigator must ensure that all investigational drug supplies are stored in a locked, safe area at room temperature (15-25°C) with access limited to authorized study staff. Investigational drug supplies should not be repackaged in any way.

Once patients are given study treatment, they will be asked to store them away from moisture at room temperature.

### 7.1.7 Side Effects

Information on pre-clinical toxicity and updated adverse event information if available are presented in the Investigational Drug Brochure.

# 8 TREATMENT PLAN

## [redacted] Patient Enrollment and Allocation to Treatment

Each patient will provide informed consent prior to any study related assessments. In some cases, procedures performed as standard of care prior to signing consent may be allowed as assessments of a patient's eligibility, e.g., scans performed on a patient's prior treatment regimen serving as baseline scans for this study so long as they will be within the 28-day screening window.

Upon determination that the patient meets all eligibility criteria, the Investigator or designee will enroll the patient according to the procedures described by the Sponsor. Each enrolled patient will be assigned a unique subject number by the Sponsor or its designee.

Recruitment into the study will be conducted in a controlled manner. No patient will be enrolled without prior authorization from the Sponsor to ensure adherence with the study design. If a patient withdraws from the study, then the subject number cannot be reused, even in cases where the patient has withdrawn prior to receiving a dose of VK-2019. Dose level assignment will be controlled by the Sponsor. The Investigator and/or designee will receive from the Sponsor confirmation of enrollment along with the assigned dose level. Sponsor will notify the other sites of slot allocation and will inform sites about the available slots, next possible enrollment dates after SRC review, etc.

Potential patients will NOT receive study drug until the entire enrollment process has been completed.

## [redacted] Dosage and Administration

### 8.2.1 Availability

Upon activation, study centers will receive a supply of VK-2019. Re-supplies of VK-2019 will be made at regular intervals during the course of the study based upon need. The Sponsor should be contacted for any issues related to drug supplies.

### 8.2.2 Preparation and Dispensing

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.

VK-2019 must be handled and administered with care. Patients should be instructed to keep their medication bottles provided at room temperature in a dry and safe place and not transfer it to any other containers.

### 8.2.3 Administration and Accountability

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.

On PK days (Tables 4-6), VK-2019 will be administered during the clinic visit to optimally control for PK times relative to dosing. On all other days, patients will be instructed to self-administer VK-2019 in the morning on an empty stomach with a glass of water at approximately the same time each day. Patients must fast for one hour before and two hours after each dose.

Patients will be instructed to swallow VK-2019 capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. When a patient is required to ingest more than six capsules per daily dose and the patient reports difficulties doing so, it is allowable to take the dose in split doses during the morning hours.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the product,
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated AEs are to be captured on an AE CRF page.

# 9 PATIENT MONITORING, TOXICITY MANAGEMENT, AND DOSE MODIFICATIONS

Each patient will be assessed for the development of any toxicity as outlined in Section 13. Dose adjustments will be made according to the system showing the greatest degree of toxicity. The table below outlines parameters for dose holds, dose reductions, resuming dosing, and study drug discontinuance for AEs assessed to be at least possibly related to VK-2019.

**Table 8: Toxicity Management and Dose Modifications for VK-2019**

| Adverse Event | Action with VK-2019 and Toxicity Management |
|---|---|
| All Grade 1 AEs | Continue VK-2019 at the same dose level. Manage with supportive therapy at the Investigator's judgment. |
| All Grade 2 AEs | Continue VK-2019 at the same dose level. Manage with supportive therapy at the Investigator's judgment. |
| All Grade ≥ 3 AEs (unless otherwise noted below) | Hold VK-2019 and administer supportive therapy as required in accordance with local practice/guidelines.<br>If AE resolves to Grade ≤ 2 within 21 days, VK-2019 may be restarted at the same dose (unless meeting criteria for a DLT) or a lower dose pending discussion between the investigator and Sponsor.<br>If AE does not resolve to Grade ≤ 2 after 21 days, permanently discontinue VK-2019 and observe the patient until the AE is resolved. |
| Grade ≥ 2 diarrhea | Manage with Loperamide (4mg at first onset, followed by 2mg every 2-4 hours (or with each loose bowel movement) until diarrhea free for 12 hours (maximum daily dose: 16 mg/24 hours). If loperamide is ineffective, consider adding Lomotil (5 mg, four times a day), or tincture of opium (15-20 drops orally every 4 hours), or octreotide (150 to 300 mcg SQ twice daily). Modifications to this regimen can be made per local standard practice. |
| Grade ≥ 3 diarrhea | Hold VK-2019 and manage as above until resolves to Grade ≤ 2.<br>If diarrhea resolves to Grade ≤ 2 within 21 days, VK-2019 may be restarted at the same dose (unless meeting criteria for a DLT) or a lower dose pending discussion between the investigator and Sponsor.<br>If diarrhea does not resolve to Grade ≤ 2 after 21 days, permanently discontinue VK-2019 and observe the patient until the AE is resolved. |

| Adverse Event | Action with VK-2019 and Toxicity Management |
|---|---|
| Nausea/vomiting, all grades | Standard antiemetics for the treatment of nausea and/or vomiting may be used. If it has been demonstrated that there is significant emetogenic potential based on individual and cumulative AE data, prophylactic anti-emetics may be used using ASCO guidelines. |
| Grade ≥ 3 nausea/vomiting | Hold VK-2019 and initiate antiemetic medication until resolves to Grade ≤ 2.<br>If nausea and/or vomiting resolves to Grade ≤ 2 within 21 days, VK-2019 may be restarted at the same dose (unless meeting criteria for a DLT) or a lower dose pending discussion between the investigator and Sponsor.<br>If nausea and/or vomiting does not resolve to Grade ≤ 2 after 21 days, permanently discontinue VK-2019 and observe the patient until the AE is resolved. |
| Grade ≥ 3 mean QTcF elongation | Hold VK-2019 and perform regular ECGs (with repeat in 24 hours or less, then as clinically indicated) until resolution to Grade ≤ 1 or baseline.<br>If QTc prolongation does not resolve to Grade ≤ 1 or baseline within 21 days, permanently discontinue VK-2019. |
| Recurrence of the same Grade ≥ 3 AE | Hold VK-2019 and restart at one dose level lower if AE resolves to Grade ≤ 2 within 21 days.<br>If recurring AE does not resolve to Grade ≤ 2 after 21 days, permanently discontinue VK-2019 and observe the patient until the AE is resolved. |

# 10 CONCOMITANT TREATMENT

## [redacted] Medication(s) or systemic treatments

All concomitant medications shall be recorded on case report forms.

No systemic anti-cancer treatment is permitted concurrently with VK-2019, including complementary, alternative, herbal, or nutritional supplement-based treatments whose purpose is for anti-cancer effect. Supportive agents such as bisphosphonates, denosumab, and RANKL inhibitors are permitted.

## [redacted] Concomitant Radiotherapy or Surgery

Focal treatment with either surgery or radiation for non-target lesions to alleviate discomfort is permitted after discussion with the study sponsor. For non-emergent, elective major surgical procedures, the investigational agent should be held one week before and one week after the procedure. G-tube placement or placement of indwelling catheters are not considered major surgical procedures.

## [redacted] Disallowed medications

*In vitro* studies have indicated that VK-2019 is a substrate for OATP1B1 and OATP1B3.

Dosing of VK-2019 in combination with OATP1B1 or OATP1B3 substrates or inhibitors are not permitted during the first two cycles of treatment with VK-2019. See Appendix 2 for a list of restricted medications. Use of OATP1B1 or OATP1B3 substrates or inhibitors after Cycle 2 should be done in consultation with the Sponsor.

It is not known how the administration of VK-2019 will affect the absorption of drugs that are transported by OATP1B3, e.g., atorvastatin, and concomitant use of these drugs should be done with caution.

# 11 STUDY PROCEDURES AND OBSERVATIONS

See Tables 1-6 for a complete schedule and descriptions of protocol specified procedures and evaluations.

## [redacted] Medical and Oncology History

A detailed medical history will be taken at Screening, including significant, relevant medical history within the past 5 years and all cancer related history, including treatment, surgical, and radiation history.

## [redacted] Physical Exam

Body systems assessed during physical exams should be performed per institutional practice

## [redacted] Lab Assessments

**Table 9: Assessments by Type and Visit**

| Lab Type | Assessment | Visits |
|---|---|---|
| Hematology | CBC with Differential | All visits (excluding LTFU) |
| Chemistry | Na, K, Cl, CO2, BUN, Cr, glucose, Ca, total bili, AST, ALT, ALP, albumin, total protein, Mg | All visits (excluding LTFU) |
| Urinalysis | pH, specific gravity, glucose, ketones, blood, protein, nitrates, leukocytes | Screening, D1 of each cycle, EOT, and Safety FU |
| Coagulation | PT, PTT, INR | Screening, D1 of each cycle, EOT, and Safety FU |
| Pregnancy | Blood or urine | EU only:<br>Screening, D1 of each cycle, EOT, and Safety FU<br>All other regions:<br>Screening and EOT |
| EBV DNA | EBV DNA in plasma | Screening, C2D0, C2D0, and EOT |

## [redacted] Electrocardiograms

ECGs using a 12-lead tracing will be collected in triplicate (i.e. three 10-second tracings approximately 1 minute apart) and should be performed in the supine position unless collecting them in this position is not feasible. A machine with the capacity to calculate standard intervals automatically should be used. At each time point, heart rate and PR, R-R, QRS, and QT intervals will be calculated.

## [redacted] Tumor Assessments

Response and progression in this study will be evaluated using RECIST 1.1 and its definitions of evaluable lesions, response, measurable disease, target lesions, non-target lesions. Tumor assessments must be performed using computed tomography (CT), positron emission tomography (PET)/CT, or magnetic resonance imaging (MRI). Assessments should include evaluation of the neck, chest, abdomen, and pelvis, however, on a case-by-case basis the investigator and Medical

Monitor may agree to limit scan volume for a given patient (e.g., due to concern over radiation exposure).

The same modality used at baseline should be used throughout the study.

**[redacted] Follow-Up**

#### 11.6.1 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.

#### 11.6.2 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.

# 12 PHARMACOKINETICS AND PHARMACODYNAMICS

## [redacted] PK and Metabolite Profiling Assessments

Specific visits and timepoints for each PK blood and urine collection are specified in Tables 3-6. See the lab manual for PK collection, processing, and shipping instructions. The PK assessments during Cycle 1 may be repeated if the PK sampling is missed for any reason or if the PK data collected are deemed non-evaluable.

Timing of sampling may be modified administratively based upon emerging PK data, but the number of samples will not increase.

PK samples used for the determination of VK-2019 concentrations and its metabolites will be analyzed by a central laboratory on behalf of the Sponsor, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

PK samples may be subjected to additional analyses by the Sponsor in order to further investigate the presence and/or identity of additional drug metabolites.

### 12.1.1 CSF for Analysis of VK-2019

If a patient undergoes a lumbar puncture while on trial as part of standard of care medical evaluation (i.e., not required per protocol), if possible, an additional sample of CSF should be collected for exploratory analysis of VK-2019 concentrations. If feasible, an unscheduled plasma PK sample should also be collected at approximately the same time. See the lab manual for CSF collection, processing, and shipping instructions.

## [redacted] Effect of EBNA1 Inhibitor VK-2019 on Plasma EBV DNA

Specific visits and timepoints for each plasma EBV DNA collection are specified in Tables 4-6. Plasma EBV DNA sample analysis will be performed by each participating institution's clinical lab.

Analysis of plasma EBV DNA will explore whether VK-2019 has any impact of NPC EBV DNA shedding into the bloodstream at time points prior to the standard of practice clinical and imaging analyses for tumor response.(24) It is possible that early changes in plasma EBV DNA in this setting may provide early hints of activity in an individual patient relative to conventional tumor response evaluations. It is also possible that early plasma EBV DNA alterations in initial cohorts of patients may reveal evidence of an impact of VK-2019 at lower dose levels than the usual clinical parameters used for evaluation of anti-cancer effect and therefore may provide evidence as a biomarker for activity in an accelerated time frame. (25) A harmonized assay for plasma EBV DNA testing will be utilized in this study and analysis will be performed at a central lab on behalf of the Sponsor.

## [redacted] Intra-Tumor EBNA1 Activity Inhibition by VK-2019

During the Phase 2a Dose Expansion, patients may elect to provide biopsies for EBNA1 activity alteration associated with VK-2019 administration. Using biopsied material before and after treatment from selected patients, DNA will be isolated and quantitative PCR (qPCR) performed on collected tissue. Using validated EBV specific primers, GAPDH control primers, and the Namalwa cell line (which has 2 EBV copies/cell), EBV genome copy number will be assessed on per cell basis. In addition, RNA will be isolated from biopsied material and Nanostring gene expression analysis of viral and cellular genes will be performed. The PanCancer Pathways panel will be used,

supplemented with 30 EBV viral genes to assess which pathways are affected by EBNA1 inhibition. These studies will help to establish proof-of-mechanism of EBNA1 inhibitors for the treatment of EBV-positive NPC.

Biopsy samples may be subjected to additional analyses by the Sponsor in order to further investigate the presence and/or identity of additional biomarkers and/or mechanisms of activity.

# 13 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

## [redacted] Definitions of an AE

An AE (also known as an adverse experience) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. More specifically, an AE can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. Laboratory values that the investigator determines to be not clinically significant should not be considered as AE. Additionally, an adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to the sponsor or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator and the sponsor concurs with that assessment.

Any AE assessed by the investigator and/or Sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical trial.

## [redacted] AE Reporting

All observed or volunteered adverse events regardless of suspected causal relationship to the investigational product will be reported as described in the following sections. For each mandated AE evaluation, there may be an AE query form developed to actively query patients and to document high priority AEs for collection, based upon preclinical AE data and emerging AE data as the study continues.

All documentation of AEs should include the following elements, further discussed below:

- AE term using the CTCAE v5.0
- AE severity grading using the CTCAE v5.0
- AE seriousness per the below guidance
- AE attribution (causality) per the below guidance
- AE expectedness for all AEs attributed to the investigational agent

## [redacted] Reporting Period

For AEs (including SAEs), the active reporting period to the sponsor or its designated representative begins from the time the patient provides informed consent, which is obtained prior to the patient's participation in the study, i.e., prior to undergoing any study-related procedure and/or receiving investigational product, until either a) 28 calendar days after the last administration of the investigational product, or b) initiation of a new anti-cancer therapy. Should an investigator be made aware of any SAE considered at least possibly related to study drug occurring any time after the active reporting period, it must be promptly reported.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as adverse events.

### [redacted] Definitions of an Adverse Reaction

An adverse reaction is defined as any AE caused by the use of a drug. Adverse reactions are a subset of all suspected adverse reactions, for which there is reason to conclude that the drug caused the event. Examples of adverse reactions include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Exposure during pregnancy;
- Exposure via breastfeeding;
- Medication error.

### [redacted] Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be considered clinically significant and therefore reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing (outside of protocol-stipulated dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

### [redacted] Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.
- Other serious (important medical event)

Each AE is to be assessed to determine if it meets the criteria for SAEs.

Progression of the malignancy under study is an AE but **should not** be reported as an SAE unless the outcome is fatal or meets other SAE criteria AND occurs within the reporting period defined in Section 13.3. In these situations, every effort should be made to report the signs and symptoms of progression as the event(s) meeting criteria as an SAE unless otherwise not feasible.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

### [redacted] SAE Reporting Requirements

If an SAE occurs, the sponsor is to be notified within 24 hours of the site investigator or other site personnel become aware of the event, using the sponsor's forms and routes pre-specified in the protocol procedures manual.

In particular, if the SAE is fatal or life-threatening and meets other reporting requirements, notification to the sponsor must be made immediately, irrespective of the extent of AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy and exposure via breastfeeding cases.

For all SAEs, the investigator is obligated to pursue and provide information to the sponsor in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by the sponsor to obtain specific additional follow-up information in an expedited fashion. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality.

Information on other possible causes of the event, such as concomitant medication and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the sponsor or its designated representative.

### [redacted] Protocol-Specified Serious Adverse Events

The following expected SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database but will not be reported individually in an expedited manner to regulatory authorities because they are anticipated to occur in the study population:

- Infections or complications from central lines or feeding tubes.
- AEs related to loco-regional or metastatic extension of the disease including central nervous system involvement of disease.

### [redacted] Hospitalization

Adverse events associated with hospitalization or prolongations of hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets these criteria. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit):

Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (e.g., caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Emergency room visit that does not result in admission;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical adverse event is not in itself a serious adverse event. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new adverse event or with a worsening of the preexisting condition (e.g., for work-up of persistent pre-treatment lab abnormality);
- Social admission (e.g., patient has no place to sleep);
- Administrative admission (e.g., for yearly physical exam);
- Protocol-specified admission during a study (e.g., for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual patient;
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### [redacted] Severity Assessment

If required on the adverse event case report forms, the investigator will use the definitions of Severity in accordance with CTCAE Version 5.0 to describe the maximum intensity of the adverse event. If the event is serious, the CTCAE grade reported in the adverse event CRF must be consistent with the description of CTCAE grade included in the narrative section of the serious adverse event report. Event-specific CTCAE grading must be used if available; otherwise the general grading system below should be applied.

**Table 10: CTCAE v5.0 general grading system for adverse events. See the CTCAE v5.0 for AE specific grading.**

| Grade | Clinical Description of Severity |
|---|---|
| 0 | No change from normal or reference range (This grade is not included in Version 4.0 document but may be used in certain circumstances.) |
| 1 | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated. |
| 2 | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living.* |
| 3 | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care Activities of Daily Living.** |
| 4 | Life-threatening consequences; urgent intervention indicated. |
| 5 | Death related to AE. |

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note the distinction between severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

### [redacted] Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements, if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE. If the investigator does

not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for IND or other regulatory authority reporting purposes, as defined by the sponsor (see Section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records and the SAE report.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

The Investigator will assign attribution of the possible association of the event with use of the investigational drug, and this information will be entered onto CRFs as either related or unrelated to the investigational agent. All AEs judged to be possibly, probably or definitely related to the investigational agent should be assigned the "related" designation. The Investigator will also assign attribution for study procedures.

#### 13.11.1 Suspected

A suspected adverse reaction is defined as any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting and reporting to other regulatory authorities, "reasonable possibility" indicates that there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

#### 13.11.2 Unexpected

An AE or suspected adverse reaction is considered *unexpected* if it is not listed in the IB or package insert(s) or is not listed at the specificity or severity that has been observed, or, if an IB is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

"Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

Except as specified in Section 13.10, AEs that would be anticipated to occur as part of the disease process are considered *unexpected* for the purposes of regulatory authority reporting because they would not be listed in the IB. For example, a certain number of non-acute deaths in a cancer trial would be anticipated as an outcome of the underlying disease, but such deaths would generally not be listed as a suspected adverse reaction in the IB.

Some AEs are listed in the IB as occurring with the same class of drugs, or as anticipated from the pharmacological properties of the drug, even though they have not been observed with the drug under investigation. Such events would be considered *unexpected* until they have been observed with the drug under investigation. For example, although angioedema is anticipated to occur in some patients exposed to drugs in the ACE inhibitor class and angioedema would be described in the IB as a class effect, the first case of angioedema observed with the drug under investigation should be considered *unexpected* for reporting purposes.

### [redacted] Exposure During Pregnancy

The definition of exposure during pregnancy (also referred to as *in utero*) is met if:

- A female becomes, or is found to be, pregnant either while receiving or being exposed to (e.g., due to treatment or environmental exposure) or after discontinuing or having been directly exposed to the investigational product;
- A male has been exposed to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If any study patient or study patient's partner becomes or is found to be pregnant during the study patient's treatment with the investigational product, the investigator must submit this information to the sponsor. In addition, the investigator must submit information regarding environmental exposure to the sponsor. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery. The investigator will follow the pregnancy until completion or until pregnancy termination. Further follow-up of birth outcomes will be handled on a case-by-case basis.

### [redacted] Withdrawal Due to an AE

Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, according to the definition of adverse event noted earlier and recorded on the appropriate adverse event CRF page.

When a patient withdraws due to an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

### [redacted] Follow-up of AEs

All adverse events will be followed with appropriate medical management until resolved. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. For selected adverse events for which administration of the investigational drug was stopped, a re-challenge of the subject with the investigational drug may be conducted if considered both safe and ethical by the Investigator.

# 14 DATA ANALYSIS/STATISTICAL METHODS

As the primary purpose of this study is to evaluate and characterize the safety profile of single agent VK-2019, and evaluate preliminary efficacy, no confirmatory inferential analyses are planned. Descriptive statistics (such as means, medians, standard deviations and ranges for continuous data and percentages for categorical data) will be used to summarize patient characteristics, treatment administration/compliance, efficacy, and safety, pharmacodynamic and pharmacokinetic parameters. Data will also be displayed graphically where appropriate.

## [redacted] Phase 1 Endpoints

### 14.1.1 Primary Endpoints

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

### 14.1.2 Secondary Endpoints

- 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 $3\text{xlog}^{10}$ reduction or a drop below the lower limit of detection of the assay [LLOD], respectively).

### 14.1.3 Exploratory Endpoints

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

## [redacted] Phase 2a Endpoints

### 14.2.1 Primary Endpoints

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

### 14.2.2 Secondary Endpoints

- 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 $3\text{xlog}^{10}$ reduction or a drop below the lower limit of detection of the assay [LLOD], respectively).
- Plasma PK parameters of VK-2019.

### 14.2.3 Exploratory Endpoints

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

### [redacted] Sample Size Determination

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.

### [redacted] Populations for Analyses

- All Enrolled Subjects: All subjects who sign informed consent form and were confirmed eligible and assigned to a treatment cohort.
- All Treated Subjects: All subjects who receive at least one dose of VK-2019.
- PK Subjects: All subjects who receive at least one dose of study medication and have available VK-2019 plasma concentration data.
- Response Evaluable Subjects: 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 Subjects: All subjects who receive at least one dose of study medication and have available biomarker data.

### [redacted] Endpoint Analysis

#### 14.5.1 Analysis of Safety Endpoints

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

**Adverse Events**

All 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 occurring after the first dose of study treatment.

TEAEs will be summarized by SOC and by preferred term. The incidence of TEAEs will be based on the numbers and percentages of patients with events and number of events. TEAEs will be further summarized by severity (according to NCI CTCAE Version 5.0) and relationship to study treatment.

An overall summary of adverse event incidence will also be presented by dose level to include the number and percentage of patients with at least one: TEAE, treatment related TEAE, Grade 3 to Grade 5 TEAE, death, SAE, treatment related SAE, DLT, TEAE leading to study treatment discontinuation, TEAE leading to dose modifications (e.g. dose reduction) and TEAE leading to study discontinuation.

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 all AE data. Listing of the first cycle DLTs for each cohort within each phase will be provided.

**Laboratory Safety Tests**

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 will be summarized using descriptive statistics.

Treatment emergent out of range results with the corresponding NCI CTCAE grade, normal ranges, baseline results and clinical significance will be separately listed. Shift tables will be used to show changes from baseline at each timepoint and the worst change in CTCAE grade for each patient.

**Vital Signs and 12-lead ECGs**

Absolute and change from baseline vital sign and 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.

14.5.2 Analysis of Efficacy Endpoints

The Response Evaluable population will be used for all efficacy endpoints with the exception of OS and rate of survival which will use the All Treated population.

The following endpoints will be summarized by dose level and across the Phase 1 and 2a Dose Expansions cohorts for selected doses.

| | |
|---|---|
| Durable ORR: | The number and percentage of patients who achieve either a complete or partial response that is maintained for at least 6 months. |
| ORR: | The number and percentage of patients whose best overall response (BOR) 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. |
| DOR: | Duration of response (applicable only to patients whose BOR is CR or PR) is defined as the time interval between the date of the earliest qualifying response (complete response or partial response) and the date of disease progression or death for any cause, whichever occurs earlier. |
| DCR-6 and DCR-12: | The number and percentage of patients who either achieve a best response of either complete response, partial response confirmed by a second scan performed at least 4 weeks later or have stable disease 6 and 12 months after dosing respectively |
| PFS: | Defined as the interval between the day of the first dose of study treatment to the first documentation of disease progression or death, whichever occurs earlier. Censoring rules will be defined in the Statistical Analysis Plan. |
| OS: | Defined as the interval between the day of the first dose of study treatment until the date of death because of any cause. Patients who discontinue the study will be censored at the date of their final study visit. |
| OS-6 and OS-12: | Kaplan-Meier estimates of the proportion of patients alive at 6 and 12 month after the first dose of study treatment respectively using the OS endpoint. |

The number and percentage of patients with Durable ORR, ORR, DCR-6 and DCR-12 will be summarized together with exact 95% confidence intervals using a binomial distribution. A Kaplan-Meier method will be used to summarize PFS and OS, from which median values will be presented if reached. Additionally, a Kaplan-Meier method will be used to estimate OS-6 and OS-12.

**[redacted] Patient Characteristics and Disposition**

All enrolled patients who receive at least one dose of any study medication will be included in the listings and summaries of demographic characteristics, study drug administration and disposition.

Demographic characteristics such as patient age, gender, height, weight, ethnicity, prior therapy, medications, medical history, ECOG performance status and signs and symptoms will be tabulated.

An accounting of the study patients will be tabulated. Patients not meeting the eligibility criteria will be identified. Patients not completing the study will be listed along with the reason for their premature discontinuation. Reasons for premature discontinuation will be summarized.

Study drug administration will be described in terms of the total number of cycles administered, the median (range) of cycles administered, dose intensity, and reasons for deviations from planned therapy.

All medications received during the treatment period will be considered as concomitant medications; patients who received concomitant medications will be listed.

**[redacted] Pharmacokinetic Analysis**

14.7.1 Single- and Multiple-Dose VK-2019 PK Analysis

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 ($C_{max}$), time to maximum plasma concentration ($T_{max}$), and area under the plasma concentration versus time curve (AUC) for VK-2019 and metabolites will be estimated using non-compartmental analysis. If data permit or if considered appropriate, minimum plasma concentration ($C_{min}$), area under the plasma concentration versus time curve to infinity ($AUC_{inf}$) terminal elimination half-life ($t_{1/2}$), oral plasma clearance (CL/F), apparent volume of distribution (Vd/F), accumulation ratio ($R_{ac}$) will be estimated. If data permit renal clearance ($CL_R$), cumulative amount recovered unchanged in the urine up to 24 hours post-dose ($AE_{24}$), and cumulative amount recovered unchanged in the urine up to 24 hours post-dose expressed as a fraction of administered dose ($AE_{24\%}$) will be also estimated. In the event of improper urine collection, the cumulative amount recovered unchanged in the urine up to 8 hours post dose (AE8) will be explored. The relative systemic exposure to VK-2019 for the metabolites will also be assessed based on AUC. 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.

For VK-2019 concentrations, individual values and descriptive statistics (N, mean, SD, CV, median, minimum, maximum, geometric mean and its associated CV) will be presented by dose, cycle, day of assessment, and nominal time in tabular form. 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.

Dose normalized VK-2019 AUC and Cmax will be plotted against dose (using a logarithmic scale) by cycle and day. These plots will include individual patient values and the geometric means for each dose. The observed accumulation ratio for VK-2019 and the linearity ratio will be summarized descriptively. The means and 90% confidence intervals (CIs) obtained from the model will be back-transformed to provide means and 90% CI for the accumulation and linearity ratios for each dose.

The attainment of steady-state for VK-2019 will be assessed by visual inspection of the pre-dose concentrations on Cycle 1 Day 14 and Cycle 2 Day 0.

14.7.2 PK/PD Modeling

Pharmacokinetic/pharmacodynamic modeling may be attempted to investigate any causal relationship between VK-2019 exposure and biomarkers or significant safety endpoints. The results of these analyses, if performed, may be reported separately.

**[redacted] Pharmacodynamic EBV DNA**

Summaries of change from baseline to treatment to post-treatment levels of cell-free plasma EBV DNA will be provided, as appropriate. Individual values and descriptive statistics (N, mean, SD, minimum, maximum, geometric mean and its associated CV) will be presented by dose and cycle in tabular form. The rate of partial response (a reduction by 3xlog10 or more) or complete response (reduction below the LLOD of the assay) will be computed as well.

**[redacted] Pharmacodynamic EBNA1 inhibition.**

Using biopsied material before and after treatment from selected patients, DNA will be isolated and quantitative PCR (qPCR) will be performed. Using validated EBV specific primers, GAPDH control primers, and the Namalwa cell line (which has 2 EBV copies/cell), EBV genome copy number per cell will be assessed. In addition, RNA will be isolated from biopsied material and Nanostring gene expression analysis of viral and cellular genes will be performed. A PanCancer Pathways panel will be used, supplemented with 30 EBV viral genes to assess which pathways are affected by EBNA1 inhibition. These studies will allow us to establish proof-of-mechanism of EBNA1 inhibitors for the treatment of EBV-positive NPC. Individual values and descriptive statistics (N, mean, SD, minimum, maximum, geometric mean and its associated CV) will be presented in tabular form.

**[redacted] Interim Analysis**

For each dose level expanded, an interim analysis of efficacy will be performed after 16 patients have been dosed. If one or fewer patients have a BOR of CR or PR (not necessarily confirmed 4 weeks later) accrual to this cohort will be stopped.

# 15 STUDY MANAGEMENT

## [redacted] Pre-study Documentation

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki as stated in 21 CFR §312.120(c)(4); consistent with GCP and all applicable regulatory requirements.

Before initiating this trial, the Investigators will have written and dated approval from the Institutional Review Boards for the protocol, written informed consent form, subject recruitment materials, and any other written information to be provided to subjects before any protocol related procedures are performed on any subjects.

The clinical investigation will not begin until either FDA has determined that the study under the IND is allowed to proceed.

The Investigator must comply with the applicable regulations in Title 21 of the Code of Federal Regulations (21 CFR §50, §54, and §312), GCP/ICH guidelines, and all applicable regulatory requirements. The IRB must comply with the regulations in 21 CFR §56 and applicable regulatory requirements.

## [redacted] Informed Consent

All participants must be provided a consent form describing the study with sufficient information for each participant to make an informed decision regarding their participation. Participants must sign the IRB/IEC-approved informed consent form prior to participation in any study specific procedure. The participant must receive a copy of the signed and dated consent document. Documentation of participant signature may be made by facsimile copy or other electronic transmission such as electronic photograph of signed consent document. A high-resolution scan or photograph of a signed consent is considered adequate documentation. The original signed copy of the consent (or scanned/ photographic copy thereof) document must be retained in the medical record or research file.

## [redacted] Changes in the Protocol

Once the protocol has been approved by the IRB/IEC, any changes to the protocol must be documented in the form of an amendment. The amendment must be approved by each site's IRB/IEC prior to implementation at that site.

If it becomes necessary to alter the protocol to eliminate an immediate hazard to patients, an amendment may be implemented prior to IRB/IEC approval. In this circumstance, however, the Investigator must then notify the IRB/IEC at each site in writing within five (5) working days after implementation. The study sponsor and the study team will be responsible for updating any participating sites.

## [redacted] Handling and Documentation of Clinical Supplies

The Principal Investigator and each participating site will maintain complete records showing the receipt, dispensation, return, or other disposition of all investigational drugs. The date, quantity and batch or code number of the drug, and the identification of patients to whom study drug has been dispensed by patient number and initials will be included.

The Investigators shall not make the investigational drug available to any individuals other than to qualified study patients. Furthermore, the investigators will not allow the investigational drug to be used in any manner other than that specified in this protocol.

### [redacted] Case Report Forms (CRFs)

The Principal Investigator at each site and/or his/her designee, will prepare and maintain adequate and accurate participant case histories with observations and data pertinent to the study. Study specific Case Report Forms (CRFs) will document safety and treatment outcomes for safety monitoring and data analysis. All study data will be entered into the clinical trial database via standardized CRFs (paper or secure electronic) in accordance with the study calendar. The investigator's designee at each site will complete the CRFs as soon as possible upon completion of the study visit.

The information collected on CRFs shall be consistent with the original source documents. Source documents will be found in the patient's medical records maintained by site personnel. In accordance with federal regulations, the Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs at their site. Each site PI will approve all completed CRFs to attest that the information contained on the CRFs is true and accurate.

All source documentation and data will be available for review/monitoring by the sponsor and regulatory agencies. A high-resolution scan or photograph of signed CRFs is considered adequate documentation and the official EMR is considered adequate primary source documentation. Not all EMR source documentation need be reproduced within separate clinical trials study materials in paper form. Storage of locked PDF documents is an acceptable alternative to paper copies of protocol related documents, including consent forms and data from the EMR.

The Principal Investigator will be responsible for ensuring the accurate capture of study data. At study completion, when the CRFs have been declared to be complete and accurate, the database will be locked. Any changes to the data entered into the CRFs after that time can only be made by joint written agreement among the PI, the Trial Statistician, and the Sponsor.

### [redacted] Study Monitoring

During the course of the trial, a monitor appointed by the Sponsor will make site visits to review protocol compliance, compare CRFs and individual patient's medical records, assess drug accountability, and ensure that the trial is being conducted according to pertinent regulatory requirements. CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

### [redacted] Inspection and Retention of Records

Cullinan Apollo or a Cullinan Apollo representative, a regulatory authority, an IRB or IEC may visit the clinical site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the International Conference on Harmonization, and any applicable regulatory requirements. Direct access to source data will be required for these audits and inspections; they will be carried out giving due consideration to data protection and medical confidentiality. The PI

or designee is responsible for providing necessary support at all times. The PI or designee should contact Cullinan or designee immediately if contacted by a regulatory agency about an inspection.

According to ICH guidelines, the PI must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval and until there are no pending or contemplated marketing applications in an ICH region or for at least 2 years following the discontinuation of clinical development of the investigational product. These documents should be retained for a longer period if required by applicable legal requirements.

### [redacted] Quality Control and Quality Assurance

The Sponsor or designee will conduct a site visit to verify the qualifications of each PI and designee, inspect the site facilities, and inform the PI of responsibilities and the procedures for ensuring adequate and correct documentation.

The CRFs for each patient will be checked against source documents at the clinical site by the monitor (Source Data Verification [SDV]).

In the case of electronic CRFs, the site monitor can also review CRFs remotely at any time during the trial and generate queries for site resolution prior to the site monitoring visit.

Instances of missing or uninterpretable data will be queried by the site monitor for site resolution.

The data management plan, to be developed during the initiation of the trial, will include specifications for consistency and plausibility checks on data. CRF completion guidelines will also be developed and include data entry instructions for the site. Queries raised during data management review of SDV data will be generated for site resolution with the PI or designee. The site will either update the CRF if original data is incorrect or will provide a confirmation that the data is correct. Data Management can also review data and generate queries prior to SDV to expedite data clean-up. The site can then update the CRF if needed and the site monitor will verify the update during SDV.

## 16 REFERENCES

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015;136(5):E359-86. Epub 2014/09/16. doi: 10.1002/ijc.29210. PubMed PMID: 25220842.

2. Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, Siu L, Sze WM, Leung TW, Sham JS, Ngan RK, Law SC, Yau TK, Au JS, O'Sullivan B, Pang ES, O SK, Au GK, Lau JT, Hong Kong Nasopharyngeal Cancer Study G. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. J Clin Oncol. 2005;23(28):6966-75. Epub 2005/09/30. doi: 10.1200/JCO.2004.00.7542. PubMed PMID: 16192584.

3. Zhang L, Huang Y, Hong S, Yang Y, Yu G, Jia J, Peng P, Wu X, Lin Q, Xi X, Peng J, Xu M, Chen D, Lu X, Wang R, Cao X, Chen X, Lin Z, Xiong J, Lin Q, Xie C, Li Z, Pan J, Li J, Wu S, Lian Y, Yang Q, Zhao C. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet. 2016;388(10054):1883-92. Epub 2016/10/19. doi: 10.1016/S0140-6736(16)31388-5. PubMed PMID: 27567279.

4. Raghupathy R, Hui EP, Chan AT. Epstein-Barr virus as a paradigm in nasopharyngeal cancer: from lab to clinic. Am Soc Clin Oncol Educ Book. 2014:149-53. Epub 2014/05/27. doi: 10.14694/EdBook_AM.2014.34.149. PubMed PMID: 24857071.

5. Henle G, Henle W. Epstein-Barr virus-specific IgA serum antibodies as an outstanding feature of nasopharyngeal carcinoma. Int J Cancer. 1976;17(1):1-7. Epub 1976/01/15. PubMed PMID: 175020.

6. Westhoff Smith D, Sugden B. Potential cellular functions of Epstein-Barr Nuclear Antigen 1 (EBNA1) of Epstein-Barr Virus. Viruses. 2013;5(1):226-40. doi: 10.3390/v5010226. PubMed PMID: 23325328; PMCID: 3564119.

7. Frappier L. EBNA1. Current topics in microbiology and immunology. 2015;391:3-34. Epub 2015/10/03. doi: 10.1007/978-3-319-22834-1_1. PubMed PMID: 26428370.

8. Nasimuzzaman M, Kuroda M, Dohno S, Yamamoto T, Iwatsuki K, Matsuzaki S, Mohammad R, Kumita W, Mizuguchi H, Hayakawa T, Nakamura H, Taguchi T, Wakiguchi H, Imai S. Eradication of Epstein-Barr virus episome and associated inhibition of infected tumor cell growth by adenovirus vector-mediated transduction of dominant-negative EBNA1. Molecular therapy : the journal of the American Society of Gene Therapy. 2005;11(4):578-90. doi: 10.1016/j.ymthe.2004.12.017. PubMed PMID: 15771960.

9. Hong M, Murai Y, Kutsuna T, Takahashi H, Nomoto K, Cheng CM, Ishizawa S, Zhao QL, Ogawa R, Harmon BV, Tsuneyama K, Takano Y. Suppression of Epstein-Barr nuclear antigen 1 (EBNA1) by RNA interference inhibits proliferation of EBV-positive Burkitt's lymphoma cells. Journal of cancer research and clinical oncology. 2006;132(1):1-8. doi: 10.1007/s00432-005-0036-x. PubMed PMID: 16180023.

10. Yin Q, Flemington EK. siRNAs against the Epstein Barr virus latency replication factor, EBNA1, inhibit its function and growth of EBV-dependent tumor cells. Virology. 2006;346(2):385-93. doi: 10.1016/j.virol.2005.11.021. PubMed PMID: 16343579.

11. Yasuda A, Noguchi K, Minoshima M, Kashiwazaki G, Kanda T, Katayama K, Mitsuhashi J, Bando T, Sugiyama H, Sugimoto Y. DNA ligand designed to antagonize EBNA1 represses Epstein-Barr virus-induced immortalization. Cancer science. 2011;102(12):2221-30. doi: 10.1111/j.1349-7006.2011.02098.x. PubMed PMID: 21910783.

12. Vereide DT, Sugden B. Lymphomas differ in their dependence on Epstein-Barr virus. Blood. 2011;117(6):1977-85. doi: 10.1182/blood-2010-05-285791. PubMed PMID: 21088132; PMCID: 3056644.

13. Noh KW, Park J, Kang MS. Targeted disruption of EBNA1 in EBV-infected cells attenuated cell growth. BMB reports. 2016;49(4):226-31. Epub 2016/02/18. PubMed PMID: 26879316; PMCID: PMC4915242.

14. Chan KC, Lo YM. Circulating EBV DNA as a tumor marker for nasopharyngeal carcinoma. Semin Cancer Biol. 2002;12(6):489-96. Epub 2002/11/27. PubMed PMID: 12450734.

15. Jahr S, Hentze H, Englisch S, Hardt D, Fackelmayer FO, Hesch RD, Knippers R. DNA fragments in the blood plasma of cancer patients: quantitations and evidence for their origin from apoptotic and necrotic cells. Cancer Res. 2001;61(4):1659-65. Epub 2001/03/14. PubMed PMID: 11245480.

16. Lo YM, Leung SF, Chan LY, Lo KW, Zhang J, Chan AT, Lee JC, Hjelm NM, Johnson PJ, Huang DP. Plasma cell-free Epstein-Barr virus DNA quantitation in patients with nasopharyngeal carcinoma. Correlation with clinical staging. Annals of the New York Academy of Sciences. 2000;906:99-101. PubMed PMID: 10818603.

17. Ma BB, King A, Lo YM, Yau YY, Zee B, Hui EP, Leung SF, Mo F, Kam MK, Ahuja A, Kwan WH, Chan AT. Relationship between pretreatment level of plasma Epstein-Barr virus DNA, tumor burden, and metabolic activity in advanced nasopharyngeal carcinoma. International journal of radiation oncology, biology, physics. 2006;66(3):714-20. doi: 10.1016/j.ijrobp.2006.05.064. PubMed PMID: 17011447.

18. Lo YM, Chan LY, Chan AT, Leung SF, Lo KW, Zhang J, Lee JC, Hjelm NM, Johnson PJ, Huang DP. Quantitative and temporal correlation between circulating cell-free Epstein-Barr virus DNA and tumor recurrence in nasopharyngeal carcinoma. Cancer research. 1999;59(21):5452-5. PubMed PMID: 10554016.

19. Lo YM, Chan AT, Chan LY, Leung SF, Lam CW, Huang DP, Johnson PJ. Molecular prognostication of nasopharyngeal carcinoma by quantitative analysis of circulating Epstein-Barr virus DNA. Cancer research. 2000;60(24):6878-81. PubMed PMID: 11156384.

20. Lin JC, Jan JS, Hsu CY, Jiang RS, Wang WY. Outpatient weekly neoadjuvant chemotherapy followed by radiotherapy for advanced nasopharyngeal carcinoma: high complete response and low toxicity rates. British journal of cancer. 2003;88(2):187-94. doi: 10.1038/sj.bjc.6600716. PubMed PMID: 12610501; PMCID: 2377053.

21. 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.

22. Skolnik JM, Barrett JS, Jayaraman 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.

23. 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.

24. Kim KY, Le QT, Yom SS, Pinsky BA, Bratman SV, Ng RH, El Mubarak HS, Chan KC, Sander M, Conley BA. Current State of PCR-Based Epstein-Barr Virus DNA Testing for Nasopharyngeal Cancer. J Natl Cancer Inst. 2017;109(4). Epub 2017/04/05. doi: 10.1093/jnci/djx007. PubMed PMID: 28376165.

25. Le QT, Zhang Q, Cao H, Cheng AJ, Pinsky BA, Hong RL, Chang JT, Wang CW, Tsao KC, Lo YD, Lee N, Ang KK, Chan AT, Chan KC. An international collaboration to harmonize the quantitative plasma Epstein-Barr virus DNA assay for future biomarker-guided trials in nasopharyngeal carcinoma. Clin Cancer Res. 2013;19(8):2208-15. Epub 2013/03/06. doi: 10.1158/1078-0432.CCR-12-3702. PubMed PMID: 23459720; PMCID: PMC3630245.

# 17 APPENDICES

## [redacted] Appendix 1 - Performance Status Criteria

| ECOG Performance Status Scale | | Karnofsky Performance Scale | |
|---|---|---|---|
| Grade | Descriptions | Percent | Description |
| 0 | Normal activity<br>Fully active, able to carry on all pre-disease performance without restriction | 100 | Normal, no complaints, no evidence of disease |
| | | 90 | Able to carry on normal activity; minor signs or symptoms of disease |
| 1 | Symptoms, but ambulatory<br>Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work) | 80 | Normal activity with effort; some signs or symptoms of disease |
| | | 70 | Cares for self, unable to carry on normal activity or to do active work |
| 2 | In bed < 50% of the time<br>Ambulatory and capable of all self-care, but unable to carry out any work activities<br>Up and about more than 50% of waking hours | 60 | Requires occasional assistance, but is able to care for most of his/her needs |
| | | 50 | Requires considerable assistance and frequent medical care |
| 3 | In bed > 50% of the time<br>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours | 40 | Disabled, requires special care and assistance |
| | | 30 | Severely disabled, hospitalization indicated<br>Death not imminent |
| 4 | 100% bedridden Completely disabled<br>Cannot carry on any self-care<br>Totally confined to bed or chair | 20 | Very sick, hospitalization indicated<br>Death not imminent |
| | | 10 | Moribund, fatal processes progressing rapidly |
| 5 | Dead | 0 | Dead |

## [redacted] Appendix 2 - Prohibited Medications During Treatment Cycle 1 and 2

| | |
|---|---|
| Aosetron: | lotronex |
| Bosentan: | Tracleer |
| Candesartan: | Atacand |
| Celecoxib: | Celebrex |
| Diclofnac: | Volaren |
| Dronabinol: | Marinol |
| Flubiprofen: | Ansaid |
| Fluvastatin: | Lescol |
| Glimepiride: | Amaryl |
| Ibuprofen: | Advil, Motrin |
| Indomethacin: | Indocin |
| Irbesartan: | Avapro |
| Losartan: | Cozaar |
| Meloxicam: | Mobic |
| Montelukast: | Singulair |
| Naproxen: | Aleve |
| Nateglinide: | Starlix Phenobarbital |
| Phenytoin: | Dilantin |
| Piroxicam: | Feldene |
| Rosiglitazone: | Avandia |
| Rosuvastatin: | Crestor Sulfmethoxazole Tolbutamide |
| Torsemide: | Demadex |
| Valsartan: | Diovan |
| Warfarin: | Coumadin |

NOTE: This list contains common drugs and is not all-inclusive. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of OATP1B3 substrate prohibited medications.

## [redacted] Appendix 3 - Effectiveness of family planning methods

https://www.cdc.gov/reproductivehealth/unintendedpregnancy/pdf/contraceptive_methods_508.pdf