2. SYNOPSIS

Name of Sponsor: BioVex, a wholly owned subsidiary of Amgen Inc.

Name of Finished Product: Talimogene laherparepvec (formerly known as OncoVEX^{GM-CSF})

Name of Active Ingredient: HSV-1 (strain JS1)/ICP34.5-/ICP47-/hGM-CSF

Title of Study: A Phase 2 Study of the Efficacy, Safety and Immunogenicity of OncoVEX^{GM-CSF} in Patients with Stage IIIc and Stage IV Malignant Melanoma

Investigator(s) and Study Center(s): This study was conducted at 7 centers in the United States (US) and 1 center in the United Kingdom (UK):

- [redacted], MD, [redacted]
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Publication(s):

Senzer NN, Kaufman HL, Amatruda T, et al. Phase II clinical trial of a granulocyte-macrophage colony-stimulating factor-encoding, second generation oncolytic herpesvirus in patients with unresectable metastatic melanoma. *J Clin Oncol*. 2009;27:5763-5771. (Additional analyses to support this publication will be provided in a supplemental report.)

Kaufman HL, Kim DW, DeRaffele G, Mitcham J, Coffin RS, Kim-Schulze S. Local and distant immunity induced by intralesional vaccination with an oncolytic herpes virus encoding GM-CSF in patients with Stage IIIc and IV melanoma. *Ann Surg Oncol*. 2010;17:718-730.

Study Period: The first subject was enrolled on 22 December 2005 and the last subject completed their last visit on 03 December 2008.

Development Phase: 2

Objectives:

Talimogene laherparepvec is an investigational, oncolytic immunotherapy containing an immune-enhanced herpes simplex virus, type-1 (HSV-1) that replicates in cancer cells. The therapeutic strategy of talimogene laherparepvec administration is to produce a direct oncolytic effect by replication of the virus in the tumor, and induction of an anti-tumor immune response enhanced by the local expression of granulocyte macrophage colony stimulating factor (GM-CSF).

The primary objective of this phase 2, open-label study was to assess the clinical efficacy of talimogene laherparepvec in terms of tumor response rates. Secondary objectives were to assess the efficacy of talimogene laherparepvec in terms of time to response, median survival time, and time to progression; and to assess the safety of talimogene laherparepvec in terms of adverse events, clinical pathology, biodistribution, and antibody responses to the vector.

Methodology:

This was a phase 2, open-label, multiple-dose evaluation of talimogene laherparepvec in patients with Stage IIIc or Stage IV melanoma.

Talimogene laherparepvec was supplied at a concentration of 10^8 plaque forming units (PFU)/mL. The first dose of talimogene laherparepvec was diluted with saline to a concentration of 10^6 PFU/mL, which was injected into 1 or more skin or subcutaneous tumors (up to 4 mL total). Subsequent doses began at least 3 weeks after the first dose and consisted of talimogene laherparepvec 10^8 PFU/mL (up to 4 mL total) every 2 weeks. This dosing schedule was based on the outcome of the previous phase 1 study (Study 001-01).

If indications of biological activity were observed after the initial 8 doses (stable disease [SD] or better and/or inflammatory response in an uninjected tumor and/or injection site reaction), subsequent treatment could continue for an additional 16 doses. Subjects with progressive disease (PD) could continue to receive study treatment for an additional 16 doses unless the investigator determined that another therapy was appropriate.

At each visit, talimogene laherparepvec was injected into 1 or more tumors. The volume of talimogene laherparepvec delivered to each tumor was dependent on the size of the tumor. The maximum total volume that was administered on any treatment day was 4 mL. If the subject had multiple tumors, the largest tumor was injected first, then the next largest, and so forth until the total dose volume had been used. If the tumor burden was below that requiring the use of the maximum of 4 mL available, less than 4 mL total of the study drug could be administered.

At least 1 tumor was left uninjected to assess uninjected response. Uninjected tumors were located at least 5 cm from the nearest injected tumor. After each dose, injected tumors were covered with a double occlusive dressing.

Treatment continued until any of the following occurred:

- complete response (CR)
- disappearance of all injectable tumors
- symptomatic disease progression requiring alternate therapy (subjects with disease progression could continue talimogene laherparepvec treatment if they did not require alternate therapy or they had disease progression for 120 days with unchanged Eastern Cooperative Oncology Group [ECOG] Performance Status)
- the maximum treatment period was achieved

Tumor size was evaluated at each visit by measurement of tumors using calipers. Photographs of injected tumors were obtained at each visit, and photographs of uninjected tumors and computed tomography (CT) scans were obtained every 12 weeks. All responses were determined objectively (ie, CT scan, clinical measurements, biopsy) at 2 visits at least 4 weeks apart.

Safety assessments at each visit included examination for active herpes labialis or other active dermatoses, ECOG Performance Status, clinical chemistry and hematology, injection site reactions, vital signs, adverse events, and concomitant medications. For the first dose only, subjects were closely monitored for 48 hours by the recording of vital signs, monitoring of adverse events, obtaining blood samples for chemistry and hematology evaluation, and blood and urine specimens for quantitative polymerase chain reaction (qPCR) for detection of talimogene laherparepvec DNA.

Prior to Amendment 4 to the study protocol, swabs for detection of live virus were required to be taken from the injected tumor and from the exterior of the occlusive dressing at 24 and 48 hours after the first dose; if one of these swabs was positive,

swabs were to be repeated every 24 hours until 3 consecutive negative swabs were obtained.

HSV-1 antibodies in serum were analyzed every 6 weeks. Antinuclear antibodies were analyzed every 12 weeks. An ophthalmology examination with slit lamp and retinal photography was performed at the screening visit, the sixth dose, and the final study visit.

The final study visit was conducted 30 days after the last dose of talimogene laherparepvec.

Number of Subjects Planned: 50

Number of Subjects Enrolled: 50

Diagnosis and Main Criteria for Eligibility:

Subjects were eligible for the study if they met all of the inclusion criteria and none of the exclusion criteria. Inclusion criteria included, but were not limited to:

- men and women ≥ 18 years of age
- histologically proven Stage IIIc (including at least 2 palpable lymph nodes, extracapsular or in-transit metastases) or Stage IV melanoma that was not eligible for curative surgery
- one or more tumors 0.5 to 10 cm in the longest diameter that were accessible and suitable for injection (ie, not bleeding or weeping)
- ECOG Performance status of 0 or 1
- total white blood cell count ≥ 3.0 x 10^9/L
- platelet count ≥ 80 x 10^9/L

Subjects were excluded from the study if they were receiving concurrent treatment with an antiviral agent or corticosteroid, or if the tumors to be injected were in mucosal regions, near dermatoses, or close to an airway, major blood vessel, or spinal cord that could cause occlusion, compression, or erosion.

A complete list of study inclusion and exclusion criteria is provided in Section 7.5.

Investigational Product, Dose and Mode of Administration, Manufacturing Batch Number:

Talimogene laherparepvec was administered by intratumoral injection at a concentration of 10^8 PFU/mL, [redacted], in [redacted] saline. The concentration was diluted with saline to 10 PFU/mL for the first dose and 10^8 PFU/mL was used for subsequent doses. Volumes of up to 0.5 mL, 1 mL, and 2 mL were injected into tumors with a longest dimension of 0.5 to 1.5 cm, > 1.5 to 2.5 cm, and > 2.5 cm, respectively. The maximum total volume that was to be given on any treatment day was 4 mL.

[redacted]

Reference Therapy, Dose and Mode of Administration, Manufacturing Batch Number:

Not applicable.

Duration of Treatment:

The initial treatment period was 8 doses administered over 15 weeks. If biological activity was observed, an additional 16 doses could be administered over the next 32 weeks.

Study Endpoints:

Efficacy endpoints were tumor response rate, time to response, duration of response, time to progression, and overall survival. Safety endpoints were adverse events, injection site reactions, clinical pathology (hematology/chemistry), antibody responses, biodistribution, herpes labialis or other active dermatoses, vital signs, and concomitant medications.

Statistical Methods:

All safety and efficacy analyses used the Intention-to-Treat (ITT) Population, which consisted of all subjects who received at least 1 dose of study drug.

All analyses were descriptive in nature. Summaries of quantitative variables included number, mean, standard deviation (SD), median, minimum, maximum, standard error, and 95% confidence interval, as appropriate. Summaries of categorical variables included frequencies and percentages.

The objective response rate (CR or partial response [PR]) was determined. Time to response from the date of first dose to the initial date of the subject's last response interval was calculated. Duration of response was calculated from the initial date of last response interval until the date of subsequent PD (or last follow up that was CR or PR). Time to progression from the date of the first dose to the first date of documented PD that was not followed by a later response of CR, PR, or SD was also calculated. Survival was calculated from the date of the first talimogene laherparepvec dose to the date of death or the date last known to be alive. Kaplan-Meier methods were used to analyze time to progression and survival. Summary statistics were provided for the other endpoints.

Study drug exposure was summarized as the number of days from first to last dose and the total dose administered. Adverse events were presented by system organ class (SOC) and preferred term. Injection site reactions were listed by subject, visit, and Common Toxicity Criteria for Adverse Events (CTCAE) grade. Separate summaries of flu-like symptoms were performed. ECOG performance status, results from the swab analysis of postinjection virus shedding, results of active herpes labialis/active dermatoses examinations, and results of slit lamp and retinal eye photography were listed by subject and assessment point and summarized. Data on vital signs, hematology, and chemistry at each time point were presented as absolute values and changes from baseline. Laboratory values above and below the normal range were flagged. HSV-1 antibody data were categorized as seropositive, seronegative or equivocal (ie, inconclusive). Antinuclear antibody data and qPCR data were listed by subject and visit.

Summary of Results:

Subject Disposition:

Fifty subjects at 8 study sites were enrolled and received at least 1 dose of talimogene laherparepvec. Of these subjects, 13 (26%) completed study treatment (ie, they received 24 doses or stopped treatment after CR) and 37 (74%) discontinued study early, most commonly due to disease progression (29 subjects).

Baseline Demographics:

Sex: There were 28 (56%) women and 22 (44%) men.

Age: Mean (SD) age was 63 (15.2) years.

Ethnicity/Race: 48 subjects were white (96%), 1 was Asian (2%), and 1 was Hispanic (2%).

Efficacy Results:

Of the 50 subjects enrolled, 14 (28%) had an objective response to talimogene laherparepvec treatment, including 8 (16%) subjects with CR and 6 (12%) with PR. Objective responses were observed in subjects with Stage IIIc or Stage IV melanoma, lactate dehydrogenase levels that were normal or elevated at baseline, ECOG Performance Status of 0 or 1 at baseline, and seropositive or seronegative HSV-1 status at baseline. In 4 of the responding subjects, early progression was observed before objective response was achieved. Among the 14 responding subjects, median time to response was 100 days (range 72 to 288).

Median duration of response was 223 days (range, 1 to 519). None of the subjects with CR and 4 subjects with PR either had PD reported by their final tumor evaluation or discontinued study due to PD. Among all 50 subjects, median time to progression or last follow-up was 146 days (range, 15 to 607). Of the 14 subjects with objective responses, 7 had ongoing response at 1 year from the first dose and 2 had ongoing response at 18 months from the first dose. Among the 36 subjects who did not meet criteria for objective response, time to progression ranged from 15 to 381 days, including > 200 days in 6 subjects, 151 to 200 days in 3 subjects, and 101 to 150 days in 4 subjects. Median overall survival was 448 days (approximately 14.7 months).

Safety Results:

All 50 subjects received at least 1 dose of talimogene laherparepvec. Subjects received a median of 6 doses of talimogene laherparepvec (range, 1 to 24). Twenty (40%) subjects continued to receive talimogene laherparepvec after the initial 8-dose period.

Most subjects (96%) experienced at least 1 adverse event during the study. The most common adverse events were pyrexia (56%), chills (46%), fatigue (34%), nausea (32%), influenza-like illness (24%), vomiting (22%), and headache (20%). These symptoms were generally mild to moderate in severity, were most marked after early doses, and usually resolved within 24 to 48 hours.

Thirty-nine (78%) subjects experienced at least 1 adverse event that was considered related to talimogene laherparepvec, most commonly pyrexia (56%) or chills (46%).

Most adverse events were mild to moderate in severity; the worst severity of adverse events was grade 3 for 28% of subjects and grade 4 for 8% of subjects. The most commonly reported grade 3 adverse events were fatigue (6%) and anemia (6%); no grade 4 adverse event was reported by more than 1 subject. Five (10%) subjects died; all fatal adverse events were attributed to disease progression. Each of the fatal adverse events began within 36 days of the last dose of talimogene laherparepvec. None of the fatal adverse events was considered to be related to treatment.

Serious adverse events were reported in 17 (34%) subjects. Serious adverse events that were reported for > 1 subject were disease progression (7 subjects, 14%) and pyrexia (2 subjects, 4%). The only serious adverse event that was considered to be related to study treatment was pyrexia in 2 (4%) subjects.

Two (4%) subjects discontinued the study early due to adverse events (gastrointestinal hemorrhage and disease progression), neither of which was considered to be related to study treatment. Twenty-seven (54%) subjects experienced at least 1 injection site

reaction (all of which were grade 1 or 2 in severity) and 42 (84%) experienced at least 1 flu-like symptom.

Talimogene laherparepvec appeared to be well-tolerated with respect to vital sign measurements, hematology and chemistry laboratory parameters, ophthalmologic examinations, and physical examinations.

Shedding of talimogene laherparepvec was evaluated by viral culture (plaque assay) on swabs of the injected tumors and the outside of the occlusive dressings after dosing. Live virus was detected on one tumor sample at 24 hours after the first dose. All other swabs of tumors and dressings were negative in all subjects tested. None of the subjects was reported to have developed herpes labialis or herpetic dermatosis. A swab that was taken from a cold sore in a subject with an adverse event of oral herpes showed that the causative agent was wild-type HSV-1, not talimogene laherparepvec. ECOG Performance Status remained 0 or 1 throughout the study for a majority of subjects.

Among the 5 subjects with a negative antinuclear antibody test at baseline and a positive titer postbaseline, no immune-mediated safety issues were identified. The qPCR data are reported separately in Addendum Clinical Study Report 002-03.

Other Results:

All subjects were seropositive for HSV-1 after the first dose. Objective responses were seen in 9 of 36 subjects (25%) who were seropositive for HSV-1 at baseline and 5 of 13 subjects (39%) who were seronegative for HSV-1 at baseline. There did not appear to be a difference in the safety profile between subjects who were seropositive for HSV-1 at baseline and those who were seronegative for HSV-1 at baseline.

Conclusions:

The results of this phase 2, open-label, single-arm, international, multiple-dose study support the efficacy of talimogene laherparepvec for the treatment of melanoma. The objective response rate was 28% and the median duration of response was 223 days (approximately 7.3 months).

The most commonly reported adverse events were a constellation of flu-like symptoms, which were generally mild to moderate in severity, were most marked after early doses, and usually resolved in 24 to 48 hours. All deaths were attributed to disease progression and were not considered related to study treatment.

Despite the seropositivity of all subjects after the first dose, objective responses were observed both in subjects who were seronegative for HSV-1 at baseline and those who were seropositive. It was uncommon for subjects with a negative antinuclear antibody test at baseline to have a positive antinuclear antibody test postbaseline, and no immune-mediated safety issues were identified.

In conclusion, biological activity was clearly observed with talimogene laherparepvec administration and treatment appeared to be generally well tolerated. Based on these findings, a randomized, controlled, phase 3 study of talimogene laherparepvec in the treatment of malignant melanoma was initiated.