INVESTIGATOR'S BROCHURE

Seviprotimut-L (formerly POL-103A; human polyvalent melanoma shed antigens vaccine, Alum adjuvanted)

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Indication:	Treatment of patients with resected melanoma, American Joint Committee on Cancer (AJCC) stages IIB, IIC, or III, who have not received prior adjuvant therapy
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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALT	Alanine transaminase
API	Active pharmaceutical ingredient
AST	Aspartate transaminase
AU	Arbitrary units
BSA	Bovine serum albumin
CT	Computed tomography
AST	Aspartate transaminase
DFS	Disease-free survival
DNA	Deoxyribonucleic acid
DTH	Delayed-type hypersensitivity
ELISA	Enzyme-linked immunosorbent assay
Elispot	Enzyme-linked immunosorbent spot
FDA	Food and Drug Administration
GLP	Good Laboratory Practices
GM-CSF	Granulocyte macrophage colony stimulating factor
HLA	Human leukocyte antigen
ID	Intradermal
IL-2	Interleukin-2
MAGE	Melanoma-associated antigen gene
MART-1	Melanoma-associated antigen recognized by T-cells 1
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed effect model repeat measurement
MSDS	Material safety data sheet
NCI-CTCAE	NCI-Common terminology criteria for adverse events
NOAEL	No-observed-adverse-effect level
OLE	Open-label extension
polyvalent-q	Formulation containing antigens from 4 cell lines (3 human and 1 hamster)
polyvalent-t	Formulation containing antigens from 3 human cell lines
RFS	Recurrence-free survival
RNA	Ribonulceic acid
SAE	Serious adverse event
TCR	Tissue cross-reactivity
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
US	United States

2 Summary

Many patients with successfully resected stage IIB, IIC, or III melanoma relapse after surgery. New therapies are needed for these high-risk patients with melanoma since the only treatment approved for these patients by the United States (US) Food and Drug Administration (FDA) and other international regulatory agencies has limited effectiveness and frequent toxicity.

Seviprotimut-L (formerly POL-103A) is an investigational, polyvalent melanoma cancer 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 (polyvalence) is believed to be important to maximize the induction of tumor-protective immune responses and to reduce a tumor cell's ability to escape the immune response.

The toxicology program of seviprotimut-L has comprised 5 studies. In immunogenicity studies in mice and rats, seviprotimut-L generated anti-seviprotimut-L antibodies after once a week dosing for 4 weeks. Tissue cross-reactivity (TCR) assay development studies led the Study Director to conclude that use of mouse or rat serum containing anti-seviprotimut-L antibodies as the test article for evaluating the TCR profiles in mouse, rat, and human tissues would not be possible.

A 3-month, Good Laboratory Practice (GLP)-compliant toxicology and immunogenicity study on seviprotimut-L was performed in the Brown Norway rat. The results showed no apparent, or very limited, signs of toxicity related to seviprotimut-L over the dose range evaluated. The anti-seviprotimut-L antibody results suggest that the male and female rats in each seviprotimut-L dose group were exposed to the test article and the exposure increased with increasing dose. Based on these findings, the no-observed-adverse-effect-level (NOAEL) for seviprotimut-L in the Brown Norway rat was 0.5 mg/kg/dose.

Results are available from Part A of an ongoing multicenter, double-blind, placebo-controlled, adaptive Phase 3 trial of seviprotimut-L polyvalent melanoma vaccine in post-resection melanoma patients with a high risk of recurrence (protocol 103A-301). A total of 157 subjects have been treated in Part A: 52, 52, and 53 in the seviprotimut-L 40 µg, 100 µg, and placebo treatment arms, respectively. The most frequent treatment-related treatment-emergent adverse events (TEAEs) have been fatigue (23%, 23%, and 26% of subjects with 40 µg, 100 µg, and placebo, respectively) and local reactions at the site of injection, including injection site erythema (21%, 29%, and 32%), injection site urticaria (12%, 14%, and 9%), injection site reaction (4%, 15%, and 6%), and injection site pruritus (10%, 12%, and 8%). Most of these reactions were Grade 1 (mild). Among the 26 subjects treated with placebo who are subsequently being treated with 40 µg in an open-label extension, fatigue has been reported for 19%, injection site erythema for 23%, injection site pain for 15%, and injection site pruritus for 12%; injection site reaction has not been reported. No deaths have been reported that were considered to be related to study drug. Excluding basal cell carcinomas, squamous cell carcinomas, and new malignant melanomas, which are no longer considered to be treatment-emergent serious adverse events (TESAEs) because they are part of the natural course of the disease under study, 17 subjects have experienced TESAEs. The

only TESAEs considered to be treatment-related by the investigator have been diverticulitis and gastroenteritis in the same subject in the 100 µg arm; the Sponsor and Medical Monitor considered these events to be unrelated. In addition to a subject who died due to myocardial infarction and a subject who died in his sleep due to unknown causes, 6 subjects in Part A have discontinued treatment due to TEAEs or TESAEs: injection site reaction (40 µg), skin lesion (100 µg), malignant melanoma (100 µg), metastatic brain cancer (100 µg), small cell lung cancer (placebo), and lymphadenopathy (placebo).

To date, 217 subjects have been treated in Part B of Protocol 103A-301, in which subjects are randomized in a 2:1 ratio to the 40 µg dose of seviprotimut-L or placebo, respectively. Enrollment is ongoing and treatment is blinded but no new safety signals have been observed.

Western blot results from 134 subjects in Part A were analyzed by analysis of variance using Mixed Model Repeated Measures (MMRM) methodology to test for a vaccine effect (bioactivity). 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 (treatment arm, baseline vs Week 10, and molecular weight bin) p-value of 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.

Supportive data are available from prior studies of shed polyvalent antigen vaccine formulations similar to the formulation of the seviprotimut-L vaccine combined with various adjuvants, which enrolled approximately 661 subjects who were treated for up to 5 years at antigen doses of 40 µg per treatment. Two basic formulations were tested, combined with various adjuvants. The original prototype vaccine was a formulation containing antigens from 4 melanoma cell lines (1 hamster and 3 human), referred to as the "prototype" or "polyvalent-q". Another formulation with just the 3 human cell lines ("polyvalent-t") was developed, which is very similar to the seviprotimut-L vaccine currently under development. Of the 661 subjects exposed to one of these vaccines, 42 received a vaccine similar to the current formulation of seviprotimut-L (3 melanoma cell lines plus alum adjuvant, in study 89-38, unpublished). An additional 56 subjects received the similar polyvalent-t vaccine with an adjuvant of liposomal IL-2 (study 96-15), and 30 subjects received the polyvalent-t vaccine with other (or unknown) adjuvants (studies 82-11 and 95-02). These subjects were treated without significant toxicity and the results demonstrated preliminary evidence of efficacy.

In a double-blind, placebo-controlled trial of a prototype of the vaccine (with 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 ($p = 0.03$). In another randomized study comparing the polyvalent-t vaccine

with the prototype and a group of subjects who received an inactive form of the vaccine, the polyvalent-t arm had a recurrence-free survival hazard ratio (compared to inactive vaccine) of 0.41. In addition, the trivalent vaccine was superior to the prototype vaccine.

Safety data are available from 5 prior clinical studies in which 260 subjects received the prototype polyvalent-q vaccine and 56 subjects received the polyvalent-t vaccine. The most frequent vaccine-related adverse events (AEs) observed in those studies were local reactions at the site of injection, including itching (4% of subjects), blistering (4%), swelling (3%), and tenderness (3%). These reactions resolved within several days. There was no ulceration or scarring of injection sites. One death was reported on-study due to disease progression. Eleven subjects experienced serious adverse events (SAEs). Eleven subjects discontinued treatment due to AEs (other than disease progression) or death, including the death reported on-study and 3 subjects who discontinued due to vaccine reactions.

3 Introduction

Polynoma is developing seviprotimut-L vaccine for the treatment of melanoma. Three unique melanoma cell lines have been developed over the last 20 years from cancer cells taken from human melanoma tumors. These melanoma cells rapidly release or "shed" numerous antigens from their external surface. The tumor-associated antigens are collected and partially purified to produce the melanoma cancer vaccine. The vaccine contains a number of melanoma tumor-associated antigens, not all of which are known. By using antigens from multiple tumors (cell lines), seviprotimut-L vaccine is "polyvalent" to increase the likelihood of an antigen being present that will stimulate effective anti-tumor responses and that some of the antigens will be present on the tumor being treated (Bystryn, 1998).

After injection into the patient, the antigens stimulate both anti-melanoma antibody and peptide-specific CD8+ T-cell responses. The vaccine is not patient-specific in that it does not require the patient's own tumor to make the vaccine and it can be used to treat all patients regardless of their genetic background.

Polyvalence is believed to be important because the tumor antigens that can stimulate immune responses that can prolong survival are unknown. To be effective, the immune responses that are induced must be directed against antigens present on the patient's own tumor. These antigens can vary between patients and within a patient during the progression of melanoma. It is believed that the greater the number of antigens in the vaccine, the greater will be the chances that the vaccine will contain the antigens relevant for a patient's tumor. Polyvalent vaccines may also more readily circumvent human leukocyte antigen (HLA)-dependent and HLA-independent heterogeneity in the ability of patients to develop T-cell mediated immune responses to individual tumor antigens.

In the ongoing Phase 3 clinical trial 103A-301, the seviprotimut-L vaccine is administered in subjects with resected (surgically removed) stage IIB, IIC, or III melanoma that has a high probability of recurrence and a poor prognosis.

Vaccines made from whole tumor cells or their lysate and vaccines made from tumor DNA, RNA, or genetically modified tumor cells contain numerous antigens. However, the bulk of the material in these vaccines consists of nuclear and cytoplasmic material (whole cell material) that is irrelevant, dilutes the concentration of relevant antigens, and/or may contain material that is detrimental or interferes with the action of the vaccine, thereby increasing its toxicity. The seviprotimut-L vaccine is partially purified, being enriched in soluble shed antigens expressed on the external surface of melanoma cells, to exclude the bulk of unrelated cellular material that is present in the cytoplasm or nucleus of cells. Purifying the vaccine and removing unnecessary (e.g., whole cell) material results in a better-tolerated and safer vaccine.

4 Physical, Chemical, and Pharmaceutical Properties and Formulation

Seviprotimut-L is a polyvalent suspension melanoma cancer vaccine that contains multiple melanoma antigens shed from 3 human melanoma cell lines (SFHM2, SFHM4, and SFHM8) as the active pharmaceutical ingredient (API). The Drug Product is a nominal 0.8 mL suspension containing 0.05 mg/mL or 0.125 mg/mL API with 1 mg/mL aluminum in aluminum hydroxide suspensions in 4 mM phosphate-buffered saline and 0.9% NaCl, at pH 6.8. The Drug Product is packaged in Type I glass vials with Teflon-coated bromobutyl stoppers and is stored at 2° to 8°C (refrigerated) until use. The vaccine is used as is and requires no reconstitution after it is warmed to room temperature.

For vaccine production the material shed into serum-free culture medium by the cells is collected, pooled, concentrated, treated with non-ionic detergent (NP-40) to break up aggregated antigens, and ultracentrifuged to remove particulate matter. The supernatant is filter sterilized, adjusted to the appropriate protein concentration, and bound to alum as an adjuvant. Seviprotimut-L is thus partially purified, being made of soluble shed antigens, to exclude the bulk of unrelated cellular material that is present in the cytoplasm or nucleus of cells.

In ongoing Protocol 103A-301, the nominal dose of 40 µg (in Parts A and B) could be administered as 24 to 56 µg and the nominal dose of 100 µg (in Part A) could be administered as 72 to 160 µg due to potential manufacturing run variation.

5 Nonclinical Studies

5.1 Nonclinical Pharmacology

In a study conducted in BALB/c mice (Johnston and Bystryn, 2005), a human melanoma vaccine was shown to induce antibody responses in mice that varied considerably from animal to animal but that were much stronger when the vaccine was administered with an adjuvant (alum) than when administered without adjuvant. BALB/c mice (5/group) were immunized with a xenogeneic human polyvalent melanoma vaccine used previously in Phase 2 clinical trials in over 600 subjects. The vaccine for this mouse study was admixed with alum by mixing equal volumes of vaccine and a 1:4 dilution of Alhydrogel 2% in sterile saline to provide 20 µg (about 1000 µg/kg for a 20-gram mouse) of vaccine and 500 µg of alum in a final volume of 0.2 mL per vaccine dose. In some mouse experiments, the same dose of vaccine (20 µg in a final volume of 0.2 mL of saline) was administered without alum. Mice were dosed 4 times a week by subcutaneous injection into the abdominal region, switching sides weekly to minimize local reactions. Blood was collected from the retroorbital sinus plexus prior to immunization and at 2, 4, and 6 weeks after immunization had begun. Antibody responses were measured by western blot. IgG antibody responses to the melanoma vaccine components with alum as adjuvant were detectable within 2 weeks after dose initiation but were much stronger (i.e., resulted in denser bands on western blot gels) at 4 and 6 weeks. The IgG antibody responses to the melanoma vaccine alone (without alum) were substantially less at 4 and 6 weeks, indicating the vaccine was more immunogenic when co-administered with an adjuvant in this animal model. When the pooled sera from mice administered vaccine plus adjuvant were further analyzed by western blot, a complex pattern of vaccine-induced antibody responses was detected. When individual sera from identically immunized mice (vaccine plus adjuvant) were assayed by western immunoblot, most mice developed antibody responses to 1 or more of a distinct set of antigens in the vaccine. Antibody responses varied widely between mice, both in the intensity of antibody produced and in the pattern of antigens recognized from animal to animal. Although immunodominant antigens that produced antibody responses in most mice were present, no single antigen induced antibody responses in all mice.

5.2 Toxicology

The nonclinical safety program for the seviprotimut-L vaccine comprises immunogenicity studies in rat and mouse, tissue cross-reactivity (TCR) assay development studies using mouse and rat serum known to contain anti-POL-103A antibodies, and a 3-month GLP-compliant toxicology and immunogenicity study in the Brown Norway rat.

5.2.1 Repeat-Dose Toxicity Study

The primary objectives of this study were to determine the toxicology and immunogenicity profiles of seviprotimut-L in the Brown Norway rat, a pigmented rat strain selected because seviprotimut-L is being developed to treat patients with malignant melanoma. During this 3-month, GLP-compliant toxicology and immunogenicity study, male and female rats were dosed with seviprotimut-L or control intradermally (ID) once every 2 weeks (on Days 1, 14, 28, 42, 56, 70, 84, and 98). On each dosing day, the test (formulated seviprotimut-L) and

control vehicle (formulation without seviprotimut-L) articles were administered using up to 6 injection sites (Days 1, 14, 28, and 42) or up to 8 injection sites (Days 56, 70, 84, and 98) with approximately 0.1 mL injected per site. The dose levels of seviprotimut-L evaluated were 0 (control), 0.1, 0.25, and 0.5 mg/kg/dose in Groups 1, 2, 3, and 4, respectively. Each dose group contained 20 rats/sex/group with 5/sex/group (interim animals) sacrificed on Day 29, 10/sex/group (main study animals) sacrificed on Day 99, and 5/sex/group (recovery animals) sacrificed on Day 126. For dosing days 1, 14, 28, and 42, the seviprotimut-L formulation (Batch No. 10083A) was designated Melanoma Vaccines in Alum, 0.2 mg/mL in vehicle (20 mg/mL alum suspension in 0.9% NaCl) and 1.1 mL per vial. For dosing days 56, 70, 84, and 98, the seviprotimut-L formulation (Lot No. TC2941) was designated Melanoma Vaccine 0.125 mg/mL in Aluminum Hydroxide gel (1 mg/mL aluminum), 0.8 mL per vial; this seviprotimut-L formulation is the same as that proposed for the Phase 3 clinical trial in subjects with resected melanoma (protocol 103A-301). Because the 2 seviprotimut-L formulations contain the same level of aluminum, the sponsor considers that the change in the seviprotimut-L formulation during this toxicology study had no apparent effect on being able to characterize the toxicology and immunogenicity profiles of seviprotimut-L in rats. The lower concentration of seviprotimut-L in the later dosing formulation required an increase from 6 injection sites/day (total injection volume per day of 2.5 mL/kg) to 8 injection sites/day (total injection volume per day of 4 mL/kg) for the control and high-dose group animals.

During this study, mortality and moribundity checks were made twice daily; cage side clinical observations were made daily from Day 1 to Day 126; detailed clinical observations, dermal scores, body weights, and food consumption were performed weekly on Days 1, 8, 15, 22, 28, 35, 42, 49, 56, 63, 70, 77, 84, 91, 98, 105, 112, 119, and 125; and ophthalmic examinations were performed prior to dose initiation, prior to the interim sacrifice, and prior to main study sacrifice. Various hematology, coagulation, clinical chemistry, and urinalysis parameters were determined for each rat in each dose group on Days 29, 99, and 126. Blood (for serum) samples for immunogenicity analyses were collected from each rat in each dose group on Days 29 (interim animals), 99 (main study animals), and 126 (recovery animals). The serum samples were analyzed for anti-seviprotimut-L antibodies using a slightly modified method 313240R (see Pharmacokinetics: Method of Analysis). No terminal procedures were conducted on animals sacrificed on Day 29 (interim). Terminal procedures for main study animals (Day 99) and recovery animals (Day 126) consisted of necropsy, tissue collection (including the injection sites), and organ weights. Histology and histopathological evaluations were conducted on all tissues from main study control and high-dose animals and on all gross lesions observed during necropsy in low and mid-dose animals. Histology and histopathological evaluations in recovery animals were conducted on all tissues with gross lesions in main study animals.

No rat administered seviprotimut-L died during the course of this study. A single (Group 1) female rat was found dead on Day 99. Clinical observation findings were limited to the injection sites (generally focal eschar) that were more frequent in rats administered POL-103A (all dose levels) than in control rats. Also noted were dose-related increases in open lesions, scabbing, and hair loss in the scapular area and away from the injection sites. Several recovery rats appeared to have some scabbing remaining including at the scapular

area. While a few statistical differences in body weights and food consumption were noted for rats in the seviprotimut-L dose groups compared to control rats, these findings were sporadic in nature (sometimes increased and sometimes decreased) and none appeared to be toxicologically relevant. While several statistical differences were found (sometimes increases, sometimes decreases, and with the majority within 5% of those in control rats or numerically small), no apparent test article-related changes were noted in any of the hematology parameters measured in interim, main study, or recovery group rats. With the exception noted below, no apparent test article-related changes were noted in any of the clinical chemistry parameters measured in interim, main study, or recovery rats. Like hematology, several statistical differences (sometimes increases, sometimes decreases, and generally within 5% of those in control rats) were noted for some clinical chemistry parameters. One Group 3 male rat on Day 99 had substantially higher ALT and AST values compared to other rats in this and other dose groups. This rat had normal ALT and AST values on Day 29. Since no gross lesions were noted in the liver of this male rat at necropsy on Day 99, no histopathology evaluations were conducted on this Group 3 male rat. Since this finding was isolated to a single male rat in the mid-dose group, the Study Director considered that this observation was incidental and not related to seviprotimut-L administration. No apparent test article-related changes were noted in any of the measured urinalysis parameters in the main study or recovery rats. Ophthalmic examinations revealed no apparent adverse effects in rats administered seviprotimut-L when compared to the findings in control rats.

Serum samples from male and female rats in each dose group on Days 29, 99, and 126 were screened, and if necessary confirmed and titrated, for the presence of anti-seviprotimut-L antibodies. Prior to the initiation of dosing, no anti-seviprotimut-L antibodies were detected in any serum sample. With the exceptions noted below, no anti-POL-130A antibodies were detected in any of the serum samples collected from Group 1 (control) animals. One female control rat had a positive antibody response on Day 99 but this rat had been incorrectly dosed and thus cannot be included in the control group. In serum collected on Day 126, another female control rat had a minimal antibody response (considerably lower than that present in animals dosed with seviprotimut-L). All serum samples collected from male and female rats in Groups 2, 3, and 4 had anti-seviprotimut-L antibodies on Days 29, 99, and 126. Table 1 summarizes the average anti-seviprotimut-L antibody titration results on each evaluation day for rats in each seviprotimut-L dose group.

Table 1 Anti-Seviprotimut-L Antibody Results from Repeat-dose Toxicity Study in the Brown Norway Rat

Rats	N	Collection Day	Average Anti-seviprotimut-L Antibody Titration Results					
			Group 2 (0.125 mg/kg)		Group 3 (0.25 mg/kg)		Group 4 (0.50 mg/kg)	
			Average	SD	Average	SD	Average	SD
Total	10	Day 29	1090	843	1980	766	2820	1320
Male	5		1150	922	2050	701	2560	1570
Female	5		1020	859	1920	905	3070	1140
Total	20	Day 99	14000	11100	20900	34300	26400	21600
Male	10		9470	6390	8960	5010	17900	10000
Female	10		18400	13300	32800	46200	34800	27000
Total	10	Day 126	5500	3520	16100	14500	16400	9890
Male	5		6660	3440	11800	16400	12300	4580
Female	5		4350	3580	20500	12500	20500	12500

Results generated using slightly modified method 313240R.

N = number of rats in each dose group, SD = standard deviation

These summary results suggest that the formation of anti-seviprotimut-L antibodies increased with increasing seviprotimut-L dose during the dosing period (from Day 29 to Day 99 – main termination) and then (as expected) decreased during the recovery period (Day 126 – recovery termination). The results also suggest a possible gender effect with female rats in each dose group generating more anti-seviprotimut-L antibodies, particularly on Day 99 with the effect still present after the recovery period on Day 126, compared male rats for the same dose group. As these anti-seviprotimut-L antibody results appear to correlate with the seviprotimut-L dose administered, the data also suggests that rats were exposed to increasing amounts of seviprotimut-L over the evaluated dose range.

While statistical decreases in absolute and relative lung weights were noted for Group 2 and Group 3 male rats, this finding was considered not likely to be test article-related because the observation was not dose-related and did not appear in Group 4 male rats. Other statistically significant changes in organ weights were sporadic and were not considered to be test article-related. No statistical differences were noted for absolute and relative organ weights in recovery animals. Other than the lesions at the injection sites (and scapular sites), necropsy evaluations of the main study rats revealed no other test article-related findings. Many apparent background findings in Brown Norway rats were observed and included consistent, slightly dilated kidney pelvis in the majority of rats in all dose groups. The necropsy findings in recovery rats were similar to those observed in main study rats.

Histopathological findings in main study rats included vehicle-related macroscopic and microscopic changes at the injection site skin and skin adjacent to the injection site with many of the changes still present following the recovery period. Microscopic changes

considered vehicle-related included granulomatous inflammation, foreign material, ulceration/erosion, epithelial hyperplasia, subacute inflammation, and serocellular crust. The epithelial hyperplasia, subacute inflammation, and serocellular crust were secondary to the ulceration/erosion. Macroscopic correlates to these findings included scabs and raised areas. Most Group 1 (control) and Group 4 (0.5 mg/kg/dose) rats had granulomatous inflammation in the lung, which is an expected normal background change in Brown Norway rats. Whether the vehicle could have contributed to this change is unclear. Similarly a few Group 1 and Group 4 female rats had granulomatous inflammation in the liver; the relationship to the vehicle administration is unclear. Pathological investigation failed to identify the cause of death of the single Group 1 female rat that died on Day 99.

In conclusion, the results generated during this 3-month toxicology and immunogenicity study on seviprotimut-L in Brown Norway rats produced no apparent, or very limited, signs of toxicity related to seviprotimut-L over the dose range evaluated. The anti-seviprotimut-L antibody results suggest that the male and female rats in each seviprotimut-L dose group were exposed to the test article and the exposure increased with increasing dose. Based on these findings, the no-observed-adverse-effect-level (NOAEL) for seviprotimut-L in the Brown Norway rat was 0.5 mg/kg/dose, which has a human equivalent dose of 0.08 mg/kg/dose or 80 µg/kg/dose. The highest dose of seviprotimut-L in the proposed Phase 3 clinical trial, 100 µg, is about 1.43 µg/kg for a 70-kg human and over 50 times lower than the NOAEL dose in rats. Thus, based on the toxicological findings in the rat, the safety margin for seviprotimut-L is considered to be at least 50.

5.2.2 Immunogenicity Studies

Generation of Anti-seviprotimut-L Antibodies During a 4-Week Intradermal Administration of seviprotimut-L in Mice (Study OZS00004)

The primary objective of this study was to determine if anti-seviprotimut-L antibodies were generated in C57/BL6 male and female mice after ID administration of seviprotimut-L at 1.0 mg/kg once a week for 4 weeks (Days 1, 7, 14, and 21). Mice (5/sex/group) were assigned to Group 1 or 2. Group 1 mice were administered placebo (20 mg/mL alum) at 5 mL/kg/dose and Group 2 mice were administered seviprotimut-L in vehicle (20 mg/mL alum) at 5 mL/kg/dose and with a seviprotimut-L concentration of 0.2 mg/mL for a dose of 1.0 mg/kg/mouse on each dosing day. The ID dose was divided between 2 injection sites (about 0.05 to 0.1 mL/per site; a 20-gram mice received a total dose volume of 0.1 mL administered ID to 2 test sites). All mice survived until scheduled euthanasia on Day 35 (study termination). Clinical evaluations were made on Day -1 and daily on Days 1 to 35.

Findings were limited to irritation at the ID injection sites in both Group 1 and Group 2 mice and included raised areas and scabbing as well as hair loss at the injection sites. In addition, 2 male mice administered seviprotimut-L exhibited some sporadic instances of rough coat during the study. Body weights were measured on Days -1, 1, 7, 14, 21, 28, and 35 and results showed that all mice gained weight during the study. The mean body weights of Group 2 mice were within 2.2% of the body weights of Group 1 mice at study termination. Serum samples collected from each mouse on Days 20 and 35 were analyzed for anti-seviprotimut-L antibodies using a screening enzyme-linked-immunosorbent assay (ELISA)-

based method. This screening ELISA detected anti-seviprotimut-L antibodies in serum collected from all Group 2 mice on Days 20 and 35 with the level of anti-seviprotimut-L antibodies increasing from Day 20 to Day 35. The absorbance value ranges (at a dilution of 1:100) at A_{450} nm were 0.556 to 1.584 AU on Day 20 and 1.820 to 3.735 AU on Day 35 for Group 2 mouse serum samples, while the Group 1 control mouse serum samples ranged in absorbance values from 0.135 to 0.516 AU on Day 20 and 0.128 to 0.934 AU on Day 35.

Based on the results of this study in male and female C57/BL6 mice, seviprotimut-L at 1.0 mg/kg administered ID (using multiple injection sites) once a week for 4 weeks produced scabbing at the injection sites but was otherwise well tolerated. Antibody analysis indicated the presence of anti-seviprotimut-L antibodies in serum samples collected from male and female mice on Day 20 and the level of anti-seviprotimut-L antibodies increased by Day 35.

Generation of Anti-Seviprotimut-L Antibodies During a 4-Week Intradermal Administration of Seviprotimut-L in Rats (Study OZS00006)

The primary objective of this study was to determine if anti-seviprotimut-L antibodies were generated in Brown Norway male and female rats after ID administration of seviprotimut-L at 0.5 mg/kg once a week for 4 weeks (Days 1, 7, 14, and 21). Rats (3/sex/group) were assigned to Group 1 or 2. Group 1 rats were administered placebo (20 mg/mL alum) at 2.5 mL/kg/dose and Group 2 rats were administered seviprotimut-L in vehicle (20 mg/mL alum) at 2.5 mL/kg/dose and with a seviprotimut-L concentration of 0.2 mg/mL for a dose of 0.5 mg/kg/rat on each dosing day. The ID dose was divided among 6 sites (about 0.1 mL/site; a 250-gram rat received a total dose of 0.6125 mL administered ID to 6 test sites). All rats survived until scheduled euthanasia on Day 35 (study termination). Clinical evaluations were made on Day -1 and daily on Days 1 to 35.

seviprotimut-L-related clinical observation findings were limited to irritation at the ID injection sites in both Group 1 and Group 2 rats and included raised areas and scabbing in male and female rats and reddened areas and open lesions in male rats only. Body weights were measured at Days -1, 1, 7, 14, 21, 28, and 35 and some instances of body weight loss were noted for both Group 1 and 2 male rats during the interval from Day 14 to Day 21, which included the Day 20 blood collection period. However, the mean body weight for Group 2 male rats was lower (-9%) compared to that for the control male rats after blood collection on Day 35 (study termination). Mean body weight for the Group 2 female rats was similar to that for control female rats throughout the study. Serum samples collected from each rat on Days 20 and 35 were analyzed for anti-seviprotimut-L antibodies using a screening ELISA-based method. This screening ELISA detected anti-seviprotimut-L antibodies in serum collected from all Group 2 rats on Days 20 and 35 with the level of anti-seviprotimut-L antibodies increasing from Day 20 to Day 35. The absorbance value ranges (at a dilution of 1:100) at A_{450} nm were 1.564 to 2.750 AU on Day 20 and 2.498 to 3.487 AU on Day 35 for Group 2 rat serum samples, while the Group 1 control rat serum samples ranged in absorbance values from 0.114 to 0.264 AU on Day 20 and 0.125 to 0.291 AU on Day 35.

Based on the results of this study in male and female Brown Norway rats, seviprotimut-L at 0.5 mg/kg administered ID (using multiple injection sites) once a week for 4 weeks produced scabbing at the injection sites and open lesions in male rats but was otherwise well tolerated. Antibody analysis indicated the presence of anti-seviprotimut-L antibodies in serum samples collected from male and female rats on Day 20 and the level of anti-seviprotimut-L antibodies increased by Day 35.

5.2.3 Tissue Cross-Reactivity Assay Development Studies

Tissue Cross-Reactivity of Mouse Anti-Seviprotimut-L Antibodies with Human and Mouse Tissues In Vitro (Study OZS00012)

The primary objective of this study was to determine the tissue binding or TCR profiles (specificity and extent) of mouse anti-seviprotimut-L antibodies to a standard set of normal human and mouse tissues. The serum containing mouse anti-seviprotimut-L antibodies and control mouse serum were obtained from Study OZS00004, in which mice were dosed weekly for 4 weeks with 1 mg/kg/dose of seviprotimut-L (Group 2) or placebo (Group 1). On Day 35, serum samples were collected from each Group 1 and Group 2 mouse, pooled by group, and used as the test and control articles, respectively, for the definition and characterization of an assay that could be used to generate the tissue binding profiles of mouse anti-seviprotimut-L antibodies to normal human and mouse tissues.

To establish the desired assay for generating the tissue binding profiles of mouse anti-seviprotimut-L antibodies, a series of method development experiments was conducted to define and characterize a sensitive and reproducible immunohistochemical assay. The test and control articles, respectively, for these experiments were the pooled Group 2 mouse serum (shown to contain anti-seviprotimut-L antibodies) and the pooled Group 1 mouse serum from Study OZS00004. The positive control was seviprotimut-L and the negative control was bovine serum albumin (BSA). Other controls were sections of melanoma cell line samples (HM4, HM8, and SFHM2).

Initial experiments showed that mouse serum containing anti-seviprotimut-L antibodies (the test article) had specific binding to the positive control and melanoma cell line samples but not to the negative control (BSA). Control mouse serum (the control article) was shown not to bind to the positive or negative controls or to any of the melanoma cell lines. When the assay was used on selected human tissues (cerebral cortex, colon, kidney, and liver), relatively high levels of staining were observed in many cell types of the human tissues examined with both the test and control articles. No dilutions of the test and control articles were identified that could sufficiently decrease the widespread staining observed in the evaluated human tissues while still maintaining a sufficient signal for the positive control sample. Based on these results, the Study Director considered that both Group 1 and Group 2 mice might be generating antibodies capable of binding to antigens common on human tissues and this nonspecific binding would limit the ability to obtain acceptable tissue binding profiles for mouse anti-seviprotimut-L antibodies for human tissues.

An additional experiment was conducted to evaluate the binding of the test article to selected mouse tissues (cerebral cortex, colon, kidney, and liver) using a biotinylated anti-mouse IgG

secondary antibody precomplex method. However, formation of the complex resulted in the elimination of any specific staining on the positive control sample or on the human melanoma cell lines, thus negating the ability to assess binding to mouse tissues. Another experiment attempted to assess the binding of the test article to selected rat tissues. The results, in the opinion of the Study Director, showed a similar widespread, nonspecific staining for both the test and control articles to various cell types in most evaluated tissues as had been observed for human tissues.

Based on the results from these method development experiments, the Study Director concluded that an assay could not be defined and characterized for determining the TCR profiles of mouse anti-seviprotimut-L antibodies in various human, mouse, or rat tissues.

Tissue Cross-Reactivity of Rat Anti-Seviprotimut-L Antiserum with Human and Rat Tissues In Vitro (Study OZS00013)

The primary objective of this study was to determine the tissue binding or TCR profiles (specificity and extent) of rat anti-seviprotimut-L antibodies to a standard set of normal human and rat tissues. The serum containing rat anti-seviprotimut-L antibodies and control rat serum were obtained from Study OZS0006, in which rats were dosed weekly for 4 weeks with 0.5 mg/kg/dose of seviprotimut-L (Group 2) or placebo (Group 1). On Day 35, serum samples were collected from each Group 1 and Group 2 rat, pooled by group, and used as the test and control articles, respectively, for the definition and characterization of an assay that could be used to generate the tissue binding profiles of rat anti-seviprotimut-L antibodies to normal human and rat tissues.

To establish the desired assay for generating the tissue binding profiles of rat anti-seviprotimut-L antibodies, a series of method development experiments was conducted to define and characterize a sensitive and reproducible immunohistochemical assay. The test and control articles, respectively, for these experiments were the pooled Group 2 rat serum (shown to contain anti-seviprotimut-L antibodies) and the pooled Group 1 rat serum from Study OZS00006. The positive control was seviprotimut-L and the negative control was BSA. Other controls were sections of melanoma cell line samples (HM4, HM8, and SFHM2).

Initial experiments showed that rat serum containing anti-seviprotimut-L antibodies (the test article) had specific binding to the positive control and melanoma cell line samples but not to the negative control (BSA). Control rat serum (the control article) was shown not to bind to positive or negative controls or to any of the melanoma cell lines. When the assay was used on selected human tissues (cerebral cortex, colon, kidney, and liver), relatively high levels of staining were observed in most cell types of the human tissues examined with both the test and control articles. No dilutions of the test and control articles were identified that could sufficiently decrease the widespread staining observed in the evaluated human tissues while still maintaining a sufficient signal for the positive control sample. Based on these results, the Study Director considered that both Group 1 and Group 2 rats might be generating antibodies capable of binding to antigens common on human tissues, thus limiting the ability

to obtain acceptable tissue binding profiles for rat anti-seviprotimut-L antibodies for human tissues.

Additional experiments were conducted to evaluate the binding to the test article to selected rat tissues (cerebral cortex, colon, kidney, and liver) using a biotinylated anti-rat IgG secondary antibody precomplex method (biotinylated rabbit anti-rat IgG antibody and biotinylated goat anti-rat IgG antibody). With both secondary antibody precomplex reagents, however, formation of the complex resulted in the elimination of any specific staining on the positive control sample or to the human melanoma cell lines, thus negating the ability to assess binding to rat tissues. Another experiment attempted to assess the binding of the test article to selected mouse tissues. The results, in the opinion of the Study Director, showed a similar widespread, nonspecific staining for both the test and control articles to various cell types in most evaluated tissues as had been observed for human tissues.

Based on the results from these method development experiments, the Study Director concluded that an assay could not be developed for determining the TCR profiles of rat anti-seviprotimut-L antibodies in various human, rat, or mouse tissues.

5.3 Nonclinical Reference

Johnston D, Bystryn J-C. Heterogeneous antibody response to polyvalent melanoma vaccines in syngeneic mice. Cancer Immunol Immunother 2005;54:345–350.

6 Effects in Humans

A multicenter, double-blind, placebo-controlled, adaptive Phase 3 trial of seviprotimut-L polyvalent melanoma vaccine is ongoing in post-resection melanoma patients with a high risk of recurrence (protocol 103A-301). The study has 2 parts. Part A is designed to determine the safety profile and immunogenicity of seviprotimut-L 40 µg and 100 µg versus placebo and to determine the dose to be used in Part B of the study. Part B allows an evaluation of efficacy using the dose of seviprotimut-L selected from Part A. The objective of the efficacy evaluation is to assess whether subjects randomized to the active arm have superior recurrence-free survival and overall survival compared with subjects randomized to the placebo arm. The safety of seviprotimut-L will also be assessed and samples will be collected for the potential correlation of exploratory biomarkers with clinical response. The safety results from Part A (up to 14 January 2015) and the bioactivity results (March 2014 analysis) are summarized in Section 6.2.1.

Previously, clinical trials in the United States had been conducted with shed polyvalent antigen vaccine formulations similar to the formulation of the seviprotimut-L vaccine combined with various adjuvants. The total number of subjects enrolled across those protocols was approximately 661, with some subjects participating in more than 1 protocol. Approximately 533 subjects were exposed to a prototype formulation (polyvalent-q) containing shed antigens from 4 melanoma cell lines (3 human and 1 hamster) and approximately 128 subjects were exposed to a formulation (polyvalent-t) containing antigens from the 3 human cell lines. Several candidate adjuvants and formulations were investigated; 42 subjects were administered polyvalent-t with alum as an adjuvant (in study 89-38), which is a formulation similar to that of seviprotimut-L being used in the ongoing clinical trial. An additional 56 subjects received the similar polyvalent-t vaccine with an adjuvant of liposomal IL-2 (study 96-15), and 30 subjects received the polyvalent-t vaccine with other (or unknown) adjuvants (studies 82-11 and 95-02).

Supportive safety information is available from 5 of those early clinical studies and is summarized in Section 6.2. Preliminary results on biological activity and efficacy are available from additional studies and are summarized in Section 6.3. Although none of the previously conducted studies used the formulation of seviprotimut-L that is being evaluated in the ongoing protocol 103A-301, the formulations were similar and therefore these safety and efficacy data are considered relevant.

6.1 Pharmacokinetics and Product Metabolism in Humans

Specific information on the absorption, distribution and excretion of the vaccine following an intradermal dose is not known.

While the disposition of the antigens in seviprotimut-L from the site of injection has not been determined, the following possibilities are considered the most likely mechanisms for clearing the seviprotimut-L antigens from the body. First, the bulk of the antigens in seviprotimut-L deposited at the site of injection will most likely be conveyed to regional nodes where these antigens will be ingested by antigen-presenting cells, macrophages, and

other phagocytic cells. Within the lymph nodes digested antigen is presented to CD8+ T cells in the context of HLA Class I molecules and other co-stimulatory molecules. Antigen presented thusly is expected to stimulate CD8+ T-cell responses (one of the mechanisms of pharmacological activity proposed for seviprotimut-L). Second, seviprotimut-L administered with adjuvant is expected to precipitate at the site of injection and this material is projected to be involved in the generation of anti-seviprotimut-L antibodies that will bind with the antigens expressed on the melanoma cells, resulting in cell death (a second proposed mechanism of pharmacological activity for seviprotimut-L). This precipitated material will have limited solubility and thus the material will most likely be cleared from the site of injection by macrophages and other phagocytic cells.

6.2 Safety

6.2.1 Protocol 103A-301 Part A Results

In Part A, subjects 18 to 75 years old with surgically resected stage IIB, IIC, or III melanoma and no prior melanoma treatment other than surgery or regional irradiation were randomized in a 1:1:1 ratio to seviprotimut-L 40 µg, 100 µg, or placebo. Seviprotimut-L or placebo is administered intradermally as 4 injections (0.2 mL per injection) into the volar surface of forearms and into the anterior upper thighs. Doses are administered every 2 weeks (after initial dose) x 4 (Weeks 0, 2, 4, 6, and 8), then monthly x 4 (Months 3, 4, 5, and 6), and then every 3 months through Month 24 (Months 9, 12, 15, 18, 21, and 24). Each subject continues to be treated with study medication until one of the following occurs: development of recurrent disease that does not meet the criteria for continued dosing, death, subject withdrawal or early termination, or study termination.

A total of 157 subjects were randomized and have been treated in Part A: 52, 52, and 53 in the seviprotimut-L 40 µg, 100 µg, and placebo treatment arms, respectively. The demographic characteristics of the 3 treatment arms are similar. Overall, the mean age is 56.2 years (range 18 to 75), the majority of subjects are male (104/157, 66%), and all subjects are white. At baseline the subjects were about evenly divided among stage IIB/IIC (31%), IIIA (33%), and IIIB/IIIC (35%), and the most common tumor locations were the extremities (43%) and the trunk (39%).

Twenty-six of the subjects from the placebo group in Part A were enrolled in an open-label extension (OLE) in which they receive seviprotimut-L 40 µg. The mean age of these subjects is 55.3 years (range 18 to 72) and 15 (58%) are male. In the following tables experience in the OLE is described as another treatment group.

6.2.1.1 Treatment-Emergent Adverse Events

Most subjects in Part A (85% to 100% in each treatment group) have experienced treatment-emergent adverse events (TEAEs). The TEAEs show a similar safety profile across the treatment groups (Table 2). TEAEs reported for more than 5% of subjects in any treatment group regardless of causality and those considered by the investigators to be possibly or probably related to study drug, or for which the relationship assessment was missing, are

summarized in Table 3 and Table 4, respectively. Because Part A is still ongoing, the results presented here are based on a cutoff date of 16 January 2016 and are not final.

The most frequently reported TEAEs have been local reactions at the site of injection, most of which were considered to be treatment-related. The most frequent local events (reported as treatment-related for subjects treated with 40 µg, 100 µg, placebo, and 40 µg OLE, respectively) have been injection site erythema (21%, 29%, 32%, and 23%), injection site urticaria (12%, 14%, 9%, and 12%), injection site pruritus (10%, 12%, 8%, and 12%), and injection site reaction (4%, 15%, 6%, and 0%). Most of these reactions were Grade 1 (mild).

Other than injection site events, the TEAE reported most frequently was fatigue, which has been reported for 35%, 25%, 30%, and 19% of subjects in the 40 µg, 100 µg, placebo, and 40 µg OLE groups, respectively, and was considered to be treatment-related for 23%, 23%, 26%, and 19%, respectively.

The most notable difference in TEAEs among the treatment groups is the higher proportion of subjects with injection site reaction in the 100 µg group (15%) compared with the 40 µg, placebo, and 40 µg OLE groups (4%, 6%, and 0%, respectively).

The majority of TEAEs have been mild or moderate (Grade 1 or Grade 2). There have been two Grade 5 (fatal) TEAEs, which are described in the following section, and two Grade 4 (life-threatening) events, pulmonary embolism in a subject treated with 40 µg and anemia in a subject treated with 40 µg in the OLE. None of these 4 events was considered to be related to study treatment.

Table 2 Overview of Treatment-Emergent Adverse Events in POL103A-301, Part A and Part A Open-label Extension

	Number (%) of Subjects			
	Part A			Part A OLE
Number of Subjects with	Seviprotimut-L 40 µg (N = 52)	Seviprotimut-L 100 µg (N =52)	Placebo (N = 53)	Seviprotimut-L 40 µg (N = 26)
At least 1 treatment-emergent adverse event (TEAE)[a]	49 (94.2)	52 (100)	51 (96.2)	22 (84.6)
At least 1 treatment-emergent serious adverse event (TESAE)	8 (15.4)	13 (25.0)	7 (13.2)	2 (7.7)
TEAEs by grade[b]				
Grade 1	14 (26.9)	20 (38.5)	20 (37.7)	11 (42.3)
Grade 2	26 (50.0)	22 (42.3)	21 (39.6)	8 (30.8)
Grade 3	7 (13.5)	9 (17.3)	9 (17.0)	2 (7.7)
Grade 4	1 (1.9)	0	0	1 (3.8)
Grade 5	1 (1.9)	1 (1.9)	0	0
TEAEs by relationship[c]				
Unlikely	12 (23.1)	10 (19.2)	7 (13.2)	4 (15.4)
Possible	10 (19.2)	12 (23.1)	15 (28.3)	5 (19.2)
Probable	27 (51.9)	30 (57.7)	29 (54.7)	13 (50.0)
At least 1 treatment-related TEAE[d]	37 (71.2)	42 (80.8)	44 (83.0)	18 (69.2)
At least 1 treatment-related TESAE	1 (1.9)	1 (1.9)	0	
At least 1 TEAE leading to discontinuation of study drug	1 (1.9)	4 (7.7)	2 (3.8)	0
Death due to TEAE by relationship to study drug				
Unlikely	1 (1.9)	1 (1.9)	0	0

Note: The data cutoff for this table was 16 January 2016 (Source Table 14.3.1.1).

[a] A treatment-emergent adverse event (TEAE) is an adverse event with onset on or after the first administration of study drug.

[b] Grading according to the NCI CTCAE Version 4. A subject was counted only once in the most severe category when multiple TEAEs were reported.

[c] A subject was counted only once in the most related category when multiple TEAEs were reported.

[d] A treatment-related TEAE is a TEAE assessed by the investigator as possibly or probably related to study drug.

Table 3 Treatment-Emergent Adverse Events in Protocol 103A-301, Part A and Part A Open-label Extension Reported for More than 5% of Subjects in Any Treatment Group

	Number (%) of Subjects			
	Part A			Part A OLE
System Organ Class Preferred Term	**Seviprotimut-L 40 µg (N = 52)**	**Seviprotimut-L 100 µg (N =52)**	**Placebo (N = 53)**	**Seviprotimut-L 40 µg (N = 26)**
Any treatment-emergent adverse event	49 (94.2)	52 (100)	51 (96.2)	22 (84.6)
Blood and Lymphatic System Disorders				
Lymphadenopathy	3 (5.8)	1 (1.9)	2 (3.8)	0
Eye Disorders				
Cataract	4 (7.7)	1 (1.9)	1 (1.9)	0
Gastrointestinal Disorders				
Constipation	1 (1.9)	1 (1.9)	3 (5.7)	0
Diarrhea	7 (13.5)	7 (13.5)	2 (3.8)	1 (3.8)
Nausea	7 (13.5)	5 (9.6)	5 (9.4)	3 (11.5)
Vomiting	3 (5.8)	2 (3.8)	1 (1.9)	1 (3.8)
General Disorders and Administration Site Conditions				
Fatigue	18 (34.6)	13 (25.0)	16 (30.2)	5 (19.2)
Influenza like illness	4 (7.7)	1 (1.9)	2 (3.8)	0
Injection site erythema	11 (21.2)	15 (28.8)	17 (32.1)	6 (23.1)
Injection site induration	3 (5.8)	3 (5.8)	2 (3.8)	1 (3.8)
Injection site nodule	1 (1.9)	4 (7.7)	5 (9.4)	1 (3.8)
Injection site pain	1 (1.9)	4 (7.7)	3 (5.7)	4 (15.4)
Injection site pruritus	5 (9.6)	6 (11.5)	4 (7.5)	3 (11.5)
Injection site reaction	2 (3.8)	8 (15.4)	3 (5.7)	0
Injection site swelling	2 (3.8)	3 (5.8)	3 (5.7)	2 (7.7)
Injection site urticaria	6 (11.5)	7 (13.5)	5 (9.4)	3 (11.5)
Edema peripheral	10 (19.2)	3 (5.8)	2 (3.8)	0
Pain	3 (5.8)	0	1 (1.9)	0
Infections and Infestations				
Bronchitis	0	1 (1.9)	4 (7.5)	1 (3.8)
Cellulitis	1 (1.9)	3 (5.8)	0	0
Diverticulitis	0	1 (1.9)	0	2 (7.7)
Influenza	0	3 (5.8)	0	0
Nasopharyngitis	2 (3.8)	2 (3.8)	3 (5.7)	4 (15.4)
Sinusitis	3 (5.8)	2 (3.8)	3 (5.7)	3 (11.5)
Upper respiratory tract infection	5 (9.6)	6 (11.5)	1 (1.9)	2 (7.7)
Urinary tract infection	1 (1.9)	2 (3.8)	5 (9.4)	0
Investigations				
Aspartate aminotransferase increased	2 (3.8)	3 (5.8)	1 (1.9)	0
Metabolism and Nutrition Disorders				

System Organ Class Preferred Term	Number (%) of Subjects			
	Part A			Part A OLE
	Seviprotimut-L 40 µg (N = 52)	Seviprotimut-L 100 µg (N =52)	Placebo (N = 53)	Seviprotimut-L 40 µg (N = 26)
Decreased appetite	4 (7.7)	0	0	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	11 (21.2)	4 (7.7)	2 (3.8)	2 (7.7)
Back pain	4 (7.7)	2 (3.8)	3 (5.7)	0
Muscle spasms	0	4 (7.7)	0	0
Myalgia	3 (5.8)	4 (7.7)	4 (7.5)	1 (3.8)
Pain in extremity	3 (5.8)	8 (15.4)	1 (1.9)	0
Neoplasms Benign, Malignant and Unspecified				
Basal cell carcinoma	4 (7.7)	6 (11.5)	2 (3.8)	1 (3.8)
Lipoma	0	3 (5.8)	0	0
Melanocytic nevus	4 (7.7)	5 (9.6)	3 (5.7)	0
Seborrheic keratosis	1 (1.9)	2 (3.8)	3 (5.7)	1 (3.8)
Squamous cell carcinoma	4 (7.7)	0	3 (5.7)	0
Nervous System Disorders				
Dizziness	5 (9.6)	7 (13.5)	1 (1.9)	0
Headache	7 (13.5)	7 (13.5)	4 (7.5)	1 (3.8)
Psychiatric Disorders				
Insomnia	2 (3.8)	3 (5.8)	0	0
Renal and Urinary Disorders				
Hematuria	3 (5.8)	0	1 (1.9)	0
Respiratory, Thoracic and Mediastinal Disorders				
Cough	6 (11.5)	3 (5.8)	0	2 (7.7)
Dyspnea	3 (5.8)	1 (1.9)	0	0
Nasal congestion	2 (3.8)	2 (2.8)	2 (3.8)	2 (7.7)
Skin and Subcutaneous Disorders				
Actinic keratosis	3 (5.8)	2 (3.8)	4 (7.5)	1 (3.8)
Dry skin	1 (1.9)	4 (7.7)	1 (1.9)	0
Erythema	1 (1.9)	6 (11.5)	2 (3.8)	0
Pruritus	5 (9.6)	5 (9.6)	4 (7.5)	0
Rash	7 (13.5)	4 (7.7)	3 (5.7)	0
Urticaria	3 (5.8)	1 (1.9)	0	0
Vascular Disorders				
Lymphedema	4 (7.7)	2 (3.8)	4 (7.5)	0

Note: The data cutoff for this table was 16 January 2016 (Source Table 14.3.1.2).
AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA version 14.1)

Table 4 Treatment-Related Treatment-Emergent Adverse Events in Protocol 103A-301, Part A and Part A Open-label Extension Reported for More than 5% of Subjects in Any Treatment Group

	Number (%) of Subjects			
	Part A			Part A OLE
System Organ Class Preferred Term	Seviprotimut-L 40 µg (N = 52)	Seviprotimut-L 100 µg (N =52)	Placebo (N = 53)	Seviprotimut-L 40 µg (N = 26)
Gastrointestinal Disorders				
Diarrhea	3 (5.8)	3 (5.8)	1 (1.9)	0
Nausea	3 (5.8)	2 (3.8)	2 (3.8)	2 (7.7)
General Disorders and Administration Site Conditions				
Fatigue	12 (23.1)	12 (23.1)	14 (26.4)	5 (19.2)
Influenza like illness	3 (5.8)	1 (1.9)	2 (3.8)	0
Injection site erythema	11 (21.2)	15 (28.8)	17 (32.1)	6 (23.1)
Injection site induration	3 (5.8)	3 (5.8)	2 (3.8)	1 (3.8)
Injection site nodule	1 (1.9)	4 (7.7)	5 (9.4)	1 (3.8)
Injection site pain	1 (1.9)	4 (7.7)	3 (5.7)	4 (15.4)
Injection site pruritus	5 (9.6)	6 (11.5)	4 (7.5)	3 (11.5)
Injection site reaction	2 (3.8)	8 (15.4)	3 (5.7)	0
Injection site swelling	2 (3.8)	3 (5.8)	3 (5.7)	2 (7.7)
Injection site urticaria	6 (11.5)	7 (13.5)	5 (9.4)	3 (11.5)
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	6 (11.5)	3 (5.8)	0	0
Myalgia	0	3 (5.8)	3 (5.7)	1 (3.8)
Nervous System Disorders				
Headache	5 (9.6)	3 (5.8)	3 (5.7)	0
Skin and Subcutaneous Disorders				
Dry skin	0	3 (5.8)	0	0
Erythema	0	5 (9.6)	1 (1.9)	0
Pruritus	4 (7.7)	4 (7.7)	3 (5.7)	0
Rash	3 (5.8)	2 (3.8)	1 (1.9)	0

Note: The data cutoff for this table was 16 January 2016 (Source Table 14.3.1.3).
A treatment-emergent adverse event (TEAE) is an adverse event with onset on or after the first administration of study drug.. TEAEs with missing relationship are included.

6.2.1.2 Deaths, Treatment-Emergent Serious Adverse Events, and Discontinuations

No deaths have been reported during Part A of the study (including the OLE) that were considered to be related to study drug. The 2 deaths that have occurred were myocardial infarction in a subject treated with 40 µg, and a death due to an unknown cause in a subject treated with 100 µg. Thirty subjects have experienced treatment-emergent serious adverse events (TESAEs), most of which were basal cell carcinoma, squamous cell carcinoma, or new malignant melanoma. Consistent with the current version of Protocol 103A-301, basal

cell and squamous cell carcinomas and new primary melanomas are no longer considered TESAEs because they are part of the natural course of the disease under study. Excluding those events, 17 subjects have experienced TESAEs (Table 5) and the only TESAEs considered by the investigator to be treatment-related gastroenteritis and diverticulitis, both of which occurred in the same subject in the 100 µg group. The Sponsor and Medical Monitor considered these events to be unrelated to study drug.

The subject who experienced gastroenteritis and diverticulitis (Subject 063-0457) was a 70-year-old male who was admitted to the hospital 5 days after his 7th (Month 4) study treatment with vomiting and diarrhea over the previous 4 days. The event was subsequently identified as acute gastroenteritis. He was treated with intravenous fluids, Pepcid (famotidine), Reglan (metoclopramide), and Zofran (ondansetron). The symptoms resolved and the subject was discharged without complications. Three days after the subject had his 8th (Month 5) study treatment he developed lower abdominal pain, constipation, and flatulence and imaging supported a diagnosis of diverticulitis. The subject was hospitalized and treated with ciprofloxacin and metronidazole and the event resolved. The investigator assessed both the gastroenteritis and diverticulitis as severe in intensity and possibly or probably related to study treatment.

Table 5 Treatment-Emergent Serious Adverse Events in Protocol 103A-301, Part A and Part A Open-label Extension

Subject (Age/Sex)	Treatment	TESAE Preferred Term	Study Days[a]	Grade[b]	Relationship to Study Treatment	Outcome
060-1014 (60/M)	40 µg	Atrial fibrillation	176-177	3	Unlikely	Resolved
061-0985 (73/M)	40 µg	Pulmonary embolism	121-127	4	Unlikely	Resolved
063-0886 (48/M)	40 µg	Malignant neoplasm of spinal cord	148-154	3	Unlikely	Resolved
069-0993 (67/M)	40 µg	Myocardial infarction	438	5	Unlikely	Fatal
012-0917 (39/M)	100 µg	Pneumonia	399-403	2	Unlikely	Resolved
016-0560 (61/M)	100 µg	Pneumonia	715-718	3	Unlikely	Resolved
022-1070 (58/M)	100 µg	Angina pectoris	583-584	2	Unlikely	Resolved
029-0464 (49/F)	100 µg	Thyroid cancer	330-331	2	Unlikely	Resolved
061-1072 (47/M)	100 µg	Deep vein thrombosis	131-138	4	Unlikely	Resolved
		Renal failure acute	136-138	3	Unlikely	Resolved
		Cellulitis	213-224	2	Unlikely	Resolved
		Death	625	5	Unlikely	Fatal

Subject (Age/Sex)	Treatment	TESAE Preferred Term	Study Days[a]	Grade[b]	Relationship to Study Treatment	Outcome
063-0457 (68/M)	100 µg	Gastroenteritis	114-120	3	Possible	Resolved
		Diverticulitis	150-186	3	Probable	Resolved
068-0995 (73/F)	100 µg	Nervous system disorder[d]	23-25	1	Unlikely	Resolved
072-0705 (65/F)	100 µg	Subarachnoid hemorrhage	635-636	2	Unlikely	Resolved
019-1015 (54/F)	Placebo	Vertigo	473-475	3	Unlikely	Resolved
020-0577 (61/M)	Placebo	Small cell lung cancer stage unspecified[c]	541-ongoing	1	Unlikely	Not resolved
060-0413 (71/M)	Placebo	Urinary retention	263-264	3	Unlikely	Resolved
025-1020 (73/M)	40 µg OLE	Anemia	693-695	4	Unlikely	Resolved
069-0908 (61/F)	40 µg OLE	Diverticulitis	931-942	3	Unlikely	Resolved

Note: Because they are part of the natural course of the disease under study, and consistent with the current version of Protocol 103A 301, basal cell carcinomas, squamous cell carcinomas, and new primary melanomas are no longer considered TESAEs and are not included in this table.

[a] Start and stop dates reported for TESAE

[b] NCI-CTCAE Grade (1 = mild, 2 = moderate, 3 = severe, 4 = life-threatening, 5 = death)

[c] TESAE led to discontinuation of study treatment.

[d] The subject had prior medical history of similar symptoms; most likely etiology was documented as poor convergence due to Parkinson's disease with low dopamine dystonia.

In addition to the subjects who died, 6 subjects discontinued treatment due to TEAEs or TESAEs: injection site reaction (40 µg), skin lesion (100 µg), malignant melanoma (100 µg), metastatic brain cancer (100 µg), small cell lung cancer (placebo), and lymphadenopathy (placebo).

- Subject 069-1083 received 12 treatments with seviprotimut-L (40 µg) through 31 Dec 2014. At Day 92, the TEAE of injection site reaction was reported as mild. Study treatment was discontinued, no other action was taken, and the event resolved. The investigator considered the TEAE probably related to study treatment.
- Subject 024-0981 received 2 treatments with seviprotimut-L (100 µg) through Week 2. At Week 3, the subject had a lesion of the left groin that was due to disease recurrence. The TEAE of skin lesion was assessed as mild. Study treatment was discontinued, no other action was taken, and the event had not resolved. The investigator considered the TEAE unlikely related to study treatment.
- Subject 029-1000 received 6 treatments with seviprotimut-L (100 µg) through Month 3. At Month 3, the subject was diagnosed with a new primary malignant melanoma. The subject had chronic sun-damaged skin and it was likely that the

lesion had been developing for some time and just became clinically evident. The lesion was attributed to the factors that had predisposed the subject to the initial diagnosis. The malignant melanoma was assessed as serious and study treatment was discontinued. The subject had local excision by outpatient surgery and the TESAE was resolved. The investigator considered the TESAE unlikely related to study treatment.

- Subject 019-0941 received 14 doses/dosing visits with seviprotimut-L (100 μg) through 21 Jan 2015. At Day 695 it was reported that the subject had progressive disease with a metastatic brain mass on the right frontal lobe. The TEAE was considered mild and study treatment was discontinued. The subject twas treated with concomitant medication and the event resolved. The investigator considered the TEAE unlikely related to study treatment.
- Subject 020-0577 received 12 treatments with placebo through 21 Jan 2014 At Day 541 it was reported that the subject had small cell lung cancer, stage unspecified. This was previously unknown to the investigator. The cancer was assessed as serious and study treatment was discontinued. The TESAE was ongoing. The investigator considered the TESAE unlikely related to study treatment.
- Subject 058-0704 received 10 treatments with placebo through Month 9. At Month 9, the subject had lymphadenopathy of the right upper thigh that was diagnosed as melanoma recurrence and confirmed by biopsy. The TEAE of lymphadenopathy was considered severe. Study treatment was discontinued, no other action was taken, and the event had not resolved. The investigator considered the TEAE unlikely related to study treatment.

6.2.2 Protocol 103A-301 Part B Results

To date, 217 subjects have been treated with seviprotimut-L 40 μg or placebo in Part B. Because enrollment is ongoing and the treatment assignment is blinded, detailed safety information is not presented. The blinded safety profile, however, is similar to that observed in Part A. Three TEAEs have led to discontinuation of study treatment: macular rash, injection site swelling, and injection site pruritus. Four TESAEs have been reported: cellulitis, neoplasm of the cervix, gastroesophageal reflux disease, and deep vein thrombosis. The investigators considered these 4 events unlikely related to study treatment.

6.2.3 Previous Clinical Studies with Similar Formulations

Safety information is available from 5 previous studies (referred to here as "prior safety studies") that included 260 subjects who received the polyvalent-q vaccine and 56 subjects who received the polyvalent-t vaccine. The polyvalent-q vaccine contains shed antigens from 4 melanoma cell lines (the 3 human cell lines used to create seviprotimut-L and 1 hamster cell line) and the polyvalent-t vaccine contains only shed antigens from the 3 human cell lines that are the same as those in the current formulation of the seviprotimut-L vaccine. Experience with those formulations is considered to provide data relevant to the current seviprotimut-L formulation. The prior safety studies are identified in Table 6.

Table 6 Polynoma Prior Clinical Studies with Safety Information

ID	Description
92-35	
Title:	Phase 1/2 clinical trial of polyvalent melanoma antigen vaccine and IL-2 encapsulated into liposomes in subjects with disseminated malignant melanoma
Design:	Subjects with AJCC stage IV melanoma and limited metastatic disease were sequentially allocated to treatment with 40 μg of polyvalent-q vaccine encapsulated in liposomes together with 2 x 10^6 units interleukin-2 (IL-2), or 6 x 10^6 units IL-2. A group of subjects who had previously received vaccine with 5 x 10^5 units IL-2 served as a control group.
Exposure:	87 subjects to polyvalent-q vaccine
96-15	
Title:	Phase 2 clinical trial of polyvalent melanoma antigen vaccine encapsulated into pH-sensitive liposomes for subjects with stage 2b and 3 malignant melanoma
Design:	Subjects with AJCC stage IIb or III resected melanoma were randomized to 2 treatment cohorts that received 40 μg of either the polyvalent-q vaccine with mycoplasma adjuvant or the polyvalent-t vaccine without mycoplasma adjuvant. Within each cohort, separate groups of subjects received a fixed dose of the vaccine encapsulated into pH-insensitive liposomes constructed from 0.4, 2.0, 8.0, or 24 mg of lipid containing 5 x 10^5 units of IL-2. Vaccine was administered every 2 weeks for 4 weeks, then monthly for 3 months, then every 3 months for 6 months, then every 6 months for 5 years or until recurrence.
Exposure:	112 subjects, 56 to polyvalent-t vaccine and 56 to polyvalent-q vaccine
96-16	
Title:	Phase 1/2 trial of the effects of interferon-alfa on the expression of Class I and II alloantigens in vivo in humans
Design:	Subjects with recurrent, AJCC stage III or IV melanoma were randomized to 1 of 4 treatment groups that received 40 μg of shed antigens from the polyvalent-q vaccine encapsulated into 1 of 4 doses of pH-sensitive liposomes (0.4, 2.0 ,8.0, or 24 mg lipid/immunization) containing 2 x 10^5 units of IL-2. Subjects also received 1 million, 3 million, 5 million, or 10 million units of interferon alpha-2, 3 times per week during the study.
Exposure:	48 subjects to polyvalent-q vaccine
97-17	
Title:	Phase 1/2 clinical trial of a polyvalent melanoma vaccine in GM-CSF liposomes in stage III melanoma
Design:	Subjects with AJCC stage III melanoma were randomized to 1 of 4 treatment groups to receive 40 μg of the polyvalent-q vaccine formulated in liposomes containing 2.5 μg, 25 μg, or 250 μg of granulocyte, macrophage colony stimulating factor (GM-CSF).
Exposure:	28 subjects to polyvalent-q vaccine

ID	Description
98-37	
Title:	Phase 2 trial of the effects of interferon alfa-2b on the immunogenicity of a polyvalent melanoma antigen vaccine in subjects with stage III malignant melanoma
Design:	Subjects with AJCC stage IIIb, resected melanoma were randomized to 1 of 3 treatment groups to receive 40 µg of the polyvalent-q vaccine formulated in IL-2-containing liposomes in addition to 0, 10 million, or 15 million units of interferon alpha-2, 3 times per week for the duration of the study.
Exposure:	41 subjects to polyvalent-q vaccine

Note: Polyvalent-q vaccine contains shed antigen from 4 melanoma cell lines (3 human cell lines and 1 hamster cell line). Polyvalent-t vaccine contains shed antigens from the 3 human cell lines.

Subject disposition in these 5 studies is summarized in Table 7. Planned enrollment across these studies was 191 subjects. A total of 316 subjects received at least 1 dose of vaccine and 179 of those subjects discontinued treatment: 158 due to disease progression, 10 due to adverse events (AEs, including vaccine reactions), and 10 for other reasons (including non-compliance, subject elected to enroll in another study, lost to follow-up, and unknown). The single death on-study was due to disease progression that was not detected during study examinations. When the studies were terminated (unrelated to subject safety), 123 subjects were still receiving treatment.

Table 7 Subject Disposition in Prior Safety Studies

	Study					
Category	**92-35**	**96-15**	**96-16**	**97-17**	**98-37**	**Total**
Planned	20	80	32	27	32	191
Treated	87	112	48	28	41	316
Completed	6	0	7	0	1	14
On study[a]	10	67	6	11	29	123
Discontinued:	71	45	35	17	11	179
Disease progression	61	40	32	14	11	158
Adverse event	3	3	3	1	0	10
Death	0	1	0	0	0	1
Other[b]	7	1	0	2	0	10

[a] When the study was terminated

[b] Non-compliance, lost to follow-up, subject elected to enroll in another study, or unknown reason

6.2.3.1 Vaccine-Related Adverse Events

Vaccine-related AEs that were reported for more than 1 subject across the 5 studies are summarized in Table 8. These were generally injection site reactions, with itching, blistering, swelling, and soreness the 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.

Table 8 Vaccine-related Adverse Events Reported for More Than 1 Subject in 5 Prior Safety Studies

Adverse Event	Study					Total (N=316) N
	92-35 (N=87) N	96-15 (N=112) N	96-16 (N=48) N	97-17 (N=28) N	98-37 (N=41) N	
Injection Site						
Itching or pruritus	3[a]	5[a]		3	3	14 (4.4%)
Blister or blistering	3[a]	7	1		2	13 (4.1%)
Swelling		6[a]		3		9 (2.8%)
Soreness and/or tenderness		7		1		8 (2.5%)
Redness or erythema		3[a]	1	1		5 (1.6%)
Discomfort or irritation		1	1	1	1	4 (1.3%)
Pain		3		1		4 (1.3%)
Induration	1	2				3 (0.9%)
Rash		1[a]		1		2 (0.6%)
Sensitivity		2				2 (0.6%)
Skin reaction		2[a]				2 (0.6%)
Urticaria or hives		1			1	2 (0.6%)
Delayed-type Hypersensitivity (DTH) Site						
Blister	1	1				2 (0.6%)
Other						
Nausea	2	1				3 (0.9%)
Myalgia	2			1		3 (0.9%)
Headache		1		1	1	3 (0.9%)
Fatigue	1				1	2 (0.6%)
Muscle aches		1		1		2 (0.6%)
Acne		2				2 (0.6%)

[a] Includes 1 subject for whom it was not specified that the event was at the injection site

Three subjects discontinued the study due to vaccine reactions:

- Subject 461 (study 96-15) had headache and skin reaction after the 4th vaccination. The subject experienced muscle aches, a severe skin reaction accompanied by redness

and swelling, and minor itching with histological evidence of drug-induced hypersensitivity following the 11th vaccination and was discontinued.

- Subject 556 (study 96-15) experienced itching at injection site after the 4th vaccination. After the 7th vaccination, the subject had swelling of both forearms, erythema and severe skin reaction with itching and pain at the injection site, and difficulty swallowing and pruritus with urticaria starting 1 hour after the injection and lasting for 24 hours. After the 8th vaccination, the subject had itching, pain, swelling, and redness at the injection site, and nausea that lasted for 12 hours after the injection. The subject experienced severe erythema and swelling at all 3 injection sites after the 9th vaccination and was discontinued.
- Subject 630 (study 96-15) experienced redness and was hot to touch at the injection site after the 4th vaccination, itching at the injection site after the 5th vaccination, swelling and blistering at the injection site after the 7th vaccination, and blistering at the injection site and severe arm swelling following the 9th vaccination, after which the subject was discontinued.

Two subjects had their vaccine dose reduced due to vaccine reactions and remained on-study until the studies were terminated. Subject 624 (study 96-15) experienced induration at the injection site and received a total of 10 treatments. Subject 630 (study 96-15) experienced swelling at the injection site after the 2nd vaccination and severe pain at injection site and leg swelling after the 3rd vaccination. For the 4th through the 9th (last) vaccinations, the dose was reduced by one-half but the subject still experienced mild itching and burning after each vaccine administration.

6.2.3.2 Adverse Events Unrelated to Vaccine

Adverse events in the combined prior safety studies that were considered to be unrelated to the vaccine or adjuvant administration and not attributable to melanoma recurrence and that were reported for at least 1% of subjects are shown in Table 9.

Table 9 Adverse Events Unrelated to Vaccine, Adjuvant, or Melanoma Recurrence Reported for At Least 1% of Subjects in 5 Prior Safety Studies

	Study					
Adverse Event	**96-16 (N=48) N**	**97-17 (N=41) N**	**98-37 (N=28) N**	**96-15 (N=112) N**	**92-35 (N=87) N**	**Total (N=316) N**
Pain	1	2	1	5	-	9 (2.8%)
Asthenia	1	1	-	4	-	6 (1.9%)
Hernia	1	-	1	3	-	5 (1.6%)
Hyperglycemia	1	2	1	1	-	5 (1.6%)
Cardiomegaly	-	1	2	1	-	4 (1.3%)
Polycystic kidney	-	-	2	2	-	4 (1.3%)

Subjects in Studies 96-16 and 98-37 were scheduled to receive 3 doses of interferon-alpha-2 each week, administered intramuscularly, in addition to the vaccine. Adverse events that the Investigator attributed to the interferon were frequent but mild or moderate in most subjects. The most frequently reported AEs related to interferon were fatigue, malaise, myalgia, fever, nausea, arthralgias, and anorexia. Interferon was reduced in dose or discontinued in 19 subjects.

6.2.3.3 Deaths, Serious Adverse Experiences, and Discontinuations

One subject died on-study due to disease progression that was not detected during routine study examinations (described among the serious adverse events [SAEs] below).

Eleven SAEs occurred in these 5 studies, one of which was considered to be related to the vaccine:

- Subject 545 (study 97-17) received 8 injections of the vaccine containing GM-CSF without incident. Two hours after the ninth injection, the subject experienced arrhythmias and syncope and was hospitalized. On admission, the subject revealed that she had experienced a similar fainting episode 2 to 3 months previously. Cardiac arrhythmias are an expected side effect of GM-CSF treatment. The subject discontinued the study because of this event. This event was considered to be related to the vaccine. This subject subsequently died of disease progression.

The 10 SAEs considered to be unrelated to the vaccine were the following.

- Subject 261 (study 96-16) was hospitalized with abdominal pain and fever approximately 2 weeks after receiving a dose of the vaccine. A CT scan identified a large necrotic mass of nodes in the pelvis. The SAE resolved with intravenous antibiotic treatment. The subject discontinued the study due to disease progression and subsequently died from recurrent melanoma.

- Subject 371 (study 96-16) complained of angina during the study and was hospitalized to undergo an angiogram and cardiac catheterization. The angina resolved and the subject completed the study.

- Subject 491 (study 96-16) was hospitalized with seizures that were believed to be due to brain metastases approximately 2 weeks after receiving a dose of the vaccine. The subject discontinued the study and died 4 months later of progressive disease.

- Subject 496 (study 97-17), who had a history of degenerative spinal disease and cardiac abnormalities including a previous myocardial infarction, was hospitalized to undergo a spinal fusion procedure due to pseudarthrosis and cardiac catheterization due to worsening angina. The subject remained on-study until the study was terminated.

- Subject 498 (study 96-15) was hospitalized with abdominal pain and cramping approximately 4 months after the last vaccination and underwent a resection of an aortic aneurysm. The subject remained on study until the study was terminated.

- Subject 499 (study 96-15) was hospitalized approximately 6 weeks after the last vaccination for abdominal pain and nausea of unexplained origin that resolved spontaneously. The subject remained on-study until the study was terminated.

- Subject 561 (study 96-15) was hospitalized 2 months after the last vaccination for a partial nephrectomy of a benign neoplasm of the renal pelvis and remained on-study until the study was terminated.

- Subject 559 (study 96-15) died of progressive melanoma several months after the last vaccination while still on-study. Although subjects with disease progression were to be discontinued from the study, the recurrence was not detected until after the subject died.

- Subject 502 (study 92-35) was hospitalized after suffering a stroke. The subject discontinued the study because of this event.

- Subject 606 (study 92-35) was hospitalized with a broken hip approximately 1 month after starting the study. The subject discontinued the study because of this event.

Eleven subjects discontinued treatment due to AEs (other than disease progression) or death, including the death reported on-study and the 3 subjects with vaccine reactions mentioned in Section 6.2.3.1:

- Six subjects were discontinued for non-serious AEs unrelated to melanoma: diabetes complications (Subject 512 in study 96-16); interferon-related toxicity (Grade 1 fever, fatigue, malaise, anorexia, and myalgia; Grade 2 leukopenia for Subject 375 in study 96-16); mental illness (Subject 297 in study 92-35); and vaccine reactions (Subjects 461, 556, and 630 in study 96-15).

- Three subjects discontinued treatment due to SAEs unrelated to melanoma, as noted above: arrhythmia (Subject 545 in study 97-17), stroke (Subject 502 in study 92-35), and a broken hip (Subject 606 in study 92-35).

- Two subjects were discontinued for an AE or death believed to be related to melanoma complications that were not prospectively identified as disease progression: seizures as a result of metastatic disease (Subject 491 in study 96-16) and death (Subject 559 in study 96-15).

6.3 Efficacy

6.3.1 Protocol 103A-301 Part A Results

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 subjects 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 seviprotimut-L dose 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, 2 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 2-way interactions between these main effects plus the 3-way interaction of these main effects.

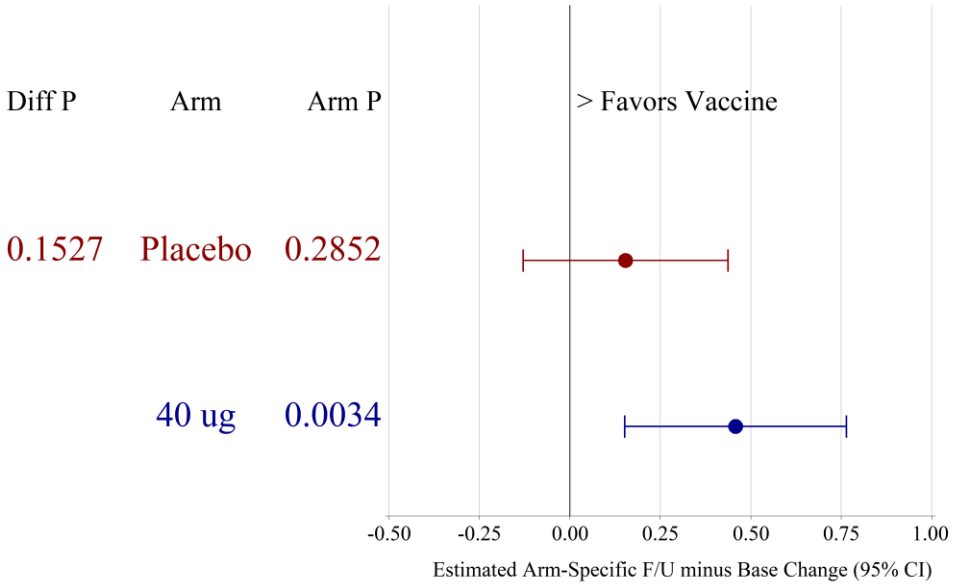
The main finding was that there is a vaccine effect. The band intensity increased on average in all 3 treatment arms with a statistically significant difference between placebo and seviprotimut-L 40 µg ($p = 0.0034$; Figure 1). The difference between placebo and the pooled vaccine arms was also statistically significant ($p = 0.0039$) while the difference between placebo and 100 µg was not statistically significant.

The vaccine effect is related to the molecular weights identified in the Western blots. The comparison between placebo and seviprotimut-L 40 µg for bin intensity change showed a statistically significant 3-way (treatment arm, baseline vs Week 10, and molecular weight bin) p-value of 0.0002 (Figure 2). Although the 3-way interaction was not statistically significant for the seviprotimut-L 100 µg arm, the similarity across doses and molecular weights strengthens the main finding of a true active vaccine effect.

An additional analysis was performed based on individual subject differences. The response for each subject was calculated based on the average percentage increase in intensity across the molecular weight bins in which the cohort results favored vaccine. The response for each

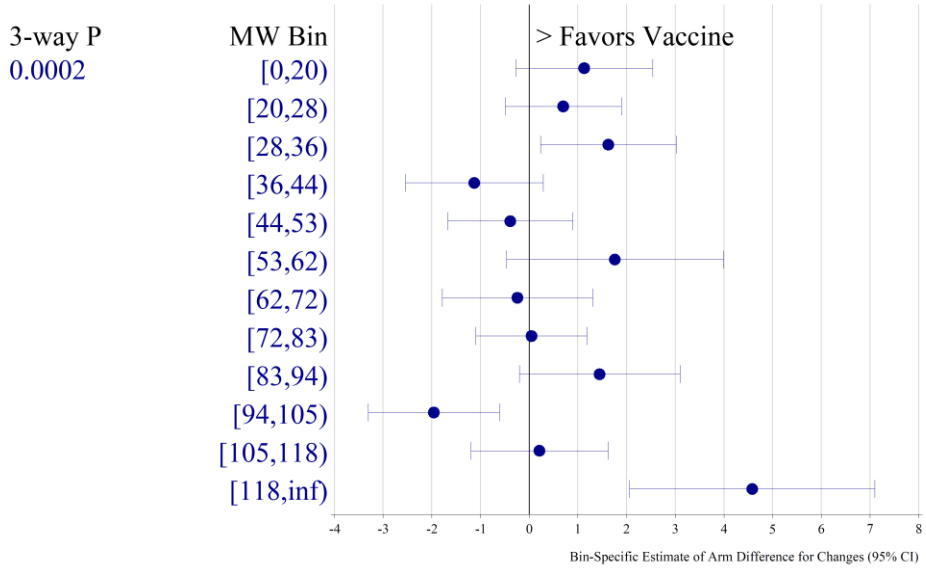
subject was computed for various thresholds in the average percentage increase: ≥ 0 (any increase), ≥ 5%, 10%, 15%, 20%, and 25%. Figure 3 shows the estimated differences between the 40 µg and placebo arms in the percentage of subjects responding over the range of immune response criteria. The one-sided 0.10 p-value level was met for all of the response criteria except ≥ 5%.

Figure 1 Band Intensity Increase from Week 0 to Week 10 (All 134 Subjects)



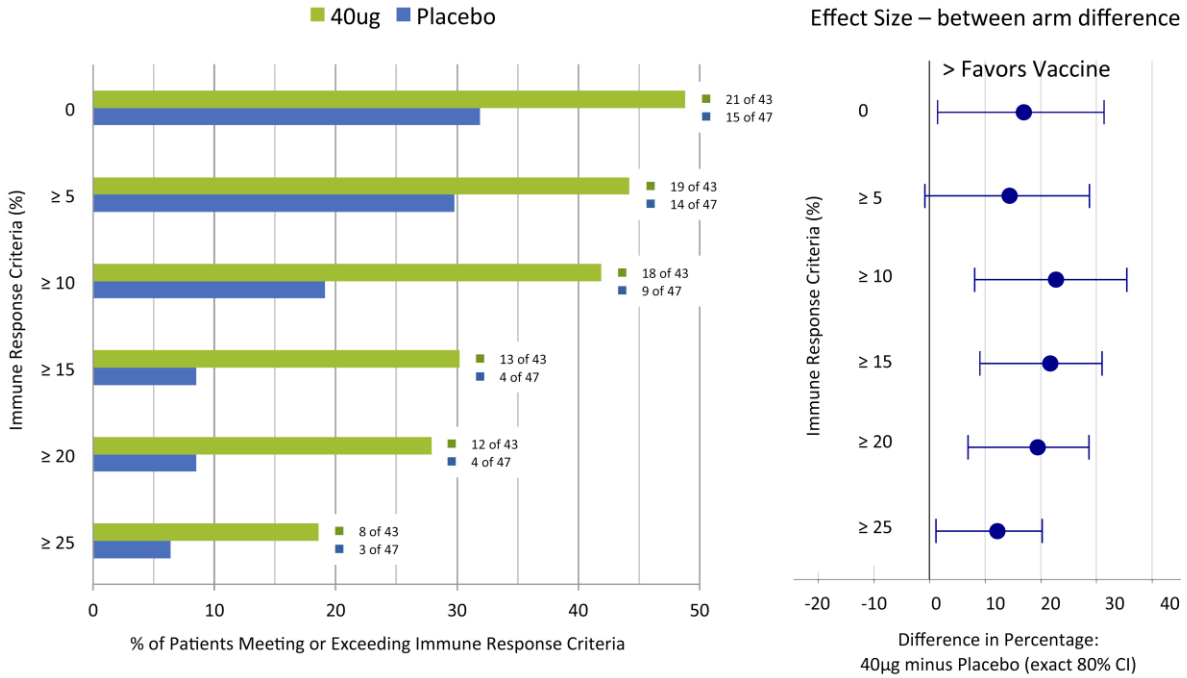
Results using the MMRM model on replicates where random effect = band within subject.
Transformation: ~sqrt = Box/Cox with Lambda = 1/2 & Shift = 1.

Figure 2 Molecular Weight Bin Intensity Change: 40 µg Compared to Placebo (All 134 Subjects)



Results using the MMRM model on replicates where random effect = band within subject.
Transformation: ~sqrt = Box/Cox with Lambda = 1/2 & Shift = 1.

Figure 3 Subject Responses: 40 µg Compared to Placebo for Molecular Weight Bins 1, 2, 3, 6, 9, and 12 Combined



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 (Bystryn et al, 2001a; Bystryn et al, 2001b; Reynolds et al, 1998; Reynolds et al, 2003).

6.3.2 Previous Clinical Studies with Similar Formulations

Results of prior studies on shed polyvalent antigen vaccines with formulations similar to that of seviprotimut-L, including the 5 studies described above for which safety information is available as well as additional studies for which safety information is not available, provide the following preliminary results suggestive of efficacy:

- The vaccine appears to stimulate antibody and CD8 T-lymphocyte responses against multiple melanoma-associated antigens in patients with a variety of different HLA phenotypes.

- Vaccine treatment appears to stimulate cellular immune responses that can recognize and infiltrate a patient's own melanoma tumors in vivo.

- Vaccine-induced anti-melanoma antibody and cellular immune responses appear to correlate with improved recurrence-free survival.

- Vaccine treatment appears to rapidly clear melanoma cells and melanoma antigens from the circulation and these changes appear to correlate with improved recurrence-free survival in some studies.

- Patients immunized with the vaccine appeared to have improved survival compared to controls in a double-blind, placebo-controlled trial in patients with resected stage III melanoma.

The main findings of studies regarding the biological activity and clinical efficacy of similar vaccine formulations are summarized briefly in Table 10. 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, by measuring the ability of vaccine treatment to clear melanoma cells and antigens from the circulation, by comparing recurrence-free survival to historical controls, and by conducting a small randomized, placebo-controlled, double-blind trial.

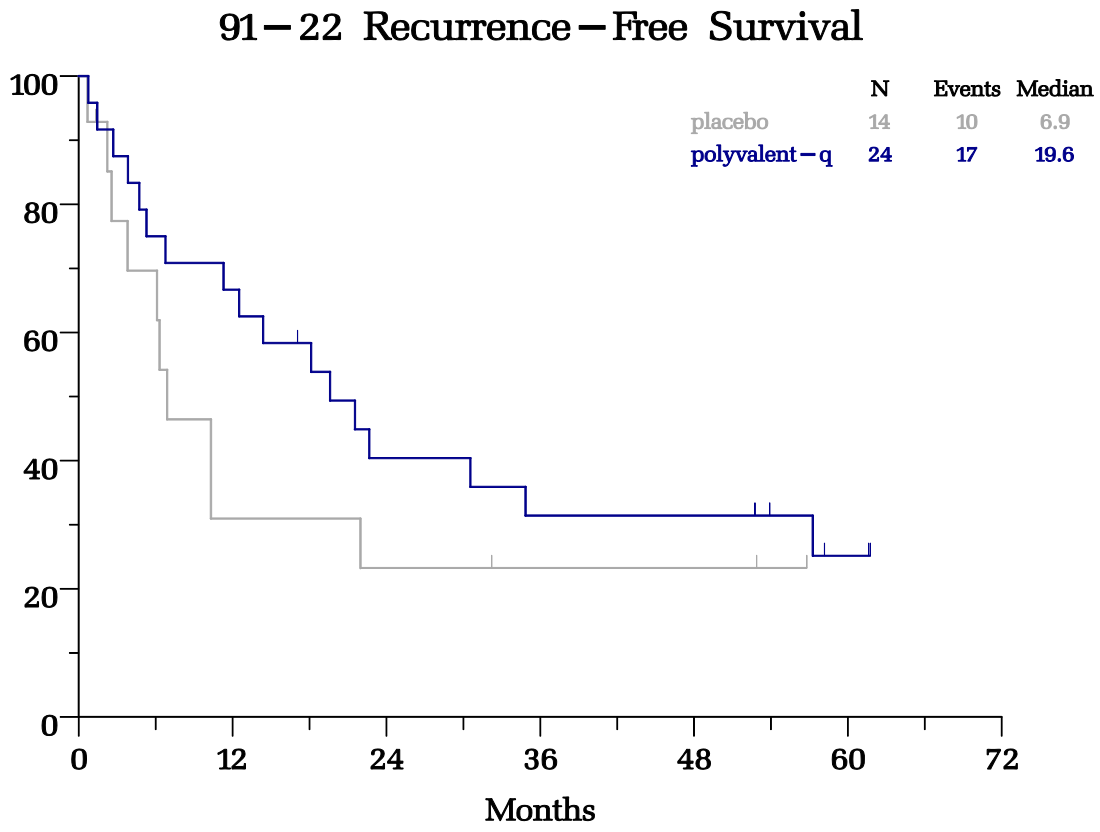
The first trial was a dose escalation study to examine the safety of escalating doses of the vaccine. Subsequently, the immunogenicity of different immunization schedules and adjuvants (alum) was examined. Most of the subsequent trials examined the ability of different adjuvants to potentiate the immunogenicity of the 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, such as the availability of serum specimens at required time points or HLA-A2 or A3 positivity for assays of CD8 responses, were sometimes used.

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 these are useful to measure the activity of different adjuvants that were being studied in these trials.

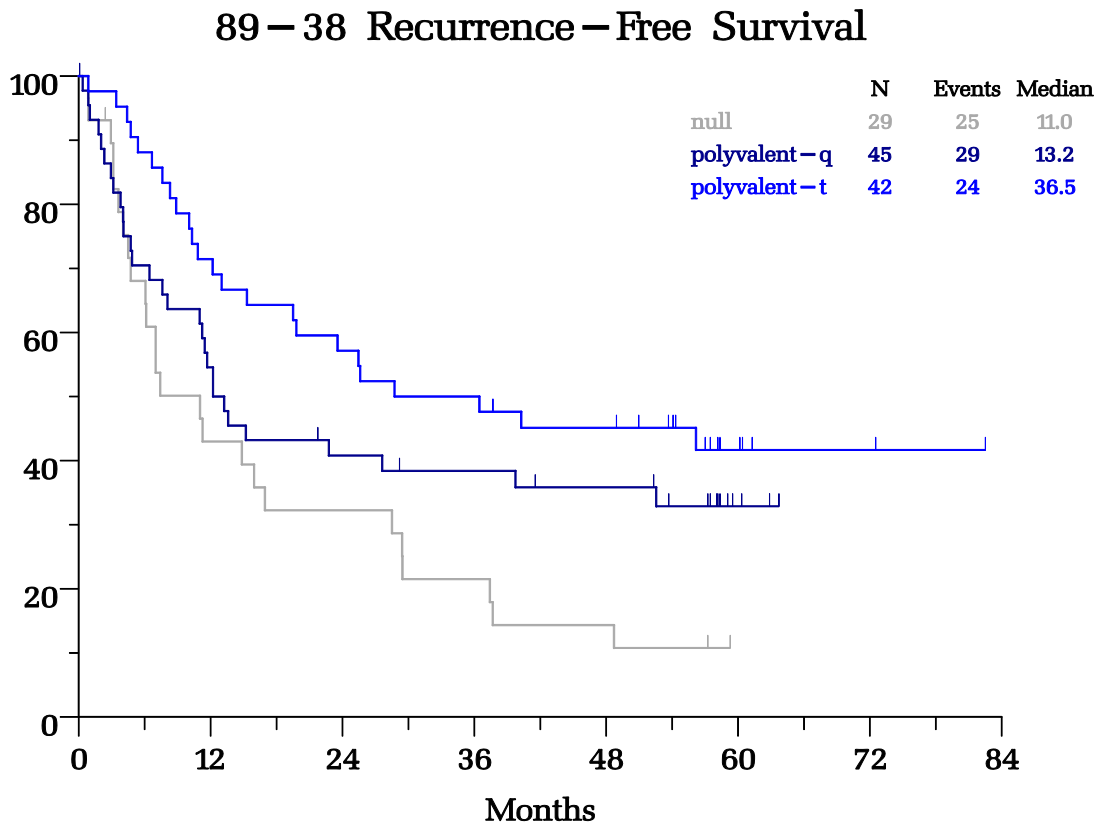
Clinical outcome data are available from two randomized controlled trials, 91-22 and 89-38. In 91-22, subjects with resected Stage IIIb-IIIc melanoma were randomized to receive either the prototype polyvalent-q vaccine (N=24) or placebo (N=14). Median recurrence-free survival (RFS) in the treated arm was 1.6 years, compared to 0.6 years in the placebo arm (Figure 4). The RFS hazard ratio estimate was 0.62, representing a 38% lower hazard rate for the vaccine (proportional hazard regression p= 0.03). Furthermore, the vaccine was shown to be immunogenic, stimulating both antibody and CD8+ responses to multiple antigens in 40-60% of subjects.

Figure 4 Recurrence-Free Survival Results from Study 91-22



In Study 89-38 (unpublished data on file at Polynoma), subjects with resected stages IIb to IV melanoma were treated with either polyvalent-t (n=42) or polyvalent-q (n=45) vaccine bound to alum as an adjuvant. Each subject was injected with 40 µg per dose intradermally into the extremities every 3 weeks x 4, monthly x 3, every 3 months x 2, and then every 6 months for 5 years or until disease progression. The results were compared to a third smaller group of subjects (n = 29) who received an inactive antigen preparation bound to alum (Null) and were immunized on the same schedule. By Kaplan-Meier analysis, subjects who received the polyvalent-t vaccine had the longest recurrence-free survival time with a median of 36.5 months versus 13.2 months for the polyvalent-q and 11.0 months for the Null vaccine. Hazard ratio estimates (and 95% confidence intervals) provide comparative effect measures: 0.63 (0.37, 1.08) for polyvalent-q over Null, 0.41 (0.23, 0.72) for polyvalent-t over null, and 0.68 (0.40, 1.18) for polyvalent-t over polyvalent-q (Figure 5). This study indicates that both the polyvalent-t and polyvalent-q may be able to increase recurrence-free survival. In addition, the polyvalent-t may be more effective than the polyvalent-q vaccine in extending recurrence-free survival.

Figure 5 Recurrence-Free Survival Results from Study 89-38



The information provided in the following table is primarily from published reports, which in many cases combine subjects from more than 1 clinical study or include a subset of study subjects. Briefly, the results show that:

- 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.
- There is a relation between vaccine-induced antibody or CD8+ T-cell responses and improved recurrence-free survival.
- Vaccine treatment is associated with induction of cellular response that infiltrates a subject's own melanoma in vivo.
- 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.
- In a double-blind, placebo-controlled, Phase 2 trial conducted in 38 subjects with resected stage IIIB and IIIC melanoma (study 91-22), 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).

Table 10 Prior Efficacy Studies of Shed Polyvalent Vaccine Formulations

Publication (Study No.)	Drug and Dosage Form	Main Findings
Bystryn et al, 1992 (82-11 and 87-22)	Various formulation/adjuvant combinations	Delayed-type hypersensitivity (DTH) responses to vaccine antigens were augmented in 40% of vaccine recipients. The median disease-free interval was 2 years longer in responding subjects than non-responding subjects although the results were not statistically significant at the time of data cut-off.
Miller et al, 1995 (82-11 and 87-22)	Various formulation/adjuvant combinations	Overall, vaccine treatment induced antibody responses in 39% of subjects. Responses were induced more often in subjects immunized to vaccine + alum compared to those immunized to the same vaccine without alum (in 39% vs 9% of subjects respectively). Median disease-free survival (DFS) was longer in subjects with compared to without a vaccine-induced antibody response (median of 5.4 vs 1.4 yrs, p=0.06) as was 5-year overall survival (71% vs 44%, respectively, p=0.01).
Schultz et al, 1995 (90-11)	Polyvalent-q vaccine + Detox	Detox potentiated vaccine-induced antibody responses, had no effect on DTH responses, and did not improve clinical responses. Median DFS was longer in subjects immunized to vaccine+alum compared to vaccine + Detox (median DFS of 32.1 mos vs 17.8 mos, respectively)
Bystryn et al, 2001b (91-22)	Polyvalent-q vaccine + Alum or placebo vaccine + Alum	By Kaplan Meier analysis, median time to disease progression was 2.5 times longer in subjects treated with melanoma compared to placebo vaccine (19.6 vs 6.9 months, respectively; p=0.03 by Cox hazard analysis). Overall survival was prolonged by 40% although the difference was not significant in this small group of subjects.
Bystryn et al, 1988 (82-11 and 87-22)	Polyvalent-q; with or without Alum; with or without cyclophosphamide pretreatment	Vaccination increased the concentration of anti-melanoma antibodies by ≥50% compared to baseline in 24% of subjects overall; frequency of DTH reactions (≥10 mm induration) was increased from 5% before vaccination to 51% afterwards.
Oratz et al, 1989 (82-11)	Formulation unknown	Subcutaneous melanoma nodules were excised from 33 subjects. Dense cellular infiltrates were seen in 10/11 nodules from 10 different vaccine-immunized subjects compared to 9/22 nodules from non-immunized subjects (p=0.02). Vaccination may augment a subject's immune response to their own tumor in vivo.

Publication (Study No.)	**Drug and Dosage Form**	**Main Findings**
Oratz et al, 1991 (87-22)	Polyvalent-q adjuvanted with alum given with or without pre-treatment with 300 mg/m^2 intravenously, 3 days prior to each vaccine immunization	There was no significant difference in the frequency of vaccine-induced antibody or DTH responses or in DFS between the 2 groups.
Unpublished: Phase I/II Clinical Trial of Polyvalent Melanoma Antigen Vaccine and IL-2 Encapsulated into Liposomes in Patients with Disseminated Malignant Melanoma (92-35)	Polyvalent-q vaccine formulated in IL-2-containing liposomes	There was an IL-2 dose-related increase in vaccine-induced DTH responses (>15 mm increase compared to baseline) that peaked at 2 x 10^6 units. IL-2 significantly increased DTH responses to the vaccine compared to subjects who received vaccine without IL-2 ($p<0.01$).
Unpublished: Phase II Clinical Trial of Polyvalent Melanoma Antigen Vaccine Encapsulated into pH-Sensitive Liposomes for Patients with stage IIb and III Malignant Melanoma (96-15)	Polyvalent-t or polyvalent-q vaccine formulated in IL-2 containing, pH-sensitive liposomes	Vaccination increased DTH responses by >15 mm compared to baseline in 37% of subjects immunized with vaccine in pH-sensitive liposomes and in 21% of subjects immunized with vaccine in conventional liposomes. The difference between regimens was not statistically significant. There was no statistically significant difference between regimens in the frequency of CD8+ T-cell responses to vaccine antigens or the frequency of anti-melanoma IgG antibody responses.
Reynolds et al, 1998 (92-35 and 96-15)	Polyvalent-t; Alum or liposome-adjuvanted	Vaccination-induced vaccine-specific CD8+ T-cell responses in peripheral blood lymphocytes in 59% of HLA-A*02 vaccine recipients to at least 1 antigen in a panel of different vaccine antigens. Different subjects tended to respond to different antigens in the vaccine mixture.
Bystryn et al, 2001a (92-35 and 96-15)	Polyvalent-q	Vaccine treatment was associated with a rapid decrease in the proportion of subjects with melanoma cells in their peripheral blood. Circulating melanoma cells were detected in peripheral blood of 32% of subjects prior to vaccination and 7% of subjects after 5-7 months of vaccine therapy. The median progression-free survival of subjects with circulating melanoma cells at baseline was 12.6 months compared to >20 months in subjects without circulating melanoma cells.
Reynolds et al, 2003 (92-35 and 96-15)	Polyvalent vaccine (formulation unknown) with alum or IL-2 liposomes	56% of subjects had a vaccine-induced CD8+ T-cell response to at least 1 of the 4 vaccine antigens. Recurrences were significantly reduced in subjects with responses to Melanoma-Associated Antigen-3 (MAGE-3) ($p=0.03$) but were unrelated to the other 3 antigens. Clinical outcome therefore appears to be correlated with CD8+ T-cells responses to MAGE-3.

Publication (Study No.)	Drug and Dosage Form	Main Findings
Unpublished: Randomized Trial of Shed Antigen Polyvalent Melanoma Vaccine Bound to Alum Shows Similar or Better Efficacy Without Inclusion of Xenogeneic Antigens (89-38)	Polyvalent-q vaccine + alum, polyvalent-t vaccine + alum, or inactive antigens + alum	Recurrence-free survival was markedly increased for subjects treated with polyvalent-q or polyvalent-t vaccine compared to subjects treated with an inactive vaccine. The recurrence-free survival seemed to be longer for subjects treated with polyvalent-t vaccine compared to polyvalent-q vaccine.

DFS = disease-free survival, DTH = delayed-type hypersensitivity, IL-2 = Interleukin-2

Notes: Polyvalent-q vaccine contains shed antigen from 4 melanoma cell lines (3 human cell lines and 1 hamster cell line). Polyvalent-t vaccine contains only shed antigens from the 3 human cell lines. In many cases the published reports listed in the table combine subjects from more than 1 clinical study or include a subset of study subjects.

Three additional published papers have reported data on biomarkers measured in samples from some of the subjects with melanoma who were treated with shed polyvalent vaccine formulations. Reynolds et al (1997) found that MAGE-3 and Melan A/Melanoma Antigen Recognized by T cell 1 (MART-1) could stimulate CD8+ T-cell responses in subjects and their results suggested that these responses are protective and could serve as surrogate markers of vaccine efficacy. Reynolds et al (2003) found that vaccine treatment was associated with clearance of melanoma cell markers (tyrosinase, gp100, MART-1, and MAGE-3) from the circulation, which was associated with an improved prognosis. Reynolds et al (2006) found that subjects whose cytoplasmic melanoma-associated antigen (CYT-MAA) serum level remained elevated during treatment were ~3 times more likely to recur or progress than subjects who were consistently below the positive cut-off.

6.4 Marketing Experience

Seviprotimut-L vaccine is not approved or marketed in any country.

6.5 Clinical References

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Schultz N, Oratz R, Chen D, et al. Effect of DETOX as an adjuvant for melanoma vaccine. Vaccine 1995;13:503-508.

7 Guidance for the Investigator

Subjects should receive full supportive care during a clinical study of seviprotimut-L, including transfusions of blood and blood products; treatment with antibiotics, antiemetics, antidiarrheals, and analgesics; and other care as deemed appropriate, and in accordance with the protocol and institutional guidelines at the investigational site.

7.1 Contraindications

The vaccine should not be used in subjects with a known allergy to alum, the adjuvant.

The vaccine should not be used by female subjects who are pregnant or lactating.

7.2 Risks

The potential risks of the seviprotimut-L melanoma vaccine include local reactions at the site of injection such as erythema, swelling, pain and/or tenderness. If severe, the reaction may progress to blistering, ulceration, and scarring, and may cause temporary limitation of motion of the inoculated extremity. These reactions normally clear completely in 2 to 5 days. An infection such as an abscess or cellulitis may occur at the site of injection. Other potential adverse reactions include swelling and/or tenderness of regional nodes, and allergic reactions that may cause a rash over part or all of the body with or without itching or with other manifestations, including difficulty in breathing or swallowing or swelling of the lips and or tongue. The vaccine may also cause malaise, fever, nausea, headaches, and muscular aches and pains. Other potential toxicities include enhancement of tumor growth, and auto-sensitization.

There is a theoretical risk that the vaccine may enhance tumor growth. Although there have been several case reports of tumor enhancement in cancer vaccine-treated subjects, all were in subjects with advanced disease, where it is difficult to dissociate tumor enhancement from tumor progression.

There is a theoretical possibility that the antigens in the vaccine may induce immune responses to antigens present in the subject's normal tissue. This risk appears to be minimal. There is no increased incidence of autoimmune reactions or of difficulty in receiving transplanted organs in recipients of blood transfusions that contain far larger quantities of alloantigens than do tumor vaccines. This risk is further minimized by the steps that have been taken to remove many alloantigens from the partially purified vaccine to be used in these studies.

Systemic allergic reactions are always a possibility when injecting subjects with foreign protein preparations. This can be minimized by observing the subject after injections and taking appropriate measures if allergic reactions develop.

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 available to the investigator.

7.3 Overdosage

To date, 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. Polynoma does not recommend specific treatment for overdose or toxicity; however, the investigator should use appropriate clinical judgment in treating the overdose. In clinical studies, 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 as vaccine is provided in single-dose vials that contain only a 20% excess of vaccine, seviprotimut-L is an investigational compound and the potential for unexpected reactions is not known. Based on nonclinical safety studies of seviprotimut-L, the anticipated toxicities from an overdose would be local injection site reactions. Appropriate supportive care measures should be provided to address these potential toxicities in the event of an overdose.

7.4 Expected Adverse Reactions

The expected adverse reactions with seviprotimut-L treatment of subjects with melanoma are shown in Table 4.