A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients with a High Risk of Recurrence

(MAVIS = Melanoma Antigen Vaccine Immunotherapy Study)

Study Drug: Seviprotimut-L (formerly POL-103A)

Protocol 103A-301 Amendment 4 – Version 10

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CLINICAL PROTOCOL SYNOPSIS

Name of Company: Polynoma LLC	**Name of Study Drug:** **S**eviprotimut-L
Title of Study: A Multicenter, Double-blind, Placebo-controlled, Adaptive Phase 3 Trial of POL-103A Polyvalent Melanoma Vaccine in Post-resection Melanoma Patients With a High Risk of Recurrence	
Population: Otherwise healthy subjects with surgically resected stage IIB, IIC, or III melanoma	
Rationale: Many patients with successfully resected stage IIB to III melanoma relapse after surgery. The only treatment approved by the US FDA and other international regulatory agencies for these patients has limited effectiveness and frequent toxicity. Thus, new therapies are needed for these high-risk patients with melanoma. Seviprotimut-L (formerly POL-103A) is an investigational, polyvalent melanoma vaccine that contains multiple melanoma-associated antigens that are shed from 3 human melanoma cell lines, admixed with alum as the adjuvant. The presence of multiple antigens is an important element in maximizing the induction of tumor-protective immune responses and reducing a tumor cell's ability to escape the immune response. The vaccine has been administered (in varied forms) to approximately 661 subjects who were treated for up to 5 years at antigen doses of 40 μg per treatment. Of these subjects, 42 received a vaccine similar to the current formulation of seviprotimut-L (3 melanoma cell lines plus alum adjuvant). An additional 56 subjects received the similar trivalent vaccine plus liposomal IL-2. These subjects were treated without significant toxicity and the results demonstrated preliminary evidence of efficacy. In study 91-22, a double-blind and placebo-controlled trial of a prototype of the vaccine (4 melanoma cell lines plus alum) in advanced stage III melanoma (n=38), the recurrence-free survival of the melanoma vaccine-treated subjects was over twice as long as that of placebo vaccine-treated subjects (p=0.03).	
Objectives: **Part A** is designed to determine the safety profile and immunogenicity of two different doses of seviprotimut-L - 40 μg or 100 μg vs placebo and to determine the dose to be used in Part B of the study. The decision to proceed to Part B will be based on evidence of immunogenicity, safety, and tolerability. **Part B** is composed of two parts: Part B1 and Part B2. Both Parts B1 and B2 allow an evaluation of efficacy using the dose of seviprotimut-L selected from Part A. The objective of the efficacy evaluations are to assess whether subjects randomized to the active arms have superior recurrence-free survival and overall survival (two primary endpoints in Part B2 of the study) in the active arm compared to subjects randomized to the placebo arm. The safety of seviprotimut-L will also be assessed, and samples collected for the potential correlation of exploratory biomarkers with clinical response.	
Methodology: This is a multi-arm, multicenter, randomized, double-blind, placebo-controlled study. In Part A (dose evaluation), subjects will receive either seviprotimut-L (at a 40 or 100 μg/dose) or placebo. The evaluation to select the seviprotimut-L dose for Part B will occur after the first 99 randomized subjects have reached Week 10 (5 doses of treatment received) and will be based on immunological biomarker response. In Part B (clinical efficacy evaluation), subjects will receive either seviprotimut-L at the dose determined from Part A (40 μg) or placebo. Subjects will be treated at different intervals (see Treatment Schedule) for up to 24 months and followed thereafter for recurrence and survival. Subjects will not be routinely unblinded following recurrence or the end of treatment except to allow the subject to pursue other treatment options.	

Name of Company:	**Name of Study Drug:**
Polynoma LLC	**S**eviprotimut-L

Number of Subjects:

Part A will randomize at least 99 subjects.
Part B1 will randomize at least 325 subjects.
Part B2 will randomize at least 800 subjects.
Note:

- An ineligibility rate of approximately 20% is assumed for the study (i.e., 20% more subjects will be screened than randomized).
- Enrollment into Part A of the study will proceed until data from 33 subjects in each treatment arm with evaluable Week 10 immunological data are collected and analyzed (i.e., it is anticipated that Part A will randomize more than 99 subjects)

Stratification:

Subjects will be stratified according to their stage of disease at enrollment (IIB/IIC vs IIIA vs IIIB/IIIC) to ensure balanced distribution between the seviprotimut-L and placebo arms.

Inclusion Criteria:

1. Histologically confirmed AJCC Stage IIB, IIC, or III cutaneous melanoma.
2. Last definitive surgical resection of all clinically evident disease within 90 days prior to the first seviprotimut-L or placebo dosing. Subjects with positive margins of resection should have re-excision prior to randomization. Previous resections are acceptable, provided that the staging of the melanoma at the time of the previous resection was AJCC Stage I or IIA.
3. Subjects with positive sentinel nodes must have a complete lymphadenectomy. Subjects randomized to the complete lymph node dissection then observation arm of the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) are eligible for enrollment.
4. Male or female subjects ≥ 18 and ≤ 80 years of age.
5. Female subjects of childbearing potential must have a negative pregnancy test within 2 weeks prior to study randomization, must agree to use adequate contraception throughout the treatment duration and for 3 months after the last seviprotimut-L or placebo dosing, and must not be breastfeeding.
6. ECOG Performance Status 0 or 1 and a reasonable expectation of living at least 2 years.
7. White blood cell (WBC) count ≥ 4,000/mm^3.
8. Absolute neutrophil count ≥ 1,500/mm^3.
9. Hemoglobin ≥ 10 g/dL.
10. Platelet count ≥ 100,000/mm^3.
11. Creatinine ≤ 2.0 mg/dL.
12. Bilirubin ≤ 1.5 times the upper limit of normal (ULN).
13. Asparate aminotransferase (AST), alanine aminotransferase (ALT) < 2.0 times ULN.
14. Subjects must have known BRAF V600E mutation tumor status or have tumor tissue (fresh or archived sample) available for testing of BRAF V600E mutation status (note: as long as it is confirmed that tumor tissue is available for testing, the subject may be considered eligible for the study; testing of BRAF mutation status on that tissue may be conducted at a later time during the study).

Name of Company: Polynoma LLC	**Name of Study Drug:** **S**eviprotimut-L

Exclusion Criteria:

1. Any prior melanoma treatment other than surgery or regional irradiation (irradiation must be completed more than 2 weeks prior to first dose of study drug), including adjuvant or neoadjuvant treatment. (Subjects who received interferon alfa-2b with adjuvant treatment intent, but discontinued within 1 week of starting treatment, at least 60 days before first dose of study drug, will be allowed to enroll.)
2. Subjects who have a history of another malignancy within the past 5 years with the exception of adequately treated in situ squamous cell carcinoma, basal cell carcinoma, stage I or IIA melanoma, or carcinoma in situ of the cervix. See treatment exclusions noted within the other exclusion criteria.
3. Use of biologic response modifiers (e.g., interleukin-2, colony-stimulating factors, other cytokines, BCG) within 60 days prior to first seviprotimut-L or placebo dosing.
4. Chronic use of systemic corticosteroids (other than inhaled or nasal steroids) or other immunosuppressants, or subjects expected to require acute systemic steroids (Medrol dose pack or other oral steroids) during the 24-month treatment course.
5. Known allergy to alum.
6. Prior use of any investigational agents within 30 days prior to first seviprotimut-L or placebo dosing.
7. History of any chronic medical or psychiatric condition or laboratory abnormality that, in the judgment of the investigator, may contraindicate study participation or study drug administration or may interfere with the interpretation of study results.
8. Any kind of disorder that compromises the ability of the subject to give written informed consent and/or comply with the study procedures.
9. Prior splenectomy.
10. Known positivity for human immunodeficiency virus (HIV).
11. Participants must not have or had prior autoimmune disorders requiring cytotoxic or immunosuppressive therapy, or autoimmune disorders with visceral involvement. The following will not be exclusionary:
    - The presence of laboratory evidence of autoimmune disease without associated symptoms unless attending physician feels such symptoms are likely to arise within ninety (90) days of laboratory evidence.
    - Clinical evidence of vitiligo.
    - Other forms of depigmenting illness.
    - Mild arthritis requiring NSAID medications or no medical therapy.

Randomization Scheme:

In Part A at least 99 subjects will be randomized to one of three arms in a 1:1:1 ratio:

- Placebo
- 40 μg seviprotimut-L vaccine
- 100 μg seviprotimut-L vaccine

In Part B of the study at least 1125 subjects will be randomized; 325 subjects will be randomized to one of two arms in a 2:1 (seviprotimut-L:placebo) ratio in Part B1 of the Study, and 800 subjects will be randomized to one of two arms in a 1:1 (seviprotimut-L:placebo) ratio in Part B2:

- Placebo
- 40 μg seviprotimut-L vaccine (the dose selected from Part A)

Treatment Schedule:

Every 2 weeks x 4 after initial dose, then monthly x 4, and then every 3 months through Month 24 (i.e., at the following time points: W0, W2, W4, W6, W8, M3, M4, M5, M6, M9, M12, M15, M18, M21, M24).

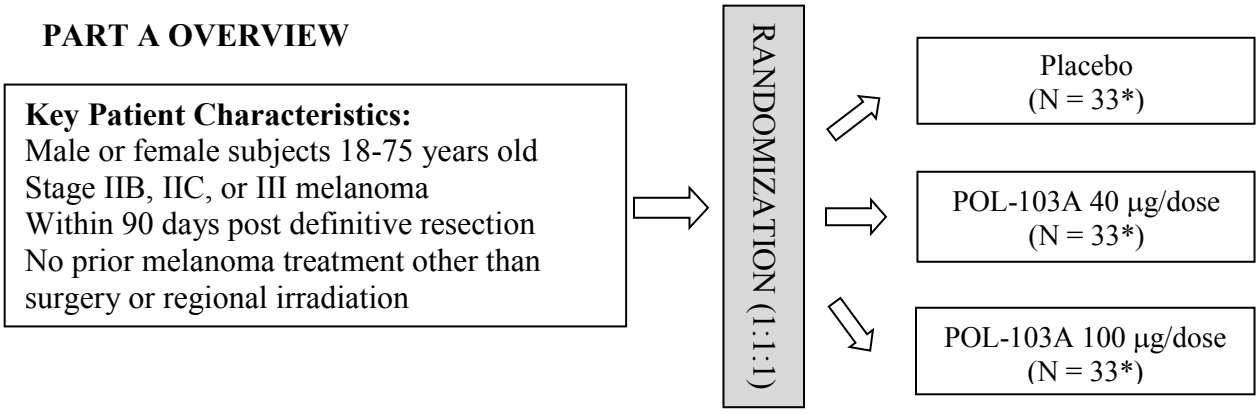
Duration of the Study:

Each subject will be treated with seviprotimut-L or placebo unless one of the following occurs: development of recurrent disease that does not meet the criteria for continued dosing, death, subject withdrawal, or study termination, whichever comes first. Subjects from all parts of the study will be monitored for disease progression and survival until 432 deaths have occurred in Part B2 of the study.

Name of Company: Polynoma LLC	**Name of Study Drug:** **S**eviprotimut-L
Concomitant Medication Restrictions: Other melanoma therapies, immunosuppressant drugs including chronic corticosteroids, and immunomodulatory drugs are prohibited.	
Statistical Considerations: Initially, subjects were randomized to 3 arms in an evaluation for immunologic endpoint signals (Part A). The interventions associated with the 3 arms in the Part A evaluation were placebo and two doses of seviprotimut-L vaccine. Part B will use the dose selected from the analysis of Part A data. Part B of the study is revised to include two Parts: Parts B1 and B2. Part B1 will consist of a recurrence-free survival (RFS) analysis when there are 126 RFS events out of the first accrued 325 patients (the Part B1 analysis set). This Part B1 RFS analysis will be conducted with one-sided alpha = 0.10. Survival is not a primary endpoint for Part B1, but all Part B1 subjects will be followed for survival. RFS is the sole primary endpoint of Part B1; Survival is a secondary endpoint. Part B2 will be based on the same treatment arms as Part B1 but with 800 patients and 1:1 randomization and with one-sided alpha = 0.025 shared between the two primary endpoints, RFS and Survival. At the time of the RFS analysis of Part B2, interim survival analyses of both superiority and futility will be performed.	

PROTOCOL SCHEMA

PART A OVERVIEW

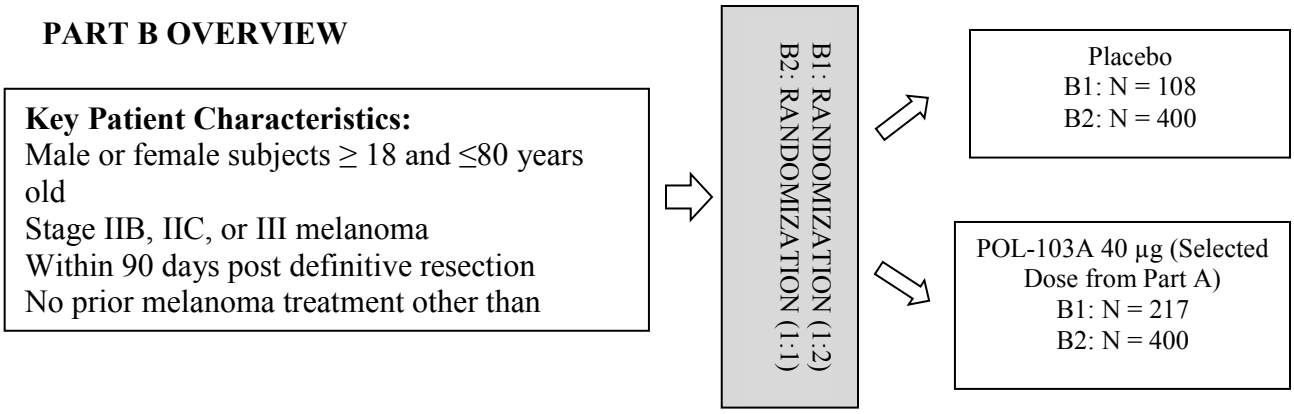


Overall Study Design:
Doses at W0, W2, W4, W6, W8, M3, M4, M5, M6, then every 3 months through M24**.
Key Assessments:

- Safety
- Immunological Response (measured at Week 10)
- Collection of blood samples over 3 years for later analysis of biological activity

* Enrollment in Part A is expected to exceed 99 subjects, as enrollment will continue until the 99th subject completes Week 10.
** At the completion of Part A analysis, subjects receiving 40 or 100 µg POL-103A will continue with the dose to which they have been initially randomized to (i.e., Part A subjects will not cross into Part B). Part A placebo subjects will be removed from the study and may be given the option of enrolling in open-label extension protocol 103A-301OL (Part B dose)

PART B OVERVIEW



Overall Study Design:
Doses at W0, W2, W4, W6, W8, M3, M4, M5, M6, then every 3 months through M24.

Key Assessment:

- Recurrence-Free Survival (B1 at 126 RFS events/325 B1 subjects, and for B2 at 310 RFS events/800 B2 subjects)
- Overall Survival (for B2 at 432 deaths/800 B2 subjects; survival is not a primary endpoint for Part B1, but all Part B1 subjects will be followed for survival)
- Safety

SCHEDULE OF ACTIVITIES: Part A

Procedure	Screening	Dosing Period																Pre-Recurrence		Post-Recurrence	End of Study[1]
		First Visit (W0)	W 2	W 4	W 6	W 8	W 10	M 3	M 4	M 5	M 6	M 9	M 12	M 15	M 18	M 21	M 24	Q 3 Mos	Q 6 Mos	Q 6 Mos	
Baseline Documentation																					
Informed Consent	X																				
Randomization		X																			
Medical History	X	X																			
Physical Exam	X	X						X			X	X	X	X	X	X	X		X		X
Pathology Review	X																				
BRAF mutation status[2]	X																				
Laboratory Studies																					
Immune Response		X					X				X		X		X		X		X[3]		X[4]
LDH	X	X						X			X	X	X	X	X	X	X	X	X		X[5]
CBC and serum chemistry	X	X	X	X	X	X	X	X			X		X		X		X		X		X
Urinalysis	X	X	X	X	X	X	X	X			X		X		X		X		X		X
Pregnancy test	X																				X
Serum FSH/estradiol	X																				
ECG	X							X					X								X
HIV test	X																				
ANA/ESR	X										X		X		X		X				
Tumor Assessments																					
Recurrence Assessment[6]	X[7]										X		X		X		X		X		
Dosing																					
Seviprotimut-L or placebo		X	X	X	X	X		X	X	X	X	X	X	X	X	X	X				
Other Clinical Assessments																					
Survival Follow-up Contact																				X	
Autoimmune Phenomena[8]	X										X		X		X		X				
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]	X

[1] At time of recurrence or study completion for subjects without recurrence - after the EOS visit, subjects from all parts of the study will be followed for disease progression and survival until 432 deaths have occurred in Part B2 of the study.
[2] BRAF tumor mutation V600E status must be either known at Screening or a tumor tissue (fresh or archived sample) must be available for testing during the Study.
[3] Blood samples for immune monitoring at visits at Months 30 and 36 only for subjects in pre-recurrence monitoring.
[4] If within 36 months of randomization into study
[5] For subjects who have not had recurrent disease
[6] See Section 9.3.1 for details
[7] To be performed if the protocol-specified assessments have not been performed after the surgical resection, or the data are not available to the Sponsor
[8] Include eye exam (by an ophthalmologist) and skin exam for vitiligo and rashes thereafter.
[9] Adverse events collected through 30 days after last dose.
[10] New cancer treatments only

SCHEDULE OF ACTIVITIES: Part B (same activities for Parts B1 and B2)

Procedure	Screening	Dosing															Pre-Recurrence		Post-Recurrence	End of Study[1]
		First Visit (W0)	W 2	W 4	W 6	W 8	M 3	M 4	M 5	M 6	M 9	M 12	M 15	M 18	M 21	M 24	Q 3 Mos	Q 6 Mos	Q 6 Mos	
Baseline Documentation																				
Informed Consent	X																			
Randomization		X																		
Medical History	X	X																		
Physical Exam	X	X					X			X	X	X	X	X	X	X		X		X
Pathology Review	X																			
BRAF mutation status[2]	X																			
Laboratory Studies																				
Biomarker[3]		X					X			X		X		X		X				X
LDH	X	X					X			X	X	X	X	X	X	X	X	X		X[4]
CBC and serum chemistry	X	X	X	X	X	X	X			X		X		X		X		X		X
Urinalysis	X	X	X	X	X	X	X			X		X		X		X		X		X
Pregnancy test	X																			X
Serum FSH/estradiol	X																			
ECG	X																			X
HIV test	X																			
ANA/ESR	X									X		X		X		X				
Tumor Assessments																				
Recurrence Assessment[5]	X[6]									X		X		X		X		X		
Dosing																				
Seviprotimut-L or placebo		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Other Clinical Assessments																				
Survival Follow-up Contact																			X	
Autoimmune Phenomena[7]	X									X		X		X		X				
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[8]			
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]	X

[1] At time of recurrence or study completion for subjects without recurrence - after the EOS visit, subjects from all parts of the study will be followed for disease progression and survival until 432 deaths have occurred in Part B2 of the study.
[2] BRAF tumor mutation V600E status must be either known at Screening or a tumor tissue (fresh or archived sample) must be available for testing during the Study.
[3] Sera samples and PBMCs will be banked at these time points for biomarker analyses (Section 9.3.2).
[4] For subjects who have not had recurrent disease
[5] See Section 9.3.1 for details
[6] To be performed if the protocol-specified assessments have not been performed after the surgical resection, or the data are not available to the Sponsor
[7] Include eye exam (by an ophthalmologist) and skin exam for vitiligo and rashes thereafter.
[8] Adverse events collected through 30 days after last dose.
[9] New cancer treatments only

TABLE OF CONTENTS

ABBREVIATIONS

AE(s)	Adverse event(s)
AJCC	American Joint Committee on Cancer
ALT	Alanine aminotransferase
ANA	Antinuclear antibodies
AST	Aspartate aminotransferase
CBC	Complete blood count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CRF(s)	Case report form(s)
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
DTH	Delayed-type hypersensitivity
ECG(s)	Electrocardiograms(s)
ECOG	Eastern Cooperative Oncology Group
Elispot	Enzyme-linked immunosorbent spot
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GM-CSF	Granulocyte macrophage colony-stimulating factor
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	Interferon
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
IUD	Intrauterine device
IVRS	Interactive voice response system
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MMRM	Mixed model repeated measures
MRI	Magnetic resonance imaging
MSDS	Material safety data sheet
MSLT-II	Multicenter Selective Lymphadenectomy Trial II
NCI	National Cancer Institute
OS	Overall survival
PET	Positron emission tomography
RBC	Red blood cell
RF	Rheumatoid factor
RFS	Recurrence-free survival
SAE(s)	Serious adverse event(s)

SAP	Statistical Analysis Plan
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World Health Organization

1 BACKGROUND

1.1 Melanoma

The incidence of primary cutaneous malignant melanoma has been increasing rapidly, with an increase of approximately 4% annually. In the United States (US) alone, over 62,000 new cases are seen annually (6). Surgery continues to offer the best curative therapy for early stage disease. The precision with which clinicians can determine prognosis has been greatly refined by the use of sentinel lymph node biopsy, which provides for accurate staging of regional lymph nodes, and by the recognition of the prognostic significance of ulceration of the tumor. Subjects with American Joint Committee on Cancer (AJCC) stage IIB, IIC, IIIA, IIIB, or IIIC melanoma have risks of relapse and death exceeding 40% at 5 years and are candidates for adjuvant systemic treatment (7).

Interferon alfa-2b is the first immunotherapy approved by the US Food and Drug Administration (FDA) and other international regulatory agencies for the adjuvant treatment of patients with stage IIB or III melanoma; and remains the only approved adjuvant therapy for these high-risk patients (8). However, side effects of interferon therapy are significant. The majority of patients receiving IFN-alfa experience constitutional symptoms, such as elevated liver enzyme levels, myelosuppression, and severe depression. These adverse events often result in dose reductions or treatment discontinuation, as seen in the up to 50% of patients in the original E1684 study (1, 2, 3, 4, 5, 8). Further, because the benefit of high-dose interferon therapy is marginal for patients with node-positive disease, patients with positive nodes must carefully weigh the risks and potential benefits of the regimen. Moreover, despite a lower risk for recurrence, there is no improvement in survival. Thus, new therapies are needed for these high-risk patients with melanoma.

1.2 Cancer Vaccine Design Strategies

Vaccines hold the potential to improve the treatment and the quality of life of patients with cancer, including melanoma. Vaccines have been demonstrated to be effective in preventing melanoma in animal models. They can selectively increase immune responses against this cancer in humans, and hence should be more effective than non-specific immunotherapies. Vaccines have little toxicity and should not have a negative impact on quality of life. In addition, they are simple to use.

The mechanism of action of cancer vaccines is stimulation of antibody and cellular immune responses that can recognize, attack, and kill cancer cells. To work, they must satisfy two critical requirements: 1) they must contain tumor antigens that can stimulate protective immune responses, and 2) some of these antigens must be present on the tumor to be treated. Unfortunately, melanoma antigens that can stimulate tumor-protective immune responses are still mostly unknown, the expression of tumor antigens by melanoma cells in different individuals is variable, and the ability of different patients to develop immune responses to the same antigens is also variable.

One strategy to minimize these problems is to prepare polyvalent cancer vaccines that contain many tumor antigens, as the greater the number the antigens the greater the chances that the

vaccine may contain antigens that can induce tumor-protective immune responses, that these responses will be induced in the patient to be treated, and that they will be directed to antigens present on the patient's own tumor. This approach has been used to construct the experimental vaccine to be studied in this protocol.

1.3 Description of Investigational Agent Seviprotimut-L

Seviprotimut-L (formerly POL-103A) is a polyvalent cancer vaccine that contains multiple melanoma antigens shed from 3 human melanoma cell lines: SFHM2, SFHM4, and SFHM8. For vaccine production the material shed into serum-free culture medium by the cells is collected, pooled, concentrated, treated with nonionic detergent NP-40 to break up aggregated antigens, and ultracentrifuged to remove particulate matter and transplantation alloantigens. The supernatant is filter-sterilized, adjusted to the appropriate protein concentration, and bound to alum as an adjuvant.

The important features of the vaccine are:

1. It contains multiple melanoma associated antigens.
2. The antigens are partially purified, as they are separated from the bulk of nuclear and cellular material that is poorly shed.
3. It is enriched in cell surface antigens that are more likely to be biologically relevant as they can be seen by and interact with the patient's anti-tumor immune responses.
4. The vaccine can stimulate immune responses against multiple antigens on cancer cells, and hence should kill these cells more effectively than vaccines that stimulate responses to only a single or limited number of antigens. It also minimizes the chances of tumor escape by down-regulation of antigen expression.
5. Polyvalent vaccines are more likely to circumvent genetic restrictions that limit the use of many vaccines.

For use, the vaccine (either 0.05 mg/mL or 0.125 mg/mL) is admixed with alum at 20 mg/mL as an adjuvant and as a suspension. This adjuvant was selected because it is approved by the FDA, is safe and simple to use, and the vaccine adjuvanted to alum appears to be immunologically active and clinically effective as described below.

1.3.1 Prior Human Experience

1.3.1.1 Summary of Findings from Part A

Safety Summary from Part A

A total of 157 subjects were treated in Part A: 52, 52, and 53 in the seviprotimut-L 40 µg, 100 µg, and placebo treatment arms, respectively. The nominal doses of 40 µg and 100 µg could be administered as 24 to 56 µg and 72 to 160 µg, respectively, due to potential manufacturing run variation. The most frequent treatment-related treatment-emergent adverse events (TEAEs, based on March 2014 analysis) were fatigue (19%, 23%, and 23% with 40 µg, 100 µg, and placebo, respectively) and local reactions at the site of injection, including injection site erythema (19%, 21%, and 26%), injection site reaction (8%, 21%, and 9%), injection site urticaria (12%, 12%, and 8%), and injection site pruritus (8%, 8%, and 8%). Almost all of these reactions were Grade 1 (mild). No deaths were reported while on study. Twenty subjects

experienced treatment-emergent serious adverse events (TESAEs); the only TESAEs considered to be treatment-related by the investigator were diverticulitis and gastroenteritis in the same subject in the 100 µg arm; the Sponsor and Medical Monitor considered these events to be unrelated. Three subjects discontinued treatment due to TEAEs, which were skin lesion (1 subject in the 100 µg group), injection site reaction (1 subject in the 100 µg group), and lymphadenopathy (1 subject in the placebo group).

Immune Response Summary from Part A

Biological activity of seviprotimut-L was measured by the percentage of subjects who generated an IgG or IgM response to antigens contained in the vaccine as measured by Western blot assay or the percentage of subjects who generated a T-cell response as measured by Elispot assay. The analyses summarized here focused on Western blot results due to issues regarding specimen holding time and artifacts for the Elispot assays. A Western blot result was considered positive (showing an increased immune response) if a ≥ 25% increase in the intensity of a band or bands at Week 10 vs Week 0 or a new/additional band at Week 10 was observed. The prespecified endpoint was that ≥ 20% of patients in a treatment arm (40 µg or 100 µg) would show an increase in immune response compared to the placebo arm. Western blot data were available for 134 subjects (43 treated with 40 µg, 44 treated with 100 µg, and 47 treated with placebo). The analysis of the data using the prespecified dichotomous success criterion (each subject's response counted as positive or negative) showed that there was not an obvious difference between placebo and either the 40 µg or 100 µg arm, i.e., placebo induced an immune response at Week 10 vs Week 0 in similar numbers (ratio) as did each active arm as determined by Western blot.

The protocol allowed for the assessment of all available data for evidence of immune response based upon exploratory analyses. The data available for analysis of Western blot results for each subject were the treatment arm, two specimen collections (Week 0 and Week 10, 3 replicates for each specimen), and molecular weight bands (categorized into intervals or "bins"). The data structure complexity together with high variability inherent in Western blot data necessitated the use of advanced statistical modeling to assess for the existence of a vaccine effect. Specifically, analysis of variance using Mixed Model Repeated Measures (MMRM) methodology was used to test for a vaccine effect. The MMRM model fit contains main effect terms for the factors listed above plus all two-way interactions between these main effects plus the three-way interaction of these main effects.

The main finding was that there is a vaccine effect. The band intensity increased on average in all 3 treatment arms with a statistically significant difference between placebo and seviprotimut-L 40 µg ($p = 0.0034$). The vaccine effect is related to the molecular weights identified in the Western blots. The comparison between placebo and seviprotimut-L 40 µg for molecular weight bin (range) intensity change showed a statistically significant 3-way interaction (treatment arm, baseline vs Week 10, and molecular weight bin; $p = 0.0002$). Although the 3-way interaction was not statistically significant for the 100 µg arm, similar patterns across the molecular weights were found for the comparison of each dose to placebo. The difference between the 40 µg arm and placebo was further supported by an analysis based on the response for each subject.

The 40 µg dose of seviprotimut-L was selected for evaluation in Part B based on the safety and statistically significant bioactivity vs placebo demonstrated for the 40 µg arm in the Western blot analysis from Part A of the study, and further supported by results of prior studies of shed polyvalent antigen vaccine formulations similar to the formulation of the seviprotimut-L vaccine combined with various adjuvants that demonstrated bioactivity, safety, and tolerability with doses of 40 µg (9, 12-14).

1.3.1.2 Summary of Historical Experience

Human clinical trials in the US were conducted with 2 forms of the seviprotimut-L vaccine combined with various adjuvants under 4 previous investigator Investigational New Drug applications (INDs) and 2 non-IND clinical studies. Those studies were completed in 2001, with a total research population comprising approximately 661 subjects: approximately 533 subjects exposed to an experimental formulation containing shed antigens from 4 cell lines (3 human and 1 hamster; polyvalent-q) and approximately 128 subjects exposed to antigens from the 3 human cell lines (polyvalent-t). Various adjuvants were tested in combination with these 2 formulations. (A limited number of subjects were treated with more than one vaccine/adjuvant combination.) Of the 128 subjects tested with a vaccine made from the 3 cell lines used in seviprotimut-L, 42 received the vaccine with alum as an adjuvant (in study 89-38), which is the formulation most similar to seviprotimut-L.

The approximately 661 subjects were treated for up to 5 years at antigen doses of 40 µg per immunization, with various dosing schedules.

See the Investigator's Brochure for a table that summarizes the prior human experience with the various forms of the seviprotimut-L vaccine.

Safety Summary from Previous Clinical Trials

All of the adverse events (AEs) attributed to the vaccine were mild or moderate. Itching (4.4%), blistering (4.1%), swelling (2.8%), and soreness (2.5%) were most frequently reported. These AEs were expected reactions to the vaccine and resolved within several days. There was no ulceration or scarring of injection sites. Most of these subjects received additional doses of the vaccine without recurrence of their AEs. However, in study 96-15 (a study of 112 subjects that used a formulation of the drug in pH-sensitive IL-12 containing liposomes), 3 subjects discontinued due to vaccine reactions and 2 subjects had their vaccine dose reduced due to vaccine reactions and remained in the study.

Only one serious adverse event (SAE) believed to be related to study drug was reported in the 661 subjects exposed to the vaccine. In study 97-17 (a study using the polyvalent-q formulated in liposomes with granulocyte macrophage colony-stimulating factor [GM-CSF] as an adjuvant), a subject was hospitalized after experiencing a fainting spell approximately 2 hours after receiving a dose of the vaccine. She was diagnosed with an arrhythmia, which is an expected side effect of treatment with GM-CSF. The subject discontinued the study because of this event. The current formulation uses polyvalent-t, not polyvalent-q, and does not use GM-CSF.

Additional information on the available safety data is included in the Investigator's Brochure.

Efficacy Summary from Previous Clinical Trials

This section summarizes analyses that were conducted to examine the biological activity and clinical efficacy of the vaccine. Biological activity was examined by measuring the presence and frequency of vaccine-induced anti-melanoma antibody and cellular immune responses and, in one case, by the ability of the vaccine to induce cellular infiltrates into tumor nodules in vivo. Clinical efficacy was evaluated by correlating vaccine-induced antibody and cellular immune responses to clinical outcome and by measuring the ability of vaccine treatment to clear melanoma cells and melanoma-associated antigens from the circulation. Clinical efficacy was also studied directly in a double-blind, placebo-controlled trial funded by the FDA under the Orphan Drug Program.

The first trial conducted was a dose escalation study to examine the safety of escalating doses of the vaccine. Most of the subsequent trials examined the ability of different adjuvants to potentiate the immunogenicity of the vaccine. One trial, the double-blind, placebo-controlled trial, focused on examining the clinical efficacy of the alum-adjuvanted vaccine.

Different analyses were often conducted at different times during the course of the same trial so that the number of subjects represented in different analyses differs from the number of subjects entered into the trial. To avoid bias, analyses were usually conducted on sequential subjects based on date of entry into the trial. Additional criteria were sometimes used, such as the availability of serum specimens at required time points or HLA-A2 or A3 positivity for assays of CD8 responses.

Vaccine-induced immune responses were usually assayed 1 week after the fourth immunization, and positivity was based on an increase in response compared to baseline measurements in the same subject. Antibody responses were measured by western immunoblotting. Cellular responses were initially measured by delayed-type hypersensitivity (DTH) responses and subsequently by enzyme-linked immunosorbent spot (Elispot) assay for melanoma peptide-specific CD8+ T cells. DTH responses were subsequently found to be directed to an artifact in the vaccine but were still used in some trials as they were useful to measure the activity of different adjuvants in these trials.

Additional information on previous studies reported in publications can be found in the Investigator's Brochure. Briefly, the results show that:

1. The vaccine stimulates both antibody and T-cell responses against multiple melanoma antigens in subjects with different genetic backgrounds. These responses are induced in approximately half of the subjects.
2. There is a relation between vaccine-induced antibody or CD8+ T-cell responses and improved recurrence-free survival.
3. Vaccine treatment is associated with induction of cellular response that infiltrates a subject's own melanoma in vivo.
4. Vaccine treatment is associated with clearance of melanoma cells and of melanoma antigens from the circulation, and clearance is associated with an improved recurrence-free survival.
5. In a double-blind, placebo-controlled Phase 2 trial conducted in 38 subjects with resected stage IIIB and IIIC melanoma (study 91-22 [9]), the recurrence-free survival of the

melanoma vaccine-treated subjects was over twice as long as that of subjects treated with a placebo vaccine, p=0.03 after Cox multivariate analysis.

2 OBJECTIVES

2.1 Part A Objectives

- To evaluate the safety of seviprotimut-L in patients with stage IIB, IIC, or III melanoma.
- To evaluate the biological activity of seviprotimut-L in patients with stage IIB, IIC, or III melanoma.
- To select the dose for Part B.
- To collect blood samples for the future investigation of the sustained biologic activity of seviprotimut-L.

2.2 Part B Objectives

2.2.1 Part B1 Objectives

Primary Objective:

- To assess the efficacy of treatment with seviprotimut-L compared to placebo with respect to recurrence-free survival

Secondary Objectives:

- To assess the efficacy of treatment with seviprotimut-L compared to placebo with respect to overall survival
- To verify the safety and tolerability of seviprotimut-L at the dose selected for Part B.
- To assess a potential correlation between biomarker shifts/baseline prognostic markers and clinical outcome

2.2.2 Part B2 Objectives

Primary Objectives:

- To assess the efficacy of treatment with seviprotimut-L compared to placebo with respect to recurrence-free survival and overall survival

Secondary Objectives:

- To verify the safety and tolerability of seviprotimut-L at the dose selected for Part B.
- To assess a potential correlation between biomarker shifts/baseline prognostic markers and clinical outcome

3 TRIAL DESIGN

3.1 Study Design Overview

The study is composed of 2 parts, Parts A and B. Part A is an evaluation of immunological activity and safety. Part B, which is also composed of two parts, Parts B1 and B2, enables a clinical efficacy evaluation.

Part A is designed to evaluate the safety and biological activity of 40 μg and 100 μg of seviprotimut-L compared to placebo, and to select a dose for Part B of the study based on immunological biomarker response (with no access to clinical outcome data). This evaluation is scheduled to take place after the first 99 randomized subjects with immune response data have reached Week 10 (5 doses of study treatment received). Enrollment into Part A will continue until completion of the Part A analysis. Missing or mishandled samples may result in not all dosed subjects being evaluable for the formal Part A analysis.

At the completion of Part A analysis, subjects receiving 40 or 100 μg seviprotimut-L will continue with the dose to which they were initially randomized in a masked manner (i.e., the subject and investigator will know the subject was receiving one of the two dose levels of seviprotimut-L, not placebo).

Subjects receiving placebo in Part A will be unmasked and removed from the study. Part A placebo subjects may be given the option of receiving treatment with seviprotimut-L (Part B dose) under open-label extension protocol 103A-301OL (Appendix C) if an investigator feels this is in the subject's best interest and the program is approved by regulatory authorities. Regardless of whether subjects receive treatment with seviprotimut-L, placebo subjects from Part A will be monitored for recurrence and vital status (survival) at least every 6 months by contacting the subjects (via telephone or at the time of routine, non-study related, office visit) until the study is terminated/completed, the subject is lost to follow-up, or the subject specifically requests to be withdrawn from vital status follow-up.

Part B implements the clinical efficacy evaluation. The clinical efficacy evaluation is double-blind with subjects randomized in Part B1 in a 2:1 ratio and in Part B2 in a 1:1 ratio to seviprotimut-L or placebo, respectively. Subjects will be treated for 24 months with either placebo or the dose selected for Part B (40 μg), and followed for recurrence and survival. A total of 1125 subjects will be enrolled into Part B, including 325 subjects in Part B1 and 800 subjects in Part B2. Individual subjects will not be unblinded at recurrence or the end of treatment for either Part B1 or Part B2 except to allow the subject to pursue other treatment options.

All subjects will be followed for disease progression and survival until 432 deaths have occurred in Part B2 of the study, at which time the study will be closed. As there is no known antidote for seviprotimut-L, knowledge of the treatment arm is unlikely to be of any benefit to patient care in the event of medical emergencies. Therefore, unblinding is discouraged. For medical emergencies where it is determined that the knowledge of the treatment arm is absolutely necessary, see Section 10.7.5.

3.2 Justification of Study Drug Administration Strategy

Study drug will be administered as 4 intradermal injections (see Section 7.2.1). The selection of the route of administration is based on the belief that split doses stimulate stronger immune responses by allowing vaccine antigens to reach more regional lymph nodes (where the immune responses are generated). Intradermal immunizations are more likely to stimulate cellular immune responses compared to subcutaneous or intramuscular immunization.

The dosing schedule to be used in the present study is slightly different from that employed in previous studies in that the vaccine will be administered every 2 weeks x 5 cycles (rather than 4 cycles), and then monthly for 4 cycles (rather than for 3 cycles), and then every 3 months for up to 2 years (rather than every 3 months for 2 cycles and then every 6 months for a total of 2 to 5 years) as more frequent dosing is expected to elicit a stronger immune response.

3.2.1 Justification for Dose Level Selected for Part B

The 40 µg dose of seviprotimut-L was selected for Part B based on the safety profile and significant bioactivity vs placebo demonstrated in Part A of this study, and further supported by the results of previous studies of similar formulations of the vaccine. The results of Part A are described in Section 1.3.1.1. Due to variability among manufacturing runs of the vials of vaccine, the nominal dose of 40 µg may actually be administered as 24 to 56 µg.

3.3 Study Population

This study will enroll subjects with stage IIB, IIC, and III cutaneous melanoma, surgically resected to clear margins.

Approximately 100 to 200 centers, including international centers, are anticipated to participate in this trial across both parts of the study.

3.4 Number of Subjects

At least 99 subjects will be randomized in the safety and dose-selection Part A and 1125 subjects will be randomized in the clinical efficacy evaluation Part B, for a minimum of 1224 subjects in Parts A and B combined.

Of note, enrollment into Part A of the study will proceed until data from 33 subjects in each treatment arm with evaluable Week 10 immunological data are collected and analyzed (i.e., it is anticipated that Part A will randomize more than 99 subjects).

3.5 Study Endpoints

3.5.1 Part A Evaluation Endpoints

The following endpoints will be evaluated on data collected through Week 10 for subjects enrolled in Part A of the study.

- The biological activity of seviprotimut-L as measured by either:
  - the percentage of subjects who have generated either an IgG or IgM response to antigens contained in the vaccine at Week 10 (Section 9.1); or
  - the percentage of subjects who have generated a T-cell response (as measured by Elispot assay) to Trp-2 antigen at Week 10 (Section 9.1).
- The safety of seviprotimut-L evaluated by safety blood and urine laboratory measurements, physical examinations, and AE reports.

3.5.2 Part B1 Evaluation Endpoints

Clinical efficacy evaluation will be performed on data collected on all subjects enrolled in Part B1 of the study. Primary and secondary endpoints will be examined in correlation with clinical prognostic factors (see the Statistical Analysis Plan for details).

Primary Endpoint:

- Recurrence-free survival (RFS)

Secondary Endpoints:

- Overall survival (OS)
- Incidence and severity of AEs
- Time to locoregional recurrence
- Time to distant recurrence

Exploratory Endpoints:

- Biomarker assessment
- Immune (antibody) responses by Western Blot to seviprotimut-L

3.5.3 Part B2 Evaluation Endpoints

Clinical efficacy evaluation will be performed on data collected on all subjects enrolled in Part B2 of the study. Primary and secondary endpoints will be examined in correlation with clinical prognostic factors (see the Statistical Analysis Plan for details).

Primary Endpoints:

- Recurrence-free survival (RFS)
- Overall survival (OS)

Secondary Endpoints:

- Incidence and severity of AEs
- Time to locoregional recurrence
- Time to distant recurrence

Exploratory Endpoints:

- Biomarker assessment
- Immune (antibody) responses by Western Blot to seviprotimut-L

3.6 Unblinding at the Completion of Part A

Subjects enrolled in Part A will continue to follow the dosing schedule in the protocol until the Part A immunogenicity data are analyzed and a decision is made regarding the dose to be brought into Part B. At this time, the placebo subjects in Part A will be unblinded, and may be offered treatment with POL-103 under open-label extension protocol 103A-301OL (Appendix C). Subjects on either dose of seviprotimut-L will continue to receive their originally randomized dose in a blinded manner.

3.7 Study Discontinuation Criteria

The sponsor may terminate the study at any time (after consultation with the Coordinating Principal Investigator) on the basis of safety considerations, other factors that may be deemed to affect the scientific validity or ethical viability of the protocol, or as a business decision. The Data Monitoring Committee (DMC) for this study may also recommend discontinuation based on periodic review of safety or efficacy data from all subjects.

4 PARTICIPANT SELECTION

The inclusion and exclusion criteria are essentially the same for Part A and Part B. However, the upper age limit of 75 years was increased to 80 years for Part B. Other minor changes in eligibility wording between Part A and Part B were to clarify the intent of the criteria, not to alter them.

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be enrolled into the study:

1. Histologically confirmed AJCC Stage IIB, IIC, or III cutaneous melanoma.
2. Last definitive surgical resection of all clinically evident disease within 90 days prior to the first seviprotimut-L or placebo dosing. Subjects with positive margins of resection should have re-excision prior to randomization. Previous resections are acceptable, provided that the staging of the melanoma at the time of the previous resection was AJCC Stage I or IIA.
3. Subjects with positive sentinel nodes must have a complete lymphadenectomy. Subjects randomized to the complete lymph node dissection then observation arm of the Multicenter Selective Lymphadenectomy Trial II (MSLT-II) are eligible for enrollment.
4. Male or female subjects ≥ 18 and ≤ 80 years of age.
5. Female subjects of childbearing potential must have a negative pregnancy test within 2 weeks prior to study randomization, must agree to use adequate contraception throughout the treatment duration and for 3 months after the last seviprotimut-L or placebo dosing, and must not be breastfeeding.
6. ECOG Performance Status 0 or 1 and a reasonable expectation of living at least 2 years.
7. White blood cell (WBC) count ≥ 4,000/mm^3.
8. Absolute neutrophil count ≥ 1,500/mm^3.
9. Hemoglobin ≥ 10 g/dL.
10. Platelet count ≥ 100,000/mm^3.
11. Creatinine ≤ 2.0 mg/dL.
12. Bilirubin ≤ 1.5 times the upper limit of normal (ULN).
13. Asparate aminotransferase (AST), alanine aminotransferase (ALT) < 2.0 times ULN.
14. Subjects must have known BRAF V600E mutation tumor status or have tumor tissue (fresh or archived sample) available for testing of BRAF V600E mutation status (note: as

long as it is confirmed that tumor tissue is available for testing, the subject may be considered eligible for the study; testing of BRAF mutation status on that tissue may be conducted at a later time during the study).

4.2 Exclusion Criteria

Subject must not meet any of the following exclusion criteria to be enrolled in the study:

1. Any prior melanoma treatment other than surgery or regional irradiation (irradiation must be completed more than 2 weeks prior to first dose of study drug), including adjuvant or neoadjuvant treatment. (Subjects who received interferon alfa-2b with adjuvant treatment intent, but discontinued within 1 week of starting treatment, at least 60 days before first dose of study drug, will be allowed to enroll)
2. Subjects who have a history of another malignancy within the past 5 years with the exception of adequately treated in situ squamous cell carcinoma, basal cell carcinoma, stage I or IIA melanoma, or carcinoma in situ of the cervix. See treatment exclusions noted within the other exclusion criteria.
3. Use of biologic response modifiers (e.g., interleukin-2, colony-stimulating factors, other cytokines, BCG) within 60 days prior to first seviprotimut-L or placebo dosing.
4. Chronic use of systemic corticosteroids (other than inhaled or nasal steroids) or other immunosuppressants, or subjects expected to require acute systemic steroids (Medrol dose pack or other oral steroids) during the 24-month treatment course.
5. Known allergy to alum.
6. Use of any investigational agents within 30 days prior to first seviprotimut-L or placebo dosing.
7. History of any chronic medical or psychiatric condition or laboratory abnormality that, in the judgment of the investigator, may contraindicate study participation or study drug administration or may interfere with the interpretation of study results.
8. Any kind of disorder that compromises the ability of the subject to give written informed consent and/or comply with the study procedures.
9. Prior splenectomy.
10. Known positivity for human immunodeficiency virus (HIV).
11. Participants must not have or had prior autoimmune disorders requiring cytotoxic or immunosuppressive therapy, or autoimmune disorders with visceral involvement. The following will not be exclusionary:
    - The presence of laboratory evidence of autoimmune disease without associated symptoms unless attending physician feels such symptoms are likely to arise within ninety (90) days of laboratory evidence.
    - Clinical evidence of vitiligo.
    - Other forms of depigmenting illness.
    - Mild arthritis requiring NSAID medications or no medical therapy.

5 STUDY PROCEDURES

A signed and dated, written informed consent form that is currently approved by an IRB or IEC must be obtained from the potential subject before he/she can participate in any study-specific procedures, including study-specific screening procedures.

Subjects will be enrolled and randomized after all screening assessments have been completed and the subject meets all eligibility criteria.

Screening assessments must be completed ≤ 6 weeks prior to Week 0. Randomization must occur at Week 0 (first visit) prior to the seviprotimut-L or placebo dosing (see Section 5.2.1). Time windows are allowed on this study for visits and study procedures as follows: Weekly assessments and visits +/- 3 days, monthly assessments and visits +/- 7 days, 3-monthly and 6-monthly assessments and visits +/- 7 days.

5.1 Screening Procedures

The following procedures must be conducted ≤ 6 weeks prior to randomization:

- Signed and dated written informed consent
- Medical history (relevant medical history (including surgeries) or ongoing conditions, within 5 years of screening only)
- Melanoma staging (pathology review)

  Documentation of stage IIB, IIC, or III shall be confirmed at screening by review of the relevant pathology and surgical reports. The date of the histological diagnosis, date of surgery, and stage should be obtained. There will be no Central Pathology Review.
- Physical examination
- Record concomitant medications
- HIV test (if not previously known)
- Autoimmune assessment (including ANA, ESR, eye exam by an ophthalmologist, and skin exam for vitiligo and rash)
- LDH
- ECG
- Obtain BRAF V600E mutation tumor status or tumor tissue (fresh or archived samples) for testing of BRAF mutation status
- Tumor Assessment (repeating scans during the screening period is not required if the specified assessments have been made within 90 days prior to enrollment. Assessments can be made before or after resection):
  - *All subjects: chest x-ray (or chest CT).*
  - *Subjects who enter with Stage IIB, IIC, or IIIA <u>and</u> also presented with lower extremity disease or a positive inguinal node will also have a pelvic CT.*
  - *Subjects who enter with Stage IIIB or IIIC <u>or</u> who had a primary lesion > 4 mm will have a CT of the chest, abdomen and pelvis AND CT (with contrast) or MRI of the brain.*

  Notes to Screening Procedures:

  Testing of ANA, ESR and LDH must occur ≤ 6 weeks before subject randomization. Randomization occurs at First Dosing (Week 0). *Note: LDH is tested twice – once at Screening, and the other at First Dosing (Week 0) (see Section 5.2.1 below).*

ANA, ESR, and LDH test results must be available and reviewed by Investigator prior to randomization. Should the designated central testing laboratory not have the test results available, samples may be redrawn with one specimen being sent to a local lab and another sent to the designated central testing laboratory, in parallel. If a test result from the designated central is not viable or interpretable, the test result obtained from the local lab may be used prior to randomization following review by the Investigator as acceptable.

The following procedures must be conducted ≤ 2 weeks prior to randomization:

- Complete blood count (CBC), chemistry, and urinalysis (within 2 weeks of randomization)
- Pregnancy test (urine or blood) for female subjects of childbearing potential, and measurement of serum follicle-stimulating hormone (FSH) and serum estradiol levels for female subjects of non-childbearing potential (within 2 weeks of randomization)

5.1.1 BRAF Mutation Status Test

BRAF V600E mutation testing will be performed. As long as it is confirmed that tumor tissue is available for testing, the subject may be considered eligible for the study; testing of BRAF mutation status on that tissue may be conducted at a later time during the study. This testing may be conducted at the site's facility as long as the BRAF assay and/or kit used is 510(k) approved or the laboratory/assay operates under Clinical Laboratory Improvement Amendments (CLIA) regulations. If desired, the site may wish to send the subject's tumor tissue (fresh or archived sample) for testing at the central laboratory. Results from existing BRAF tests of subjects (if available) will be accepted if they were performed under CLIA regulations or a commercially approved 510(k) kit.

5.2 On-Study Procedures

Study-related procedures and assessments performed during treatment on study are detailed as follows and in the Schedule of Activities table. In addition, any non-study related procedures that are performed during the study will be documented.

5.2.1 Baseline Assessment and First Dosing (Week 0)

The following baseline procedures will be performed prior to dosing:

- Physical examination (including height, weight, vital signs, and ECOG performance status)
- Update of medical history (all untoward findings between consent and randomization are to be recorded as medical history, not adverse events)
- Blood draw for immune monitoring (Part A subjects only)
- CBC, serum chemistry, urinalysis
- LDH
- Record concomitant medications
- Biomarker Panel (Part B only)

Notes to Baseline Assessment and First Dosing (Week 0):

Testing of LDH must have occurred as part of Screening (see Section 5.1) and as part of the subject's baseline assessment prior to randomization or first dosing. *Thus, LDH must be tested twice prior to randomization.*

LDH test results must be available and reviewed by Investigator prior to subject randomization. Should the designated central testing laboratory not have LDH test results available, samples may be redrawn with one specimen being sent to a local lab and another sent to the designated central testing laboratory, in parallel. If a LDH test result from the designated central is not viable or interpretable, the test result obtained from the local lab may be used prior to randomization following review by the Investigator as acceptable.

The following procedures will be performed after all the previous baseline procedures are completed:

- Randomization
- Seviprotimut-L or placebo administration

5.2.2 Assessments at Weeks 2, 4, 6, and 8 (± 3 days)

At the specified visit, the following procedures will be performed. *Note: Subjects with recurrent disease may, under certain conditions, continue to receive study medications. See Section 7.2.4 for details.*

- Record adverse events
- CBC, serum chemistry, urinalysis
- Record concomitant medications
- Seviprotimut-L or placebo administration

5.2.3 Assessments at Week 10 (± 3 days) for Part A Subjects ONLY

At the specified visit, the following procedures will be performed. *Note: Subjects with recurrent disease may, under certain conditions, continue to receive study medications. See Section 7.2.4 for details.*

- Blood draw for immune monitoring (Part A subjects only)
- Record adverse events
- CBC, serum chemistry, urinalysis
- Record concomitant medications

5.2.4 Assessments at Month 3 (± 7 days)

At the specified visit, the following procedures will be performed. *Note: Subjects with recurrent disease may, under certain conditions, continue to receive study medications. See Section 7.2.4 for details.*

- Record concomitant medications
- Record adverse events
- Physical examination (including weight, vital signs, and ECOG performance status)

- LDH, CBC, serum chemistry, urinalysis
- ECG (Part A only)
- Biomarker Panel (Part B only)
- Seviprotimut-L or placebo administration

5.2.5 Assessments at Months 4 and 5 (± 7 days)

At the specified visits, the following procedures will be performed, unless the subject has had disease recurrence and terminated study intervention. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10. Subjects who discontinue study intervention (see Section 6.2.1) but have not progressed should continue to be assessed as described.

- Record concomitant medications
- Record adverse events
- Seviprotimut-L or placebo administration

5.2.6 Assessments at Months 6, 12, 18, 24 (± 7 days for Month 6, and ± 14 days for Month 12, 18, and 24)

At the specified visits, the following procedures will be performed, unless the subject has had disease recurrence and terminated study intervention. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10. Subjects who discontinue study intervention (see Section 6.2.1) but have not progressed should continue to be assessed as described.

- Record concomitant medications
- Physical examination (including weight, vital signs, and ECOG performance status)
- CBC, serum chemistry, urinalysis
- LDH
- Biomarker Panel (at M6, M12, M18, and M24; Part B only)
- Tumor assessments (see Section 9.3.1)
- Seviprotimut-L or placebo administration
- Record adverse events
- Blood draw for immune monitoring (Part A subjects only)
- Physical examination for autoimmune phenomena (including eye exam by ophthalmologist, and skin exam for vitiligo and rash)
- Autoimmune labs ANA and erythrocyte sedimentation rate (ESR). Other tests (e.g., rheumatoid factor [RF], T4, thyroid-stimulating hormone [TSH]) to be performed only as clinically indicated.
- ECG (Month 12 only, Part A only)

5.2.7 Assessments at Months 9, 15, 21 (± 14 days)

At the specified visits, the following procedures will be performed, unless the subject has had disease recurrence and terminated study intervention. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10. Subjects who discontinue study intervention (see Section 6.2.1) but have not progressed should continue to be assessed as described.

- Record concomitant medications
- Physical examination (including weight, vital signs and ECOG performance status)
- LDH
- Seviprotimut-L or placebo administration
- Record adverse events

5.2.8 Pre-Recurrence Monitoring after Month 24

At the specified visits, the following procedures will be performed, unless the subject has had disease recurrence. In this case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10.

5.2.8.1 Pre-Recurrence Monitoring Every 3 Months (± 7 days)

- LDH (every 3 months)

5.2.8.2 Pre-Recurrence Monitoring Every 6 Months (± 7 days for Month 6, and ± 14 days for every 6 months thereafter)

- Physical examination (including weight, vital signs, and ECOG performance status)
- CBC, serum chemistry, urinalysis
- Tumor assessments (see Section 9.3.1)
- Concomitant Medications

At Months 30 and 36 only (± 14 days):

- Blood draw for immune monitoring (Part A subjects only)

At Month 36 only (± 14 days):

- Biomarker panel (Part B subjects only)

5.2.9 Assessments to be Conducted at Recurrence (or at Study Completion for Subjects Without Recurrence)

After a subject has had recurrence or the study is completed through the documentation of the pre-specified number of survival events, subjects will report to the clinic within 28 days (± 7 days) for a final follow-up (end of study) visit. Assessments are as follows:

- Physical examination (including weight, vital signs and ECOG performance status)
- CBC, serum chemistry, urinalysis
- ECG
- Pregnancy test (urine or blood) for female subjects of childbearing potential
- Blood draw for immune monitoring studies (Part A subjects only), if within 36 months of randomization into study
- Biomarker Panel (Part B only) (see Section 9.3.2)
- Adverse Events (within 30 days of last dose of study drug)
- Concomitant medications

For subjects with tumor assessments that indicate recurrence:

- Confirmation of recurrence through biopsy, if not previously conducted (see Section 9.3)

If survival events have been met, and there is no previous indication of subject disease recurrence:

- LDH (to be followed up by tumor assessments for LDH elevations of 1.5XULN (or greater), provided there are no other obvious medical reasons for the elevated LDH.)

5.2.10 Survival Monitoring of Subjects after Recurrence

Subjects with confirmed recurrent disease (see Section 9.3) (and who are not continuing to receive study drug per section 7.2.4) will no longer attend study visits, but will be monitored for survival at least every 6 months (+/- 14 days) through telephone contact until the study is terminated/completed or the subject is withdrawn or lost to follow-up. At the telephone contact, the subject will be asked for information on any additional cancer therapy he/she has started. Contact in-person is acceptable in lieu of a telephone contact. Survival of subjects lost to follow-up by telephone will be tracked by the investigator through the Social Security Death Index in the US, or other similar database outside the US if available.

5.2.11 Monitoring of Subjects after Premature Termination of Study Drug

Subjects who discontinue treatment with study drug in the first 24 months will continue to attend all remaining study visits as noted for subjects in Section 5.2.8 (study visits that include LDH and/or tumor assessments). Beyond Month 24, they should be monitored as described in 5.2.8 (if prior to recurrence).

5.3 Enrollment Strategy and Minimization of Bias

5.3.1 Randomization

Subjects in Part A will be randomized in a 1:1:1 ratio to placebo or one of two doses of seviprotimut-L. Subjects in Part B will be randomized in a 2:1 ratio in Part B1 and a 1:1 ratio in Part B2 to the dose selected from Part A or placebo, respectively. Randomization will take place across all study sites using a centralized Interactive Voice/Web Response System (IVRS/IWRS).

5.3.2 Stratification

At the time of randomization, the IVRS/IWRS system will be used to stratify the population according to disease state (IIB/IIC vs IIIA vs IIIB/IIIC) to ensure balanced distribution between the seviprotimut-L and placebo arms.

5.3.3 Blinding

The investigator and subject will be blinded as to treatment assignment; the placebo injections will appear identical to the seviprotimut-L injections.

5.3.4 Enrollment Strategy

Recruitment will continue in Part A until the analysis of Week 10 data has been completed on the first 99 randomized subjects. This will result in an “over enrollment” for Part A to avoid a discontinuation of recruitment and ensure a complete data set for Part A evaluation.

Subjects receiving 40 or 100 μg seviprotimut-L will continue with the dose to which they were initially randomized (i.e., Part A subjects will not cross into Part B). Subjects receiving placebo in Part A will be removed from the study and may be given the option of receiving treatment with seviprotimut-L (Part B dose) under open-label extension protocol 103A-301OL (Appendix C) if an investigator feels this is in the subject's best interest and the program is approved by regulatory authorities. Regardless of whether subjects receive treatment with seviprotimut-L, placebo subjects from Part A will be monitored for recurrence and vital status (survival) at least every 6 months through telephone (or in-person) contact until the study is terminated/completed, the subject is lost to follow-up, or the subject specifically requests to be withdrawn from vital status follow-up.

6 SUBJECT COMPLETION AND WITHDRAWAL

6.1 Subject Completion

Subjects may continue to receive seviprotimut-L or placebo dosing until they meet the criteria for treatment discontinuation described in Section 6.2.1 or complete the dosing phase of the study. Subjects who have recurrent disease in the first 3 months on study may, in some cases, continue to receive seviprotimut-L or placebo dosing. See Section 7.2.4 for details.

6.2 Subject Withdrawal From Study

In accordance with the Declaration of Helsinki, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines, and the US FDA regulations, a subject has the right to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The investigator and sponsor also have the right to withdraw subjects from the study treatment, as described below or for safety, behavioral or administrative reasons.

6.2.1 Subject Withdrawal from Study Intervention

Every effort must be made by study personnel to keep subjects on study intervention. However, a subject may discontinue or be discontinued prior to completion of the study intervention for any of the following reasons:

Subject may be removed from the study intervention for any of the following events.

- Grade 4 AE or Grade 3 AE, at the investigator's discretion (subject treatment assignment will not be routinely unmasked in the case of treatment discontinuation due to AEs/SAEs. See Section 10.7.5 for details).
- Recurrent disease with the exceptions described in Section 7.2.4.
- Positive pregnancy test (urine or blood)
- Significant deviation from protocol on the part of the subject (includes lack of compliance)
- Significant protocol violation on the part of the investigator or his/her staff
- Termination of the study by Polynoma LLC
- Intercurrent illness that prevents further administration of treatment

If a subject prematurely discontinues study intervention for any reason, the investigator must make every effort to perform the study follow-up assessments, including the scheduled tumor assessments, even if the subject has initiated other anti-cancer therapy without documented recurrence.

A complete final evaluation must be made at the time of the subject's withdrawal from study intervention. The explanation of why the subject is withdrawing will be documented in the case report form (CRF). If the subject withdraws from treatment due to toxicity, "Adverse Event" will be recorded as the primary reason for withdrawal. If a subject is prematurely discontinued from the study at any time due to an AE or SAE, the subject must be followed until resolution to Grade 2 or less, unless it is unlikely to improve because of his/her underlying disease.

6.2.2 Subject Withdrawal from Recurrence Assessments

Even in the case of termination of study intervention, subjects will be encouraged to continue to attend follow-up assessments as outlined in Section 5.

6.2.3 Subject Withdrawal from Vital Status Follow-up

Subjects will only be withdrawn from vital status follow-up at the specific request of the subject. Subjects who are withdrawn from study intervention will not automatically be withdrawn from vital status follow-up.

6.2.4 Replacement of Subjects

Subjects prematurely withdrawing from the study will not be replaced.

7 INVESTIGATIONAL PRODUCT

7.1 Description of Investigational Product

All production, formulation, and packaging of the investigational agent will be in accordance with applicable current Good Manufacturing Practice and meet applicable criteria for use in humans.

7.1.1 Seviprotimut-L

Seviprotimut-L (a human polyvalent melanoma shed antigen vaccine, alum adjuvanted) contains pooled soluble melanoma antigens shed from 3 human melanoma cell lines: SFHM2, SFHM4, and SFHM8. Seviprotimut-L is a suspension product provided at a concentration of 0.05 mg/mL (for the 40 µg dose) and 0.125 mg/mL (for the 100 µg dose) admixed with 20 mg/mL alum in sterile pyrogen-free isotonic saline (0.9% NaCl). The volume of the final product vials is 1.0 mL.

The nominal doses of 40 µg and 100 µg could be administered as 24 to 56 µg and 72 to 160 µg, respectively, due to potential manufacturing run variation.

7.1.2 Placebo

The placebo contains the same concentration of alum as in seviprotimut-L but without shed antigens.

7.2 Dosage and Administration

7.2.1 Route of Administration - Intradermal Injection

Seviprotimut-L or placebo is administered intradermally, in 4 injections (0.2 mL each injection) into the volar surface of forearms and into the anterior upper thighs, with the following exceptions:

- If the subject has had a complete node dissection in the node basin draining the extremity to be injected, then an additional vaccination will be given into the contralateral extremity.
- If the subject has a bilateral node dissection, then 2 injections will be given into each of the other extremities.

These exceptions will be documented in the CRF.

The number of syringes used may be determined per individual institutional guidelines.

7.2.2. Treatment Assignment

The study interventions to be administered will be blinded as to content and identified using codes unique to individual subjects. Clinical site workers should have no expectation of knowing the content of the intervention administered to individual subjects either initially, at recurrence, or at the end of study intervention. Furthermore, only emergency unblinding of the contents of individual subjects interventions will be allowed. See Section 10.7.5 for a description of emergency unblinding procedures.

The definitions of the randomized arms relative to the intended intervention to be used in those arms are as follows:

Part A: Randomization to 1 of 3 treatment arms:

- 0 µg (placebo containing alum but not shed antigens)
- 40 µg seviprotimut-L vaccine
- 100 µg seviprotimut-L vaccine

Part B: Randomization to 1 of 2 treatment arms:

- 0 µg (placebo containing alum but not shed antigens)
- 40 µg seviprotimut-L (dose selected from Part A)

7.2.3 Schedule and Duration of Treatment

Each subject will be treated with seviprotimut-L or placebo until one of the following occurs: development of recurrent disease that does not meet the criteria for continued dosing (see Section 7.2.4), death, subject withdrawal or early termination, or study termination.

Doses will be administered according to the following schedule: the initial dose then every 2 weeks x 4, then monthly x 4, and then every 3 months through Month 24 (i.e., at the following time points: W0, W2, W4, W6, W8, M3, M4, M5, M6, M9, M12, M15, M18, M21, and M24).

The outcome of the Part A evaluation will not change the dose level or regimen for subjects enrolled in Part A, except for placebo subjects. Subjects receiving 40 or 100 µg seviprotimut-L will continue with the dose to which they were initially randomized (i.e., Part A subjects will not cross into Part B). Subjects receiving placebo in Part A will be removed from the study and may be given the option of receiving treatment with seviprotimut-L (Part B dose) under open-label extension protocol 103A-301OL (Appendix C) if an investigator feels this is in the subject's best interest and the program is approved by regulatory authorities. Regardless of whether subjects receive treatment with seviprotimut-L, placebo subjects from Part A will be monitored for vital status (survival) at least every 6 months through telephone (or in-person) contact until the study is terminated/completed, the subject is lost to follow-up, or the subject specifically requests to be withdrawn from vital status follow-up.

Safety information from all subjects will be included in the final analysis, but only efficacy data from Part B subjects will be included in the clinical efficacy analysis for the study.

7.2.3.1 Handling Missed Doses

There is a ± 3 day window for dosing in the first 8 weeks of dosing, a ± 7 day window for dosing M3, M4, M5 and M6, and a ± 14 day window for M9, M12, M15, M18, M21, and M24 doses. If a subject cannot be dosed in these time windows for any reason, the dose in question should be skipped, and the subject should resume dosing at the next planned dosing date. The missed dose will be documented in the CRF.

7.2.4 Provisions for Continued Treatment Following Disease Recurrence

Treatment with seviprotimut-L or placebo will not be automatically discontinued in the case of early disease recurrence or the identification of a new primary melanoma. Treatment will be continued according to the pre-specified schedule if all of the following conditions are met:

- The recurrence (or new primary) occurred within 3 months of first dose of study drug
- The lesion was completely resectable
- The subject continued to meet all the other inclusion/exclusion criteria
- The investigator and the subject agree that there is no other therapy required or appropriate except surgical resection
- The subject continues to be willing to participate in the study

The procedures outlined in Section 5.2.9 do not have to be performed for these subjects.

7.3 Study Drug Handling and Accountability

7.3.1 Preparation

The study drug is packaged in type-1 glass vials with Teflon-coated bromobutyl stoppers and stored at 2-8°C until use. Study drug is used as is and requires no reconstitution. Prior to administration, the product should be warmed to room temperature, gently inverted, then rolled between the hands to re-suspend the contents. The study drug should be drawn into syringes as described in the study manual and used within 4 hours of removal from refrigeration.

7.3.2 Labeling

Study drug vials will be labeled with the name of the sponsor, the vial identification number, date of manufacturing, storage condition, volume, and the statement "Caution: New Drug--Limited by United States law to investigational use" (or in compliance with local regulatory requirements).

7.3.3 Storage

Study drug should be stored at 2-8°C. All investigational products must be stored in a secure area with access limited to the investigator and authorized site staff and under physical conditions that are consistent with investigational product-specific requirements. Investigational product must be dispensed or administered according to procedures described herein. Only authorized site staff may supply or administer investigational product.

7.3.4 Product Accountability

The investigator, institution, or the head of the medical institution (where applicable) is responsible for investigational product accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or the head of the medical institution (where applicable), or designated site staff (e.g., storage manager, where applicable) must maintain current investigational product accountability records throughout the course of the study. These records will contain the following information:

- Subject ID number
- Date, quantity, and vial ID number of investigational product dispensed
- Date and quantity of investigational product returned to the investigator/pharmacy (if applicable)
- Date and quantity of accidental loss of investigational product (if any)
- Documentation of storage conditions
- Amount of investigational product received from and returned to the sponsor (when applicable)

These inventories must be made available for inspection by the study monitor. The investigator is responsible for ensuring that all used and unused trial supplies are accounted for. While the used vials need not be retained, the outer packaging should be kept at the study site for clinical monitoring review. At the end of the study the study monitor will also collect the original investigational product dispensing record.

7.4 Assessment of Compliance

Study treatments will be administered under the supervision of clinic staff. On clinic visit days, clinic staff will observe and record the date and time (first intradermal injection only) of seviprotimut-L or placebo administration on the CRF.

7.5 Treatment of Investigational Product Overdose

There have been no cases of overdose with seviprotimut-L. Treatment of any suspected or confirmed overdose with seviprotimut-L should be symptomatic, and supportive care is recommended in cases where overdose is suspected. As described in the Investigator's Brochure for seviprotimut-L, Polynoma LLC does not recommend specific treatment for overdose or

toxicity; however, the investigator should use appropriate clinical judgment in treating the overdose. For the purposes of this study, an overdose of seviprotimut-L is defined as any dose 50% greater than the intended dose for that subject. While the potential for overdose is considered small since the vaccine is provided in single-dose vials that contain only a 20% excess of vaccine, seviprotimut-L is an investigational product and the potential for unexpected reactions is not known. Appropriate supportive care measures will need to be provided to address these potential toxicities in the event of an overdose.

7.6 Occupational Safety

Precautions should be taken to avoid direct contact with the investigational product. A Material Safety Data Sheet (MSDS) describing occupational hazards and recommended handling precautions will be made available to the investigator.

8 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

8.1 Permitted Medications

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (follow-up visit).

Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the CRF. The minimum requirement is that the drug name, dose, and the dates of administration are to be recorded. Additionally, a complete list of all prior melanoma cancer therapies will be recorded in the CRF.

8.2 Prohibited Medications

Prohibited medications include other melanoma therapies, chronic use of systemic corticosteroids (other than inhaled or nasal steroids) or other immunosuppressant or immunomodulatory medications (see Prohibited Medication List in the Study Manual). The following restrictions of other steroid use apply:

- Topical steroids are permitted, with the exception of topical steroids on the injection sites.
- Steroid injections into joints are permitted, with a limit of no more than one set of injections every three months. It is strongly encouraged that the steroid used in these injections has a low systemic absorption.

8.2.1 Subject Management Following Emergency Steroid Use

- Subjects in Part A who unexpectedly require systemic steroids (other than inhaled or nasal) within the first 10 weeks of the study will be withdrawn from study treatment. Between Week 10 and Month 24, the subject may receive up the 3 such acute steroid courses without being withdrawn from study treatment. All such treatments will be documented as protocol violations, and all subjects will continue to be followed for recurrence and survival.
- Subjects in Part B who unexpectedly require acute treatment with systemic steroids (other than inhaled or nasal) will not be withdrawn from study treatment. All such treatments

will be documented as protocol violations, and all subjects will continue to be followed for recurrence and survival.

- If a Subject in either Part A or Part B unexpectedly needs chronic systemic steroids (other than inhaled or nasal), the subject will be withdrawn from study treatment, unless the investigator determines that it is in the best interest of the subject to remain on study treatment. All such treatments will be documented as protocol violations, and all subjects will continue to be followed for recurrence and survival.

8.3 Supportive Care

Subjects may receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, antiemetics, antidiarrheals, and analgesics, and other care as deemed appropriate by the investigator, and in accordance with their institutional guidelines. Please see Section 8.2 for prohibited medications.

9 ASSESSMENT OF EFFICACY

9.1 Part A Evaluation Endpoint

The principal method used to evaluate the immunogenicity of the vaccine is a vaccine-induced anti-melanoma IgG/IgM antibody response. The responses will be measured by Western immunoblot using the vaccine as the antigen source, patient sera as the primary probe, and a secondary probe that binds to IgG and IgM but does not distinguish between the two. This endpoint is based on prior work with a similar formulation of the vaccine. Elispot assays (for Trp-2-specific T-cell responses) will be used as a secondary measure to demonstrate an immune response. A Patient with either a positive result by Western Blot or Elispot will be considered as having an immune response to study drug.

9.1.1 Immune Monitoring

Blood samples will be collected from Part A and Part B subjects over the course of 3 years for immunological investigations and possible correlation with clinical response. These samples will be banked and analyzed separately from this protocol.

9.2 Initiation of Part B

The initiation of Part B will be based on all aspects of the analysis of the data collected and available from Part A. The primary consideration will be evidence of biologic activity in Part A in the absence of safety concerns. Failure to meet these criteria will not automatically preclude the initiation of Part B, The charter will instruct the DMC to make a recommendation regarding initiation of Part B based in part on toxicity of the seviprotimut-L vaccine treatment compared to current approved treatment for resected melanoma.

The decision to initiate Part B at the seviprotimut-L dose of 40 µg was made by the sponsor consistent with recommendations from the DMC, which were based on pooled unblinded safety and immunogenicity findings of Part A, which are summarized briefly in Section 1.3.1.1. This decision was also previously agreed upon by the FDA.

9.3 Part B Clinical Efficacy Parameters

Survival time is computed based on the date of death if the subject is known dead or the date last known to be alive (censored). Zero time for a subject is the date of randomization.

Recurrence-free survival time (RFS) is computed from the earliest of the date of recurrence or death or, if without recurrence or death, the date last assessed for recurrence without a diagnosis of recurrence (censored). The date of recurrence is specified as the first date a recurrence is suspected, which is later confirmed by biopsy. In the rare cases where biopsies are not clinically appropriate (e.g., brain metastases), the recurrence date will be set by the treating clinician's medical judgment. Zero time for a subject is the date of randomization.

Recurrence will be monitored through tumor imaging (as specified in Section 9.3.1) every 6 months until recurrence, death, subject withdrawal, early termination or completion of the study.

LDH is also monitored every 3 months for early indication of possible recurrence. LDH elevations of 1.5 X ULN (or greater) will be followed up with radiological scans, provided there are no other obvious medical reasons for the elevated LDH.

Recurrence is defined as the occurrence of the following events:

- Loco-regional relapse
- Distant metastasis
- A new melanoma that is likely unrelated to the original primary lesion

Investigators are required to obtain biopsies of recurrent tumors to provide pathologic evidence of recurrence unless the recurrence is in the brain. In the case of multiple lesions during an imaging examination, biopsy of at least one lesion should be obtained.

As the determination of recurrence will primarily rely on biopsies, there will be no central reading of CT scans to confirm recurrence.

9.3.1 Tumor Assessments

For all subjects a chest x-ray (or chest CT with contrast) will be performed every 6 months, and additional CT/MRI scans with contrast will be performed as clinically indicated.

Subjects who enter with Stage IIB, IIC, or IIIA and also presented with lower extremity disease or a positive inguinal node will also have a pelvic CT with contrast done every 6 months.

Subjects who enter with Stage IIIB or IIIC or who had a primary lesion > 4 mm will have a CT with contrast of the chest, abdomen and pelvis AND MRI or CT, with contrast, of the brain every 6 months. For the brain scans, the modality used at screening (MRI or CT) must be carried through the remainder of the study, for comparability.

9.3.2 Immune Monitoring and Biomarker Analysis

Humoral immune responses will be analyzed to evaluate immunogenicity and monitor Part A subjects' responses to seviprotimut-L. Antibodies specific to seviprotimut-L will be measured by Western blot methodology as in Part A of the study. Serum will be collected for Western blot testing and analysis. Subject responses will be tested at day 0 (baseline) and at M3, M6, M12, M18, M24, M30 and M36. Subjects with recurrence prior to M36 will have a final analysis performed at the time of recurrence (see Section 5.2.9). Western Blot results will be used in the evaluation of the potential clinical effectiveness seviprotimut-L.

Additional blood samples, including both sera and PBMCs, will be collected over the course of the study (Part B1 and B2) for biomarker analysis, specifically at day 0 (Baseline) and M3, M6, M12, M18, M24, and M36. Subjects with recurrence prior to M36 will have final samples collected at the time of recurrence (see Section 5.2.9). Immunological-based tests for possible subject selection and correlation with clinical response will be investigated. These subject specimens/samples will be banked, tested and analyzed separately from this study protocol. These samples may be tested and analyzed to assess a potential correlation between biomarker shifts/baseline prognostic markers and clinical outcome (Part B1 and B2 Secondary Objective).

10 ASSESSMENT OF SAFETY

Safety will be assessed throughout the study by a physician, physician designate, or nursing staff. Measurements used to evaluate safety will include history, physical examination, vital signs (blood pressure, heart rate, respiratory rate, and temperature), clinical laboratory tests (hematology and clinical chemistry), urinalysis, 12-lead ECG, and monitoring for AEs. Safety will be assessed by physical examination, AE reports, clinical chemistry evaluation, and hematology evaluation. AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 4 (NCI-CTCAE v4) [NCI, 2009].

Laboratory measurements that deviate significantly (as determined by the investigator) from previous measurements may be repeated. If warranted, additional or more frequent testing than is specified in the protocol should be done to provide adequate documentation of AEs and the resolution of AEs.

10.1 Physical Examination

Medical and physical examinations must be performed by a qualified physician, nurse practitioner, or physician assistant and should include a thorough review of all body systems. Examinations should be performed as listed on the schedule of activities. Physical examinations will include vital signs (blood pressure, heart rate, respiratory rate and temperature).). For height and body weight measurements, the subject may wear indoor, daytime clothing with no shoes.

10.1.1 Injection Site Reactions

Injection site reactions will be assessed. All injection site reactions should be recorded as adverse events.

10.2 Clinical Laboratory Tests

Subjects will have blood samples collected for routine clinical laboratory testing. The clinical laboratory parameters will be analyzed at a central laboratory. Laboratory assessments to be completed will include hematology (complete CBC with differential and platelet count), chemistry, and pregnancy test (urine or blood for females of childbearing potential).

The chemistry panel will include: sodium, calcium, magnesium, total protein, albumin, creatinine, blood urea nitrogen, total bilirubin, alkaline phosphatase, AST, ALT, potassium, chloride, bicarbonate, LDH, and glucose.

Additional laboratory assessments may be conducted throughout the study as medically necessary.

10.3 Urinalysis

Subjects will have urine samples collected for routine urinalysis. The urinalysis will include color, appearance, dipstick for specific gravity, protein, white blood cell-esterase, glucose, ketones, urobilinogen, nitrite, WBC, red blood cells (RBC), and pH. Microscopic analysis of urine will be performed if indicated based on macroscopic examination and urine dipstick results.

10.4 Autoimmune Monitoring

Autoimmune monitoring will occur through laboratory measurements of ANA and ESR. Other tests, such as RF, TSH, and T4, may be performed as clinically indicated. Furthermore, periodic physical examinations, including eye exam (performed by an ophthalmologist) and skin exam for vitiligo and rashes will be performed.

10.5 Performance Status

The performance status assessment is based on the ECOG scale.

10.6 Pregnancy and Contraception

All female subjects of childbearing potential will have a pregnancy test (urine or blood) performed at screening and at the post-treatment follow-up visit. Measurement of serum FSH and serum estradiol levels will be performed at screening in female subjects believed to not be of childbearing potential to confirm this status.

Female subjects of childbearing potential must agree to use adequate contraception throughout the treatment duration and for 3 months after the last seviprotimut-L or placebo dosing. Acceptable contraceptive methods for female subjects of childbearing potential include one of the following:

1. Abstinence
2. One of the following methods:
    a. Tubal ligation
    b. Placement of a copper-containing intrauterine device (IUD)
    c. Condom with spermicidal foam/gel/film/cream/suppository
    d. Male partner who has had a vasectomy for at least 6 months

e. Hormonal contraceptives (oral, injected, intrauterine, transdermal, or implanted) provided the subject remains on treatment throughout the entire study and has been using hormonal contraceptives for an adequate period of time to ensure effectiveness (e.g., 3 months).

If a female subject becomes pregnant during the study, treatment will be immediately discontinued and the subject will be removed from study-mandated procedures, except follow-up for survival. The subject will receive counseling from the investigator or designee regarding the nature of the study medication and the potential risk on fetal development.

10.6.1 Time Period for Collecting Pregnancy Information

The time period for collecting information on whether a pregnancy occurs is from the screening visit to 3 months after the last seviprotimut-L or placebo dosing. Information on pregnancies identified prior to randomization does not need to be reported to Polynoma LLC or designee.

10.6.2 Action to be Taken if Pregnancy Occurs

The investigator will collect pregnancy information on any female subject who becomes pregnant while participating in this study and for up to 3 months post the last seviprotimut-L or placebo dosing. Treatment and study-related procedures will be terminated, and the investigator will record pregnancy information on the appropriate form and submit it to Polynoma LLC (or designee) within 2 weeks of learning of a subject's pregnancy. The subject will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to Polynoma LLC or designee. Generally, follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE (see Section 10.7).

A spontaneous abortion is always considered to be an SAE and will be reported as such. Furthermore, any SAE occurring as a result of a post-study pregnancy and that is considered reasonably related to the investigational product by the investigator will be reported to Polynoma LLC or designee. While the investigator is not obligated to actively seek this information on former study participants, he or she may learn of an SAE through spontaneous reporting.

Subjects who become pregnant and discontinue study treatment will still be followed for overall survival.

10.7 Adverse Events (AE) and Serious Adverse Events (SAE)

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE, as provided in this protocol. When there is a safety evaluation during this study, the investigator or site staff will be responsible for detecting, documenting, and reporting AEs and SAEs, as detailed in both this section of the protocol and in the AE/SAE section of the study manual.

10.7.1 Definition of an AE

An adverse event can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality.

Only events that occur between randomization and 30 days following the completion of study drug administration for the subject will be reported as adverse events (i.e., 30 days after either the Month 24 dose or premature study drug termination). Events that occur between study of enrollment (signing of informed consent) and randomization will be documented as medical history.

For patients that roll over into the Open Label Extension Study, AEs that occurred >30 days from last dose of placebo will not be documented. However, AEs present on the day of but prior to the first dose of active drug will be documented as AEs.

10.7.2 Definition of an SAE

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. 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 inpatient hospitalization, or the development of drug dependency or drug abuse.

10.7.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

An event that is part of the natural course of the disease under study (i.e., disease progression) should not be reported as an SAE. Progression of melanoma, basal and squamous cell skin cancers (non-melanoma skin cancer), or a new primary melanoma will be recorded in the clinical assessments in the CRF. Death due to disease progression is to be recorded in the eCRF and not as an SAE. However, if the progression of the underlying disease is greater than what would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with seviprotimut-L or protocol design/procedures and the disease progression, then it must be reported as an SAE.

10.7.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments (e.g., ECGs or vital signs) that are judged by the investigator as **clinically significant** will be recorded as AEs and SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start

of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will **not** be reported as AEs or SAEs.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

10.7.5 Breaking of Study Blind for Medical Emergencies

As there is no known antidote for seviprotimut-L, knowledge of the treatment arm is unlikely to be of any benefit to patient care in the event of medical emergencies. Therefore, unblinding is discouraged. Patients should be treated with best supportive care in the event of medical emergencies thought to be caused by study drug.

If it is determined that knowledge of the treatment arm is absolutely necessary, the option of code break may be performed using the IVRS only by the Medical Monitor assigned to the study (the option to access the code break will not be made available to the investigator or his/her staff). After unblinding the subject will not receive any more seviprotimut-L or placebo dosing, but will continue to be followed according to the original schedule for disease recurrence and survival.

10.7.6 Reporting Adverse Events

The investigator is to record all directly observed AEs and all AEs spontaneously reported by the study subject on the Adverse Event CRF. In addition, each study subject will be questioned about AEs.

Each AE should be described in detail on the Adverse Event CRF and SAEs on a Serious Adverse Event form and include the following information: start and stop dates, CTCAE grading, relationship to study medication, action taken, and outcome.

The investigator will also assess the possible relationship between the AE and the study medication as well as any concomitant medications according to the following criteria (WHO definitions):

- Probable: A clinical event - including laboratory test abnormality - with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and that follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possible: A clinical event - including laboratory test abnormality - with a reasonable time sequence to administration of the drug, but that could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

- Unlikely: A clinical event - including laboratory test abnormality - with a temporal relationship to drug administration that makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations. If the relationship is judged unlikely, an explanation for this decision should be made.

10.7.7 Prompt Reporting of SAEs to Polynoma LLC or Designee

All SAEs, whether or not considered related to the investigational drug, must be reported within 24 hours through electronic data capture system. The initial report will require a brief narrative of the symptoms, course, and treatment of the event. The Medical Monitor will review the information provided, and the investigator will be contacted as needed to obtain additional information on the event, and to determine whether the event requires expedited reporting per regulatory requirements. The sponsor will promptly report to the FDA and other applicable regulatory agencies SAEs which are both unexpected and suspected to be related to the study drug, in accordance with Title 21 of the Code of Federal Regulations (CFR), Part 312.32 (21 CFR 312.32) and local regulatory requirements. The investigator should also comply with any applicable requirements related to the reporting of SAEs to the IRB/IEC.

Any SAE occurring while on study shall be reported for the period from randomization through 30 days post discontinuation of the active treatment portion of the study or the last injection, whichever is longer.

The investigator will provide an SAE follow-up report to the sponsor. In this report, the investigator is to assess and record the SAE in detail, including the date and time of onset, description, intensity, duration, outcome, etiology, relationship to study drug, and action taken. Any SAEs that continue at the subject's last study visit must be followed until the event resolves or follow-up is agreed to be adequate by the investigator, Medical Monitor, and sponsor.

The investigator and the Medical Monitor will review each SAE report and evaluate the relationship of the SAE to study treatment and to underlying disease. Based on the investigator’s and sponsor’s assessment of the SAE, a decision will be made concerning the need for further action. The primary consideration governing further action is whether new findings affect the safety of subjects participating in the clinical study. If the discovery of a new SAE related to seviprotimut-L raises concern over the safety of continued administration of study drug to subjects, the sponsor will take immediate steps to notify the FDA and all investigators participating in clinical studies of seviprotimut-L.

Further action that may be required includes the following:

- Modification of the protocol
- Discontinuation or suspension of the study
- Modification of the existing consent form and informing current study participants of new findings
- Addition of any newly identified seviprotimut-L-related AEs to the list of expected AEs

11 STATISTICAL CONSIDERATIONS

The details of the statistical considerations and specific statistical analyses to be performed are provided in a separate Statistical Analysis Plan (SAP). This section of the protocol provides an overview of the statistical design of the study with a focus on justifying the size of the study.

11.1 Data Monitoring Committee

A Data Monitoring Committee (DMC) will monitor subject safety and assess analyses of efficacy measures. The DMC's role in efficacy monitoring role will be to make a recommendation regarding initiation of Part B, evaluation of interim analyses in Part B, and monitoring for threats to the validity of the planned analyses of Part B data. The criteria to be used by the DMC are specified in the SAP.

11.2 Part A Methods

The statistical goal in Part A is the assessment of vaccine biologic activity based on immunologic biomarkers. The signal of biologic activity will be based on measures of immune activity to the vaccine where signals of immune activity are putative evidence of ultimate clinical benefit.

The immunology data to be used in the statistical criterion for Part A come from two assessments: (1) IgG/IgM Western blot method, and (2) T-Cell Elispot method. Each method provides an immune response dichotomous outcome for each patient (0 = negative, 1 = positive). Both assays will be performed in triplicate, and be based on a comparison of a pre-vaccination baseline (T_0) to the post-vaccination Week 10 visit (T_{10w}). A subject will be regarded as having a positive immune response if either method (Western blot or Elispot) is positive. For the Western blot assay, a value of 1 (success) indicates the presence of an antibody reactive band in the follow-up assessments that was either absent in pre-vaccination serum or whose intensity was at least 25% greater than the corresponding band in the baseline serum. A value of 0 indicates all other outcomes, including missing or failed assessments.

Details for the Western blot and Elispot assay procedures and analysis are included in the Endpoint Charter and Statistical Analysis Plan, respectively.

Overall success is defined as evidence that frequency of a positive immune response (by Western blot OR Elispot) in seviprotimut-L dosing arms is 20 percentage points or higher than those in the placebo arm (e.g., Arm 0 has a 25% "positive" response rate and Arm 2 has a 45% "positive" response rate). Thus, the null hypothesis is that the proportion of success in the seviprotimut-L dose arm is the same as or lower than the proportion of successes in the placebo arm. The specific alternative for each endpoint is evidence that the seviprotimut-L dose arm proportion of successes is 20 points or more higher than that for Arm 0. The number of subjects required per arm is computed to be 33. This computation takes into account 2 arms and 2 endpoints, an attenuated type I error probability of 0.1 because this is not a regulatory endpoint, and 80% power.

11.3 Part B

Part B of the Study is revised to include two Parts: Parts B1 and B2. Part B1 will consist of a recurrence-free survival (RFS) analysis of the first accrued 325 patients with one-sided alpha = 0.10 and 80% power; RFS is the sole primary endpoint for Part B1. Part B2 will be based on the same treatment arms as Part B1 but with 1:1 randomization of 800 patients and with one-sided alpha = 0.025 shared between RFS and Survival, and with 90% power for RFS and 80% power for survival.

At the time of the RFS analysis of Part B2, interim survival analyses of both superiority and futility will be performed. The RFS endpoint and survival (Part B2) are defined previously in this protocol.

Subjects in Parts B1 and B2 will be randomly partitioned into two arms, designated P (for Placebo) and V (for vaccine) for statistical purposes. The primary analysis will be an ITT between-arm comparison using the stratified logrank test.

The reference data are based on the control arm outcome from recent interferon trials accruing similar subjects and a projection of the stage distribution of the patients to be enrolled updated using the patients currently accrued.

Evidence of a 37.5% lower RFS hazard rate for Arm V subjects is considered clinically consequential in both Parts B1 and B2, corresponding to a hazard ratio (Arm V over Arm P) of 0.625. In Part B2 evidence of a 33.33% smaller death hazard rate for Arm V subjects is considered clinically consequential. The corresponding hazard ratio (Arm V over Arm P) is 0.6667.

Based on visual inspection of the survival Kaplan-Meier graphs from randomized adjuvant melanoma studies (10, 11) it is conjectured that there exists the possibility of a delay of the vaccine effect. The existence of a delayed effect would mean that early deaths will not differentiate between the arms and therefore the computation of the required number of events for both Parts B1 and B2 take into account the possibility of delayed effect.

11.3.1 Part B1

Part B1 is an RFS analysis of the first accrued 325 patients. The Part B1 RFS analysis will be done after the realization of 126 RFS events with significance level one-sided 0.10 and power 80%. The projected time of this analysis is 3.21 years following the initiation of accrual. The critical hazard ratio is projected to be 0.792. Overall survival will be tracked for Part B1 subjects and will be reported in the final report.

11.3.2 Part B2

Part B2 will be based on the same arms as Part B1 but with 1:1 randomization. Part B2 will have two primary endpoints (RFS and overall survival) with an overall one-sided alpha of 0.025. The significance level to be used for RFS is specified to be one-sided 0.02, and the significance level to be used for the subsequent survival analysis is specified to be 0.005. Part B2 is planned with 90% power for RFS and 80% power for survival.

Part B2 is planned with the specific alternative RFS HR = 0.625, and the specific alternative survival HR = 0.6667 as was originally planned.

The RFS analysis is planned using the same delayed effect specifications as were used to plan the Part B1 analysis and accrual of 800 patients in 3 years.

Simulations with 10,000 replications find a requirement for 310 RFS events and the last of these events is projected to occur 3.93 years following the start of accrual. The critical RFS hazard ratio region is estimated to be ≤ 0.791, corresponding roughly to a 26% or longer median RFS.

The statistical operating characteristics for the survival endpoint assessment requires 432 deaths and the last of these events is projected to occur 13.0 years following the start of accrual. The simulation estimate of the critical survival hazard ratio region is estimated to be ≤ 0.764, corresponding roughly to 30.1% or longer experimental arm median survival.

11.3.3 Futility Analyses in Part B2

At the time of the RFS analysis of Part B2, interim survival analyses of both superiority and futility will be performed. The details of this analysis are specified in the SAP.

12 STUDY CONDUCT CONSIDERATIONS

12.1 Regulatory and Ethical Considerations, Including the Informed Consent Process

The sponsor or designee will obtain favorable opinion/approval to conduct the study from the appropriate regulatory agency in accordance with applicable country-specific regulatory requirements or local regulations where applicable prior to a site initiating the study in that country.

The study will be conducted in accordance with all applicable regulatory requirements, including a US IND.

The study will also be conducted in accordance with GCP, all applicable subject privacy requirements, and, the guiding principles of the Declaration of Helsinki. This includes, but is not limited to, the following:

- IRB/IEC review and favorable opinion/approval to conduct the study and of any subsequent relevant amending documents
- Subject informed consent
- Investigator reporting requirements

The sponsor will provide full details of the above either verbally, in writing or both.

Signed and dated written informed consent will be obtained for each subject before he or she can participate in the study.

12.2 Quality Control (Study Monitoring)

In accordance with applicable regulations, GCP, and Polynoma LLC procedures, study monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and Polynoma LLC requirements. When reviewing data collection procedures, the discussion will also include identification, agreement, and documentation of data items for which the CRF will serve as the source document.

Polynoma LLC or designee will monitor the study consistent with the demands of the study and site activity to verify that the:

- Data are authentic, accurate and complete.
- Safety and rights of subjects are being protected.
- Study is conducted in accordance with the currently approved protocol and any other study agreements, GCP, and all applicable regulatory requirements.

The investigator and the head of the medical institution (where applicable) agrees to allow the study monitor direct access to all relevant documents.

12.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, Polynoma LLC or designee may conduct one or more quality assurance audits. Regulatory agencies may also conduct regulatory inspection of this study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

12.4 Study and Site Closure

Upon completion or premature discontinuation of the study, the study monitor will conduct site closure activities with the investigator or site staff, as appropriate, in accordance with applicable regulations, GCP, and Polynoma LLC procedures.

In addition, Polynoma LLC reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. For this multicenter study, this may occur at one or more sites. If Polynoma LLC determines such action is needed, Polynoma LLC will discuss this with the investigator or the head of the medical institution (where applicable), including the reasons for taking such action, at that time. When feasible, Polynoma LLC will provide advance notification to the investigator or the head of the medical institution, where applicable, of the impending action prior to it taking effect.

Polynoma LLC (or designee) will promptly inform all other investigators or the head of the medical institution (where applicable), and/or institutions conducting the study if the study is suspended or prematurely discontinued for safety reasons. Polynoma LLC (or designee) will also promptly inform the regulatory authorities of the suspension or premature discontinuation of the

study and the reason(s) for the action. If required by applicable regulations, the investigator or the head of the medical institution (where applicable) must inform the IEC/IRB promptly and provide the reason for the suspension or premature discontinuation.

12.5 Records Retention

Following closure of the study, the investigator or the head of the medical institution (where applicable) must maintain all site study records, except for those required by local regulations to be maintained by someone else, in a safe and secure location. The records must be maintained to allow easy and timely retrieval, when needed (e.g., audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (e.g., microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible and are a true and accurate copy of the original and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

Polynoma LLC or designee will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study, as dictated by any institutional requirements or local laws or regulations, or Polynoma LLC standards/procedures; otherwise, the retention period will default to 15 years.

The investigator must notify Polynoma LLC or designee of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site.

12.6 Provision of Study Results and Information to Investigators

When required by applicable regulations, the Principal Coordinating Investigator (as listed on the cover page of this protocol) will be the investigator signatory for the clinical study report. When the clinical study report is completed, Polynoma LLC will provide the investigator with a full summary of the study results. The investigator may share the summary results with the subjects, as appropriate. In addition the investigator may be given reasonable access to review the relevant statistical tables, figures, and reports and will be able to review the results for the entire study at the Polynoma LLC facility or other mutually agreeable location.

12.7 Data Management

The data collection tool for this study will be Polynoma LLC-defined CRFs via electronic data capture. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system. Clinical data management will be performed in accordance with applicable Polynoma LLC or designee standards and data cleaning procedures.

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APPENDIX A: ECOG PERFORMANCE STATUS SCALE

ECOG PERFORMANCE STATUS*

Grade	Description
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, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

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

Credit: the Eastern Cooperative Oncology Group, Robert Comis MD, Group Chair.

APPENDIX B: AJCC STAGING SYSTEM (2009)

Source: Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol. 2009 Dec 20;27(36):6199-206.

Table 1. TNM Staging Categories for Cutaneous Melanoma

Classification	Thickness (mm)	Ulceration Status/Mitoses
T		
Tis	NA	NA
T1	≤ 1.00	a: Without ulceration and mitosis < 1/mm^2 b: With ulceration or mitoses ≥ 1/mm^2
T2	1.01-2.00	a: Without ulceration b: With ulceration
T3	2.01-4.00	a: Without ulceration b: With ulceration
T4	> 4.00	a: Without ulceration b: With ulceration
N	**No. of Metastatic Nodes**	**Nodal Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis* b: Macrometastasis†
N2	2-3	a: Micrometastasis* b: Macrometastasis† c: In transit metastases/satellites without metastatic nodes
N3	4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes	
M	**Site**	**Serum LDH**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastases	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases	Normal
	Any distant metastasis	Elevated

Abbreviations: NA, not applicable; LDH, lactate dehydrogenase.
*Micrometastases are diagnosed after sentinel lymph node biopsy.
†Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.

Table 2. Anatomic Stage Groupings for Cutaneous Melanoma

	Clinical Staging*				Pathologic Staging†		
	T	N	M		T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
IA	T1a	N0	M0	IA	T1a	N0	M0
IB	T1b	N0	M0	IB	T1b	N0	M0
	T2a	N0	M0		T2a	N0	M0
IIA	T2b	N0	M0	IIA	T2b	N0	M0
	T3a	N0	M0		T3a	N0	M0
IIB	T3b	N0	M0	IIB	T3b	N0	M0
	T4a	N0	M0		T4a	N0	M0
IIC	T4b	N0	M0	IIC	T4b	N0	M0
III	Any T	N > N0	M0	IIIA	T1-4a	N1a	M0
					T1-4a	N2a	M0
				IIIB	T1-4b	N1a	M0
					T1-4b	N2a	M0
					T1-4a	N1b	M0
					T1-4a	N2b	M0
					T1-4a	N2c	M0
				IIIC	T1-4b	N1b	M0
					T1-4b	N2b	M0
					T1-4b	N2c	M0
					Any T	N3	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

*Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

†Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (ie, sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or stage IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.

APPENDIX C: OPEN LABEL PROTOCOL 103A-301OL

A Multicenter Open Label Extension Study for Placebo Subjects in Part A of Protocol 103A-301 to Receive Seviprotimut-L

Study Drug: Seviprotimut-L (formerly POL-103A)

Protocol 103A-301OL

Original Protocol: 25 July 2014

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TABLE OF CONTENTS

1 BACKGROUND

Refer to the corresponding section in Protocol 103A-301.

2 OBJECTIVES

- To evaluate the safety of seviprotimut-L in subjects who received placebo in Part A of Protocol 103A-301.
- To assess the efficacy (defined as recurrence-free survival [RFS] and overall survival [OS]) of treatment with seviprotimut-L in subjects who received placebo in Part A of Protocol 103A-301.

3 TRIAL DESIGN

3.1 Study Design Overview

This is an open-label extension (OLE) study available exclusively to subjects in Part A of Protocol 103A-301 who were randomized to receive placebo.

3.2 Justification of Study Drug Administration Strategy

Refer to the corresponding section in Protocol 103A-301.

3.3 Study Population

This study is open to subjects in Part A of Protocol 103A-301 who were randomized to receive placebo and who were active on the protocol at the time of the Part A analysis and unblinding.

3.4 Number of Subjects

Up to 53 subjects may be enrolled.

3.5 Study Endpoints

- The safety of seviprotimut-L evaluated by safety blood and urine laboratory measurements, physical examinations, and adverse event (AE) reports.
- Recurrence-free survival (RFS)
- Overall survival (OS)

3.6 Study Discontinuation Criteria

The sponsor may terminate the study at any time (after consultation with the Coordinating Principal Investigator) on the basis of safety considerations, other factors that may be deemed to affect the scientific validity or ethical viability of the protocol, or as a business decision. The Data Monitoring Committee (DMC) for this study may also recommend discontinuation based on periodic review of safety or efficacy data from all subjects.

4 PARTICIPANT SELECTION

To be eligible for this OLE study, all of the following conditions must be met:

1. Subject was randomized into the placebo arm of Part A of Protocol 103A-301.

2. Subject is eligible to receive study drug at the time of IRB approval for this OLE study, i.e., disease has not recurred and the subject has been actively participating in the Part A portion of the trial.
3. Subject is an appropriate candidate for treatment with seviprotimut-L, in the opinion of the site investigator.
4. Subject must have known BRAF V600E mutation tumor status or have tumor tissue (fresh or archived sample) available for testing of BRAF V600E mutation status (note: as long as it is confirmed that tumor tissue is available for testing, the subject may be considered eligible for the study; testing of BRAF mutation status on that tissue may be conducted at a later time during the study). A new sample is not needed if the sample has already been tested or reconciled prior during the Part A portion of the trial.
5. Subject is able to give written informed consent and/or comply with the study procedures.

5 STUDY PROCEDURES

A signed and dated, written informed consent form that is currently approved by an IRB or IEC must be obtained from the potential subject before he/she can participate in any study-specific procedures, including study-specific screening procedures.

5.1 Pre-Dosing Visit Procedures

If not performed within 30 days of Week 0 of the OLE protocol, the following procedures must be conducted prior to Week 0:

- Tumor assessments (see Section 9.3.1 in Protocol 103A-301)
- Autoimmune assessment (including antinuclear antibodies [ANA], erythrocyte sedimentation rate [ESR], eye examination by an ophthalmologist, and skin examination for vitiligo and rash)

5.2 On-Study Procedures

Study-related procedures and assessments performed during treatment on study are detailed as follows and in the Schedule of Activities table. In addition, any non study-related procedures that are performed during the study will be documented.

5.2.1 Baseline Assessment and First Dosing (Week 0)

The following baseline procedures will be performed prior to dosing:

- Physical examination (including height, weight, vital signs, and ECOG performance status)
- CBC, serum chemistry, urinalysis
- LDH
- Record concomitant medications

The following procedures will be performed after all the previous baseline procedures have been completed:

- Seviprotimut-L administration
- Record adverse events

5.2.2 Assessments at Weeks 2, 4, 6, and 8 (± 3 days)

The following procedures will be performed at the specified visits:

- Record adverse events
- CBC, serum chemistry, urinalysis
- Record concomitant medications
- Seviprotimut-L administration

5.2.3 Assessments at Month 3 (± 7 days)

The following procedures will be performed at the specified visits:

- Record concomitant medications
- Record adverse events
- Physical examination (including weight, vital signs, and ECOG performance status)
- LDH, CBC, serum chemistry, urinalysis
- Seviprotimut-L administration

5.2.4 Assessments at Months 4 and 5 (± 7 days)

The following procedures will be performed at the specified visits unless the subject has had disease recurrence and terminated study intervention. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10. Subjects who discontinue study intervention (see Section 6.2.1 in Protocol 103A-301) but have not progressed should continue to be assessed as described.

- Record concomitant medications
- Record adverse events
- Seviprotimut-L administration

5.2.5 Assessments at Months 6, 12, 18, and 24 (± 7 days)

The following procedures will be performed at the specified visits unless the subject has had disease recurrence and terminated study intervention. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10. Subjects who discontinue study intervention (see Section 6.2.1 in Protocol 103A-301) but have not progressed should continue to be assessed as described.

- Record concomitant medications
- Physical examination (including weight, vital signs, and ECOG performance status)
- CBC, serum chemistry, urinalysis
- LDH
- Tumor assessments (see Section 9.3.1 in Protocol 103A-301)
- Seviprotimut-L administration
- Record adverse events
- Physical examination for autoimmune phenomena (including eye examination by ophthalmologist, and skin examination for vitiligo and rash)
- Autoimmune labs ANA and ESR. Other tests (e.g., rheumatoid factor [RF], T4, thyroid-stimulating hormone [TSH]) to be performed only as clinically indicated.

5.2.6 Assessments at Months 9, 15, and 21 (± 7 days)

The following procedures will be performed at the specified visits unless the subject has had disease recurrence and terminated study intervention. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10. Subjects who discontinue study intervention (see Section 6.2.1 in Protocol 103A-301) but have not progressed should continue to be assessed as described.

- Record concomitant medications
- Physical examination (including weight, vital signs and ECOG performance status)
- LDH
- Seviprotimut-L administration
- Record adverse events

5.2.7 Pre-Recurrence Monitoring After Month 24

The following procedures will be performed at the specified visits unless the subject has had disease recurrence. In that case, the subject will have the procedures outlined in Section 5.2.9 performed, and then enter into a vital status assessment as outlined in Section 5.2.10.

5.2.7.1 Pre-Recurrence Monitoring Every 3 Months (± 7 days)

- LDH
- Record concomitant medications
- Record adverse events (through 30 days after the last dose of seviprotimut-L)

5.2.7.2 Pre-Recurrence Monitoring Every 6 Months (± 7 days)

- Physical examination (including weight, vital signs, and ECOG performance status)
- LDH
- CBC, serum chemistry, urinalysis
- Autoimmune labs ANA and ESR
- Tumor assessments (see Section 9.3.1 in Protocol 103A-301)
- Record concomitant medications

5.2.8 Assessments to be Conducted at Recurrence (or at Study Completion for Subjects Without Recurrence)

After a subject has had recurrence, he/she will report to the clinic within 28 days (± 7 days) for a final follow-up (end of study) visit. Assessments are as follows:

- Physical examination (including weight, vital signs and ECOG performance status)
- LDH (for subjects who have not had recurrent disease)
- CBC, serum chemistry, urinalysis
- ECG
- Pregnancy test (urine or blood) for female subjects of childbearing potential
- Record adverse events (through 30 days after last dose of seviprotimut-L)
- Record concomitant medications

For subjects with tumor assessments that indicate recurrence:

- Confirm recurrence through biopsy, if not previously conducted (see Section 9.3 in Protocol 103A-301)

If survival events have been met, and there is no previous indication of subject disease recurrence:

- LDH (to be followed up by tumor assessments for LDH elevations of 1.5X upper limit of normal (or greater), provided there are no other obvious medical reasons for the elevated LDH.)

5.2.9 Survival Monitoring of Subjects after Recurrence

Every 6 months post-recurrence, follow-up contact will be made for survival and new cancer treatments. Refer to the corresponding section in Protocol 103A-301.

5.2.10 Monitoring of Subjects after Premature Termination of Study Drug

Refer to the corresponding section in Protocol 103A-301.

5.3 Enrollment Strategy and Minimization of Bias

This is an OLE study and minimization of bias is not applicable.

6 SUBJECT COMPLETION AND WITHDRAWAL

6.1 Subject Completion

Subjects may continue to receive seviprotimut-L dosing until they meet the criteria for treatment discontinuation described in Section 6.2.1 in Protocol 103A-301 or complete the dosing phase of the study.

6.2 Subject Withdrawal From Study

Refer to the corresponding section in Protocol 103A-301.

7 INVESTIGATIONAL PRODUCT

Refer to the corresponding section in Protocol 103A-301. All subjects in this OLE study will receive seviprotimut-L. Subjects will not be dosed following a documented disease recurrence.

8 CONCOMITANT MEDICATIONS AND NON-DRUG THERAPIES

Refer to the corresponding section in Protocol 103A-301.

9 ASSESSMENT OF EFFICACY

Subjects will be assessed for efficacy as described in Section 9.3 of Protocol 103A-301.

10 ASSESSMENT OF SAFETY

Refer to the corresponding section in Protocol 103A-301.

11 STATISTICAL CONSIDERATIONS

Safety data will be tabulated and descriptive statistics will be used to summarize all other results.

12 STUDY CONDUCT CONSIDERATIONS

Refer to the corresponding section in Protocol 103A-301.

13 REFERENCES

Refer to the corresponding section in Protocol 103A-301.

SCHEDULE OF ACTIVITIES FOR PROTOCOL 103A-301OL

Procedure	Pre-Dosing	Dosing Period															Pre-Recurrence		Post-Recurrence	End of Study[1]
		First Visit (W0)	W 2	W 4	W 6	W 8	M 3	M 4	M 5	M 6	M 9	M 12	M 15	M 18	M 21	M 24	Q 3 Mos	Q 6 Mos	Q 6 Mos	
Baseline Documentation																				
Informed Consent	X																			
Physical Exam		X[2]					X			X	X	X	X	X	X	X		X		X
BRAF mutation status[3]	X																			
Laboratory Studies																				
LDH		X					X			X	X	X	X	X	X	X	X	X		X[4]
CBC and serum chemistry		X	X	X	X	X	X			X		X		X		X		X		X
Urinalysis		X	X	X	X	X	X			X		X		X		X		X		X
Pregnancy test																				X
ECG																				X
ANA/ESR	X[5]									X		X		X		X		X		
Tumor Assessments																				
Recurrence Assessment	X[6]									X		X		X		X		X		
Dosing																				
Seviprotimut-L		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Other Clinical Assessments																				
Survival Follow-up Contact																			X	
Autoimmune Phenomena[7]	X[8]									X		X		X		X				
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[9]			
Concomitant Medications		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[10]	X

Note: Visit windows are ± 3 days for Weeks 2, 4, 6, and 8; and ± 7 days for subsequent visits.
[1] At time of recurrence or study completion for subjects without recurrence
[2] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[3] BRAF tumor mutation V600E status must be either known at Screening or a tumor tissue (fresh or archived sample) must be available for testing during the Study.
[4] For subjects who have not had recurrent disease
[5] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[6] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[7] Include eye exam (by an ophthalmologist) and skin exam for vitiligo and rashes thereafter.
[8] If not performed within 30 days prior to planned first dose under Protocol 103A-301OL
[9] Adverse events collected through 30 days after last dose.
[10] New cancer treatments only