

3.0 INTRODUCTION

3.1 Metastatic Melanoma

Cutaneous melanoma has one of the most rapidly increasing incidence rates of any cancer in the United States⁽¹⁾. Melanoma accounts for 4% of all skin cancers, but is responsible for 79% of skin cancer deaths. The American Cancer Society estimated that in 2004 there would be 55,000 new cases of melanoma in the United States, and an estimated 8,000 people will die from this disease⁽²⁾. Surgical excision of early stage melanomas can be curative, but the outlook for subjects with advanced metastatic melanoma remains poor. Median survival ranges from 6–10 months, with few long-term survivors^(3,4). The prognosis is dismal even for those subjects with metastatic disease limited to the skin or lymph nodes, for which the median survival is only 10.6 months⁽⁵⁾.

Currently in the United States, two single-agent products are indicated for first-line non-surgical treatment of metastatic melanoma, DTIC-Dome[®] (dacarbazine) and Proleukin[®] (aldesleukin, a human recombinant interleukin-2 product)^(6,7). Response rates for DTIC in Stage IV disease range from 9.9 to 12.1% in two recent randomized trials^(8,9). Proleukin[®] and combination chemotherapy and biochemotherapy regimes appear to offer increased response rates at the expense of increased toxicity^(8,9,10). Given the limitations of the current licensed therapies, an alternative therapy whereby efficacy and safety synchronize to provide the melanoma subject a palliative treatment for this devastating disease is warranted.

3.2 Prior Clinical Experience with Allovectin-7[®]

Extensive clinical experience with Allovectin-7[®] exists with over 700 subject participants across numerous trials. This database has provided strong evidence to support the ongoing development of this product in an attempt to achieve a safe and effective treatment for metastatic melanoma subjects. Details of the clinical experience with Allovectin-7[®] are contained in the Allovectin-7[®] Investigator's Brochure, with the highlights provided below.

Preliminary research in melanoma subjects using a DNA/lipid complex demonstrated that gene transfer enhanced the immune response to tumors using the allogeneic Class I MHC cell surface antigen, HLA-B7. There was evidence of response without significant adverse events when injecting plasmid DNA into melanoma tumors^(11, 12, 13, 14).

In these early Phase 1/2 studies a total of 36 melanoma subjects were treated. Thirty-six percent of subjects showed regression of the injected nodule of >25% and 19% had systemic objective responses with regression of non-injected, distant nodules. These encouraging results in melanoma subjects prompted additional research and additional Phase 2/3 trials designed to confirm responses in larger subject populations and in multi-center settings. In addition to evaluating the safety of Allovectin-7[®], subsequent protocols were designed to

determine the response rate and duration of response of the injected and non-injected metastatic tumors.

VCL-1005-201 was an open-label Phase 2 trial that prescribed four intralesional injections of 10 µg of Allovectin-7[®]. Melanoma subjects comprised 38 of the 124 subjects, of which 25 were evaluable according to the protocol criteria. This required a subject to have received at least two of four planned injections, to have been evaluated at the 6-week time point, and to have had a tumor biopsy collected at six weeks. Based on preliminary and unaudited data, Allovectin-7[®] associated adverse events were reported in 13 of the 25 evaluable subjects, and categorized as mild or moderate. Of the 25 evaluable melanoma subjects, 11 were classified with disease limited to subcutaneous or lymph node involvement and 14 had visceral involvement. In the subgroup of subjects with limited disease, five of 11 (45%) subjects responded, while responses were observed in two of 14 (14%) subjects with visceral involvement. Of these seven responding subjects, five also showed systemic effects, two of which were partial responses, both in subjects with limited disease. The partial responses in these two subjects persisted for four months in one subject, and 14+ months in the other.

Another Phase 2 Clinical trial, **VCL-1005-205**, was an open-label, multi-center trial of low-dose (10 µg) Allovectin-7[®] as an immunotherapeutic agent in subjects with Stage III or IV melanoma and no treatment alternatives. The trial was designed to demonstrate an objective clinical response in a subject population for whom there are minimal treatment alternatives. Key eligibility criteria for VCL-1005-205 were as follows: at least one injectable lesion (cutaneous, subcutaneous, or nodal) at least 1 x 1 cm, and no larger than 5 x 5 cm; Stage III or IV melanoma and failure or relapse from chemotherapy, biochemotherapy or a combination of the two; Karnofsky Performance Status ≥ 80 and adequate organ function. Subjects with brain or visceral (except lung) metastases were excluded.

This trial was completed with 77 subjects in the intent-to-treat population. Fifty-eight subjects completed at least one cycle of therapy. There were nine responders reported by the investigators, however, sponsor review reduced this number to seven based on lack of response confirmation at the 4-week follow-up period of two cases. Two subjects achieved a complete response and five achieved a partial response. The overall response rate according to the sponsor's review was 9.1% with a median duration of response of 5.9 months. Eighteen subjects were classified as having stable disease and 52 as having progressive disease. Median time to progression was 2.1 months (range: 0.5 – 54.5+) and the estimated median survival in this trial was 14.2 months.

The Allovectin-7[®] treatment was well tolerated. Some of the most common adverse events considered to be associated with the product included: injection site pain, injection site burning, fatigue, injection site hemorrhage and injection site reaction. Most were rated as Grade 1. Fewer than 3% of subjects experienced an Allovectin-7[®]-associated toxicity of Grade 3 or higher.

A Phase 3 trial, **VCL-1005-301** was undertaken as a randomized, controlled trial for first-line therapy. In this trial, low-dose (10 µg) Allovectin-7[®] plus DTIC-Dome[®] was compared to DTIC-Dome[®] alone in chemotherapy naïve subjects, most of whom had Stage IV disease. DTIC-Dome[®] was given intravenously (800 mg/m²) on Day 0 of each 28-day cycle and 10 µg of Allovectin-7[®] was administered intratumorally into a single lesion on Days 3 and 10 of the cycle. This trial differed from VCL-1005-205 in that the indication in VCL-1005-301 was for first-line, rather than second-line therapy, the treatment cycle length was short and the potential cumulative dose was less than in VCL-1005-205, and the inclusion of subjects with visceral metastases (other than lung) or abnormal LDH was permitted. In the VCL-1005-301 trial, no statistically significant difference was observed in the response rates (DTIC-Dome[®] alone = 11.5% vs. DTIC-Dome[®] plus Allovectin-7[®] = 13.3%; p=0.926) or overall survival (DTIC-Dome[®] alone = 9.6 months median survival vs. DTIC-Dome[®] plus Allovectin-7[®] = 11.3 months median survival; p=0.297) between treatment arms. In addition, there was no increased toxicity in the Allovectin-7[®] plus DTIC-Dome[®] arm, which continued to support the safety profile for Allovectin-7[®]. Consistent with other recent studies which have shown no advantage of biochemotherapy plus chemotherapy over chemotherapy alone⁽⁹⁾, Allovectin-7[®] did not show any improvement when combined with chemotherapy.

Having gained valuable safety and efficacy information in the previous two multi-center trials (VCL-1005-205 and VCL-1005-301), it was determined that evaluation of Allovectin-7[®] at a higher dose to enhance efficacy was warranted. Therefore, the Phase 2 dose-escalation trial, **VCL-1005-208**, was designed to evaluate safety and antitumor activity up to a maximum dose of 2 mg of Allovectin-7[®]. In this Phase 2, open-label, multi-center trial, the 2 mg dose was studied in 127 melanoma subjects enrolled with either Stage III or IV (M1a or M1b) melanoma.

The VCL-1005-208 data confirmed the efficacy seen in earlier clinical trials of Allovectin-7[®], as well as reinforced the robust tolerability and safety profile seen previously. Fewer than 1% of subjects experienced a drug-related toxicity of Grade 3 or higher. The most common adverse events considered to be associated with the product were: injection site pain, fatigue, rigors, injection site erythema, myalgia, pyrexia, arthralgia and headache. The 127 subjects who received the 2 mg dose demonstrated an overall response rate of 11.8%, a median duration of response of 12.7 months, and overall estimated median survival of 21.3 months (follow up for survival ongoing). Response rates were higher in subjects with single injectable lesions, and when the injection was given into one rather than multiple lesions. Of note, four subjects in this trial developed vitiligo. In addition, resection of residual nodules in injected lesions in four subjects revealed no residual melanoma.

With the clinical experience of Allovectin-7[®] collected to date, Vical (the sponsor) now proposes a pivotal Phase 3 clinical trial that will incorporate the

critical elements of this cumulative knowledge in order to definitively establish the clinical benefit with minimal toxicity of Allovectin-7[®] to address the pressing unmet medical need for metastatic melanoma patients.

4.0 PHYSICAL, CHEMICAL, AND BIOLOGICAL CHARACTERISTICS OF THE INVESTIGATIONAL AND CONTROL PRODUCTS

4.1 Investigational and Control Product(s)

Investigational Product - Allovectin-7[®] is a bicistronic plasmid DNA encoding HLA-B7 and β -2 microglobulin proteins formulated in cationic lipids.

Control Products - consist of one of the following options:

- DTIC-Dome[®] (dacarbazine) ⁽⁶⁾
- Temodar[®] (temozolomide) ⁽¹⁵⁾

4.2 Formulation

4.2.1 Allovectin-7[®]

Allovectin-7[®] is manufactured as a 2 mg/mL plasmid DNA formulated with the cationic lipid-based system, DMRIE/DOPE. DMRIE is DMRIE-Br (CAS name: (+)-N-(2-hydroxyethyl)-N, N-dimethyl-2,3-bis(tetradecyloxy)-1-propanaminium bromide) and DOPE is CAS name: 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine. The two are mixed to form DMRIE/DOPE. Allovectin-7[®] is administered in a 1 mL dose directly into the lesion via a needle by syringe injection.

4.2.2 Dacarbazine (DTIC-Dome[®])

Sterile dacarbazine is a colorless to ivory colored solid which is light sensitive and reconstituted and administered intravenously over one hour. DTIC-Dome[®] is indicated in the treatment of metastatic melanoma.

4.2.3 Temozolomide (Temodar[®])

Temodar[®] is a white to light tan/light pink powder contained in capsules for oral administration that metabolizes to 3-methyl-(triazene-1-yl)imidazole-4-carboxamide (MTIC), the same intermediate metabolized after DTIC-Dome[®] infusion. Temodar[®] is indicated for treatment of refractory anaplastic astrocytoma.

4.3 Rationale for Dose Regimen

Allovectin-7[®] has shown minimal toxicity in all human studies to date at doses ranging from 5 μ g to 2 mg. The safety of Allovectin-7[®] has been demonstrated in animals at doses substantially higher (on a mg/kg basis) than the 2 mg dose.

In the Phase 2 trial **VCL-1005-208**, it was demonstrated that the maximum tolerated intralesional injected dose of Allovectin-7[®] is at least 2 mg. Although