SUMMARY OF CHANGES

A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma

Version 4.0

NCI Protocol #: AMC-098
Local Protocol #: AMC-098

NCI Version Date: 08DEC2020
Protocol Date: 08DEC2020

I. Scientific and Substantive Changes:

#	Section	Comments
1.	4.5 5.1 5.1.2	The protocol was updated to clarify that participants who experience a cumulative dose delay of > 14 days throughout the course of the trial must discontinue study drug.
2.	7.2	Drug dispensing procedures have been revised to comply with Pfizer policy. Pharmacists are no longer permitted to break bottles and must dispense nelfinavir in the original container, destroying any nelfinavir removed from the bottle prior to dispensing. Additionally, pharmacists must only supply enough nelfinavir to last the participant until the subsequent study visit. Instructions for documenting dispensed nelfinavir via DARF have also been included, and requirements for US sites to complete a separate DARF documenting drug accountability for each protocol using nelfinavir has been removed as sites are permitted document using a single DARF. In addition, locally sourced supplies of FDA-approved Viracept® (nelfinavir mesylate) 625 mg tablets may be sourced by the clinical site and reimbursed by the AMC with prior approval from the AMC ODMC, as permitted by the AMC Executive Committee.
3.	8.1.12.2 Appendix X	Prolonged storage in formalin may affect biopsy tissue specimen viability and result in the inability to perform immunohistochemistry (IHC) studies. To ensure specimen viability, the protocol has been updated to require that tissue for ICH studies be processed locally to a FFPE block and shipped at ambient temperature to the AMC Biorepository. Centers are instructed to refer to the MOP for processing requirements. If the previously submitted baseline tissue samples are inadequate to perform IHC studies, 6 additional slides from the diagnostic punch biopsy will be requested.
4.	8.4.1	The window for post-treatment follow up has been revised to permit evaluations earlier than 8 weeks post treatment discontinuation, if in the

#	Section	Comments
		opinion of the treating investigator the participant needs to begin alternative therapy sooner. All participants must complete the follow up evaluations prior to starting alternative therapy.
5.	9.0	This section has been revised to allow CTEP-registered physician investigators and CTEP-registered advanced practice clinicians who are non-physician investigators (i.e., NP or PA) to perform toxicity assessment per local licensure requirements. Delegation of these tasks must be recorded on the institution's AMC delegation of task log (DTL) or local equivalent.
6.	Appendix XI	Sulfamethoxazole and trimethoprim (Bactrim) have been removed from Appendix XI as drugs that may potentially interact with nelfinavir, as there is limited scientific evidence suggesting potential interactions. Clinically, Bactrim and nelfinavir are often taken concurrently when nelfinavir is the primary ART regimen.

II. Administrative and Editorial Changes:

#	Section	Comments
7.	Global	Version number and version date has been updated from v3.0 / 13FEB2019 to v4.0 / 08DEC2020.
8.	Global	Grammar and spelling have been updated throughout.
9.	Title Page	CTEP IVR numbers have been added for the chairs/co-chairs.
10.	Protocol Roster	The protocol roster has been updated to accurately reflect investigator qualifications, credentials, address/contact information, and titles. In addition, amipm@emmes.com has replaced amcpm@emmes.com as the contact email for AMC ODMC.
11.	Protocol Schema 10.1	Phrasing that the study will need to enroll 18 HIV positive and 18 HIV negative participants to achieve sufficient power when completing the primary analysis has been removed from Section 10.1. and the protocol schema has been revised to indicate approximately 18 participants HIV positive and 18 HIV negative participants will be enrolled. These updates were made for consistency throughout the protocol as the enrollment of 18 HIV positive and 18 HIV negative participants is the enrollment goal (see "Population" under the Protocol Synopsis).
12.	2.4.2	Protocol references to the Michelle Rudek Lab have been replaced with the AMC core lab title, the AMC Pharmacology Core Lab at Johns Hopkins University (Lab PI: Michelle Rudek).
13.	3.1.2	Eligibility requirements for documenting HIV-1 negative status have

#	Section	Comments
		been clarified. A negative result on any of the nationally approved tests (including rapid tests) is sufficient to satisfy inclusion the criterion.
14.	3.5	This section has been updated to reflect that enrollment is now open to international centers, provided that the site satisfies all regulatory and site activation requirements.
15.	List of Abbreviations 8.1.10 8.2.5 8.3.1.3 8.4.1.3 Appendix I	The individual chemistry tests required throughout the course of the study (based on a typical U.S. chemistry panel) and timepoints for collection were clarified. CBCs and chemistries performed for eligibility must be completed within 4 weeks prior to enrollment, while baseline/screening chemistries must be collected within 4 weeks prior to starting treatment. Select chemistries have been added to the List of Abbreviations.
16.	8.1.12.3 8.2.8.3	Blood collections for PK analysis have been removed from the baseline/screening evaluations, as the first timepoint of collection is included in the during treatment evaluations per Section 8.2.8.3 and Appendix II.
17.	8.2.8.3 Appendix II Appendix IX	Added clarification that blood collection for PKs may occur within 3 days before dose administration (i.e., - 3 day window), and listed the cycle numbers corresponding to the study week.
18.	8.3.1.2 8.4.1.2	The requirement that KS tumor assessments must be completed at each study visit (every 2 weeks) and at the early treatment discontinuation and follow-up visits has been clarified. Because there is only one early treatment discontinuation visit and one follow-up visit, KS response assessment will only be completed once for each timepoint.
19.	12.4 12.5	CTEP registration procedures for the investigator, research associate, and for site participation have been added to align with the CTEP template and to require that the AMC DTL must be updated contemporaneously as personnel are added or removed and/or study roles and delegated tasks change. Changes must be approved by the CI, and documented by his/her initials and date, before they are implemented.
20.	Appendix II	Specimen handling instructions for IHC studies has been replaced with a reference/link to Appendix X.
21.	Appendix VI	The AMC Data and Safety Monitoring plan was updated from version 6.0 to the current version (9.0). Key revisions include the addition of an introduction to address the variety of systems the AMC uses for individual trials, changes to the data entry systems used by some AMC trials (OPEN/Rave), participation with NCI CIRB for new AMC protocols, procedures for data reporting, administrative changes

#	Section	Comments
		(updates to document organization, external links, and group terminology), and to state that the IRB review plan is identified in the protocol, as the AMC is opening international studies subject to review/requirements per their respective regions.
22.	Appendix VII	The study diary was reorganized for clarity. "Capsules" were updated to "tablets."
23.	Appendix X	This Appendix has been updated to indicate that RNA*later* for gene expression profiling may be sourced locally or provided by the AMC.

AIDS MALIGNANCY CONSORTIUM

AMC PROTOCOL #098

A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma

A Trial of the AIDS Malignancy Consortium (AMC)

Sponsored by:	National Cancer Institute Office of HIV and AIDS Malignancy (OHAM)
NCT Registration Number:	NCT03077451
Pharmaceutical Support Provided by:	Pfizer Inc. IND Status: Exempt
Commercially Available Agents:	Viracept® (nelfinavir mesylate) NSC #: 722664
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Version 4.0, 08DEC20202
NCI Version Date 08DEC2020

AMC PROTOCOL SIGNATURE PAGE

I, _____, Principal Investigator at site _____, agree to conduct and follow this protocol: **AMC Protocol # 098 – A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma (Version 4.0, 08DEC2020),** as written according to AMC, NCI, and FDA guidelines. I understand that no deviations from the protocol eligibility criteria or waivers for protocol deviations will be permitted.

_____ _____

PI Signature Date (DDMMMYYYY)

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PROTOCOL ROSTER

AMC Protocol # 098

A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma

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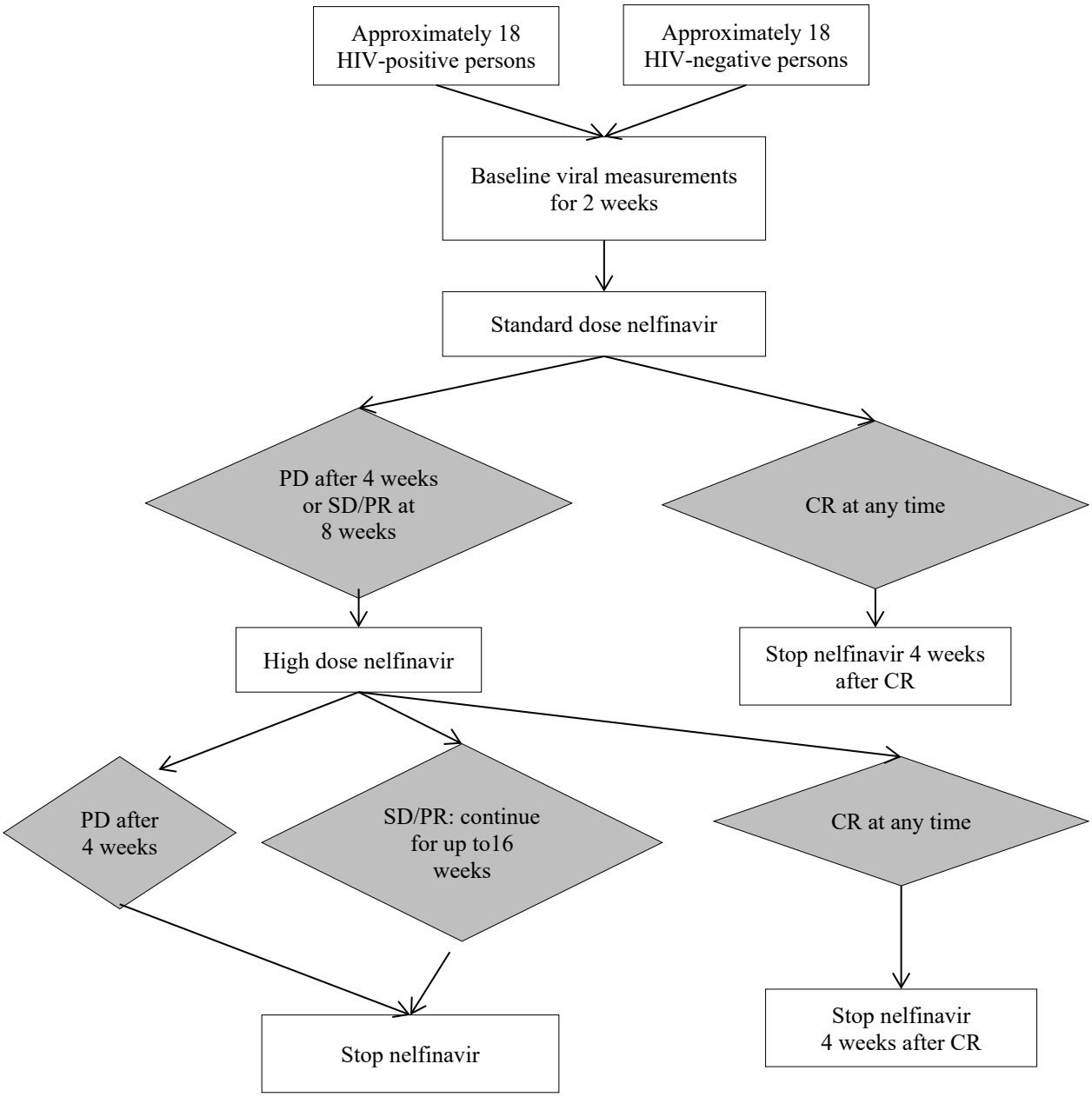
PROTOCOL SYNOPSIS

Title:	A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma
Phase of Study:	Phase II
Participating Institutions:	This protocol will be open to all AMC domestic member sites and AMC sub-Saharan Africa sites.
Accrual Target:	36 participants
Population:	Participants with Kaposi sarcoma (KS). Enrollment will target but will not be limited to 18 participants with HIV infection and 18 without HIV infection.
Regimen:	Nelfinavir 1250 mg twice daily for up to 8 weeks, followed by escalation to nelfinavir 3125 mg twice daily for up to 16 weeks (up to 24 weeks of treatment). Participants will be followed for up to 8 weeks following treatment discontinuation.
Anticipated Trial Duration:	Up to 3 years
Primary Objective:	To determine the efficacy of a therapeutic escalation strategy consisting of standard dose nelfinavir, followed by high dose nelfinavir, for the treatment of KS tumor lesions.
Secondary Objectives:	1. To evaluate the safety of high dose nelfinavir among participants with KS. 2. To assess the effect of nelfinavir on Kaposi sarcoma-associated herpesvirus (KSHV) lytic gene expression in tumor tissue. 3. To correlate nelfinavir and the primary active metabolite, M8, concentrations with tumor response, antiviral response, and adverse effects in participants with KS. 4. To assess the effect of nelfinavir on KSHV copy number in saliva.
Exploratory Objectives:	1. To assess the effect of nelfinavir on KSHV and Epstein-Barr virus (EBV) copy number in peripheral blood mononuclear cells (PBMC) and plasma. 2. To assess the effect of nelfinavir on herpes simplex virus (HSV), cytomegalovirus (CMV), and EBV copy number in saliva.

PROTOCOL SCHEMA



Standard dose nelfinavir, (1250 mg twice daily); high dose nelfinavir, (3125 mg twice daily); PD, progressive disease; CR, complete response; SD, stable disease; PR, partial response.

LIST OF ABBREVIATIONS

ACSR ..... AIDS and Cancer Specimen Resource
ACTG ..... AIDS Clinical Trials Group
AE ..... adverse event
AIDS ..... Acquired Immunodeficiency Syndrome
ALT (SGPT) ..... alanine transaminase
AMC ..... AIDS Malignancy Consortium
ART ..... antiretroviral therapy
AST (SGOT) ..... aspartate transaminase
AUC ..... area under the curve
BID ..... bis in die (twice a day)
BUN ..... blood urea nitrogen
CBC ..... complete blood count
CDC ..... Centers for Disease Control and Prevention
CDUS ..... Clinical Data Update System
CMV ..... cytomegalovirus
CO2 ..... carbon dioxide
CR ..... complete response
CRF ..... case report form
CTCAE ..... Common Terminology Criteria for Adverse Events
CTEP ..... Cancer Therapy Evaluation Program
CTEP-AERS ..... CTEP Adverse Event Reporting System
DARF ..... Drug Accountability Record Form
DHHS ..... Department of Health and Human Services
DLT ..... dose-limiting toxicity
DNA ..... deoxyribonucleic acid
DSMB ..... Data Safety Monitoring Board
EBV ..... Epstein-Barr Virus
EIACD ..... enzyme inducing anti-convulsant drug
EKG ..... electrocardiogram
ELISA ..... enzyme-linked immunosorbent assay
ER ..... endoplasmic reticulum
FIAU ..... fialuridine
FDA ..... Food and Drug Administration
GEE ..... generalized estimating equations
HD-NFV ..... high dose nelfinavir
HHV-8 ..... human herpesvirus-8
HIV ..... Human Immunodeficiency Virus
HSV ..... herpes simplex virus

IDB ..... Investigational Drug Branch
IHC ..... immunohistochemistry
IRB ..... institutional review board
KS ..... Kaposi sarcoma
KSHV ..... Kaposi sarcoma-associated herpesvirus
LANA ..... latency-associated nuclear antigen
MMP2 ..... matrix metalloprotease 2
MOP ..... manual of procedures
MTD ..... maximum tolerated dose
NCI ..... National Cancer Institute
NCT ..... National Clinical Trials [Registry]
NFV ..... nelfinavir
NIH ..... National Institutes of Health
NRTI ..... nucleoside/nucleotide reverse transcriptase inhibitor
NNRTI ..... non-nucleoside reverse transcriptase inhibitor
ODMC ..... Operations and Data Management Center
OHAM ..... Office of HIV AIDS Malignancy
PBMC ..... peripheral blood mononuclear cells
PD… ..... progressive disease
PI ..... protease inhibitor
PIO ..... Protocol Information Office
PK ..... pharmacokinetics
PR ..... partial response
qPCR ..... quantitative polymerase chain reaction
RNA ..... ribose nucleic acid
SAE ..... serious adverse event
SD ..... stable disease
SD-NFV ..... standard dose nelfinavir
SOC ..... system organ class
SOP ..... standard operating procedure
SUSAR ..... serious and unexpected suspected adverse drug reaction
ULN ..... upper limit of normal

1.0 OBJECTIVES

1.1 Primary Objective

To determine the efficacy of a therapeutic escalation strategy consisting of standard dose nelfinavir, followed by high dose nelfinavir, for the treatment of Kaposi sarcoma tumor lesions.

1.2 Secondary Objectives

1.2.1 To evaluate the safety of high dose nelfinavir among participants with KS.

1.2.2 To assess the effect of nelfinavir on KSHV lytic gene expression in tumor tissue.

1.2.3 To correlate nelfinavir and the primary active metabolite, M8, concentrations with tumor response, antiviral response, and adverse effects in participants with KS.

1.2.4 To assess the effect of nelfinavir on KSHV copy number in saliva.

1.3 Exploratory Objectives

1.3.1 To assess the effect of nelfinavir on KSHV and EBV copy number in PBMC and plasma.

1.3.2 To assess the effect of nelfinavir on HSV, CMV, and EBV copy number in saliva.

2.0 BACKGROUND

2.1 Study Disease

Kaposi sarcoma is a vascular inflammatory tumor of endothelial origin caused by Kaposi sarcoma-associated herpesvirus, also known as human herpesvirus 8 (HHV-8)[1]. HIV infection and immunosuppression dramatically increase the risk of KS among people infected with KSHV. KS is the most common AIDS-defining malignancy. Due to in part to the low prevalence of KSHV infection, KS is rare among HIV-uninfected individuals in the U.S. However, in parts of East Africa where KSHV is endemic, KS is common among people with and without HIV infection[2]. Like all herpesviruses, HHV-8 infection of cells results in one of two discrete viral programs, latency and lytic replication.

During latent infection, few viral genes are expressed and the HHV-8 genome is maintained as an episome. KS tumor ("spindle") cells are predominately (~99%) latently infected with KSHV. However, a portion of spindle cells undergo lytic replication and produce virions[3-5]. Most infected cell types in culture display a progressive loss of the HHV-8 episomal genome within 5-10 divisions in the absence of genetic selection or reinfection[6], such that the KSHV genome is eventually lost from most spindle cell lines isolated from KS lesions[7-9]. This indicates that persistence of KSHV within KS tumors requires ongoing lytic replication and infection of new cells[6]. In addition, numerous lytic viral gene products detected in KS tumors appear central to KS pathogenesis. Proteins expressed by spindle cells during lytic replication directly or indirectly mediate several aspects of KS pathogenesis; including inflammation (vGPCR, vIL-6, K15), angiogenesis (vIL-6, vGPCR, K1, vCCL1, vCCL2), cell growth (vIL-6, vGPCR, K1), and inhibition of apoptosis (vCCL1, vCCL2, vBcl2, vIRF1, K1), among others[10, 11]. Of note, lytically infected cells are destroyed, and thus, their effects in KS lesions should be limited to either increasing the number of infected cells or paracrine effects of lytic viral gene products.

KSHV DNA is detected more frequently and at higher copy numbers in blood of KS patients compared to controls with asymptomatic KSHV infection[12-15]. A large proportion of KSHV DNA in plasma is encapsidated in virions[14, 16], indicating an association between KS and systemic viral replication and dissemination. KSHV viremia appears to be in the causal pathway for KS, rather than a consequence, since KSHV viremia predicts subsequent KS in cohorts of asymptomatic people with KSHV and Human Immunodeficiency Virus (HIV) co-infection[17, 18]. In addition, ganciclovir, which inhibits KSHV lytic replication, prevents incident KS (see below). Therefore, inhibiting KSHV replication may interfere with KS progression.

A large number of drugs that block herpesvirus DNA synthesis have been reported to inhibit HHV-8 replication[19-23]. Of these agents, ganciclovir (or its oral pro-drug valganciclovir) is the only one proven to either suppress HHV-8 replication *in vivo* or prevent the development of KS in randomized trials. In a randomized, placebo-controlled, cross-over trial, valganciclovir was shown to reduce HHV-8 oral shedding frequency by 46% and quantity by 0.44 log copies/mL[24]. In a randomized trial, Ganciclovir treatment of cytomegalovirus retinitis in HIV-infected patients statistically significantly reduced the incidence of KS by 75% when given orally and 93% when given intravenously compared to intraocular treatment alone[25]. Numerous observational studies have also suggested that ganciclovir and foscarnet, but not acyclovir, may prevent KS[26-29]. The efficacy of antivirals

for the treatment, as opposed to prevention, of KS is less clear. Case reports have suggested that cidofovir or foscarnet may have improved KS treatment outcomes[30-32]. However, data from small observational studies did not indicate better KS outcomes with inhibitors of HHV-8 DNA synthesis[33,34]. Furthermore, the largest trial of cidofovir to date, which included seven patients with KS, found no apparent effect on progression or HHV-8 viremia[35].

2.2 Study Agent

2.2.1 Nelfinavir mesylate (Viracept®)

Nelfinavir is an orally administered aspartyl-protease inhibitor (PI) approved for the treatment of HIV. More recently off-target effects have led investigators to repurpose nelfinavir as a potential anticancer agent[36-38]. Several early phase clinical trials have resulted. In a phase I dose escalation trial in lung cancer, nelfinavir was studied in combination with combination chemotherapy (cisplatin and etoposide)/radiation therapy[39]. Two dose levels were studied, 625 mg bis in die (BID [twice daily]) and 1250 mg BID. No dose limiting toxicities (DLTs) were seen at either dose level and there was no grade 3 or 4 diarrhea reported.

In a National Cancer Institute (NCI) phase I trial in participants with refractory solid tumors, 3125 mg BID was found to be the maximum tolerated dose (MTD)[40]. The 3125 mg BID dosing leads to plasma levels of 18 μM. Some participants have continued this dose level for more than 18 months. In contrast to the early experiences with nelfinavir in the United States, in which secretory diarrhea was identified as a common adverse effect[41], diarrhea was unusual in this study[40]. Additionally, there were no cumulative toxicities noted, and no participants developed greater than grade 2 changes in lipids or fasting glucose, despite 11 participants receiving the MTD of 3125 mg BID for a median of 6.6 months. Two of three participants receiving 3750 mg BID of nelfinavir experienced grade 4 neutropenia, but the drug was well tolerated at other doses. It should also be noted that in previous HIV treatment trials of nelfinavir in Sub-Saharan Africa, the frequency with which diarrhea was reported ranged from 2-11% and did not require discontinuation of treatment[42-45]. While non-linearity in the pharmacokinetics was noted at doses above 1875 mg, greater than 50% of the patients at 3125 mg had higher maximal (Cmax) and total area under the curve (AUC) exposure compared with the 1875 mg dose.

In another phase I study of nelfinavir, for liposarcoma, there were no DLTs at the highest evaluated dose of 4250 mg BID[46]. In that study, episodes of diarrhea occurred in a minority of courses, all episodes were mild, and were not associated with higher nelfinavir doses. However, there was no measurable increase (and perhaps a slight decrease) in the peak plasma levels of nelfinavir or the primary active metabolite, M8, between 3000 mg BID and 4250 mg BID, suggesting that higher levels may not be achievable, perhaps due to autoinduction of metabolism[46]. Therefore, in this trial of nelfinavir for KS, we will cap the high dose at 3125 mg BID and obtain trough levels to account for the potentially large variability in nelfinavir exposure.

2.3 Study Design and Rationale

The off-target effects of nelfinavir are highly relevant for KS[47]. Several studies show that nelfinavir can inhibit PI3K/Akt signaling and induce endoplasmic reticulum (ER) stress with activation of the unfolded protein response[38, 48-50]. In addition, antiangiogenic effects of nelfinavir are well documented, including down regulating hypoxia-inducible factor 1 alpha (HIF-1-α), VEGF and matrix metalloprotease 2 (MMP2) activity, and inhibition of STAT3 signaling and of γ-secretase activity[50,51]. Nelfinavir has activity against a broad range of cancer cell lines and in animal models[36,37]. These diverse tumors include liposarcoma[52,53], multiple myeloma[48], primary effusion lymphoma and Burkitt lymphoma. All of these activities suggest the possibility of a direct antitumor effect in KS.

In addition, nelfinavir both reactivates lytic KSHV gene expression and inhibits production of infectious KSHV *in vitro*. Consistent with activation of the unfolded protein response, nelfinavir activates KSHV lytic gene expression[54]. Activation of viral lytic gene expression might directly result in tumor cell killing as viral replication activates DNA damage pathways and apoptosis or might lead to increased viral antigen expression and increased susceptibility to immune killing. Although viral lytic gene expression is induced in latently infected cells, nelfinavir potently blocks *in vitro* production of infectious KSHV, and other herpesviruses, at concentrations that are achieved in plasma of patients after oral administration[55]. Thus, we hypothesize that nelfinavir will decrease measurable viral loads. Protease inhibitor-based antiretroviral therapy (ART) has recently been shown to decrease shedding of KSHV, though this study was not able to demonstrate a superior effect of nelfinavir compared with other PIs[56]. In herpes simplex virus 1 (HSV-1), nelfinavir prevents envelopment and release of mature virus from infected cells[54,57], suggesting that that nelfinavir may act similarly against KSHV. Although initial induction of KSHV lytic gene expression by nelfinavir might theoretically cause transient exacerbation of KS, which we will monitor for, we expect that the combination of antitumor and antiviral activities will result in KS responses.

Proposals to evaluate the effects of nelfinavir on KSHV infection and KS in HIV-infected individuals have focused on the potential confounding by the antiretroviral activity of nelfinavir; even with adjustment for HIV viral load and CD4 counts, any effect of nelfinavir might still be due to enhanced control of HIV infection. By including participants with KS but without HIV, we have the ability to definitively examine the direct clinical antitumor and antiviral effects of nelfinavir, which may provide valuable clinical information regarding the treatment of KS in HIV-negative individuals, as well as those who are HIV-infected. Additionally, because all prior studies in reducing incident KS or treating KS with PIs have focused on ART-naïve persons, it is difficult to compare studies of persons receiving modern highly-active ART regimens, that do or do not include PIs, directly for their effects on KS and KSHV, because it is known that PIs provide more rapid virologic and immunologic responses than triple nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) regimens or non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens (unclear vs. recently utilized integrase inhibitors). Therefore, in this study, we propose to add nelfinavir to stable complete ART regimens in HIV-infected persons and in HIV-negative KS participants, in order to remove the HIV virologic and immunologic confounding implied in PI use. This is distinct from modern trials, which evaluate cytotoxic chemotherapy plus ART-initiation in previously ART-naïve persons. Thus, we expect we

may see less robust responses in persons with stable disease (SD) despite ongoing ART usage[58-60]. Comparable trials of novel agents, such as valproic acid or VEGF inhibitors in persons already on stable ART at enrollment, showed much smaller effect sizes between 20-30%[61-64].

The proposed trial is based on the hypothesis that nelfinavir might be repurposed as an anticancer agent, and that among all cancers that might be targeted, the effects of nelfinavir on Akt signaling, angiogenesis pathways, viral gene expression, and infectious virion production seem almost tailored to the treatment of KS. And, save for (likely undue) concerns about diarrhea, the side effect profile is gentler than for any of the approved treatments (paclitaxel, liposomal doxorubicin) or those presently being investigated by the AMC (bortezomib, lenalidomide). Therefore, we propose to evaluate a treatment strategy of nelfinavir in AIDS-associated and in HIV-negative KS participants to determine tumor response and virologic suppression. The strategy starts with standard dose (1250 mg BID) nelfinavir to determine whether KS patients may demonstrate a tumor response and to determine the antiviral activity of the FDA-approved regimen. Those participants with tumor progression or no response to standard dose nelfinavir will receive high dose (3125 mg BID) nelfinavir therapy, which has been found to be well tolerated in clinical trials of cancer patients. In addition to tumor and virologic outcomes, these participants will be assessed for the possibility of bone marrow suppression and other toxicities that can occur with nelfinavir, especially in combination with a full ART regimen.

Clinical tumor responses would pave the way for further evaluation of nelfinavir alone as an antitumor agent. Given the possibility of activation of viral lytic gene expression, evaluation of the combination of nelfinavir with an agent such as ganciclovir or fialuridine (FIAU) that would kill infected cells might be pursued. This study will evaluate the safety and efficacy of nelfinavir to treat KS. Furthermore, findings regarding the tumor and virologic response in participants may provide valuable insights into KS pathogenesis and the mechanism(s) of action of nelfinavir, which may translate into knowledge to guide therapy of KS worldwide. Finally, if nelfinavir was found to have an antiviral effect on KSHV *in vivo*, the drug may play a role in strategies to prevent the development of KS among persons deemed to be at high risk.

High-Dose Safety Review

As outlined in Section 3.5, the first three domestic participants on high-dose nelfinavir treatment were evaluated for safety on November 29, 2017. In accordance with the protocol, the Protocol Chair, AMC Medical Monitor, and Protocol Statistician participated in this review, along with the protocol co-chairs. All participants experienced grade 2 or 3 diarrhea; however, several participants continued treatment during the AE and did not report diarrhea until the next visit, and the providers continued treatment with appropriate medical management in some cases without holding the dose for resolution to grade 1. No other grade 3 adverse events were reported among these participants. Available relevant safety data for the other three domestic participants on high-dose nelfinavir was also reviewed and did not reflect significant toxicity. The safety review team agreed that the safety data for AMC-098 does not reflect significant toxicities or toxicity that requires supportive care exceeding capabilities of the international sites, and that the protocol stopping rule for safety had not been exceeded. The protocol team's recommendation to

proceed with enrollment at Sub-Saharan African AMC sites remains contingent upon site satisfaction of all regulatory and site activation requirements.

2.4 Correlative Studies

Additional details and methods are provided in Appendix II, Appendix IX, and Appendix X.

2.4.1 Assessment of the effect of nelfinavir on KSHV lytic gene expression in tumor tissue.

As described in Section 2.1, KSHV lytic gene expression may contribute to tumor development and progression. We hypothesize that nelfinavir will decrease lytic gene expression in tumors. This will be ascertained by whole genome mRNA profiling at the AMC Genomics Core and immunohistochemistry (IHC) on a subset of viral proteins at the AMC Pathology Core Laboratory.

2.4.2 Correlation of nelfinavir and the primary active metabolite, M8, concentrations with tumor response, antiviral response, and adverse effects in participants with KS.

The pharmacokinetics (PK) of nelfinavir are non-linear and show considerable inter-patient variability. We hypothesize that higher drug levels will be associated with tumor response, as well as lower levels of viral lytic gene expression in tumors (Section 2.4.1) and KSHV copy number in saliva, PBMC, and plasma (Sections 2.4.3 and 2.4.4). Because nelfinavir is metabolized by CYP3A and CYP2C19, genotyping will be performed to identify predictors of nelfinavir levels and response to treatment. Nelfinavir/M8 concentrations will be performed at the AMC Pharmacology Core Lab at Johns Hopkins University and genotyping will be performed at the AMC Genomics Core by targeted sequencing.

2.4.3 Assessment of the effect of nelfinavir on KSHV copy number in saliva.

KSHV lytic replication is common in the oropharynx[15] and decreases with active antiviral treatment[24]. As such, KSHV copy number will be measured in saliva using quantitative polymerase chain reaction (qPCR) as a convenient estimate of antiviral activity. KSHV qPCR will be conducted at the AMC Genomics Core Laboratory.

2.4.4. Exploratory: Assessment of the effect of nelfinavir on KSHV and EBV copy number in PBMC and plasma; and HSV, CMV, and EBV viral load in saliva.

KSHV replication in blood may be a more relevant predictor of response to nelfinavir than oral replication. As such, qPCR may be used to measure KSHV in stored PBMC and plasma from participants. EBV viral load will also be evaluated in these samples.

Additionally, HSV, CMV, and EBV viral load will be assessed in saliva at the AMC Virology Core. KSHV qPCR for plasma and PBMC viral load will be performed at the AMC Virology Core.

PBMC/Plasma viremia: Because KSHV can reactivate sporadically, and viremia is not always persistent in persons with KS (present on median of 20% of days in endemic KS and on 67% of days in HIV-associated KS in Uganda[1] the more

samples obtained, the more stability and precision in estimates. Therefore, we would like to obtain 2 samples pre-treatment and 8 samples on treatment. The timing of those samples is not important in a Poisson mixed effects model, so we are basing the timing on feasibility. For example, 2 samples can be achieved through weekly sampling during the 4 weeks pre-treatment. Eight samples on treatment can be obtained twice monthly in order to coordinate the blood draw schedule with clinical/tumor assessment visits and safety lab blood draws, which will also occur on this schedule (safety labs monthly but coordinated with bi-weekly visits); this will reduce burden on participant and maximize study resources. Effect of the study drug on KSHV replication is an important outcome of this study.

3.0 PARTICIPANT SELECTION

A rostered AMC investigator (CTEP-registered physician investigator) must document that each protocol participant meets all stated eligibility criteria. Participating sites must have documentation that each eligibility requirement is satisfied prior to participant enrollment. In compliance with CTEP policy, no exceptions to eligibility criteria will be granted under any circumstance.

NOTE: Institutions may use this section of the protocol as an eligibility checklist for source documentation if it has been reviewed, signed, and dated before registration/randomization by the study investigator. If used as source documentation, this checklist must be printed, the investigator must check each item to document their assessment that the participant meets each eligibility criterion, and the completed checklist must be maintained in the participant's chart.

Participant ID Number: 098 - ___ ___ ___ - ___ ___ ___ ___ ___

Patient's Initials (F, M (optional), L): ___ ___ ___

3.1 Eligibility Criteria

__ 3.1.1 Biopsy-proven KS involving skin (with or without visceral involvement) without need for urgent cytotoxic therapy. There should be no evidence of improvement in KS in the 4 weeks immediately prior to study enrollment and treatment.

__ 3.1.2 Known HIV-1 infection status, as documented by any nationally approved, licensed HIV rapid test performed in conjunction with screening (or enzyme-linked immunosorbent assay [ELISA] test kit) and confirmed by an approved test at each study site[1].

U.S. participants only: Alternatively, this documentation may include a record demonstrating that another physician has documented the participant's HIV status based on either:

1. Approved diagnostic tests, or
2. The referring physician's written record that HIV infection was documented, with supporting information on the participant's relevant medical history and/or current management of HIV infection.

Participants enrolled outside the U.S. must have a confirmatory diagnostic test sequence as appropriate per national standards, detailed as above, performed regardless of prior documented HIV status.

[1] NOTE: The term "licensed" refers to a U.S. FDA-approved kit or for sites located in countries other than the United States, a kit that has been certified or licensed by an oversight body within that country and validated internally.

WHO (World Health Organization) and CDC (Centers for Disease Control and Prevention) guidelines mandate that confirmation of the initial test result must use a test that is different from the one used for the initial assessment. A reactive initial rapid test should be confirmed by either another type of rapid assay or an E/CIA that is based on a different antigen preparation and/or different test principle (e.g., indirect versus competitive), or a Western blot or a plasma HIV-1 RNA viral load.

For HIV-negative participants, a negative result must be documented by any one of the nationally approved or licensed tests, including rapid tests, and must be performed no more than 4 weeks before enrolling to the treatment segment

__ 3.1.3 Participant may be either previously untreated for KS or refractory to or intolerant of any one or more prior KS therapies.

__ 3.1.4 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of high dose nelfinavir in participants < 18 years of age, children are excluded from this study.

__ 3.1.5 ECOG performance status ≤ 2 (Karnofsky ≥ 50%, see Appendix III).

__ 3.1.6 Life expectancy of greater than 3 months as assessed by the investigator.

__ 3.1.7 Participants must have organ and marrow function within the following parameters (within 4 weeks before enrolling for study treatment):

- Leukocytes: ≥ 3,000/mm^3
- Absolute neutrophil count: ≥ 1,500/mm^3
- Platelets: ≥ 100,000/mm^3
- Total bilirubin: within normal limits at each study site local laboratory
- AST (SGOT) / ALT (SGPT): ≤ 2.5 X institutional upper limit of normal (ULN)
- Creatinine:
  - Creatinine levels ≤ upper limit of institutional normal; or
  - Creatinine clearance ≥ 60 mL/min/1.73 m^2 for participants with serum creatinine levels above institutional normal.

__ 3.1.8 HIV seropositive participants must be on ART with the following criteria:

- A complete ART regimen that adheres to the current DHHS Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (https://aidsinfo.nih.gov/guidelines/html/1/adult-and-adolescent-arv/0) or any co-formulated combination that is FDA approved for the treatment of HIV. See Section 3.2.5 for details regarding eligible antiretroviral drugs.
- The ART regimen must not include PIs (including nelfinavir); participants must not have received a PI-based regimen for at least 4 weeks prior to study enrollment.
- Modification of ART regimen limited to eligible antiretroviral drugs while on study is allowable.
- Participants must either have an undetectable HIV plasma RNA, or if plasma RNA detectable, it must be decreasing while on the same stable regimen for a minimum of 12 weeks prior to study enrollment.
- No evidence of incomplete virologic response or virologic failure (two consecutive HIV RNA levels ≥ 200 copies/mL after 24 weeks on a stable regimen or after achieving an undetectable viral load) within 12 weeks before

study enrollment.

__ 3.1.9 The effects of high dose nelfinavir on the developing human fetus are unknown. For this reason, women of child-bearing potential must agree to use adequate contraception (barrier or other non-hormonal method of birth control, or abstinence) prior to study enrollment and for the duration of study participation. Hormonal contraception alone is contraindicated for pregnancy prevention in this study due to potential loss of efficacy from drug interactions with nelfinavir. Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform her treating physician immediately.

__ 3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

Participants who do not fulfill the criteria as listed in Section 3.1 above, are ineligible. Additionally, the presence of any of the following conditions will exclude a participant from study enrollment:

__ 3.2.1 Participants who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin-C) prior to study enrollment or those who have not recovered from adverse events due to agents administered more than 4 weeks prior to study enrollment.

__ 3.2.2 Participants who are receiving any other investigational agents.

__ 3.2.3 Participants with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.

__ 3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nelfinavir.

__ 3.2.5 Participants receiving any medications or substances that have antiviral activity against KSHV or that are strong inhibitors or inducers of CYP3A or 2C19 are ineligible. Nelfinavir (NFV) also inhibits CYP3A4 and therefore sensitive substrates should be avoided. Of the antiretroviral drugs, only delaviridine, nevirapine, cobicistat-boosted antiretrovirals (strong CYP3A4 inhibitor), maraviroc (sensitive CYP3A4 substrate), and protease inhibitors (strong CYP3A4 inhibitor) are excluded. For women of child-bearing potential, hormonal contraception is permitted if the participant agrees to use barrier or non-hormonal methods of birth control or abstinence prior to enrollment and for the duration of the study, due to the effect of nelfinavir on contraceptive effectiveness. The following drugs are also prohibited:

Strong Inhibitors of CYP3A4:

- Antibiotics: clarithromycin, erythromycin, telithromycin, troleandomycin
- HIV: non-nucleoside reverse transcriptase inhibitors (delaviridine, nevirapine), protease inhibitors (ritonavir, indinavir, lopinavir/ritonavir, saquinavir),

cobicistat-boosted antiretrovirals (e.g., elvitegravir). **NOTE:** Clinical trials have demonstrated that there are no clinically significant drug-drug interactions between nelfinavir and the following antiretrovirals: efavirenz (strong CYP3A4 inhibitor), etravirine (strong CYP3A4 inhibitor). Therefore, these antiretrovirals will not be excluded.

- Antifungals: itraconzaole, ketoconazole, voriconazole, fluconazole, posaconazole
- Antidepressants: nefazodone
- Antidiuretic: conivaptan
- GI: cimetidine, aprepitant
- Hepatitis C: boceprevir, telaprevir
- Miscellaneous: Seville oranges, grapefruit, or grapefruit juice and/or pummelos, star fruit, exotic citrus fruits, or grapefruit hybrids

Strong Inducers of CYP3A4:

- Glucocorticoids: cortisone (> 50 mg), hydrocortisone (> 40 mg), prednisone (> 10 mg), methylprednisolone (> 8 mg), dexamethasone (> 1.5 mg)
- Anticonvulsants: phenytoin, carbamazepine, primidone, phenobarbital and other enzyme inducing anti-convulsant drugs (EIACD)
- Antibiotics: rifampin (rifampicin), rifabutin, rifapentine
- Miscellaneous: St. John's Wort, modafinil

Strong Inhibitors of CYP2C19:

- Antifungals: fluconazole

Strong Inducers of CYP2C19:

- Antibiotics: rifampin (rifampicin)

Lists including medications and substances known or with the potential to interact with the CYP3A or 2C19, isoenzymes are provided in Appendix XI.

Drugs with KSHV antiviral activity:

- Participants receiving any medications or substances that may interfere with KSHV replication are ineligible.

Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated list such as http://medicine.iupui.edu/clinpharm/ddis. Medical reference texts such as the Physicians' Desk Reference may also provide this information. Sites are encouraged to contact Michelle Rudek with any questions regarding eligible ART regimens.

As part of the enrollment/informed consent procedures, the participant will be counseled on the risk of interactions with other agents, and what to do if new

medications need to be prescribed or if the participant is considering a new over-the-counter medicine or herbal product.

Lists including medications and substances known or with the potential to interfere with KSHV replication, are provided in Appendix XII.

__ 3.2.6 Uncontrolled intercurrent illness including, but not limited to, hepatitis C infection requiring treatment during the study, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that in the opinion of the investigator would limit compliance with study requirements.

__ 3.2.7 Pregnant women are excluded from this study because nelfinavir is a Pregnancy Category B agent that has not been studied at high doses in pregnant women. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with high dose nelfinavir, breastfeeding should be discontinued if the mother is treated with high dose nelfinavir.

__ 3.2.8 Chronic diarrhea as defined by loose or watery stools occurring more than 3 times daily at baseline lasting more than 4 weeks or not abating on condition-appropriate therapy prior to study enrollment.

__ 3.2.9 Participant is < 2 years free of another primary malignancy. Exceptions include basal cell skin cancer, Stage 0-I squamous cell cancer of the skin, cervical carcinoma in situ, anal carcinoma in situ.

__ 3.2.10 Use of systemic corticosteroid therapy (except for replacement doses of glucocorticoid and/or mineralocorticoid for adrenal insufficiency). Inhaled or intranasal corticosteroids for allergic or bronchospastic conditions are permitted.

Physician Signature: _____ Date: _____

(Optional unless this section is used as an eligibility checklist)

3.3 Number of Participants to be Enrolled

3.3.1 Proposed sample size

This study will enroll a minimum of 3 participants and a maximum of 36 participants (planned enrollment of 18 participants with HIV infection and 18 participants without HIV infection).

3.3.2 Accrual rate

Approximately 1-2 participants per month.

3.4 Participant Enrollment Procedures

Sites must have this protocol approved by their Institutional Review Boards (IRB) and be registered for study participation with the AIDS Malignancy Consortium (AMC) Operations and Data Management Center (ODMC) before they may enroll participants. Enrollment and data collection will occur via Advantage eClinical.

3.4.1 Registration for screening

After an informed consent form has been signed by the participant and the protocol-

specific eligibility checklist for Segment A has been completed, the participant must be registered for screening (AMC-098, Segment A, Screening Enrollment) on-line via Advantage eClinical. After successful registration into screening, the participant will receive an eleven-digit participant ID and will then enter the screening process (screening and pre-entry visits). A system generated confirmation email will be sent to the enroller upon successful completion of the participant enrollment into Segment A. If the on-line system is inaccessible, the site should notify the AMC ODMC (via email at amcpm@emmes.com or via phone at 301-251-1161) for further instructions.

3.4.2 Enrollment

After the screening evaluations have been obtained and the participant is determined to be eligible, the participating site will enroll the participant into AMC-098 Segment B (Treatment Enrollment) on-line via Advantage eClinical. Enrollment into Segment B should occur no more than 1 week prior to administration of the first dose of the protocol agent (enrollment 1 day prior to or on the day of treatment is strongly encouraged).

Participants must be enrolled into AMC-098 Segment B (Treatment Enrollment) prior to receiving the first dose of the protocol agent.

3.5 Enrollment at International Sites

Enrollment is open at all sub-Saharan Africa AMC international sites contingent upon site satisfaction of all regulatory and site activation requirements.

4.0 TREATMENT PLAN

4.1 Agent Administration

The protocol agent will be administered on an outpatient basis. A cycle is 2 weeks of continuous treatment (+/- 3 days according to timing of study visit/evaluations within window). Reported adverse events and potential risks for nelfinavir are described in Section 6.0. Appropriate dose modifications for nelfinavir are described in Section 5.0. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

All participants will initiate protocol treatment with nelfinavir 1250 mg BID continuously for up to 8 weeks, and then, depending on response at the standard dose, advance to high dose nelfinavir at 3125 mg BID continuously (i.e., intrapatient dose escalation) for up to 16 weeks (up to 24 weeks of treatment).

NOTES: The participant will be requested to maintain a medication diary of each dose of medication (See Appendix VII). The medication diary will be returned to clinic staff at the end of each cycle (every two-week study visit).

The site will be required to document study agent return by participant in source documents. Non-compliance with study agent administration should be noted at the time of diary collection and the participant should be instructed again regarding dosing instructions.

Dose delays and modifications for participants experiencing toxicity are described in Section 5.0. Due to the known food-effects on the bioavailability of nelfinavir, clinical staff will provide nutritional counseling for agent administration to ensure that the participant is aware the drug must be consumed with a moderately-high fat meal, to increase absorption and decrease pharmacokinetic variability, and that acidic foods/fruit juices are avoided at time of administration.

Treatment intensification will depend on the response at each treatment level:

4.1.1 Standard dose nelfinavir (1250 mg BID)

- Each participant must be observed for a minimum period of at least 4 weeks on standard dose nelfinavir before escalation to the high dose nelfinavir treatment level.
- If after 4 weeks there is progressive disease (PD), the participant will advance to the high dose nelfinavir level.
- If by 8 weeks there is stable disease (SD) or partial response (PR) at the standard dose, the participant will advance to the high dose level.
- If there is complete response (CR) at any time at the standard dose level, nelfinavir will be discontinued 4 weeks after documentation of complete response.
- Because dosing of study drug is continuous both during and between cycles, care should be taken to avoid study drug interruption. Therefore, if the study visit/study evaluations occur within the +/- 3 day visit window, the appropriate

amount of drug should be provided at that visit for the study interval (i.e., if the study visit occurs 3 days before the 14th day of the cycle, the sufficient drug should be provided to prevent to last 17 days, or until the date of next scheduled visit)

4.1.2 High dose nelfinavir (3125 mg BID)

- High dose nelfinavir treatment will be continued for at least 4 weeks.
- If there is progressive disease (PD) documented after 4 weeks at the high dose level, nelfinavir will be discontinued.
- If there is stable disease (SD) or partial response (PR) at the high dose level, high dose nelfinavir will be continued for up to 16 weeks.
- If there is a complete response (CR), high dose treatment will be discontinued 4 weeks after documentation of complete response.

4.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of nelfinavir with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. A patient drug information and wallet card for potential drug-interactions will be provided to participants (See Appendix XIV). The site Principal Investigator should be alerted if the participant is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes. Questions regarding ART regimens may be directed to Michelle Rudek. Appendix XI presents guidelines for identifying medications/substances that could potentially interact with the study agent.

Antiretroviral therapy is required for HIV-infected participants, with the stipulations detailed in Section 3.1.8. Participants may not have received a PI for at least 4 weeks prior to enrollment. Management of HIV will be left to the discretion of the investigator. Modification of antiretroviral therapy to eligible antiretroviral drugs is allowed after study entry and will be made at the discretion of the investigators. Any changes to antiretroviral therapy must be documented in the case report form (CRF).

4.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for a minimum of 8 weeks as per Section 4.1 or until one of the following criteria in Section 4.5 applies.

4.4 Duration of Follow Up

All participants will be followed for 8 weeks after removal from study or until death, whichever occurs first. Participants removed from study for unacceptable adverse event(s) (see Section 4.5) will be followed until resolution or stabilization of the adverse event(s).

4.5 Criteria for Removal from Treatment

Participants will be removed from study treatment according to the criteria listed in Section 5.0. The reason for study treatment removal and the date the participant was removed must be documented in the Case Report Form in Advantage eClinical.

- Disease progression after 4 weeks on high dose nelfinavir;
- Rapid progression of disease that is deemed to be life-threatening;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Participant decides to withdraw from the study;
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the investigator;
- Participants who become pregnant or need to breast-feed;
- The Investigator has the right to remove participants from the study for clinical reasons which he/she believes are life threatening to the participant even if such reasons do not fall into the toxicity classifications discussed in Section 5.0;
- Participants requiring a cumulative delay of > 2 weeks (i.e., across cycles) or, participants requiring > two dose reduction (i.e., requiring reduction to < 1875 mg BID) throughout the duration of the study.

5.0 DOSING DELAYS/DOSE MODIFICATIONS

5.1 Dose Modifications for Nelfinavir

There will be no dosage modifications for participants receiving standard dose nelfinavir (1250 mg BID) as this dose is currently FDA approved for treatment of HIV infection and has been studied extensively in Phase I-IV studies, with clinical experience over the last two decades[65-67].

If at any time during administration of standard dose nelfinavir (1250 mg BID) the participant experiences an adverse event at a severity (grade) that requires dose interruptions per the tables below, study treatment will be terminated.

Unless noted otherwise for a specific event, if at any time during administration of high dose nelfinavir (3125 mg BID) the participant experiences an adverse event grade that requires dose interruptions per the tables below, study drug will be held until the event resolves or improves to the specified grade, and then reduced by 625 mg BID (at 2500 mg BID) and continued as above unless the adverse event recurs, in which case the dose is reduced by another 625 mg to a minimum of 1875 mg BID if required. If the participant experiences an adverse event on high dose nelfinavir that does not resolve or improve to the specified grade after reducing the dose to 1875 mg BID, study treatment will be terminated.

If any participant requires a cumulative treatment delay of > 2 weeks throughout the duration of the study (i.e. total across cycles), then the participant must discontinue study treatment.

5.1.1 Table of Nelfinavir Dose Levels and Number of Tablets

Dose Level	Nelfinavir Dose	Number of 625 mg Tablets
1 (Standard Dose)	1250 mg, BID	2 tablets BID
2	1875 mg, BID	3 tablets BID
3	2500 mg BID	4 tablets BID
4 (High Dose)	3125 mg, BID	5 tablets BID

5.1.2 Tables of adverse events, and indications for dose modifications and management

The AEs and corresponding severity definitions below are as classified in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, as required in protocol Section 6.0.

Event Name	Nausea	
Grade of Event	**Management/Next Dose for Standard Dose-Nelfinavir**	**Management/Next Dose for High Dose-Nelfinavir**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a cumulative delay of > 2 weeks should go off protocol therapy. **Participants requiring > two dose reductions should go off protocol therapy.		
Recommended management: antiemetics.		

Event Name	Vomiting	
Grade of Event	**Management/Next Dose for Standard Dose-Nelfinavir**	**Management/Next Dose for High Dose-Nelfinavir**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at same dose level.	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a cumulative delay of > 2 weeks shall go off protocol therapy. **Participants requiring > two dose reductions shall go off protocol therapy.		
Recommended management: antiemetics.		

Event Name	Diarrhea	
Grade of Event	**Management/Next Dose for Standard Dose-Nelfinavir**	**Management/Next Dose for High Dose-Nelfinavir**
≤ Grade 1	No change in dose	No change in dose
Grade 2 considered tolerable or easily managed	Add supportive care as indicated. No change in dose.	Add supportive care as indicated. No change in dose.
Grade 2 considered intolerable to participant or deemed unacceptable in the investigator's judgment	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 2 if tolerable, or ≤ Grade 1 if considered intolerable at Grade 2. Resume at same dose level.	Hold* until ≤ Grade 2 if tolerable, or ≤ Grade 1 if considered intolerable at Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a cumulative delay of >2 weeks shall go off protocol therapy. **Participants requiring > two dose reductions shall go off protocol therapy.		
Recommended management: loperamide antidiarrheal therapy. Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours). Adjunct anti-diarrheal therapy is permitted and shall be recorded when used.		

Event Name	Neutropenia	
Grade of Event	**Management/Next Dose for Standard Dose-Nelfinavir**	**Management/Next Dose for High Dose-Nelfinavir**
≤ Grade 1	No change in dose	No change in dose
Grade 2	No change in dose	No change in dose

Event Name	Neutropenia	
Grade of Event	**Management/Next Dose for Standard Dose-Nelfinavir**	**Management/Next Dose for High Dose-Nelfinavir**
Grade 3	Hold* until ≤ Grade 2. Resume at same dose level.	Hold* until ≤ Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a cumulative delay of > 2 weeks shall go off protocol therapy. **Participants requiring > two dose reductions shall go off protocol therapy.		

Event Name	Thrombocytopenia	
Grade of Event	**Management/Next Dose for Standard Dose-Nelfinavir**	**Management/Next Dose for High Dose-Nelfinavir**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol therapy	Off protocol therapy
*Participants requiring a cumulative delay of > 2 weeks shall go off protocol therapy. **Participants requiring > two dose reductions shall go off protocol therapy.		

6.0 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 6.1) and the characteristics of an observed AE (Section 6.2) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (via CTEP-AERS) **in addition** to routine reporting.

CTEP-registered physician investigators and CTEP-registered advanced practice clinicians who are non-physician investigators (i.e.,, NP or PA) may perform toxicity assessment per local licensure requirements.

The CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5.0 of the CTCAE is identified and located on the CTEP website at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

All appropriate treatment areas should have access to a copy of the CTEP Version 5.0 of CTCAE.

This study will be monitored by the Clinical Data Update System (CDUS). Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

6.1 Comprehensive Adverse Events and Potential Risks Lists

6.1.1 Adverse event list for nelfinavir

Agent not supplied by CTEP: Refer to Section 7.0 or the Viracept® package insert(s) for the comprehensive list of adverse events.

Listed below are adverse events occurring in > 2% of participants receiving standard dose nelfinavir (Viracept®).

- Diarrhea
- Nausea
- Flatulence
- Rash

With high dose nelfinavir, neutropenia has been observed.

6.2 Classification of AEs by Severity and Relationship to Study Drug Administration

6.2.1 Adverse Event: Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite).

6.2.2 Life-threatening Adverse Event: Any AE that places the participant or participant, in view of the Investigator, at immediate risk of death from the reaction.

6.2.3 Serious Adverse Event (SAE): Any AE occurring at any dose that results in any of the following outcomes: Death, a life-threatening AE, inpatient hospitalization or

prolongation of existing hospitalization, a persistent or significant disability/ incapacity, or a congenital anomaly/birth defect.

6.2.4 Please note for hospitalization – All hospitalizations (or prolongation of existing hospitalization) for medical events equivalent to CTCAE Grade 3, 4, 5 must be reported regardless of the requirements for Phase of study, expected or unexpected, and attribution. For example, do not report an admission for pharmacokinetic sampling, but do report an admission for a myocardial infarction.

6.2.5 Toxicity: Toxicity is a term NOT clearly defined by regulatory organizations. Toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to investigational treatment. To minimize confusion the NCI would recommend that the term toxicity NOT be utilized for AE reporting purposes. The CTCAE continues to use the term 'toxicity' because of familiarity.

6.2.6 Unexpected Adverse Event: Any AE that is not listed in available sources including the package insert, the Investigator's Brochure, or the protocol.

6.2.7 CTEP Adverse Event Reporting System (CTEP-AERS): An electronic system for expedited submission of AE reports.

6.2.8 Attribution: The determination of whether an AE is related to a medical treatment or procedure. Attribution categories:

Definite – The AE is clearly related to the investigational agent.
Probable – The AE is likely related to the investigational agent.
Possible – The AE may be related to the investigational agent.
Unlikely – The AE is doubtfully related to the investigational agent.
Unrelated – The AE is clearly NOT related to the investigational agent.

6.3 Expedited Adverse Event Reporting

6.3.1 Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov). These requirements are briefly outlined in the table below (Section 6.3.3).

A 24-hour notification is to be made to AMC ODMC by telephone at 301-251-1161, only when Internet connectivity is disrupted. Once Internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

6.3.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

6.3.3 Expedited reporting guidelines

Use the NCI protocol number and the protocol-specific participant ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "General disorders and administration site conditions – Disease Progression."** Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Expedited Reporting Requirements for Adverse Events that Occur in a Non-IND/IDE trial within 30 Days of the Last Administration of a Commercial Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the participant or participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs.	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs.	Not required		10 Calendar Days	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 5 calendar days for:
All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

Grade 3 adverse events

[2] For studies using PET or SPECT agents, the AE reporting period is limited to 10 radioactive half-lives, rounded

UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.
Effective Date: May 5, 2011

6.3.4 Additional protocol-specific expedited adverse event reporting exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 6.4):

CTCAE SOC	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization
Gastrointestinal Disorders	Nausea	≤ 2	Prolongation of Hospitalization
Gastrointestinal Disorders	Diarrhea	≤ 2	Prolongation of Hospitalization
Gastrointestinal Disorders	Vomiting	≤ 2	Prolongation of Hospitalization
*AEs considered with an attribution to NFV of possible or greater			

6.3.5 For Uganda Cancer Institute Only: SAE reporting to the Ugandan National Drug Authority

Once the trial is opened in Uganda, this protocol will also comply with the National Drug Authority's requirements for safety reporting.

The requirement for the investigator to notify the sponsor of any serious adverse event that occurs in a participant during a clinical trial will occur via Adverse Event form in Advantage eClinical (see Section 6.4), which will include any suspected unexpected serious adverse reactions.

The sponsor shall, within seven days of becoming aware, report to the Authority and the Uganda National Council of Science and Technology or an institution authorized to receive the report by the Uganda National Council of Science and Technology, any suspected unexpected serious adverse reactions.

Where urgent safety measures are taken to protect the participants against any immediate hazard to the health or safety of trial participants due to participation in this investigation, the sponsor shall within three working days from the date the safety measures are taken, give written notice to the Authority of the measures taken and the circumstances that give rise to the measures.

6.3.6 SAE reporting to Pfizer Inc.

The following incidents will be reported to Pfizer Inc. within 24 hours of the AMC ODMC's awareness, in accordance with the agent supply agreement:

- All deaths
- Non-fatal SAEs in reporting period assessed as related to nelfinavir and unexpected
- Related SAEs that occur after the reporting period

- Exposure during pregnancy or lactation, occupational exposure, or lack of effect

As the manufacturer of the agent, Pfizer will be responsible for reporting any serious and unexpected suspected adverse drug reactions (SUSAR) to the FDA in accordance with 21 CFR 314.80.

6.4 Routine Adverse Event Reporting

All adverse events must be reported in routine study data submissions. AEs reported through CTEP-AERS must also be reported in routine study data submissions. All SAEs must be entered in an Adverse Event form within 24 hours of the investigator's awareness.

In assessing laboratory results, an abnormal laboratory value will be considered clinically significant if it is characterized by one or more of the following criteria:

1. Is judged by the investigator to have a causal relationship to the investigational agent
2. Requires clinical intervention or monitoring, such as: close observation, more frequent follow-up assessments, further diagnostic intervention, treatment/therapeutic intervention, or protocol therapy dose modification
3. Is associated with clinical signs or symptoms, which may suggest a disease and/or organ toxicity, or may represent a new condition or worsening of a baseline condition
4. Is associated with a serious adverse event, or is otherwise judged by the Investigator to be of significant clinical impact

Laboratory results that are proven erroneous by repeat testing will not be considered clinically significant.

In general, a laboratory abnormality that is not clinically significant will be consistent with CTCAE grade 1 (mild) or 2 (moderate) severity, as categorized by the relevant severity description in the Investigations System Organ Class (SOC) or Metabolism and Nutrition Disorders SOC. Investigators may not designate laboratory abnormalities that are consistent with grade 3 or greater severity as not clinically significant.

All laboratory values deemed clinically significant will be subsequently reported as AEs unless the result is a sign of a clinical diagnosis that is reported as an AE. For example, clinically relevant laboratory results for electrolyte abnormalities would not require separate reporting as AEs if they are signs of a clinical diagnosis and reported AE for dehydration.

6.5 Secondary Malignancy

Not relevant for nelfinavir.

6.6 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine adverse event reporting.

7.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 6.1.

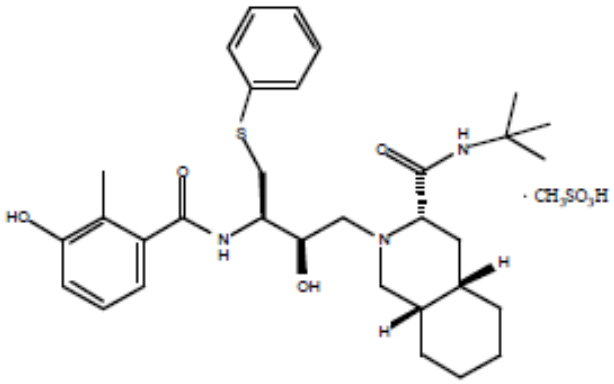
7.1 Nelfinavir (Viracept®, nelfinavir mesylate)

[NOTE: Please refer to the commercial package insert for more information.]

7.1.1 Other Names: Viracept®; 159989-64-7; VRX496; UNII-HO3OGH5D7.

The chemical name for nelfinavir mesylate is

[3*S*-[2(2*S**, 3*S**), 3α, 4aβ, 8aβ]]-*N*-(1, 1-dimethylethyl)decahydro-2-[2-hydroxy-3-[(3-hydroxy2-methylbenzoyl)amino]-4-(phenylthio)butyl]-3-isoquinoline carboxamide monomethanesulfonate (salt) and the molecular weight is 663.90 (567.79 as the free base).



7.1.2 Classification: human immunodeficiency virus (HIV-1) protease inhibitor.

7.1.3 Mode of action

Nelfinavir is an inhibitor of the HIV-1 protease. Inhibition of the viral protease prevents cleavage of the *gag* and *gag-pol* polyprotein resulting in the production of immature, non-infectious virus. Nelfinavir also has activity against a number of tumor types and herpesvirus replication *in vitro* (see Section 2.2.1).

7.1.4 Ingredients

Nelfinavir tablets are available for oral administration as a white oval tablet with a clear film coating in 625 mg strength (as nelfinavir free base).

Each tablet contains the following common inactive ingredients: calcium silicate, crospovidone, magnesium stearate, hypromellose, and triacetin. In addition, the 625 mg tablet contains colloidal silicon dioxide.

7.1.5 Storage and stability

Nelfinavir tablets and should be stored at 15° to 30°C (59° to 86°F) away from sources of heat and moisture. **Keep container tightly closed.**

7.1.6 Dose specifics and administration

Nelfinavir should be taken with a meal. Participants unable to swallow the 625 mg tablets should dissolve the tablets in a small amount of water. Once dissolved, participants should mix the cloudy liquid well, and consume it immediately. The glass should be rinsed with water and the rinse swallowed to ensure the entire dose is consumed.

7.1.7 Preparation: 625 mg tablets.

7.1.8 Route of administration: Oral

7.1.9 Incompatibilities: Not applicable (oral).

7.1.10 Availability: VIRACEPT® (nelfinavir mesylate) 625 mg: White oval tablet with a clear film coating engraved with "V" on one side and "625" on the other. Bottles of 120 (625 mg) tablets – NDC 63010-027-70 VIRACEPT® (nelfinavir mesylate).

7.1.11 Side Effects: Most common adverse reactions (≥ 2%) of moderate or severe intensity in adults and adolescents (13 years and older) are diarrhea, nausea, rash, and flatulence.

Adverse events occurring in less than 2% of participants receiving VIRACEPT® in all phase II and III clinical trials and considered at least possibly related or of unknown relationship to treatment and of at least moderate severity are listed below.

Body as a Whole: abdominal pain, accidental injury, allergic reaction, asthenia, back pain, fever, headache, malaise, pain, and redistribution/accumulation of body fat.

Digestive System: anorexia, dyspepsia, epigastric pain, gastrointestinal bleeding, hepatitis, mouth ulceration, pancreatitis, and vomiting.

Hemic/Lymphatic System: anemia, leukopenia, and thrombocytopenia.

Metabolic/Nutritional System: increases in alkaline phosphatase, amylase, creatine phosphokinase, lactic dehydrogenase, SGOT, SGPT, and gamma-glutamyl transpeptidase; hyperlipemia, hyperuricemia, hyperglycemia, hypoglycemia, dehydration, and liver function tests abnormal.

Musculoskeletal System: arthralgia, arthritis, cramps, myalgia, myasthenia, and myopathy.

Nervous System: anxiety, depression, dizziness, emotional lability, hyperkinesia, insomnia, migraine, paresthesia, seizures, sleep disorder, somnolence, and suicide ideation.

Respiratory System: dyspnea, pharyngitis, rhinitis, and sinusitis.

Skin/Appendages: dermatitis, folliculitis, fungal dermatitis, maculopapular rash, pruritus, sweating, and urticaria.

Special Senses: acute iritis and eye disorder.

Urogenital System: kidney calculus, sexual dysfunction, and urine abnormality.

The following adverse reactions have been identified during post-approval use of VIRACEPT®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Body as a Whole: hypersensitivity reactions (including bronchospasm, moderate to severe rash, fever, and edema).

Cardiovascular System: QTc prolongation, torsades de pointes.

Digestive System: jaundice.

Metabolic/Nutritional System: bilirubinemia, metabolic acidosis.

7.1.12 Nursing Implications: Women receiving high dose nelfinavir should not breastfeed.

7.1.13 References: PubChem: Open Chemistry Database; VIRACEPT® Highlights of Prescribing Information (ViiV Healthcare Company, updated 05/2013)

7.2 Drug Orders, Transfers, Returns, and Accountability

Nelfinavir mesylate is being supplied by Pfizer, Inc. for this trial. Locally-sourced supplies of a FDA-approved Viracept (nelfinavir mesylate) 625 mg tablets may be sourced by the clinical site and reimbursed by the AMC with prior approval from the AMC Operations and Data Management Center. The principal investigator (or his/her authorized designee) at each study site will request study agent from the AMC's vendor for study agent distribution. International sites must consult the Manual of Procedures for drug ordering instructions. Information and forms for ordering study agent will be maintained in the password-protected section of the AMC Operations website for protocol AMC-098 (www.AIDSCancer.org).

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Participants should be instructed to keep medication in its original container and stored at room temperature (15-30°C), away from heat and moisture. The site is responsible for the destruction of study agent returned by study participants according to local procedures.

The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all drugs received using the NCI Drug Accountability Record Form (Oral DARF) (available on the CTEP home page (http://ctep.cancer.gov) or contacting the Pharmaceutical Management Branch by email at **pmbafterhours@mail.nih.gov**). The DARFs document the drug delivery date to the site, inventory at the site, use by each study participant, and disposal of the drug (if applicable). A site-specific accountability record, either manual or electronic, may be used if it includes all the information required on the NCI Investigational Drug Accountability Record and if the paper printout is identical to the NCI accountability record. Institutional pharmacists must only supply participants enough study drug to last until their subsequent study visit (i.e., no extra study drug should be given. The pharmacist must dispense nelfinavir in the original container. The nelfinavir removed from the bottle prior to dispensing should be destroyed according to local policy. Pharmacists must log the number of capsules being dispensed on the first line of the oral DARF. On the next line, record the number of capsules wasted and connect the two lines with a bracket (either '{' or '[') outside of the table on

the left side.

8.0 CLINICAL AND LABORATORY EVALUATIONS

Schedules shown in the Study Calendar below are provided in Appendix I.

8.1 Screening/Baseline Evaluations

Baseline evaluations (including scans and x-rays) are to be conducted within 4 weeks prior to study enrollment into Segment B (Treatment Enrollment), unless otherwise specified below.

8.1.1 Recording of demographics, medical history, history of Centers for Disease Control and Prevention (CDC) HIV risk group and AIDS defining illnesses, physical examination (including vital signs, height, and weight), nutrition assessment, ECOG or KPS score, assessment of KS sign and symptoms, and medication review.

8.1.2 Diagnostic KS biopsy if not previously done at any time (can be the same biopsy collected for immunohistochemistry correlative studies). Any biopsy report is sufficient for the domestic sites; participants at the international sites require diagnosis by the AMC-approved pathologist identified for that site.

8.1.3 Tumor assessments with photographic record must be performed prior to initiating treatment. These may be performed on Day 0, but no earlier than 7 days before initiating study treatment. Tumor assessments and photographs should be performed as outlined in the Kaposi's Sarcoma (KS) Tumor Assessment Manual of Procedures (MOP).

8.1.4 Staging criteria (to be done within 4 weeks prior to study enrollment): KS staging will be based on the modified AIDS Clinical Trials Group (ACTG) Oncology Committee Staging Criteria as outlined in the KS Tumor Assessment MOP.

8.1.5 HIV serology if negative or not previously done.

8.1.6 HIV plasma viral load, and CD4 count and percentage if HIV-positive.

8.1.7 Chest X-ray.

8.1.8 Pregnancy testing by beta-HCG if female of childbearing age. Repeat pregnancy testing required immediately prior to starting standard dose nelfinavir (on Day 0) if previously performed within the 4 weeks before Day 0.

8.1.9 Electrocardiogram (EKG).

8.1.10 Complete blood count (CBC) with differential and chemistries must be performed within 4 weeks before starting treatment. Chemistries include calcium, sodium, potassium, carbon dioxide (CO2), chloride, AST (SGOT)/ALT(SGPT), BUN, creatinine, direct and total bilirubin, fasting glucose, and triglycerides.

8.1.11 Optional donation to the AIDS and Cancer Specimen Resource (ACSR). (See Appendix V for ACSR Informed Consent Form and Appendix IV for ACSR Specimen Preparation and Shipping Instructions) (**for U.S. participants only**).

8.1.12 Correlative Studies (see Section 2.4, Appendix II, Appendix IX, and Appendix X)

8.1.12.1 Oral swabs for KSHV, HSV, EBV, and CMV qPCR collected on 14 separate days pre-treatment (14 samples total) between weeks -4 and 0. Sample collection will be performed between study visits and will be self-

collected by the participant and returned at the visit to the study clinician. See Appendix XIII for participant instructions for the oral swab collection. Training and any re-training provided to the participant must be documented in the participant's study record.

8.1.12.2 Baseline biopsies: two biopsy specimens will be obtained prior to initiating nelfinavir: one 3 mm KS biopsy for immunohistochemistry (collected in formalin) AND one 3 mm for viral gene expression arrays (collected in RNA*later*). For IHC, the same biopsy may be used for those participants that require a diagnostic KS biopsy for study entry (see Section 8.1.2). If biopsy specimens for ICH studies are deemed unusable or are inadequate to perform IHC studies, 6 additional slides from the diagnostic biopsy may be collected for analysis.

8.1.12.3 Blood (8.5 mL in a yellow top ACD tube) sample collected once per week during pre-treatment for a total of 2 samples for KSHV and EBV qPCR of PBMC and plasma. PBMC DNA from this sample will also be used for genotyping of CYP3A/CYP2C19 will be performed to assess nelfinavir/M8 metabolism/pharmacogenomics.

The timing of these samples is based on feasibility. For example, 2 samples can be achieved through weekly sampling in the 4 weeks pre-treatment.

8.1.13 Provide study drug, nutritional counseling, Participant Drug Information Handout and Wallet Card (Appendix XIV), Participant Instructions for Oral Swabs (Appendix XIII), and Participant Drug Diary (see Appendix VII). Nutritional counseling is required to ensure that participants are consuming nelfinavir with the appropriate foods. The site must query the participant regarding this information (open-ended questions are recommended) and capture the response in the source. The AMC-098 Documentation of Nutrition Assessment and Counseling source document provided on the AMC member's only website or an equivalent document may be used for this purpose.

8.2 Evaluations during Treatment

Efforts should be made to keep participants on the proper study visit schedule. Each study visit while on treatment may be conducted +/- 3 days from the evaluation schedule.

8.2.1 Medical history, physical exam (including vital signs and weight), medication review (adherence review), nutrition assessment, and assessment of KS sign and symptoms.

8.2.2 KS tumor response assessment with photographic documentation to be completed each visit, every 2 weeks as outlined in the KS Tumor Assessment MOP. Response of KS to treatment is described in Section 9.0.

A chest X-ray should be performed to evaluate tumor response only for participants with pulmonary KS or new pulmonary symptoms.

8.2.3 Pregnancy testing by beta-HCG if female of childbearing age immediately prior to starting high-dose nelfinavir.

8.2.4 HIV plasma viral load if HIV-positive every 8 weeks while on nelfinavir.

8.2.5 Complete blood count with differential and chemistries described in Section 8.1.10 every 4 weeks while on high dose nelfinavir.

8.2.6 Fasting glucose and triglycerides every 8 weeks while on high dose nelfinavir.

8.2.7 EKG 2 weeks after starting standard dose nelfinavir, and 2 weeks after starting high dose nelfinavir.

8.2.8 Correlative Studies (see Section 2.4, Appendix II, Appendix IX, and Appendix X)

8.2.8.1 Oral swabs for KSHV, HSV, EBV, and CMV, qPCR collected twice weekly for 7 weeks (14 samples) starting one week after initiation of high dose nelfinavir treatment. Sample collection between study visits will be self-collected by the participant. See Appendix XIII for participant instructions for the oral swab collection.

8.2.8.2 On-treatment biopsies

- Two weeks after initiating standard dose nelfinavir, two 3 mm KS biopsies will be obtained: one for immunohistochemistry (collected in formalin) AND one for viral gene expression arrays (collected in RNA*later*).
- Two weeks after initiating high dose nelfinavir, two 3 mm KS biopsies will be obtained: one for immunohistochemistry (collected in formalin) AND one for viral gene expression arrays (collected in RNA*later*).

8.2.8.3 Blood (6 mL in a lavender top EDTA tube) for assessment of nelfinavir/M8 concentrations (pharmacokinetics), prior to dosing at each study visit (every 2 weeks) while on treatment, starting on Week 1/cycle 1 through the completion of Week 15/cycle 9 (a total of 9 samples will be collected) A -3 day window is permitted.

8.2.8.4 Blood (8.5 mL in a yellow top ACD tube) sample collected at each clinic visit (every 2 weeks) while on high dose nelfinavir for KSHV and EBV qPCR of PBMC and plasma.

The timing of these samples is basing the timing on feasibility. The eight samples on treatment can be obtained twice monthly in order to coordinate the blood draw schedule with clinical/tumor assessment visits and safety lab blood draws, which will also occur on this schedule (safety labs monthly but coordinated with bi-weekly visits); this will reduce burden on participant and maximize study resources.

8.2.9 Provide study drug, nutritional counseling, Participant Instructions for Oral Swabs (one week after initiation of high dose nelfinavir, Appendix XIII), and Participant Drug Diary (see Appendix VII). Sufficient drug to provide continuous dosing between cycles/study visits should be provided as long as visits lie within the visit window.

8.3 Early Treatment Discontinuation Evaluations

8.3.1 Participants who discontinue protocol treatment for adverse events as outlined in Section 5.0 should have the following evaluations and laboratory tests within 7 days after discontinuation of nelfinavir:

8.3.1.1 Medical history, physical exam (including vital signs and weight), medication review (adherence review), nutrition assessment.

8.3.1.2 KS tumor assessment with photographic documentation as outlined in the KS Tumor Assessment MOP. Response of KS to treatment is described in Section 9.0.

A chest X-ray should be performed to evaluate tumor response only for participants with pulmonary KS or new pulmonary symptoms.

8.3.1.3 Complete blood count with differential, and chemistries as described in Section 8.1.10.

8.3.1.4 Fasting glucose and triglycerides.

8.3.1.5 HIV plasma viral load and CD4 count if HIV-positive.

8.4 Follow-up Evaluations

8.4.1 All participants will have the following evaluations and laboratory tests 8 weeks (± 7 days) after discontinuation of nelfinavir. Follow-up evaluations must occur before beginning alternative therapy. If in the opinion of the treating investigator the participant needs to begin alternative therapy prior to follow up, then the follow up visit may occur earlier than 8 weeks (± 7 days) after discontinuation of nelfinavir.

8.4.1.1 Medical history, physical exam (including vital signs and weight).

8.4.1.2 KS tumor assessment with photographic documentation as outlined in the KS Tumor Assessment MOP. Response of KS to treatment is described in Section 9.0.

A chest X-ray should be performed to evaluate tumor response only for participants with pulmonary KS or new pulmonary symptoms.

8.4.1.3 Complete blood count with differential, and chemistries as described in Section 8.1.10.

8.4.1.4 Fasting glucose and triglycerides.

8.4.1.5 HIV plasma viral load and CD4 count if HIV-positive.

8.5 Final Evaluations, Off Study

At the completion of all follow-up evaluations described in Section 8.4, the Off-Study Summary Form should be completed in Advantage eClinical.

8.5.1 Participants completing study per-protocol.

8.5.2 Participants who discontinue the study early.

9.0 MEASUREMENT OF EFFECT

For the purposes of this study, participants should be re-evaluated for response every 2 weeks. See Appendix I for the KS Tumor Assessment schedule.

CTEP-registered physician investigators and CTEP-registered advanced practice clinicians who are non-physician investigators (i.e., NP or PA) may perform toxicity and response assessment per local licensure requirements.

Evaluable for Toxicity: All participants will be evaluable for toxicity from the time of their first treatment with nelfinavir.

Evaluable for Objective Response: Only those participants who have measurable disease present at baseline and have received study drug will be considered evaluable for response.

Response status will be classified as complete response **(CR),** partial response **(PR)**, stable disease (**SD**), or progressive disease (**PD**).

9.1 Definition of Response

Response and progression will be evaluated in this study using the AIDS Clinical Trials Groups (ACTG) response criteria for Kaposi sarcoma.

9.1.1 Complete response: Complete response (CR) is defined as the absence of any detectable residual disease, including tumor-associated edema, persisting for at least 4 weeks. In participants with pigmented (brown or tan) macular skin lesions persist after apparent complete response, biopsy of at least one representative lesion is required in order to document the absence of malignant cells. In participants known to have had visceral disease, an assessment at restaging with appropriate endoscopic or radiographic procedures should be made.

9.1.2 Partial response (PR) is defined as no new lesions (skin or oral), or new visceral sites of involvement (or the appearance or worsening of tumor-associated edema or effusions); AND

- A 50% or greater decrease in the number of all previously existing lesions lasting for at least 4 weeks; OR
- Complete flattening of at least 50% of all previously raised lesions (i.e., 50% of all previously nodular or plaque-like lesion become macules); OR
- A 50% decrease in the sum of the products of the largest perpendicular diameters of the marker lesions.

Note: Participants with residual tumor-associated edema or effusion who otherwise meet the criteria for complete response will be classified as having a partial response.

9.1.3 Stable disease is defined as any response not meeting the criteria for CR, PR, or progressive disease.

9.1.4 Progressive disease (PD) is defined as follows:

For participants with ≤ 50 cutaneous lesions

- 25% increase in the sum of perpendicular diameters of the indicator lesions, OR

- ≥ 25% increase in the total lesion count, or a minimum of 5 new lesions, whichever is greater, OR
- ≥ 25% increase in the number of raised lesions (minimum of 5 new raised lesions if there are very few raised lesions, for example ≤ 8), whichever is greater.

Note: There are body sites where disease is particularly difficult to evaluate, and a few new lesions may be counted in spite of the fact that a participant is not actually progressing. For example, lesions of the foot, particularly those which are flat, are difficult to evaluate because their intensity may be variable based on how much edema is present, how much the person walked the day before, how long their feet have been in a dependent position prior to the physical exam, etc.

For participants with > 50 cutaneous lesions

- ≥ 25% increase in the sum of the perpendicular diameters of the indicator lesions, OR
- ≥ 25% increase in the total number of lesions in the prospectively defined anatomic sites containing representative numbers of lesions, OR
- A total of 5 new lesions in anatomic sites which were previously documented as having no evidence of cutaneous disease on the whole body diagram, OR
- ≥ 25% increase in the number of raised lesions (minimum of 5 raised lesions if there are very few raised lesions, for example < 8) whichever is greater. Photographic documentation of "gross" or significant progression, particularly in areas that were not being followed, will be of particular value.

In order to classify a response as PR, the participant must have at least a PR in either the cutaneous or noncutaneous sites of disease, and no evidence of progression as defined in the above criteria. In order to classify a response as a CR, the participant must have a CR in both the cutaneous (if applicable) and noncutaneous (if applicable) sites of disease, and no evidence of progression as defined by the above criteria.

9.1.5 Noncutaneous progression

Progressive disease includes new visceral sites of involvement or progression of visceral disease or the development of new or increasing tumor-associated edema or effusion lasting at least 1 week, which interferes with the participant's normal activities. Progressive visceral disease, for measurable and evaluable disease, should be analogous to non-KS response criteria.

9.1.6 Recurrent disease

Recurrent disease is defined as the appearance of tumor following documentation of a complete remission.

9.1.7 Time to response

Time to response is defined as time from the first dose of chemotherapy until

documentation of first response.

9.1.8 Time to progression

Time to progression is defined as time from initiation of chemotherapy to documentation of first progression.

9.1.9 Response duration

Response duration is defined as the time from first documentation of response to documentation of first progression.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Endpoints

Currently approved cytotoxic chemotherapy regimens result in a roughly 40% partial or complete response (total response) rate in persons who are not ART-naïve (who initiate ART and chemotherapy concurrently). Our hypothesis is that the dose-escalation regimen will result in at least a 20% improvement in PR or CR above the historically defined rate of spontaneous KS regression, which is 20%. We chose to evaluate a 20% improvement in total response rate because we felt that this would be both a clinically significant improvement and at least equivalent to current chemotherapy. Because NFV has many fewer toxicities and requires less monitoring, oral administration, and less cost and potential for better access compared to chemotherapy, a finding of at least equivalence could be considered an improvement over the standard-of-care. Because the cost and feasibility of using an all-oral NFV regimen in resource-limited settings would provide a significant implementation and access benefit over cytotoxic chemotherapy, we feel strongly that NFV should be proven similarly efficacious to current chemotherapy, rather than superior to it. Therefore, we have chosen a design with 90% power at a one-sided 10% significance level to test the hypothesis that 40% of participants receiving NFV at standard followed by high-dosing regimens will be able to attain PR or CR. The null hypothesis is that we will fail to detect a response superior to the rate of spontaneous tumor regression (20%). Participants from both the international and domestic protocol will contribute to the single analysis plan, which is based on HIV status and not site of recruitment.

Primary objective

To determine the efficacy of a therapeutic escalation strategy consisting of standard dose nelfinavir, followed by high dose nelfinavir, for the treatment of Kaposi sarcoma (KS) tumor lesions. The binomial proportion and its exact 95% confidence interval will be used to estimate the response rate in the study. With 36 evaluable participants, the null hypothesis will be rejected if 11 or more participants respond. Response rates will be estimated using the binomial proportion and its exact 95% confidence interval separately for HIV positive and HIV negative participants.

Secondary objectives

- To evaluate the safety of high dose nelfinavir among participants with KS.
- The frequency of adverse events and their severity will be tabulated to evaluate tolerance of high dose NFV in the treatment of KS in both HIV-negative and HIV-positive participants.
- To correlate nelfinavir and the primary active metabolite, M8, concentrations with tumor response, antiviral response, and adverse effects in participants with KS. Trough nelfinavir/M8 concentrations will be summarized using descriptive statistics and 95% confidence intervals. This outcome will also be displayed graphically as a trend in drug levels over time. The relationship between dose and drug exposure of nelfinavir/M8 and the pharmacodynamic effects will be determined using Pearson's correlation coefficient (r^2) or appropriate non-parametric statistics for dichotomous and categorical variables (e.g., Mann–Whitney U-test or Kruskal-Wallis analysis of variance by ranks).

- To assess the effect of nelfinavir on KSHV lytic gene expression in tumor tissue. Descriptive statistics will be used for changes in the relative abundance of all latent and lytic viral mRNA relative to cellular mRNA by expression array, and changes in the percentage of cells staining for K8.1 (lytic) and LANA (latency-associated nuclear antigen) antigens by immunohistochemistry. Generalized estimating equations will be used to evaluate these changes over time. Normalizing transformations will be used as needed.
- To assess the effect of nelfinavir on KSHV copy number in saliva. Prior studies demonstrate stability of estimates of herpesvirus shedding rate in mucosal swabs with 14 or more samples. Therefore, pre-treatment oral samples and oral samples during treatment will be collected from each participant. The sampling frequency is irrelevant as long as the quantity is sufficient. With 36 participants, a decrease in the proportion of participants with detectable KSHV DNA from 50% at baseline to 1% on treatment can be detected at the one-sided 0.05 significance level with 0.99 power using McNemar's test.
- K8.1 will be measured by immunohistochemistry. A study participant's K8.1 expression will be considered to have increased with treatment if the percentage of cells with K8.1 staining is at least 20% and has increased at least 50% from baseline measures. With 36 study participants, the null hypothesis that the proportion of study participants who demonstrate an increase is 1% and can be tested against the alternative that it is 20% or greater at the one-sided significance level of 0.10 with power of 0.92 using the exact test for a single proportion (REF: Chernick MR, Liu CY: The saw-toothed behavior of power versus sample size and software solutions: single binomial proportion using exact methods. The American Statistician 56: 149-155, 2002.) Thus, the proportion of study participants who demonstrate an increase in K8.1 expression will be estimated using the binomial proportion and its exact 95% confidence interval.

Exploratory objectives

- To assess the effect of nelfinavir on KSHV and EBV copy number in PBMC and plasma.
- To assess the effect of nelfinavir on HSV, CMV, and EBV in saliva.
- KSHV detection in plasma (viremia) and oral shedding will be calculated at baseline and on NFV treatment. An analysis will also be performed for shedding of HSV, CMV, and EBV. Kaplan-Meier curves will also be created to demonstrate percent of participants demonstrating the presence of each of the above viruses in blood and saliva as a function of time and stage of treatment. For each herpesvirus and source of samples (oral or plasma), the following analyses will be done:
- McNemar's chi-square test will be used to evaluate the detection of the herpesvirus prior to treatment and during treatment.
- Generalized estimating equations (GEE) using a binomial distribution will be used to evaluate the detection of KSHV in plasma and oral specimens over time. Log10 transformations will be applied to the viral load data, and the median log viral load will be estimated for each participant prior to treatment and at time points post treatment. Generalized estimating equations (GEE) will be used to assess change over time with

respect to these measures.

10.2 Sample Size/Accrual Rate

The study is designed to test the null hypothesis that the response rate is less than or equal to 20% against the alternative that it is 40% or greater with 90% power at a one-sided 10% significance level which will require a sample size of 36 evaluable participants using the exact test for a single proportion[3,4].

The plan is to enroll 18 participants who are HIV-positive and 18 who are HIV-negative, at an estimated accrual rate of 1-2 participants/month. Participants from both the international and domestic sites will contribute to the single analysis plan, which is based on HIV status and not site of recruitment.

Evaluable participants for all endpoints are defined as participants who meet all the eligibility criteria, enroll on the study, and receive at least one dose of treatment. Participants who enroll but are not treated will be replaced.

10.3 Reporting and Exclusions

10.3.1 Evaluation of toxicity – All participants will be evaluable for toxicity from the time of their first treatment with nelfinavir.

10.3.2 Evaluation of response – All participants included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each participant will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the participants who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Participants in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible participants. Subanalyses may then be performed on the basis of a subset of participants, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding participants from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

10.4 Stopping Rule for Feasibility

The stopping rule is based on an underlying proportion of participants with adverse events that require treatment termination of 0.05. Thus, the stopping rule is derived by determining the number of participants with adverse events that require treatment termination which would occur ≤ 5% of the time of the true underlying rate of treatment terminations due to adverse events was 0.05. The trial will be stopped if the number of participants who terminate treatment due to adverse events is greater than or equal to X out of N participants:

X	N
2	3-7
3	8-16
4	17-28
5	29-36

11.0 ROLE OF DATA MANAGEMENT

11.1 CRF Instructions

Access to the internet data entry system for this study, Advantage eClinical, and instructions for recording of study data on CRFs will be provided by the AMC ODMC at www.AIDSCancer.org. Participating institutions are responsible for submitting data and/or data forms via Advantage eClinical in accordance with the AMC Data Entry Guide and specific form instructions, within the timelines specified by the AMC's Standards of Procedure for Site Performance Measures.

11.2 Data Quality

It is the responsibility of the AMC ODMC to assure the quality of data for the study (See Appendix VI, AMC Data and Safety Monitoring Plan). This role extends from protocol development to generation of the final study database.

11.3 Data Monitoring

This study will be monitored in compliance with AMC policies and by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and participant-specific CDUS data will be submitted electronically to CTEP on a quarterly basis. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html). The AMC ODMC is responsible for compiling and submitting CDUS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.0 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 IRB Approval and Informed Consent

The principles of Institutional Review Board (IRB) approval and informed consent described in the Food and Drug Administration (FDA) regulations (21 CFR Part 50 and 56) and Department of Health and Human Services (DHHS) regulations for the Protection of Human Subjects regulations (45 CFR Part 46) must be followed. IRB approval of the protocol and the informed consent form must be given in writing.

The sponsor's designee (AMC ODMC) must receive a copy of the letter of approval from the IRB, which specifically approves the protocol and informed consent, before participant enrollment. The IRB must also approve any significant changes to the protocol and documentation of this approval must be sent to the AMC ODMC. The IRB must review the research project at least once every 365 days during the duration of the project. Continuing approval of the project must also be given in writing and provided to the AMC ODMC.

Records of all study review and approval documents must be kept on file by the Investigator and are participant to inspection during or after completion of the study. AEs must be reported to the IRB according to local procedures. The IRB should receive notification of completion of the study and final report within 3 months of study completion and termination. The Investigator will maintain an accurate and complete record of all submissions made to the IRB, including a list of all reports and documents submitted.

Written informed consent will be obtained from the participant. The nature and significance of the risks associated with the study must be explained to the participant. The informed consent will describe the purpose of the study, the procedures to be followed, the risks and benefits of participation, all risks of the investigational agent(s) and/or study participation as listed in the model informed consent form, and all other elements of informed consent as required by regulation. A copy of the consent form will be given to the participant to keep.

In addition, any institution(s) conducting research according to the guidelines of this protocol is required to adhere to local and national laws and regulations governing the confidentiality and disclosure of health information.

12.2 Changes to the Protocol

Any change or addition to this protocol requires a written protocol amendment that must be approved by CTEP and the Investigator before implementation. All amendments require approval by the IRB/IEC of the treating institution. A copy of the written approval of the IRB/IEC and the national regulatory body (if applicable) must be sent to the ODMC.

12.3 Women and Minorities

This study is being conducted by the NCI-sponsored AIDS Malignancy Consortium (AMC). As part of their contractual obligations, each participating site within the AMC and the AMC as a whole is required to assure that the participation of women and minority participants reflects the percentage representation of these populations in their geographic region and, for the AMC, the United States as a whole. As such, it is expected that the representation of participants on this trial will reflect the constitution of the respective

populations.

Accrual Targets

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	12	0	1	16
White	1	5	1	3	10
More Than One Race	0	0	0	0	0
Total	4	17	1	4	26

INTERNATIONAL PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	7	0	0	10
White	0	0	0	0	0
More Than One Race	0	0	0	0	0
Total	3	7	0	0	10

12.4 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to the electronic data entry system for this protocol or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five-person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU and/or AMC applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave; Advantage eClinical for this protocol),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

Table 12-B: CTEP investigator registration documentation requirements

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites

on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL; the AMC DTL template will be used for this study; see Section 12.5).

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

12.5 Protocol Registration and Delegation of Tasks Log

Each site must complete a protocol-specific registration packet, including an AMC DTL using the provided AMC template or local equivalent. The Clinical Investigator (CI) is required to review and sign the AMC DTL prior to the site receiving an approved site registration status and enrolling participants to the study. The AMC DTL template is provided in the protocol registration packet for this protocol, located on the AMC Operations web site at www.AIDSCancer.org. Any individual at the enrolling site on a participating roster may initiate the site DTL. Instructions on completing the DTL are embedded in the AMC DTL template.

The AMC DTL must be updated contemporaneously as personnel are added or removed and/or study roles and delegated tasks change. Changes must be approved by the CI, and documented by his/her initials and date, before they are implemented.

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APPENDIX I: SCHEDULE OF PROCEDURES

The schedule of evaluations below applies to all participants on study. Baseline evaluations (including scans and x-rays) are to be conducted within 4 weeks prior to study enrollment into Segment B (Treatment Enrollment), unless specified below.

Assessment Type	Study Stage	Baseline/ Screening	Treatment Start	SD-NFV[1]	HD-NFV[1]	Early Discontinuation and Follow-Up
	Study Visit	Up to 4 Weeks Before NFV Unless Noted	Treatment Day 0	Every 2 Weeks Through Week 8 Unless Noted	Every 2 Weeks Through Week 24 Unless Noted	Within 7 Days After Stopping NFV for Early Disc. +8 Weeks (± 3 days) After Stopping NFV for Follow-Up
Informed Consent (2 to 4 weeks before NFV)		X				
Optional ACSR Donation		X				
Demographics, Height, Diagnostic KS Biopsy[2], ECOG/KPS score		X				
Medical History (including documentation of HIV diagnosis if positive), Concurrent meds, Physical Exam, Vital Signs, Weight		X		X	X	X
Confirmatory HIV Test if Previously HIV-negative		X				
Chest X-Ray		X		X[7]	X[7]	X[7]
CBC w/ Differential Safety Labs/Chemistries: calcium, sodium, potassium, CO2, chloride, AST (SGOT)/ALT(, SGPT), BUN, creatinine, direct and total bilirubin, fasting glucose, and triglycerides.		X			X (every 4 wks.)	X
Fasting Glucose and Triglycerides		X			X (every 8 wks.)	X

Assessment Type	Study Stage	Baseline/ Screening	Treatment Start	SD-NFV[1]	HD-NFV[1]	Early Discontinuation and Follow-Up
	Study Visit	Up to 4 Weeks Before NFV Unless Noted	Treatment Day 0	Every 2 Weeks Through Week 8 Unless Noted	Every 2 Weeks Through Week 24 Unless Noted	Within 7 Days After Stopping NFV for Early Disc. +8 Weeks (± 3 days) After Stopping NFV for Follow-Up
Adherence Review Nutrition Assess. KS Sign/Symp. Assessment		X		X	X	X[3]
KS Staging		X				
Standardized Assessment of Tumor Response with Photographs			X[8]	X	X	X
If HIV-positive: CD4 Count, and %		X				X
If HIV-positive: HIV Plasma Viral Load		X		X (every 8 wks.)	X (every 8 wks.)	X
beta-HCG if of Childbearing Potential		X	X[5]		X[5]	
EKG		X		X[6]	X[6]	
Provide and Review Drug Diary, Provide Study Drug, and Nutritional Counseling			X	X[4]	X[4]	
Provide Participant Instructions for Oral swabs		X			X[4] (once after starting HD-NFV)	

1. Study weeks and timing of standard dose nelfinavir (SD-NFV) and high dose nelfinavir (HD-NFV) may vary based on response; see Section 4.1. Scheduled study visits will be every 2 weeks +/- 3 days. Sufficient drug to provide continuous dosing between cycles/study visits should be provided as long as visits lie within the visit window.
2. Can be the same biopsy collected for immunohistochemistry correlative studies. May be performed any time prior to study enrollment.
3. Medication adherence review and nutrition assessment not required at Early Discontinuation or Follow-up visit.
4. Providing drug diary, study drug, participant instructions for oral swabs, and nutritional counseling not required if participant is discontinued.
5. Pregnancy testing for females of childbearing potential immediately prior to starting SD-NFV (day 0) and again immediately prior to starting HD-NFV.
6. EKG **only** required once 2 weeks after starting SD-NVF and once 2 weeks after starting HD-NFV.

7. A chest X-Ray should be performed to evaluate tumor response only for participants with pulmonary KS or new pulmonary symptoms.
8. Tumor assessment with photographs may be performed on Day 0, but no earlier than 7 days before initiating study treatment.

APPENDIX II: BIOMARKERS AND CORRELATIVE STUDIES

Sample	Collected in	Baseline/Screening Weeks -4 to 0	Treatment start/ Day 0	SD-NFV[1]	HD-NFV[1]	Special Handling	Where to Send
3mm skin biopsies for immunohistochemistry expression of LANA and 3 lytic gene products; KSHV gene expression arrays	1 biopsy in formalin (for IHC); 1 biopsy in RNA*later* (for gene expression)	Weeks -4 to 0, once	--	2 weeks after starting SD-NFV	2 weeks after starting HD-NFV	See Appendix X	See Appendix X
Whole blood for separation into plasma and PBMCs for KSHV and EBV qPCR	One 8.5 ml ACD (yellow top) tube	2 total blood samples during weeks -4 to 0	--	--	Each visit (every 2 weeks) after starting HD-NFV (8 samples total)	See Appendix X	See Appendix X
Oral swabs for KSHV, EBV, CMV, and HSV	Study-specific swabs/tubes	14 total daily swabs, collected during weeks -4 to 0	--	--	2 swabs per week while on HD-NFV for a total of 14 swabs	Stored at room temperature. Ship in batches bi-weekly (Sun-Wed);	See Appendix X
Genotyping	To be performed using DNA from PBMC	Once	--	--	--	See Appendix X	See Appendix X
Peripheral blood for PK	~6 ml of whole blood processed as plasma (one 6 ml potassium EDTA lavender top tube)	--	Immediately (- 3 days) pre-dose at each visit (every 2 weeks) starting on Week 1/cycle 1 through the completion of Week 15/cycle 9 (9 total samples)			Stored on ice, plasma separated within 30 minutes and frozen at ~ -70. Ship in batches (Mon-Wed)	See Appendix IX

1. Study weeks and timing of SD-NFV and HD-NFV may vary based on response; see Section 4.1. Scheduled study visits will be every 2 weeks.

APPENDIX III: PERFORMANCE STATUS SCALES

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

APPENDIX IV: AIDS AND CANCER SPECIMEN RESOURCE (ACSR) SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS

A. GENERAL

To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website: www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Mondays** through **Thursdays** an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON SATURDAYS OR SUNDAYS** in the ACSR.

B. SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

Blood specimens

Draw two 8.5 cc (mL) yellow top [acid citrate dextrose (ACD)] tubes from study participant. With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol # 098
- AMC Participant ID#
- Date and time of collection
- Specimen type, i.e., WB=Whole Blood, P=Plasma, S=Serum, or Tissue
- Specimen purpose: Donation

Specimen shipment

- Seal the tops of the two 8.5 cc yellow tops with Parafilm.
- Place the two sealed tubes into bubble wrap (provided in STP-210 kit).
- Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
- Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal."
- Place poly-bag containing tubes into the white TYVEK bag and seal.
- Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
- Affix the FED-EX air bill on blank side of the shipper making sure that it is marked "FED-EX PRIORITY OVERNIGHT."
- Mark "OTHER" in the air bill under "Packaging." Please use the FedEx # available on the AMC member's only website.

- Under air bill section "Special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."
- Place "From/To" information onto areas provided on the shipper.

Blood specimens should be shipped by overnight express at room temperature to:

Sylvia Silver, DA
AMC Biorepository
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: 202-994-5056
Email: ssilver@gwu.edu

- Make certain that shipper is already either pre-labeled with 'UN#3373' stamp or make a paper label with 'UN#3373" and affix it to the shipper.
- Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in ml and affix to the shipper.
- Affix air bill to shipper so that the 'UN' and 'VOLUME' labels are visible.
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

INSTRUCTIONS FOR BLOOD SPECIMENS COLLECTED ON FRIDAY OR SATURDAY

Preparation of plasma and mononuclear cells

Refer to the ACSR's Standard Operating Procedure (SOP) on Separation of Plasma and Mononuclear Cells on the AMC Operations web site for instructions on preparing plasma and PBMC aliquots. It is preferable that separation occurs as soon as possible. If necessary, whole blood in ACD (yellow top tubes) can be held at room temperature for no more than 24 hours.

Freeze the cell suspension in 0.5 mL aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

*****PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.**

Preparation of tissue samples

Tissue specimens to be fresh frozen should be placed in OCT and then on dry ice immediately. The specimens may stay on dry ice until being transferred to a -80ºC freezer.

Tissue specimens for donation may be batched for shipping after storage in -80ºC freezer. *NOTE: Specimens can only be accepted Monday through **Friday**. Therefore, specimens can only be shipped **Sunday-Thursday** for delivery the next day. Shipping frozen tissue requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

TISSUE specimens should be shipped by overnight express to:

Sylvia Silver, DA
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: (202) 994-5056

C. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace[SM], a component of the AMC Advantage eClinical system. The GlobalTrace shipment manifest must accompany all specimen shipments.

APPENDIX V: ACSR INFORMED CONSENT

Study Title for Study Participants:	Collecting Blood and Tissue Sample Donations for Research for HIV/AIDS-Related Cancers
Official Study Title:	Biospecimen Collection and Donation to the AIDS and Cancer Specimen Resource (ACSR)

What is the usual approach to donate blood and/or tissue to the ACSR?

You are being asked to donate blood and/or tissue for future research. You are being asked to donate your blood and/or tissue samples to the ACSR because you have HIV infection and are being considered for participation in an AIDS Malignancy Consortium (AMC) clinical trial. The AMC works with the ACSR to collect donated samples from persons with HIV infection for research studies. People who do not take part in an AMC clinical trial can also donate samples to the ACSR.

What are my other choices if I do not take part in this study?

It is your choice to donate or not donate your blood and/or tissue samples. You may still take part in the AMC clinical study if you choose not to donate blood or biopsy samples to the ACSR.

You may also choose to donate:

- Blood but not tissue, or
- Tissue but not blood.

What is the AIDS and Cancer Specimen Resource (ACSR)?

The ACSR is a biorepository (biobank) that collects human biological specimens (samples) from persons who have HIV or cancers related to HIV/AIDS. The ACSR stores the samples and some of the donor's medical information for use by researchers in future research studies. The National Cancer Institute (NCI) has set up the ACSR to assist researchers locate samples needed for their studies.

The ACSR has an independent research panel that approves researchers' requests to use the ACSR's stored samples for research studies. The ACSR only gives samples and medical information to researchers after their projects have been approved. Researchers may use the samples to study cancers and other diseases associated with HIV disease. This information may help us learn more about the causes of HIV-related diseases and cancers and to develop better ways to screen, diagnose, and treat them.

Why is this study being done?

The purpose of this study is to collect samples for the ACSR for future research studies. Researchers may study samples from the ACSR in combination with hundreds or thousands of other samples to explore how biologic or genetic factors may be related to HIV-related diseases and cancer. The information might help doctors in the future to identify who will or will not benefit from treatment. The samples may be used to learn more about how HIV-related diseases and cancers develop. The samples may also lead to new tests or discoveries. Finally, researchers may use the samples to study the genetic material from your cancer tissue and compare it to the material from your normal tissue (blood) to try to find the differences that exist. These studies could make it possible to identify many of the changes that are associated with diseases such as cancers. It may

also help us tailor treatments to a patient's unique genetic make-up and/or to the genetic markers of the tumors.

What extra tests and procedures will I have if I take part in this study?

1) If you agree to donate blood, the medical team will draw about 2 tablespoons of blood to give to the ACSR. This takes about 10 minutes.
2) If you agree to donate tissue, your leftover tissue biopsy material will be donated to and stored by the ACSR.
3) Some of your clinical information will be released to the ACSR and entered into their database. The information given to the ACSR will not include your name or any information that could personally identify you.

We will only give the ACSR tissue that is left over after making decisions about your treatment or diagnosis. The study doctor will not take any extra biopsies just for the ACSR.

We cannot tell you right now what future research these samples would be used for. Instead, we are asking that you give approval to give your samples for future testing without contacting you again. The results of whatever research is done on your samples will *not* be told to you or your doctor. The results of the tests will *not* be placed in your study records.

How long will ACSR keep my samples?

Your blood and/or tissue sample will be stored until it is used for research. The samples may be stored indefinitely.

What possible risks can I expect from taking part in this study?

- Blood Draw: The risks of drawing blood include temporary discomfort from the needle stick, bruising, and, rarely, infection.
- Confidentiality: The ACSR will receive study samples with code numbers. There will be no personal identifiers on the samples. Then the samples will be re-labeled with a barcode and stored for future testing. While the ACSR and researchers who study ACSR samples will have no information that could identify you, there is a risk that someone could use information from genetic studies to trace your samples back to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information. In some cases, this information could be used to make it harder for you to get or keep a job. There are laws against misuse of genetic information, but they may not give full protection. The researchers believe the chance these things will happen is very small but cannot promise that they will not occur.

Let your study doctor know of any questions you have about these possible risks. You can ask the study doctor questions about side effects at any time.

What possible benefits can I expect from taking part in this study?

This study is unlikely to help you. This study may help us learn things that may help people in the future.

The information may help to identify those who are at increased risk and those who may benefit from targeted treatment and screening. In turn, these studies could help find ways to prevent or improve treatments for HIV-related diseases and AIDS-related cancers.

Can I stop taking part in this study?

Yes, you may withdraw your samples from the ACSR at any time. You may contact your AMC study coordinator if you would like to withdraw your samples. The coordinator can ask in writing that your sample be removed from research use and that any identifiable sample and information still in their possession be destroyed. However, if any research has already been done using some of your samples, the data will be kept and analyzed as part of those studies.

What are my rights in this study?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

What are the costs of taking part in this study?

There will be no cost to you for donating your samples to the ACSR. You will not be paid for taking part in this study.

What happens if I am injured or hurt because I took part in this study?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The AMC will not offer to pay for medical treatment for injury. Your insurance company may not be willing to pay for study-related injury. If you have no insurance, you would be responsible for any costs.

If you feel this injury was a result of medical error, you keep all your legal rights to seek payment for injury even though you are in a study.

Who will see my medical information?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The AIDS Malignancy Consortium (AMC)
- The Institutional Review Board, IRB, is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Office for Human Research Protections and the National Cancer Institute in the U.S.

To protect your privacy, the AMC does not keep identifying information that links study participants to specific samples. As a result, the AMC and ACSR will not be able to link the results from studies that use your samples back to you. Thus, information, including genetic information, that researchers may obtain in studies that use your samples may not be directly linked to you and will not be placed in your medical record. However, some clinical and basic information obtained confidentially from the AMC will be attached with these data. It is possible that findings may one day help, for example, people of the same race or sex as you. It also is possible that genetic factors might come to be associated with people who have HIV and cancer through these kinds of studies.

Where can I get more information?

You may visit the NCI Web site at **http://cancer.gov/** for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at 1-800-4-CANCER (1-800-422-6237).

Who can answer my questions about this study?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

Please circle your answer to show whether or not you would like to take part in each option:

1) I agree to donate my blood to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

2) I agree to donate my blood to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

3) I agree to donate some of my tissue biopsy material that is not required for my treatment or diagnosis to the ACSR for future research that may be used to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

4) I agree to donate some of my tissue biopsy material to the ACSR for future research that may include genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

   YES NO

My Signature Agreeing to Take Part in The Study

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the optional study.

Participant's signature_____

Date of signature_____

Signature of person(s) conducting the informed consent discussion_____

Date of signature_____

APPENDIX VI: AMC DATA AND SAFETY MONITORING PLAN

(Version 9.0 • October 6, 2020)

Introduction

The AIDS Malignancy Consortium (AMC) Data and Safety Monitoring Plan (DSMP) outlines the measures employed by the group to monitor the safety of participants and ensure the data validity and integrity for all clinical trials it conducts. This includes methods to: 1) monitor the progress of trials and the safety of participants; 2) comply with regulatory requirements for adverse event (AE) reporting; 3) processes for trial termination or temporary suspension and major modifications; and 4) plans for ensuring data accuracy and protocol compliance. As the AMC conducts protocols of varying research phase, region of conduct (which may include trials conducted in the U.S., international sites, or both), IND sponsor (AMC investigator, CTEP, or industry-sponsored) and clinical data entry system use, this plan addresses broad processes applying to the range of trial designs and requirements. Refer to the individual AMC protocol to identify the applicable study characteristics for the relevant requirements described in this plan.

Monitoring the Progress of Trials and the Safety of Participants

Routine and expedited AE reporting

All AMC protocols that collect safety data adhere to the *National Cancer Institute (NCI), Cancer Therapy Evaluation Program (CTEP) Guidelines: Adverse Event Reporting Requirements* (https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm), as applicable to the clinical protocol. AEs are to be recorded in the source documents, assessed by a clinical investigator for the AE reporting criteria, and promptly reported in the clinical data entry system as required by each protocol. For AMC trials conducted under a CTEP IND and AMC trials conducted within the U.S., all AEs that meet the NCI's expedited reporting requirements are reported to the NCI via the CTEP Adverse Event Reporting System (CTEP-AERS) web application, either directly or through integration with Medidata Rave where this system is employed for AMC protocols. Use of this system ensures notification to the protocol chair and Investigational Drug Branch (IDB) at CTEP, as required for trials conducted under a CTEP IND, and a uniform expedited reporting and safety review process for AMC domestic trials. The system may also be programmed to include sponsor notification as required for trials with industry support. Alternate process for expedited AE reporting to the AMC protocol chairs and AMC Operations and Data Management Center (ODMC) within the clinical data entry system (AdvantageEDC or Advantage eClinical only) may be defined in the protocol for select trials (international studies and The ANCHOR Study).

All serious adverse events (SAEs) received by the AMC ODMC will be reviewed by the AMC medical monitor at the AMC ODMC for consideration of individual participant safety, safe trial conduct, data reporting quality for AE term selection, and appropriate application of the regulatory criteria for seriousness, expectedness, and relatedness to the investigational therapy. If alternate procedures are followed for SAE review, the process for adequate medical monitoring will be defined in the AMC protocol and the Transfer of Regulatory Obligations (TORO) with the sponsor. AMC medical monitor review includes review of the CTEP-AERS report before CTEP submission for IDB review (if applicable), or review of the SAE report in the data entry system for trials not using CTEP-AERS for expedited reporting. The IND sponsor or its designee will issue the determination as to whether the AE requires IND safety reporting to FDA as a serious and

unexpected suspected adverse drug reaction (SUSAR). For protocols not conducted under an IND, in the event of disagreement between the reporting physician and the AMC medical monitor regarding the relationship of the AE to the investigational agent(s) (i.e., determination of whether the attribution is unrelated or unlikely, or possible, probable, or definite), the AMC medical monitor will provide the final determination of the relationship. IND safety reporting to FDA is performed by CTEP for trials conducted under a CTEP IND; IND safety reporting is performed by the sponsor or sponsor's designee (AMC ODMC or other party defined in the study agreement or TORO) for IND studies sponsored by AMC investigators or industry sponsors.

Expedited reporting to the Institutional Review Board (IRB)

The requirements for IRB review will be identified in the protocol section on ethical and regulatory obligations. All AMC trials initiated before September 1, 2020 and all international sites for all AMC studies are subject to local IRB review; only U.S. sites are subject to the NCI requirement to use a single IRB for protocols initiated on or after September 1, 2020. For trials subject to local IRB review, the site principal investigator is responsible for ensuring that expedited AE reports for its trial participants and any unanticipated problems that affect the local institution only are submitted to the local IRB of the reporting institution, per the local IRB's requirements for such reporting. For studies reviewed by the single IRB, the protocol chair will render a determination as to whether a SAE or other problem constitutes a trial-wide unanticipated problem that requires reporting to that IRB, in accordance with its standards of procedure.

To comply with investigator notification requirements for IND studies under 21 CFR 312.32 and 312.55, IND safety reports from all trials the AMC conducts and reports from external sponsors investigating the same agents are made available to all investigators upon receipt from the sponsor or its designee, either via the password-protected section of the AMC Operations web site (AMC trials subject to local IRB review only) or the CTSU website (U.S. trials subject to single IRB review/CTEP IND agents). The site clinical investigator responsible for the applicable AMC protocol(s) is responsible for reviewing any IND safety reports received and documenting submission to the IRB of record (if required by local policy) within the timeline defined by the Clinical Trials Monitoring Branch (CTMB) audit guidelines.

Procedures for monitoring trial progress and pharmacovigilance

For trials using AdvantageEDC or Advantage eClinical for clinical data entry, the AMC ODMC provides on demand tabular listings of all reported AEs and SAEs on a participant level to the protocol chair and co-chair(s) for review via the password-protected section of the AMC Operations web site, www.AIDScancer.org. For trials using OPEN and Medidata Rave for clinical data collection, data listing will be made available using that system. Summary reports of AEs by frequency and relationship to the investigational agent(s) are provided to all AMC investigators and their staff It is the responsibility of each site to provide trial-specific AE listings to their respective IRB, if required by its policies. For blinded studies, the AE and SAE listings are reviewed and tabulated without treatment assignment.

Accrual summaries for each AMC trial are updated nightly on the password-protected section of the AMC web site. The progress of each AMC trial is reviewed regularly by the protocol chair and also by the appropriate Scientific Working Group (SWG) during scheduled conference calls (monthly SWG calls and as required, protocol-specific monitoring conference calls). Summary accrual, summary AE, and individual SAE reports are provided to SWG leadership and protocol chairs to monitor participant safety during these monthly calls.

The AMC medical monitor reviews listings of all reported AEs on a quarterly basis for assuring compliance with the protocol requirements for AE reporting and the identification of any safety concerns (individual AE or increased frequency/severity of expected AEs) for the agents under investigation. Findings from these reviews are communicated to the protocol chairs and all AMC investigators, and posted to the AMC Operations web site.

Data and Safety Monitoring Board(DSMB) review

The AMC has formed an independent Data and Safety Monitoring Board (DSMB) for AMC trials and for the ANCHOR Study. As required by NCI policy, the AMC requires DSMB review for all phase III randomized trials. All other clinical trials that the AMC initiates will be reviewed by the AMC ODMC and AMC Statistical Center during protocol development to issue a recommendation as to whether the study requires DSMB oversight, which will require the approval of the AMC Executive Committee. This determination will be based on the phase of the study, experimental design, risk posed by the investigational approach, extent of data available on the safety of an investigational agent, risk posed by the natural course of the health condition under research, and the categories of vulnerable populations involved. The involvement of a DSMB in reviewing an AMC protocol will be identified in each clinical protocol as approved by CTEP and, as applicable, required by the IRB of record.

Regarding the composition of the AMC DSMB, voting members usually include physicians, statisticians, an ethicist, and a patient advocate. All voting members have no other affiliation to the AMC and are appointed by the AMC Executive Committee with the approval of the OHAM Director. Nonvoting members are the AMC group statistician, the protocol statistician, an AMC ODMC staff member, two representatives (normally a clinician or statistician) from CTEP, and the grant program directors from the NCI Office of HIV and AIDS Malignancy (OHAM).

The DSMB reviews all applicable AMC studies in accordance with the National Cancer Institute's Policy for Data and Safety Monitoring. Confidential reports of all trials under review are prepared by the AMC group statistician with support from the AMC ODMC. A written report containing the current status of each trial monitored, and when appropriate, any toxicity and outcome data, are sent to DSMB members by the AMC ODMC within the timelines specified by the DSMB charter. This report addresses specific toxicity issues and any other concerns about the conduct of the trial, as defined by the protocol plan for DSMB review. The report may contain information for the DSMB to render determinations for participant safety, early trial termination, results reporting, or continuing accrual or follow-up.

The results of each DSMB meeting are summarized in a formal report sent by the DSMB chair to the AMC group chair and AMC ODMC. The DSMB report contains recommendations on whether to close each study reviewed, whether to report the results, and whether to continue accrual or follow-up. A primary recommendation (e.g., continue with no change; recommended or required modification; stop) must be included in the document. The group chair or designee is then responsible for notifying the protocol chair and relevant SWG chair before the recommendations of the DSMB are carried out. In the unlikely event that the protocol chair does not concur with the DSMB, then the OHAM program directors and the NCI division director or designee must be informed of the reason for the disagreement. The protocol chair, relevant SWG chair, group chair, DSMB chair, and NCI division director or designee will be responsible for reaching a mutually acceptable decision about the study. CTEP approval of a protocol amendment will be required prior to any implementation of a change to the study.

Following a DSMB meeting, the DSMB's recommendations are provided to all AMC investigators and staff. It is each site principal investigator's responsibility for conveying this information to its local IRB as relevant for its protocol participation. For trials reviewed by a single IRB, the AMC ODMC will support notification to the IRB as required per its procedures.

Cohort trial reviews not subject to DSMB review

For phase I dose escalation trials, dose escalation (or dose de-escalation) is based on the rules in the protocol and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met based on a review of all safety data for the protocol-defined evaluation period. If applicable for phase II trials, stopping the trial for toxicity or efficacy, or suspending enrollment pending observation of responses in a multi-stage phase II trial, is based on meeting criteria stated in the protocol, and the protocol chair, AMC medical monitor, and protocol statistician determine whether these criteria have been met.

Plans for Assuring Compliance with Requirements Regarding AE Reporting

The protocol chair, AMC group chair, and the AMC ODMC share responsibility in assuring that participating investigators comply with applicable regulatory and protocol requirements for AE reporting. The AMC site principal investigator certifies compliance with NCI and FDA requirements for trial conduct by signing the site subaward agreement for the grant and the AMC Adherence Statement for site membership; clinical investigators also certify compliance in completing the protocol signature page for each protocol active at the site, and Form FDA-1572 for CTEP investigator registration, and also for AMC IND studies sponsored by AMC investigators or industry sponsors. Protocol compliance with AE identification, assessment and reporting requirements is assessed by the AMC ODMC using several methods: 1) programmed system checks and messages to instruct the site to complete routine and/or expedited reporting when certain criteria are reported in the clinical data entry system; 2) programmed data reports provided to the protocol chairs that identify reports requiring expedited AE reporting; 3) remote review of data entry or data reports to ensure compliance with protocol and NCI AE reporting requirements; 4) AMC medical monitor review described in the section above; and, 5) routine site audits by reviewing the site's source documentation.

The clinical data entry systems used for AMC studies include the Oncology Patient Enrollment Network, OPEN for enrollment, and Medidata Rave for clinical data entry for enrolled participants; trials activated before September 1, 2020 or that involve only AMC international sites may be reported in AdvantageEDC/Advantage eClinical, a web-based data entry and enrollment system. These data entry systems are programmed to notify the site investigator, protocol chair, AMC medical monitor, and AMC ODMC via email in the event that a site reports an AE that meets expedited reporting criteria to NCI and/or FDA. Additional reporting conditions may be programmed depending on the sponsor reporting requirements of a given protocol (e.g., adverse events of special interest [AESI]). If the site does not follow with an expedited report, the AMC ODMC contacts sites to request compliance with reporting requirements. Additionally, the protocol chair, AMC ODMC, and the AMC medical monitor review reported AEs on a routine basis to identify AEs reported by sites that require expedited reporting. The protocol chair, AMC SWG chairs, AMC group chair, and IND sponsors have general oversight for assuring that routine and expedited adverse reporting requirements are met by the responsible parties.

For studies monitored by CTEP using the Data Mapping Utility (DMU), cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. For trials

monitored by the NCI's Clinical Data Update System (CDUS), AE information is transmitted electronically to NCI on a quarterly basis. For trials monitored by NCI's Clinical Trials Monitoring Service (CTMS), AE information is transmitted electronically to NCI every two weeks.

Plans for Assuring that any Action Resulting in a Temporary or Permanent Suspension of an NCI-Funded Clinical Trial is Reported to the NCI Grant Program Director Responsible for the Grant

In the event that temporary or permanent suspension of a trial, or major modification to the protocol is under consideration, the protocol chair will convene the AMC ODMC, AMC Statistical Center, and SWG chair by conference call to discuss the options. Suspension actions will also be reviewed by the AMC Executive Committee for program oversight and direct communication of the action with the OHAM program directors. For phase III trials, closure decisions are typically rendered by the AMC DSMB; if the trial in question is under AMC DSMB oversight but rendered by the AMC investigators, the AMC DSMB will be notified of the suspension and the reason. For phase I and II trials, the protocol chair also has the option of asking the DSMB to review the study. The AMC ODMC will inform the CTEP Protocol Information Office (PIO), with copy to OHAM Directors, when studies are temporarily or permanently closed. In the event of major trial modification, CTEP must approve all protocol amendments prior to distributing to the AMC sites.

Plans for Assuring Data Accuracy and Protocol Compliance

All study data for AMC clinical trials are entered directly by AMC clinical site staff into the applicable clinical data entry system for the trial. During data entry, the system performs validation checks on many fields and performs consistency checks between select fields. Range checks are placed on each field to eliminate entry of out-of-range values. Edit check programs are run on the database on a set schedule to identify and resolve inconsistencies between forms or data collected at different points in time. Submitted data entry forms are reviewed for compliance with the protocol and data entry instructions according to the AMC ODMC's standards for data quality processes. AMC ODMC staff routinely interacts with site staff to resolve any data submission problems.

In accordance with NCI guidelines, the AMC ODMC conducts audits at the AMC sites to evaluate compliance with regulatory issues, and to review data for specific cases by checking source documents. These reports are sent to the site principal investigator and to the NCI. In the event that major violations are identified, sites are asked to provide a written corrective and preventative action plan to correct deficiencies. If needed, a repeat site audit is conducted. In the event that a site does not correct deficiencies in a pre-determined time frame, the AMC Executive Committee has the option to implement remedial action(s) for the site. Possible actions include, but are not limited to, suspending enrollment of new patients to AMC trials until deficiencies are corrected; recommending a decrease in funding to the site; and requiring specific training for site investigators or staff members.

APPENDIX VII: PARTICIPANT DRUG DIARY

YOU MUST KEEP THIS DIARY AND BRING IT TO EVERY APPOINTMENT

Instructions for participants:

Please record the date and time that your nelfinavir dose was taken. Be sure to record the doses when you take them and avoid writing entries for several days at once.

In the "Comments" section write any problems you are having with the medicines or if you missed a dose and why or if you only took part of the medicine.

When you are finished, bring this diary with you when you next see the Doctor or Study Staff.

Your nelfinavir tablets should be taken with a meal, twice daily (once in the morning and once in the evening).

Nelfinavir should be taken with a moderately high fat meal, for example that includes oil, butter, eggs, or meat.

If you cannot swallow the tablet whole, you may dissolve the tablet in a small amount of water. Drink all of the mixture after the table dissolves. Then refill your glass with water and drink all of the water right away. Do not mix with acidic foods or juice (apple juice, applesauce, or orange juice) because it will make it taste bad. Someone in the clinic will talk to you about the diet requirements.

Missed nelfinavir doses, regardless of reason, SHOULD be made up if it is within 6 hours of the missed dose. Do not make up the missed dose if within an hour from the next dose. If you vomit, do not take more pills to make up the dose.

AMC-098 Drug Diary **Participant ID #: 098- ___ ___ ___ - ___ ___ ___ ___ ___**

Day	Date DD/MMM/YYYY	Time Nelfinavir Taken (circle AM/PM)	# of Tablets Taken	Time Nelfinavir Taken (circle AM/PM)	# of Tablets Taken	Comments
Week #: _____		**Take _____ tablets twice a day (morning and evening) with a moderately high fat meal.**				
1	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
2	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
3	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
4	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
5	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
6	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
7	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
Week #: _____		**Take _____ tablets twice a day (morning and evening) with a moderately high fat meal.**				
1	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
2	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
3	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
4	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
5	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
6	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
7	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
8	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
9	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	
10	___/_____/_____	___:___ AM PM	_____	___:___ AM PM	_____	

Please return the unused tablets to your doctor with your diary at your next appointment.

FOR STUDY TEAM USE ONLY

AMC-098 Drug Diary **Participant ID #: 098- ___ ___ ___ - ___ ___ ___ ___ ___**

Number of tablets dispensed	
Date returned	
Number of tablets returned	
Number of days in this cycle (14 days +/- 3 days)	
Number of tablets that should have been taken	
Number of tablets reported taken	
Discrepancy Notes:	

Staff Signature: _____ Date: _____ (DDMMMYYYY)

NOTE: Non-compliance with study agent administration and/or diary completion should be noted at the time of diary collection and the participant should be instructed again regarding dosing instructions.

APPENDIX VIII: CENTRAL PATHOLOGY REVIEW

Required Tissues

Participants must have measurable cutaneous Kaposi sarcoma (KS) that has been pathologically confirmed by the local pathologist. Participants must have one of the following for the purposes of central pathology review:

- Diagnostic tissue block or H&E plus five blank FFPE sections for LANA staining , or
- High quality images of the LANA staining for electronic submission for pathology review and H&E is available on site

Handling of Tissues

Domestic tissues should be submitted to the following address:

Sylvia Silver, DA
George Washington University Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: 202-994-5056

International tissues should be submitted to the following address:

Johann Schneider, MMed Anat Path
Division of Anatomical Pathology
National Health Laboratory Service
10th Floor Green Avenue, Room 52
Tygerberg Hospital
Tygerberg
7535 South Africa
Phone: 27-21-938-4041
Fax: 27-21-938-6559
Email: jws2@sun.ac.za

Record of Specimens: This study will track specimens via GlobalTrace[SM], a component of the AMC Advantage eClinical system. The GlobalTrace[SM] shipment manifest must accompany all specimen shipments.

Pathology Review

Ethel Cesarman, MD
Weill Medical College of Cornell University
Department of Pathology

APPENDIX IX: SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS FOR NELFINAVIR AND METABOLITE PHARMACOKINETIC STUDIES

Blood for nelfinavir and metabolite PK assessments will be collected immediately prior to dose administration (- 3 day window) at week 1/cycle 1 through completion of week 15/cycle 9. A maximum of nine (9) specimens will be collected. .A window of - 3 days is allowed. The actual sample collection times should be recorded on a pharmacokinetic worksheet that also documents the time of nelfinavir administration (previous and current dose; along with the use of a participant dosing diary (See Appendix VII).

In addition, when feasible, samples will be requested from the participant at the time of disease progression and in the event of DLT or other persistent and severe toxicity. For these optional samples, a blood sample should be drawn as close as possible to the time of the event with documentation of the last nelfinavir dose administered.

Collection, Processing and Storage (only 1 tube is necessary for the PK assessment for nelfinavir)

1) Each sample will comprise ~ 6 mL of venous blood drawn into a 6-mL lavender top tube with K_2-EDTA as the anticoagulant. Immediately after collection, the tube should be gently inverted 8 to 10 times to mix the anticoagulant with the blood sample. The tube should be stored upright on ice until centrifugation; centrifugation and sample processing should be performed within 30 minutes of sample collection.
2) The plasma fraction should be separated by placing the collection tube into a refrigerated centrifuge (4 to 8°C) in a horizontal rotor (with a swing-out head) for a minimum of 10 minutes at 1500 to 1800 relative centrifugal force (RCF).
3) The plasma fraction will be withdrawn by pipette and divided into 3 polypropylene freezing tubes (with each tube receiving approximately equal aliquots and at least 0.5 mL volume).
4) All sample collection and freezing tubes will be clearly labeled in a fashion that identifies the participant, the study period, and the collection date and time. Labels will be fixed to freezing tubes in a manner that will prevent the label from becoming detached after freezing.
5) After processing, samples should be placed into a freezer at approximately –70°C.

With a black, water resistant, fine-tipped sharpie pen, label each specimen label with the following information:

- Protocol #: AMC-098
- 11-digit Participant ID #
- Specimen type: “Plasma”
- Specimen purpose: “Pharmacokinetic Analysis” (for the 3 aliquots)
- Date/Time collected:

*The nominal time point of the blood draw should be written on the specimen label (e.g., day, and pre-dose, 1 hour, 2 hours, etc.) In GlobalTrace^{SM}, enter the time collected and be sure to indicate the nominal time point in the comments section when adding specimens.

If there were samples not obtained at the required time points, please inform the Analytical Pharmacology Core (APC) Laboratory prior to shipping.

Shipment

Samples will be kept at the study site and shipped periodically during the study to the APC Laboratory. Unless otherwise stated, samples will be shipped to the APC Laboratory under the direction of Michelle A. Rudek, Pharm.D., Ph.D.

Specimens should be stored through the duration of the PK study (through Week 15) and shipped as a batch by participant (more than one participant/shipment is acceptable if the site has > 1 participant on-study).

A participant's samples should be shipped to the APC lab within 1 month of the last sample's collection date. (i.e., if the Week 15 sample is collected on 1/1/2016, all of that participant's samples should be at the APC lab by 2/1/2016). If a second set of participant samples can be batched by waiting up to 2 weeks (i.e., 1.5 months).

Please ship 2 aliquots to the APC laboratory. Once receipt is confirmed, the third/back-up aliquot may be shipped (after 2 successful shipments, all 3 aliquots can be shipped at once).

Overnight shipments should occur on **Monday** through **Wednesday** (**Tuesday** is the preferred day) except when the following day is a holiday. A fax or call should be place to the Analytical Pharmacology Core Laboratory prior to shipment providing the shipment tracking information.

Samples should be shipped on dry ice to:

Analytical Pharmacology Core Laboratory*
Attn: AMC Nelfinavir Study Samples
1650 Orleans St. CRB1 Rm 184
Baltimore, MD 21231-1000
Phone: 410-502-7192 or 410-955-1129
Fax: 410-502-0895
Email: onc-pharmacology@lists.johnshopkins.edu

Record of Specimens

This study will track specimens via GlobalTrace^{SM}, a component of the AMC Advantage eClinical system. The GlobalTrace^{SM} shipment manifest must accompany all specimen shipments.

APPENDIX X: AMC BIOREPOSITORY SPECIMEN PREPARATION AND SHIPPING INSTRUCTIONS FOR CORRELATIVE STUDIES

Regimen: Required study specimens are included in Appendix II. All specimens will be banked at the domestic or international AMC biorepository, which will serve as a tissue source site for processing samples for all AMC sites, for testing at AMC core labs and outside labs. Test will be conducted at the end of enrollment for each phase or within one year of acquisition of sample.

Assays procedures are described in the AMC manual of operation(s) and available from the network core laboratories. Assays details may change as technology progresses.

Assays as proposed in exploratory objectives (Section 2.4):

- Plasma for herpesvirus (KSHV) and EBV viral load (AMC Virology Core)
- PBMC for herpesvirus (KSHV) latent virus (AMC Virology Core)
- PBMC for drug metabolism profile (Genotyping) (AMC Genomics Core)
- Tissue (skin of KS) biopsies: RNA*later* for gene expression profiling (AMC Genomics Core)
- Tissue (skin of KS) biopsies: formalin for IHC (AMC Pathology Core)
- Saliva swabs for multiple herpesvirus (KSHV, HSV, EBV, HCMV) (AMC Genomics Core)
- Nelfinavir PK (AMC Pharmacology Core) (See Appendix IX)

GENERAL

A. To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website: www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Sunday** through **Thursday** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON SATURDAYS OR SUNDAYS** in the AMC biorepository.

B. ***INSTRUCTIONS FOR PERIPHERAL BLOOD SPECIMENS FOR PLASMA AND PBMCS (FOR RESEARCH) COLLECTED ON SUNDAY – THURSDAY***

From study participant, draw:

One 8.5 cc (mL) yellow top [acid citrate dextrose (ACD)] tube at two time points: prior to initiation of study drug (enrollment visit and prior to first dose, timing not important); and at each biweekly study visit while on high dose nelfinavir treatment.

With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol # 098
- AMC Participant ID#
- Date and time of collection

- Specimen type, i.e., WB = Whole Blood
- Specimen purpose: Research

Specimen Shipment

- Seal the tops of the tube(s) with Parafilm.
- Place the sealed tube(s) into bubble wrap (provided in STP-210 kit).
- Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
- Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal."
- Place poly-bag containing tubes into the white TYVEK bag and seal.
- Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
- Affix the FEDEX air bill on blank side of the shipper making sure that it is marked "FEDEX PRIORITY OVERNIGHT."
- Mark "OTHER" in the air bill under "Packaging." Please use the FedEx # available on the AMC member's only website.
- Under air bill section "Special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."
- Place "From/To" information onto areas provided on the shipper.

DOMESTIC BLOOD SPECIMENS should be shipped by overnight express at room temperature to:

Sylvia Silver, DA
AMC Biorepository
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: 202-994-5056
Email: ssilver@gwu.edu

- Make certain that shipper is already either pre-labeled with 'UN#3373' stamp or make a paper label with 'UN#3373" and affix it to the shipper.
- Make certain that the net volume of the specimen being shipped is written in the space provided on the shipper or make a separate label with the volume in mL and affix to the shipper.
- Affix air bill to shipper so that the 'UN' and 'VOLUME' labels are visible.
- RETAIN THE TOP COPY OF THE AIRWAY BILL FOR YOUR RECORDS.
- Place the box in the FedEx pickup area at your site or call to request a package pickup.

Please Note: The shippers will be mailed back to each AMC site.

Specimens should be sent by 24-hour shipment at room temperature. If collecting on a Friday through Saturday where 24-hour shipment is not possible, please see Section C below for instructions regarding separation of Plasma and PBMCs from blood. In this case separation will need to occur on site and within 2 hours of blood collection.

C. INSTRUCTIONS FOR SEPARATION OF BLOOD FOR PLASMA AND PBMCS (FOR RESEARCH) COLLECTED ON FRIDAY - SATURDAY

In the event that blood samples are drawn on Friday through Saturday, the samples must be processed into plasma and peripheral blood mononuclear cells (PBMC) immediately to maintain their viability for analysis.

From study participant, draw:

One 8.5 cc (mL) yellow top [acid citrate dextrose (ACD)] tube for PBMCs and plasma (see below for PBMC and plasma separation directions) at two time points: prior to study drug initiation (enrollment and prior to first drug dose acceptable, exact timing not important); and at each biweekly study visit while on nelfinavir treatment.

With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol # 098
- AMC Participant ID#
- Date and time of collection
- Specimen type, i.e., WB = Whole Blood
- Specimen purpose: Research

Preparation of plasma and peripheral blood mononuclear cells (PBMCs)

Blood is to be processed on site within 6 hours of collection.

Materials

- Lymphocyte Separation Medium (LSM Solution, Ficoll-Hypaque - sterile)
- 15 mL conical centrifuge tubes (sterile)
- PBS (sterile)
- 1 mL, 5 mL and 10 mL serologic pipettes (sterile)
- 1.5 mL NUNC tubes
- Alcohol-saturated, control rate freezer container
- DMSO freezing media
- Lonza BioWhittaker TM Cryoprotective Medium (catalog BW12-132A)
- 50% Heat Inactivated Fetal Bovine Serum

Plasma separation and freezing procedures

1. The 10 mL tubes of whole blood in acid citrate dextrose should be rotated gently two or three times before being centrifuged. Do not transfer before centrifugation.
2. Separate the cells by centrifugation at 500 g for 10 minutes.
3. Remove 0.5 mL aliquots of plasma and put into separate 1.5 mL NUNC tubes and transfer to liquid nitrogen storage.

PBMC separation and freezing procedures

1. The cells and plasma remaining from the previous step are transferred into a 15 mL conical tube or 50 mL centrifuge tube depending on volume.
2. Sterile PBS should be added to the suspended whole blood cells in an equal volume and pipetted up and down to mix (1:1).
3. The whole blood-PBS mixture should be carefully overlaid onto 4-5 mL of room temperature LSM or Ficoll-Hypaque solution in a sterile 15 ml conical centrifuge tube. A sharp interface should exist between the LSM and the whole blood mixture. (If the layer of LSM gets mixed with the blood-PBS, the tube should be gently rotated to mix the blood, PBS, and LSM, and transfer to a 50 mL sterile conical tube. An equal volume of PBS is added, and the cells are separated at 600 g for 15 minutes. After removal of LSM-PBS supernatant, return to Step 2).
4. Centrifuge the 15 mL conical tube for 30 minutes at 900 g at room temperature. The mononuclear leukocytes (principally lymphocytes and monocytes) will band at plasma/LSM interface.
5. The fluffy white layer just below the plasma layer should be aspirated off and transferred to an appropriately labeled 15 mL sterile conical centrifuge tube. Be careful to remove only the interface and a minimum amount of the LSM or Ficoll-Hypaque.
6. Add three volumes of PBS to the cell suspension and or enough to fill conical and mix by pipetting up and down.
7. Centrifuge at 500 g for 10 minutes.
8. Aspirate off and discard supernatant, taking care not to disturb pellet.
9. Resuspend in 12 mL of PBS. Take 10 µl of suspension for cell counting (dilute accordingly whether using a hemocytometer or automated cell counter). Centrifuge again for 10 minutes at 500g to wash cells.
10. Using a 1 ml pipette, the *DMSO freezing mixture should be added dropwise to the cell pellet suspension. Gently finger-tap between drops to resuspend cells. If the cell pellet is small, only 0.5 mL of freezing media is added (and only one aliquot of cells is frozen). If the cell pellet is large, up to 2 mL of freezing media can be added in a drop wise fashion. (Cell densities of 1-10 million PBMC/ml are best for cryopreservation. If a hemocytometer is available, the optimal concentration is 5 x 10^6 PBMC/mL).

***Important: Do not put the DMSO containing media on the cell button all at once.**

Freeze the cell suspension in 0.5 mL aliquots in sterile NUNC vials by placing the NUNC tubes in a room temperature, alcohol saturated, control rate freezer container and store in

the -80°C freezer overnight. Transfer the cell suspension into the liquid nitrogen temperature freezer for long-term storage the next working day.

GENERAL

Plasma and PBMC specimens may be shipped in batches monthly. To ship blood specimens, use a diagnostic shipper approved for a volume of at least 30 cc. The use of the SAF-T-PAK STP 210 diagnostic cardboard shipper is recommended. These shippers may be ordered at the SAF-T-PAK website www.saftpak.com. The following instructions below are for use with the recommended STP-210 shipper. If using another federally approved diagnostic shipper, please follow instructions provided for that specific shipper.

NOTE: Specimens MUST BE SHIPPED **Sundays** through **Thursday** as an OVERNIGHT PRIORITY shipment. Specimens are **NOT ACCEPTED ON SATURDAYS OR SUNDAYS**.

SPECIMEN PREPARATION, PACKAGING, AND SHIPMENT

Blood specimens

With a black, water resistant, sharpie pen, label each specimen with the following information:

- AMC Protocol #098
- AMC Participant ID#
- Date and time of collection
- Specimen type: i.e., P = Plasma; PBMCs= Peripheral Blood Mononuclear Cells
- Specimen purpose: Research

Specimen shipment

- Seal the tops of the tube(s) with Parafilm.
- Place the sealed tube(s) into bubble wrap (provided in STP-210 kit).
- Tape around the bubble wrap so that the roll stays together and the tubes cannot fall out or break.
- Place absorbent material sheet around the bubble wrapped tubes and slip into a biohazard poly-bag and "self-seal."
- Place poly-bag containing tubes into the white TYVEK bag and seal.
- Place the TYVEK bag into the STP-210 diagnostic cardboard shipper. Seal the cardboard shipper with clear packing/shipping tape.
- Affix the FEDEX airbill on blank side of the shipper making sure that it is marked "FEDEX PRIORITY OVERNIGHT."
- Mark "OTHER" in the airbill under "Packaging." Please use the FedEx # available on the AMC member's only website.
- Under airbill section "Special Handling" indicate "YES-SHIPPERS DECLARATION NOT REQUIRED."

- Place “From/To” information onto areas provided on the shipper.

***PLEASE DOUBLE CHECK PACKAGING OF SHIPPER AND DO NOT DEVIATE FROM REQUESTED LABELING. Shipping frozen aliquots requires the use of packaging acceptable for dry ice and Class 9 label with weight of dry ice written on package.

Mail to:

Sylvia Silver, DA
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Tel: 202-994-2945
Fax: 202-994-5056

D. ***PREPARATION OF TISSUE SAMPLES***

From KS study participant, obtain:

Skin biopsy; formalin-fixed

Three will be obtained: 1). One at baseline; 2). Another at 2 weeks after beginning standard dose NFV; and 3). A third at 2 weeks after beginning high dose NFV. Tissue specimens (punch biopsies) must be placed into no more than 5 mL buffered formalin and processed locally to FFPE. Please refer to the MOP for processing instructions.

Skin biopsy; RNA*later*

Three will be obtained: 1). One at baseline; 2). Another at 2 weeks after beginning standard dose NFV; and 3). A third at 2 weeks after beginning high dose NFV. Tissue specimens (punch biopsies) should be placed into 1 mL RNA later (locally sourced or provided to each site by the AMC Biorepository in batches of 20).

***NOTE**: Specimens can only be accepted **Monday through Friday**. Therefore, specimens can only be shipped **Sunday-Thursday** for delivery the next day. Samples in RNA*later* are to be shipped on cold packs and FFPE block is to be shipped in ambient temperature.

TISSUE specimens from U.S. sites should be shipped to:

Sylvia Silver, DA
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: 202-994-5056

TISSUE specimens from international sites should be shipped to:

Johann Schneider, MMed Anat Path
Division of Anatomical Pathology
National Health Laboratory Service
10th Floor Green Avenue, Room 52
Tygerberg Hospital
Tygerberg
7535 South Africa
Phone: 27-21-938-4041
Fax: 27-21-938-6559
Email: jws2@sun.ac.za

E. ***ORAL SWAB SAMPLES***

Oral swabs will be self-collected by participants daily for 14 days prior to starting study drug (14 baseline swabs) and twice weekly beginning on high dose nelfinavir (14 on-treatment swabs) for quantification of KSHV, EBV, CMV and HSV by qPCR. Swabs and tubes containing buffer will be provided to the sites.

Swabs: Puritan Swabs, Fisher Scientific Polyester; Plastic shaft; 6 x 1/10 in.; 10 pack sterile; 1000/CS Catalog #25-806 1PD.

Buffer: 5X recipe as follows (500 mL):

- KCL, ACS Reagent Sigma #P3911-500G 18.65g
- Tris-HCl, 1M, pH8 Sigma #T3038 25 mL
- EDTA, 0.5M, PH8 Sigma #3690 125 mL
- Igepal CA_630 Sigma #l3021-500mL 25mL

With a black, water resistant, sharpie pen, label each tube with the following information:

- AMC Protocol # 098
- AMC Participant ID#
- Date and time of collection
- Specimen type: Oral swabs

Participants will be instructed how to collect swabs in the following manner (See Appendix XIII):

- Rub the tip of the swabs over the inside of the both cheeks (buccal mucosa), along the upper and lower gum-lines inside and outside of the teeth, around the hard palate and across the soft palate; end with the posterior wall as tolerated by the participant.
- Place the swab into opened buffer tube labeled with the participant's identification number.
- Break off the long cardboard handle so that the lid can be put on tightly.
- Complete the swab collection portion of the visit CRF.

- Place the buffer tubes from one participant in one plastic bag.

Swabs should be stored and shipped at room temperature.

SWAB specimens from U.S. sites should be shipped to:

Sylvia Silver, DA
George Washington Medical Center
Ross Hall, Room 118
2300 I Street, NW
Washington, DC 20037
Phone: 202-994-2945
Fax: 202-994-5056

SWAB specimens from international sites should be shipped to:

Johann Schneider, MMed Anat Path
Division of Anatomical Pathology
National Health Laboratory Service
10th Floor Green Avenue, Room 52
Tygerberg Hospital
Tygerberg
7535 South Africa
Phone: 27-21-938-4041
Fax: 27-21-938-6559
Email: jws2@sun.ac.za

F. RECORD OF SPECIMENS

This study will track specimens via GlobalTrace℠, a component of the AMC Advantage eClinical system. The GlobalTrace℠ shipment manifest must accompany all specimen shipments.

APPENDIX XI: DRUGS KNOWN TO BE METABOLIZED BY SELECTED CYP450 ISOENZYMES

When drugs classified as "substrates" are co-administered with nelfinavir there is the potential for higher concentrations of the "substrate." When nelfinavir is co-administered with compounds classified as "inhibitors," increased plasma concentrations of nelfinavir is the potential outcome. The co-administration of "inducers" would potentially lower plasma nelfinavir concentrations. See Section 3.2.5 for exact recommendations relating to administration of agents that interact with the CYP450 system.

Comprehensive List of Drugs That May Have Potential Interactions

CYP3A4 Substrates			
Albuterol	Docetaxel	Ketoconazole	Quetiapine
Alfentanil	Doxepin	Lansoprazole	Quinidine
Alprazolam	Doxorubicin	Letrozole	Rabeprazole
Amlodipine	Doxycycline	Levomethadyl acetate hydrochloride	Repaglinide
Amprenavir	Efavirenz	Levonorgestrel	Rifabutin
Aprepitant	Eletriptan	Lidocaine	Rifampin
Aripiprazole	Enalapril	Losartan	Ritonavir
Atazanavir	Eplerenone	Lovastatin	Saquinavir
Atorvastatin	Ergoloid mesylates	Medroxyprogesterone	Sertraline
Benzphetamine	Ergonovine	Mefloquine	Sibutramine
Bisoprolol	Ergotamine	Mestranol	Sildenafil
Bortezomib	Erythromycin	Methadone	Simvastatin
Bosentan	Escitalopram	Methylergonovine	Sirolimus
Bromazepam	Estradiol	Methysergide	Sufentanil
Bromocriptine	Estrogens, conj., synthetic	Miconazole	Tacrolimus
Buprenorphine	Estrogens, conj., equine	Midazolam	Tamoxifen
Buspirone	Estrogens, conj., esterified	Miglustat	Tamsulosin

CYP3A4 Substrates			
Busulfan	Estrone	Mirtazapine	Telithromycin
Carbamazapine	Estropipate	Modafinil	Teniposide
Cerivastatin	Ethinyl estradiol	Montelukast	Terbinafine
Chlordiazepoxide	Ethosuximide	Moricizine	Tetracycline
Chloroquine	Etoposide	Nateglinide	Theophylline
Chlorpheniramine	Felbamate	Nefazodone	Tiagabine
Cisapride	Felodipine	Nelfinavir	Ticlopidine
Citalopram	Fentanyl	Nevirapine	Tolterodine
Clarithromycin	Flurazepam	Nicardipine	Toremifene
Clobazam	Flutamide	Nifedipine	Trazodone
Clonazepam	Fosamprenavir	Nimodipine	Triazolam
Clorazepate	Fulvestrant	Nisoldipine	Trimipramine
Cocaine	Gefitinib	Nitrendipine	Troleandomycin
Colchicine	Halofantrine	Norethindrone	Vardenafil
Cyclophosphamide	Haloperidol	Norgestrel	Venlafaxine
Cyclosporine	Ifosfamide	Ondansetron	Verapamil
Dantrolene	Imatinib	Paclitaxel	Vinblastine
Dapsone	Indinavir	Pergolide	Vincristine
Delavirdine	Irinotecan	Phencyclidine	Vinorelbine
Diazepam	Isosorbide dinitrate	Pimozide	Zolpidem
Digitoxin	Isosorbide mononitrate	Pioglitazone	Zonisamide
Dihydroergotamine	Isradipine	Primaquine	Zopiclone

CYP3A4 Substrates			
Diltiazem Disopyramide	Itraconazole Ketamine	Progesterone	

CYP3A4 Inhibitors			
Acetominophen	Diclofenac	Lopinavir	Prednisolone
Acetazolamide	Dihydroergotamine Diltiazem	Losartan	Primaquine
Amioderone	Disulfiram	Lovastatin	Progesterone
Amlodipine	Docetaxel	Mefloquine	Propofol
Amprenavir	Doxorubicin	Mestranol	Propoxyphene
Anastrozole	Doxycycline	Methadone	Quinidine
Aprepitant	Drospirenone	Methimazole	Quinine
Atazanavir	Efavirenz	Methoxsalen	Quinupristin
Atorvastatin	Enoxacin	Methylprednisolone	Rabeprazole
Azelastine	Entacapone	Metronidazole	Risperidone
Azithromycin	Ergotamine	Miconazole	Ritonavir
Betamethasone	Erythromycin	Midazolam	Saquinavir
Boceprevir	Ethinyl estradiol	Mifepristone	Selegiline
Bortezomib	Etoposide	Mirtazapine	Sertraline
Bromocriptine	Felodipine	Mitoxantrone	Sildenafil
Caffiene	Fentanyl	Modafinil	Sirolimus
Cerivastatin	Fluconazole	Nefazodone	Sulconazole
Chloramphenicol	Fluoxetine	Nelfinavir	Tacrolimus

CYP3A4 Inhibitors			
Chlorzoxazone	Fluvastatin	Nevirapine	Tamoxifen
Cimetadine	Fluvoxamine	Nicardipine	Telaprevir
Ciprofloxacin	Fosamprenavir	Nifedipine	Telithromycin
Cisapride	Glyburide	Nisoldipine	Teniposide
Clarithromycin	Grapefruit juice	Nitrendipine	Testosterone
Clemastine	Haloperidol	Nizatidine	Tetracycline
Clofazimine	Hydralazine	Norfloxacin	Ticlopidine
Clotrimazole	Ifosfamide	Olanzapine	Tranylcypromine
Clozapine	Imatinib	Ombitasvir	Trazodone
Cobicistat	Indinavir	Omeprazole	Troleandomycin
Cocaine	Irbesartan	Orphenadrine	Valproic acid
Conivaptan	Isoniazid	Oxybutynin	Venlafaxine
Cyclophosphamide	Isradapine	Paritaprevir	Verapimil
Cyclosporine	Itraconazole	Paroxetine	Vinblastine
Danazol	Ketoconazole	Pentamidine	Vincristine
Danoprevir	Lansoprazole	Pergolide	Vinorelbine
Darunavir	Lidocaine	Phencyclidine	Voriconazole
Dasabuvir	Lomustine	Pilocarpine	Zafirlukast
Delavirdine		Pimozide	Ziprasidone
Desipramine		Posaconazole	
Dexmedetomidine		Pravastatin	
Diazepam			

CYP3A4 Inducers			
Aminoglutethimide	Hydrocortisone (high dose)	Phenobarbital	Rifapentine
Carbamazapine	Methylprednisolone (high dose)	Phenytoin	St. John's wort
Cortisone (high dose)	Modafinil	Prednisone (high dose)	
Dexamethasone (high dose)	Nevirapine	Primidone	
Efavirenz	Oxcarbazepine	Rifabutin	
Fosphenytoin	Pentobarbital	Rifampin	

CYP2C19 Substrates			
Amitriptyline	Glimepiride	Losartan	Suprofen
Celecoxib	Glipizide	Meloxicam	Tamoxifen
Diclofenac[1]	Glyburide	S-naproxen→Norpiroxicam	Tolbutamide[1]
Fluoxetine	Ibuprofen	Nateglinide	Torsemide
Fluvastatin	Irbesartan	Phenytoin-4-OH2	Valproic acid
Glibenclamide	Lornoxicam	Rosiglitazone	S-warfarin[1]
			Zafirlukast

CYP2C19 Inhibitors			
Amiodarone	Fluvoxamine[2]	Phenylbutazone	Teniposide
Efavirenz	Isoniazid	Probenicid	Voriconazole
Fenofibrate	Lovastatin	Sertraline	Zafirlukast
Fluconazole	Metronidazole	Sulfaphenazole[1]	
Fluvastatin	Paroxetine		

CYP2C19 Inducers			
Carbamazepine	Nevirapine	Rifampin	St. John's Wort
Enzalutamide	Phenobarbital	Secobarbital	

Adapted from Cytochrome P-450 Enzymes and Drug metabolism. In: Lacy CF, Armstrong LL, Goldman MP, Lance LL eds. Drug Information Handbook 12TH ed. Hudson, OH; LexiComp Inc. 2004: 1619-1631.

(1). Malhorta *et al*. (2000). Clin Pharmacol Ther. 69:14-23

(2). Mathijssen *et al*. (2002). J Natl Cancer Inst. 94:1247-1249

(3). Frye *et al*. (2004). Clin Pharmacol Ther. 76:323-329

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

APPENDIX XII: DRUGS KNOWN OR SUSPECTED TO INHIBIT KSHV REPLICATION

Direct Acting Antivirals
acyclovir
adefovir
cidofovir
foscarnet
ganciclovir
valacyclovir
valganciclovir

HIV Protease Inhibitors
atazanivir
darunivir
fosempranavir
lopinavir
ritonavir
tipranavir

APPENDIX XIII: PARTICIPANT INSTRUCTIONS FOR ORAL SWABS

YOU MUST KEEP THIS DIARY AND BRING IT TO YOUR APPOINTMENT

Study Participant ID #: _____

You will collect one oral swab on 14 separate days before you start nelfinavir (14 swabs total).

If you begin taking a higher dose of nelfinavir, you will collect more oral swabs after one week of taking the higher dose. You will collect two oral swabs every week for seven weeks (14 swabs total).

How to collect the oral swabs

1) Collect the oral swabs in the morning before brushing your teeth or eating.

   If you not able to collect the swab in the morning, wait one hour after eating, drinking, or brushing your teeth to collect the oral swabs.

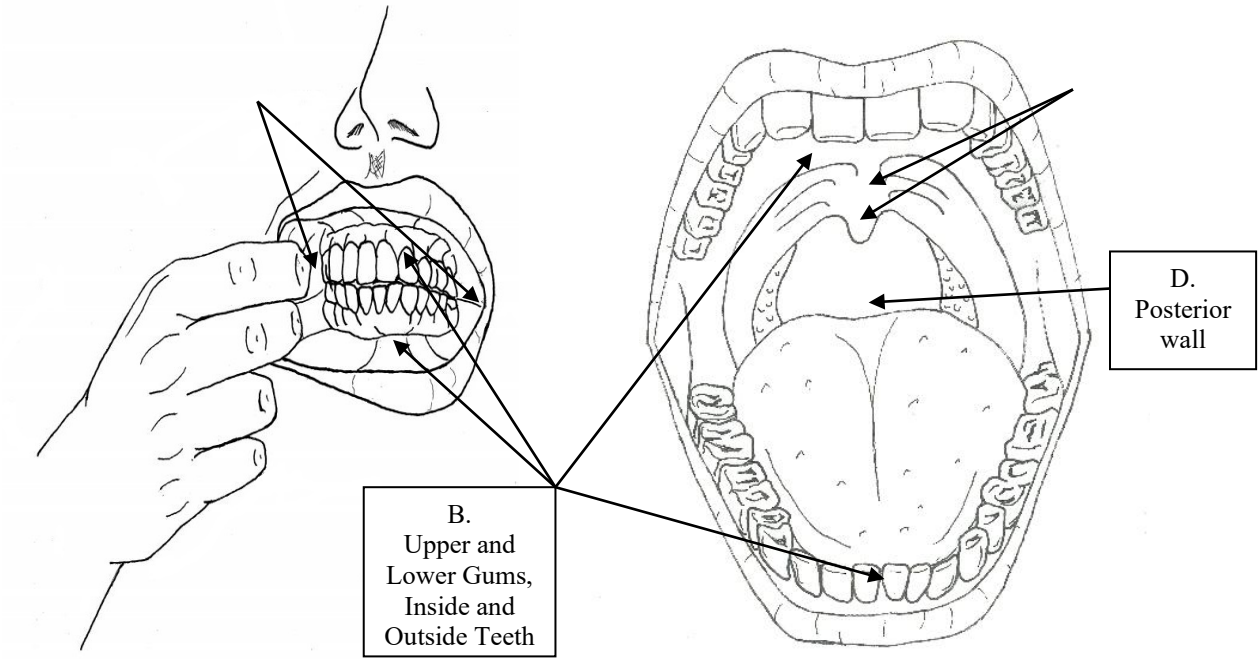
2) Rub the tip of the swab **over each of these areas** in your mouth as shown below:

   A. The inside of the both cheeks

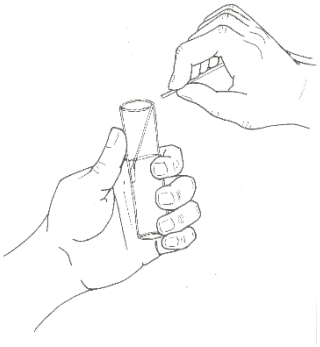
   B. Along the upper and lower gum-lines inside and outside of the teeth

   C. Around the hard palate and across the soft palate

   D. End with the posterior wall (*if you are able*)



Study Participant ID #: _____



3) Place the swab into an opened tube.
4) Break off the long cardboard handle so that the lid can be put on tightly.
5) Place the tubes into the plastic bag and keep the swabs at room temperature to bring to your next study visit.

Please record in the diary below the date that oral swab was done. Be sure to record the swabs when you do them and avoid writing entries for several days at once. When you are finished, bring this diary with you to your next study visit. In the "Comments" section write any problems you are having collecting the swabs or if you missed a swab.

Oral Swab Collection Before Starting Nelfinavir			
Day of Collection	**Date MM/DD/YYYY**	**Time Swab Collected (circle AM/PM)**	**Comments**
1	___/___/_____	___:___ AM PM	
2	___/___/_____	___:___ AM PM	
3	___/___/_____	___:___ AM PM	
4	___/___/_____	___:___ AM PM	
5	___/___/_____	___:___ AM PM	
6	___/___/_____	___:___ AM PM	
7	___/___/_____	___:___ AM PM	
8	___/___/_____	___:___ AM PM	
9	___/___/_____	___:___ AM PM	
10	___/___/_____	___:___ AM PM	
11	___/___/_____	___:___ AM PM	
12	___/___/_____	___:___ AM PM	
13	___/___/_____	___:___ AM PM	
14	___/___/_____	___:___ AM PM	

Please return the swabs to your doctor with your diary at your next study visit.

Study Participant ID #: _____

Please record in the diary below the date that oral swab was done. Be sure to record the swabs when you do them and avoid writing entries for several days at once. When you are finished, bring this diary with you to your next study visit. In the "Comments" section write any problems you are having collecting the swabs or if you missed a swab.

Oral Swab Collection on High Dose Nelfinavir				
Weeks	**Swabs**	**Date MM/DD/YYYY**	**Time Swab Collected (circle AM/PM)**	**Comments**
Week 1	**No Swabs**			
Week 2	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	
Week 3	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	
Week 4	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	
Week 5	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	
Week 6	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	
Week 7	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	
Week 8	Swab 1	___/___/_____	___:___ AM PM	
	Swab 2	___/___/_____	___:___ AM PM	

Please return the swabs to your doctor with your diary at your next study visit.

APPENDIX XIV: PARTICIPANT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Participants, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The participant _____ is enrolled on a clinical trial using the experimental study drug, nelfinavir. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Nelfinavir interacts with certain specific enzymes in your liver* and may affect the heart's electrical activity (QTc prolongation)**.

* The enzyme(s) in question is/are **CYP3A and CYP2C19**. Nelfinavir is broken down by this enzyme and may be affected by other drugs that inhibit or induce this enzyme.

** The heart's electrical activity may be affected by nelfinavir. The study doctor may be concerned about QTc prolongation and any other medicine that is associated with greater risk for having QTc prolongation.

To the participant: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Nelfinavir may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Nelfinavir must be used very carefully with other medicines that use certain liver enzymes or that may affect your heart's electrical activity. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inducers/inhibitors or substrates of CYP3A or CYP2C19, or any medicine associated with greater risk for having QTc prolongation.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.
- Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **nelfinavir.** This clinical trial is sponsored by the NCI. **Nelfinavir** may interact with drugs that are **processed by your liver, or affects the electrical activity of your heart**. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Nelfinavir interacts with a **specific liver enzymes called CYP3A and CYP2C19, heart's electrical activity (QTc prolongation)**, and must be used very carefully with other medicines that interact with **Nelfinavir**.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **"strong inducers/inhibitors or substrates of CYP3A and CYP2C19, or affect the heart's electrical activity.**"
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____ and can be contacted at _____.

SUMMARY OF CHANGES

A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma

Version 4.0

NCI Protocol #: AMC-098
Local Protocol #: AMC-098

NCI Version Date: 08DEC2020
Protocol Date: 08DEC2020

I. Scientific and Substantive Changes

#	Section	Comments
1.	WHAT EXTRA TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?	Added statements communicating that if previously submitted baseline tissue samples are inadequate to perform IHC studies, additional slides from the diagnostic punch biopsy may be requested to perform such studies. See protocol summary of changes item 3 regarding this change.

II. Administrative and Editorial Changes:

#	Section	Comments
2.	Global	Version number and version date were updated from v3.0 dated 13FEB2019 to v4.0 dated 08DEC2020
3.	HOW LONG WILL I BE IN THIS STUDY?	Participants will be followed for 8 weeks after discontinuing nelfinavir unless in the opinion of the treating physician, the participant should start an alternative therapy sooner for treatment of KS. Instructions were added requiring follow-up evaluations to be completed before participants start a new therapy to treat KS.
4.	WHERE CAN I GET MORE INFORMATION?	Dr. Gantt's (Protocol Chair) address and contact information have been updated.

AMC-098 MODEL INFORMED CONSENT FORM

Study Title for Study Participants**: A Study of Nelfinavir for Treating Kaposi Sarcoma**

Official Study Title for Internet Search on **http://www.ClinicalTrials.gov**: **A Pilot Study of Nelfinavir for the Treatment of Kaposi Sarcoma**

A Clinical Trial of the AIDS Malignancy Consortium (AMC)

WHAT IS THE USUAL APPROACH TO MY CANCER?

People with Kaposi sarcoma who are not in this study are usually treated with intravenous chemotherapy (cancer fighting drugs given through a needle in a vein), cryotherapy (freezing of the cancer), radiation, or other treatments depending on how severe the disease is. Sometimes combinations or sequences of these treatments are used, and your doctor can explain which may be best for you. These treatments can reduce symptoms and may stop the tumor from growing for several months or more.

WHAT ARE MY OTHER CHOICES IF I DO NOT TAKE PART IN THIS STUDY?

If you decide not to take part in this study, you have other choices. For example:

- you may choose to have the usual approach described above
- you may choose to take part in a different study, if one is available, or
- you may choose not to be treated for cancer

WHY IS THIS STUDY BEING DONE?

You are being asked to participate in this study because you are an adult with Kaposi sarcoma that has not been improving. The purpose of this study is to test the good and bad effects of the medicine called nelfinavir. Nelfinavir could shrink or cure your cancer, but it could also cause side effects. Nelfinavir is FDA approved to treat HIV, but it has not yet been tested or FDA approved to treat people who already have Kaposi sarcoma. Nelfinavir has also been shown to kill the Kaposi sarcoma-associated herpes virus (KSHV) that causes Kaposi sarcoma, and has been found to be safe when used at higher doses to treat people with other cancers.

We will test whether regular or higher doses of nelfinavir help shrink your Kaposi sarcoma or cause any side effects. Another purpose of this study is for researchers to learn how well nelfinavir blocks the KSHV virus in people taking the study medicine. There will be about 36 people taking part in this study.

WHAT ARE THE STUDY GROUPS?

All people in the study will get the same study treatment with nelfinavir in the form of pills. Some of the people in the study will have HIV and some will not have HIV. If you join the study, you will first get the regular approved dose of nelfinavir (1250 mg by mouth twice daily). If the regular dose of nelfinavir does not cause your Kaposi sarcoma to shrink enough then you will be given a higher dose of nelfinavir (3125 mg by mouth twice daily). If nelfinavir causes bad side effects, the dose might be lowered or stopped.

Nelfinavir should be taken with a moderately high fat meal, for example that includes oil, butter, eggs, or meat. If you cannot swallow the tablet whole, you may dissolve the tablet in a small amount of water. Drink all of the mixture after the tablet dissolves. Then refill your glass with

water and drink all of the water right away. Do not mix with acidic food or juice (apple juice, applesauce, or orange juice) because it will make it taste bad. Someone in the clinic will talk with you about the diet requirements. If you vomit after taking nelfinavir, do not take more pills to make up the dose.

HOW LONG WILL I BE IN THIS STUDY?

You will be given the regular dose of nelfinavir for up to 8 weeks. After that, you may be given the higher dose of nelfinavir for up to an additional 16 weeks. You may be on nelfinavir for less time if you are not having good effects from it or if your cancer gets bigger, or if your cancer goes away. After you finish the medicine, your doctor will continue to watch you for bad effects and follow your Kaposi sarcoma for up to 8 more weeks. You may be followed for less than 8 weeks if your doctor thinks you should start a new therapy sooner. If you start a new therapy to treat your KS you will no longer be followed as part of this study. You will be in this study for up to 32 weeks, during which time you will track your doses of nelfinavir in a drug diary.

WHAT EXTRA TESTS AND PROCEDURES WILL I HAVE IF I TAKE PART IN THIS STUDY?

Most of the tests that you will have done are part of the usual way people with Kaposi sarcoma are treated. However, there are some extra tests and exams that you will need to do if you join in this study.

Before the study:

- You will need to take a HIV test unless you have had one recently or your usual doctor knows for sure that you do have or do not have HIV.
- If your Kaposi sarcoma was diagnosed without a biopsy (small piece of the Kaposi sarcoma removed by surgery) we will ask your doctor to take a biopsy to make sure that you have Kaposi sarcoma.
- We will ask questions related to the risk of getting HIV, including drug use and sexual behavior.
- You will have an electrocardiogram (EKG) within 4 weeks of starting the study
- You will have a chest X-ray within 4 weeks of starting the study
- If you are a female who may become pregnant, you will have a pregnancy test

During the study:

- You will come to the study clinic every 2 weeks.
- You will have a nutrition assessment in addition to routine physical examinations.
- You will have an EKG two weeks after starting standard dose nelfinavir and two weeks after starting high dose nelfinavir.
- You may receive chest X-rays while on treatment if the doctor thinks you need them.
- If you are a female who may become pregnant you will have a pregnancy test prior to starting standard dose nelfinavir and again prior to starting high dose nelfinavir
- Two Kaposi sarcoma biopsies will be taken before you start nelfinavir, during the regular dose

treatment, and during the higher dose treatment. You will have a total of 6 biopsies. These samples are required in order for you to take part in this study because the research on the sample is an important part of the study. We will use the biopsies to see how nelfinavir works on Kaposi sarcoma and the KSHV virus that causes Kaposi sarcoma. The biopsy for the study is done in a similar way to biopsies done for cancer diagnosis. Local anesthesia will be used for your comfort. If the tissue from the biopsy is not adequate, the study doctors may need to use some additional the tissue left over from your biopsy when you were diagnosed with cancer to perform these tests.

- The biopsies will be very small (only a few millimeters across). Adverse effects from these biopsies are very uncommon and include mild pain, bruising, bleeding and low risk of infection.
- We will ask you to collect saliva with a swab in your mouth daily for 14 days before you start the nelfinavir treatment. During treatment we will ask you to collect saliva with a swab twice a week for 7 weeks, during weeks 10-16 of the study. We will use these swabs to see how the nelfinavir works against the KSHV virus that causes Kaposi sarcoma. This virus is found in the saliva of many people with Kaposi sarcoma. Collecting these swabs is painless.
- Before you start nelfinavir, we will draw blood samples (about 2 tablespoons total) at separate screening visits for research tests. While you are taking nelfinavir, we will draw about 1 tablespoon of blood every two weeks for research tests. These tests will monitor the good and bad effects of nelfinavir. These tests also measure how nelfinavir works against the KSHV virus that causes Kaposi sarcoma. We will also use these samples to test for other viruses that occur with HIV infection and Kaposi sarcoma.

Neither you nor your health care plan/insurance carrier will be billed for the collection of the biopsies, saliva swabs, or any blood tests that are not part of usual care for Kaposi sarcoma. Results from these tests will not be shared with you or your study doctor.

WHAT POSSIBLE RISKS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual.
- You may be asked sensitive or private questions which you normally do not discuss.

If you are taking certain medicines, you may not be able to take part in the study.

If you have HIV, you will continue taking your regular HIV medications throughout the course of the study. If you are on certain HIV medications, you may need to change regimens for safety with the nelfinavir during the time you are in the study and for a short time after. If you choose not to switch to one of the allowed regimens, you may not be able to take part in the study.

If you take part in the study, you will be given a Participant Drug Information and Wallet Card that has information about drugs may interact with nelfinavir which can cause side effects.

It is possible that your Kaposi sarcoma could get worse while taking nelfinavir. Nelfinavir may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have other side effects from nelfinavir or the tests that will be done.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon; some may last a long time.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust nelfinavir to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

COMMON, SOME MAY BE SERIOUS In 100 people receiving nelfinavir, more than 20 and up to 50 may have:
• Diarrhea • Low red blood cell count (anemia) • Low white cell blood cell count

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving nelfinavir, from 2 to 20 may have:
• Fatigue • Dehydration • Heartburn • Nausea • Bloating or gas • Rash • Low platelets • Increase in cholesterol and triglycerides • High blood sugar or diabetes

RARE, AND SERIOUS In 100 people receiving nelfinavir, 3 or fewer may have:
• Infection, especially when white blood cell count is low • Electrical changes in the heart causing abnormal or dangerous heart rhythm

Let your study doctor know of any questions you have about possible side effects. You can ask the study doctor questions about side effects at any time.

Reproductive risks: Reproductive risks have not been seen with nelfinavir. However, higher doses of nelfinavir have not been studied in pregnant or breastfeeding women. You should not get pregnant or breastfeed a baby while in this study. Check with the study doctor about what types of birth control, or pregnancy prevention, to use while in this study. If you are a woman who could become pregnant and are taking hormonal birth control, talk to the study doctor. Nelfinavir can cause hormonal birth control to fail, and may lead to unplanned pregnancy. To take part in this study, you will need to agree to use other non-hormonal birth control methods like condoms or abstinence while taking nelfinavir.

WHAT POSSIBLE BENEFITS CAN I EXPECT FROM TAKING PART IN THIS STUDY?

It is not possible to know at this time if nelfinavir is better than the usual ways Kaposi sarcoma is treated, so this study may or may not help treat your Kaposi sarcoma. This study will help researchers learn things that will help people in the future.

CAN I STOP TAKING PART IN THIS STUDY?

Yes. You can decide to stop at any time. If you decide to stop for any reason, it is important to let the study doctor know as soon as possible so you can stop safely. If you stop, you can decide whether or not to let the study doctor continue to provide your medical information to the organization running the study.

The study doctor will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

The study doctor may take you out of the study:

- If your health changes and the study is no longer in your best interest,
- If new information becomes available,
- If you do not follow the study rules,
- If the study is stopped by the sponsor, IRB, or *(insert as appropriate:* FDA/National Drug Authority of Uganda).

WHAT ARE MY RIGHTS IN THIS STUDY?

Taking part in this study is your choice. No matter what decision you make, and even if your decision changes, there will be no penalty to you. You will not lose medical care or any legal rights.

For questions about your rights while in this study, call the _____ *(insert name of center)* Institutional Review Board at _____ *(insert telephone number). (Note to Local Investigator: Contact information for patient representatives or other individuals at a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can also be listed here.)*

WHAT ARE THE COSTS OF TAKING PART IN THIS STUDY?

Nelfinavir will be supplied to you at no charge by Pfizer, Inc. while you take part in this study. It is possible that the nelfinavir may not continue to be supplied while you are on the study. Although not likely, if this occurs, your study doctor will talk to you about your options.

You and/or your health plan/insurance company will not be billed for the tumor biopsies, saliva

swabs, or extra research blood tests that are not part of usual cancer care.

You and/or your health plan/insurance company will need to pay for all of the other costs of treating your cancer while in this study, including the cost of usual tests, procedures, or medicines to manage any side effects, unless you are told that certain tests are supplied at no charge. Before you decide to be in the study, you should check with your health plan or insurance company to find out exactly what they will pay for.

You will receive $(insert amount) for each study visit you attend. (Note to Local Investigator: retain this information and insert amount as applicable in the local consent. If your site will not be compensating the participant, please use the following language instead: There will not be any monetary compensation for participation in this study.)

WHAT HAPPENS IF I AM INJURED OR HURT BECAUSE I TOOK PART IN THIS STUDY?

If you are injured or hurt as a result of taking part in this study and need medical treatment, please tell your study doctor. The AIDS Malignancy Consortium will not offer to pay for medical treatment for injury. *(Note to SSA site: add appropriate language for coverage of research-related injury costs).* Your insurance company may not be willing to pay for study-related injury. If you feel this injury was a result of medical error, you keep all your legal rights to receive payment for this even though you are in a study.

WHO WILL SEE MY MEDICAL INFORMATION?

Your privacy is very important to us and the researchers will make every effort to protect it. Your information may be given out if required by law. For example, certain states require doctors to report to health boards if they find a disease like tuberculosis. However, the researchers will do their best to make sure that any information that is released will not identify you. Some of your health information, and/or information about your specimen, from this study will be kept in a central database for research. Your name or contact information will not be put in the database.

There are organizations that may inspect your records. These organizations are required to make sure your information is kept private, unless required by law to provide information. Some of these organizations are:

- The sponsor, the AIDS Malignancy Consortium (AMC)
- The drug company supporting the study, Pfizer Inc.
- The Institutional Review Board (IRB) is a group of people who review the research with the goal of protecting the people who take part in the study.
- The Food and Drug Administration (FDA) and the National Cancer Institute (NCI) in the U.S., *(international sites: insert name of national and/or local regulatory authorities who will review study records)*

WHERE CAN I GET MORE INFORMATION?

You may visit the NCI Web site at http://cancer.gov/ for more information about studies or general information about cancer. You may also call the NCI Cancer Information Service to get the same information at: 1-800-4-CANCER (1-800-422-6237).

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

WHO CAN ANSWER MY QUESTIONS ABOUT THIS STUDY?

You can talk to the study doctor about any questions or concerns you have about this study or to report side effects or injuries. Contact the study doctor _____ *(insert name of study doctor[s])* at _____ *(insert telephone number).*

You can also contact the Principal Investigator or Protocol Co-Chairs for the AIDS Malignancy Consortium:

Dr. Soren Gantt
Centre de recherche du CHU Sainte-Just
3175 Côte Sainte-Catherine
Montréal Qc H3T 1C5, Canada
Tel: (604) 875-2151
Email: soren.gantt.hsj@ssss.gouv.qc.ca

Dr. Rachel Bender Ignacio
Child & Family Research Institute
1100 Fairview Ave N, Mailstop E2-112
Seattle, WA 98109
Tel: (206) 667-4628
Email: rbenderi@fredhutch.org

Dr. Richard Ambinder
Room 389, Cancer Research Building
1650 Orleans Street
Baltimore, MD 21287
Tel: (410)-955-8839
Email: Rambind1@jhmu.edu

OPTIONAL SAMPLE COLLECTIONS FOR LABORATORY STUDIES AND DONATION OF LEFTOVER TISSUE SAMPLES TO THE AIDS AND CANCER SPECIMEN RESOURCE (ACSR)

This section is about optional studies you can choose to take part in

Researchers are trying to learn more about cancer, HIV/AIDS, and other health problems. Much of this research is done using samples from your tissue, blood, urine, or other fluids. Through these studies, researchers hope to find new ways to prevent, detect, treat, or cure health problems. Some of these studies may be about genes. Genes carry information about features that are found in you and in people who are related to you. Researchers are interested in the way that genes affect how your body responds to treatment.

If you choose to take part in this study, the study doctor for the main study would like to collect unused blood and biopsy tissue left over after the study is done. The researchers ask your permission to store and use your samples and related health information (for example, your response to cancer treatment, results of study tests and medicines you are given) for medical research. The research that may be done is unknown at this time. Storing samples for future studies is called "biobanking." The Biobank is being run by the **AIDS and Cancer Specimen Resource** and is supported by the National Cancer Institute.

What is involved?

If you agree to take part, here is what will happen next:

1) Your sample and some related health information will be stored in the ACSR Biobank, along with samples and information from other people who take part. The samples will be kept until they are used up. Information from your medical record may be updated after the study is over.
2) Qualified researchers can submit a request to use the materials stored in the ACSR. A science committee at the ACSR will review each request. There will also be an ethics review to ensure that the request is necessary and proper. Researchers will not be given your name or any other information that could directly identify you.
3) Neither you nor your study doctor will be notified when research will be conducted or given reports or other information about any research that is done using your samples.
4) Some of your genetic and health information may be placed in central databases that may be public, along with information from many other people. Information that could directly identify you will not be included.

What are the possible risks?

1) There is a risk that someone could get access to the personal information in your medical records or other information researchers have stored about you.
2) There is a risk that someone could trace the information in a central database back to you. Even without your name or other identifiers, your genetic information is unique to you. The researchers believe the chance that someone will identify you is very small, but the risk may change in the future as people come up with new ways of tracing information.
3) In some cases, this information could be used to make it harder for you to get or keep a job or insurance. There are laws against the misuse of genetic information, but they may not give full protection. There can also be a risk in knowing genetic information. New health information about inherited traits that might affect you or your blood relatives could be found during a study. The researchers believe the chance these things will happen is very small, but cannot promise that they will not occur.

How will information about me be kept private?

Your privacy is very important to the researchers and they will make every effort to protect it. Here are just a few of the steps they will take:

1) When your sample(s) is sent to the researchers, no information identifying you (such as your name) will be sent. Samples will be identified by a unique code only.
2) The list that links the unique code to your name will be kept separate from your sample and health information. The ACSR and AMC staff with access to the list must sign an agreement to keep your identity confidential.
3) Researchers to whom the ACSR and the AMC send your sample and information will not know who you are. They must also sign an agreement that they will not try to find out who you are.
4) Information that identifies you will not be given to anyone, unless required by law.
5) If research results are published, your name and other personal information will not be used.

What are the possible benefits?

You will not benefit from taking part. The researchers, using the samples from you and others, might make discoveries that could help people in the future.

Are there any costs or payments?

There are no additional costs to you or your insurance for these optional studies. You will not be paid for taking part. If any of the research leads to new tests, drugs, or other commercial products, you will not share in any profits.

What if I change my mind?

If you decide you no longer want your samples to be used, you can call the study doctor, _____, *(insert name of study doctor for main trial)* at _____ *(insert telephone number of study doctor for main trial)* who will let the researchers know. Then, any sample that remains in the bank will no longer be used and related health information will no longer be collected. Samples or related information that have already been given to or used by researchers will not be returned.

What if I have more questions?

If you have questions about the use of your samples for research, contact the study doctor, _____, *(insert name of study doctor for main trial)*, at _____ *(insert telephone number of study doctor for main trial)*.

Please circle your answer to show whether or not you would like to take part in each option:

Samples for future research studies:

My samples and related information may be donated to ACSR Biobank for use in future health research.

YES NO

I agree to have my samples undergo genetic testing to learn about, prevent, diagnose, or treat HIV-related diseases and cancer.

YES NO

This is the end of the section about optional studies.

MY SIGNATURE AGREEING TO TAKE PART IN THE MAIN STUDY

I have read this consent form or had it read to me. I have discussed it with the study doctor and my questions have been answered. I will be given a signed copy of this form. I agree to take part in the study.

Participant's signature: _____

Date of signature: _____

Signature of person(s) conducting the informed consent discussion: _____

Date of signature: _____

ATTACHMENT 1: AMC CERTIFICATE OF CONFIDENTIALITY STATEMENT

The NIH has given the AMC a Certificate of Confidentiality. The Certificate does not mean that the NIH or the U.S. Government recommend that you take part in this study. This Certificate helps us keep your health information private.

Your records for this study will have information that may identify you. This Certificate lets us turn down legal demands for your study records. We can use the Certificate to turn down demands for records from a U.S. court. The Certificate can be used in any federal, state, or local legal matters. We will use the Certificate to turn down any demands for your study records. The cases where we cannot use the Certificate are explained below.

We cannot use the Certificate to turn down a demand from the U.S. Government for study records. This applies to audits or reviews of the AMC. This also applies to study records that we have to report to the FDA.

The Certificate does not stop you or your family members from sharing your health information. It does not stop you from talking about taking part in this study. You may give written permission for an insurer, employer, or other person to get copies of your study records. If you give permission, we cannot use the Certificate to say no to a request for your study records.