OncoPep, Inc.

A Phase 1/2a Dose Escalation Study of PVX-410, a Multi-Peptide Cancer Vaccine, in Patients with Smoldering Multiple Myeloma

Protocol Number: 2010-001

This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

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INVESTIGATOR STATEMENT

I understand that all documentation provided to me by OncoPep, Inc., or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB). No changes will be made to the study protocol without the prior written approval of OncoPep, Inc., and the IRB, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

_____ _____

Investigator Signature Date

CLINICAL STUDY SYNOPSIS

Protocol Title:	A Phase 1/2a Dose Escalation Study of PVX-410, a Multi-Peptide Cancer Vaccine, in Patients with Smoldering Multiple Myeloma
Protocol Number:	2010-001
Study Phase:	1/2a
Primary Objective:	Determine the safety and tolerability of the PVX-410 tumor vaccine regimen alone and in combination with lenalidomide in patients with smoldering multiple myeloma (SMM).
Study Design:	Study 2010-001 is a phase 1/2a, multi-arm, open-label, multi-center, dose escalation study of PVX-410 for injection, a multi-peptide cancer vaccine. All patients must provide written informed consent before any samples are collected or evaluations performed in this study. A Screening blood sample for HLA typing with sequence-based subtyping is to be collected before the performance of any other Screening procedures. If the patient has had HLA typing previously performed by an accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for Screening. If the patient has not had HLA typing performed previously or an acceptable result is not available from the previous test, then a blood sample for HLA typing with sequence-based subtyping may be collected under the auspices of this protocol >4 weeks before Week 0, but only after the patient provides consent to participate in this study. Patients must be determined to be HLA-A2-positive (HLA-$A2^+$) in order to proceed with Screening; if the patient is demonstrated to be HLA-$A2^+$, then the Screening process may continue, with all other Screening assessments to be performed within 4 weeks before Week 0. Patients who are demonstrated to be HLA-$A2^-$ will be considered screen failures, and no additional Screening assessments will be performed. Patients determined to be eligible, based on Screening assessments, will be assigned to 1 of 3 treatment cohorts, enrolled in the study, and assigned a baseline date (Week 0, first study treatment). The 3 treatment cohorts are as follows: • Low-dose cohort, in which all patients are to

receive PVX-410 at the low-dose of 0.4 mg (total peptide dose).

- Target-dose cohort, in which all patients are to receive PVX-410 at the target dose of 0.8 mg (0.2 mg/peptide or 0.8 mg total).
- PVX-410 + lenalidomide cohort, in which all patients are to receive PVX-410 at the target dose of 0.8 mg (0.2 mg/peptide or 0.8 mg total) plus 3 cycles of lenalidomide 25 mg.

All patients will also receive 0.5 mL (1 mg) Hiltonol® (poly-ICLC) (2 mg/mL) via intramuscular (IM) injection at the time of PVX-410 administration.

The first 3 patients enrolled are to receive PVX-410 at the low-dose of 0.4 mg (total peptide dose). These 3 patients are to be treated sequentially. Each patient in the low-dose cohort must complete the Week 2 visit, with safety data reviewed by the Dose Escalation Safety Cohort Committee, before the next patient may be treated.

- If 0 of 3 patients experiences a dose-limiting toxicity (DLT), then dose escalation will proceed to the target dose level.
- If 1 of 3 patients experiences a DLT, then 3 additional patients will be enrolled at the current dose level. Escalation to the target dose will continue if 1 of 6 patients experienced a DLT. No more than 1 out of 6 patients may experience a DLT for the dose level to be considered acceptable.
- If ≥2 patients experience a DLT at the low-dose level, then the enrollment and treatment of patients will be stopped.

After the last patient in the low-dose cohort receives the 6th study vaccine dose, treatment of patients at the target-dose cohort may commence. A total of 10[1] patients are planned to be enrolled sequentially at

[1] At the time of this amendment; enrollment in the low-dose and target-dose cohorts is complete; a total of 3 and 9 patients were enrolled, respectively. Although 10 patients were planned to be enrolled in the target-dose cohort, the Sponsor elected not to enroll the 10th patient, as the Sponsor determined sufficient safety and efficacy data to support this amendment were available from the 12 treated patients.

the target dose (0.8 mg; 0.2 mg/peptide or 0.8 mg total). The next 2 patients must complete the Week 2 visit, with safety data reviewed by the Dose Escalation Safety Cohort Committee, before the next patient may be enrolled. Thereafter, the remaining patients in the target-dose cohort are to be treated sequentially after a 2-day interval from the previous patient's first dose.

After the last patient in the target-dose cohort receives their final vaccination (6^{th}), treatment in the PVX-410 + lenalidomide cohort may commence. A total of 10 patients are planned to be enrolled sequentially in this cohort and receive PVX-410 at the target dose (0.8 mg; 0.2 mg/peptide or 0.8mg total) plus 3 cycles of lenalidomide, with a cycle consisting of lenalidomide 25 mg orally (PO) daily for 21 days (Days 1-21) followed by a 7-day rest period; thus, each lenalidomide cycle is 28 days. Enrollment in this cohort (ie, the PVX-410+lenalidomide cohort) will commence after review of safety data and Baseline to Month 1 follow-up enzyme-linked immunosorbent spot (ELISPOT) and tetramer data from the low-dose and target-dose cohort. Furthermore, enrollment will be staggered by 2 days; thus, the previous patient must be followed for 2 days after the first PVX-410 dose given in combination with lenalidomide before the next patient can start treatment.

The Dose Escalation Safety Cohort Committee will not be formally reviewing the safety data for the last 8 patients in the target-dose cohort (PVX-410 alone) or the PVX-410 + lenalidomide cohort, unless a DLT is observed or any event is observed that requires review by the committee. If a DLT occurs, enrollment will be interrupted and a safety review meeting convened. A decision regarding modification or discontinuation of study vaccine and/or patient enrollment will be made by the sponsor in consultation with the investigators and medical monitor.

During treatment, patients will attend study center visits at Weeks 2 (±3 days), 4 (±3 days), 6 (±3 days), 8 (±3 days), and 10 (±3 days) for study vaccine administration and safety, activity, and immunologic assessments. After completion of treatment, patients will attend follow-up study center visits at post-treatment Months 1 (± 1 week), 2 (± 1 week), 3 (± 1 week), 6 (± 1 week), 9 (± 1 week), and 12 (± 1 week). Month 12 is the final study visit.

Number of Patients Planned:	Approximately 20 to 22 patients are planned to be enrolled.
Diagnosis and Main Criteria for Inclusion:	Patients meeting all of the following criteria will be considered eligible for study entry:

1. Patient has confirmed SMM according to a definition derived from the International Myeloma Working Group (IMWG) definition: serum M-protein ≥3 g/dL or bone marrow clonal plasma cells (BMPC) >10%, or both, along with normal organ and marrow function (CRAB) within 4 weeks before baseline.
   - C: Absence of hypercalcemia, evidenced by a calcium <10.5 mg/dL.
   - R: Absence of renal failure, evidenced by a creatinine <2.0 mg/dL or calculated creatinine clearance (using the Modification of Diet in Renal Disease [MDRD] formula) >50 mL/min.
   - A: Absence of anemia, evidenced by a hemoglobin >10 g/dL.
   - B: Absence of lytic bone lesions on standard skeletal survey.
2. Patient is at higher than average risk of progression to active MM, defined as having 2 or more of the following features:
   - Serum monoclonal (M)-protein ≥3 g/dL.
   - BMPC >10%.
   - Abnormal serum free light chain (FLC) ratio (0.26-1.65).
3. Patient is aged 18 years or older.
4. Patient has a life expectancy of greater than 6 months
5. Patient is HLA-A2 positive.
6. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
7. Patient has adequate bone marrow function, evidenced by a platelet count $\geq 75\times10^9$/L and an absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L within 2 weeks before baseline.
8. Patient has adequate hepatic function, evidenced by a bilirubin ≤2.0 mg/dL and an alanine

transaminase (ALT), and aspartate transaminase (AST) ≤2.5× the upper limit of normal (ULN) within 2 weeks before baseline.

9. If of child-bearing potential, patient agrees to use adequate birth control measures during study participation.
10. If a female of child-bearing potential, patient has negative urine pregnancy test results within 2 weeks before baseline and is not lactating.

    In the PVX-410 + lenalidomide cohort, females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
11. Patient (or his or her legally accepted representative) has provided written informed consent to participate in the study.
12. In the PVX-410 + lenalidomide cohort, all study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.

Patients meeting any of the following criteria are not eligible for study entry:

1. Patient has symptomatic multiple myeloma, as defined by any of the following:
   - Lytic lesions or pathologic fractures.
   - Anemia (hemoglobin <10 g/dL).
   - Hypercalcemia (corrected serum calcium >11.5 mg/dL).
   - Renal insufficiency (creatinine >2 mg/dL).
   - Other: symptomatic hyperviscosity, amyloidosis.
2. Patient has a history of a prior malignancy within the past 5 years (excluding resected basal cell carcinoma of the skin or in situ cervical cancer).
3. Patient has abnormal cardiac status, evidenced by any of the following:
   - New York Heart Association (NYHA) stage III or IV congestive heart failure (CHF).
   - Myocardial infarction within the previous 6 months.

- Symptomatic cardiac arrhythmia requiring treatment or persisting despite treatment.

4. Patient is receiving any other investigational agent.
5. Patient has a current active infectious disease or positive serology for human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
6. Patient has a history of or current auto-immune disease.
7. Patient has been vaccinated with live attenuated vaccines within 4 weeks before study vaccination.

Test Products, Doses, and Mode of Administration:

Each patient will receive 6 doses of PVX-410 0.4 mg (0.1 mg/peptide or 0.4 mg total) or 0.8 mg (0.2 mg/peptide or 0.8 mg total) emulsified in Montanide ISA 720 VG (Seppic, Inc.), biweekly (Weeks 0, 2, 4, 6, 8, and 10) via subcutaneous (SC) injection.

Patients enrolled in the PVX-410+lenalidomide cohort also will receive 3 cycles of lenalidomide, with a cycle consisting of lenalidomide 25 mg orally (PO) daily for 21 days (Days 1-21) followed by a 7-day rest period; thus, each lenalidomide cycle is 28 days.

All patients also will receive 0.5 mL (1 mg) Hiltonol® (poly-ICLC) (2 mg/mL) via intramuscular (IM) injection at the time of PVX-410 administration.

Patients will be observed in the clinic for 1 hour after each study vaccine dose.

No PVX-410 dose modifications will be allowed. The lenalidomide dose may be modified for the management of toxicities as described in the protocol (Section 7.5.1.2).

Duration of Treatment:

For all patients, the minimum duration of study participation is approximately 15.5 months, accounting for a 4-week screening period, a 10-week treatment period, and a 12-month post-treatment follow-up period. The duration of participation in the study may be longer, depending on when the Screening sample for HLA typing is collected.

Study Endpoints:

Safety:	Safety will be assessed by documentation of adverse events, including serious adverse events (SAEs), vaccination site examinations, clinical laboratory tests (hematology, clinical chemistry, and coagulation studies), vital signs, physical examination findings, and ECOG performance status.
Immunogenicity:	The immunogenicity of study vaccine will be determined by assessment of peptide-specific T lymphocytes using interferon-gamma (IFN-γ) ELISPOT and tetramer assays and other relevant assays identified by the Sponsor.
Efficacy:	The anti-tumor activity of study vaccine will be determined by assessment of disease response using the IMWG criteria. In order to assess response, M protein component is to be measured in serum and urine, FLC testing is to be performed and, as applicable, bone marrow aspirate and biopsies, appropriate imaging studies (eg, computed tomography, magnetic resonance imaging) are to be performed.
Statistical Methods:	Statistical analyses will be descriptive, since the primary goal of the study is to determine the safety and tolerability of PVX-410 alone and in combination with lenalidomide. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification. Time to event analyses (ie, time to progression, progression-free survival, and duration of response) will use standard survival analysis techniques such as Kaplan-Meier life test methods.

LIST OF ABBREVIATIONS

Abbreviation	Definition
β-HCG	Beta-human chorionic gonadotropin
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
APC	Antigen-presenting cells
aPTT	Activated partial thromboplastin time
ASO-PCR	Allele-specific oligonucleotide-polymerase chain reaction
AST	Aspartate transaminase
BM	Bone marrow
BMPC	Bone marrow clonal plasma cells
BP	Blood pressure
CD	Compact disc
CFR	Code of Federal Regulations.
CHF	Congestive heart failure
CR	Complete response
CRA	Clinical research associate

Abbreviation	Definition
CRAB	C = calcium (elevated); R = renal failure; A = anemia; B = bone lesions
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTL	Cytotoxic T lymphocyte
DC	Dendritic cell
Dex	Dexamethasone
DFCI	Dana Farber Cancer Institute
DFS	Disease-free survival
DLT	Dose-limiting toxicity
dsRNA	Double-stranded ribonucleic acid
DUR	Duration of response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ELISPOT	Enzyme-linked immunosorbent spot
EM	Effector memory
F/U	Follow-up
FACS	Fluorescent activated cell sorting
FDA	Food and Drug Administration
FIH	First in human
FISH	Fluorescent *in situ* hybridization

Abbreviation	Definition
FLC	Free light chain
G	Grade
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
GM-CSF	Granulocyte macrophage-colony stimulating factor
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA $A2^+$	Human leukocyte antigen A2 positive
ICH	International Conference on Harmonisation
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular
IMPCL	Immunologic Monitoring and Cellular Products Laboratory
IMWG	International Myeloma Working Group
IR	Immune response

Abbreviation	Definition
IRB	Institutional Review Board
ISR	Injection site reaction
IV	Intravenous
LD_{10}	Dose lethal to 10% of animals
LDH	Lactic dehydrogenase
Len	Lenalidomide
M	Monoclonal
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MNC	Mononuclear cell
MP	Multi-peptide
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NOAEL	No observed adverse effect level
NYHA	New York Heart Association
PBMC	Peripheral blood mononuclear cell
PC	Plasma cells
PD	Progressive disease
PFS	Progression-free survival
PR	Partial response

Abbreviation	Definition
PT	Prothrombin time
RBC	Red blood cell (count)
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SC	Subcutaneous
sCR	Stringent complete response
SD	Stable disease
SMM	Smoldering multiple myeloma
SP	Spliced
TAA	Tumor-associated antigen
TTP	Time to progression
ULN	Upper limit of normal
US	United States
US	Unspliced
VGPR	Very good partial response
WBC	White blood cell (count)

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1. STUDY PERSONNEL AND ADMINISTRATIVE STRUCTURE

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2. ETHICAL, LEGAL, AND ADMINISTRATIVE CONSIDERATIONS

2.1. Good Clinical Practice

This study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

The investigator confirms this by signing the protocol.

2.2. Informed Consent

Each investigator must submit an informed consent form to the Institutional Review Board (IRB) for their review and approval before enrolling patients. A copy of the IRB approval of the informed consent form must be forwarded to OncoPep, Inc., or its designated representative, before initiation of the study. OncoPep, Inc., will maintain a copy of the approved informed consent form.

Informed consent must be obtained from each patient or their legal guardian before initiation of any protocol-specified study procedures and enrollment in the study. Each investigator must retain the original signed informed consent form. A copy of the signed informed consent form will be given to the patient.

The investigator will not undertake any investigation specifically required by the protocol until valid informed consent has been obtained. The terms of the consent and the date obtained must be documented in the electronic case report form (eCRF).

If a protocol amendment is made, then the informed consent form must be revised to reflect the changes made to the protocol. After receiving IRB approval, the revised informed consent form must be signed by patients currently participating in the study and also by potential patients before initiation of study procedures.

2.3. Institutional Review Board

Approval to conduct the study will be obtained by each investigator from the local IRB at his or her institution before commencement of study procedures.

2.4. Approval of Study Protocol

Before the start of the study, the study protocol will be submitted to the IRB and national regulatory authorities in accordance with local requirements.

2.5. Amending the Protocol

This protocol is to be followed exactly. To alter the protocol, amendments must be written by OncoPep, Inc., and receive required regulatory approvals before implementation.

OncoPep, Inc., may make administrative changes (ie, changes that do not significantly affect patient safety or the study's scope or scientific quality) without any further approvals.

All amendments will be distributed to all protocol recipients with instructions to append them to the protocol.

2.6. Confidentiality

All study findings and documents will be regarded as confidential. The investigator and other study personnel must not disclose such information without prior written approval from OncoPep, Inc.

Patient confidentiality will be strictly maintained to the extent possible under the law. Patient names must not be disclosed. Patients will be identified in the eCRFs and other documents submitted to OncoPep, Inc., or its designated representative, by their initials, birth date, and/or assigned patient number. Documents that identify the patient (eg, the signed informed consent form) should not to be submitted to OncoPep, Inc., or its designated representative, and must be maintained in confidence by the investigator.

2.7. Publication Policy

Publications or presentations of data from individual study centers will not be allowed without explicit permission of OncoPep, Inc. Data for publication or presentation must receive approval from OncoPep, Inc., before submission. OncoPep, Inc., will determine authorship in conjunction with the investigator(s).

3. INTRODUCTION

3.1. Smoldering Multiple Myeloma

Smoldering multiple myeloma (SMM) is an asymptomatic, plasma cell proliferative disorder characterized by monoclonal plasma cell proliferation in the bone marrow and monoclonal proteins in the blood and/or urine without renal dysfunction, hypercalcemia, bone disease, or anemia. The diagnosis of SMM requires a serum monoclonal (M) protein level ≥3 g/dL and/or bone marrow clonal plasma cells (BMPC) >10%, and the absence of end-organ damage (ie, hypercalcemia, renal insufficiency, anemia, or bone lesions [CRAB]).(1) Although asymptomatic, SMM is associated with a high-risk of progression to symptomatic multiple myeloma (MM) or amyloidosis.

At present, it has been estimated that SMM accounts for approximately 15% of all newly diagnosed cases of MM. The median time to progression from diagnosis to symptomatic MM ranges from 2 to 3 years (2,3), and the annual risk of progression from SMM to symptomatic MM requiring treatment is estimated to be 10%. The risk of progression is contingent on 1) monoclonal protein levels ≥3 g/dL; 2) BMPC ≥10%; and 3) the presence of abnormal serum free light chain (FLC) ratio. As shown in Table 3-1, the median time to progression is notably shorter in patients meeting all 3 of these prognostic criteria (1.9 years) compared to those meeting only 1 of these criteria (10 years) or 2 of these criteria (5.1 years). Similarly, the proportion of patients progressing to symptomatic MM by 5 years is notably higher in those meeting all 3 prognostic criteria (76%) compared to those meeting only 1 or 2 of these criteria (25% and 51%, respectively).

Table 3-1 SMM Prognosis

Number of Risk Factors	Number of Patients (N)	Median Time to Progression (Years)	Progression at 5 Years (%)
1	81	10	25
2	114	5.1	51
3	78	1.9	76

Source: Kyle RA, et al, 2010.(4)

Recent data have demonstrated the importance of other prognostic criteria for SMM, including the presence of an aberrant phenotype of BMPC (2), defined as a decrease in 1 or 2 of the uninvolved immunoglobulin (Ig) isotypes as well as whether M protein remains stable or progressively worsens over time. In this latter case, referred to as evolving SMM, patients with a progressive increase in serum M protein levels have shorter median time to progression (TTP) compared to those with a stable M protein of 1.3 versus 3.9 years, respectively.(5)

Currently, there is no active treatment for SMM. Instead, a "watchful" waiting approach is taken, with treatment initiated after progression to symptomatic disease. For most patients, progression is indicated by an increase in anemia (hemoglobin lower than 2 g/dL below the lower limit of normal or <10 g/dL) and/or skeletal involvement, including bone lesions and/or diffuse osteoporosis.(3)

Although a watchful waiting approach is typical, several treatment approaches intended to delay or prevent progression to symptomatic MM have been investigated, with limited

success. Findings from small, randomized studies have failed to show benefit with early treatment with alkylating agents compared to observation until progression.(6,7,8). Results of preliminary Phase 2 studies of thalidomide alone and in combination with pamidronate and Anakinra (anti interleukin[IL]-1 receptor antagonist combined with dexamethasone) revealed no impact on disease progression.(9,10,11) Further, while treatment with bisphosphonates has been shown to reduce the number of skeletal events, such treatment has not been shown to prolong TTP or overall survival.(12)

More recently, the results of a Phase 3 study evaluating whether early treatment with lenalidomide plus dexamethasone (len/dex) versus no treatment prolonged TTP in SMM patients at high risk of progression to active MM showed that early treatment of patients with high-risk SMM with lenalidomide delayed progression to active disease, as evidenced by a significantly prolonged TTP with lenalidomide compared to observation (median not reached versus 21 months, respectively; $p<0.001$). The 3-year survival rate also was longer with lenalidomide than with observation (94% versus 80%, respectively).(13) These encouraging findings provide support for the investigation of PVX-410 in combination with lenalidomide in this study (see Section 5.2).

3.2. PVX-410 for Injection, a Multi-peptide Cancer Vaccine

Predicated on research performed at the Dana Farber Cancer Institute (DFCI), Boston, MA, on MM-associated epitopes, OncoPep, Inc., is developing a multi-peptide therapeutic cancer vaccine, PVX-410, for subcutaneous (SC) administration to patients diagnosed with SMM. The goal of treatment with PVX-410 is to induce immunity against MM cells by selectively stimulating tumor-associated antigen-specific cytotoxic T lymphocytes (CTLs). The rationale for the use of multiple peptides is to 1) target the tumor cell heterogeneity observed in all cancers, particularly MM, and 2) decrease the likelihood of tumor cells developing resistance to CTLs by targeting multiple antigens simultaneously. Furthermore, targeting multiple antigens increases the probability of an immune response against all subsets of MM.

PVX-410 is composed of 4, 9-mer chemically synthesized peptides from unique regions of 3 MM-associated antigens (XBP1, CD138, and CS1). XBP1 is a basic leucine zipper-containing transcription factor required for the terminal differentiation of B lymphocytes to plasma cells. Splicing of XBP1 occurs in terminal B cell differentiation and correlates with plasma cell differentiation. XBP1 is highly expressed in plasma cells, with regulation through both transcriptional and post-transcriptional mechanisms. The unique tissue expression profile of XBP1 provides an opportunity to develop an antigen-specific immunotherapy for SMM. CD138 is an integral membrane protein acting as a receptor for the extracellular matrix. Within the normal hematopoietic compartment, CD138 is expressed on differentiated plasma cells and is a primary diagnostic marker of MM. Antibody responses to CD138 *in vitro* indicate it is a clinical target for an immunotherapeutic. CS1 is a member of the immunoglobulin gene super-family and is universally present and highly expressed on MM cells. These characteristics support the choice of these 3 peptides as appropriate target antigens for this vaccine.

OncoPep's collaborators at DFCI performed a series of studies with human T-lymphocytes in culture to select MM-specific peptides for inclusion in the multi-peptide candidate vaccine for development. Results of these investigations showed that certain synthetic peptides from 3 MM associated antigens (XBP1, CD138, and CS1) are able to elicit a cellular immune response. Specifically, these peptides stimulated antigen-specific CTLs that demonstrated MM-specific T lymphocyte responses including cell

proliferation, interferon-gamma (IFN-γ) secretion, and cytotoxic activity in response to MM tumor cells. These investigators also examined whether multiple immunogenic peptides (XBP1 $US_{184-192}$, XBP1 $SP_{367-375}$, $CD138_{260-268}$, and $CS1_{239-247}$) could be used simultaneously to generate immune competent CTLs. The CTLs exposed to the combined/multiple peptides were able to produce IFN-γ proliferate and show evidence of degranulation in response to both MM cell lines and primary $CD138^+$ cells from MM patients. In addition, these CTLs stimulated with the multiple peptides induced cytotoxic activity against MM cell lines and primary cells from MM patients.

The results of *in vitro* studies examining stimulation by single and multiple peptides are summarized in Section 3.2.1.

3.2.1. Preclinical Pharmacology Studies: *In Vitro* Proof-of-Concept

3.2.1.1. CD-138

To identify CD138 peptide specific to human leukocyte antigen (HLA)-A2 molecules, the full-length CD138 protein sequence (a total of 310 amino acids) was screened using the search software SYFPEITHI program to predict peptides having affinity to HLA-A2. Following this initial screening process, BIMAS software was used to select peptides with extended half-time disassociation rates and avoid the sequences of amino acid residues that potentially cause reduced binding to HLA-A2 molecules. Based on this bioinformatics search, 4 CD138 peptides were selected and synthesized for HLA-A2 binding. Among the peptides, $CD138_{260-268}$ (GLVGLIFAV) was shown to have the highest binding affinity as well as stability to HLA-A2 molecules.

Based on the high level of HLA-A2 affinity and specificity of the $CD138_{260-268}$ peptide, its immunogenicity was evaluated without further modification of the epitope.(14) This 9-mer peptide induced CTLs specific to primary $CD138^+$ MM cells. Repeated CD138 peptide stimulation induced CTLs with a distinct phenotype changes characterized by a high percentage of $CD8^+$ activated/memory T cells with a low percentage of $CD4^+$ T cell and naive $CD8^+$ T cell subsets. Repeated stimulation also produce CTLs displaying HLA-A2-restricted and antigen-specific cytotoxicity against MM cell lines. CD138-CTLs demonstrated increased degranulation, proliferation and IFN-γ secretion in response to HLA-$A2^+$/$CD138^+$ myeloma cells, but not HLA-$A2^-$/$CD138^+$ or HLA-$A2^+$/$CD138^-$ cells. The immune functional properties of the CD138-CTLs were also demonstrated using primary HLA-$A2^+$/$CD138^+$ cells isolated from myeloma patients.

These data provided evidence that the $CD138_{260-268}$ (GLVGLIFAV) peptide can induce antigen-specific CTLs and be a candidate for a peptide-based vaccine for the treatment of MM or its pre-malignant condition.

3.2.1.2. XBP1

Studies were performed to identify HLA-A2+ immunogenic peptides derived from XBP1 antigens to induce an MM-specific immune response. Peptide identification was performed by screening the full-length sequences of non-spliced (260 amino acids) or spliced (375 amino acids) XBP1 protein to predict HLA-A2-specific peptides. The HLA-A2 anchor residues were screened to avoid epitopes containing amino acids that can negatively affect HLA-A2 binding, and optimal peptides were selected from spliced or non-spliced XBP1 protein and evaluated for their HLA-A2 affinity. Six native peptides from non-spliced XBP1 antigen and 3 native peptides from spliced XBP1 antigen were selected and evaluated for their HLA-A2 specificity. Among them, the heteroclitic

peptides, YISPWILAV or YLFPQLISV, demonstrated improved HLA-A2 stability from their native $XBP1_{184-192}$ or XBP1 $SP_{367-375}$ peptide, respectively.

CTLs generated by repeated stimulation of $CD3^+$ T cells with each HLA-A2-specific heteroclitic peptide showed an increased percentage of $CD8^+$ (cytotoxic) and $CD69^+/CD45RO^+$ (activated memory) T cells and a lower percentage of $CD4^+$ (helper) and $CD45RA^+/CCR7^+$ (naïve) T cells, that were distinct from the control T cells.(15) CTLs demonstrated MM-specific and HLA-A2-restricted proliferation, IFN-γ secretion, degranulation, and cytotoxicity against both established MM cell lines and primary MM cells. These data demonstrated the distinct immunogenic characteristics of unique heteroclitic XBP1 peptides, which induce MM-specific CTLs supporting their potential application for immunotherapy to treat patients with MM or its pre-malignant condition.

3.2.1.3. CS1

Four CS1 peptide sequences with the potential to bind to HLA-A*0201 were predicted based upon the high binding scores among 3 databases (RANKPEP, BIMAS, and NetMHC). High affinity binding to HLA-A*0201 was confirmed using the peptide-T2 cell binding assay. Autologous dendritic cells (DCs) or T2 cells, pulsed with candidate CS1-peptides, were used to stimulate HLA-A*0201-positive normal human $CD8^+$ T lymphocytes and generate peptide-specific CTLs. CTL cell lines were established after several rounds of re-stimulation.

The proliferative activity of CS1-CTLs was assessed by ^{3}H-TdR incorporation. Stimulation by peptide-pulsed T2 cells increased proliferation of CS1-specific CTLs ~55-fold compared with unstimulated cells.(16) The activation of CS1-CTLs was monitored by the expression of CD25 (IL-2R chain) on peptide-stimulated CS1-CTLs, with results showing 98% and 13% CD25+ cells in pulsed versus unpulsed cells, respectively. Furthermore, CS1-CTLs secreted significantly higher levels of IFN-γ in response to peptide-pulsed T2 cells (615 and 46 pg/mL in pulsed versus unpulsed cells, respectively, a 14-fold difference). The expanded CS1-CTLs were highly cytotoxic (93%) in response to peptide pulsed T2 cells. Furthermore, more than 30% of killing activity by CS1-CTLs against HLA-A*0201+CS1+ MCCAR cells was observed at the effector: target ratio of 20:1. In contrast, these CS1-CTLs did not kill HLA-A*0201+/CS1– U266 and HLA-A*0201–/CS1+ MM1S target cells. These results support CS1 as an antigenic target for the induction of peptide-specific CTLs against MM cells.

3.2.1.4. Multi-peptide Cocktail

Studies were performed to evaluate the ability to elicit MM-specific responses of a cocktail containing heteroclitic XBP1 $US_{184-192}$ (YISPWILAV), heteroclitic XBP1 $SP_{367-375}$ (YLFPQLISV), native $CD138_{260-268}$ (GLVGLIFAV) and native $CS1_{239-247}$ (SLFVLGLFL) peptides with strong HLA-A2 affinity and immunogenicity. Multipeptide-specific CTLs (MP-CTLs) were generated by stimulation of T lymphocytes from $HLA\text{-}A2^+$ individuals with autologous mature dendritic cells or T2 cells by pulsing with a cocktail containing the four peptides. The strategy used to minimize competition between peptides for HLA-A2 binding was to use much lower concentrations (6.25 µg/ml versus 50 µg/mL) of each peptide in the cocktail. Combining the 4 peptides in this manner to produce simultaneous pulsing did not compromise tumor-specific activity of CTLs.

The MP-CTLs displayed an increased percentage of total, effector memory ($CCR7^-$ $CD45RO^+$) and activated ($CD69^+$) $CD3^+CD8^+$ T lymphocytes and functional activities including IFN- γ production, degranulation, cell proliferation, and cytotoxicity against $HLA\text{-}A2^+$ MM cells in an antigen-specific and HLA-A2-restricted manner. The MP-CTLs demonstrated specific responses to each relevant peptide, but not to an irrelevant CMV pp65 (NLVPMVATV) peptide in various functional assays. These results demonstrate the potential therapeutic application of a cocktail of HLA-A2 specific peptides to induce CTLs with a broad spectrum of immune responses against tumor-associated antigens (TAAs) involved with MM pathogenesis.

3.2.2. Other Data with PVX-410

PVX-410 is composed of 4, 9-mer chemically synthesized peptides from unique regions of 3 MM-associated antigens (XBP1, CD138, and CS1). Evidence of anti-MM activity and a tolerable safety profile have been seen in clinical studies of other investigational agents targeting CD138 and CS1. The effects of XBP1 inhibition in the clinical setting are currently unknown. However, OncoPep has conducted a Good Laboratory Practice (GLP), repeat-dose nonclinical toxicology study to assess the safety profile of the XBP1-derived peptides in HLA-A*0201 transgenic mice. Findings showed that 6 weekly injections of XBP1 derived peptides at 90 or 180 µg/occasion was tolerated, with no apparent effect on the overall health of the animals based on clinical observations, body weight, or food consumption. The only treatment-related effects directly attributable to XBP1derived peptides were higher phosphorus values in males at 180 µg/occasion and females (90 and 180 µg dose) and creatinine concentrations in males receiving 180 µg/occasion. These effects were not considered to be adverse in nature due to magnitude of changes, reversibility, and lack of changes in related test parameters. The no-observed adverse level (NOAEL) was considered to be greater than 180 µg/occasion. Immunologic response specific to the XBP1-derived peptides were evaluated with an enzyme-linked immunosorbent spot (ELISPOT) assay. The main study and recovery group animals receiving the XPB1 derived peptides demonstrated a positive ELISPOT response, thereby supporting the use of the HLA-A*0201 transgenic mouse as a relevant animal species to assess the potential toxicity of XBP1 derived peptides.

Adjuvant-related effects were apparent in all treatment groups receiving the adjuvant or either concentration of XBP1 derived peptides and were attributed to Montanide (an oil-based vehicle) and/or the contributions of poly-ICLC. Treatment related hematological and blood chemical changes observed amongst animals receiving adjuvant and/or XBP1 peptides were not considered to be of toxicological significance. The more notable findings were mainly associated with the subcutaneous injection sites (clinical, macroscopic and histopathological findings) with associated secondary pathological changes in the lung and bronchi, spleen, and lymph nodes. In general, there was no significant recovery from these histopathological findings. These effects were considered to represent exaggerated pharmacology of immune stimulation of Montanide and/or poly-ICLC. Furthermore, these effects were observed at dose levels that are at high multiples of the clinical doses based on body weight and surface area.

Based on these data as well as other nonclinical data, XBP1 inhibition in this therapeutic approach is anticipated to result in anti-MM activity without significant safety risks.

PVX-410 is anticipated to be well tolerated, given that other tumor antigen-based peptide vaccines have been well tolerated in the clinical setting. Review of data from 13 recent clinical studies of tumor-specific peptide vaccines in both solid tumor and hematologic

cancers revealed the predominant effects of such treatment to be local injection site reactions, including swelling, erythema, and induration at the injection site; as well as systemic effects typically associated with vaccines including fatigue, headache, myalgia/arthralgia, fever, malaise, and urticaria. Safety findings from these 13 clinical studies are summarized in Appendix 1.

The current study represents the first clinical investigation of PVX-410. A total of approximately 20 to 22 patients with SMM are planned to be enrolled in the study at 3 study centers in the United States. PVX-410 initially will be administered at a low dose of 0.4 mg (0.1 mg/peptide or 0.4 mg total), with escalation to the target dose of 0.8 mg (0.2 mg/peptide or 0.8 mg total) planned thereafter. The primary goal of this study is to demonstrate the safety and tolerability of PVX-410. The immunologic and anti-tumor activity of the vaccine will also be evaluated with respect to development of immune response and any impact on clinical course during the 12-month post-treatment period.

In the 2013 Annual Report for PVX-410, safety data were summarized for 10 patients treated with PVX-410 in this study, of whom 3 received the low-dose of 0.4 mg and 0.5 mL (1 mg) Hiltonol and 7 received the target-dose of 0.8 mg and 0.5 mL (1 mg) Hiltonol.

Overall, a total of 59 adverse events were experienced among the 10 PVX-410-treated patients, with all 10 patients experiencing adverse events. All adverse events reported to date were mild or moderate (Grade 1 or 2) in intensity. Three Grade 2 adverse events were reported, including one case each of headache, upper respiratory infection, and fatigue; none of these events were considered by the Investigator to be study vaccine-related. No apparent dose relationship was seen with regard to the incidence of adverse events.

Overall, 43 of the 59 adverse events reported were considered by the Investigator to be study vaccine-related. Most such events occurred within the first 2 days after study injection and consisted of systemic symptoms and local reactions commonly seen with vaccines. Systemic symptoms included fever, chills, fatigue, nausea, and other flu-like symptoms, and local reactions included erythema, induration, pain at the injection site, rash, and localized pruritus. Two adverse events not commonly seen with vaccines, dry eye and blurred vision, also have been reported. These adverse events resolved, and no patient discontinued study vaccine because of an adverse event.

No deaths or other serious adverse events have been reported among PVX-410-treated patients. Furthermore, no clinically significantly abnormal clinical laboratory test results have been seen.

Immunogenicity data at Baseline, Weeks 4 and 8, and post-treatment Month 1, as determined by the ELISPOT and tetramer assays, are available for the first 6 patients in the study, of whom 3 each were in the low-dose and target-dose cohorts.

Immunogenicity data, as determined by the ELISPOT assay, are presented in Table 3-2. Response is recorded as the percentage of signal change in the presence of peptide compared to signal in the absence of peptide (background). Values are rounded to the nearest 10%.

Table 3-2 ELISPOT Results

Patient / Cohort	Timepoint	Peptide			
		XBP1(US)	**XBP1(S)**	**CD138**	**CS1**
03-004 (Low-dose)	Baseline	30%	10%	10%	NA[1]
	Week 4	20%	70%	10%	
	Week 8	40%	30%	0%	
	Month 1	0%	40%	0%	
04-006 (Low-dose)	Baseline	10%	50%	100%	NA[1]
	Week 4	90%	70%	20%	
	Week 8	40%	0%	0%	
	Month 1	30%	60%	20%	
04-008 (Low-dose)	Baseline	60%	90%	40%	NA[1]
	Week 4	250%	410%	130%	
	Week 8	50%	240%	80%	
	Month 1	110%	340%	40%	
01-010 (Target dose)	Baseline	40%	0%	0%	0%
	Week 4	50%	100%	70%	80%
	Week 8	160%	250%	240%	280%
	Month 1	20%	40%	50%	40%
01-017[2] (Target dose)	Baseline	190%	150%	120%	280%
	Week 8	180%	400%	600%	350%
	Month 1	300%	110%	320%	450%
01-018 (Target dose)	Baseline	70%	30%	40%	130%
	Week 4	20%	100%	40%	120%
	Week 8	30%	50%	51%	140%
	Month 1	20%	20%	-20%	-10%

1 Results for CS1 for the Low-dose cohort could not be analyzed due to assay error.

2 Patient sample not available from study center.

Signal increases over Baseline values were noted for multiple patients with multiple peptides at the treatment and follow-up time points. The results for the tetramer assays for all peptides for all 6 patients were not significantly elevated compared to control samples.

4. STUDY OBJECTIVES/ENDPOINTS

4.1. Primary Objective

The primary objective of this study is to:

- Determine the safety and tolerability of the PVX-410 tumor vaccine regimen alone and in combination with lenalidomide in patients with SMM.

4.2. Secondary Objectives

Secondary objectives of this study are to:

- Assess immune responses of lymphocytes to human leukocyte antigen A2 positive (HLA $A2^+$) MM cells from patients with SMM via IFN-γ ELISPOT assay, and $CD8^+$ CTLs specific to XBP1, CD138, and CS1 peptides, by tetramer assays.
- Measure the change in M serum protein or FLC and urinary FLC levels, as appropriate.
- Correlate immune response with clinical anti-tumor responses.

4.3. Study Endpoints

4.3.1. Safety Endpoints

The safety endpoints of this study are:

- Incidence of adverse events during the drug administration and for 24 hours and 2 weeks post-administration.
- Incidence of serious adverse events (SAEs).
- Incidence and types of dose-limiting toxicities (DLTs).
- Change from baseline in physical examination, vital sign, and clinical laboratory test findings.

4.3.2. Activity Endpoints

Clinical disease response is to be determined by the investigator using the International Myeloma Working Group (IMWG) Uniform Response Criteria.(17) The clinical response endpoints, based on the investigator's assessment, of this study are:

- Change from baseline in serum or urine M protein levels.
- Change from baseline in FLC ratio.

Additional activity endpoints include:

- Duration of response (DUR).
- Progression-free survival (PFS).
- Time to progression (TTP).

4.3.3. Immunogenicity Endpoints

Immunogenicity endpoints of this study are:

- Immune response in lymphocytes to HLA $A2^+$ MM cells, as determined by IFN-γ ELISPOT.

- Immune response by assessment of peptide-specific $CD8^+$ cells specific to XBP1, CD138, and CS1 peptides, as determined by tetramer assays.

Peripheral blood mononuclear cells (PBMCs) will be collected for future immunologic analyses. Such samples will be stored indefinitely until such time that appropriate analyses are developed / identified and will not be used for genomic testing.

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design and Plan

Study 2010-001 is a phase 1/2a, multi-arm, open-label, multi-center, dose escalation study of PVX-410 for injection, a multi-peptide cancer vaccine. Approximately 20 to 22 adults with SMM are to be enrolled at 3 study centers in the United States. The primary objective is to determine the safety and tolerability of PVX-410 in this patient population. Secondary objectives include determination of the immune response to the study vaccine alone and in combination with lenalidomide as well as evaluate changes in M protein and/or FLC in serum and/or urine, as appropriate.

All patients must provide written informed consent before any samples are collected or evaluations are performed in this study. A Screening blood sample for HLA typing with sequence-based subtyping is to be collected before the performance of other Screening assessments. If the patient has had HLA typing previously performed by an accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for Screening. If the patient has not had HLA typing performed previously or an acceptable result is not available from the previous test, then a blood sample for HLA typing with sequence-based subtyping may be collected under the auspices of this protocol >4 weeks before Week 0, but only after the patient provides consent to participate in this study. Patients must be demonstrated to be HLA-$A2^+$ to proceed with Screening; if the patient is demonstrated to be HLA-$A2^+$, then the Screening process may continue, with all other Screening assessments to be performed within 4 weeks before Week 0. Patients who are demonstrated to be HLA-$A2^-$ will be considered screen failures, and no additional Screening assessments will be performed.

Patients who are determined to be eligible, based on Screening assessments, will be assigned to 1 of 3 treatment cohorts, enrolled in the study, and assigned a baseline date (Week 0, first study treatment). The 3 treatment cohorts are as follows:

- Low-dose cohort, in which all patients are to receive PVX-410 at the low-dose of 0.4 mg (total peptide dose).
- Target-dose cohort, in which all patients are to receive PVX-410 at the target dose of 0.8 mg (0.2 mg/peptide or 0.8 mg total).
- PVX-410 + lenalidomide cohort, in which all patients are to receive PVX-410 at the target dose of 0.8 mg (0.2 mg/peptide or 0.8 mg total) plus 3 cycles of lenalidomide 25 mg.

All patients will also receive 0.5 mL (1 mg) Hiltonol® (poly-ICLC) (2 mg/mL) via intramuscular (IM) injection at the time of PVX-410 administration.

The first 3 patients enrolled are to receive PVX-410 at the low-dose of 0.4 mg (0.1 mg/peptide or 0.4 mg total). These 3 patients are to be treated sequentially. Each patient in the low-dose cohort must complete the Week 2 visit, with safety data reviewed by the Dose Escalation Safety Cohort Committee, before the next patient may be treated.

- If 0 of 3 patients experiences a DLT, then dose escalation will proceed to the target dose level.
- If 1 of 3 patients experiences a DLT, then 3 additional patients will be enrolled at the current dose level. Escalation to the target dose will continue if 1 of 6 patients

experienced a DLT. No more than 1 out of 6 patients may experience a DLT for a dose level to be considered acceptable.

- If ≥2 patients at the low-dose level experience a DLT, then the enrollment and treatment of patients will be stopped.

After the last patient in the low-dose cohort receives the 6th study vaccine dose, treatment of patients at the target-dose cohort may commence. A total of 10[2] patients are planned to be enrolled sequentially at the target dose (0.8 mg; 0.2 mg/peptide or 0.8 mg total). The next 2 patients must complete the Week 2 visit, with safety data reviewed by the Dose Escalation Safety Cohort Committee, before the next patient may be treated. Thereafter, the remaining patients are to be treated sequentially after a 2-day interval from the previous patient's first dose.

After the last patient in the target-dose cohort receives their final vaccination (6th), treatment in the PVX-410 + lenalidomide cohort may commence. A total of 10 patients are planned to be enrolled sequentially in this cohort and receive PVX-410 at the target dose (0.8 mg; 0.2 mg/peptide or 0.8mg total) plus 3 cycles of lenalidomide, with a cycle consisting of lenalidomide 25 mg orally (PO) daily for 21 days (Days 1-21) followed by a 7-day rest period; thus, each lenalidomide cycle is 28 days. Enrollment in this cohort (ie, the PVX-410+lenalidomide cohort) will commence after review of safety data and Baseline to Month 1 follow-up ELISPOT and tetramer data from the low-dose and target-dose cohort. Furthermore, enrollment will be staggered by 2 days; thus, the previous patient must be followed for 2 days after the first PVX-410 dose given in combination with lenalidomide before the next patient can start treatment.

The Dose Escalation Safety Cohort Committee will not be formally reviewing the safety data for the last 8 patients in the target-dose cohort (PVX-410 alone) or PVX-410 + lenalidomide cohort unless a DLT is observed or any event is observed that requires review by the committee. If a DLT occurs, enrollment will be interrupted and a safety review meeting convened. A decision regarding modification or discontinuation of study vaccine and/or patient enrollment will be made by the sponsor in consultation with the investigators and medical monitor.

Patients are to receive a total of 6 doses of study vaccine via SC injection on a biweekly basis (Weeks 0, 2, 4, 6, 8, and 10). Patients will be observed by study center personnel for at least 1 hour after study vaccine administration.

During treatment, patients will attend study center visits at Weeks 2, 4, 6, 8, and 10 for study vaccine administration and safety, activity, and immunologic assessments.

After completion of treatment, patients will attend follow-up study center visits at post-treatment Months 1, 2, 3, 6, and 9, and 12. Month 12 is the final study visit.

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2 At the time of this amendment; enrollment in the low-dose and target-dose cohorts is complete; a total of 3 and 9 patients were enrolled, respectively. Although 10 patients were planned to be enrolled in the target-dose cohort, the Sponsor elected not to enroll the 10th patient, as the Sponsor determined sufficient safety and efficacy data were available to support this amendment from the 12 treated patients.

During the study, safety will be assessed by documentation of adverse events, including SAEs, vaccination site examinations, clinical laboratory tests (hematology, clinical chemistry, and coagulation studies), vital signs, physical examination findings, and Eastern Cooperative Oncology Group (ECOG) performance status.

The anti-tumor activity of study vaccine will be determined by assessment of disease response using the IMWG criteria. In order to assess response, M protein component is to be measured in serum and urine, FLC testing is to be performed and, as applicable, bone marrow aspirate and biopsies, or appropriate imaging studies (eg, computed tomography, magnetic resonance imaging).

The immunogenicity of study vaccine will be determined by assessment of peptide-specific T lymphocytes using IFN-γ ELISPOT and tetramer assays and other relevant assays identified by the Sponsor at Weeks 2, 4 and 8 and Months 1, 3, 6, 9 and 12.

5.2. Justification for the Study Design

Goals of Phase 1 studies include determination of a recommended dose for evaluation in Phase 2 studies (18,19); the primary objectives of the current study are consistent with those typical of Phase 1 studies. Consistent with the objectives of many Phase 1 studies, preliminary evaluation of the potential activity of PVX-410 is a secondary objective of this study.

The study design employed in the current study is consistent with regulatory guidance regarding clinical considerations for therapeutic cancer vaccines.(20)

In order to determine a maximum tolerated dose (MTD) as well as a recommended Phase 2 dose (RP2D), a "3+3 design" dose-escalation design is typically employed in Phase 1 studies of anti-cancer treatments. However, as noted in the regulatory guidance, a typical "3+3 design" typically does not result in identification of an MTD for therapeutic cancer vaccines, given that the dose-toxicity curve may be so flat that the highest dose that can be feasibly administered is limited by manufacturing or other issues rather than toxicity; thus, an alternate study design should be employed. Accordingly, in the current study, a cohort of 3 patients will be enrolled and treated with a low starting dose of 0.4 mg. In order to better monitor the safety of patients, treatment will be sequential, with a minimum delay of 2 weeks between each patient treated at the low starting dose. Treatment of patients at the target-dose cohort may commence after the last patient in the low-dose cohort receives the 6th study vaccine dose. Approximately ten patients are to be enrolled at the target dose of 0.8 mg, with a minimum of a 2-week delay between the next 2 patients and a minimum of a 2-day delay between the subsequent 7 patients treated at the target dose.

Combining cancer vaccines with conventional therapy (eg, chemotherapy, radiation therapy) is emerging as a strategy to maximize anti-tumor activity, with the addition of chemotherapy leading to improved clinical efficacy by clearing suppressor cells, rebooting the immune system, rendering tumor cells more susceptible to immune-mediated killing, or by activation of cells of the immune system.(21) In particular, it has been demonstrated that chemotherapy renders tumors cells more susceptible to lysis by CTLs *in vivo*.(22) To investigate whether co-administration of a conventional therapy improves the immune response / activity seen with PVX-410, a cohort of patients will be enrolled and treated with PVX-410 plus lenalidomide (Revlimid®), a commercially available analogue of thalidomide with immunomodulatory, antiangiogenic, and

antineoplastic properties.(23) The immunomodulatory effects of lenalidomide include inhibition of pro-inflammatory cytokines (eg, IL-1, IL-6, IL-10, and IL-12 and tumor necrosis factor-alpha), stimulation of $CD8^+$ and $CD4^+$ cells, and modulation of natural killer cells. Given these immunomodulatory properties, it is hypothesized that co-administration of lenalidomide would enhance the T cell-mediated immune response induced by PVX-410.

Lenalidomide, which is indicated for the treatment of MM patients who have received 1 prior therapy, has been shown to be well-tolerated and efficacious in patients with high-risk SMM. Lenalidomide induction therapy (9 cycles of lenalidomide 25 mg/day on Days 1-21 plus dexamethasone 20 mg/day on Days 1-4 and 12-15 of a 28-day cycle) followed by maintenance therapy (lenalidomide 10 mg/day on Days 1-21 of a 28-day cycle for 2 years) (n=57) was compared with observation (n=62) in a Phase 3, open-label, randomized, comparative study in 119 patients with high-risk SMM, with patients followed for a median of 40 months.(13) Findings showed that early treatment of patients with high-risk SMM with lenalidomide delayed progression to active disease, as evidenced by a significantly prolonged time to progression with lenalidomide compared to observation (median not reached versus 21 months, respectively; $p<0.001$). The 3-year survival rate also was longer with lenalidomide than with observation (94% versus 80%, respectively). The incidence of adverse events in this patient population was lower than that seen in previous studies of lenalidomide and dexamethasone in patients with symptomatic MM.

In the PVX-410 + lenalidomide cohort, patients will receive PVX-410 at the target dose (0.8 mg; 0.2 mg/peptide or 0.8mg total) plus 3 cycles of lenalidomide. In accordance with the prescribing information (available at: http://www.revlimid.com/pdf/PI.pdf) (23), lenalidomide will be administered in 28-day cycles, with each cycle consisting of lenalidomide 25 mg PO daily for 21 days (Days 1-21) followed by a 7-day rest period. The lenalidomide dose will be adjusted for the management of toxicities as described in the prescribing information.(23) Enrollment in this cohort (ie, the PVX-410+lenalidomide cohort) will commence after review of safety data and Baseline to Month 1 follow-up ELISPOT and tetramer data from the low-dose and target-dose cohort. Furthermore, enrollment will be staggered by 2 days; thus, the previous patient must be followed for 2 days after the first PVX-410 dose given in combination with lenalidomide before the next patient can start treatment.

The conventional model for clinical development of anti-cancer treatment involves initial testing in patients with advanced/metastatic diseases and different tumor types. However, as noted in the regulatory guidance, this conventional strategy is not considered appropriate for cancer vaccine studies, as there may not be sufficient time for the development and assessment of an anti-tumor immune response needed to determine vaccine activity because of the potentially short time interval from administration of study vaccine to subsequent disease progression in patients with advanced disease. Accordingly, patients with SMM, which is by definition an asymptomatic form of MM, will be treated in the current study.

6. STUDY POPULATION

Approximately 20 to 22 patients with SMM meeting the protocol entrance criteria are to be enrolled in this study.

6.1. Inclusion Criteria

Patients meeting all of the following criteria will be considered eligible for study entry:

1. Patient has confirmed SMM according to a definition derived from the IMWG definition (1): serum M-protein ≥3 g/dL or BMPC >10%, or both, along with normal organ and marrow function (CRAB) within 4 weeks before baseline.
    - C: Absence of hypercalcemia, evidenced by a calcium <10.5 mg/dL.
    - R: Absence of renal failure, evidenced by a creatinine < 1.5 mg/dL (177 μmol/L) or calculated creatinine clearance (using the Modification of Diet in Renal Disease [MDRD] formula) >50 mL/min.
    - A: Absence of anemia, evidenced by a hemoglobin >10 g/dL.
    - B: Absence of lytic bone lesions on standard skeletal survey.
2. Patient is at higher than average risk of progression to active MM, defined as having 2 or more of the following features:
    - Serum M-protein ≥3 g/dL.
    - BMPC >10%.
    - Abnormal serum FLC ratio (0.26-1.65).
3. Patient is aged 18 years or older.
4. Patient has a life expectancy of greater than 6 months.
5. Patient is HLA-A2+.
6. Patient has an ECOG performance status of 0 or 1.
7. Patient has adequate bone marrow function, evidenced by a platelet count $\geq 75\times10^9$/L and an absolute neutrophil count (ANC) $\geq 1.0\times10^9$/L within 2 weeks before baseline.
8. Patient has adequate hepatic function, evidenced by a bilirubin ≤2.0 mg/dL and an alanine transaminase (ALT), and aspartate transaminase (AST) ≤2.5× the upper limit of normal (ULN) within 2 weeks before baseline.
9. If of child-bearing potential, patient agrees to use adequate birth control measures during study participation.

10. If a female of child-bearing potential, patient has negative urine pregnancy test results within 2 weeks before baseline and is not lactating.

    In the PVX-410 + lenalidomide cohort, females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

11. Patient (or his or her legally accepted representative) has provided written informed consent to participate in the study.

12. In the PVX-410 + lenalidomide cohort, all study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.

6.2. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patient has symptomatic multiple myeloma, as defined by any of the following:
    - Lytic lesions or pathologic fractures.
    - Anemia (hemoglobin <10 g/dL).
    - Hypercalcemia (corrected serum calcium > 11.5 mg/dL).
    - Renal insufficiency (creatinine > 2 mg/dL).
    - Other: symptomatic hyperviscosity, amyloidosis.
2. Patient has a history of a prior malignancy within the past 5 years (excluding resected basal cell carcinoma of the skin or in situ cervical cancer).
3. Patient has abnormal cardiac status, evidenced by any of the following:
    - New York Heart Association (NYHA) stage III or IV congestive heart failure (CHF).
    - Myocardial infarction within the previous 6 months.
    - Symptomatic cardiac arrhythmia requiring treatment or persisting despite treatment.
4. Patient is receiving any other investigational agent.
5. Patient has a current active infectious disease or positive serology for human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
6. Patient has a history of or current auto-immune disease.

7. Patient has been vaccinated with live attenuated vaccines within 4 weeks before study vaccination.

6.3. Source of Patients

This will be a multi-center study conducted at 3 study centers in the United States. Each study center is required to obtain local IRB and national regulatory approval to conduct the study before enrollment of patients may commence. Patients meeting the entrance criteria who are known or referred to the study center will be eligible for enrollment.

6.4. Withdrawal and Replacement of Patients

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Occurrence of an unacceptable adverse event.
- Patient, investigator, or sponsor request.
- Patient non-adherence to study treatment or protocol requirements.
- Pregnancy.
- Progression of disease that, in the opinion of the investigator, precludes further study treatment.

Patients who withdraw from the study prior to completing the Month 12/Final Study visit are to have the evaluations scheduled for Final Study visit performed at the time of study withdrawal.

The reason for study withdrawal is to be documented in the patient's source documents and eCRF.

Patients who discontinue from the study for administrative or other non-safety related reasons (eg, non-compliance, patient request) before receiving at least 4 of 6 study vaccine doses will be replaced.

Study treatment discontinuation criteria are described in Section 7.7.

6.5. Study Termination

If the sponsor or investigator discovers conditions arising during the study that suggest the study should be halted, then this can happen only after appropriate consultation between the sponsor and investigator. Conditions that may warrant study termination include, but are not limited to:

- Occurrence of DLT (see Section 7.5.3) in ≥2 patients.
- The discovery of any other unexpected, significant, or unacceptable risk to the patients treated with PVX-410 in this study.
- Failure of the investigator to enter patients at an acceptable rate.
- Insufficient adherence to the protocol requirements.
- A decision on the part of the sponsor to suspend or discontinue development of study vaccine.

6.6. Statistical Basis for Sample Size

No formal sample size calculation was performed.

Approximately 20 to 22 patients are to be enrolled in this study, of whom 3 will be treated at the low vaccine dose (0.4 mg total peptide dose) 9 will be treated at the target vaccine dose (0.8 mg total peptide dose) and approximately 10 will be treated with the target vaccine dose (0.8 mg total peptide dose) plus lenalidomide (3 courses, 25 mg).

6.7. Patient Identification and Randomization

To ensure accurate and timely monitoring of patient enrollment, the following procedures will be implemented:

- Patients who are candidates for enrollment into the study will be evaluated for eligibility by the investigator to ensure that the inclusion and exclusion criteria (see Sections 6.1 and 6.2) have been satisfied and that the patient is eligible for participation in this clinical study.
- The investigator or the investigator's research staff will provide eligibility information to OncoPep, Inc., or designee. The patient will be registered and assigned a sequential and unique patient number by the study electronic data capture system. Once a patient number has been assigned, it cannot be reused. In the dose escalation portion of the study, OncoPep, Inc., or designee will provide the investigator with written verification of each patient's registration and the target date on which treatment can commence, based on the status of the previously enrolled patient.
- No patient may be enrolled or begin treatment prior to registration and assignment of a patient number.
- OncoPep, Inc., or designee will notify the investigator when the registered patient can begin treatment.
- Patients who are registered, but not treated will be replaced.
- Patients who receive less than 4 of the 6 vaccine doses will be replaced.
- OncoPep, Inc., or designee will notify investigators when enrollment in the current cohort is closed and enrollment in the next group can begin.
- Investigators will be notified by OncoPep, Inc., or designee if the study is placed on administrative hold, when it is completed, or is closed to further patient enrollment.

6.8. Patient Management

All patients must provide written informed consent before any samples are collected or evaluations performed in this study. A Screening blood sample for HLA typing with sequence-based subtyping is to be collected prior to the performance of other Screening assessments. If the patient has had HLA typing previously performed by an accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for Screening. If the patient has not had HLA typing performed previously or an acceptable result is not available from the previous test, then a blood sample for HLA typing with sequence-based subtyping may be collected under the auspices of this protocol >4 weeks before Week 0, but only after the patient provides consent to participate in this study. Patients must be demonstrated to be HLA-$A2^{+}$ to proceed with

Screening; if the patient is demonstrated to be HLA-$A2^+$, then the Screening process may continue, with all other Screening assessments to be performed within 4 weeks before Week 0. Patients who are demonstrated to be HLA-$A2^-$ will be considered screen failures, and no additional Screening assessments will be performed.

Patients who are determined to be eligible for the study will be enrolled in the study at baseline (Week 0, first study treatment). Thereafter, during treatment, patients will be evaluated at the study center at Weeks 2, 4, 6, 8, and 10. After completion of treatment, patients will attend follow-up study center visits at post-treatment Months 1, 2, 3, 6, and 9, and 12. Month 12 is the final study visit.

The minimum duration of study participation is approximately 15.5 months, accounting for a 4-week screening period, a 10-week treatment period, and a 12-month post-treatment follow-up period. The duration of participation in the study may be longer, depending on when the Screening sample for HLA typing is collected.

6.9. Investigator Compliance

The investigator at each study center is responsible for ensuring the accuracy and completeness of all research records, the accountability of study treatment, and the conduct of clinical and laboratory evaluations as outlined in the protocol. Study centers that deviate significantly from the protocol without prior approval from the sponsor and regulatory authorities may be discontinued from the study.

6.10. Patient Adherence

All patients are required to adhere to the protocol-specified visit schedule. If a patient misses a scheduled visit during the treatment period, attempts should be made to reschedule the visit within the following 3 days. Failure to attend scheduled study visits may result in discontinuation from the study.

7. STUDY TREATMENT

OncoPep, Inc., will supply study treatment (vaccine and adjuvant) to all participating patients. Lenalidomide also will be provided to participating patients. Before administration to patients, study treatment must be maintained in a locked cabinet that can be accessed only by appropriate study center personnel.

7.1. Study Treatment Supply

7.1.1. PVX-410 and Adjuvants

PVX-410 is composed of four, 9-mer chemically synthesized peptides from unique regions of 3 MM-associated antigens (XBP1, CD138, and CS1), as follows:

Peptide 1: H-Tyr-Ile-Ser-Pro-Trp-Ile-Leu-Ala-Val-OH (XBP1 $US_{184-192}$)

Peptide 2: H-Tyr-Leu-Phe-Pro-Gln-Leu-Ile-Ser-Val-OH (XBP1 $SP_{367-375}$)

Peptide 3: H-Gly-Leu-Val-Gly-Leu-Ile-Phe-Ala-Val-OH ($CD138_{260-268}$)

Peptide 4: H-Ser-Leu-Phe-Val-Leu-Gly-Leu-Phe-Leu-OH ($CS1_{239-247}$)

These 4 peptides, administered together as a fixed combination, constitute PVX-410 Multi-Peptide Vaccine.

PVX-410 will be supplied by the sponsor in sterile glass stoppered vial containing a lyophilized cake containing 0.2 mg/mL of each peptide (for a total of 0.8 mg total peptide).

Montanide ISA 720 VG will be supplied in a separate vial. At the point of use, the vaccine will be reconstituted in sterile water for injection, and then emulsified in 30:70 volume of Montanide ISA 720 VG. PVX-410 will be administered as an SC injection.

Instructions for PVX-410 dose preparation and administration will be provided in the Pharmacy Manual.

Hiltonol® will be supplied by the sponsor as a 2 mL sterile liquid in a glass stoppered vial. The clinician or designee is to draw the equivalent of 0.5 mL (1 mg) of Hiltonol® into the syringe and administer via IM injection in the same body region of the PVX-410 administration.

7.1.2. Lenalidomide

Lenalidomide (Revlimid®) will be provided to research patients for the duration of their participation in this study at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this study, and all research patients enrolled into this study, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Drug will be shipped on a per patient basis by the contract pharmacy to the study center. Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

7.2. Study Treatment Labeling

Study treatment labels will not bear any statement that is false or misleading in any manner or that represents that the study treatment is safe or effective for the purposes for which it is being investigated.

7.2.1. Procedures for Breaking the Blind

This is an open-label study; no blinding methods will be employed.

7.3. Study Treatment Storage

All study treatment is to be stored in a locked cabinet accessible only to appropriate study center personnel.

Study vaccine, Montanide, and Hiltonol® are to be stored at 2 to 8ºC.

Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

7.4. Study Treatment Accountability

The United States Food and Drug Administration (FDA) requires accounting of all investigational treatment (vaccine, adjuvant, and lenalidomide) received by each study center. Records of treatment disposition required by federal law include the date received by the center, date administered, quantity administered, and the patient to whom study treatment was administered. The investigator is responsible for the accountability of all used and unused study treatment containers and unused study treatment.

Each study center is to use a study treatment accountability log to document study treatment disposition. All items on this form are to be completed in full. The clinical research associate (CRA) is to approve the area where study treatment accountability records are to be maintained. The CRA is to review study treatment accountability records during routine monitoring visits.

7.5. Study Treatment Dose and Administration

All patients will receive 6 doses of PVX-410 emulsified in Montanide ISA 720 VG (Seppic, Inc.), one each at Weeks 0, 2, 4, 6, 8, and 10, via SC injection.

Three dose cohorts are planned:

- Low-dose cohort: 0.4 mg (0.1 mg/peptide or 0.4 mg total dose)
- Target–dose cohort: 0.8 mg (0.2 mg/peptide or 0.8 mg total dose)
- PVX-410+lenalidomide cohort: 0.8 mg (0.2 mg/peptide or 0.8 mg total dose) plus 25 mg lenalidomide

All patients also will receive 0.5 mL (1 mg) Hiltonol® (poly-ICLC) (2 mg/mL) via IM injection at the time of PVX-410 administration.

Study treatments will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will prepare the study treatments under aseptic conditions.

The emulsion should be administered to the patient within 4 hours of formulation. It is recommended to first administer PVX-410 followed by Hiltonol®. The 2 study

treatments (PVX-410 and Hiltonol®) do not have to be administered at the same injection site, but must be administered in the same body part (eg, left upper arm, left thigh).

Study centers will be provided with an instruction document developed by the sponsor titled "Instructions for Reconstitution of Study Drug (PVX-410), Emulsification Process with Montanide™ ISA 720 VG and Injection of Emulsion and Hiltonol®". This document provides detailed instructions for study drug preparation and administration.

Pre-medication prior to PVX-410 with an anti-histamine (eg, diphenhydramine) and/or acetaminophen is recommended. The dose(s) to be administered are at the Investigator's discretion.

Patients will be observed by study center personnel for 1 hour after each study vaccine administration.

Patients in the PVX-410+lenalidomide cohort also will receive 3 cycles of lenalidomide 25 mg PO daily for 21 days (Days 1-21) followed by a 7-day rest period; thus, each lenalidomide cycle is 28 days. Dosing will be in the morning at approximately the same time each day. Prescriptions must be filled within 7 days for females of child bearing potential and 14 days for all other risk categories. Patients are to swallow lenalidomide capsules whole with water at the same time each day. Patients are not to break, chew, or open the capsules. If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

7.5.1. Toxicity Management Recommendations

7.5.1.1. PVX-410

No PVX-410 dose modifications are allowed.

7.5.1.2. Lenalidomide

The Investigator must notify MedSource of any change in a patient's lenalidomide dosing regimen. MedSource will provide instruction regarding the return of any unused lenalidomide, and an alternate lenalidomide capsule strength will be provided, as applicable.

Lenalidomide dose reduction steps are summarized in Table 7-1.

Table 7-1 Lenalidomide Dose Reduction Steps

Starting Dose	25 mg daily on Days 1-21 every 28 days
Dose Level – 1	20 mg daily on Days 1-21 every 28 days
Dose Level – 2	15 mg daily on Days 1-21 every 28 days
Dose Level – 3	10 mg daily on Days 1-21 every 28 days

* Lenalidomide 10 mg daily on Days 1-21 every 28 days is the minimum lenalidomide dose. Lenalidomide will be discontinued in patients who cannot tolerate this dose. However, patients who experience toxicity requiring dose reduction while receiving lenalidomide 10 mg daily on Days 1-21 every 28 days may, at the discretion of their physician, have their dose held until toxicity resolves as described in Section 7.5.1.2.2 and then restart lenalidomide 10 mg daily on Days 1-21 every 28 days. If the same toxicity recurs at lenalidomide 10 mg daily on Days 1-21 every 28 days, consideration should be given to discontinuing lenalidomide.

7.5.1.2.1. Instructions for Initiation of a New Lenalidomide Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is $\geq 1.0 \times 10^9$/L
- The platelet count is $\geq 50 \times 10^9$/L
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤Grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the patient will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above.

7.5.1.2.2. Lenalidomide Dose Modifications or Interruption During a Cycle

Instructions for lenalidomide dose modifications or interruption during a cycle are summarized in Table 7-2.

Table 7-2 Lenalidomide Dose Modifications

NCI CTC Toxicity Grade	Dose Modification Instructions
Grade 3 neutropenia associated with fever (temperature ≥38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.
Thrombocytopenia ≥Grade 3 (platelet count <50 × 10^9/L)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤Grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Platelet count <25 × 10^9/L	• Hold prophylactic anti-coagulation, if applicable. • Restart prophylactic anti-coagulation when platelet count is ≥25 × 10^9/L.
Non-blistering rash Grade 3 Grade 4	 • If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤Grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove patient from study.

NCI CTC Toxicity Grade	**Dose Modification Instructions**
Neuropathy Grade 3	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤Grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4	• If Grade 4, discontinue lenalidomide. Remove patient from study.
Venous thrombosis/embolism ≥Grade 3	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate. • Restart lenalidomide at investigator's discretion (maintain dose level).
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Other non-hematologic toxicity ≥Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤Grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.

7.5.2. Dose Escalation Procedure

The first 3 patients enrolled are to receive PVX-410 at the low-dose of 0.4 mg (0.1 mg/peptide or 0.4 mg total). These 3 patients are to be treated sequentially. Each patient in the low-dose cohort must complete the Week 2 visit and safety data reviewed by the Dose Escalation Safety Cohort Committee before the next patient may be treated.

- If 0 of 3 patients experiences a dose-limiting toxicity (DLT), then dose escalation will proceed to the target dose level.
- If 1 of 3 patients experiences a DLT, then 3 additional patients will be enrolled at the current dose level. Escalation to the target dose will continue if 1 of 6 patients experienced a DLT. No more than 1 out 6 patients may experience a DLT for the dose level to be considered acceptable.
- If ≥2 patients at the low-dose level experience a DLT, then the enrollment and treatment of patients will be stopped.

After the last patient in the low-dose cohort receives the 6th study vaccine dose, treatment of patients at the target-dose cohort may commence. A total of 10 patients are planned to be enrolled sequentially at the target dose cohort (0.8 mg; 0.2 mg/peptide or 0.8 mg total). The next 2 patients must complete the Week 2 visit, with safety data reviewed by

the Dose Escalation Safety Cohort Committee, before the next patient may be treated. Thereafter, the remaining 7 patients are to be treated sequentially after a 2-day interval from the previous patient's first dose.

The Dose Escalation Safety Cohort Committee will not be formally reviewing the safety data for the last 8 patients in the target-dose cohort (PVX-410 alone) or the PVX-410 + lenalidomide cohort, unless a DLT is observed or any event is observed that deems review of the committee. If a DLT occurs, enrollment will be interrupted and a safety review meeting convened. A decision regarding modification or discontinuation of study vaccine and/or patient enrollment will be made by the sponsor in consultation with the investigators and medical monitor.

7.5.3. Dose-Limiting Toxicity

Toxicities are to be assessed using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. Any toxicity listed below that is, in the investigator's opinion, related to study vaccine (see Section 8.2.7.2) will be considered a DLT:

- ≥Grade 2 allergic reaction accompanied by dyspnea, urticaria (non-localized / present on both sides of the body or oropharynx), and/or vital sign changes that, in the investigator's opinion, requires intervention.
- ≥Grade 2 autoimmune or hypersensitivity reaction.
- Any other ≥Grade 3 hematologic or non-hematologic toxicity.

7.6. Rationale for the Dose(s) Selected

Typically, nonclinical data from toxicology studies permit estimation of the maximum safe starting dose for first in human (FIH) clinical studies. The maximum safe starting dose is usually based upon some fraction of the NOAEL or dose lethal to 10% of animals (LD_{10}), as determined in a pivotal GLP toxicology study in the most sensitive species. This generally involves using a fraction (1/10th) of this dose extrapolated to the human clinical setting using accepted allometric conversion factors expressing dose in terms of body surface area.

In the case of vaccines, there is no generally accepted allometric method for translating dose in nonclinical studies to a dose for use in clinical studies. However, consistent with regulatory guidance (20), the dose of the study vaccine in this case is predicated on findings from previous clinical studies using peptide vaccines targeting multiple TAAs. The target dose for this clinical study is 0.2 mg/peptide (0.8 mg total dose). This dose was chosen primarily because it was the lowest dose that was both safe and active in a previous clinical study in hematologic cancer (AML) patients.(24) Furthermore, this target dose is on the low end of total exposures in recent peptide vaccine studies, as shown in Table 7-3.

Table 7-3 Comparison of Highest Peptide Dose Evaluated in Recent Clinical Studies

Parameter	Study / Number of Peptides					
	2010-001 (Current Study) / 4 (A2)	**AML Phase 1 (24) / 4 (A2, T Helper)**	**Breast Phase 1 (25) / 2 (A2)**	**AML/MDS Phase 1 (26) / 2 (A2)**	**Melanoma Phase 2 (27) / 3 (A2)**	**Melanoma Phase 2 (28) / 13**
Peptide dose (each)	0.2 mg	0.2 mg	0.5 mg	0.5mg, 200 µg	2.0 mg	0.201 mg
Peptide dose (total)	0.8 mg	0.8 mg	1.0 mg	0.7 mg	6.0 mg	1.390 mg
Adjuvant	Montanide Hiltonol	GM-CSF	GM-CSF	GM-CSF, Montanide	GM-CSF, Montanide, interferon-α	GM-CSF, Montanide
Adjuvant Dose	1 mg	0.07 mg	0.25 mg	0.2 mg	0.25 mg	0.11 mg
No. of vaccinations	6	6	6	6	13	14
Comments	-	7/9 evaluable pts showed IR. Mean F/U 30 months. median DFS not reached	GM-CSF dose reduced to 0.125 mg –IR in all pt treated	Loss of high avidity peptide-specific CD8+ T cells	Neither GM-CSF nor IFN-α improved IR	High IR rate but CD8+ and CD4+ lower with GM-CSF

Key: F/U = follow-up; DFS = disease-free survival; GM-CSF = granulocyte macrophage-colony stimulating factor; IR = immune response.

In order to better ensure the safety of patients, a lower starting dose of 0.4 mg (0.1 mg/peptide; 0.4 mg total dose) will first be investigated in the first 3 patients enrolled before escalation to the target dose of 0.8 mg.

In addition to using a conservative dosing schedule in the human clinical trial, a GLP toxicity study was conducted to evaluate the safety of the XBP1 peptides (XBP1u and XPB1s) in a transgenic mouse model (Protocol HUD0225, Huntingdon Life Sciences). The CD138 and CS1 peptides were not included in this toxicity study as these antigens are well known MM targets whereas XBP1 is a novel target for this disease. The details of this study are provided in the Investigators Brochure. In summary, the XBP1 peptide cocktail was administered at approximately 35× and 70× of the human equivalent dose once a week for a total of 6 weeks or 6 doses. The peptides were emulsified in Montanide and a co-injection of Poly ICLC was administered to mimic the treatment regimen described in this protocol. There were no safety concerns related to the XPB1 peptides identified in this study.

The dose regimen of lenalidomide to be administered to patients in the PVX-410+lenalidomide cohort, 25 mg once daily on Days 1-21 of a 28-day cycle, is that recommended in the lenalidomide prescribing information (available at: http://www.revlimid.com/pdf/PI.pdf).(23) Per the prescribing information, lenalidomide

is given in combination with dexamethasone; however, systemic corticosteroids such as dexamethasone are prohibited in this study as they would be expected to attenuate a PVX-410-induced immune response. Accordingly, lenalidomide will not be given in combination with dexamethasone.

Historically, peptides have been weakly immunogenic on their own and thus require an adjuvant to appropriately stimulate the immune system.(29,30) Montanide ISA 720 VG, a ready-to-use adjuvant, is based on squalene oil and is used in vaccines for the treatment of cancer and infectious disease. Montanide is being employed in the current study to create a depot effect for the peptides in PVX-410. Montanide provides both a stimulant in that it is a foreign irritant (squalene oil) and allows the peptides to reside at the site of injection to be presented to the antigen-presenting-cells.

At the time of PVX-410 administration, all patients will receive the immunostimulant 0.5 mL (1 mg) Hiltonol® (poly-ICLC), a synthetic double-stranded ribonucleic acid (dsRNA) 'host-targeted' therapeutic viral-mimic with broad innate and adaptive vaccine adjuvant, immune enhancing, as well as antiviral and antiproliferative effects.

Initially, poly-ICLC was investigated as an IFN inducer in cancer studies. In early Phase 1 studies, the MTD was determined to be 12 mg/m^2 in patients with cancer who were not terminally ill.(31) Subsequently, Phase 1 and 2 clinical studies were conducted in a variety of solid tumors and hematologic malignancies, with poly-ICLC administered intravenously at a dose ~6 mg/m^2 in most studies.(32,33,34,35,36,37,38,39,40) Subsequently, it was determined that lower poly-ICLC doses of 10 to 50 µg/kg resulted in a broader host defense stimulation and potent adjuvant effect mediated by the 2'5'OAS and PKR nuclear enzyme systems.(41) Based on these findings, poly-ICLC (Hiltonol®) is currently being developed by Oncovir, Inc., for use only at doses up to 50 µg/kg. To date, 7 clinical studies of Hiltonol® at doses ranging from 0.50 to 4 mg as an adjuvant for cancer vaccines have been initiated, as shown in Table 7-4. In these studies, low-dose Hiltonol® has been well tolerated, with the most common adverse events including discomfort at the injection site associated with induration and mild tenderness; mild, transient fever and fatigue; and nausea and vomiting. In the current study, Hiltonol® will be administered at a dose of 0.5 mL (1 mg), which is within the range of doses employed and shown to be well tolerated in these previous clinical cancer vaccine studies.

Table 7-4 Clinical Studies of Poly-ICLC as a Vaccine Adjuvant

Protocol Title	Phase	Indication	N	Dose Schedule
PSMA and TARP peptide with poly ICLC adjuvant in prostate cancer	1/2	Prostate cancer	30	1 mg
CDX 1307 vaccine with poly-ICLC in metastatic cancers	1	Metastatic cancers	20	2 mg IM
Poly-ICLC with glioma associated peptide vaccine	1/2	Grade 2 gliomas	20	20 µg/kg IM 2× Wk
MUC1 Hundred-mer and poly-ICLC vaccine for triple-negative breast cancer	1/2	Triple negative breast cancer	37	50 mg IM
MUC1 hundred-mer and poly-ICLC vaccine for colonic polyposis	1/2	Colonic adenoma	45	0.5 mg SC
Hiltonol +NYEso protein vaccine in ovarian cancer	1/2	Ovarian cancer	10	1.4 mg SC

7.7. Study Treatment Discontinuation Criteria

Study vaccine may be discontinued for any of the following reasons:

- Occurrence of a DLT, as defined in Section 7.5.3.
- A treatment delay for > 2 weeks or missing >2 study vaccine doses.
- Patient, investigator, or sponsor request because of an unacceptable adverse event or other reason.
- Patient non-adherence to study vaccine or protocol requirements.
- Pregnancy.
- Progression of disease that, in the opinion of the investigator, precludes further study treatment.

Patients who discontinue study vaccine are to continue to attend post-treatment follow-up visits through Month 12 unless a study withdrawal criterion is met (see Section 6.4). In such cases, evaluations scheduled to be performed at the Month 12/Final Study visit are to be performed at the time of study withdrawal.

Patients who discontinue from the study for administrative or other non-safety related reasons (eg, non-compliance, patient request) before receiving at least 4 of 6 study vaccine doses will be replaced.

Lenalidomide is to be discontinued per the instructions in Section 7.5.1.2.2 and in the prescribing information (available at: http://www.revlimid.com/pdf/PI.pdf).(23) If lenalidomide is discontinued, the Investigator is to notify MedSource, as specified in the REMS® program. In such cases, the patient is to continue treatment with PVX-410.

7.8. Concurrent Medications

7.8.1. Prohibited Concurrent Medications

The following medications are prohibited during the study:

- Systemic corticosteroids.
- Any other treatment for MM, including conventional chemotherapies, proteasome inhibitors, thalidomide, and IMiDs.
- Intravenous (IV) bisphosphonates. (Oral bisphosphonates are allowed.)
- Live vaccines are prohibited within 4 weeks prior to the first study vaccine dose and during the course of the study.

Refer to the lenalidomide prescribing information (available at: http://www.revlimid.com/pdf/PI.pdf) for drug interaction information with lenalidomide.(23)

7.8.2. Permitted Concurrent Medications

Medications and treatments other than those specified in Section 7.8.1 are permitted during the study.

All medications and supportive therapies that are administered during the active treatment period of the study through the Month 1 follow-up visit, including the start and stop date(s), dose/amount administered, and indication, must be recorded in the patient's eCRF and in the source documents. Medications and supportive therapies administered after the Month 1 follow-up visit are to be recorded in the patient's eCRF and in the source documents if, at the Investigator's discretion, the medication or supportive therapy is required to treat symptoms related to study treatment.

8. VARIABLES AND METHODS

8.1. Efficacy Measurements

The following section describes the anti-tumor measurements that will be obtained during the study. All anti-tumor measurements collected on the same day as study vaccine administration must be collected before study vaccine is administered.

8.1.1. Myeloma Protein Measurements in Serum and Urine

8.1.1.1. Serum

Blood samples for quantitation of Ig (IgA, IgG, and IgM are required; IgD and IgE are optional) and M-protein and assessment of M-protein by immunofixation in serum are to be collected from all patients during Screening. Such samples also are to be collected at Weeks 0, 4, and 8 and at post-treatment Months 1, 3, 6, 9, and 12.

All samples will be analyzed by the local laboratory.

8.1.1.2. Urine

Twenty-four hour urine samples for quantitation of M-protein and assessment of M-protein by immunofixation are to be collected from all patients during Screening. For patients with positive findings at Screening, such samples also are to be collected Weeks 0, 4, and 8 and at post-treatment Months 1, 3, 6, 9, and 12. Patients with negative Screening results need not provide urine samples for M-protein quantitation and assessment after Screening.

All samples will be analyzed by the local laboratory.

8.1.2. Free Light Chain Testing

Serum samples for FLC testing are to be collected from all patients during Screening and Weeks 0, 4, and 8 and at post-treatment Months 1, 3, 6, 9, and 12. The free kappa/lambda ratio is to be recorded in the eCRF.

A serum sample for FLC testing also is to be collected in order to confirm stringent complete response (sCR).

8.1.3. Bone Marrow Examination

Bone marrow aspiration and trephine biopsy are to be performed for all patients during Screening. Bone marrow aspiration and biopsy are to be repeated during treatment as clinically indicated, at the investigator's discretion, in order to confirm complete response (CR).

8.1.4. Skeletal Survey and Other Imaging Studies

Skeletal surveys are to be performed during Screening. If a skeletal survey has been performed within 3 months before baseline, then this evaluation need not be repeated during Screening.

A skeletal survey is to be repeated during the study as clinically indicated.

Other appropriate imaging studies (eg, magnetic resonance imaging [MRI], computed tomography [CT], X-ray) to evaluate the patient's disease are to be performed during

Screening per standard of care, as determined by the investigator. Appropriate imaging studies are to be repeated as necessary to confirm CR.

8.1.5. Assessment of Disease Response

The investigator will perform tests that will allow evaluation of response to therapy according to Table 8-1. Patients who are determined to have CR are then to have additional tests performed that will allow further characterization of the CR.

Assessment of disease response using non-invasive procedures will be performed at Weeks 4 and 8 and at post-treatment Months 1, 3, 6, 9, and 12. Appropriate imaging studies and bone marrow aspirates/biopsies must be repeated only in patients suspected of having a CR, based on non-invasive procedures.

Table 8-1 International Myeloma Working Group Disease Response Criteria

Response	IMWG Criteria
Complete response (CR)[1]	• Negative immunofixation of serum and urine, and • Disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in bone marrow
Stringent complete response (sCR)	CR as defined above plus • Normal FLC ratio, and • Absence of clonal plasma cells (PC) by immunohistochemistry or 2-4 color flow cytometry.
Immunophenotypic CR	Stringent CR plus • Absence of phenotypically aberrant PC (clonal) in bone marrow (BM) with a minimum of one million of total BM cells analyzed by multiparametric flow cytometry (with >4 colors)
Molecular CR	CR plus • Negative allele-specific oligonucleotide-polymerase chain reaction (ASO-PCR), sensitivity 10^{-5}
Very good partial response (VGPR)[1]	• Serum and urine M-component detectable by immunofixation but not on electrophoresis, or • ≥90% or greater reduction in serum M-component plus urine M component <100 mg per 24 hours
Partial response (PR)	• ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 hours • If the serum and urine M-protein are unmeasurable a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30% • In addition to the above criteria, if present at baseline, ≥50% reduction in the size of soft tissue plasmacytomas is also required
Stable disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease.

Response	IMWG Criteria

Progressive disease (PD)[2]	• Increase of 25% from lowest response value in any one or more of the following:
	  • Serum M-component (absolute increase must be ≥0.5 g/dL) and/or
	  • Urine M-component (absolute increase must be ≥200 mg/24 hours) and/or
	  • Only in patients without measurable serum and urine M protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL)
	  • Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be >10%)
	• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	• Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

Source: Rajkumar, et al. Blood 2011;117(18):4691-5.

All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

1 Note clarifications to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients requires in addition a >90% decrease in the difference between involved and uninvolved free light chain FLC levels.

2 Note clarifications to IMWG criteria for coding PD: Clarified than bone marrow criteria for progressive disease are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that "25% increase" refers to M protein, FLC, and bone marrow results, and does not refer to bone lesions, soft tissue plasmacytomas, or hypercalcemia. Note that the "lowest response value" does not need to be a confirmed value.

8.1.6. Immune Response

The University of Pittsburgh Medical Center Cancer Centers, Immunologic Monitoring and Cellular Products Laboratory (IMPCL) is the central laboratory for immune monitoring assessments and will provide blood collection kits and instructions for sample shipment to the study centers. Contact information for IMPCL and detailed instructions regarding sample shipment to IMPCL are provided in the study reference manual.

Blood samples for measurement of cytokine measurements are to be collected prior to the study vaccine dose at Weeks 0, 4, and 8 and post-treatment Months 1, 3, 6, 9, and 12.

Blood samples for T-cell assays are to be collected prior to the study vaccine dose at Weeks 0, 2, 4, and 8 and post-treatment Months 1, 3, 6, 9, and 12.

Aliquots of blood collected at each timepoint will be stored or future immunologic analyses. Such samples will be stored indefinitely until such time that appropriate analyses are developed / identified and will not be used for genomic testing.

A blood collection kit will be provided for each patient for each visit at which samples for immune response are to be collected (Weeks 0, 4, and 8 and Months 1, 3, 6, 9, and 12). Overall, a minimum of 70 mL, with a target of 100 mL of blood, will be drawn over these visits.

Samples will be packaged according to instructions provided in the specimen kit. The kit is to be sent via overnight courier (Monday through Thursday) to the University of Pittsburgh Medical Center Cancer Centers, IMPCL; samples must be sent to IMPCL via overnight courier on the same day they are collected. Plasma will be collected from the samples and the blood will be ficolled according to IMPCL standard operating procedures to obtain mononuclear cells (MNC). If a sample is not collected as required according to the sample collection schedule, the study center representative must notify the Sponsor within 24 hours of the study visit.

Monitoring assays to assay immune response is planned to be performed in batches, with the first batch containing all patient samples through Month 1 and the second batch containing the remaining samples up to Month 12. All samples will be tested for IFN-γ production by ELISPOT and for T cell response to the specific study peptides by a tetramer flow cytometry assay. Other relevant assays identified by the Sponsor also may be used for immunogenicity assessments.

8.2. Safety Measurements

8.2.1. Demographics and Medical History

A medical history will be obtained during the Screening period for all patients. The medical history is to include demographic and background information and SMM history, including date of diagnosis, and any previous treatment for SMM.

8.2.1.1. Historical Cytogenetic Findings

As part of the patient's SMM history, study centers are to submit a local cytogenetics report and fluorescent *in situ* hybridization (FISH) analysis report obtained prior to enrollment, if available. The FISH panel ideally should include assessment of t(4;14), t(14;16), and del 17p.

8.2.2. Human Leukocyte Antigen Typing

A Screening blood sample for HLA typing with sequence-based subtyping is to be collected prior to the performance of any other Screening assessments. If the patient has had HLA typing previously performed by an accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for Screening. If the patient has not had HLA typing performed previously or an acceptable result is not available from the previous test, then a blood sample for HLA typing with sequence-based subtyping may be collected under the auspices of this protocol >4 weeks before

Week 0, but only after the patient provides consent to participate in this study. Patients must be demonstrated to be HLA-$A2^+$ to proceed with Screening; if the patient is demonstrated to be HLA-$A2^+$, then the Screening process may continue, with all other Screening assessments to be performed within 4 weeks before Week 0. Patients who are demonstrated to be HLA-$A2^-$ will be considered screen failures, and no additional Screening assessments will be performed.

8.2.3. Physical Examination

A complete physical examination will be conducted for all patients during Screening. Any abnormal findings are to be documented as part of the patient's medical history.

Abbreviated physical examinations are to be performed at all subsequent visits, including Weeks 0, 2, 4, 6, 8, and 10 and at post-treatment Months 1, 2, 3, 6, 9, and 12. An examination of the injection site is included in the abbreviated physical examination. Abnormal physical examination findings that represent a change from baseline are to be reported as adverse events.

8.2.4. Vital Signs and Weight

Vital signs, including systolic and diastolic blood pressure (mmHg), pulse (beats per minute), respiration rate (breaths per minute), and temperature (ºC) as well as weight (kg), are to be measured during Screening and at Weeks 0, 2, 4, 6, 8, and 10 and at post-treatment Months 1, 2, 3, 6, 9, and 12.

The mode of temperature recording will be documented (ie, oral or axillary).

Blood pressure (BP) and pulse will be measured using a BP recording device with an appropriate cuff size. Measurements will be made after the patient has been resting supine for a minimum of 5 minutes.

If an abnormality is considered by the investigator to be clinically significant, then the abnormality is to be recorded as part of the patient's medical history if occurring prior to the start of study treatment and as an adverse event if occurring after the start of study treatment, where the finding represents a change from baseline.

8.2.5. ECOG Performance Status

ECOG performance status is to be determined during Screening and at Weeks 0, 2, 4, 6, 8, and 10 and at post-treatment Months 1, 2, 3, 6, 9, and 12 (see Table 8-2).

Table 8-2 ECOG Performance Status Scale

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey, DC, Horton J, Davis, TE, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.

8.2.6. Safety Laboratory Assessments

8.2.6.1. Screening Serology

A blood sample for serologies, including hepatitis B surface antigen (HBsAg), anti-HCV, and HIV, is to be collected from all patients during Screening. Results must be negative for the patient to be enrolled in the study.

8.2.6.2. Pregnancy Testing for Female Patients of Child-bearing Potential

For patients in the low-dose and target-dose cohorts, a urine or serum β-human chorionic gonadotropin (hCG) pregnancy test is to be performed for women of child-bearing potential during Screening and repeated as needed if the patient has had unprotected intercourse.

For patients in the PVX-410 + lenalidomide cohort, patients must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.
Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to initiating lenalidomide therapy. During lenalidomide treatment, pregnancy testing is to be performed weekly during the first month, and then monthly thereafter for women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles during the active treatment period and for 1 month post-treatment. Females of reproductive potential must also be tested for pregnancy during the 7-day rest period before the start of any new lenalidomide cycle. The pregnancy tests administered must be sensitive to at least 50 mIU/mL, and may be performed locally.

Males must agree to always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking lenalidomide and for up to 28 days after discontinuing lenalidomide, even if they have undergone a successful vasectomy and also must agree not to donate sperm while taking lenalidomide.

Regardless of cohort, if a woman becomes pregnant or suspects she is pregnant while participating in this study, she must inform her treating physician immediately and permanently discontinue all study treatment.

8.2.6.3. Hematology, Clinical Chemistries, and Coagulation Studies

Blood samples for hematology and clinical chemistry are to be collected for all patients during Screening and at Weeks 0, 2, 4, 6, 8, and 10 and at post-treatment Months 1, 2, 3, 6, 9, and 12. On study vaccine administration days, hematology and clinical chemistry results must be available and reviewed by the investigator prior to study vaccine administration.

The following clinical laboratory parameters are to be measured:

Hematology

- Hemoglobin
- Red blood cell count (RBC)
- Platelet count
- White blood cell count (WBC) with differential

Chemistry

- Glucose
- Calcium
- Albumin
- Total protein
- Sodium
- Potassium
- Lactic dehydrogenase (LDH)
- Creatinine
- Fibrinogen
- Alkaline phosphatase (ALP)
- AST
- ALT
- Total bilirubin
- Gamma-glutamyl transferase (GGT)
- C-reactive protein (CRP) (non-high sensitivity)
- Amylase
- Phosphate
- Urea
- Uric acid

Coagulation Studies

- Prothrombin time (PT)
- Activated partial thromboplastin time (aPTT)

Clinical laboratory evaluations are to be repeated as necessary during treatment at a schedule determined by the investigator, based on the patient's clinical status.

Laboratory abnormalities that are considered by the investigator to be clinically significant for a particular patient during Screening and before study treatment at Week 0 be reported as part of the patient's medical history and as an adverse event after the start of study treatment at Week 0, where the finding represents a change from baseline.

8.2.7. Adverse Events

8.2.7.1. Definitions

An adverse event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, and which does not necessarily have to have a causal relationship with the study treatment. An adverse event can therefore be any unfavorable and unintended sign (including abnormal laboratory

findings), symptom, or disease temporally associated with the use of study treatment, whether or not related to study treatment.

Injection site reactions (ISRs) and flu-like symptoms are expected adverse events with study vaccine administration. In order to accurately capture the incidence and duration of these events, the Sponsor will provide patient cards (see Appendix 2) on which the patient is to record ISRs and flu-like symptoms for up to 7 days after each study vaccine dose. Patients will be instructed to bring the completed patient card to the study center visit after each study vaccine dose.

An unexpected adverse event is any event for which the nature or severity is not consistent with the information in the current Investigator's Brochure.

International Conference on Harmonization (ICH) guidelines define an SAE as any untoward medical occurrence that at any dose and regardless of causality that:

- Results in death.
- Is life-threatening. Life-threatening means that the subject was at immediate risk of death from the reaction as it occurred, ie, it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form.
- Requires in-patient hospitalization or prolongation of existing hospitalization. Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected manner during the study (eg, surgery performed earlier than planned).
- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a persons' ability to conduct normal life functions.
- Is a congenital anomaly/birth defect.
- Is an important medical event. An important medical event is an event that may not result in death, be life-threatening, or require hospitalization but may be considered an SAE when, based upon appropriate medical judgment, it may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definitions for SAEs. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

8.2.7.2. Adverse Event Assessment

All non-serious adverse events will be recorded from the time the patient signs the informed consent form through the Month 1 follow up visit, and SAEs will be recorded from the start of study treatment dose through the Month 1 follow up visit. This includes adverse events the patient reports spontaneously, those observed by the investigator, those elicited by the investigator in response to open-ended questions during scheduled study center visits, and ISRs and flu-like symptoms recorded on the patient card.

Each adverse event is to be assessed by the investigator with regard to the following categories.

Serious/Non-Serious

Adverse events that meet the criteria specified in Section 8.2.7.1 are to be considered serious.

Relationship to Study Treatment

The relationship of each adverse event to study treatment is to be assessed by the investigator according to the following criteria:

Reasonably or Possibly Related to Study Treatment

This category applies to those adverse events that, after careful medical consideration at the time they are evaluated, are considered by the investigator to have at least a possible relationship to study treatment.

The adverse event may be considered reasonably or possibly related to study treatment if the event:

- Follows a reasonable temporal sequence after administration of the study treatment,
- Could not be reasonably explained by the known characteristics of the patient's clinical state, environmental, or toxic factors, or other modes of therapy administered to the patient,
- Disappears or decreases on cessation or reduction in dose, or
- Follows a known pattern of response to study treatment.

Not Reasonably or Possibly Related to Study Treatment

This category applies to those adverse events that, after careful medical consideration at the time they are evaluated, are considered by the investigator to have no reasonable or possible relationship to study treatment.

The adverse event may be considered not reasonably or possibly related to study treatment if the event:

- Does not follow a reasonable temporal sequence after administration of the study treatment,
- Could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient,
- Does not follow a known pattern of response to the study treatment,
- Does not reappear or worsen when the study treatment is readministered, or
- Is clearly and incontrovertibly due to causes other than the study treatment (eg, disease, environment).

Intensity

The intensity of each adverse event is to be assessed by the investigator according to the NCI CTCAE, Version 4.03. If the adverse event is not included in the NCI CTCAE, then the investigator is to determine the intensity of the adverse event according to the following criteria:

Mild (Grade 1):	Adverse event that disappears or is easily tolerated on continuation of study treatment.

Moderate (Grade 2):	Adverse event sufficiently discomforting to cause interference with usual work activities.
Severe (Grade 3):	Adverse event that is incapacitating, with inability to work or perform daily activities.
Life-Threatening (Grade 4):	Adverse event that is *potentially* life-threatening.[3]

8.2.7.3. Recording Adverse Events

All non-serious adverse events occurring from the time the patient signs the informed consent form through the Month 1 follow up visit, and SAEs occurring from the start of the first study treatment dose through the Month 1 follow up visit, regardless of relationship to study treatment, are to be recorded in the Adverse Events eCRF. All adverse event reports are to contain the following details regarding the adverse event: a brief description, onset date, duration, intensity, treatment required, relationship to study treatment, study treatment action taken, outcome, and whether the event is classified as serious.

8.2.7.4. Reporting Serious Adverse Events

The investigator must report all serious adverse events to the medical monitor within 24 hours of discovery.

Medical Monitor

James F. Balsey, MD

Telephone: 410.708.7609

Fax: 919.844.6948

E-mail: saereports@drugsafety.biz

A completed SAE report is to be sent to the medical monitor's attention within 24 hours of discovering the event. The medical monitor will contact the investigator via telephone for follow-up information regarding the SAE, as appropriate.

Refer to Section 8.2.7.5 for additional reporting requirements for patients in the PVX-410+lenalidomide cohort.

8.2.7.5. Expedited Reporting by Investigator to Celgene: PVX-410+Lenalidomide Cohort

Serious adverse events (SAE) are defined in Section 8.2.7.1. The Investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not

[3]. If a life-threatening (grade 4) adverse event is *immediately* life-threatening, the event is, by definition, serious and is to be reported as described in Section 8.2.7.4.

available at the time of the initial report (eg, an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-XX-PI-###) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

8.2.7.6. Follow-Up of Adverse Events

The investigator must continue to follow all SAEs and non-serious adverse events considered to be reasonably or possibly related to study treatment either until resolution or the investigator assesses them as chronic or stable. This follow-up may extend after the end of the study.

8.2.7.7. Reporting Safety Information

The investigator must promptly report to his or her IRB all unanticipated problems involving risks to patients. This includes death from any cause and all SAEs reasonably or possibly associated with the use of study treatment.

The sponsor will promptly notify FDA and all participating investigators in a safety report of potential serious risks deriving from this clinical study or any other sources in accordance with 21 Code of Federal Regulations (CFR) 312.32.

8.2.7.8. Protocol Deviations Due to an Emergency or Adverse Event

Departures from the protocol will be determined as allowable on a case-by-case basis and only in the event of an emergency. The investigator or other physician in attendance in such an emergency must contact the medical monitor as soon as possible to discuss the circumstances of the emergency.

The medical monitor, in conjunction with the investigator, will decide whether the patient should continue to participate in the study. All protocol deviations and reasons for such deviations must be noted in the eCRF.

8.2.7.9. Pregnancies: PVX-410+Lenalidomide Cohort

Female Patients:

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (eg, spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety

immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Patients:

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

9. SCHEDULE OF EVALUATIONS

Patients are to attend study centers visits during Screening within 4 weeks before baseline, with the exception of HLA typing, which may be performed any time before baseline, provided written informed consent has been obtained (see Section 8.2.2). Other Screening assessments should be performed only after the patient is demonstrated to be HLA-A2^{+}.

Patients who are determined to be eligible for the study, based on Screening assessments, will be enrolled in the study and receive their first study vaccine dose at Week 0 (baseline). During the treatment period, patients will attend study center visits on an every 2-week basis (Weeks 2 [±3 days], 4 [±3 days], 6 [±3 days], 8 [±3 days], and 10 [±3 days]) to receive study vaccine and have study assessments performed. After completion of the treatment period, patients are to attend follow-up visits at post-treatment Month 1 (±1 week), 2 (±1 week), 3 (±1 week), 6 (±1 week), 9 (±1 week), and 12 (±1 week). The post-treatment Month 12 visit represents the final study visit.

Table 9-1 presents the schedule of evaluations for this study.

Table 9-1 Schedule of Evaluations

	Study Period / Visit (Window) / Timepoint												
	Screening	**Treatment**						**Post-treatment Follow-up**					**Final Visit**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Evaluation	**W-4[1] to 0**	**W0**	**W2 (±3 D)**	**W4 (±3 D)**	**W6 (±3 D)**	**W8 (±3 D)**	**W10 (±3 D)**	**M1 (±1 W)**	**M2 (±1 W)**	**M3 (±1 W)**	**M6 (±1 W)**	**M9 (±1 W)**	**M12 (±1 W)**
Provision of written informed consent	X												
Review entrance criteria	X												
Medical history, including SMM history, and demographics	X												
HLA typing	X[1]												
Skeletal survey[2]	X												
Baseline medical conditions	X												
Baseline medications	X												
Physical examination	X												
Vaccination		X	X	X	X	X	X						
Abbreviated physical examination, including injection site examination		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs and weight	X	X	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X
Clinical laboratory testing													
Urine or serum pregnancy testing	X[3]				X[3]								
Screening serologies[4]	X												
Hematology, clinical chemistries, and coagulation studies[5]	X	X	X	X	X	X	X	X	X	X	X	X	X

	Study Period / Visit (Window) / Timepoint												
	Screening	**Treatment**						**Post-treatment Follow-up**					**Final Visit**
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**
Evaluation	**W-4[1] to 0**	**W0**	**W2 (±3 D)**	**W4 (±3 D)**	**W6 (±3 D)**	**W8 (±3 D)**	**W10 (±3 D)**	**M1 (±1 W)**	**M2 (±1 W)**	**M3 (±1 W)**	**M6 (±1 W)**	**M9 (±1 W)**	**M12 (±1 W)**
Clinical disease response-													
Bone marrow aspirate and biopsy[6]	X												
Serum / urine M protein quantitation[7]	X	X		X		X		X		X	X	X	X
Immunoglobulin quantitation (IgA, IgG, and IgM [required]; IgD, IgE [optional])	X	X		X		X		X		X	X	X	X
Free light chain analysis[9]	X	X		X		X		X		X	X	X	X
Disease response assessment				X		X		X		X	X	X	X
Immune response assessment													
Cytokines[8]		X	X	X		X		X		X	X	X	X
T-cell assays[8]		X	X	X		X		X		X	X	X	X
Concomitant medications[10]		X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[11]	X	X	X	X	X	X	X	X	X	X	X	X	X

Table footnotes appear on the following page.

1 Screening blood sample for HLA typing with sequence-based subtyping is to be collected. If the patient has had HLA typing previously performed by an accredited testing facility, with results determined to be acceptable by the Investigator, those results may be used for Screening. If the patient has not had HLA typing performed previously or an acceptable result is not available from the previous test, then a blood sample for HLA typing with sequence-based subtyping may be collected under the auspices of this protocol >4 weeks before Week 0, but only after the patient provides consent to participate in this study. If the patient is demonstrated to be HLA-$A2^{+}$, then the Screening process may continue, with all other Screening assessments to be performed within 4 weeks before Week 0.

2 If a skeletal survey has been performed within 3 months before baseline, then this evaluation need not be repeated. Skeletal survey is to be repeated during the study as clinically indicated.

3 For women in the low-dose and target dose cohorts, urine or serum pregnancy testing is to be performed for female patients of childbearing potential within 2 weeks before baseline; results must be negative to be eligible for study participation. Pregnancy testing is to be repeated any time pregnancy is suspected. For patients in the PVX-410 + lenalidomide cohort, pregnancy testing requirements as outlined in the Revlimid REMS® program material must be followed. Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing lenalidomide therapy. During lenalidomide treatment, pregnancy testing is to be performed weekly during the first month, and then monthly thereafter for women with regular menstrual cycles or every 2 weeks for women with irregular menstrual cycles during the active treatment period and for 1 month post-treatment. Females of reproductive potential must also be tested for pregnancy during the 7-day rest period before the start of any new lenalidomide cycle. The pregnancy tests administered must be sensitive to at least 50 mIU/mL, and may be performed locally. Regardless of cohort, all study treatment is to be permanently discontinued for any patient with positive pregnancy test results during the treatment period.

4 Screening serologies include testing for HIV, HBsAg, and HCV. Results must be negative to be eligible for study participation.

5 Hematology parameters RBC, WBC with differential count, platelets, hemoglobin. Coagulation studies include aPTT, PT, Serum chemistries include sodium, potassium, urea, creatinine, glucose, uric acid, calcium, phosphates, total proteins, and albumin, total bilirubin, AST, ALT, ALP, GGT, amylase, LDH, CRP, and fibrinogen. Screening laboratory tests must be performed and results reviewed within 2 weeks before baseline.

6 Bone marrow aspirate and trephine biopsy are to be performed during Screening. Bone marrow aspirate and biopsy are to be repeated during treatment as clinically indicated, at the Investigator's discretion, and at any time CR is suspected.

7 Serum will be tested at all scheduled time points. Urine (24-hour sample) testing will be conducted screening. If positive, testing will continue as detailed on the chart. If negative, no further urine testing is needed.

8 Immunomonitoring assays will be performed by the University of Pittsburg Medical Center, Pittsburgh, PA.

9 The free light chain assay provides qualitative measurement of the free kappa and free lambda level and free kappa/lambda ratio. The free kappa/lambda ratio is to be recorded in the eCRF.

10 All medications and supportive therapies that are administered during the active treatment period of the study through the Month 1 follow-up visit, including the start and stop date(s), dose/amount administered, and indication, must be recorded in the patient's eCRF and in the source documents. Medications and supportive therapies administered after the Month 1 follow-up visit are to be recorded in the patient's eCRF and in the source documents if, at the Investigator's discretion, the medication or supportive therapy is required to treat symptoms related to study treatment.

11 All non-serious adverse events occurring from the time the patient signs the informed consent form through the Month 1 follow up visit, and SAEs occurring from the start of study treatment dose through the Month 1 follow up visit, regardless of relationship to study vaccine, are to be documented.

10. STATISTICAL ANALYSES

10.1. Missing, Unused, and Spurious Data

All available safety, immunogenicity, and activity data will be included in data listings and tabulations. No imputation of values for missing data will be performed.

10.2. Patient Disposition

Patients who are screened for study entry and do not meet the eligibility criteria will be listed. Reasons for study discontinuation after the start of study treatment will be tabulated by dose group. Reasons for discontinuation that are the basis for DLT will be categorized in distinction from other reasons for discontinuation.

10.3. Populations for Analysis

Safety analyses will be performed on the safety population, defined as all patients who receive at least 1 dose of study vaccine at either the low or target concentration.

Activity and immunogenicity evaluations will be performed on the evaluable population, defined as all patients who receive at least 4 of 6 study vaccine doses and have at least 1 post-baseline assessment.

10.4. Statistical Methods

Statistical analyses will be descriptive, since the primary goal of the study is to determine the safety and tolerability of PVX-410 alone and in combination with lenalidomide.

Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, median, minimum, and maximum). Categorical variables will be summarized showing the number and percentage (n, %) of patients within each classification.

10.4.1. Demographic and Baseline Characteristics

Demographic and baseline disease characteristic data summarization will be performed in order to descriptively assess the comparability of dose groups. Data to be tabulated will include at least demographic features such as sex, age, and race as well as weight and disease-specific status and medical history.

10.4.2. Extent of Exposure

Descriptive statistics for patients treated, including the number of doses received, total dose given, and doses delayed or missed, will be presented for each treatment cycle. A by-patient listing of the date and time of study vaccine administration and the dose administered will be presented.

10.4.3. Concomitant Medications

All concomitant medications administered will be presented in a data listing.

10.4.4. Safety Analyses

Safety evaluations will be based on the incidence, intensity, and type of adverse events, and changes in the patient's physical examination findings, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all patients who receive any amount of study vaccine and have follow-up safety data. Summarization will focus on occurrence rates of any SAEs; treatment-emergent adverse events by

system/organ classification and preferred term; discontinuation rates of study vaccine due to adverse event or toxicity based on clinical laboratory test results. The frequency of DLT by dose group also will be summarized.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization.

Treatment-emergent events will be tabulated, where treatment-emergent is defined as any adverse event that occurs after administration of the first dose of study treatment and through 30 days after the last dose of study treatment, any event that is considered study treatment-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered study treatment-related by the investigator.

Events that are considered study treatment-related will also be tabulated; it should be noted, however, that without a control, the primary safety conclusions must be based on overall incidence rates, not those considered treatment-related.

A tabulation will also be provided that enumerates treatment-emergent adverse events by maximum severity.

All adverse events, including treatment-emergent adverse events and post-treatment adverse events, will be listed in patient data listings.

Deaths, SAEs, and events resulting in study discontinuation will be tabulated. As applicable, SAEs attributable to disease progression will be tabulated in combination and separately from all other SAEs.

Change from baseline in clinical laboratory parameters will be summarized across time on study, and the frequency of clinically significant abnormal laboratory values will be tabulated. Shift tables will be produced for selected laboratory parameters, to include at least hemoglobin, WBC count, ANC, lymphocytes, platelet count, AST, ALT, bilirubin, creatinine, ALP, and electrolytes. These tables will summarize by cycle the number of patients with each baseline CTCAE grade and changes to the maximum CTCAE grade in the cycle.

Changes in vital sign parameters (including systolic and diastolic blood pressure, heart rate, respiration rate, and temperature) will be summarized over time in a similar fashion to laboratory parameters, and any abnormal values will be tabulated.

ECOG performance status will be summarized for changes from baseline to the End of Therapy visit; ECOG performance status at each time point will be presented in data listing format.

Additional safety analyses may be determined at any time without prejudice, in order to most clearly enumerate rates of toxicities and to define further the safety profile of PVX-410.

10.4.5. Activity Analyses

Changes from baseline to successive measurement intervals in M protein component will be analyzed by dose group. Other metrics such as area under the curve methodology may be used, if appropriate; specific details of analyses will be documented in a formal statistical analysis plan.

Disease response is to be determined by the investigator according to the IMWG criteria.

For responding patients, DUR will be defined as time in weeks from the date of the first observation of PR or better to the date of PD/relapse.

TTP will be defined as the duration in weeks from the date of the first PVX-410 dose until the date of confirmed progressive disease or relapse from CR.

PFS will be defined as the time in weeks from the date of the first PVX-410 dose to the date of PD or death, whichever occurs first.

Time to event analyses (ie, TTP, PFS, DUR) will use standard survival analysis techniques such as Kaplan-Meier life test methods. The durations of DUR, TTP, and PFS will be listed on a per-patient basis.

Data that may further characterize the activity of PVX-410 will be summarized and assessed for a potential dose-response relationship.

10.4.6. Immunogenicity Analyses

Immunogenicity data will be summarized descriptively. Other metrics may be used, if appropriate; specific details of analyses will be documented in a formal statistical analysis plan.

10.5. Interim Analyses

No formal interim analysis for the purposes of modifying the study is planned.

10.6. Changes to the Planned Statistical Methods

Changes to the planned statistical methods will be documented in the clinical study report.

11. DATA QUALITY CONTROL AND QUALITY ASSURANCE

11.1. Data Quality Assurance

OncoPep, Inc., or its designated representative will conduct a study center visit to verify the qualifications of each investigator, inspect study center facilities, and inform the investigator of responsibilities and procedures for ensuring adequate and correct study documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded in the eCRFs for this study must be consistent with the patient's source documentation.

11.2. Case Report Forms and Source Documentation

OncoPep, Inc., or designee will provide the study centers with secure access to and training on the EDC application, sufficient to permit site personnel to enter or correct information in the eCRFs for the patients for whom they are responsible.

eCRFs will be completed for each study patient. It is the investigator's responsibility to ensure the accuracy, completeness, clarity, and timeliness of the data reported in the patient's eCRF.

The investigator, or designated representative, should complete the eCRF as soon as possible after information is collected.

The investigator must provide through the EDC application formal approval of all the information in the eCRFs and changes to the eCRFs to endorse the final submitted data for the patients for which he or she is responsible. The audit trail entry will show the user's identification information and the date and time of the correction.

OncoPep, Inc., or a designee, will retain the eCRF data and corresponding audit trails. A copy of the final archival eCRF in the form of a compact disc (CD) or other electronic media will be placed in the investigator's study file.

11.3. Direct Access to Source Data

During the course of the study, the CRA will make study center visits to review protocol compliance, compare eCRFs and individual patient's medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. The eCRFs will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRFs for completeness and cross-checking with source documentation will be required to monitor the progress of the study. Moreover, regulatory authorities and/or quality assurance personnel from OncoPep, Inc., or its designated representative, may wish to carry out such source data checks and/or in-center audit inspections. The investigator assures OncoPep, Inc., of the necessary support at all times.

11.4. Archiving Study Records

Essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed

since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if required by the applicable local requirements.

12. REFERENCES

1 International Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121 (5):749-57.

2 Pérez-Persona E, Vidriales MB, Mateo G, García-Sanz R, Mateos MV, de Coca AG, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. Blood 2007;110:2586-92.

3 Bladé J, Dimopoulos M, Rosiñol L, Rajkumar SV, Kyle RA. Smoldering (asymptomatic) multiple myeloma: current diagnostic criteria, new predictors of outcome, and follow-up recommendations. J Clin Oncol 2010;28(4):690-97.

4 Kyle RA, Durie BG, Rajkumar SV, Landgren O, Bladé J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. Leukemia 2010;(6):1121-7.

5 Rosiñol L, Bladé J, Esteve J, Aymerich M, Rozman M, Montoto S, et al. Smoldering multiple myeloma: natural history and recognition of an evolving type. Br J Haematol 2003;123(4):631-36.

6 Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rödjer S, Westin J. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage 1-a randomized study. Myeloma group of Western Sweden. Eur J Hematol 1993;50:95-102.

7 Grignani G, Gobbi PG, Formisano R, Pieresca C, Ucci G, Brugnatelli S, et al. A prognostic index for multiple myeloma. Br J Cancer 1996;73:1101-1107.

8 Riccardi A, Mora O, Tinelli C, Valentini D, Brugnatelli S, Spanedda R, et al. Long term survival of stage 1 multiple myeloma given chemotherapy just after diagnosis or at progression of the disease: a multi-center randomized study. Cooperative Group of Study and Treatment of Multiple Myeloma. Br J Cancer 2000;82(7):1254-60.

9 Lust JA, Lacy MQ, Zeldenrust SR, Dispenzieri A, Gertz MA, Witzig TE, et al. Induction of a chronic disease state in patients with smoldering or indolent multiple myeloma by targeting interleukin-1 (beta)-inducted interleukin 6 production and the myeloma proliferative component. Mayo Clin Proc 2009;84:114-22.

10 Rajkumar SV, Dispenzieri A, Fonseca R, Lacy MQ, Geyer S, Lust JA, et al. Thalidomide for previously untreated indolent or smoldering multiple myeloma. Leukemia 2001;15(8):1274-76.

11 Rajkumar SV, Gertz MA, Lacy MQ, Dispenzieri A, Fonseca R, Geyer SM, et al. Thalidomide as initial therapy for early-stage myeloma. Leukemia 2003;17: 775-79.

12 D'Arena G, Gobbi PG, Broglia C, Sacchi S, Quarta G, Baldini L, et al. Pamidronate versus observation in asymptomatic myeloma: final results with long-term follow-up of a randomized study. Leuk Lymphoma 2011;52(5):771-5.

13 Mateos M-V, Hernández M-T, Giraldo P, de la Rubia J, de Arriba F, López Corral L, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-47.

14 Bae J, Tai Y-T, Anderson K, Munshi N. Novel epitope evoking CD138 antigen-specific cytotoxic T lymphocytes targeting multiple myeloma and other plasma cell disorders. Br J Haematol 2011.

15 Bae J, Carrasco R, Lee A-H, Prabhala R, Tai1 Y-T, Anderson KC, et al. Identification of novel myeloma-specific XBP1 peptides able to generate cytotoxic T lymphocytes: a potential therapeutic application in multiple myeloma. Leukemia 2011.

16 Bae J, Song W, Smith R, Daley J, Tai Y-T, Anderson KC, et al (2011). A novel immunogenic CS1-specific peptide inducing antigen-specific cytotoxic T lymphocytes targeting multiple myeloma. In Press.

17 Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117(18):4691-5.

18 Ahn C. An evaluation of phase I cancer clinical trial designs. Statistics in Medicine 1998; 17 (14):1537-49.

19 Dillman RO, Koziol JA. Phase I cancer trials: limitations and implications. Molecular Biotherapy 1992; 4 (3):117-21.

20 US Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research. Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines, September 2009.

21 Andersen MH, Junker N, Ellebaek E, Svane IM, Thor Straten P. Therapeutic cancer vaccines in combination with conventional therapy. J Biomed Biotechnol. 2010;2010:237623.

22 Ramakrishnan R, Huang C, Cho HI, Lloyd M, Johnson J, Ren X, et al. Autophagy induced by conventional chemotherapy mediates tumor cell sensitivity to immunotherapy. Cancer Res. 2012;72(21):5483-93.

23 Revlimid (lenalidomide) prescribing information. Celgene Corporation, June, 2013.

24 Maslak PG, Dao T, Krug LM, Chanel S, Krontsvit T, Zakhaleva, et al. Vaccination with synthetic analog peptides derived from WTI oncoprotein induces T-cell responses in patients with remission from acute myeloid leukemia Blood 2010;116:171-179.

25 Carmichael MG, Benavides LC, Holmes JP, Gates JD, Mittendorf EA, Ponniah S, et al. Results of the first phase 1 clinical trial of the HER-2/neu peptide (GP2) vaccine in disease-free breast cancer patients: United States Military Cancer Institute Clinical Trials Group Study I-04 Cancer 2009;116:292-301.

26 Rezvani K, Yong AS, Mielke S, Jafarpour B, Savani BN, Le RQ, et al. Repeated PR1 and WT1 peptide vaccination in Montanide-adjuvant fails to induce sustained high-avidity, epitope-specific CD8+ T-cells in myeloid malignancies. Haematologica 2011;96(3):432-440.

27 Kirkwood JM, Lee S, Moschos SJ, Albertini MR, Michalak JC, Sander C, et al. Immunogenicity and antitumor effects of vaccination with peptide vaccine +/- granulocyte-monocyte colony-stimulating factor and/or IFN-α2b in advanced metastatic melanoma: Eastern Cooperative Oncology Group phase II trial E1696 Clin Cancer Res 2009;15:1443-1451.

28 Slingluff CL Jr, Petroni GR, Olson WC, Smolkin ME, Ross MI, Haas NB, et al. Effect of granulocyte/macrophage colony-stimulating factor on circulating CD8+ and CD4+ T-cell responses to a multipeptide melanoma vaccine: outcome of a multicenter randomized trial Clin Cancer Res. 2009 Nov 15;15(22):7036-7044.

29 Zhang YQ, Tsai YC, Monie A, Hung CF, Wu TC. Carrageenan as an adjuvant to enhance peptide-based vaccine potency. Vaccine 2010;28(32):5212-9.

30 Tefit JN, Serra V. Outlining novel cellular adjuvant products for therapeutic vaccines against cancer. Expert Rev Vaccines 2011;10(8):1207-20.

31 Levine AS, Sivulich M, Wiernik PH, Levy HB. Initial clinical trials in cancer patients of polyriboinosinic-polyribocytidylic acid stabilized with poly-L-lysine, in carboxymethylcellulose [poly(ICLC)], a highly effective interferon inducer. Cancer Res 1979;39(5):1645-50.

32 Droller MJ. Immunotherapy of metastatic renal cell carcinoma with polyinosinic-polycytidylic acid. J Urol 1987;137(2):202-6.

33 Hawkins MJ, Levin M, Borden EC. An Eastern Cooperative Oncology Group phase I-II pilot study of polyriboinosinic-polyribocytidylic acid poly-L-lysine complex in patients with metastatic malignant melanoma. J Biol Response Mod 1985;4(6):664-8.

34 Krown SE, Kerr D, Stewart WE 2nd, Field AK, Oettgen HF. Phase I trials of poly(I,C) complexes in advanced cancer. J Biol Response Mod 1985;4(6):640-9.

35 Lampkin BC, Levine AS, Levy H, Krivit W, Hammond D. Phase II trial of poly(I,C)-LC, an interferon inducer, in the treatment of children with acute leukemia and neuroblastoma: a report from the Children's Cancer Study Group. J Biol Response Mod 1985;4(5):531-7.

36 Levine AS, Levy HB. Phase I-II trials of poly IC stabilized with poly-L-lysine. Cancer Treat Rep 1978;62(11):1907-12.

37 Nakamura O, Shitara N, Matsutani M, Takakura K, Machida H. Phase I-II trials of poly(ICLC) in malignant brain tumor patients. J Interferon Res 1982;2(1):1-4.

38 Rettenmaier MA, Berman ML, DiSaia PJ. Treatment of advanced ovarian cancer with polyinosinic-polycytidylic lysine carboxymethylcellulose (poly(ICLC]. Gynecol Oncol 1986l;24(3):359-61.

39 Stevenson HC, Abrams PG, Schoenberger CS, Smalley RB, Herberman RB, Foon KA. A phase I evaluation of poly(I,C)-LC in cancer patients. J Biol Response Mod 1985;4(6):650-5.

40 Theriault RL, Hortobagyi GN, Buzdar AU, Levy HB, Hersh EM. Evaluation of polyinosinic-polycytidylic and poly-L-lysine in metastatic breast cancer. Cancer Treat Rep 1986;70(11):1341-2.

41 Ewel CH, Urba WJ, Kopp WC, Smith JW 2nd, Steis RG, Rossio JL, et al. Polyinosinic-polycytidylic acid complexed with poly-L-lysine and carboxymethylcellulose in combination with interleukin 2 in patients with cancer: clinical and immunological effects. Cancer Res 1992;52(11):3005-10.

13. APPENDICES

Appendix 1 Safety Findings from Clinical Studies of Peptide Vaccines in Oncologic Indications

Reference	Vaccine (Dose)	Adjuvant	Indication (N)	Adverse Event Summary
Baba 2010[1]	HLA-A*2402 gp100 (1mg/dose)	Montanide	Melanoma (6)	AEs in all pts, including hemorrhage at brain metastasis site (1), hypoxia (1), G3 anemia (1), all related to PD. G1 injection site induration, rubor, local pain, and itching seen in all pts. Vitiligo in 2 pts.
Barve 2008[2]	IDM-2101; 10 peptides (0.5mg/mL each)	Montanide	NSCLC (63)	G1 to 2 AEs included injection site erythema (21%), fatigue (16%), injection site pain (14%), fever (14%). G3 fever/chills (1 pt).
Carmichael 2009[3]	GP2 peptide (250µg/0.5mL)	GM-CSF	Breast cancer (18)	Local toxicities, G1 in 38.9%, G2 in 61.1%. Max systemic toxicity G0 (5.6%), 1 (61.1%), and 2 (33.3%). Most common local reactions: erythema and induration (100%), pruritus (25%), and inflammation (23%). Most common systemic reactions: G1 fatigue (40%) and arthralgia/myalgia (15%). No G3-5 AEs.
Diefenbach, 2008[4]	NY-ESO-1b peptide (100µg/dose)	Montanide	Ovarian cancer (9)	G1 anemia, injection site pruritus, and rash (11%); grade 1 fatigue and myalgia (22%); G2 hypothyroidism (11%). No G3/4 AEs or treatment interruption or delay secondary to AEs.
Jain 2000[5]	5 peptides (200-500 µg/dose)	GM-CSF	CML	G1 or 2 injection site (9), fatigue (4), skin rash (3), diarrhea (3), bone pain (2), nausea (2), sinus drainage, headache, leg pain, dizziness, tachycardia, myalgia, scalp itching, and burning sensation in extremities (1 each). No tx interruptions or discontinuations.
Keilholz 2009[6]	WT1 peptide (0.2 mg/dose)	GM-CSF/KLM	AML and MDS (10)	Transient local erythema and induration; G1 and 2 fatigue, G1 fever, and G1 and 2 pruritus. Erythema-nodosum-like lesions (3). Persistent G2 cough without radiologic abnormalities of the lungs (1).
Kirkwood 2009[7]	4 peptides (total 1mg/mL)	Montanide GM-CSF	Melanoma (120)	≥G3 toxicity rates 41.9% to 83.3% across arms, most commonly lymphopenia, fatigue, and neutropenia.

Reference	Vaccine (Dose)	Adjuvant	Indication (N)	Adverse Event Summary
Maslak 2010[8]	4 WTI peptides (200µg/peptide)	Montanide ISA 51 UFCH/GM-CSF	AML (10)	Minimal toxicity (G2) generally consistent with local irritation, swelling, redness, tenderness or pruritus; 1 delayed G2 allergic reaction (generalized urticaria and perceived laryngeal spasm) treated with antihistamines; 1 pt with localized hypersensitivity reaction to GM-CSF.
Rahma 2010[9]	von Hippel-Lindau peptide (1000µg/dose)	Montanide	Renal cell carcinoma (6)	Most common AEs: G1 fatigue (83%) and local skin reaction, incl. mild skin redness and swelling (83%). No G3 or 4 AEs. No signs or symptoms of autoimmune disease through 88 months of f/u.
Slingluff 2009[10]	12 MHC class I & II-restricted peptides (100 µg/peptide)	Tetanus helper peptide/Montanide or +GM-CSF	Melanoma (121)	Unexpected G3 vaccine-related AEs requiring IRB review: fever (1); syncope (1) rash (2), headache/myalgia/arthralgia (1), injection site pain (1), fever/cellulitis (1); fatigue (1), diarrhea (1). G3 injection site reactions (4). Tx stopped treatment due to AEs (4). Autoimmune toxicities in 24%, similar across all study groups.
Solares 2011[11]	HPV16 E7 (100 µg)	Very small size proteoliposomes (VSSP)	Cervical intra-epithelial neoplasa (7)	Injection site pain (7), burning sensation (6) and local redness and swelling, fever, tremors, cramps, all G1. Lower abdominal pain due to urinary sepsis unrelated to vaccine (1). No late AEs.
Speetjens 2009[12]	10 p53 peptides (0.3mg/peptide)	Montanide	Colorectal cancer (10)	Transient vaccination pain, flu-like symptoms (2), injection site swelling and /or redness (5), injection site pain and/or itching (4), all ≤G2. G2 prostatitis, resolved with antibiotics, and atrial fibrillation, returning to normal sinus rhythm after 0.5 hours; both unrelated.
Tsuruma 2008[13]	Survivin-2B80-88 (0.1/1.0 mg/dose)	Montanide (IFA)	Breast cancer (10)	No AEs with vaccine alone. AEs with vaccine+IFA included induration at injection site (2), general malaise (1), and fever (1). No SAEs.

Key: AE = adverse event; F/U = follow-up; G = grade; GM-CSF = granulocyte macrophage-colony stimulating factor; IRB = institutional review board; SAE = serious adverse event; Tx = treatment.

1 Baba T, Sato-Matsushita M, Kanamoto A, Itoh A, Oyaizu N, Inoue Y, et al. Phase 1 clinical trial of the vaccination for the patients with metastatic melanoma using gp100-derived epitope peptide restricted to HLA-A*2402 J. Translational Med 2010;8:84.

2 Barve M, Bender J, Senzer N, Cunningham C, Greco FA, McCune D, et al. Induction of immune responses and clinical efficacy in a phase II trial of IDM-2101, a 10-epitope cytotoxic T-lymphocyte vaccine, metastatic non-small lung cancer. J Clin Oncol 2008;26:4418-4425.

3 Carmichael MG, Benavides LC, Holmes JP, Gates JD, Mittendorf EA, Ponniah S, et al. Results of the first phase 1 clinical trial of the HER-2/neu peptide (GP2) vaccine in disease-free breast cancer patients: United States Military Cancer Institute Clinical Trials Group Study I-04 Cancer 2009;116:292-301.

4 Diefenbach CS, Gnjatic S, Sabbatini P, Aghajanian C, Hensley ML, Spriggs DR, et al. Safety and immunogenicity study of NY-ESO-1b peptide and montanide ISA-51 vaccination of patients with epithelial ovarian cancer in high-risk first remission. Clin Cancer Res 2008;14(9):2740-2748

5 Jain N, Reuben JM, Kantarjian H, Li C, Gao H, Lee BN, et al. Synthetic tumor-specific breakpoint peptide vaccine in patients with chronic myeloid Leukemia and minimal residual disease J Cancer 2009;115:3924-39-34.

6 Keilholz U, Letsch A, Busse A, Asemissen AM, Bauer S, Blau IW et al. A clinical and immunologic phase 2 trial of Wilms tumor gene product 1 (WT1) peptide vaccination in patients with AML and MDS. Blood 2009;113:6541-6548.

7 Kirkwood JM, Lee S, Moschos SJ, Albertini MR, Michalak JC, Sander C, et al. Immunogenicity and antitumor effects of vaccination with peptide vaccine +/- granulocyte-monocyte colony-stimulating factor and/or IFN-α2b in advanced metastatic melanoma: Eastern Cooperative Oncology Group phase II trial E1696 Clin Cancer Res 2009;15:1443-1451.

8 Maslak PG, Dao T, Krug LM, Chanel S, Krontsvit T, Zakhaleva, et al. Vaccination with synthetic analog peptides derived from WTI oncoprotein induces T-cell responses in patients with remission from acute myeloid leukemia Blood 2010;116:171-179.

9 Rahma OE, Ashtar E, Ibrahim R, Toubaji A, Gause B, Herrin VE, et al. A pilot clinical trial testing mutant von Hippel-Lindau peptide as a novel immune therapy in metastatic renal cell carcinoma. J Translational Med 2010;8:8.

10 Slingluff CL Jr, Petroni GR, Olson WC, Smolkin ME, Ross MI, Haas NB, et al. Effect of granulocyte/macrophage colony-stimulating factor on circulating CD8+ and CD4+ T-cell responses to a multipeptide melanoma vaccine: outcome of a multicenter randomized trial Clin Cancer Res. 2009;15(22):7036-7044.

11 Solares AM, Baladron I, Ramos T, Valenzuela C, Borbon Z, Fanjull S, et al. Safety and Immunogenicity of a Human Papillomavirus Peptide Vaccine (CIGB-228) in Women with High-Grade Cervical Intraepithelial Neoplasia: First-in-Human, Proof-of-Concept ISRN Obstetrics and Gynecology Volume 2011, Article ID 292951, 9 pages.

12 Speetjens FM, Kuppen PJ, Welters MJ, Essahsah F, Voet van den Brink AM, Lantrua MG, et al. Induction of p53-specific immunity by a p53 synthetic long peptide vaccine in patients treated for metastatic colorectal cancer. Clin Cancer Res. 2009 Feb 1;15(3):1086-95.

13 Tsuruma T, Iwayama Y, Ohmura T, Katsuramaki T, Hata F, Furuhata T, et al. Clinical and immunological evaluation of anti-apoptosis protein, surviving-derived peptide vaccine in phase I clinical study for patients with advanced or recurrent breast cancer J Translational Med 2008;6:24.

Appendix 2 Patient Card

INJECTION SITE REACTIONS			
Patient Number:	**Patient Initials:**	**Study Visit:**	**Date of Study Visit:**

Please complete any REACTIONS ON OR NEAR WHERE YOU RECEVIED THE VACCINE INJECTION for 7 days from the time you receive the vaccine injection and return to your clinical study nurse at your next study visit.

- ✓ **Fill in every box in grey below and do not leave any blank.**
- ✓ **Rate how bad the reaction felt with 0 being the lowest pain and 3 being the most severe pain.**

  0 = No Pain 1 = Sensitive to touch 2 = Some restriction of activity 3 = Pain restricts activity
- ✓ **Circle YES or NO to confirm which symptoms you have experienced since your last vaccine injection.**
- ✓ **Circle LEFT or RIGHT and ARM or LEG to confirm where you have experienced these symptoms.**

Days After Vaccine	Date	Injection Site Pain (please circle one)	Arm or Leg	Rash or Redness	Itching or Skin Irritation	Pain	Soreness or Discomfort or Tenderness	Swelling
Same Day of Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
1 Day After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
2 Days After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
3 Days After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
4 Days After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
5 Days After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
6 Days After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No
7 Days After Vaccine		0 1 2 3	Arm or Leg	Yes or No	Yes or No	Yes or No	Yes or No	Yes or No

SYMPTOMS

Patient Number:	Patient Initials:	Study Visit:	Date of Study Visit:

Please complete any SYMPTOMS you experience for 7 days from the time you receive the vaccine injection and return to your clinical trial nurse at your next study visit.

- ✓ **Fill in every box in grey below and do not leave any blank.**
- ✓ **Circle YES or NO to confirm which symptoms you have experienced since your last vaccine injection. If you have experienced fever, record the highest temperature. If you have experienced vomiting and/or fever, record the number of episodes of each.**

Days After Vaccine	Date	General Muscle Aches	Fever	Chills	More Tired than Usual	Headache	Nausea or Vomiting	Diarrhea
Same Day of Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
1 Day After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
2 Days After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
3 Days After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
4 Days After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
5 Days After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
6 Days After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____
7 Days After Vaccine		Yes or No	Yes or No If Yes, temp: ____	Yes or No	Yes or No	Yes or No	Yes or No If Yes, # ep: ____	Yes or No If Yes, # ep: ____

ep = episodes; temp = temperature,