CLINICAL STUDY PROTOCOL

A Phase 1b/2 Open-Label, Dose Escalation and Expansion Study of Orally Administered VRx-3996 and Valganciclovir in Subjects with Epstein-Barr Virus-Associated Lymphoid Malignancies

Protocol Number:	VT3996-201
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Study Drugs:	Nanatinostat (VRx-3996) and Valganciclovir
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ABBREVIATIONS

Abbreviation	Description
Ab	antibody
AE	adverse event
AIDS	acquired immunodeficiency syndrome
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	asparagine aminotransferase
AUC	area under the curve
$AUC_{0-\infty}$	area under the concentration-time curve from administration to infinity
AUC_{0-t}	area under the concentration-time curve from administration to time t
BID	twice daily
CBC	complete blood count
CFR	Code of Federal Regulations
CHR-3996	former name for VRx-3996
CI	confidence interval
CL/F	apparent clearance
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CMV	cytomegalovirus
CNS	central nervous system
CR	complete response
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	cytotoxic T-lymphocyte
CV	coefficient of variation
CV%	percent coefficient of variation
DLBCL	diffuse large B-cell lymphoma
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
EBER	Epstein-Barr Virus-encoding region

Abbreviation	Description
EBV	Epstein-Barr Virus
EC	Ethics Committee
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report forms
eGFR	estimated glomerular filtration rate
ET	End of Treatment
FDA	Food and Drug Administration
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GvHD	graft versus host disease
HCT	hematocrit
HDAC	histone deacetylase
HGB	hemoglobin
HHV	human herpesvirus
HIV	human immunodeficiency virus
HL	Hodgkin's lymphoma
HLA	human leukocyte antigen
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Council for Harmonisation
ICMJE	International Committee of Medical Journal Editors
INR	international normalized ratio
IP	investigational product
IRB	Institutional Review Board
IV	intravenous
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
MCH	mean corpuscular hemoglobin
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Description
MMF	mycophenolate mofetil
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NHL	non-Hodgkin's lymphoma
NK	natural killer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PLT	platelet
PO	by mouth
PR	partial response
PS	performance status
PT	prothrombin time
PTLD	post-transplant lymphoproliferative disease
PTT	partial thromboplastin time
QD	once daily
qPCR	quantitative polymerase chain reaction
QTcF	corrected QT interval using Fridericia's method
RBC	red blood cell
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAHA	suberoylanilide hydroxamic acid
SD	stable disease
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SOP	Standard Operating Procedure

Abbreviation	Description
SRC	Safety Review Committee
$t_{½}$	terminal elimination half-life
TK	thymidine kinase
TLS	tumor lysis syndrome
T_{max}	time to maximum concentration
TTR	time to response
ULN	upper limit of normal
UPS	United Parcel Service
US	United States
Vz/F	apparent volume of distribution
WBC	white blood cell
WHO	World Health Organization

SPONSOR'S PROTOCOL APPROVAL SIGNATURE PAGE

By signing below, the Sponsor declares that this study will be conducted in accordance with current United States (US) Food and Drug Administration Code of Federal Regulations, International Council for Harmonisation (ICH) Guidelines, Good Clinical Practice (GCP) standards, the Declaration of Helsinki (Scotland 2000, as clarified 2002), the Medical Research Council's "Code of Ethics for Research Involving Humans – May 1997", and local ethical and legal requirements.

This protocol has been reviewed and approved by:

7 Jan 21

Lisa Rojkjaer, MD
Chief Medical Officer
Date

7 Jan 2021

Susan Spruill, MS, PStat®
Statistician
Date

INVESTIGATOR'S SIGNATURE PAGE

By signing below, the Investigator agrees to adhere to the protocol as written and agrees that any changes to the protocol must be approved by Viracta Therapeutics, Inc. before seeking approval from the Institutional Review Board (IRB).

The study will be conducted in accordance with the current International Council for Harmonisation (ICH) Guidelines, the Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, and local ethical and regulatory requirements.

The information contained in this protocol is proprietary and provided to me in confidence, and may not be disclosed to any other party, in any form, without prior authorization from Viracta Therapeutics, except to the extent necessary for the conduct of the study at this study site.

_____

Investigator - Signature Date

_____

Investigator - Printed name

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Institution

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Address

PROTOCOL SYNOPSIS

Title	A Phase 1b/2 Open-Label, Dose Escalation and Expansion Study of Orally Administered VRx-3996 and Valganciclovir in Subjects with Epstein-Barr Virus-Associated Lymphoid Malignancies
Sponsor Study No.	VT3996-201
Phase	1b/2
Sponsor	Viracta Therapeutics, Inc.
Study Drug	VRx-3996 (nanatinostat) and Valganciclovir
Study Population	Relapsed/refractory, pathologically confirmed Epstein-Barr virus-positive (EBV^+) lymphoid malignancy or lymphoproliferative disease regardless of histologic subtype.
Primary Objectives	• Determine the safety and tolerability of VRx-3996/valganciclovir • Determine a recommended Phase 2 dose (RP2D) of VRx-3996/valganciclovir • Assess activity based on overall response rate (ORR)
Secondary Objectives	• Evaluate pharmacokinetic (PK) parameters of varying doses of VRx-3996 in capsule and in tablet form • Evaluate PK parameters of varying doses of valganciclovir • Evaluate time to response (TTR) • Evaluate duration of response (DoR) • Determine progression-free survival (PFS) and overall survival (OS)
Exploratory Objectives	• Evaluate changes in viral loads (cytomegalovirus, EBV) by quantitative polymerase chain reaction (qPCR) with treatment, where applicable • Evaluate EBV latency/lytic profile • Evaluate changes in histone acetylation in peripheral blood mononuclear cells (PBMCs) • Evaluate immunophenotype and immune function in PBMCs
Treatment Regimen	VRx-3996 by mouth (PO) once daily (QD) or twice daily (BID) Valganciclovir PO QD or BID

Study Design	An open-label, 2-part, Phase 1b/2 study to define a RP2D of VRx-3996 in combination with valganciclovir (Phase 1b) designed to evaluate the efficacy of this combination in relapsed/refractory EBV^+ lymphomas (Phase 2). Phase 1b (dose escalation) will follow a modified oncology 3+3 design. Phase 2 (dose expansion) will evaluate the RP2D in patients with EBV^+ lymphomas or lymphoproliferative disease using capsule and tablet forms of VRx-3996. All patients (Phase 1b and 2) will be assessed for response using imaging modalities appropriate for their specific lymphomas.
Number of Patients	Phase 1b: 25 Phase 2: 30 patients. An additional cohort of 10 patients will be enrolled after the 30 phase 2 patients are enrolled. These 10 patients will meet the same inclusion/exclusion criteria of the Phase 2 cohort, but will receive VRx-3996 in the tablet formulation instead of capsules.
Number of Sites	~30
Key Inclusion Criteria (see Section 4.1 for complete list of criteria)	• Age 18+ years • Relapsed/refractory, pathologically confirmed EBV^+ lymphoid malignancy or lymphoproliferative disease regardless of histologic subtype • Absence of available therapy with reasonable likelihood of cure or significant clinical benefit
Key Exclusion Criteria (see Section 4.2 for complete list of criteria)	• Known primary central nervous system (CNS) lymphoma • CNS metastases or leptomeningeal disease unless appropriately treated and neurologically stable for at least 4 weeks • Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy • Refractory graft versus host disease (GvHD) not responding to treatment (e.g., steroid refractory and not responding to second-line agents) • Positive hepatitis B core antibody or surface antigen unless quantitative DNA PCR is negative and patient will be receiving prophylaxis for reactivation • Positive hepatitis C virus on RNA PCR (if serology is positive) • Known history of human immunodeficiency virus (HIV) infection

1. BACKGROUND

1.1. EBV and Cancer

Epstein-Barr virus (EBV), a member of the γ-herpesvirus family, was the first virus directly implicated in the development of a human tumor,[1] and is formally classified as a carcinogenic agent by the World Health Organization (WHO). Primary infection with EBV typically occurs in childhood and is generally asymptomatic; however, infection later in life may manifest as infectious mononucleosis.[2] Once infected, individuals remain life-long carriers of the virus, with >90% of the world's population asymptomatically infected with EBV.

Latent infection and intermittent reactivation are 2 important characteristics of the EBV lifecycle. The maintenance of latent EBV infection requires the expression of a small subset of genes, and specific expression patterns (Types I–III) of these genes are associated with specific EBV-driven malignancies.[3] EBV has been shown to infect B-cells, T/natural killer (NK)-cells, and epithelial cells, though its greatest predilection is for B-cells.[3,4] EBV has been associated with a wide spectrum of human malignancies, though B-cell lymphomas are the most common and include Hodgkin's lymphoma (HL), Burkitt's lymphoma, post-transplant lymphoproliferative diseases (PTLDs), lymphomatoid granulomatosis, senile EBV-associated B-cell lymphoproliferative disorders, and many acquired immune deficiency syndrome (AIDS)-associated B-cell lymphomas.[3]

1.2. EBV-Associated Lymphomas

EBV-associated lymphomas are a heterogeneous group of malignancies that harbor latent EBV within the tumor. Within a specific histologic subtype of lymphoma, the frequency of EBV positivity may vary considerably. Diffuse large B-cell lymphoma (DLBCL) is rarely EBV^+, whereas 30% of HLs within North America are EBV^+ and endemic Burkitt's lymphomas are almost always EBV^+.[5]

The risk for developing an EBV-associated lymphoma is higher in the setting of immunodeficiency, as is present in patients with human immunodeficiency virus (HIV), congenital immunodeficiencies, post-transplant immunosuppression, or chronic active EBV infection.

EBV-associated lymphomas express a limited number of viral genes, with latency expression patterns associated with specific lymphoma subtypes.[2] The limited expression of EBV genes may allow for persistence of the viral DNA in cells by restricting the visibility of the virus to the immune system. Supportive of this concept is the observation that lymphomas in patients with impaired immune function are more likely to express a greater number of viral genes.

EBV-associated lymphomas in patients who are immunosuppressed may respond to therapies that improve immune function such as reduced immunosuppression (e.g., transplant patients) or adoptive immunotherapy.[5] In contrast, EBV-associated lymphomas that arise in patients who are immunocompetent generally express fewer viral genes, and as a result are less prone to immune attack.

While outcomes vary based on the specific EBV-associated malignancy, given the tumors associated with EBV (e.g., HL, Burkitt's lymphoma, DLBCL, lymphomatoid granulomatosis, primary DLBCL of the central nervous system (CNS), and a number of T-cell based malignancies), effective regimens are only available for a subset of affected patients.

The presence of EBV in lymphomas is a poor prognostic indicator. Across a series of patients with DLBCL, those who were EBV^+ generally presented more aggressive disease, had lower response rates to first-line therapy, and poorer progression-free and overall survival (OS) times.[6] In a meta-analysis evaluating survival outcomes across several lymphoma types (HL, DLBCL, T/NK-cell lymphoma, peripheral T-cell lymphoma), EBV^+ disease was associated with significantly worse OS times.[7]

1.3. Use of Antivirals in EBV-Associated Lymphomas

Several antiviral compounds have been tested in the clinic against EBV-associated lymphomas, and in general, reproducible activity has been difficult to document.[2] Antivirals that require the presence of functional viral thymidine kinase (TK) or viral protein kinase, such as the synthetic nucleosides ganciclovir, famciclovir, acyclovir, valaciclovir (a prodrug of acyclovir), and valganciclovir (a prodrug of ganciclovir) are less effective at eliminating EBV in chronically infected hosts because the virus can persist in a latent state of infection and lytic-phase proteins, including viral kinases, are required to convert these drugs to active antivirals.[2] Foscarnet and cidofovir are active against viral DNA polymerase and are not dependent on expression of the viral kinases. As such, these antivirals have shown some activity against EBV-associated tumors both as single agents and in combination with the anti-CD20 monoclonal antibody rituximab.

1.4. Human Herpesviruses

There are 9 distinct herpesviruses known to cause disease in humans. These viruses are further subdivided into 3 subfamilies as outlined in Table 1.

Among the herpesviruses, only members of the γ family (namely EBV and Kaposi's associated human herpesvirus (HHV-8) have been associated with the development of malignancies. As outlined under Section 1.2 and in Table 1, EBV-associated malignancies are typically of lymphoid nature (e.g., Burkitt's lymphoma, PTLD, and others). Similarly, primary effusion lymphoma and Kaposi's sarcoma are known to be driven by HHV-8.

The initial lytic infection caused by EBV and HHV-8 is generally cleared within a few weeks via a robust cytotoxic T-lymphocyte (CTL) response in immunocompetent individuals. However, a few infected cells survive and the virus down-regulates lytic genes and enters latency, which persists for the life of the infected host. However, viral reactivation can periodically occur during immunodeficiency states that may be associated, in some patients, with the development of malignancy. Immunodeficiency can be related to HIV infection, a known risk factor for the development of EBV and/or HHV-8 related malignancy[3,5](Table 1).

Post-transplant immunosuppression is yet another setting permissive for the development of EBV and/or HHV-8 related PTLD. Keys to the development of cancer are the type of immunosuppressant used, the total drug exposure (dosage and duration of dosing), and type of organ transplant, as well as genetic and pathogenic causes.[8]

The immunosuppressive agents typically used in these settings include corticosteroids, calcineurin inhibitors (e.g., cyclosporine and tacrolimus), the antithymocyte globulins, and others.[8,9] Post-transplant immunosuppression is also known to cause the reactivation of α herpesviruses (herpes simplex virus [HSV]-1 and -2, and Varicella Zoster Virus) and β herpesviruses (cytomegalovirus [CMV] and HHV-6).[9]

Because of this close interplay between the oncogenic viruses (namely EBV and HHV-8), immunodeficiency states (HIV or drug-induced) and reactivation of non-various human herpesviruses (Table 1), of non-γ human herpesviruses, both α and β, and the diseases that such -γ human herpesviruses can cause in this patient population, a close monitoring of viral reactivation for all herpesviruses with circulating quantitative polymerase chain reaction (qPCR) tests is clearly needed.

Table 1: Human Herpesviruses

Virus	Family	Primary Target	Primary pathophysiology	Latency site
HSV-1	α	Mucoepithelial	Oral and/or genital herpes	Neuron
HSV-2	α	Mucoepithelial	Oral and/or genital herpes	Neuron
Varicella zoster	α	Mucoepithelial	Chickenpox and shingles	Neuron
CMV	β	Monocytes, lymphocytes, epithelial cells	Infectious mononucleosis-like syndrome, retinitis	Monocyte, lymphocyte
HHV-6A and 6B	β	T cells	*Sixth disease* (roseola infantum or *exanthem subitum*)	T cells
HHV-7	β	T cells	drug-induced hypersensitivity, encephalopathy, hemiconvulsion-hemiplegia-epilepsy syndrome, hepatitis infection, postinfectious myeloradiculoneuropathy, pityriasis rosea, and the reactivation of HHV-4, leading to "mononucleosis-like illness"	T cells
EBV	γ	B cells, epithelial cells	Infectious mononucleosis, Burkitt's lymphoma, CNS lymphoma in AIDS patients, post-transplant lymphoproliferative syndrome (PTLD), nasopharyngeal carcinoma, HIV-associated hairy leukoplakia	B cell
Kaposi's-associated herpesvirus (HHV-8)	γ	Lymphocytes, other cells	Kaposi's sarcoma, primary effusion lymphoma, some types of multicentric Castleman's disease	B cell

**Source https://en.wikipedia.org/wiki/Herpesviridae on 28-Aug 2017*

1.5. Rationale for the Combination of HDAC Inhibitors and Antivirals for the Treatment of EBV-Associated Lymphomas

Induction of EBV TK within EBV^+ lymphomas is predicted to result in sensitization of these tumor cells to antiviral agents such as ganciclovir.[10] This approach is predicted to have high tumor specificity based on targeting of EBV-containing cells. Support for this approach was first demonstrated in a patient with an EBV-associated immunoblastic lymphoma in a donor lung 4 months following transplantation.[11] Based on work demonstrating that butyrate congeners could induce EBV lytic phase genes, including viral TK,[12,13] a cell line derived from the patient's tumor was exposed to arginine butyrate resulting in induction of EBV TK transcription. The combination of arginine butyrate and ganciclovir resulted in inhibition of cell proliferation and cell death.[11] Arginine butyrate was added to the patient's existing treatment with ganciclovir with no apparent increase in toxicity. Though the patient succumbed to a systemic aspergillus

infection that had preceded the administration of arginine butyrate therapy, pathologic examination of the tumor demonstrated substantial necrosis compared to pre-therapy histology. A definitive causal relationship could not be established based on prior treatment with chemotherapy.

Several histone deacetylase (HDAC) inhibitors in addition to arginine butyrate can induce expression of EBV lytic phase genes *in vitro*, leading to the sensitization of EBV^+ lymphoma cells to nucleoside antivirals.[10,11] These HDAC inhibitors include the short-chain fatty acids sodium butyrate and valproic acid, the hydroxamic acids oxamflatin, panobinostat, and belinostat, the benzamide entinostat, the cyclic tetrapeptide apcidin, and the macrocyclic depsipeptide largazole. In addition, the investigational compound VRx-3996, a hydroxamic acid, has also been shown to induce EBV lytic phase genes expression, including TK, *in vitro*. Ongoing studies are evaluating the ability of VRx-3996 to sensitize EBV^+ lymphoma cells to ganciclovir *in vivo*.

Evidence from clinical studies supporting the use of an HDAC inhibitor to sensitize EBV^+ tumor cells to nucleoside antivirals was demonstrated in a Phase 1/2 study of arginine butyrate combined with ganciclovir in 15 patients with EBV^+ tumors previously treated with chemotherapy and/or radiation.[14] Arginine butyrate was administered by continuous intravenous (IV) infusion daily on an escalating dose schedule within each patient for 21 days of a 28-day treatment course, combined with a fixed dose of daily ganciclovir continuously. Eleven patients received at least 28 days of arginine butyrate and ganciclovir, and all 15 patients were evaluable for response. Significant antitumor activity was seen in 10 patients, with 4 complete responses (CRs) and 6 partial responses (PRs). Three of the patients demonstrating complete clinical responses died shortly after completing therapy due to comorbid conditions and complications of tumor lysis. On pathological examination, there was complete disappearance of tumor in 2 patients, and the third had significant necrosis of the residual tumor.

1.6. HDAC Enzymes

Currently, 18 HDAC enzymes have been identified in mammalian cells, varying in function, localization, and substrates as illustrated in Table 2.[15,16] Class III enzymes appear relevant to certain human diseases but are not implicated in cancer.

Table 2: HDAC Enzymes[16]

Class	HDAC Enzymes	Zn^{2+} Dependent	Localization	Expression
I	1, 2, 3, 8	Yes	Nucleus	Ubiquitous
IIa	4, 5, 7, 9	Yes	Nucleus and Cytoplasm	Tissue specific
IIb	6, 10	Yes	Cytoplasm	Tissue specific
III	Sirtuins 1-7	No	Variable	Variable
IV	11	Yes	Nucleus and cytoplasm	Ubiquitous

1.7. HDAC Inhibitors

Epigenetic modulation of gene expression is an essential biological process, with chromatin structure and gene transcription tightly regulated by the acetylation state of histones within the nucleosome.[15,16] The degree of histone acetylation is a balance between the actions of histone acetyltransferases and HDACs. In general, acetylation of histones is associated with induction

of gene transcription and deacetylation with decreases in gene transcription. However, HDAC inhibition can also have effects on many processes independent of chromatin structure. In tumor cells, the most commonly reported effects of HDAC inhibitors relate to induction of apoptosis, though they have also been shown to interfere with cell growth and differentiation and inhibit angiogenesis. In addition, HDAC inhibitors have been shown to modulate immune responses which, in turn, affect many diverse cellular functions.

To date, at least 15 HDAC inhibitors have been tested in preclinical and clinical studies. These HDAC inhibitors are broadly classified into 4 main groups based on their structure as illustrated in Table 3. The common mechanism of action of these drugs is to bind a critical Zn^{2+} ion required for catalytic function of the HDAC enzyme.

Four HDAC inhibitors are currently approved by the United States (US) Food and Drug Administration (FDA) for oncology indications. These are:

- Vorinostat (2006) for the treatment of cutaneous T-cell lymphoma,
- Romidepsin (2009) for the treatment of cutaneous T-cell lymphoma,
- Belinostat (2014) for the treatment of peripheral T-cell lymphoma, and
- Panobinostat (2015) for the treatment of multiple myeloma.

Common side effects seen with HDAC inhibitors include thrombocytopenia, neutropenia, anemia, fatigue, and diarrhea. While HDAC inhibitors have displayed antitumor activity as single agents, data suggest that the HDAC inhibitors may have a greater role as part of combination regimens.[16,17]

Table 3: Selected HDAC Inhibitors in Clinical Use or Development*

Class	Class members	HDAC Class Specificity
Hydroxamic acid	VRx-3996 (CHR-3996)	I
	Vorinostat (SAHA, Zolinza®)	I, II, IV
	Belinostat (PXD101, Beleodaq®)	I, II, IV
	Panobinostat (LBH589, Farydak®)	I, II, IV
Cyclic peptides/ depsipeptides	Romidepsin (Istodax®)	I
Benzamide	Entinostat (SNDX-275/MS-275)	I
	Mocetinostat (MGCD0103)	I
Short-chain fatty acids	Valproic acid	I, IIa
	Butyrate	I, IIa

**Adapted from Lane et al.*[16]

1.8. VRx-3996 (nanatinostat)

VRx-3996 (formerly CHR-3996) is a selective HDAC Class I inhibitor with activity against HDAC1, HDAC2, and HDAC3. In both tumor cell lines and tumor xenograft models, VRx-3996 inhibited growth across a wide spectrum of human tumor types and demonstrated synergistic activity in combination with agents such as erlotinib, decitabine, and tosedostat.[18]

A Phase 1 study of VRx-3996 as a single-agent was performed in 39 patients with refractory solid tumors.[19] The study included 26 men and 13 women with a mean age of 56 years (range 24–77). Most patients had an Eastern Cooperative Oncology Group (ECOG) performance

status (PS) of 0 or 1 (1 patient was PS 2). All patients had received prior treatment with a median number of prior systemic chemotherapy regimens of 2 (range 0–7).

VRx-3996 was administered once daily (QD) orally at doses ranging from 5 to 160 mg on a 28-day cycle. The median number of completed cycles was 2 (range 1-18), with 12 patients receiving 3 or more cycles.

Dose-limiting toxicities (DLTs) were thrombocytopenia (160 mg), fatigue (80 and 120 mg), elevations in serum creatinine (80 and 120 mg), and atrial fibrillation (40 mg). The maximum tolerated dose (MTD) for QD continuous dosing of VRx-3996 was established as 80 mg.

Most adverse events (AEs) were low grade (Grade 1 or 2), though Grade 3 or 4 events were seen in 27 patients. The most prevalent AEs were fatigue and nausea. Incidences of nausea, thrombocytopenia, and increased creatinine appeared to be dose related, while fatigue appeared unassociated with dose.

Of the 39 patients receiving at least 1 dose of VRx-3996, 1 patient (2.5%) in the 160 mg dose group had a PR and continued study treatment for 12 months. An additional 9 patients (23%) had stable disease (SD).

The pharmacokinetics (PK) of VRx-3996 demonstrated rapid absorption with a median time to maximum concentration (T_{max}) of 1 hour (range 1–4 hours). The maximum concentration (C_{max}) achieved ranged from 18.5 ng/mL at 5 mg to 774.3 ng/mL at 160 mg. The median terminal elimination half-life ($t_{½}$) for was 1.8 hours (range 1.1–7.8 hours).

Exposure to VRx-3996 (area under the curve [AUC]) was broadly proportional over the dose range tested. At 40 mg daily, plasma concentrations exceeded 10 ng/mL for approximately 8 hours, a concentration associated with antitumor efficacy in preclinical models. There was no apparent accumulation between Day 1 and 28. The use of proton pump inhibitors did not appear to reduce absorption.

Table 4: PK Parameters of VRx-3996

Dose (mg/day)	5	10	20	40	80	120	160
Number of patients	3	4	3	10	10	4	5
Mean C_{max} ng/mL (CV%)	18 (121)	34 (91)	54 (68)	259 (100)	359 (167)	340 (114)	774 (74)
Median T_{max} h (range)	4 (2–4)	1 (0.3–4)	4 (0.3–4)	1 (0.3–4)	1 (0.3–4)	1 (1–2)	1 (0.3–4)
Mean $AUC_{0-\infty}$ ng×h/mL (CV)	*	111 (57)	93#	630 (74)	1214 (138)	888 (103)	1985 (66)

Abbreviations: $AUC_{0-\infty}$ = area under the concentration-time curve from administration to infinity; C_{max} = maximum concentration; T_{max} = time to maximum concentration.

** No reliable estimate of terminal elimination rate constant for this cohort.*

 # Only one reliable observation.

The pharmacodynamic effect of VRx-3996 was evaluated by acetylation of histone H3 in peripheral blood mononuclear cells (PBMCs). Samples were collected on Days 1 and 28 of the first course of therapy, and values normalized to pretreatment levels. Increased histone acetylation was apparent 4 hours after drug administration and returned towards baseline by 24 hours. Increases in histone acetylation were first seen at 20 mg per day and appeared to plateau at 40 mg per day.

1.9. Valganciclovir

Valganciclovir (VALCYTE®), an oral prodrug of ganciclovir, is approved for treatment of CMV retinitis in patients with AIDS and prevention of CMV disease in high-risk transplant patients. Outside of its approved indications, valganciclovir has been shown to be effective in mitigating EBV viral load in EBV^+ pediatric liver transplant patients at risk for development of post-transplant proliferative disorder.[20] Recommended adult dosing for treatment of CMV retinitis is 900 mg orally twice daily (BID) for 21 days followed by a maintenance dose of 900 mg once a day.

Oral valganciclovir is well absorbed (~60%) and converted to ganciclovir by first-pass intestinal or hepatic metabolism with peak plasma concentrations achieved in 1 to 3 hours. The major elimination pathway is renal excretion of ganciclovir through glomerular filtration and active tubular secretion. Dosage reductions, based on creatinine clearance, are recommended for patients with renal impairment. The antiviral activity of valganciclovir is based on the generation of ganciclovir-triphosphate, which is a competitive substrate for the CMV DNA polymerase. Significant AEs include hematologic toxicity and acute renal failure. Hematologic toxicity may result in leukopenia, neutropenia, anemia, and thrombocytopenia. The VALCYTE® package insert includes guidance regarding pre-treatment hematologic assessment and complete blood count (CBC) monitoring. Elderly patients, patients receiving nephrotoxic drugs and inadequately hydrated patients are at higher risk for renal failure. Other common AEs include gastrointestinal manifestations, such as diarrhea, nausea, and vomiting.

1.10. Rationale for Starting Dose

The dose for valganciclovir will follow the approved dose as described in the label or a modified dose based on agreement between the Investigator and the Medical Monitor to manage known valganciclovir-associated AEs. The safety profile for this dose of valganciclovir is well defined and appears acceptable as part of a treatment regimen for patients with relapsed/refractory lymphoma.

The starting dose for VRx-3996 (20 mg per day) is 25% of the MTD determined in a prior clinical study of VRx-3996 and 50% of the recommended Phase 2 dose (RP2D) from the same study. While overlapping toxicities exist (e.g., renal dysfunction and thrombocytopenia), the reduced dose of VRx-3996 and close monitoring of patients during the study should provide for acceptable safety.

1.11. Rationale for Study

VRx-3996 in combination with valganciclovir appears appropriate for evaluation in humans based on the following:

- EBV-associated lymphomas are often aggressive malignancies that respond poorly to conventional treatments
- VRx-3996 has been administered previously to patients with advanced solid tumors and demonstrated acceptable safety but limited anti-tumor activity
- Valganciclovir is an approved antiviral medication with a well understood safety profile at its approved dose and schedule (i.e., 900 mg PO BID)
- Clinical proof of concept exists for the combination of an HDAC inhibitor (i.e., arginine butyrate) and an EBV antiviral (i.e., ganciclovir) in patients with EBV^+ lymphomas that demonstrated promising antitumor activity with an acceptable safety profile
- VRx-3996 combined with valganciclovir should demonstrate at least equivalent activity and safety compared to arginine butyrate and ganciclovir at the proposed starting doses for this study

1.12. Potential Risks and Benefits

1.12.1. Potential Risks

Both VRx-3996 and valganciclovir exhibit overlapping toxicities (i.e., thrombocytopenia and renal dysfunction) that may be increased in rate or severity with this combination.

In addition, in prior clinical studies other toxicities reported for one or both agents include fatigue, atrial fibrillation, nausea/vomiting, anemia, leukopenia, and neutropenia.

While not all have been reported for VRx-3996, toxicities reported for other HDAC inhibitors include, thrombocytopenia, neutropenia, anemia, fatigue and diarrhea.[21]

As with any new combination, toxicities, which have not been seen with either agent alone or with combinations of similar agents, may become manifest. Similar combinations (arginine butyrate combined with ganciclovir)[14] have resulted in rapid tumor destruction and loss of tissue integrity resulting in death.

1.12.2. Potential Benefits

VRx-3996 combined with valganciclovir may benefit patients by reducing lymphoma volume and/or slowing lymphoma growth. Patients who experience a CR following administration of VRx-3996 and valganciclovir could experience substantial benefit. In patients with symptoms related to the presence of lymphoma, VRx-3996 and valganciclovir may result in a reduction of symptoms.

2. OBJECTIVES

2.1. Primary Objective

- Determine the safety and tolerability of VRx-3996/valganciclovir
- Determine a RP2D of VRx-3996/valganciclovir
- Assess activity based on overall response rate (ORR)

2.2. Secondary Objectives

- Evaluate PK parameters of varying doses of VRx-3996 in capsule form and in tablet form (at RP2D only for tablet form)
- Evaluate PK parameters of varying doses of valganciclovir
- Evaluate time to response (TTR)
- Evaluate duration of response (DoR)
- Determine progression-free survival (PFS) and overall survival (OS)

2.3. Exploratory Objectives

- Evaluate changes in viral loads (CMV, EBV) by qPCR with treatment, where applicable
- Evaluate EBV latency/lytic profile
- Evaluate changes in histone acetylation in PBMCs
- Evaluate immunophenotype and immune function in PBMCs

3. STUDY DESIGN

This is an open-label, 2-part (Phase 1b = dose escalation, Phase 2 = dose expansion) Phase 1b/2 study of VRx-3996 and valganciclovir. The Phase 1b portion of the study will evaluate safety and define a recommended Phase 2 dose (RP2D) using a modified 3+3 design for oncology studies in patients with EBV^+ lymphomas. The Phase 2 portion of the study will evaluate the RP2D in 30 patients with EBV-associated lymphomas or lymphoproliferative disease, using a Simon's 2-stage design to allow for early stopping for futility. The study defines a cycle length as 28 days. Valganciclovir will be administered at no higher than the approved dose of 900 mg PO BID.

During the Phase 1b portion of the study, dosing will be based on assigned cohort. During the Phase 2 expansion portion, patients will receive the RP2D of VRx-3996 defined previously in the Phase 1b portion of the study. In both phases, patients will continue to receive VRx-3996/ valganciclovir if they may still have clinical benefit in the opinion of the Investigator, and in the absence of unacceptable toxicity.

Safety assessments will make use of all available data including using vital signs, physical exams, electrocardiograms (ECGs), PS assessments, and clinical laboratory parameters. Response assessments will be performed using imaging modalities appropriate for the patients' specific lymphoma (e.g., positron emission tomography [PET]-computed tomography (CT), CT scans, magnetic resonance imaging [MRI]) based on the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: the Lugano Classification.[22]

Patients considered at risk for tumor lysis syndrome will receive prophylactic medications and interventions.

3.1. Phase 1b (Dose Escalation)

3.1.1. Cohort Size

Cohort size during the Phase 1b portion of the study will be up to 7 patients using a conventional modified 3+3 design for dose escalation studies in oncology. The first cycle (28 days) is defined as the DLT assessment period. At each dose level, 3 or 4 patients will initially be enrolled and followed through the DLT assessment period. If 1 patient in the initial 3 or 4 patients experiences a DLT, the cohort will be expanded to 6 or 7 total patients.

3.1.2. Cohort Enrollment

Enrollment will begin with the Phase 1b portion of the study at the starting cohort as indicated in Table 5.

In the interest of safety, the patient enrollment rate will be limited to no more than 1 patient per week in the starting cohort. The enrollment rate in subsequent cohorts will not be limited.

A patient who experiences clinical benefit while on study treatment, and then experiences progressive disease while not receiving VRx-3996/valganciclovir, may have study drugs restarted if the following conditions are met:

- Restarting study drugs is considered in the patient's best interest by the Investigator,
- The patient has not developed any contraindications to either study drug,
- The Investigator has discussed restarting study drugs with the study Medical Monitor who agrees that restarting of study drugs is appropriate, and
- The study has not been closed by the Sponsor.

The patient should restart study drugs at the RP2D if this dose is tolerated.

3.1.3. Cohort Doses and Regimens

During the Phase 1b portion of the study, the doses of VRx-3996 and valganciclovir will follow those outlined in Table 5. On Cycle 1 Day 1, in an effort to ensure that patients tolerate oral valganciclovir prior to receiving VRx-3996, valganciclovir will be taken first, followed by VRx-3996 approximately 1 hour later. For all subsequent administrations, the sequence of VRx-3996 and valganciclovir can be dictated by patient convenience (e.g., both drugs may be taken together if tolerated by the patient). With the implementation of Protocol Amendment 4.0, VRx-3996 and valganciclovir are taken together at all timepoints, including Cycle 1 Day 1.

The Safety Review Committee (SRC) (Section 3.10) will have the option of defining additional cohorts and doses either below, above, or intermediate to the doses listed in Table 5 as needed based on data generated from prior cohorts. The SRC may also define additional cohorts based on alternative dosing schedules (e.g., QD versus BID).

Table 5: Phase 1b Cohort Doses

Cohort Number	Dose VRx-3996**	Dose valganciclovir**
1	10 mg BID (20 mg daily dose)	900 mg BID
2a	5 mg BID (10 mg daily dose)	450 mg BID
2b	10 mg QD (10 mg daily dose)	450 mg BID
2c	10 mg QD (10 mg daily dose)	900 mg QD
3	20 mg QD (20 mg daily dose)[#]	900 mg QD

Abbreviations: BID = bis in die (twice daily; PO = per os (oral); QD = quaque die (once daily); SRC = Safety Review Committee

*** The Schedule used (e.g., QD, BID) for either VRx-3996 or valganciclovir may be modified by the SRC as required to accommodate different dosage strengths and patient convenience. However, when the schedule is adjusted, the total daily dose will remain unchanged.*

[#] *In Cohort 3, VRx-3996 will be administered PO QD for 4 days on and 3 days off in a 7-day regimen. The dosing holiday is not considered a dosing hold; if a dose is held for any length of time beyond the 3-day dosing holiday (e.g., dosing does not resume on Cycle 1 Day 8), those subsequent days will constitute a dose hold. Please refer to Section 3.5 Dose Adjustments/Modifications/Delays. If the next dose of VRx-3996 following a dosing holiday (e.g., Cycle 1 Day 8) does not coincide with a scheduled visit, the patient should take the next scheduled dose at home.*

3.1.4. Dose Escalation Procedure

Dose escalation during the Phase 1b portion of the study will follow commonly accepted criteria used in a modified 3+3 Phase 1 study design.

Dose levels of VRx-3996 and valganciclovir in sequential cohorts will be defined prior to the start of each cohort. If the MTD is exceeded, de-escalation may occur to a lower dose level. Each cohort will initially consist of 3 to 4 patients (See Section 3.1.1).

If none of the first 3 or 4 patients in a cohort demonstrates a DLT during the first cycle (28 days), then the cohort will be declared safe and the next higher cohort will be opened for enrollment.

If 1 of the first 3 or 4 patients in a cohort demonstrates a DLT during the first cycle (28 days), then an additional 2 or 3 patients will be enrolled to that cohort for a total of 6 patients.

If 1 out of 6 patients in an expanded cohort demonstrates a DLT during the first cycle (28 days), then the cohort will be declared safe and the next cohort will be opened for enrollment.

If 2 or more patients in an expanded cohort demonstrate a DLT, that cohort will be declared to exceed the MTD.

The MTD (if reached) will be defined as the highest dose level at which no more than 1 of 6 patients demonstrates a DLT.

If the MTD is exceeded, then the next lowest dose cohort, or an intermediate dose level (as determined by the SRC) will be expanded to at least 6 patients.

3.1.5. Dose Limiting Toxicity

Grading of DLTs will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.

To be considered a DLT, an AE must meet all of the following criteria:

- Occurs during the first cycle (28 days) of study drug administration in Phase 1b only
- Is not incontrovertibly related to underlying disease

In addition, to be considered a DLT, the AE will meet at least one of the criteria listed below:

- Grade 4 anemia unexplained by underlying disease
- Grade 4 febrile neutropenia
- Grade 4 neutropenia lasting >5 days
- Any other Grade 4 hematologic toxicity of any duration
- Grade 4 or higher tumor lysis syndrome
- Grade 3 or higher thrombocytopenia (with or without bleeding)
- Any requirement for platelet transfusion
- Grade 3 or higher non-hematologic toxicity despite adequate supportive care
- Results in a dose hold of >7 consecutive days

Adverse events may be excluded from the definition of DLT if they meet the following criterion:

- AEs that persist <72 hours and are able to be managed with supportive care

The SRC (Section 3.10) will have the option of declaring other toxicities, not listed above, as DLTs if necessary to ensure patient safety.

3.1.6. Continued Study Drugs Following DLT

In the Phase 1b portion of the study, patients experiencing a DLT will not receive additional study drugs unless all the following conditions are met:

- The DLT has returned to at least Grade 2 or clinically insignificant from baseline
- The DLT is not expected, in the opinion of the Investigator, Medical Monitor and Sponsor representative, to recur based on an intervention such as prophylactic use of appropriate treatment (e.g., prophylactic anti-emetics), or dose reduction from the prior dose
- Continued administration of study drugs is considered to be in the patient's best interest based on the opinion of the Investigator and the study Sponsor

3.1.7. Maximum Tolerated Dose

While this study is not designed to define a MTD for this combination of study drugs, in the event that a DLT is observed, the MTD of VRx-3996 with valganciclovir will be defined as the highest dose administered during Cycle 1 of Phase 1b at which no more than 33% (i.e., ≤1 of 6 or 7 patients) experiences a DLT.

3.1.8. Dose Increases for Individual Patients

In an effort to afford patients the greatest likelihood of benefit from study participation, if judged to be in the best interest of the patient by the Investigator, Medical Monitor, and Sponsor representative, patients may receive an escalated dose of VRx-3996 in subsequent cycles. This escalated dose will generally follow the dose levels previously explored in the study and may not exceed the highest dose shown to be safe (i.e., the highest dose that has been demonstrated not to exceed the MTD based on evaluation of at least 3 patients at that level). In addition, no patient

may undergo a dose escalation until having completed at least 2 cycles at their initial assigned dose.

3.1.9. Replacement of Patients during Phase 1b Portion of Study

Patients who are unable to complete the DLT assessment period for reasons other than study drug related toxicity may be replaced if needed to achieve at least 3 patients evaluable for DLTs. The final decision on replacement will rest with the SRC.

In the event that a cohort is filled with 4 patients, and if 1 of the 4 patients is considered not evaluable for safety or for reasons other than study drug related toxicity, this 4th patient will not be replaced, and a decision will be made by the SRC on the safety of the current cohort based on the remaining 3 patients.

3.2. Phase 2 (Dose Expansion)

3.2.1. Phase 2 Sample Size

The Phase 2 portion of the study will accrue 30 patients. Any patients in screening at the time that the 30th patient is enrolled will be permitted to enroll, should they be eligible. This sample size is based on a Simon's 2-stage design where the Phase 2 portion of the study may be stopped if none of the first 10 treated patients have a response. The hypothesized response rate of a poor drug is 5%, while the hypothesized response rate of a good drug would be at least 20%. Using a 1-sided alpha of 0.05 and power of 80%, if at least 1 of the first 10 patients has a response, the Simon's design recommends accruing up to at least 29 total subjects to test the null hypothesis. The probability of stopping early is 59.9% with a type I error rate of 0.0468 (http://cancer.unc.edu/biostatistics/program/ivanova/SimonsTwoStageDesign.aspx).

3.2.2. Phase 2 Dose

The dose and schedule of VRx-3996 and valganciclovir used during the Phase 2 portion of the study will be the RP2D for VRx-3996 and valganciclovir as determined by the SRC at the conclusion of the Phase 1b portion of the study.

Based on accumulating efficacy and safety data, the SRC may elect to declare a RP2D prior to defining an MTD or prior to exploring all cohorts listed in Table 5.

The RP2D may be modified later during the Phase 2 portion of the study by the SRC (see Section 3.2.3 and Section 3.10) if information arises suggesting that the initial RP2D was not appropriate. In the event that the RP2D is adjusted mid-study, all subsequent patients entering the study will receive study drugs at the adjusted RP2D. Patients currently on study at the time of a dose modification may continue with their current dose at the discretion of the Investigator.

3.2.3. Assessment of Toxicity During Phase 2 Dose Expansion

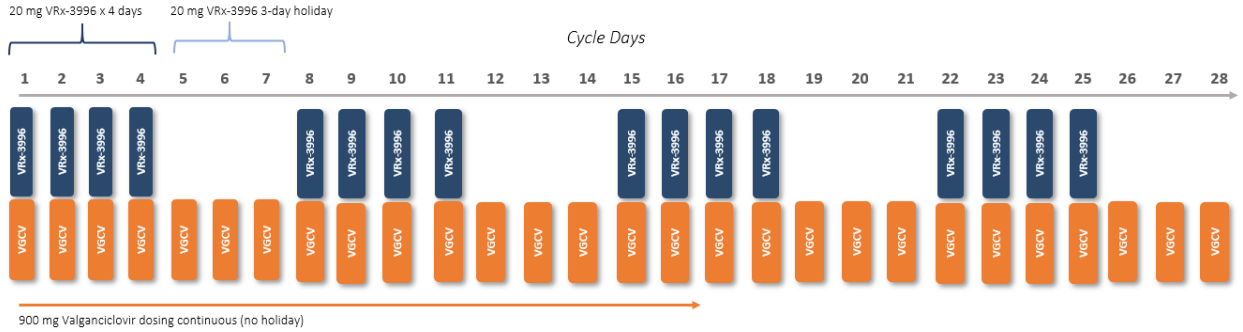
Sequential boundaries will be used to monitor the DLT rate during the dose expansion phase of the study.[29] If an excessive number of DLTs are seen, the SRC will have the option of either halting study accrual or reducing the RP2D to reduce the level of toxicity. The boundaries at which the study is halted or the RP2D is reduced are listed in Table 6. This is a Pocock-type

boundary that yields at most a 5% probability of crossing the boundary when the rate of DLT is equal to the acceptable rate of 30%.

Table 6: Early Stopping Boundaries for Toxicity

# Patients	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Boundary	-	-	-	4	5	5	6	6	7	7	8	8	9	9	9
# Patients	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
Boundary	10	10	11	11	12	12	12	13	13	14	14	14	15	15	15

3.2.4. Phase 2 Study Drug(s) Administration Schedule



In the Phase 2 portion of the study VRx-3996 will be administered 20 mg PO QD for 4 days on and 3 days off in a 7-day regimen. Valganciclovir will be administered 900 mg PO QD. VRx-3996 and valganciclovir will be taken at the same time for all visits.

The administration schedule used for VRx-3996 and/or valganciclovir may be modified as appropriate by the SRC during the course of the study. Changes to the schedule will be enacted with minimal or no change in the total daily dose.

If employed during the study, the following schedule definitions will be used:

- QD – Once each day at approximately the same time
- Q12 hours – Twice each day at between a 10 to 14-hour interval
- BID – Twice each day at between 8- and 12-hour intervals (preferably at 12-hour intervals when possible)

The SRC may define and employ other schedules as appropriate based on data accumulated during the course of the study.

3.3. Tablet Cohort

Once the Phase 2 arm has completed enrollment, approximately 10 patients will be enrolled into a cohort to receive VRx-3996 tablets instead of capsules. Approximately 10 patients will be needed to provide an assessment of systemic exposures to VRx-3996. The dose and schedule of VRx-3996 and valganciclovir administered to patients in the tablet cohort will be the RP2D

(VRx-3996 20 mg PO QD for 4 days on and 3 days off in a 7-day regimen with valganciclovir 900 mg PO QD starting at C1D1). VRx-3996 and valganciclovir will be taken at the same time for all visits.

The intent of these evaluations will be important to the clinical development program for assessing comparability of exposures to VRx-3996 administered as a tablet presentation, for comparison to delivery of the oral capsule product. The tablet form of VRx-3996 allows for a reduction from four 5 mg capsules to two 10 mg VRx-3996 tablets per dose on a daily basis and is expected to be less of a burden for patients.

With exceptions as described in the protocol, patients will follow the protocol/assessments as detailed for the Phase 2 expansion cohort patients.

3.4. Continuation of VRx-3996/Valganciclovir

Patients may continue to receive VRx-3996/valganciclovir provided the following criteria are met:

- Patient does not demonstrate progressive disease (in the absence of clinical deterioration, patients may continue on study drug until a repeat scan confirms progression)
- Patient has not experienced unacceptable toxicity that cannot be resolved with supportive treatment, a dose reduction, or interruption
- The Investigator considers additional VRx-3996/valganciclovir to be in the best interest of the patient

3.5. Dose Adjustments/Modifications/Delays

Details on dose adjustments, modifications, and delays are outlined in Section 5.1.8 and Section 5.2.5.

Patients who have had a dose hold should continue to follow all assessments called for in the Schedule of Events (i.e., if a patient undergoes a dose interruption, this will not delay conduct of any study procedures).

3.6. Central Pathology Review

A central review of pathology may be performed on available (archived or fresh) tumor samples taken from patients. This will include any historical diagnostic samples and samples available at the time of study entry in addition to samples taken per standard of care during study participation and samples taken at the time of relapse. Archived samples will be used to further characterize the tumor. Presence of EBV for eligibility will be determined by either a local or central pathology lab. Patients enrolled on the basis of a local result will have repeat testing at a central laboratory. The process for submitting archived tissue and procedures for central pathology review will be covered in a separate Study Manual.

3.7. Laboratory Procedures

Sites may elect to use either central or local laboratory tests for purposes of eligibility, safety, and other study required tests. The central laboratory kits should be utilized for the protocol-specified exploratory tests.

Any local labs collected for eligibility, or required by the study protocol, or to make treatment decisions will be entered into the electronic case report forms (eCRF).

The process for submitting central laboratory samples will be covered in the Laboratory Manual.

3.8. Central Radiology Review

Central review of patient scans (CT, MRI, PET-CT) will be performed by the Sponsor. A de-identified digital copy of each scan accompanied by the local radiology report will be generated by the site and sent to the Sponsor for review. The specific scan format and method of transfer will be arranged with each site. The review performed centrally may include an assessment based on both the Lugano[23] and RECIL[23] criteria.

3.9. Central ECG Review

Central review of patient ECGs will be performed by the Sponsor. A de-identified copy of each scan will sent to the Sponsor for review. The specific format and method of transfer will be arranged with each site. The Sponsor may elect to review all ECGs or a subset.

3.10. Safety Review Committee (SRC)

An SRC will govern the conduct of the study. The SRC will consist of the following individuals appointed by the Sponsor:

- Study Investigators
- The Study Medical Monitor
- A Sponsor representative

Responsibilities of the SRC will include:

- Reviewing study safety data throughout conduct of the study
- Confirming or modifying the specific dose escalations between cohorts
- Defining intermediate dose levels as appropriate
- Declaring the MTD (if reached)
- Determining the RP2D
- Providing guidance on treatment-related issues raised by an Investigator

The SRC will meet at the end of each cohort during the Phase 1b portion and approximately quarterly during the Phase 2 portion, or as needed based on the rate of enrollment.

A Core SRC consisting of 2 investigators and 1 clinical expert appointed by the Sponsor will assess the toxicity during Phase 2 dose expansion (Section 3.2.3).

3.11. Concomitant Medications, Treatments, and Procedures

Drug-interaction studies with VRx-3996 have not been conducted. During their participation on this study, patients may continue to use concomitant mediations, treatments, and procedures previously prescribed to treat non-cancer related conditions provided that, in the Investigator's judgment, they will not interfere with the study outcomes. Concomitant medications will be documented until 28 days following the last dose of study drug, or until a new anti-cancer therapy is started if sooner than 28 days.

3.11.1. Cytochrome P450 Substrates

A study with recombinant human cytochrome P450 isoforms (CYP450) suggests that VRx-3996 is a direct inhibitor of CYP3A4 isoform. *In vitro* studies indicated that VRx-3996 is not metabolized by or induces the activity of CYP3A4. A potential for drug interactions between VRx-3996 and drugs that are substrates of CYP3A4 is low but cannot be ruled out (see Table 18a in the Appendix). Please refer to the Investigator Brochure for detailed description.

3.11.2. Transporter Substrates and Inhibitors

Transporter studies indicate VRx-3996 is likely a substrate of MDR1 and BCRP transporters, but not an inhibitor of these transporters. Therefore, the protocol should limit or restrict strong MDR1/P-gp and BCRP inhibitors relevant to the patient population when administered with VRx-3996 (see Table 18b in the Appendix).

The effect of gastric pH on study drug absorption is not known. Unless necessary for patient care, proton pump inhibitors and H2 antagonists should be avoided, and antacids should not be given in the 2 hours prior to or within 4 hours post VRx-3996 administration.

3.12. Prophylactic Medications, Treatments, and Procedures

With the exception of prophylactic medications intended to reduce the risk of Tumor Lysis Syndrome (TLS) in patients at risk for TLS, the use of prophylactic medications intended to reduce toxicity associated with VRx-3996/valganciclovir will not initially be allowed.

The SRC may elect to institute the use of prophylactic medications (e.g., for prevention of nausea and vomiting secondary to study drugs) during the study. The specific medications used will be in keeping with generally accepted standards of care and the institutional guidelines of the participating sites.

Prophylaxis for Tumor Lysis Syndrome (TLS)

Patients considered to be at risk for TLS based on specific characteristics (e.g., specific diagnosis, renal insufficiency, bulky disease, elevated lactate dehydrogenase [LDH]) should receive TLS prophylaxis.[24]

The determination of a patient's risk for TLS can be estimated based on Table 7.

Table 7: Patient Stratification by Risk (adapted from Coiffier 2008)[24]

Type of Cancer	High risk	Intermediate risk	Low risk
NHL	Burkitt's, lymphoblastic, B-ALL	DLBCL	Indolent NHL
ALL	WBC ≥100,000	WBC 50,000–100,000	WBC ≤50,000
CLL		WBC 10,000–100,000	WBC ≤10,000

Abbreviations: *ALL = acute lymphoblastic leukemia; B-ALL = Burkitt's acute lymphoblastic leukemia; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma;* ***NHL = non-Hodgkin's lymphoma****.*

Patients considered at high risk for TLS should be managed in the inpatient setting with increased laboratory monitoring during the first 48 hours. Patients should receive rasburicase based on the recommended dosing outlined in Table 8.

Table 8: Recommended Rasburicase Dosing (adapted from Coiffier 2008)[24]

Risk profile	Baseline uric acid		Dose (mg/kg)*	Duration
	mg/dL	mmol/L		
High	>7.5	>450	0.20	Based on plasma uric acid levels
Intermediate	<7.5	<450	0.15	Based on plasma uric acid levels
Low	<7.5	<450	0.10	Clinical judgement

* ***Sites may choose to follow institutional standards for dosing rasburicase if they differ from those outlined in Table 8.***

Patients should also receive hydration with fluid intake maintained at approximately 1 to 2 times maintenance, with a urine output of 80 to 100 mL/m^2/hour.[24]

3.13. Rescue Medications, Treatments, and Procedures

The Investigator will determine the appropriateness and use of any medications, treatments, or procedures required to adequately treat study-related toxicities or complications (e.g., treatment of drug-induced nausea or vomiting, treatment of myelosuppression or anemia). Any rescue medication, treatments, or procedures will be consistent with accepted medical practice and institutional guidelines.

3.14. Prohibited Cancer Treatments

The following medications/therapies intended to treat the patients' underlying cancer are prohibited during the study

- Other investigational agents
- Other cancer therapies other than those which the patient has received for at least 6 months and which the Investigator, Medical Monitor, and Sponsor representative agree are unlikely to interfere with the study objectives (e.g., hormonal therapy for prostate cancer)

3.15. Discontinuation of VRx-3996/Valganciclovir

VRx-3996/valganciclovir may be discontinued in the event of any of the following:

- Clinically significant progressive disease (sites may elect to allow patients to continue study drug administration and confirm progressive disease with a follow-up evaluation to rule out pseudoprogression as outlined in the RECIL criteria)[23]
- Unacceptable AE(s) considered secondary to VRx-3996/valganciclovir despite appropriate therapy
- Withdrawal of consent for study drug administration by the patient (patient may agree to continue to be followed for safety and survival)
- Noncompliance by the patient at the discretion of the Investigator and Medical Monitor with agreement by the Sponsor representative

- Termination of study by the Sponsor

If the patient withdraws consent for treatment, it is important to continue to collect follow-up data, if possible. The Investigator must discuss this option with the patient.

3.16. Restarting Study Drugs at Relapse

Patients who experienced clinical benefit while on study treatment, and then experience progressive disease while not receiving VRx-3996/valganciclovir, may have study drugs restarted if the following conditions are met:

- Restarting study drugs is considered in the patient's best interest by the Investigator
- The patient has not developed any contraindications to either study drug
- The Investigator has discussed restarting study drugs with the study Medical Monitor who agrees that restarting of study drugs is appropriate
- The study has not been closed by the Sponsor

Patients will generally restart study drugs at the RP2D; however, the dose and schedule may be altered if considered in the best interest of the patient by the Investigator, Medical Monitor, and Sponsor representative.

3.17. Removal of Patients from Study Follow-Up

No additional follow-up of a patient will occur in the event of any of the following:

- Request by the patient to no longer be followed (e.g., withdrawal of consent for follow-up)
- Patient is lost to follow-up
- Termination of study by Sponsor

3.18. Replacement of Patients During Phase 2 Portion of Study

Patients who are unable to complete at least 1 disease assessment to evaluate efficacy during the Phase 2 portion of the study may be replaced.

3.19. Handling of Patient Withdrawal or Termination

Data generated from patients prior to withdrawal from the study will be maintained and utilized in the final study analysis. No data generated from patients after their withdrawal from the study will be collected.

3.20. Premature Termination or Suspension of Study

In the event that the Sponsor elects to terminate or suspend this study prior to completion, the Sponsor will discuss the feasibility of continued administration of VRx-3996/valganciclovir with each participating Investigator for those patients that appear to be benefitting from VRx-3996/valganciclovir.

The Sponsor will also cooperate with participating sites in terms of collecting outstanding study data sufficiently to allow for the generation of a study manuscript.

In the interest of avoiding the administration of VRx-3996 to more patients than is reasonable in the dose expansion phase of the study, this study will utilize a Simon's 2-stage design.[25] See Section 3.2.1 for sample size details and stopping rules of the Simon's 2-stage design.

4. STUDY ELIGIBILITY

4.1. Inclusion Criteria

1. Signed, informed consent
2. Age 18 or more years
3. ECOG PS[26] of 0 to 2 or Karnofsky Performance scale (KPS) ≥60%
4. Failed any available standard therapy with a reasonable likelihood of clinical benefit (e.g., anti-CD20 monoclonal antibody, withdrawal of immunosuppression, cytotoxic chemotherapy)
5. Relapsed/refractory, pathologically confirmed EBV^+ lymphoid malignancy or lymphoproliferative disease regardless of histologic subtype
6. EBV^+ as determined by institution's usual testing method or by the Sponsor's central laboratory on a specimen that is representative of the current disease (e.g., for patients who have relapsed the biopsy specimen should have been taken post-relapse). For questions on the suitability of particular specimens, please consult the Medical Monitor
7. Absence of available therapy with reasonable likelihood of cure or significant clinical benefit
8. Evaluable [Phase 1b only] or measurable [Phase 1b and Phase 2] disease based on Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification[22]
9. If previously treated:
    a. Treatment-related toxicity resolved to at least Grade 1 (alopecia excepted), or
    b. Treatment-related toxicity resolved to at least Grade 2 with prior approval of the Medical Monitor, or
    c. Treatment related toxicity resolved to at least the levels outlined in inclusion criterion #10, without transfusion support.
10. Adequate laboratory parameters including:
    a. Absolute neutrophil count (ANC) ≥1000/mm^3
    b. Platelet (PLT) count ≥50,000/mm^3
    c. Hemoglobin ≥8.0 g/dL
    d. Asparagine aminotransferase (AST)/serum glutamine oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic-pyruvic transaminase (SGPT) ≤3.0 × upper limit of normal (ULN) (≤5 × ULN if known liver involvement)
    e. Total bilirubin ≤2.0 × ULN unless considered due to Gilbert's syndrome in which case, ≤3.5 × ULN

f. Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.732 m^2 by Modification of Diet in Renal Disease (MDRD) equation

g. Prothrombin time (PT) ≤1.5 × ULN

h. International normalized ratio (INR) ≤1.5 × ULN

i. Serum potassium and magnesium should be within normal limits for institution or treatment to correct out of range values should be instituted

11. Willingness to participate in collection of all required laboratory testing as defined in the protocol
12. Females must be surgically sterile, postmenopausal, or agree to use adequate contraception (adequate as determined by the judgement of the Investigator) throughout the study and for a period of 6 months after last dose of VRx-3996
13. Males must be surgically sterile or must agree to use of effective contraception throughout the study and for a period of 3 months after last dose of VRx-3996

4.2. Exclusion Criteria

1. Fewer than 14 days from prior anti-lymphoma therapy (chemotherapy, irradiation, biological, or investigational therapy), or fewer than 7 days from prior therapies if approved by the Medical Monitor. Corticosteroid treatment at doses of ≤20 mg/day of prednisone or its equivalent, granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) are permitted up to 2 weeks prior to start of study treatment.
2. Fewer than 28 days from receipt of prior HDAC inhibitor
3. Fewer than 60 days from prior hematopoietic stem cell transplantation or solid organ transplantation
4. Known primary CNS lymphoma
5. CNS metastases or leptomeningeal disease unless appropriately treated and neurologically stable for at least 4 weeks
6. Other known active cancer(s) likely to require treatment in the next year that would impact the assessment of any study endpoints
7. Refractory graft versus host disease (GvHD) not responding to treatment (e.g., steroid refractory and not responding to second-line agents)
8. Active, uncontrolled bacterial, viral, or fungal infection(s) requiring systemic therapy
9. Pregnant or currently breastfeeding
10. Positive hepatitis B core antibody or surface antigen unless quantitative DNA PCR is negative and patient will be receiving prophylaxis for reactivation
11. Positive hepatitis C viral RNA (if serology is positive for infection)
12. History of allergic reactions attributed to compounds of similar chemical or biologic composition to valganciclovir

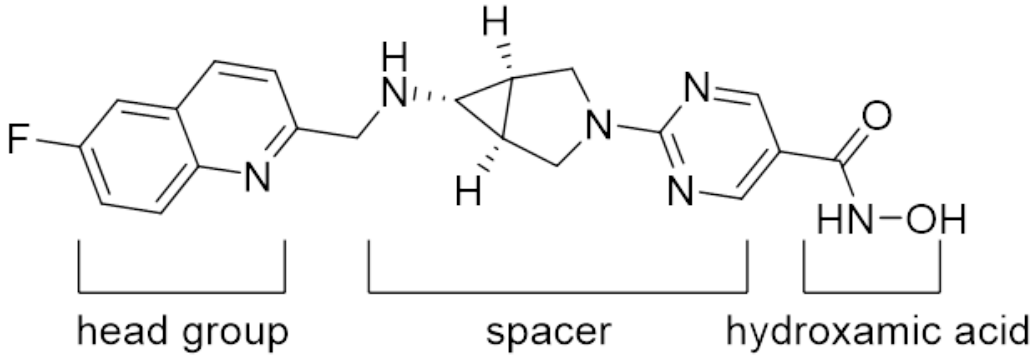
13. Psychiatric illness/social situations that would interfere with compliance with study requirements
14. Clinically significant cardiovascular abnormalities such as uncontrolled hypertension, congestive heart failure (New York Heart Association classification ≥ II), unstable angina, poorly controlled arrhythmias, or myocardial infarction within 6 months of study entry. Congenital long QT syndrome or corrected QT interval using Fridericia's method (QTcF) interval of ≥470 msec, average of triplicate readings at screening.
15. Other severe acute or chronic medical or psychiatric conditions or laboratory abnormalities that would impart, in the judgement of the Investigator, Medical Monitor, and/or Sponsor representative, excess risk associated with study participation or would interfere with study outcome assessments
16. Known involvement of critical structures by lymphoma that is considered highly likely to result in serious outcome in the event of rapid tumor destruction
17. Known history of HHV-6 chromosomal integration (ciHHV-6)
18. Known history of HIV infection

5. INVESTIGATIONAL PRODUCTS

5.1. VRx-3996 Drug Substance

VRx-3996 is a hydroxamic acid-based HDAC inhibitor.[18] As is typical of this class, the structure of VRx-3996 has 3 main components: a hydroxamic acid that coordinates with the Zn^{2+} ion in the active pocket of the enzyme, a spacer (azabicyclo pyrimidine) that fills out the narrow channel of the binding site, and a hydrophobic head group, amino methyl(fluoroquinoline), that interacts with the rim surrounding the pocket of the active site.

Figure 1: Structural Formula and Key Features of VRx-3996



Specific characteristics of VRx-3996 are outlined in Table 9.

Table 9: Drug Substance Properties

Molecular formula	$C_{20}H_{19}FN_6O_2$
Molecular weight	394.40
Physical description	Off-white to pale orange solid
LogP	1.60 (neutral); -1.0 (cationic)

5.1.1. Acquisition

VRx-3996 will be provided by the Sponsor to each clinical site. Instructions for requesting and receiving VRx-3996 will be included in the Study Manual.

5.1.2. Dosage Form

VRx-3996 drug product is currently supplied as 5 mg strength capsules. In addition to active ingredient nanatinostat, inactive excipients consist of silicified microcrystalline cellulose and sodium stearyl fumarate, which are dry-filled into size 2, white to off-white, opaque, hard gelatin capsules for oral administration.

Viracta intends to introduce film-coated immediate-release (IR) tablets of 5 mg and 10 mg strengths in this study, replacing the capsule product. The tablets are dose proportional, consisting of the active VRx-3996, and inactive excipients (i.e., mannitol, microcrystalline cellulose, croscarmellose sodium, and sodium stearyl fumarate). The tablets are film coated with non-functional Opadry II white. The comparability between the tablets and capsules has been established via *in vitro* dissolution studies and *in vivo* dog pharmacokinetic studies and no dose adjustment is needed.

All of the inactive ingredients in the drug product meet compendial requirements of the United States Pharmacopeia and/or National Formulary.

5.1.3. Composition

The quantitative compositions for 5 mg VRx-3996 capsules are presented in Table 10.

Table 10: Quantitative Composition of VRx-3996 Capsules

Components	5 mg	
	Amount per Capsule (mg)	**Weight (%)**
VRx-3996	5.0[1]	2.5
Silicified microcrystalline cellulose	194.0	97.0
Sodium stearyl fumarate	1.0	0.50
Total (Blend)	**200.0**	**100.00**
Capsule Size	61.0[2]	---
Total (filled capsule)	**261.0**	---

[1] *Exact amount is corrected for drug substance assay (free base on the anhydrous, solvent free basis)*

[2] *Average capsule weights as provided by manufacturer*

The quantitative compositions for the dose proportional 5 mg and 10 mg VRx-3996 tablets are presented in Table 11.

Table 11: Quantitative Composition of Film-Coated, Immediate-Release VRx-3996 Tablets (5 and 10 mg Strengths)

Component	Function	% w/w	5 mg strength (mg/tablet)	10 mg strength (mg/tablet)
VRx-3996	Drug substance	5.0	5	10
Mannitol	Filler	25.0	25	50
Microcrystalline cellulose	Filler	65.5	65.5	131
Croscarmellose sodium	Disintegrant	4.0	4.0	8.0
Sodium stearyl fumarate	Lubricant	0.5	0.5	1.0
Total (core)		100	100	200
Opadry II coating powder	Film coating	3.0	3.0	6.0
Purified water*	Film coating	-	-	-
Total			103	206

** Used to make the coating solution and removed during processing*

5.1.4. Product Packaging

VRx-3996 Capsules, 5 mg, are packaged in 30-count high-density polyethylene bottles, sealed and closed with child-resistant caps.

VRx-3996 film-coated Tablets, 10 mg and 5 mg, are packaged in 45-count high-density polyethylene bottles, sealed and closed with child-resistant caps.

5.1.5. Product Storage and Stability

VRx-3996 should be stored at controlled room temperature 20–25ºC (68–77ºF), with excursions permitted to 15–30ºC (59–86ºF) in a secure location. Once the bottle seal is broken, bottles should be stored tightly capped.

5.1.6. Dosing and Administration

VRx-3996 will be administered in the Phase 1b portion of the study at a dose and schedule determined by the assigned cohort.

In the Phase 2 portion of the study, patients will receive VRx-3996 at the RP2D and schedule determined in the Phase 1b portion of the study.

5.1.7. Dietary Requirements

There are no special dietary restrictions or requirements associated with VRx-3996; however, valganciclovir absorption is affected by food and should be taken with food (see Section 5.2.4 for additional clarification).

5.1.8. Dose Adjustments/Modifications/Delays

Given the expectation that both study drugs are required for activity, both agents will be held and restarted in parallel unless toxicity is clearly associated with VRx-3996 and there is clinical justification to continue dosing with valganciclovir alone. For non-hematologic toxicity requiring dose modification see Table 12.

Table 12: Requirements for Dose Hold Secondary to Non-Hematologic Toxicity

Toxicity (CTCAE)	Requirement for Dose Hold
Grade 1 or 2	No dose hold required
Grade 3+	Hold subsequent dosing until toxicity has resolved to at least Grade 1 or baseline

In the event that any of the following hematologic AEs are observed on study, the dose of VRx-3996 and valganciclovir will be held:

- ANC <500 cells/µL
- PLT count <35,000/µL
- Hemoglobin (HGB) is <8 g/dL

If a hold is implemented for study drug-related toxicity, patients may restart study drugs only if the following conditions are met or if agreed with the Medical Monitor:

- The AE has resolved to at least Grade 1 or baseline for non-hematologic AEs and Grade ≤2 hematologic toxicity related to study drug
- The AE is not expected to recur in the opinion of the Investigator with subsequent study drug administration based on an intervention such as prophylactic use of appropriate treatment (e.g., prophylactic anti-emetics), or a reduction in the dose of one or both of the study drugs
- Continued administration of study drugs is considered to be in the patient's best interest based on the opinion of the study Investigator

Patients should be followed up approximately twice weekly for resolution of the toxicity. Study days will continue to accrue during dose holds and other scheduled procedures as per Table 15 should not be delayed. If the dose is held for more than 14 days, the Investigator should consult with the Medical Monitor before dosing resumes.

If a patient has multiple dose interruptions for study drug toxicity or has had to interrupt for more than 14 days, a dose reduction should be considered. Dose reduction for VRx-3996 will be in 10 mg increments and for valganciclovir from 900 mg to 450 mg. Re-escalation of study drug dose may only be performed after approval by Medical Monitor.

There are additional criteria for modification of the valganciclovir dose based on renal function as outlined in Section 5.2.3.

5.2. Valganciclovir

5.2.1. Acquisition

Valganciclovir tablets will be provided to the clinical sites from commercial sources by the Sponsor. Instructions for requesting and receiving valganciclovir will be included in the Pharmacy Manual.

5.2.2. Product Storage and Stability

Valganciclovir should be stored at controlled room temperature 20–25ºC (68–77ºF), with excursions permitted to 15–30ºC (59–86ºF) in a secure location.

5.2.3. Dosing and Administration

In the Phase 1b portion of the study, the starting dose of valganciclovir is listed in Table 5. If a patient is on valganciclovir prior to study entry, the dose of valganciclovir should be increased to the dose and schedule listed for their assigned cohort in Table 5. Patients who have previously shown intolerance to a given dose of valganciclovir, should start at their highest tolerable dose of valganciclovir or their assigned dose (whichever is lower) following discussion with the Medical Monitor. For those patients with evidence of renal impairment at study entry, the starting dose of valganciclovir should be discussed with the Medical Monitor but should be no higher than the doses listed in Table 13.

In the Phase 2 portion of the study, the starting dose and schedule of valganciclovir (i.e., RP2D) will be determined by the SRC at the conclusion of the Phase 1b portion of the study. If a patient is on valganciclovir prior to study entry, the dose of valganciclovir should be increased to the RP2D. Patients who have previously shown intolerance to a given dose of valganciclovir, should start at their highest tolerable dose of valganciclovir or the RP2D (whichever is lower) following discussion with the Medical Monitor. For those patients with evidence of renal impairment at study entry, the starting dose of valganciclovir should be discussed with the Medical Monitor but should be no higher than the dose listed in Table 13.

In either phase of the study, patients who develop an elevated creatinine while on study should have their dose of valganciclovir reduced to no higher than the doses listed in Table 13. For patients already receiving a dose of valganciclovir lower than that recommended in Table 13, the Investigator should discuss the amount of dose reduction with the Medical Monitor.

Table 13: Valganciclovir Dose Adjustments for Adult Renal Impairment

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

In patients who are unable to tolerate oral dosing of valganciclovir, the Investigator will have the option of administering ganciclovir IV at 5 mg/kg IV BID. In patients who are receiving a dose of valganciclovir less than 900 mg PO BID, the dose of ganciclovir will be reduced accordingly using the ratio of 900 mg valganciclovir to 5 mg/kg ganciclovir.

The SRC may elect to adjust the starting dose or schedule of valganciclovir as appropriate during the conduct of the study.

5.2.4. Dietary Requirements

Valganciclovir absorption is affected by food. Therefore, patients should be instructed to take both valganciclovir and VRx-3996 with food.

In an effort to standardize food intake for the PK assessments, patients will be asked to consume one can of Ensure® or equivalent prior to the dose of study drugs on days with pre- and post-dose PK assessments as outlined in Section 6.4.1. Note that valganciclovir and VRx-3996 should be taken at the same time, including on Cycle 1 Day 1. An Ensure equivalent is defined as any liquid nutrition that is at least 8 ounces in size containing at least 8 grams of protein and at least 6 grams of fat. Alternatively, patients may consume a light breakfast in place of consuming an Ensure equivalent.

Patients are free to determine what food to take prior to all subsequent study drug administrations. On study visit days requiring PK trough levels, patients should be instructed to bring food to consume prior to dosing in order to avoid taking study drugs on an empty stomach and reduce disruption in their dosing schedule.

5.2.5. Dose Adjustments/Modifications/Delays

Dose adjustments for valganciclovir will be made in concert with adjustments to VRx-3996. See Section 5.1.8 for specific details.

For patients with renal impairment, dose adjustments for valganciclovir will be made in accordance with valganciclovir prescribing guidelines as outlined in Table 13.

5.2.6. Drug Interactions

The drug-drug interactions for valganciclovir are those seen with ganciclovir. Drug-drug interaction studies with ganciclovir were conducted in patients with normal renal function. Therefore, with concomitant administration of valganciclovir and other renally excreted drugs, patients with impaired renal function may have increased concentrations of ganciclovir and/or the co-administered drug. Such patients should be closely monitored for toxicity of ganciclovir and the co-administered drug. Established and other potentially significant drug interactions conducted with ganciclovir are listed in Table 17 in the Appendix.

In patients that are receiving a concomitant medication considered to pose a significant drug interaction with valganciclovir, additional monitoring should be conducted as outlined in Table 17.

5.3. Missed Doses

If a scheduled dose of VRx-3996 or valganciclovir is missed, the patient should take the missed dose(s) as soon as possible during the same day, but within 8 hours of the missed dose. If more than 8 hours or an entire day has passed, the normal dosing schedule will be resumed the following day without a change in the daily dose or schedule.

5.4. Vomited Doses

If a scheduled dose of VRx-3996 or valganciclovir is vomited, the patient should contact the site for consideration of anti-nausea medication and dosing should resume with the next scheduled dose. No replacement dose should be given.

5.5. Assessment of Study Drug Compliance

Patient compliance with study drugs will be assessed during study participation. The specific method used to assess study drug compliance may include paper diaries or an automated phone-based system to collect study drugs capsule/tablet counts. Details on the specific method used will be included in the Study Manual.

5.6. Study Drug Accountability

The Investigator or their representative will account for all study drugs supplied by the Sponsor. The Investigator shall maintain adequate records of the disposition of study drug, including dates, quantity, and use by patients. Upon completion of the study, all remaining study drugs will be accounted for and returned to the Sponsor via a traceable method (UPS, FedEx, Marken, etc.) or disposed following the institution's Standard Operating Procedures (SOPs), if instructed by the Sponsor.

6. STUDY PROCEDURES AND SCHEDULE

6.1. Informed Consent

Written informed consent (ICF) in a language fully comprehensible to the prospective patient will be obtained from each patient prior to performing any study-related procedures. A copy of the signed ICF will be provided to the patient. The study site will retain all original versions of signed ICFs.

6.2. Patient Registration

Clinical sites will submit Patient Registration materials through an electronic system for Medical Monitor approval prior to the initial administration of study drugs. Details on the specific electronic system and procedures will be included in the Study and Pharmacy Manuals.

Administration of study drugs should begin within 14 days of approval by the Sponsor (or designee).

6.3. Study Specific Procedures

Study procedures will follow those outlined in the Schedule of Events in Table 15.

6.3.1. End of Treatment Visit

The End of Treatment (ET) Visit is the visit at which the decision is made to discontinue administration of VRx-3996.

If the decision is made to discontinue administration of VRx-3996 outside of a scheduled visit, an attempt will be made to have the patient return for an ET visit.

6.3.2. Safety Follow-Up Visit

Safety will be assessed at the Safety Follow-Up Visit, approximately 28 days following the final administration of VRx-3996/valganciclovir.

6.3.3. Survival and Follow-up Assessment

Survival and follow-up assessment will be conducted at least every 3 months for assessment of additional therapy, response status, and survival following the safety follow-up assessment.

This assessment may be conducted by review of the patient records or by patient contact (e.g., telephone, email). Patients who are unable to be contacted following at least 3 attempts (one of which is contact by registered mail) will be considered lost to follow-up.

6.3.4. Unscheduled Visit

Unscheduled visits will be recorded in the database. The specific tests and evaluations performed during an unscheduled visit will be determined by the Investigator.

6.4. Clinical Laboratory Evaluations

Clinical laboratory evaluations will follow those outlined in the Schedule of Events in Table 15.

Clinical laboratory evaluations will be performed using a central laboratory or a local laboratory. In addition, the clinical sites will provide archived or fresh tissue samples at baseline and in the event of a relapse, if diagnostic biopsies are performed.

6.4.1. Pharmacokinetics

Phase 1b/2 and Tablet Cohorts

A PK assessment of both VRx-3996 and valganciclovir will be performed following the first administration of VRx-3996/valganciclovir in all patients. The scheduled timepoints are shown in Table 14.

Table 14: Pharmacokinetic Sampling and ECG Schedule for Valganciclovir and VRx-3996

Time	Administration	PK Sampling and ECG Schedule		
Cycle 1 & 2, Day 1		**Plasma**	**ECG**	**Urine (Cycle 1 only)**
Pre-dose***	Meal supplement*	X	X (triplicate)	Void
0 hour	Valganciclovir and VRx-3996			N/A
0.5 hour (±15 min)		X	X (triplicate)	0–3 hr collection
1 hour (±15 min)		X	X (triplicate)	
2 hour (±15 min)		X	X (triplicate)	
4 hour (±15 min)		X	X (triplicate)	3–8 hr collection
6 hour (±15 min)		X	X (triplicate)	
8 hour (±30 min)		X		
Cycle 1 Day 2**				
Pre-dose***	Meal supplement*	X	X (triplicate)	N/A
0 hour	Valganciclovir and VRx-3996			N/A
2 hour (±15 min)		X	X (triplicate)	N/A
Cycle 1 & 2, Day 15**				
Pre-dose***	Meal supplement*	X	X (triplicate)	N/A
0 hour	Valganciclovir and VRx-3996			N/A
2 hour (±15 min)		X	X (triplicate)	N/A

* *Ensure or equivalent should be consumed prior to dosing. Alternatively, patients may consume a light breakfast in place of consuming an Ensure or equivalent.*

** *Patients should be reminded **not to take their dose at home** prior to coming into the clinic on these days. Study visits with PK assessments should occur on days that the patient will take both study drugs, VRx-3996 and valganciclovir.*

*** *Pre-dose ECG should be conducted prior to meal supplement. If possible, patients should not consume additional food between dose and last ECG timepoint. If 6 hr fasting time for ECGs is not feasible for patients, a high protein, low carb snack immediately following an ECG to maximize the time between food and the next ECG.*

At selected sites, urine will be collected for levels of VRx-3996 and its metabolites Cycle 1 Day 1. Patients will be instructed to void urine prior to administration of study drug, then all urine will be collected between 0 and 3 hours, and 3 and 8 hours. Detailed instructions are included in the Study Manual.

Pharmacokinetic analysis will be performed at a central laboratory designated by the Sponsor.

Instructions on the collection, processing, and shipment of patient PK samples for these assays will be provided in the Laboratory Manual.

If available, back-up PK aliquots may be used for future assessment of VRx-3996 metabolites (if identified).

6.4.2. Exploratory Biomarkers

Exploratory biomarkers will be evaluated in this study as indicated in Table 15. Archived blood, PBMCs, plasma, and/or tissue samples may be used for assessment of other exploratory biomarkers (if identified).

Details on the collection procedure and timing for each exploratory biomarker will be provided in the Study Manual.

7. SCHEDULE OF EVENTS

The study procedures for the Phase 1b and Phase 2 portions of the study will follow those outlined in Table 15.

Table 15: Schedule of Events

Cycle	SR	1					2		3+		ET	ST	SV
Cycle Day		**1**	**2**	**8**	**15**	**22**	**1**	**15**	**1**	**15**			
Assessment													
Informed consent	X												
Medical history (includes donor data)	X												
EBER/histology sample	X						[X]		[X]		[X]		
Height	X												
Physical examination	X												
Symptom-directed exam		X	X	X	X	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	
Performance status	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X		X	X	X	X	X	X	X	X	X	
Hematology	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	
Coagulation	X	X		X	X	X	X	X	X	X	X	X	
Serum pregnancy test	X												
Urine pregnancy test		X					X		X				
12-lead ECG	X	X	X	X	X	X	X	X	X	X	X	X	
Head CT/MRI	X												
Disease assessment	X								X		X		
PK sample(s)		X	X		X		X	X					
Urine PK sample collection		X											
Hepatitis B antigen/antibodies	X												
Hepatitis B DNA PCR	X												
Hepatitis C antibodies	X												
Hepatitis C qPCR	X												

Cycle	SR	1					2		3+		ET	ST	SV
HLA testing		X											
Exploratory Biomarkers													
-Histone H3 acetylation		X	X	X			X						
-Immune profile		X			X		X		X		X		
-EBV and CMV qPCR		X	X	X	X	X	X		X				
VRx-3996/valganciclovir distribution		X					X		X				
VRx-3996/valganciclovir return							X				X		
VRx-3996/valganciclovir compliance assessment		X	X	X	X	X	X	X	X	X	X		
Survival and follow-up assessment and disease status													X

Study assessments may be performed ±3 days of the recommended date (however the DLT assessment period should include a full 28 days). Study visits with PK assessments should occur on days that the patient will take both study drugs, VRx-3996 and valganciclovir. End of Treatment (ET) Visit assessments (if needed) will be the same as for the Safety Follow-Up Visit. Safety Follow-Up Visit will be performed 28 ±7 days after last dose.

***SR** – Screening (within 21 days of Cycle 1 Day 1)*

***ET** – End of Treatment*

***ST** – Safety follow-up*

***SV** – Survival follow-up contact (performed at least every 3 months after safety follow-up assessment)*

***X** – Required*

***[X]** – Biopsy tissue samples taken per standard of care during study participation and samples taken at the time of relapse should be submitted to the central pathology lab for review.*

***Informed consent –** Informed consent may be performed at any time prior to the start of screening procedures.*

***EBER/histology Sample** – Histology sample, indicative of current disease, to be sent to central pathology lab at the time of screening. Central pathology review/results not required for enrollment. Pathology review will include detection of EBV gene products.*

***Medical history** – Record all cancer-related history over the patient's lifetime and collect non-cancer related history for the 2 years prior to study entry. For transplant recipients (except auto-SCT), collect the following historical information on donors: HIV1, HIV2, hepatitis B surface Ag, hepatitis B surface Ab, hepatitis B core Ab, hepatitis C Ab, HSV-1 Ab, HSV-2 Ab, CMV Ab IgG, CMV Ab IgM, EBV IgG-VCA (viral capsid antigen).*

***Vital signs** – Performed just prior to first dose of valganciclovir and VRx-3996, and in concert with (but prior to) PK draws on Cycle 1 Day 1. On other indicated visit days, perform vital signs once (prior to study drugs dosing if administered in clinic). Vital signs include weight (in pounds), heart rate, respiratory rate, blood pressure, temperature, and oxygen saturation by pulse oximeter. Note that weight only needs to be recorded once daily.*

***Performance status** – Either ECOG or KPS (See Table 16 in the Appendix for conversion table).*

***Concomitant medications** – Recorded from 28 days prior to Cycle 1 Day 1 to 28 days after last dose of study drugs, except for concomitant medications related to cancer treatment, for which lifetime history prior to entering the study will be recorded.*

***Urinalysis** – [Urine] Color, appearance, glucose, bilirubin, ketone, specific gravity, blood, pH, protein, urobilinogen, nitrite, leukocyte esterase, RBC, WBC, epithelial cells.*

***Hematology** - [Blood] Complete blood count with differential to include WBC, RBC, HGB, HCT, platelets, MCV, MCH and differential.*

***Chemistry** - [Blood] Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, phosphate, magnesium, AST, ALT, total bilirubin, alkaline phosphatase, total protein, albumin, uric acid, and LDH.*

Coagulation *– [Blood] PT, PTT, and INR.*

Serum pregnancy test *– Only required for females of child-bearing potential.*

Urine pregnancy test *– Only required for females of child-bearing potential at the beginning of every cycle.*

12-lead ECG *– Careful skin preparation should be done to assure high quality ECGs and all ECGs should be collected on the same ECG machines. ECGs should be performed in as calm an environment as possible and not immediately following stressful procedures (i.e., biopsies, etc.) and distractions should be minimized, such as talking, TV, etc. Prior to each ECG, the patient should lie in a supine position in a calm environment for at least 5 minutes. When performed in triplicate, the ECGs should be performed ~1 minute apart. ECGs should be conducted prior to and as close to PK blood draws when timepoints coincide, followed by vital signs, when all 3 assessments are scheduled for the same time (in order: ECG, vital signs, then blood draw).*

ECGs should be performed in triplicate at the following times:

- *Screening*
- *Cycle 1 Day 1 pre-dose, and post-dose at 0.5 hr, 1 hr, 2 hr, 4 hr, and 6 hr*
- *Cycle 1 Day 2 pre-dose and post-dose at 2 hr*
- *Cycle 1 Day 15 pre-dose and post-dose at 2 hr*
- *Cycle 2 Day 1 pre-dose and post dose at 0.5 hr, 1 hr, 2 hr, 4 hr, and 6 hr*
- *Cycle 2 Day 15 pre-dose and post dose at 2 hr*

Average corrected QT interval using Fridericia's method (QTcF) to be calculated to confirm eligibility.

At times not listed above, single ECGs should be performed. When performed on days that include PK draws, a single ECG should be performed as close as possible to each PK draw. For days when there are no scheduled PK draws, the ECG can be performed at any time during the clinic visit, irrespective of the time of study drug dosing. On study days requiring a single ECG, if ECG indicates an increased QTcF interval (i.e., >450 msec), 2 additional ECGs should be performed at least 2 minutes apart.

Head CT/MRI *– Performed to rule out occult CNS disease prior to study entry.*

Disease assessment *– Performed at least every 2 cycles with initial assessment after Cycle 2 (may be adjusted based on Investigator discretion following discussion with Medical Monitor). Disease assessment performed using a modality appropriate for the patient's tumor (e.g., PET-CT scan, CT scans, MRI). Use a consistent modality for the same patient throughout the study. May include assessment of bone marrow (e.g., aspirate, biopsy) with cytogenetics and/or fluorescence in situ hybridization (FISH) as indicated. Disease assessment data including actual scan data and radiology reports will be submitted to the Sponsor as it becomes available for evaluation by a central radiologist reader. Investigator assessment of clinical response will be documented in the source and in Electronic Data Capture. When available, tumor tissue collected during the study should be provided to the central pathology lab.*

PK sample(s) *– [Blood] Collected for both valganciclovir and VRx-3996. Timepoints per Section 6.4.1. Collection procedure outlined in the Study Manual for all sites. Study visits with PK assessments should occur on days that the patient will take both study drugs, VRx-3996 and valganciclovir.*

Urine PK collections *– At selected sites only urine will be collected for levels of VRx-3996 and its metabolites on Cycle 1 Day 1. Patients will be instructed to void urine prior to administration of study drug, then all urine will be collected as described in Table 14 depending on the patient Cohort. Detailed instructions are included in the Study Manual.*

Hepatitis B antigen/antibodies *– [Blood] Includes surface antigen, core antibody, and surface antibody. Collection procedure outlined in the Study Manual.*

Hepatitis B DNA PCR *– [Blood] Collected on patients with positive hepatitis B core Ab or surface Ag.*

Hepatitis C antibodies *– [Blood] Collection procedure outlined in Study Manual. Any patient positive for hepatitis C Ab will be evaluated for hepatitis C circulating virus by qPCR.*

Hepatitis C qPCR *– [Blood] Required only for patients with evidence of hepatitis C based on serology.*

Human leukocyte antigen (HLA) testing *– [Blood] Determination of HLA class I and II. Collection procedure outlined in the Study Manual.*

Exploratory biomarkers:

- ***-Histone H3 acetylation*** *– [Blood] Evaluates acetylation on PBMCs. Samples collected prior to administration of study drugs on Cycle 1 Day 1 (baseline), Cycle 1 Day 2, Cycle 1 Day 8. Collection procedure outlined in the Study Manual.*
- ***-Immune profile –*** *[Blood] Evaluates immunophenotype and immune function in PBMCs. Samples are collected prior to administration of study drugs on Cycle 1 Day 1 (baseline), Cycle 1 Day 15, Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1, and ET. Collection procedure outlined in the Study Manual.*
- ***-EBV and CMV qPCR****- [Blood] Collected prior to administration of study drugs on Cycle 1 Day 1 (baseline), Cycle 1 Days 2, 8, 15, 22, and Cycles 2–12 Day 1. Collection procedures are outlined in the Study Manual.*

8. STUDY COMPLETION

8.1. Early Study Termination

If the Sponsor elects to terminate the study prematurely, the Sponsor will provide appropriate notification to the Investigators, Institutional Review Boards (IRBs), and FDA and other relevant regulatory authorities as applicable. The notification will include instructions for handling patients still on study drug, data collection procedures, and requirements for study close-down.

8.2. Patient Discontinuation

Prior to discontinuing a patient, every effort should be made to contact the patient, schedule a final study visit, obtain as much follow-up data as possible, and retrieve all study material. An attempt will be made to collect survival data whenever possible, unless the patient has withdrawn consent for all study-related activities.

8.3. Lost to Follow-Up

Patients who do not return for scheduled visits and who cannot be contacted, will be considered lost to follow-up. Follow-up attempts will be documented in the source documents and the applicable sections of the eCRF.

9. ASSESSMENT OF SAFETY

9.1. Specification of Safety Parameters

9.1.1. Adverse Event (AE) Definition

An AE is any untoward medical event that occurs to a patient following the start of investigational product (IP) administration, whether the event is considered IP-related or not.

Pre-existing conditions are not considered an AE unless the condition worsens by at least 1 grade following the start of IP administration.

Adverse events will be captured with the first dose of study drugs (on Cycle 1 Day 1) and continue until 28 days after the last dose of study drugs or until a new anticancer treatment is started.

Death considered related to disease progression will not be considered an AE. However, all deaths within 28 days of last study drug administration or assessed as related to study drug, must be reported on a serious adverse event (SAE) form within 24 hours.

9.1.2. Abnormal Laboratory Tests

Laboratory test abnormalities that constitute an adverse event (i.e., are considered to be clinically significant, induce clinical signs or symptoms, require concomitant therapy or require changes in study treatment) should be recorded in the eCRF. If possible, a diagnosis rather than a symptom should be provided (e.g., anemia instead of low hemoglobin). Laboratory abnormalities that meet the criteria for AEs should be followed until they return to normal or an explanation for the abnormality is determined. When abnormal results are due to toxicity, patients should be assessed twice weekly for resolution.

Laboratory abnormalities that do not meet the definition of an AE should not be reported as adverse events. If a dose hold or concomitant medication for the lab abnormality is required, this would be considered an AE by definition and must be reported as such.

9.1.3. Definition of Serious Adverse Events (SAE)

An SAE is any AE that results in any of the following outcomes:

- Death
- A life-threatening experience
- An inpatient hospitalization or prolongation of an existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- An event that is not listed above but that requires intervention to prevent one of the outcomes listed above also is considered a SAE

Elective hospitalizations for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent should not be reported as a SAE.

Hospitalizations related to disease progression should not be reported as a SAE.

9.2. Classification of an Adverse Event

9.2.1. Severity of Event

All AEs will be assessed by the Investigator using NCI CTCAE version 5.0.

9.2.2. Relationship to Study Drugs

The Investigator will use his/her best medical judgment to determine the relationship of an AE to one or both study drugs.

The relationship of an AE or SAE to study drugs will be classified using the following 3 categories:

- Definitely related
- Possibly related

- Unrelated

To be classified as "Definitely related", an AE should occur in a timeframe relative to administration of study drugs that suggests a strong causal relationship between study drugs and the AE. In addition, there should be no other reasonable explanations for the AE, such as underlying disease or other concurrent conditions.

To be classified as "Unrelated", an AE should occur in a timeframe relative to administration of study drugs that suggests a causal relationship between study drugs and the AE is very unlikely. In addition, there should be a reasonable explanation for the AE, such as underlying disease or other concurrent condition.

To be classified as "Possibly related", an AE should not fall clearly into 1 of the above 2 categories. This would include, for example, an AE that does not seem to occur in close temporal proximity to administration of study drugs, but also has no other reasonable explanation.

9.2.3. Expectedness

The Investigator will make an assessment of whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the reference safety information described in the Investigator Brochure for the study drugs.

Expectedness refers to AEs previously observed, not to what might be anticipated from the properties of the study agent or what has been seen with agents of the same class.

9.3. Time Period for AE Reporting

Adverse Events will be recorded that occur following the first administration of study drugs (on Cycle 1 Day 1) up to and including 28 days after the last dose of study drugs or until the start of a new anticancer therapy.

10. ASSESSMENT OF EFFICACY

Response will be assessed locally using a combination of physical exam and imaging (e.g., PET-CT scan, CT scan MRI, bone marrow/aspirate) as appropriate for each patient.

Response assessments will follow the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification.[22]

Response assessments may also be conducted centrally using the RECIL criteria.[23]

11. REPORTING PROCEDURES

11.1. Serious Adverse Event Reporting

All SAEs must be reported to the Sponsor within 24 hours of the Investigator becoming aware of the SAE. The time period for reporting SAEs will follow that for AEs as outlined in Section 9.3.

To report a SAE, sites will complete an SAE Report Form and email the report to:

CTISafety@ctifacts.com

or

Fax to 1-866-366-2329

The Investigator should discuss with the Medical Monitor any SAEs for which the issue of seriousness is unclear or questioned. Contact information for the Medical Monitor is:

Name: John Gutheil, MD
Phone: 1-858-248-0639
Email: jgutheil@sciquus.com

SAEs must be reported by each site to their appropriate IRB/Ethics Committee (EC) in accordance with the timeframes and procedures required by their IRB Policy.

The Sponsor will report SAEs to the US FDA and any other relevant regulatory authorities.

11.2. Reporting of Pregnancy

Pregnancies occurring in study patients will be reported to the Sponsor within 24 hours of becoming known to the site. A Pregnancy Report Form provided by the Sponsor will be completed. Pregnancies may also be reported to the IRB as per the IRB's requirements.

All pregnancies will be followed to term. Every effort will be made to obtain the health status of the mother and infant or the fetus (in cases of miscarriage or therapeutic abortion).

11.3. Overdose

An overdose is defined as the intake of a study drug in excess of the prescribed daily dose. Since both study drugs are in solid form, this would involve taking an additional 5 mg capsule of VRx-3996 or an additional 450 mg tablet of valganciclovir over the intended dose.

All overdoses, whether accidental or intentional, should be reported on an SAE form whether or not an AE occurred. If an overdose resulted in an AE, the SAE form should specify the event and explain in the narrative that the event was associated with an overdose.

12. STATISTICAL CONSIDERATIONS

12.1. Analysis Datasets

This study will identify the following datasets:

- Intent to treat dataset: All patients who have enrolled in the study
- Safety dataset: All patients who receive at least 1 dose of VRx-3996.
- Efficacy dataset: All patients with measurable disease at Screening who have met all inclusion criteria and have received at least 1 post-baseline tumor assessment for efficacy.

12.2. Description of Statistical Methods

Analyses performed for this study will utilize descriptive statistics. For continuous variables, the following information will be presented by cohort and study phase: n, mean, standard deviation, median, minimum, and maximum. Baseline will be the last observation prior to treatment. For categorical variables counts and percentages will be used.

The clinical outcomes of primary interest are overall response rate (ORR: complete or partial response) and duration of response (DoR). Efficacy will be presented as the percentage of patients with CRs, PRs, and SD. ORR will be calculated as CR + PR; disease control rate will be calculated as CR + PR + SD. Response criteria will follow the recommendations of Cheson et al., 2014.[28] The analysis of study data will be based on patient data from both the dose escalation (Phase 1b) and dose expansion (Phase 2 and Tablet cohort) parts up to the time when: i) all Phase 1b patients have completed at least 12 months of follow-up from their first disease response assessment after 2 cycles of therapy or have discontinued from the study, and ii) all patients have been followed for DoR for a maximum period of 12 months from the first dose of study medication, have died, withdrawn consent, discontinued, or are lost to follow up, whichever occurs first. The additional data for any patients continuing to receive study drugs or remaining in safety or survival follow-up beyond the final cutoff point will be summarized in a final Clinical Study Report.

The ORR and CR rates will be summarized by cohort and study phase with exact 95% confidence Intervals (CIs).

Duration of response is defined as time from date of first observed complete or partial response to the date of disease progression, death due to any cause, or last adequate (radiographic) response assessment. The DoR will be estimated for the RP2D dose patients using Kaplan-Meier estimates where patients still on treatment after 12 months will be censored.

12.3. Analysis of the Primary Endpoints

12.3.1. Safety Profile

The safety dataset will be used for all the safety summaries.

The incidence of all AEs will be tabulated by dose received. These AEs will be classified by System Organ Class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

For incidence reporting, if a patient reported more than 1 AE that was coded to the same System Organ Class or Preferred Term, the patient will be counted only once at the highest observed grade for that specific system organ class or preferred term.

An overview of AEs, which includes patient incidence of AEs, AEs by severity, SAEs, deaths, and AEs leading to discontinuation, will be presented.

A summary of the number DLTs per cohort will be provided.

Serious adverse events will be listed and summarized in a similar manner to AEs.

12.3.2. Recommended Phase 2 Dose

The RP2D will be determined by the SRC after review of all safety and efficacy data available at the end of the Phase 1b portion of the study. The RP2D may be no higher than then MTD as traditionally determined in oncology studies (e.g., dose at which DLTs are seen in fewer than 33% of patients).

12.4. Analysis of the Secondary Endpoints

12.4.1. Pharmacokinetics (PK)

For all cohorts in Phase 1b and the Tablet cohort of Phase 2, the PK of VRx-3996 and valganciclovir will be summarized by descriptive statistics. For valganciclovir, PK analysis will be conducted on ganciclovir. Pharmacokinetic parameters will be estimated, where appropriate, by non-compartmental analysis using statistical computer packages as specified in the Statistical Analysis Plan. Graphic evaluation will be used for data analysis where appropriate. Pharmacokinetics and fit will be evaluated graphically, and by modeling if sufficient data are available.

Serial blood samples for PK analysis will be collected from all subjects at pre-specified timepoints. The following PK parameters of VRx-3996 and ganciclovir may be calculated but are not limited to:

- Area under the concentration-time curve from administration to time t ($AUC_{0\text{-}t}$)
- Area under the concentration-time curve from administration to infinity ($AUC_{0\text{-}\infty}$)
- Maximum concentration (C_{max})
- Time to maximum concentration (T_{max})
- terminal elimination half-life ($t_{½}$)
- Apparent volume of distribution (V_z/F)
- Apparent clearance (CL/F)

Individual elapsed sampling times will be used in the pharmacokinetic analysis. C_{max} and T_{max} will be obtained directly from the experimental observations. $AUC_{0\text{-}t}$ will be calculated using the linear trapezoidal rule.

$AUC_{0\text{-}\infty}$ will be calculated according to the following equation:

$$AUC_{0-\infty} = AUC_{0-t} + \left(\frac{C_{last}}{\lambda_Z}\right)$$

where the C_{last} is the last quantifiable concentration.

For the purpose of calculating $AUC_{0\text{-}t}$, when two consecutive plasma concentrations below the lower limit of quantification (LLOQ) are encountered after T_{max}, all subsequent values will be excluded from the analysis. When embedded missing values occur, they will be excluded from the analysis. Any quantifiable concentrations at pre-dose will be set to zero.

12.4.2. Time to Response, PFS, and OS

- Time to response (TTR): defined as the interval from the start of study drug treatment to the first documentation of CR or PR
- Progression free survival (PFS): defined as the interval from the start of study treatment to the first documented date of disease progression or death from any cause, whichever occurs first.
- Overall survival (OS): defined as the time from date of first study drug treatment to date of death, for any reason.

Kaplan Meier statistics will be used to display TTR, PFS and OS.

12.5. Analysis of Exploratory Endpoints

Analysis of all exploratory endpoints will be outlined in subsequent materials provided by the Sponsor.

12.6. Baseline Descriptive Statistics

The characteristics of all patients entered into the study will be summarized with descriptive statistics.

13. CLINICAL MONITORING

The clinical monitoring plan outlines the nature and frequency of site monitoring.

14. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Each participating site will develop source documents and maintain appropriate medical and research records for this study, in compliance with ICH E6 and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when permitted by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

15. QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented against data collected centrally. Missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Applicable procedures will follow written SOPs in compliance with the protocol, GCP, and the applicable regulatory requirements.

The investigational site will provide direct access to all study-related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor, and inspection by local and regulatory authorities.

16. ETHICS/PROTECTION OF HUMAN PATIENTS

16.1. Ethical Standard

The Investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Patients of Research codified in:

- US Code of Federal Regulations (CFR) applicable to clinical studies: 45 CFR Part 46, 21 CFR Parts 11, 50, 54, 56, 312
- ICH E6
- Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013)
- Applicable local legal and regulatory requirements

16.2. Institutional Review Board

Each participating institution must provide for the review and approval of this protocol and the associated informed consent documents on an annual basis and approve any recruitment material by an appropriate IRB or EC.

Protocol amendments require review and approval by the applicable IRB prior to implementation.

Changes to the ICF will be submitted to the appropriate IRB for review and approval.

At the time of any protocol amendment or change to the informed consent document, an assessment will be made regarding the need for re-consenting existing patients.

16.3. Patient and Data Confidentiality

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor.

The study patient's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study patient research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored by the Sponsor. This will not include the patient's contact or identifying information. Rather, individual patients and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Sponsor will be secured and password protected. At the end of the study, all study databases will be de-identified and archived by the Sponsor.

16.4. Research Use of Stored Human Samples, Specimens or Data

The Sponsor will be responsible for all stored samples generated during this study. Some samples will be stored with specific vendors as appropriate (e.g., PK samples). Samples and data will be stored using codes assigned by the clinical data system. Data will be kept in password-protected computers.

16.5. Future Use of Stored Specimens

Data collected for this study will be analyzed and stored by the Sponsor. After the study is completed, the de-identified, archived data will be maintained by the Sponsor and may be made available for use by other researchers including those outside of the study.

With the patient's approval and as approved by local IRBs, de-identified biological samples will be stored by the Sponsor with the same goal as the sharing of data with other researchers, some of whom may be outside of this study.

During the conduct of the study, an individual patient can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biological sample storage will not be possible after the study is completed.

17. DATA HANDLING AND RECORD KEEPING

17.1. Data Collection Responsibilities

The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

This study will utilize a 21 CFR Part 11-compliant data capture system provided by the Sponsor for the purposes of data collection. Specific instructions on the system used for data collection will be provided in the Study Manual. Clinical data will be entered directly from the source documents.

17.2. Study Records Retention

Study documents should be retained for a minimum of 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. These documents may be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

17.3. Publication and Data Sharing Policy

The Sponsor intends that the data from this study will be presented and published following completion of data analysis. This study is registered on clinicaltrials.gov by the Sponsor (NCT03397706), and the results will be reported per the International Committee of Medical Journal Editors (ICMJE) guidelines for clinical trial reporting (http://www.icmje.org/recommendations/). Authorship will be based upon the principles outlined in the ICJME guidelines (http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). As a broad guideline, to ensure representation of centers making substantial contributions to this study, centers enrolling at least 2 patients will be invited to suggest an investigator for publication co-authorship. Other contributors not meeting authorship criteria will be acknowledged individually should they agree. Data derived from the study are the exclusive property of the Sponsor.

The results of the study may be published or presented by the Investigator(s) following review and agreement by the Sponsor. Any publication or presentation of ancillary reports or local site outcome data must wait until the primary clinical publication is “in press”. The Sponsor reserves the right to withhold the presentation of confidential or proprietary information.

18. COVID-19 PANDEMIC

18.1. Introduction

The current pandemic caused by the COVID-19 virus has created, and will continue to cause, challenges to health care providers and institutions for the foreseeable future. These challenges may interfere with the conduct of clinical studies and may necessitate deviations from the approved clinical protocol. Viracta has considered the potential risks and benefits of completing this study. The study population comprises patients with a likely fatal outcome and a high unmet

medical need, and the Sponsor considers it appropriate to continue the study. However, patients must not be placed at an unacceptable risk and the critical scientific value of the study must be preserved. This section describes potential modifications to the protocol which will generally be considered as acceptable although planned changes must be discussed and agreed with the Sponsor.

The FDA has provided guidance to Industry, Investigators, and IRBs, entitled, "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Pandemic." (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/fda-guidance-conduct-clinical-trials-medical-products-during-covid-19-pandemic)

18.2. Protocol Modifications

If, due to the COVID-19 pandemic, the Investigator is unable to follow all protocol procedures or considers it against the best interest of the patient to complete all study required visits and procedures, the Investigator must develop a plan to ensure patient safety and to be as close as possible to compliance with study procedures to preserve the scientific integrity of the study.

This plan must be reviewed and agreed to by the Sponsor. The patient must be fully informed of these changes and information pertaining to how the patient was informed must be recorded in source documents. If appropriate, sites may formally document re-consent on an IRB-approved consent form or consent addendum to be provided and signed by the patient.

The following are considered acceptable modifications to the protocol after discussion and approval by the Sponsor:

- The acceptable window around scheduled visits may be adjusted on a patient-by-patient basis.
- For patients in a clinically stable condition after Cycle 1, visits may be reduced to no less frequently than once every 2 weeks, and after Cycle 4, to no less frequently than once every month. If alternate visit frequencies appear appropriate, the Investigator should discuss these with the Medical Monitor and obtain approval.
- Visits may be conducted virtually by telephone, Google, FaceTime, or another appropriate modality. Patient confidentiality must be maintained to the extent possible (see https://www.hhs.gov/hipaa/for-professionals/special-topics/emergency-preparedness/notification-enforcement-discretion-telehealth/index.html).
- For remote visits, laboratory tests may be conducted at a local facility; standard ranges from that laboratory must be appended to the results. Results corresponding to the visit must be entered into the eCRF. During these circumstances, it may be feasible to only collect safety laboratory tests (chemistry, hematology, and coagulation parameters)
- The patient should attend the study center at least once every 2 cycles for PET-CT assessment of disease status. A PET-CT scan at another center may be acceptable.
- Study drug required for 2 cycles may be dispensed to the patient. Alternatively, study drug may be shipped directly to a patient's home.

It is also recommended that any potential new study patient should be screened for COVID-19 symptoms and asked about travel within the past 21 days or contact with people likely to have placed them at risk of infection. If indicated and feasible, potential patients should be tested for the virus. Patients who are considered to be at a high risk of COVID-19 virus infection or to have confirmed infection, should not be enrolled per exclusion criterion #15.

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APPENDIX

Table 16: Conversions for ECOG and Karnofsky Grades[30]

Karnofsky Status	Karnofsky Grade	ECOG Grade	ECOG Status
Normal, no complaints	100	0	Fully active, able to carry on all pre-disease performance without restriction
Able to carry on normal activities. Minor signs or symptoms of disease	90	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Normal activity with effort	80	1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Care for self. Unable to carry on normal activity or to do active work	70	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires occasional assistance, but able to care for most of his needs	60	2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
Requires considerable assistance and frequent medical care	50	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Disabled. Requires special care and assistance	40	3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Severely disabled. Hospitalization indicated though death nonimminent	30	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Very sick. Hospitalization necessary. Active supportive treatment necessary	20	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Moribund	10	4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
Dead	0	5	Dead

Abbreviation: ECOG = Eastern Cooperative Oncology Group

Table 17: Established and Other Potentially Significant Drug Interactions with Ganciclovir*

Concomitant Drug	Change in the Concentration of Ganciclovir or Concomitant Drug	Increased monitoring required	Clinical Comment
Imipenem-cilastatin	Unknown	If required, only administer as inpatient with close monitoring for seizure activity	Risk of generalized seizures
Cyclosporine or amphotericin B	Unknown	Monitor serum creatinine at least twice weekly for first week, followed by monitoring every week thereafter	Risk of renal toxicity
Mycophenolate Mofetil (MMF)	No change in levels of ganciclovir or MMF in patients with normal renal function	Monitor serum creatinine and CBC at least twice weekly for first week, followed by monitoring every week thereafter	Risk for hematological and renal toxicity
Other drugs associated with myelosuppression or nephrotoxicity[1]	Unknown	Monitor serum creatinine and CBC at least twice weekly for first week, followed by monitoring every week thereafter	Risk for increased hematological and renal toxicity
Didanosine	No change in ganciclovir Increased didanosine	Serum amylase weekly for first month on combination, monthly thereafter	Monitor closely for didanosine toxicity (e.g., pancreatitis)
Probenecid	Increased ganciclovir	Monitor CBC at least twice weekly for first week, followed by monitoring every week thereafter	May require dose reduction of valganciclovir

Abbreviation: CBC = complete blood count

* *Adapted from Prescribing information for valganciclovir (Genentech 2017)*[31]

[1] adriamycin, dapsone, doxorubicin, flucytosine, hydroxyurea, pentamidine, tacrolimus, trimethoprim/sulfamethoxazole, vinblastine, vincristine, and zidovudine

Table 18a: Examples of Sensitive Substrates of CYP3A

Enzyme	Therapeutic
CYP3A	alfentanil, avanafil, buspirone, conivaptan, darifenacin, darunavir, ebastine, everolimus, ibrutinib, lomitapide, lovastatin, midazolam, naloxegol, nisoldipine, saquinavir, simvastatin, sirolimus, tacrolimus, tipranavir, triazolam, vardenafil, budesonide, dasatinib, dronedarone, eletriptan, eplerenone, felodipine, indinavir, lurasidone, maraviroc, quetiapine, sildenafil, ticagrelor, tolvaptan

Abbreviation: CYP = cytochrome P450

Table 19b: Examples of Strong Inhibitors of P-gp and BCRP Transporters

Enzyme	Therapeutic
P-gp	amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil
BCRP	curcumin, cyclosporine A, eltrombopag

Abbreviations: BCRP Breast Cancer Resistance Protein = P-gp = P-glycoprotein