

BIOLOGICS LICENSE APPLICATION (BLA) MEDICAL REVIEW

Submission Number: BLA125197

Product: Autologous Antigen Presenting Cells Pulsed with PAP-GM-CSF Fusion Protein

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Proposed Trade Name: Provenge

Therapeutic Class: Somatic Cell Therapy/Tumor Vaccines

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Proposed Indication: For the treatment of men with asymptomatic metastatic androgen independent prostate cancer

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1 RECOMMENDATIONS

1.1 Recommendation for regulatory action

A: Issuance of a Complete Response letter (non approval)

B: Clinical comments in the Complete Response letter to the applicant

- a. Your submission did not provide sufficient evidence to support the effectiveness claim of a prolongation of overall survival of treatment with sipuleucel-T in men with asymptomatic metastatic androgen independent prostate cancer. Both randomized controlled trials, D9901 and D9902A, failed to demonstrate efficacy of sipuleucel-T on the protocol-specified primary endpoint of time to disease progression. Since these trials failed to achieve their primary endpoint, subsequent survival analyses were *post hoc* in nature and were performed in a relatively small number of subjects. Therefore the submitted clinical data were not sufficiently persuasive to support licensure at this time.
- b. The African-American population was underrepresented in the phase 3 trials submitted as well as in the on-going D9902B, accounting for < 10% of the total trial subjects. Since the biology and prognosis of prostate cancer and cardiovascular diseases in African-Americans may be different from those in the Caucasian population, the trial results may not be applicable to the general prostate cancer population. Therefore, we recommend that you increase the enrollment of African-American subjects in the current 9902B trial, or propose an alternative plan to investigate the safety and efficacy of sipuleucel-T in minority populations.
- c. Data submitted did not provide sufficient information about the magnitude and risk factors for cerebrovascular accidents (strokes) in sipuleucel T- and APC-placebo treated-subjects. In addition, data currently available are insufficient to clarify sipuleucel T's efficacy and safety in African American men with prostate cancer as described in item 10. If subsequently developed clinical trial data do not provide clarification on these issues, a detailed pharmacovigilance plan should be established to address these questions after licensure.
- d. We recommend that you request a meeting with the review Divisions to address these deficiencies in detail, to facilitate the overall clinical development for

sipuleucel T and to explore possible means to provide rapid access to this promising therapy.

1.2 Basis for the recommendation

1.3 Summary of the efficacy and safety results

Efficacy:

The efficacy claim of this BLA submission is based on the survival difference favoring Sipuleucel T (APC8015) treatment seen in two completed phase 3 studies, D9901 and D9902A. D9901 enrolled 82 subjects who received Sipuleucel T (APC8015) and 45 who received placebo. D9902A was terminated early with 65 subjects enrolled to Sipuleucel T (APC8015) and 33 subjects to placebo. Both studies failed to demonstrate a sipuleucel T (APC8015) treatment effect on pre-specified efficacy endpoints including time to disease and pain progression. *Post hoc* survival analyses showed that compared to placebo, sipuleucel T (APC8015) treated subjects sustained a 4.5-month median survival time (MST) increase in D9901 and a 3.3 month MST increase in D9902A, respectively. Only D9901 survival difference reached statistical significance by log-rank test.

A review of the data submitted, including sensitivity analyses and review of death events, confirmed the 4.5 month survival difference in study D9901 favoring sipuleucel T (APC8015) treatment. This survival difference is clinically meaningful, and compares favorably with other therapeutic options in this disease setting. There was no apparent excess of deaths attributable to causes other than prostate cancer in the control arm.

Notable imbalances were observed in the distribution of some prognostic factors such as the Gleason score and soft tissue diseases. However, sensitivity analyses indicated that these imbalances did not have an impact on the increased survival in Sipuleucel T treated subjects in D9901. Potential confounding effect of subsequent chemotherapy on survival, albeit unlikely, cannot be completely ruled out.

However, neither study defined the survival as an efficacy endpoint, nor the primary method for survival analysis was pre-specified.

Although CD54 upregulation appeared to be correlated with survival, clinical reviewer could not make a conclusion that the correlated survival was due to the treatment effect since CD54 upregulation could be simply one of patient prognostic factors to predict for a better survival.

Safety

Sipuleucel T (APC8015) appeared to be well tolerated compared to placebo. There were 1.3% more cerebrovascular accidents (CVAs) observed in subjects who received Sipuleucel T compared to placebo subjects in four randomized phase 3 trials. Review of the case summaries did not reveal a clear association of these CVA events with the administration of Sipuleucel T (APC8015) or placebo.

1.4 Major efficacy deficiency

The information submitted in the BLA did not provide substantial evidence to demonstrate the effectiveness for sipuleucel T (APC8015) treatment in the intended patient population. Specifically, both studies failed to demonstrate the efficacy of Sipuleucel T (APC8015) treatment on protocol prespecified primary endpoint of time to progression. Therefore, subsequent survival analyses were *post hoc* in nature and performed in a relatively small sample size. The results from these analyses were hypothesis-generating: there is no way to determine the type I error (falsely claiming the treatment effect even there were none) since all type I errors had been spent in the analyses for the primary endpoint. In conclusion, the purported survival effect from sipuleucel T treatment in the intended population cannot be determined.

2 EXECUTIVE SUMMARY

2.1 Brief Overview of Clinical Program

- Product name:
 - Proposed name: PROVENGE®
 - Used name: APC8015
 - Established name: Sipuleucel T
- Product class: an autologous active cellular immunotherapy
- Route of Administration: intravenous infusion
- Proposed Dosage: The recommended course of therapy for PROVENGE® is 3 doses, given at approximately 2-week intervals by intravenous infusion. Each dose of PROVENGE® is preceded by a standard leukapheresis procedure approximately 2 to 3 days prior to the infusion date. Each dose must be administered to the patient from whom the cells were obtained. It is important that the physician and patient adhere to the personalized leukapheresis and infusion schedule.

- Proposed Indication: for the treatment of men with asymptomatic metastatic androgen independent prostate cancer.
- Number of pivotal efficacy and safety trials: 2 (D9901 and D9902A)
- Number of patients enrolled in the primary trials: D9901: 127 patients. D9902A: 98 patients.
- Overall number of patients in the safety database: 731 patients exposed to APC8015 from the following 14 clinical trials:
 - PB 01 (25)
 - D9903 (56)
 - P-11 (175): 117 APC8015 subjects
 - D9801 (15)
 - 9801-015 (1)
 - D9706 (1)
 - 9168-067 (1)
 - ACT 9610 (31)
 - D9905 (19)
 - ACT 9702 (33)
 - D9901 (127): 82 APC8015 subjects
 - D9902A (98): 65 APC8015 subjects
 - D9906 (18)
 - D9902B (400) as of April 2007: (based on 2:1 randomization, estimated 270 subjects treated with APC8015). On-going.

2.2 Studies submitted

PROVENGE[®] (Sipuleucel T, APC8015) is an active cellular immunotherapy product proposed for the treatment of men with asymptomatic metastatic androgen independent prostate cancer (AIPC). The product consists of peripheral blood mononuclear cells (PBMCs), which are obtained from patients by leukapheresis and activated *in vitro* with a recombinant fusion protein (prostatic acid phosphatase fused with GM-CSF). These activated cells including antigen presenting cells (APCs) are then re-infused intravenously into the autologous patients.

Two similarly designed, randomized, double-blind, placebo-controlled phase 3 trials, D9901 and D9902A, and evidence from additional non-randomized studies are submitted in support of efficacy and safety in this BLA. The efficacy claim is primarily based on a finding of an increased survival in APC8015-treated subjects from D9901, a single study of 127 patients. The stated primary objective of D9901 and D9902A was to test whether the treatment with APC8015 could increase the time to disease progression by 3.7 months in patients with asymptomatic metastatic AIPC. Disease progression was defined by objective radiographical, clinical and pain progression criteria. Prostate-Specific Antigen (PSA) was measured, but not used as a criterion for disease progression. The trials were not powered to detect a survival

difference and the primary method for survival analysis was not pre-defined. Major eligibility criteria included histologically documented adenocarcinoma of the prostate, >25% of tumor cells staining positive for PAP, asymptomatic metastatic disease either in the soft tissue or bone, and evidence of tumor progression after hormonal therapy either by radiographic or PSA criteria. Subjects were stratified by study center and bisphosphonate use, centrally randomized in a 2:1 ratio of APC8015 to APC-Placebo, and scheduled to receive three intravenous infusions of either APC8015 or APC-placebo preceded by leukapheresis 2 to 3 days prior to the infusion date on weeks 0, 2 and 4. Patients were evaluated at weeks 2, 4, 12, and clinical evaluations were combined with radiographic tumor staging at baseline, weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression. Staging scans were reviewed by an independent radiology facility to confirm objective disease progression. Subjects were monitored for delayed treatment-related adverse events (AEs) and for survival for 36 months or until death.

2.3 Efficacy Results

D9901: Study D9901 screened 186 patients to enroll 127 subjects. Eighty-two were randomized to the APC8015 arm and 45 to the APC-Placebo arm. Some imbalances were noted in the baseline demographic and prognostic characteristics including Gleason grading and disease location (bone, soft tissue or both) between the two arms. Sensitivity analyses did not suggest that these imbalances confounded the survival results. African-American and Hispanic subjects were underrepresented in this patient population. The primary efficacy analysis of D9901 results showed that the study did not achieve its primary objective of prolonging time to objective disease progression or any other pre-specified efficacy endpoint. The estimated median time to disease progression was 11.0 weeks in the APC8015 arm compared to 9.1 weeks in the APC-Placebo arm. This 1.9-week delay in the time to objective disease progression did not reach statistical significance ($p = 0.085$).

A 3-year survival analysis of D9901 was performed as part of the follow up, although a primary method for survival analysis was not pre-specified in the protocol. The analysis showed that the median survival times in the subjects treated with APC8015 and APC-Placebo were 25.9 and 21.4 months, respectively, a difference of 4.5 months. Overall survival difference reached statistical significance ($p = 0.010$) by log rank test. The unadjusted HR was 1.71 [95% confidence interval (CI): 1.13, 2.58]. Therefore, study D9901 failed in achieving its primary objective, but a *post hoc* analysis demonstrated an apparent survival increase in APC8015-treated subjects, the basis for the efficacy claim in this BLA submission.

D9902A: The D9902A trial was originally designed to be a companion trial to D9901: eligibility, endpoints, treatment plan, monitoring, accrual goals and statistical analysis plans were initially the same in both studies. Study D9902A was terminated early because of the overall negative findings from D9901. Ninety-eight patients were enrolled out of a planned 120 patients: 65 were randomized to receive APC 8015 and 33 to APC-Placebo. As a result of this early termination, D9902A was underpowered to reach its primary objective of improved time to progression. The

estimated median time to disease progression in D9902A was 10.9 weeks in the APC8015 arm compared with 9.9 weeks in the APC- Placebo arm ($p=0.72$); median survival times were 19.0 months and 15.7 months, respectively ($p = 0.331$, log rank test).

2.4 Safety results

The safety database was mainly derived from 147 patients who received APC8015 and 78 patients who received APC-placebo; a total of 225 subjects in trials D9901 and D9902A. Since these studies were similar in design and eligibility, safety results were pooled from the two studies. More than 88% of the subjects received the scheduled 3 infusions of either APC8015 or APC-Placebo. Overall, APC8015 treatment was relatively well tolerated. Most APC8015 treated patients developed Adverse Events (AEs), but most of these were grade 1 to 2 and resolved within 48 hours. Chills, fatigue pyrexia, and back pain were the most common AE's (> 25% of subjects who received APC8015). These events generally occurred within 1 day of an infusion with APC8015, were Grade 1 or 2, were managed on an outpatient basis, and had median durations of 24 to 48 hours. No deaths were reported to be related to the infusion of APC8015 and no deaths occurred within 30 days after the infusion. Twenty-four percent (23.8%) of APC8015 treated subjects developed Serious Adverse Events (SAEs) other than death, not different from 23% of APC-Placebo treated subjects. These SAEs included life-threatening adverse events, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity. However, 5.4% (8 out of 147) APC8015 treated subjects experienced CVA-related SAEs, compared to 2.6% (2 out of 78) in APC-Placebo treated subjects in D9901 and D9902A.

The sponsor subsequently submitted summarized results for CVA events observed in all phase 3 trials, including P-11 in androgen dependent prostate cancer and D9901, D9902A and ongoing study D9902B in the proposed indication. Eighteen out of 461 (3.9%) subjects treated with APC8015 developed CVA events compared to 6 out of 231 (2.6%) in the APC-Placebo treated subjects, an absolute increase of 1.3% (odds ratio = 1.5). Two percent (7/345) of subjects in the APC8015 arm died from CVA events compared to 1.2 % of subjects in the APC- Placebo arm (2/172), an absolute increase of 0.8%. In the proposed indication, approximately three times as many subjects experienced CVA's in the treatment group (17/345 or 4.9%) compared with controls (3/172 or 1.7%). Although these differences did not reach statistical significance, the increased CVA frequency in APC8015 treated subjects is a potential safety concern that warrants further investigation.

2.5 Conclusions

Neither study D9901 nor study D9902A achieved any study objectives (Table 1).

Table 1: Combined Summary of Efficacy, D9901 and D9902A

Study	Median Time to Progression (weeks)		Median Survival (months)	
	APC8015	APC Placebo	APC8015	APC Placebo
D9901	11.0	9.1 (p = 0.085)	25.9	21.4 (p = 0.010)
D9902A	10.9	9.9 (p = 0.72)	19.0	15.7 (p = 0.33)

A review and analyses of the data submitted, including sensitivity analyses and review of death events, supported the finding of an increase in the median survival reported by the sponsor in APC8015 arm compared with the APC-Placebo in study D9901. However, the lack of a pre-specified primary method for survival analyses renders it impossible to estimate the type I error of this survival difference. In addition, the six month difference in median survival times between D9901 and D9902A despite similar study design, inclusion criteria, and baseline characteristics, suggest that the eligibility criteria did not define a homogenous population in these small studies. These observations increase the possibility that the survival difference in D9901 might be attributable to chance.

Safety and tolerability: APC8015 was generally well tolerated; approximately 90% of subjects in the two studies received the 3 infusions specified by the protocol. The most frequently reported adverse events in APC8015 treated subjects were transient chills, fatigue, and pyrexia. However, the increased CVA frequency reported in subjects treated with APC8015 constitutes a potential safety concern.

2.6 Special Populations

The African-American population was underrepresented in the phase 3 trials accounting for < 10% of the total trial subjects. Since the biology, prognosis of the African-American are different from Caucasian population, the submitted trial results may not be applicable to the entire prostate cancer population.

2.7 FDA advisory committee meeting

On March 29, 2007, FDA held an advisory committee meeting (Cellular, Tissue and Gene Therapies Advisory Committee, supplemented by members of the Oncology Drugs Advisory Committee and several prostate cancer specialists) to seek its advice on the persuasiveness of the submitted sipuleucel T efficacy and safety results. In addition, several questions regarding product potency, variability and mechanism of action were also discussed.

After extensive discussions regarding the significance of the CVA's reported in the submitted studies, as well as in additional studies with APC-8015, the committee voted unanimously (17-0) that safety had been established. The Committee recommended that post-marketing pharmacovigilance studies be performed to monitor the incidence of CVA's with attention to the African- American population and other minorities

The Committee was asked to vote whether or not submitted data established the efficacy of sipuleucel-T (APC-8015) in the intended population. The official record shows that the

vote was 13 yes and 4 no in favor of evidence of efficacy, however most of the advisory committee members expressed misgivings about the persuasiveness of the efficacy data. After two members initially voted against efficacy, the committee requested clarification, and the question was changed from 'establish efficacy' to 'substantial evidence.' The two members then changed their vote from no to yes and an additional member stated that he would have voted no to the original question but yes to the revised question. Only seven out of the 17 voting Committee members voiced an opinion that the data clearly demonstrated efficacy, and one member stated that he voted yes to "promote this type of research." The interpretation of the advisory committee vote on efficacy is therefore highly problematic, however Committee members did agree that the phase 3 study must be completed, and that the under representation of the African American population should be addressed (1).

3 BACKGROUND

3.1 Currently Available Treatment for Indication

- Prostate cancer

Prostate cancer is the most common malignancy and 2nd most common cause of cancer mortality in men. In 2007, American Cancer Society estimates that 218,890 new cases of prostate cancer will be diagnosed in the United States with 27,050 annual deaths from this disease (2).

Initial primary treatment modalities for subjects with localized prostate cancer include expectant management (watchful waiting), surgery, radiation therapy, brachytherapy, cryotherapy (3). However, approximately 20 to 40% of men will eventually experience disease recurrence after the initial treatment. Prognostic factors for prostate carcinoma include anatomic stage, histologic grade, PSA level, age, and comorbidity (4). One of the most important prognostic factors is the histologic grading of prostate cancer, Gleason score (5). High Gleason score (≥ 8) portends an unfavorable factor for recurrence and overall survival. Standard therapy for prostate cancer patients with disease recurrence, typically presenting with elevated prostate-specific antigen (PSA) but no detectable metastases, is androgen deprivation with either luteinizing hormone-releasing hormone (LHRH) agonist and/or androgen receptor blocker. Despite hormonal therapy, virtually all patients will progress and their disease will spread to distant sites (most commonly regional lymph nodes and/or bones) and will become refractory to hormone therapy. This stage of disease is known as androgen independent prostate cancer (AIPC), or hormone refractory prostate cancer (HRPC). Median survivals of patients with AIPC reported in the literature varies from 9 months to over 16 months depending on prognosis (6-8)

- Treatment options for metastatic AIPC

Once metastatic and androgen-independent, prostate cancer is usually incurable. Currently available therapies are intended for palliation and/or prolonging survival.

These therapeutic options include no treatment, chemotherapy, secondary hormonal treatment or local radiation

- *Chemotherapy*

A number of chemotherapeutic agents have been approved for the treatment of subjects with HRPC. Mitoxantrone was approved in the United States for use in combination with corticosteroids as initial chemotherapy for hormone refractory prostate cancer based on findings from a randomized multicenter trial comparing mitoxantrone plus prednisone 5 mg twice a day to prednisone alone. A total of 161 patients were randomized to this study which had palliative response as a primary endpoint (9).

Three other agents approved for the treatment of advanced prostate cancer are estramustine phosphate, zoledronate and docetaxel in combination with prednisone. Only docetaxel treatment has been demonstrated to confer a survival benefit (6).

Table 2: Drugs for metastatic prostate cancer

Drug	Approval date	Drug class	Endpoint
Docetaxel	2004	Taxane	Overall survival
Zoledronate	2002	Bisphosphonate	Prolongation in time to Skeletal Related Events (SRE)
Mitoxantrone	1996	Anthracenedione	Palliative response (pain)
Estramustine	1974	Estrogen/Alkylator	Endocrine effect

Docetaxel (taxotere) was approved based on the results from a randomized, multi-center global clinical trial (TAX327) designed to evaluate chemotherapy with Taxotere and prednisone in the treatment of men with metastatic, hormone-refractory prostate cancer. One thousand and six patients were randomized to one of three treatment arms: (1) mitoxantrone + prednisone (MTX + P), (2) weekly Taxotere (TXT qw) + prednisone, or (3) Taxotere once every three weeks (TXT q3w) + prednisone. The primary efficacy endpoint was survival. The treatment arm of TXT q3w + prednisone demonstrated a statistically significant survival advantage over MTX+P control (median survival 18.9 vs. 16.5 months, respectively, $p = 0.0094$). The TXT qw + prednisone arm did not demonstrate an advantage in overall survival over the control arm (6;10).

Adverse events included anemia, neutropenia, infection, nausea, vomiting, anorexia, and fatigue. Adverse events occurring more frequently with TXT q3w compared to MTX+P included allergic reactions, fluid retention, sensory neuropathy, alopecia, nail changes, diarrhea, and stomatitis.

- *“Watchful Waiting”*

Many patients who are asymptomatic or minimally symptomatic may be simply monitored. When symptoms develop or increase, they may be treated with prescription analgesics, including opioids, or palliative chemotherapy or local radiation.

- *Secondary Hormone Therapy*

Secondary hormonal maneuvers, such as anti-androgen addition or withdrawal, ketoconazole, aminoglutethimide, megestrol acetate or corticosteroids may produce PSA responses in some patients, but have not been demonstrated to prolong survival (11).

3.2 Clinical Trial Endpoints in Prostate Cancer

Clinical Trial Endpoints in Prostate Cancer were discussed in an FDA Public Workshop in June 2004, followed by an FDA Oncology Drug Advisory Committee (ODAC) meeting discussion in March 2005 (12;13). A summary of discussions on several prostate cancer endpoints relevant to the current BLA submission is described below:

Prostate Specific Antigen (PSA)-related endpoints

PSA based endpoints (reduction, double time or PSA velocity) have been proposed to overcome some of the difficulties encountered in assessing outcome by means of other endpoints, e.g. bone scans or pain relief. In current clinical practice, patient management decisions are frequently dictated by changes observed in the PSA level; PSA determination is reproducible and quantitative; rising PSA levels often precede other manifestations of disease progression; and except in some rare circumstances rising PSA level means disease progression. Thus, the PSA based endpoints may accelerate both the development of promising agents and the discontinuation of inactive ones. However, none of the PSA based endpoints has been validated as a surrogate for clinical benefit so far. Correlation of PSA based endpoints with prognosis can support their use for patient selection and stratification in clinical trials. However, correlation of a tumor marker such as PSA with clinical outcome, although a necessary first step, by itself does not provide validation for a tumor marker to serve as a surrogate of clinical benefit.

Time to progression (TTP)

The use of TTP as a trial endpoint presents several challenging study design issues. TTP is a difficult endpoint to measure; meticulous care must be taken prospectively to ensure that a TTP endpoint has validity. When possible, trials should be blinded. Tumor assessments must be symmetrical on all study arms. Tumor progression must be prospectively defined and prospective methods must be in place for handling missing data. If progression is to be determined radiographically, independent radiology review plays a key role in the analysis and interpretation of trial results. Review of radiographic progression by blinded radiology panels provide credence to the endpoint. Randomized trials are necessary to demonstrate

benefit in all time-dependant endpoints such as survival, progression-free survival and time to tumor progression.

Overall survival (OS)

Survival is the gold standard in oncology trials and often serves as the basis for product licensure. It is a universally accepted direct measure of benefit in cancer patients, and is relatively easily and precisely measured and is less subject to bias. Trials that use survival as their endpoint take a longer to perform and must enroll larger numbers of patients. In addition, the true survival effect of a treatment may be obscured by secondary treatment and crossover. The inability of OS to capture cause of death may be relevant in prostate cancer patients, where patients may die of other causes and cause-specific death allows a bias in the adjudication of cause of death. The median survival of patients with androgen independent prostate cancer is less than two years, making survival a very feasible endpoint in advanced prostate cancer as compared with more indolent indications.

3.3 APC8015 (Sipuleucel T) immunotherapy

- Pre-clinical studies

The development of APC8015 was based on the pre-clinical results from rodent experiments suggesting that infusion of rat APC ex vivo cultured with prostatic acid phosphatase (PAP) fused to GM-CSF (PAP-GM-CSF) could elicit immunity attacking normal rat prostate, inducing autoimmune prostatitis. PAP is a normal prostate tissue antigen found in both rat and human species, and is highly expressed in human prostate cancer (14). It was thus hypothesized that immunization to human prostate cancer could break immune tolerance, leading the destruction of prostate cancer cells. A fusion protein encoding the human PAP sequence fused to human granulocyte-macrophage colony-stimulating factor (GM-CSF) was engineered. This recombinant protein was named PA2024.

- Phase 1 and 2 trials using APC8015

- In a phase I/II trial, 31 men with hormone-refractory prostate cancer (HRPC) (12 patients with metastatic disease and 19 with nonmetastatic disease) were treated with sipuleucel-T on weeks 0, 4 and 8, with a fourth infusion administered on week 24 to patients whose disease was stable or improving. All patients appeared to have developed immune response to the target antigen PA2024, as measured by lymphocyte proliferation assays. Three patients had a more than 50% decline in PSA level and another three had PSA declines by 25 to 49%. Median time to progression in the Phase II study was 29 weeks (15).
- In a separate Phase I trial, 13 patients with metastatic HRPC were treated with sipuleucel-T and three subcutaneous PA2024 injections to boost immune responses. Sipuleucel-T was administered on weeks 0 and 4, while PA2024 was given on weeks 8, 12 and 16. Out of 12 patients evaluable for response to

treatment, three patients had a more than 50% decline in PSA, and three patients experienced drops in circulating PAP levels. With regards to immune response, there was evidence of specific T-cell responses as well as antibody generation. The administration of three subcutaneous injections of PA2024 contributed little to the T-cell proliferation response. All evaluable patients developed antibodies (low in titer) to PA2024, with nine patients after sipuleucel-T alone, but before PA2024 injections (16).

- Phase II studies --- Metastatic setting
In a Phase II trial, 21 patients with metastatic HRPC were treated with sipuleucel-T. Sipuleucel-T was infused twice, 2 weeks apart, with three subcutaneous injections of PA2024 one month apart starting 2 weeks after the second sipuleucel-T infusion. Of the 19 patients who received both sipuleucel-T infusions and at least one PA2024 injection, two of these patients exhibited a transient 25–50% decrease in PSA. In a third patient, PSA fell from 221 ng/ml at baseline to undetectable levels at week 24 and metastatic retroperitoneal and pelvic adenopathy resolved. Median time to progression was 118 days. The addition of PA2024 injections once again did not confer any apparent immunological clinical responses over and beyond Sipeuleucel T alone (17).
- Phase II studies --- biochemical progression
An additional phase II trial was conducted in men with androgen-dependent prostate cancer with biochemical progression after definitive therapy. 18 men with a PSA of 0.4–6 ng/ml were treated with sipuleucel-T as single therapy. No prior immuno-, chemo-, or steroid therapy was allowed. Sipuleucel-T was administered on weeks 0, 2 and 4. PSA was measured at baseline and monthly until disease progression, which was defined as a doubling of the baseline or nadir PSA value. Of the 18 patients, 13 had an increase in PSA doubling time (PSADT), with a median increase of 62% (4.9 months before treatment vs. 7.9 months after treatment; $p = 0.09$), but did not result in a 50% or larger decrease in PSA from baseline (18).

3.4 Proposed indication

For the treatment of men with asymptomatic, metastatic androgen independent prostate cancer (AIPC).

3.5 Presubmission Regulatory Activity

Table 3 below summarizes the major agreements and meetings between FDA and the Applicant.

Table 3: Summary of Relevant Regulatory Milestones

Date	Milestone Description	Outcome
22 DEC 1996	IND Original submission, BB-IND 6933, in effect.	Phase 1 trial initiated.

Date	Milestone Description	Outcome
03 NOV 1998	End of Phase 2 Meeting to discuss a prospective Phase 3 trial including product issues, clinical target population, study endpoints, assessment of treatment benefit, and appropriate controls.	FDA provided recommendations regarding the design of the Phase 3 trial efficacy endpoints (including a requirement for survival data submission and concerns about the crossover design), patient population, control arm, maintenance of blinding. FDA reminded sponsor that a single trial with a TTP endpoint would be unlikely to support licensure that additional studies would be likely to be required, and that comparisons of survival between study arms would have to be performed.
04 MAR 1999	Follow-Up to End of Phase 2 Teleconference to discuss a prospective Phase 3 trial and a Phase 2 open-label salvage trial	FDA provided additional recommendations regarding the design of the Phase 3 (progression endpoints, study procedures, analytical plan). Dendreon agreed to capture survival data although the primary endpoint was time to disease progression.
03 SEP 1999	Follow-Up to End of Phase 2 Teleconference on Phase 3 Protocols D9901 and D9902, discussing study design and statistical analysis plan	FDA agreed to the design of Studies D9901 and D9902 (including the efficacy endpoints, patient population, control arm, and study procedures) and the proposed analyses. FDA stated that original population was insufficient for safety database, agreed that a 2:1 ratio of drug to placebo would provide sufficient safety data.
20 JUL 2001	Sipuleucel-T Clinical Development Plan and new Phase 3 study P-11	FDA agreed that the clinical development plan (D9901 and D9902) was sufficient to support a license application for sipuleucel-T; FDA requested clarification of objective disease progression endpoint.
26 JUL 2002	D9901 Final Statistical Analysis Plan (SAP) submitted to FDA	SAP approved by FDA
Oct 2002	D9901 Primary Analysis	Results of Study D9901 analysis demonstrated that overall study results were negative, but sipuleucel-T delayed time to objective disease progression in the ITT population with a statistically significant treatment effect of delaying time to objective disease progression in the non pre-specified subgroup of patients with Gleason score ≤ 7 . Data submitted to FDA and discussed at the Type A Meeting as noted below.
22 NOV 2002	Type A Meeting to discuss results of D9901 and proposed changes to D9902	Based on the above findings of the D9901 primary analysis, FDA agreed that Study D9902 could be split into 2 parts: D9902A would include subjects already enrolled regardless of Gleason score; D9902B would be initiated, to include subjects with Gleason scores of ≤ 7 . These study populations could not be combined for efficacy analysis.
30 MAY 2003	Special Protocol Assessment agreement received for Protocol D9902B	Time to objective disease progression and time to disease related pain were co-primary endpoints.
30 JUL 2003	Sipuleucel-T received Fast Track designation for the treatment of asymptomatic patients with metastatic, Gleason Sum ≤ 7 AIPC	Received Fast Track designation based on the potential of sipuleucel-T to prolong TTP and time to disease related pain (TDRP) in men with asymptomatic, metastatic, Gleason Sum ≤ 7 AIPC
October 2004	D9901 Survival Analysis Performed	Analysis demonstrated a survival increase of sipuleucel-T compared with APC-Placebo in the ITT population
24 NOV 2004	D9902A Final Statistical Analysis Plan submitted to FDA	FDA agreed to the proposed D9902A SAP with primary endpoint of time to disease progression and adding overall survival as secondary endpoint.
28 JUL 2005	Type C Meeting (CMC Licensing Strategy)	FDA agreed that the to-be-licensed manufacturing process is consistent with that used for studies that will serve as the clinical basis for the BLA
25 NOV 2005	SPA Amendment for Protocol D9902B	Major changes included elimination of the Gleason score restriction, expansion of the eligibility criteria to include minimally symptomatic patients, and elevation of survival to the primary endpoint.
21 Aug 2006	Clinical section of BLA submitted electronically	

4 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing and Control (CMC):

See separate CMC review

4.2 Animal Pharmacology/Toxicology

See separate Pharmacology and toxicology review

4.3 Statistics

See separate statistical review

5 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

5.1 Sources of Clinical Data

- The regulatory history of the application
- Electronic submission of the BLA and its amendments
- Relevant published literature
- Relevant submissions in response to clinical reviewer's questions.

5.2 Tables of Clinical Studies

Table 4: Clinical Studies Pertinent to the Claimed Indication

A: Controlled studies:

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Controlled Clinical Studies Pertinent to the Claimed Indication									
Phase 3; Safety and Efficacy	D9901	clinical\aipe\controlled\csr-d9901.pdf	<ul style="list-style-type: none"> • Safety of APC8015 • Survival • TTP • TDRP • Response rate and duration of response • Immune response 	Double-blind, multicenter, randomized (2:1); Placebo-controlled	APC8015 or APC-Placebo; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (minimum 3×10^6 CD54 ⁺ cells); Intravenous infusion	127 (82:45)	Asymptomatic, metastatic, AIPC	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4	Complete; Full CSR
Phase 3; Safety and Efficacy	D9902A	clinical\aipe\controlled\csr-d9902a.pdf	<ul style="list-style-type: none"> • Safety of APC8015 • Survival • TTP • TDRP • Response rate and duration of response 	Double-blind, multicenter, randomized (2:1); Placebo-controlled	APC8015 or APC-Placebo; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (minimum 3×10^6 CD54 ⁺ cells); Intravenous infusion	98 (65:33)	Asymptomatic, metastatic, AIPC	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4	Complete; Full CSR

B: Uncontrolled studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Uncontrolled Clinical Studies									
Phase 1/2; Safety	9610	clinical\aicp\uncontrolled\csr-d9610.pdf	<ul style="list-style-type: none"> Safety of APC8015 Immune response Tumor response 	Open-label, dose escalation; No control	APC8015; 3 dose level cohorts: 1) 0.2×10^9 cells/m ² 2) 0.6×10^9 cells/m ² 3) 1.2×10^9 cells/m ² ; Intravenous infusion	Phase 1: 12 Phase 2: 19	Phase 1: Metastatic AIPC Phase 2: Non-Metastatic AIPC	Approximately 24 weeks, with 1 dose given in Weeks 0, 4, 8 and 24	Complete; Abbreviated CSR
Phase 1/2; Safety	9702	clinical\aicp\uncontrolled\csr-d9702.pdf	<ul style="list-style-type: none"> Safety of APC8015 and PA2024 Immune response Tumor response 	Open-label, dose escalation; No control	APC8015; Approximately 1.2×10^9 nucleated cells/m ² ; Intravenous infusion PA2024; Phase 1: 3 dose level cohorts: 1) 0.3 mg 2) 0.6 mg 3) 1.0 mg; Phase 2: 1.0 mg; Subcutaneous (sc) injection	Phase 1: 13 Phase 2: 21	Metastatic AIPC	Phase 1: Approximately 16 weeks, with one IV dose given in Weeks 0 and 4 and sc antigen injections given at Weeks 8, 12, and 16 Phase 2: Approximately 12 weeks, with one IV dose given in Weeks 0 and 2 and sc antigen injections given at Weeks 4, 8, and 12	Complete; Abbreviated CSR
Phase 2; Safety	D9903	clinical\aicp\uncontrolled\csr-d9903.pdf	<ul style="list-style-type: none"> Safety of APC8015F Response rate and duration Time to disease progression 	Open-label, multicenter, salvage; No control	APC8015F; 3 autologous cell doses, each dose prepared from cryopreserved PBMCs, including APCs, (minimum 3×10^6 CD54 ⁺ cells); Intravenous infusion	56	AIPC subjects with objective disease progression following participation in the APC-Placebo arm of Studies D9901 or D9902A	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4	Complete; Abbreviated CSR

C: Completed Studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Other Clinical Studies – Completed Studies									
Phase 2; Safety	D9905	clinical\other\csr-d9905.pdf	<ul style="list-style-type: none"> Safety of APC8015 Tumor response TTP 	Open-label; No control	APC8015; 3 autologous doses, each dose the maximum that could be prepared from a single leukapheresis (approximately 1.2×10^9 cells/m ²); Intravenous infusion	18	Non-metastatic prostate cancer with PSA progression after definitive local therapy	Approximately 4 weeks, with 1 dose given in Weeks 0, 2, and 4	Complete; CSR Synopsis
Phase 1; Safety	D9801	clinical\other\csr-d9801.pdf	<ul style="list-style-type: none"> Safety of APC8026 Immune response Relationship between cell dose and immune response 	Open-label; No control	APC8026; 3 dose level cohorts: 1) 1.0×10^9 cells/m ² 2) 2.5×10^9 cells/m ² 3) 4.0×10^9 cells/m ² ; Intravenous infusion	15	Advanced AIPC	Approximately 16 weeks, with 1 dose given in Week 0, 2, 4, and 16	Complete; CSR Synopsis

D: On-going studies (see Appendix 6)

5.3 Review Strategy

The efficacy review is primarily based on the data from the trial D9901 and integrated data of the trial D9901 and D9902A with the emphasis on the data from D9901. All death dates were reviewed by examinations of both case report forms (CFRs) and available death certificates. A consultant reviewer examined all D9901 CRFs to evaluate the patient eligibility, distribution of tumor locations and tumor evaluations.

The safety review is primarily based on the data of 225 subjects from D9901, D9902A. CVA events review included additional information from P-11 and D9902B.

5.4 Data Quality, Integrity and Compliance with Good Clinical Practices

Generally adequate. See BiMO's separate review memo.

5.5 Financial Disclosures

Certification of financial disclosure (Form 3454) was provided by the sponsor. Documentation of financial disclosure was provided for all investigators except one (the applicant did not have financial disclosure information available). The applicant certified that as the sponsor of the submitted studies, the applicant has not entered into any financial arrangement with the clinical investigators listed whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a).

However, the results from BiMO inspection revealed that one of the primary investigators for both studies is a consultant to the sponsor and owns -b(4)-Dendreon stock shares worth about -b(4)-------. He did not report this financial interest to the IRB and the informed consent document does not mention the investigator's financial interest in the clinical study. There is no evidence to suggest that the clinical data from this investigator biased the studies.

6 ANALYSES OF EFFICACY

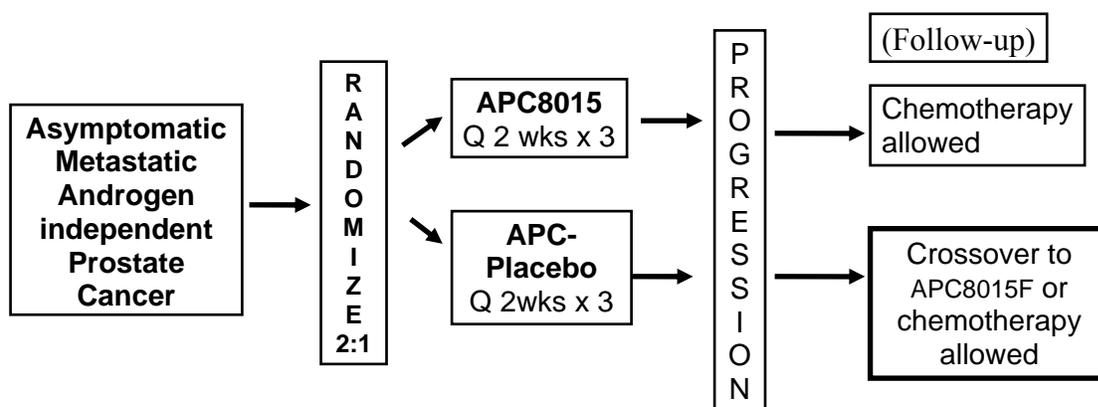
6.1 Methods

The data from two randomized phase 3 trials, D9901 and D9902A were used for the evaluation of the efficacy. The objective study protocol information was reviewed first, followed by integrated analyses. Case report forms, death events and primary datasets were analyzed.

6.2 Study Design, D9901 and D9902A

Studies D9901 and D9902A were similarly designed randomized, double-blind, placebo-controlled trials in men with asymptomatic metastatic hormone-refractory prostate cancer. Subjects were randomized following eligibility determination and assigned to receive three intravenous infusions of either APC8015 or APC-placebo at weeks 0, 2 and 4. Following progression, subjects were allowed to receive chemotherapy. Subjects assigned to placebo could alternatively “cross over” to receive APC8015F. “APC 8015 F” was similarly prepared as APC 8015 except that the frozen PBMCs were used as the starting material (see section 6.2.E). The study design is outlined in Figure 1:

Figure 1: D9901 and D9902A study design



During the study, hormonal treatment and Bisphosphonates were continued. RT and Chemotherapy were prohibited while on study.

D9901 and D9902A shared the same study title; study design; patient entry criteria primary and secondary endpoints; treatment; follow up; and evaluation plans with D9902A enrolling patients shortly after D9901 (see regulatory history). However, D9902A endpoints and statistical analytical plan were later revised before the final analyses to change the efficacy endpoints as described in section 6.6.B.

Summary of clinical trial design and protocol review is described below.

A. Study title

A Randomized, Double Blind, Placebo Controlled Trial of Immunotherapy with Autologous Antigen-Loaded Dendritic Cells (Provence™, APC8015) for Asymptomatic Metastatic Hormone-Refractory Prostate Cancer

B. Primary and secondary objectives

D9901

- **The primary objective** was to compare the **time to disease progression**, defined as the time from randomization to the first observation of disease progression.
- **Secondary objectives** included comparison between the two arms:
 - a) Time to onset of disease-related pain (The planned analysis of D9901 and D9902A included a pooled analysis in order to have sufficient power for this endpoint.);
 - b) Response rate and duration of response;
 - c) Time to first evidence of clinical progression;
 - d) Time to treatment failure; and
 - e) Incidence of Grade 3 and greater treatment-related AEs.

D9902A

The primary objective: same as D9901

Secondary objectives: same as D9901 initially, but revised in November 2004 as described in section 6.6.B.

C. Key Eligibility criteria

- **Inclusion criteria**
 - ❖ Histologically documented adenocarcinoma of the prostate >25% of tumor cells staining positive for PAP by immunohistochemistry.
 - ❖ Current hormonal therapy consisting of castration by orchiectomy or LHRH agonists documented by castrate levels of testosterone (<50 ng/dl).
 - ❖ Metastatic disease as evidenced by soft tissue and/or bony metastases.
 - ❖ Baseline PSA value > 5 ng/mL, stable or rising,
 - ❖ Tumor progression (see definition in section 6.2.F.i)
 - Progression of measurable disease, or
 - Progression of evaluable disease, or
 - PSA progression: PSA evidence for progressive disease requires a PSA >5 ng/mL and two consecutive PSA values, at least 14 days apart, each > 50% above the minimum PSA observed during initial castration therapy or above the pretreatment value if there was no response. In addition, the patient must have rising PSA on two determinations at least 14 days apart on current therapy if any.
 - ❖ ECOG Performance Status of 0 or 1.

- ❖ Adequate hematologic, renal and liver function evidenced by laboratory parameters
- ❖ Prior and concurrent therapy allowed:
 - Prior chemotherapy was allowed provided at least 6 months had elapsed from the last dose to the time of registration or 3 months if the patient's CD4+ T-cell count was greater than 400.
 - Primary radiation therapy and surgery was allowed. At least 4 weeks must have elapsed since the completion of radiation therapy or surgery and the patient must have recovered from acute side effects.
 - Prior antiandrogen therapy with non-steroidal antiandrogens (e.g., flutamide, nilutamide or bicalutamide) was permitted provided therapy was stopped at least four weeks prior to enrollment for flutamide or nilutamide and six weeks prior to enrollment for bicalutamide.
 - Prior herbal therapy was permitted.
 - Concurrent bisphosphonate therapy was permitted provided treatment started at least 30 days before enrollment. Patients may not start or stop bisphosphonates within 30 days before enrollment or during the time patients are on this protocol.
- **Exclusion Criteria**
 - ❖ Cancer-related pain.
 - ❖ Visceral organ metastases (e.g., liver, lung, brain) or cytologically positive effusions (e.g., pleural effusions or ascites).
 - ❖ Prior radiation therapy or anticipated need for radiation therapy in the next four months.
 - ❖ Concurrent therapy with experimental agents.
 - ❖ Concurrent herbal therapy (e.g., PC-SPES or Saw Palmetto) was prohibited.
 - ❖ Prior radiopharmaceutical therapy (e.g. strontium therapy) was excluded unless at least one year has elapsed since treatment.
 - ❖ Systemic corticosteroids at doses greater than 40 mg hydrocortisone/day other than for treatment of prostate cancer within the last 6 months.
 - ❖ History of prior malignancy.
 - ❖ Ongoing active bacterial, viral or fungal infection.

D. Randomization and blinding

Patients were randomized 2:1 to APC8015 and to APC-Placebo. Two strata were used in the randomization: bisphosphonate use and study center. The randomization was performed by the sponsor's contract organization. Both studies were blinded to

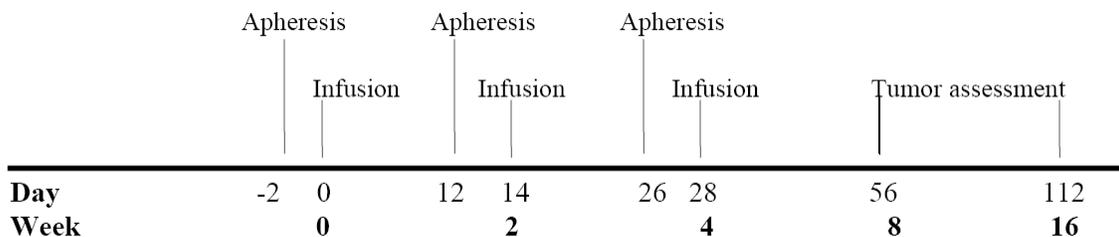
the sponsor’s clinical personnel, investigators and patients. This blinding was maintained throughout the trial. However, the sponsor’s manufacturing personnel were not blinded.

E. Treatment regimens

Each subject underwent apheresis procedure to harvest peripheral blood mononuclear cells (PBMCs) 2 to 3 days prior to the infusion date. For subjects in the APC 8015 arm, these cells were cultured *ex vivo* and activated with PA2024, a recombinant protein consisting of Prostate Acid Phosphatase fused to Granulocyte Macrophage Colony Stimulating Factor (PAP-GM-CSF). Cells were washed, tested for sterility, identity and potency before the intravenous infusion to subjects. The cell manufacturing process took approximately 2 days to complete from harvesting cells by apheresis to fresh administration to subjects. Subjects in the APC placebo arm underwent the same apheresis procedure as those in APC 8015 arm to harvest PBMCs. However, these cells were not activated with any material. Instead, one-third of the total PBMCs were freshly administered to subjects and the other two third were frozen. If a subject in the placebo arm had disease progression, these frozen cells would be thawed and loaded with PA2024 (APC8015F) and infused.

The study agent, either APC8015 or APC-Placebo, was administered intravenously every 2 weeks for 3 doses. The cell counts in each individual dose varied depending on the apheresis yield. The minimum APC8015 dose was approximately 3×10^6 CD54+ cells for each infusion. The dose for APC-Placebo was 1/3 of the total cells harvested from the apheresis. The two phase 3 trials did not evaluate the effectiveness or safety in subjects who received different doses of APC8015. Hormonal treatment and bisphosphonates were continued during the study if the patient was initially enrolled on these therapies. Figure 2 outlines the schedule of leukapheresis and infusions.

Figure 2: Schedule of leukapheresis and infusions



F. Clinical endpoint definitions

i. Primary endpoint:

The primary endpoint was the time to objective disease progression, defined as the time from randomization to the development of objective disease progression.

“Objective” disease progression: defined as any of the following:

- **Radiological Progression**
- **Clinical Progression**
- **Pain progression**

Radiological progression: defined by any of the following:

- *Measurable disease:* > 50% increase in the sum of the products of the perpendicular diameters of all bidimensionally measurable lesions. The change will be measured against the best response to prior therapy or against the pretreatment value if there was no response.
- *Evaluable disease:* Unidimensionally measurable disease: > 50% increase in the sum of the measurements of all unidimensionally measurable lesions. The change will be measured against the best response to prior therapy or against the pretreatment value if there was no response.
- *Non-measurable disease:* Clear worsening of non-measurable disease.
- *“Scan only” bone disease:* an appearance of 2 or more new areas of abnormal uptake on bone scan. Increased uptake of pre-existing lesions on bone scan does not constitute progression.
- Appearance of any new lesions on X-ray, CT scan or MRI, or reappearance of any lesion which had disappeared constitutes progression

○ **Definitions of disease status**

- *Measurable disease (radiological scans):*
 - Tumor masses with clearly defined margins
 - Three lesions should be chosen for follow-up, additional lesions will be considered evaluable
- *Evaluable Disease (radiological scans):*
 - Unidimensionally measurable disease
 - Non-measurable disease
 - “Scan only” bone disease
- *Non-measurable Disease:* Disease that is not measurable or evaluable
- The prostate may be a site of measurable disease, evaluable disease or non-evaluable disease.

Clinical progression: Defined by development of prostate cancer-related events (e.g., spinal cord compression or a pathologic fracture or the development of a requirement for radiation therapy or other clinically significant disease-specific events)

Pain Progression: Defined by development of prostate cancer-related pain, corresponding to the site of disease, as demonstrated by objective radiographic means.

ii. Secondary endpoints

D9901

- Time to onset of disease-related pain (The D9901 and D9902A results were pooled in order to have sufficient power for this endpoint.);
- Time to first evidence of clinical progression;
- Time to treatment failure;
- Incidence of Grade 3 and greater treatment-related AEs.
- Response rate and duration of response;

D9902A

The secondary endpoints were initially the same as D9901 in the clinical protocol. However, in November 2004 after the analyses of D9901 overall survival demonstrating a survival difference between the two arms, the sponsor revised the secondary endpoints to be the following

- Overall survival
- The time to objective disease progression confirmed by imaging studies

D9902A Tertiary endpoints

The original protocol did not have tertiary endpoints. The revised statistical analyses before unblinding the data included the following as tertiary endpoints

- The time to the development of disease-related pain in subjects treated with APC8015 versus APC-Placebo.
- The time to disease progression with treatment, cell processing center (CPC), and their interaction tested in subjects treated with APC8015 versus APC-Placebo
- The incidence of Grade 3 and greater treatment-related adverse events (AEs) in subjects treated with APC8015 versus APC-Placebo
- Response rate.
- **PSA progression** was not used as a study endpoint

iii. Survival: Survival was not a pre-specified efficacy endpoint in either D9901 or D9902A. The primary method for survival analysis was not pre-specified in the protocol. The D9901 protocol stated that “This study is not powered to show a survival effect. However, survival data will be summarized descriptively.”

In addition, the statistical analytical plan of the clinical protocol contained the following description regarding the use of survival as supporting analyses in the analysis methodology section for the primary endpoint of time to disease progression:

“Primary endpoint

The analysis of time to disease progression will be conducted on the ITT and Efficacy Evaluable Populations. The primary analysis will be on the ITT population.

The primary null hypothesis is that the time to disease progression curve of the APC8015 group is not different from that of the control group. The corresponding alternative hypothesis is that there is a difference between these curves. Time to disease progression curves will be constructed using Kaplan- Meier technique for the two treatment groups and the primary hypothesis tested using the log-rank test.

“As supporting analyses, estimates of survival rate and progression free frequencies at three, six, nine, twelve and every six months thereafter, and median survival will be provided based on the Kaplan-Meier curves, with corresponding confidence intervals; and the Cox proportional hazards model will be used to adjust for prognostic variables.”

F. Sample size and statistical assumptions

Based on the sponsor’s past experience and a review of the literature, the median time to objective disease progression was estimated to be 16 weeks for control patients and 31 weeks for APC8015 treated subject, a delay in the time to objective disease progression of 3.7 months (from 4 to 7.7 months). All subjects were followed for 36 months or until death for safety.

Both studies were designed to have a two-sided 5% level of significance and 2:1 ratio between the treatment and control group. A total of 120 patients would be needed to achieve 80% power to detect the specified difference of 3.7 months in median time to objective disease progression.

A total of 240 patients for pooled analysis, 120 from each study, would be needed to achieve 80% power for time to pain progression --- one of the secondary endpoints. Derived from these assumptions, each study was designed to enroll 120 patients.

G. Study Evaluations

○ Efficacy Evaluations

Medical histories, physical examinations, laboratory evaluations, pain status, and survival status were performed at baseline, weeks 2, 4, 8, 12, 16, 24, and 32, and every 12 weeks thereafter until disease progression. To assess the efficacy of treatment (disease progression), bone scan was performed at baseline, weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression. CT and/or MRI was performed at baseline and, if positive, at weeks 8, 16, 24 and 32 and every 12 weeks thereafter until disease progression. It should be noted that this design could miss the detection of soft tissue tumor progression in subjects with bone only disease due to the lack of CT and/or MRI scans. Prostate-specific antigen (PSA) was measured every 16 weeks before disease progression.

Subjects were monitored for survival at 2 months following disease progression and every 6 months after randomization until death or for 36 months, whichever occurred first.

○ Safety Evaluations

Safety measurements included AE assessments, laboratory measurements, and vital sign measurements. Adverse events were collected at each study visit, or whenever they occurred, through Week 16. Adverse events deemed by the Investigator as related to the study product were collected for the duration of each subject's participation in the trial. Serious adverse events (SAEs) were defined as events that resulted in death, were life-threatening, or resulted in hospitalization; important medical events that required medical or surgical intervention to prevent one of these outcomes could also have been considered SAEs. Subjects were monitored for delayed treatment-related AEs at 2 months following disease progression and every 6 months after randomization until death or for 36 months.

Table 5. Evaluation schedule

	Base-line	0	2	4	8	12	16	24, 32 then Q12 weeks before disease progression ^a	Q16 weeks before disease progression ^a	2 months and Q6 months after disease progression ^b
Apheresis		X	X	X						
Clinical										
ECOG	X									
History and Physical ^c	X		X	X	X	X	X	X		

	Base-line	0	2	4	8	12	16	24, 32 then Q12 weeks before disease progression ^a	Q16 weeks before disease progression ^a	2 months and Q6 months after disease progression ^b
Survival and adverse events (up to 3 years or death)			X	X	X	X	X	X		X
Pain Log ^d	X		X	X	X	X	X	X		
Staging ^{a,e,f} : Bone Scan, CT or MRI of abdomen and pelvis	X ^a				X ^a		X ^a	X ^a		
Lab Tests										
PSA ^f	X						X		X	
PAP blood test	X						X			
CBC	X		X	X	X	X	X	X		
Testosterone	X									
Bun/Creatinine	X						X			
Na, K, Ca ⁺⁺ , Mg ⁺⁺	X									
LFTs: Total bilirubin, AST, ALT, Alkaline Phosphatase	X				X		X			
LDH, Albumin, Total Protein	X									
Serology: HIV 1 and 2, Hepatitis B and C, HTLV-1	X									
Urinalysis	X									
EKG	X									
Chest x-ray	X									
Immunohistochemistry (tumor tissue staining for PAP)	X									
Blinding Assessment					X					
antibody and/or T-cell immune response		X			X		X			

- a. Baseline staging must include CT or MRI of the abdomen and pelvis and a bone scan. Perform follow up CT/MRI only if baseline is positive for tumor. Follow up bone scan is required regardless of baseline result.
- b. At the time patients develop objective disease progression, follow-up will be limited to survival and delayed treatment-related adverse events. Follow-up after disease progression and pain status will be at 2 months and every 6 months for 3 years or until death, whichever is shorter.
- c. A full history, physical exam and pain assessment must be performed at Baseline. At subsequent time points, a problem-oriented history, physical exam and pain assessments are required.
- d. Patients will complete the Weekly Pain and Analgesic Use log weekly. Patients developing disease-related pain before or at the time of objective disease progression will stop the pain log. Patients who are pain-free at the time of objective disease progression will continue the pain log 4 additional weeks.
- e. To ensure comparability, the Baseline scans/x-rays and subsequent scans/x-rays to assess response must be performed using identical techniques.
- f. Patients who have a Partial or Complete Response at any time point should have a repeated tumor assessment and PSA test 4 weeks later to confirm the response status.
- g. Tests must be performed but treatment may begin before the results are available. Antibody response means antibodies to the PAP antigen assessed by specific ELISA. T-cell response means T-cell response to the PAP antigen assessed by proliferation.

H. Analysis plan for the primary efficacy endpoint

The primary efficacy endpoint was time to objective disease progression, defined as the time from randomization to the first observation of disease progression. For patients without disease progression by the cutoff date (April 30, 2002), this time was censored at the cutoff date. For patients lost to follow-up without disease progression before the cutoff date, this time was censored at the time of last follow-up visit.

The following procedures were used to determine the date of disease progression:

- o For patients with objective (i.e., radiographic) evidence for disease progression, the date of the objective evidence was the date of progression.
- o For patients with clinical evidence for disease progression but no objective evidence, the date of onset of the clinical event was the date of progression.
- o For patients with both objective and clinical evidence for progression, the date of objective evidence is the date of progression.

All imaging scans used to determine the dates of progression were reviewed and confirmed by a third party independent radiology facility

The database was locked, then unblinded in June 2002 for the final analysis when 109 progression events had occurred during the study. In October 2004, supplemental analysis of safety and survival was performed at 36 months after the last patient was entered into the study.

I. Key amendments

Amendment #2 (3-27-00) Baseline procedures expanded to include CT or MRI of the pelvis and abdomen in addition to bone scan. The tumor staging was more frequent; Q8 weeks for CT or MRI vs. Q16 weeks.

Amendment #5 (3-12-01) clarified inclusion criteria to allow prior palliative radiation therapy (RT) including strontium therapy if at least 1 year had elapsed and the patient remained pain-free.

Amendment #6: (9-27-01) Added statistical plans for performing an unblinded interim analysis conducted on data entered as of 28 September 2001. “Although no claims of efficacy for purposes of regulatory submission will be made, attention to the type-I error probability is warranted. The interim analysis will therefore employ a Haybittle-Peto approach with a nominal significance level of 0.001 at the interim and 0.05 at the final analysis, for a two-sided test of the hypothesis. The final data analysis will be conducted when 109 events have occurred during the study and will be followed by a supplemental analysis of safety and survival at three years after the last patient was entered into the study. Additional supplemental analyses may be performed without amending the protocol if the FDA or another regulatory agency requests the analyses.”

Amendment # 7 (7-25-02) revised the SAP, including the description on survival analysis under the analysis methodology section for the primary endpoint of TTP (see section 6.2.F.iv).

J. Protocol milestones

Table 6. D9901 protocol milestones

Date	Submission	Changes
09-22-1999	Original	N/A
10-22-1999	Amendment #1	Clarified that subjects with prior radiation therapy were eligible for the study if 4 weeks had elapsed since the completion of therapy and if the subject had recovered from any acute side effects.
03-27-2000	Amendment# 2	Added baseline CT or MRI of the pelvis and abdomen as part of the study assessments. This amendment also increased the frequency of follow-up CT and MRI scanning from every 16 weeks to every 8 weeks. (The timing of bone scans remained every 8 weeks.); Added a long-term follow-up visit at 2 months following disease progression.
6-6-2000	Amendment 3	Several administrative changes were made to the protocol, as well as the following major points: the inclusion criterion 5.1.3 was revised to indicate that all subjects were to have stable or rising PSA levels; the testosterone level in inclusion criterion 5.1.5 was changed from < 30 ng/dL to < 50 ng/dL based on NCI criteria; and the timing for several baseline assessments was clarified.
3-12-2001	Amendment 5	The following specific revisions were made: (1) clarified the composition of the placebo control, the expiration time of the

Date	Submission	Changes
		study products, and product storage requirements; (2) revised inclusion criterion 5.1.9 to allow subjects previously treated for painful metastases more than 1 year before registration and who continued to be pain free; (3) amended exclusion criterion 5.2.3 to allow subjects who had previously received experimental therapy, at the discretion of the Dendreon Medical Monitor; (4) amended exclusion criterion 5.2.4 to exclude prior radiopharmaceutical therapy unless at least 1 year had elapsed since treatment, the subject remained pain-free, and the subject was approved by the Dendreon Medical Monitor; (5) further clarified in the exclusion criteria that the use of systemic corticosteroids was permitted unless the treatment was for prostate cancer within 6 months prior to registration unless approved by the Dendreon Medical Monitor; and (6) provided clarification for the timing of specific study-related procedures.
9-27-2001	Amendment 6	Added details of the statistical methodology employed in the analysis of unblinded data for the second interim analysis and clarified the timing of the final data analysis and supplemental analyses.
7-25-2002	Amendment 7	Described changes made to the final reporting and analysis plan. This amendment was not sent to the investigators since the study was closed.

6.3 Efficacy Findings

Since the application depends primarily upon the survival findings reported in study D9901, and D9902A was primarily supportive, the efficacy findings for D9901 will be discussed in more detail and the findings in D9902A will be summarized.

6.4 Efficacy population

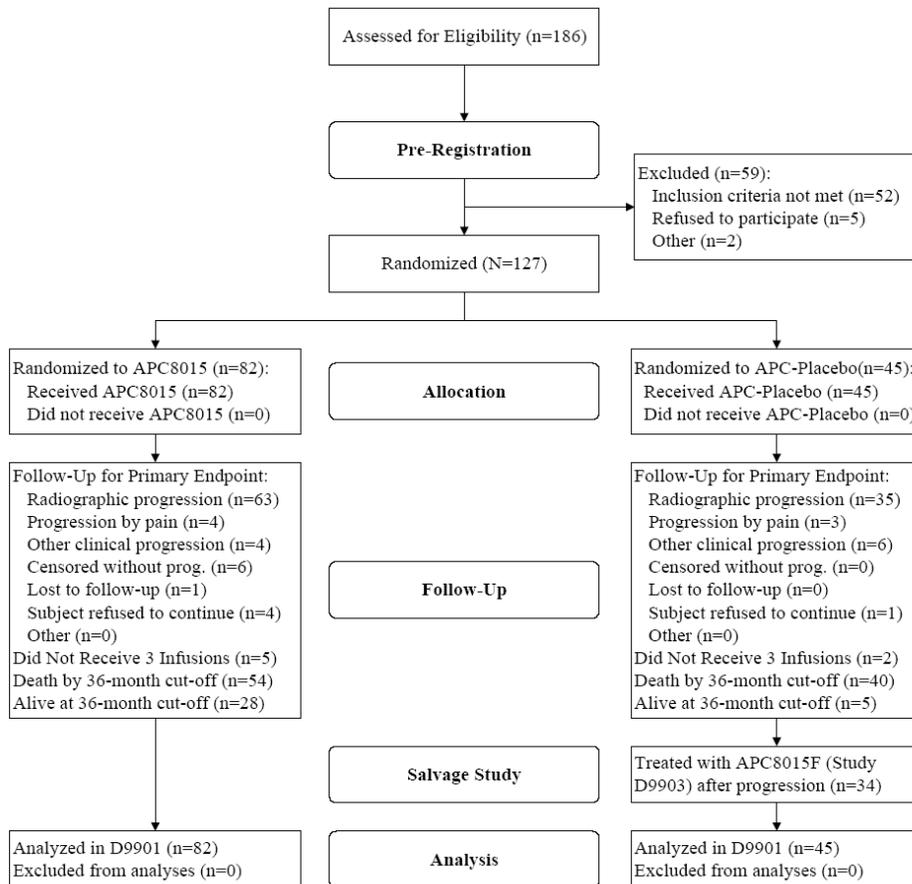
D9901 enrolled a total of 127 subjects with 82 subjects randomized to APC8015 and 45 subjects to APC-Placebo. D9902A randomized 65 subjects to APC 8015 and 33 subjects to APC-Placebo, a total of 98 subjects. The smaller number of subjects in the study D9902 was a result of early termination in March 2003, after the results from D9901 became available showing that there was no statistical significance for any of the pre-specified efficacy endpoints. Therefore, D9902A was insufficient in sample size to detect any difference in any of the pre-specified endpoints.

6.5 D9901 Efficacy Results

A. Patient Disposition

Of 186 subjects screened for eligibility, 127 subjects were randomized between 04 JAN 2000 and 08 OCT 2001. Of these, 82 subjects were randomized to receive APC8015 and 45 subjects were randomized to receive APC-Placebo. All 127 subjects underwent at least 1 leukapheresis procedure and received at least 1 infusion. Of the 59 subjects who were screened for the trial but were not randomized, the majority of subjects failed to satisfy the inclusion criteria (52 of 59 subjects, 88%). Five subjects (8.5%) chose not to participate in the trial following their registration visit. Two additional subjects (3.4%) withdrew for other reasons (aortic aneurysm and participation in a separate clinical trial). One subject was initially considered to have failed the screening process due to no measurable disease, but he later entered the trial after radiographic scans revealed measurable disease and he was therefore included with the 127 randomized subjects. The Sponsor’s summary of the disposition of subjects is presented in Figure 3 below:

Figure 3: Study subject disposition in D9901



B. Patient Baseline Demographic Characteristics

The median age in this population was 73.0 years; ages ranged from 47 years to 86 years. Demographic characteristics of the D9901 study population are summarized in the Table 7 below.

Table 7: Patient Baseline Demographic Characteristics in D9901

Parameter	APC8015 (N = 82)	APC- Placebo (N = 45)	Total (N = 127)
N	82	45	127
Age (years)			
Mean	72.1	71.1	71.7
Range	(47, 85)	(50, 86)	
Race, n (%)			
Caucasian	73 (89.0)	42 (93.3)	115 (90.6)
African American	8 (9.8)	1 (2.2)	9 (7.1)
Hispanic	1 (1.2)	1 (2.2)	2 (1.6)
Unknown	0 (0.0)	1 (2.2)	1 (0.8)
Weight (lbs)			
Mean	199.9	191.2	196.9
Maximum	334.4	272.1	334.4
Unknown		1	1
ECOG Performance Status, n (%)			
0	62 (75.6)	37 (82.2)	99 (78.0)
1	20 (24.4)	8 (17.8)	28 (22.0)
Serum PSA (ng/mL)			
Mean	181.8	168.0	176.9
Median	46.0	47.9	47.3
Minimum	3.5	7.9	3.5
Unknown	1	0	1

There were no significant imbalances between the two arms in ethnicity, PSA, weight and ECOG performance status. In the study, 90.6% of subjects were Caucasians, 7.1% were African-American and 1.6% were Hispanic. Therefore, caution should be exercised when extrapolating the trial data to general population of prostate cancer patients since African-American subjects were underrepresented.

All patients had a pathological diagnosis of prostate adenocarcinoma. Table 8 summarizes Gleason score distributions.

Table 8: Gleason Score distribution in D9901 study subjects

Gleason Score	APC8015 N (%)	Placebo N (%)
N	82	45
≤ 6	22 (26.8)	7 (15.6)
= 7	28 (34.1)	18 (40)
≥ 8	32 (39.0)	20 (44.5)

There were 11.2% more subjects in APC8015 arm who had lower Gleason score compared to APC placebo. Conversely, placebo arm had 11.4% more subjects who had higher Gleason score (≥ 7). The Gleason score is one of the prognostic factors for the patients with prostate cancer.

Table 9 shows the disease distribution between the two arms in study subjects. All subjects in APC8015 arm had a baseline bone scan. One subject in APC 8015 and 3 subjects in APC placebo did not have scans for soft tissue diseases. There were 15.2% more subjects in APC 8015 who had >10 bony metastatic lesions per subject.

Table 9: Disease location and distribution D9901

Localization of Disease		
N	81	42
Bone metastases only	34 (42)	10 (23.8)
Soft tissue metastasis/pelvis recurrence only	5 (6.2)	3 (7.1)
Both bone metastasis and soft tissue metastasis/pelvic recurrence	42 (51.9)	29 (69)
Number of bone metastases per subject	N = 82	N = 45
0	5 (6.1)	4 (8.9)
1-5	31 (37.8)	17 (37.8)
6-10	12 (14.6)	12 (26.7)
> 10	34 (41.5)	12 (26.7)

Table 10 lists the prior treatment regimens the study subject had received prior to the study. There were no imbalances seen between the two arms.

Table 10: Prior treatment regimen D9901

Prior treatment Regimen	APC 8015 N = 82	APC- Placebo N = 45
Hormone Therapies,	n (%)	n (%)
Castration	5 (6.1)	3 (6.6)
Combined androgen blockade	76 (93)	42 (93)
Unknown	1 (1.2)	0 (0.0)
Prior Chemotherapy	3 (3.7)	4 (8.9)
Radiotherapy, Intent of Therapy		
Curative	32 (39.0)	12 (26.7)
Palliative	6 (7.3)	3 (6.7)
Unknown/other	7 (8.5)	4 (8.8)
No radiotherapy received	37 (45.1)	26 (57.8)
Orchiectomy	22 (26.8)	11 (24.4)
Bisphosphonates	3 (3.7)	3 (6.7)

Distribution of Prostate Acid Phosphatase (PAP) between two arms by Immunohistochemistry, a required entry criterion is shown below:

Table 11: Distribution of Prostate Acid Phosphatase (PAP) between two arms

	APC8015 (n = 82)	APC-Placebo (n = 45)	Total (N = 127)	p-value ^a
Percent PAP Positive, n (%)				0.0618
25% - 74%	19 (23.2)	17 (37.8)	36 (28.3)	
≥ 75%	63 (76.8)	28 (62.2)	91 (71.7)	

- There were 14.6% more patients who have $\geq 75\%$ of tumor cells stained positive in APC 8015 arm than APC placebo. APC-placebo arm has 14.6% more patients who have 25-74% of tumor cells stained positive for PAP than APC 8015 arm. The significance of this imbalance is unknown.
- In subsequent communication between the sponsor and FDA, the sponsor indicated that PAP is not a major factor for the study entry criteria and proposed to drop this criterion in subsequent trials (FDA telecom minutes 11-22-2002)

Consultant FDA review of baseline disease status

A detailed review of case report forms was performed by a consultant clinical reviewer to evaluate patient eligibility and baseline imbalances of soft tissue diseases or other factors between the two treatment arms (see Appendix 1).

The consultant clinical reviewer identified considerable variability in the study population in terms of primary therapy and prior antiandrogen use. However, these variations were fairly well-balanced between study arms and were consistent with study entry criteria. In addition, the consultant identified a percentage of patients who may not have been truly refractory to anti-androgen therapy. However, 125/127 (98%) of patients had castrate levels of testosterone (< 50 ng/dl) and had been treated with either orchiectomy or gonadotropic suppression as per study protocol. Thus, the status of D9901 subjects at the study entry was consistent with the generally accepted definition of “hormone refractory” and with other studies in androgen independent prostate cancer such as the TAX 327 study which formed the base for docetaxel approval in hormone refractory, androgen independent metastatic prostate cancer (19). Additionally, all subjects who were on anti-androgens withdrew these therapies prior to study enrollment, eliminating the potential confounding factor on the survival results.

An exploratory analysis of the consultant reviewer’s estimate of the extent of baseline soft tissue disease suggested larger imbalances in baseline extensive soft tissue disease than was originally appreciated: 30% extensive soft tissue disease was observed in the Sipuleucel T patients versus 51% in the placebo patients (see Appendix 1). Despite these imbalances, the estimated survival in the group with more severe soft tissue disease was similar to that of the rest of the study population (p= 0.6857, HR = 1.089, 95% CI: 0.72 -1.65). Therefore, there was no statistical evidence to indicate that this imbalance confounded results. Nonetheless, there may be additional unknown baseline differences between the treatment arms (FDA statistical reviewer’s calculation).

- **Summary of D9901 subject demographic and baseline characteristics:** Study 9901 enrolled 127 patients with AIPC; the median age was 73 years; African-American and Hispanic subjects were underrepresented. The treatment arms appeared well balanced in terms of demographic characteristics; however some imbalances were noted in some of the prognostic characteristics including the Gleason grading and disease location (bone, soft tissue or both) between the two arms. Although these imbalances could have led to biases to the study results, the sensitivity analyses performed did not suggest that they confounded the survival results. See statistical review for details.

C. Study conduct

- **---Information withheld per the Privacy Act-----**

Site	Subject enrolled
Site 21	7
Site 22	2
Site 23	6
Site 24	12
Site 25	14
Site 26	9
Site 27	9
Site 28	3
Site 37	6
Site 44	6
Site 59	2
Site 60	6
Site 62	1
Site 64	9
Site 65	1
Site 68	4
Site 69	20
Site 70	8
Site 73	2

- **Randomization Errors:** Study center and bisphosphonate were used as stratification factors for randomization. Fifteen randomization errors occurred. The majority of errors consisted of subjects not being assigned to the randomization slots expected based on the sequence of enrollment. There were no subjects who were randomized to APC-Placebo actually received APC8015 or vice visa. A sensitivity analysis removing these subjects from the survival analyses did not have an impact on the survival difference seen between APC8015 and APC Placebo.
- **Protocol Deviations:** Major and minor protocol deviations are summarized below:

Table 12: Protocol deviations D9901

Deviations		
	N = 82	N = 45
Major	10 (12.2%)	2 (4.4%)
Testosterone ≥ 50 ng/dl or unknown	4	
Receive XRT during the study	1	
PSA ≥ 5 ng/ml or increase not ≥ 50% from previous value	1	1
Pleural effusion at the entry	1	
No metastatic diseases	1	1
Hormone treatment not continued during the study	1	
Received Prednisone during the study	1	
Minor	24 (29.2%)	14 (31.1)

Eight (8%) more patients in APC8015 arm had major protocol deviations than those in APC-Placebo. Removal of these subjects from the survival analyses did not have an impact on the survival difference observed between APC8015 and APC Placebo. Major protocol eligibility violations included the following:

- no evidence of metastatic disease at entry
- evidence of pleural effusion at study entry
- not medically or surgically castrate at study entry or medical castration therapy discontinued during trial
- PSA values demonstrating or confirming androgen independence obtained outside the protocol-specified window, and radiation therapy received during the active period.

- **Exposure:** The number of leukaphereses and infusions for D9901 study subjects are summarized in Table 13. In the ITT population, 95.3% and 94.5% of patients underwent 3 or more leukapheresis and 3 infusions respectively.

Table 13: Leukaphereses and infusions D9901

Treatment			
Number of Leukaphereses, n (%)			
1 leukapheresis	0 (0.0)	0 (0.0)	0 (0.0)
2 leukaphereses	5 (6.1)	1 (2.2)	6 (4.7)
3 or more leukaphereses	77 (93.9)	44 (97.8)	121 (95.3)
Number of Infusions, n (%)			
1 infusion	2 (2.4)	0 (0.0)	2 (1.6)
2 infusions	3 (3.7)	2 (4.4)	5 (3.9)
3 infusions	77 (93.9)	43 (95.6)	120 (94.5)

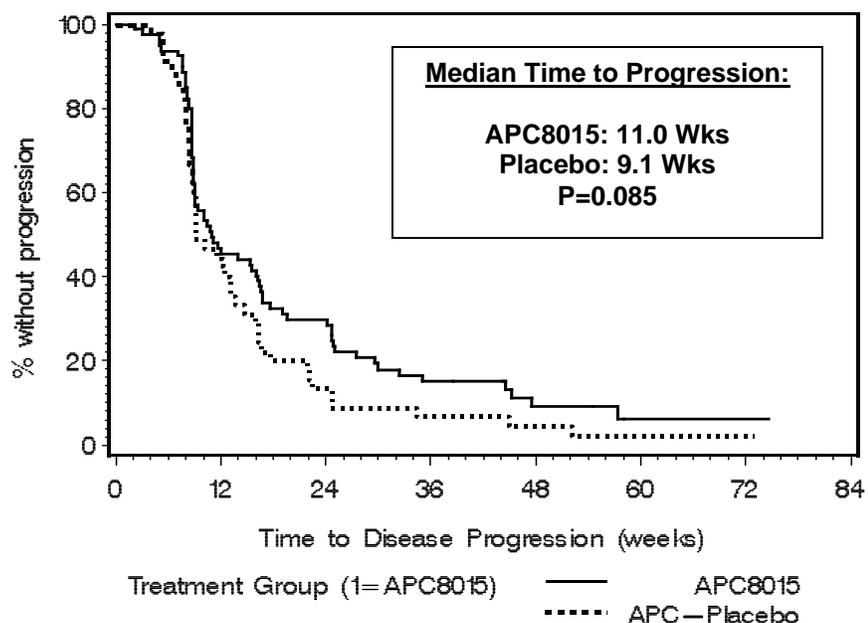
The percentage of subjects who received scheduled infusions and the number of missed administrations were similar between study and control arms, suggesting product tolerability and adequate treatment compliance.

- **Study blinding**

The study was a double blind study: investigators, other clinical study center personnel, subjects, and Dendreon clinical personnel were blinded to treatment assignment. An independent third party contract randomized subjects, and information regarding treatment assignment was sent directly to the manufacturing center personnel. However, the Dendreon's manufacturing center personnel was not blinded to the patient assignment.

D. D9901 Primary efficacy endpoint analysis

Study D9901 primary analysis was performed in October 2002, after 115 progression events had occurred. The analyses of the time to disease progression are depicted in the Figure 4 below:

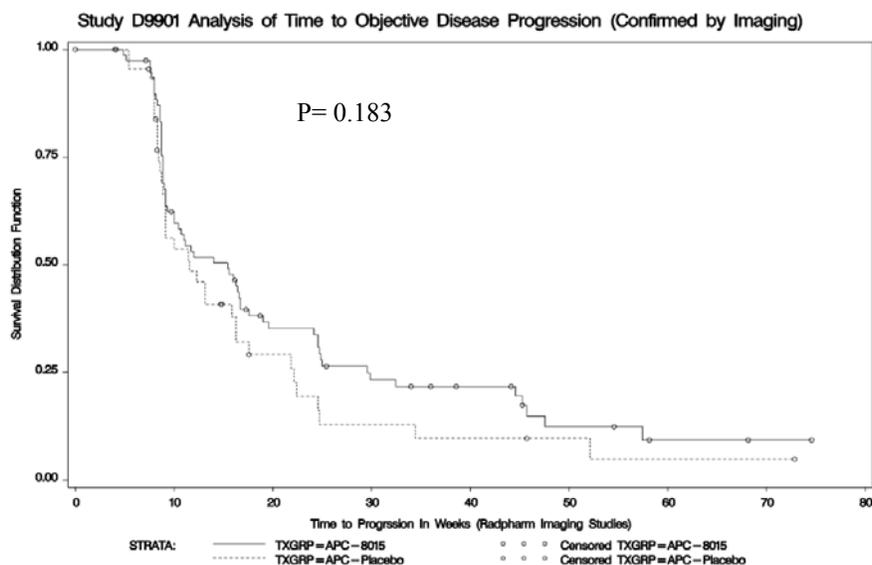
Figure 4: Kaplan-Meier Plot for time to disease progression D9901

Progression events: Out of 127 subjects randomized, 114 developed disease progression. Ninety-eight subjects were documented to have disease progression based on the imaging studies. Ten subjects had clinical events of disease progression and 7 subjects developed new onset of disease pain correlated with imaging studies. There were 12 censored events (13.4%) for APC8015 arm and 1 (2.2%) censored event for APC-placebo. Although the curves appeared to separate at week 10, there was no overall statistical difference between the two curves; Estimated median time to disease progression was 11.0 weeks (ranging from 2.1 weeks to 57.4) for APC8015 and 9.1 weeks (ranging from 3.9 weeks to 52.1) for placebo. Progression events are presented in Table 14.

Table 14: Summary of Progression Events D9901

Progression Event			
Objective Disease Progression Observed			
Radiological progression	71 (86.6)	44 (97.8)	115 (90.6)
Clinical progression	4 (4.9)	6 (13.3)	10 (7.9)
Objective Pain Progression	4 (4.9)	3 (6.7)	7 (5.5)
No Disease Progression Observed	11 (13.4)	1 (2.2)	12 (9.4)
Off Study	4 (4.9)	1 (2.2)	5 (3.9)
No Follow-up After Randomization	1 (1.2)	0 (0.0)	1 (0.8)
Censored (no events as of the data cut-off date)	6 (7.3)	0 (0.0)	6 (4.7)

Objective disease progression: Sponsor's analysis of the primary endpoint using the imaging progression date (objective disease progression) is shown below. No difference between the two arms.



APC8015 treatment effects on subgroups: The sponsor performed subgroup analyses for the primary endpoint of time to objective disease progression. Results suggested that that sipuleucel-T therapy may be associated with a delayed time to objective disease progression in the Gleason score ≤ 7 subgroup. FDA informed the sponsor that this was a *post hoc* hypothesis-generating analysis that could be used to design a future phase 3 study. The sponsor subsequently terminated D9902A in March 2003 prior to its reaching accrual objectives and initiated a new study 9902B to enroll patients with Gleason score ≤ 7 . D9902B was subsequently revised in October 2005 to enroll both asymptomatic and minimally symptomatic patients without Gleason score restriction. In addition, the primary endpoint was revised to be overall survival (Appendix 6).

E. Revision of primary efficacy endpoint results

After the unblinding and primary analyses of the database locked in July 2002, the difference in the time to disease progression (TTP) seen between the two arms in the ITT population did not reach statistical significance ($p = 0.085$ by log-rank test).

Subsequently, a complete clinical audit was performed to compare source documentation at the clinical study centers to the clinical database, resulting in the changes of progression dates in six subjects. An additional modification was done to change the date of progression in an additional subject. This audit was not prespecified in the imaging charter. Based upon this unblinded audit and revision of progression dates, the applicant re-analyzed the primary endpoint results and reported a p-value of 0.052 for the primary TTP endpoint difference (20). FDA's detailed

review of the revised progression dates from case report forms and sponsor's additional information showed that the changes in the progression dates from two APC8015 subjects [9170-147 (+118 days) and 9125-072 (+303 days)] were primarily responsible for lowering p-value to 0.052 (see detailed CRF review in Appendix 2).

In addition, there were a number of the difficulties in the interpretation of TTP data. First, overestimation of TTP; the predicted TTP for Sipuleucel T arm was 31 weeks, but actually observed time was 11.1 weeks, about one third of the prediction, illustrating the overestimation of median time to progression based on non-randomized phase 2 data. Second, median progression occurred before scheduled second assessment for progression. Third, lack of soft tissues scans in some bone only subjects according to the study design may have missed the detection of soft tissue progressions in these subjects. Lastly, some progression dates were uninterpretable because of protocol violations.

Thus, the 0.052 p-value is derived from an analysis resulting from an unblinded study audit. The reduction in the p-value was primarily driven by the revision of progression dates or censoring from two subjects in a study with a small sample size. FDA considers a p-value of 0.085 by log-rank test to be the result from the primary analysis specified in the protocol, and the p-value of 0.052 by log-rank test to be derived from an exploratory analysis. Since the BLA claim is based on a survival advantage in favor of APC8015 treatment, not on the results of the primary endpoint, FDA did not require a complete reassessment of the time to disease progression data.

In sum, D9901 failed to demonstrate an APC8015 treatment effect on the primary endpoint in delaying the time to disease progression. In addition, the FDA clinical consultant reviewer's detailed review of case report forms showed that a number of patients whose tumor status was not adequately evaluated at baseline or subsequently, making the dates of tumor progression in these subjects difficult to interpret (see Appendix 1)

F. Secondary Endpoints

There was no difference for the following secondary endpoints: a) the time to pain progression; b) the time to clinical progression; c) the time to treatment failure; and d) the response rate and duration of response.

a) Time to Pain Progression

i. Collection of disease-related pain data:

All of the following criteria were required for disease-related pain: pain that had the quality and consistency of cancer-related pain, pain that occurred since enrollment in the trial, and pain that occurred in a location that correlated with a site of cancer, as demonstrated by objective radiographic means. Subjects were required to complete a Weekly Pain and Analgesic Use log until disease progression occurred. If disease-

related pain was not present at the time of disease progression, subjects were required to complete a Weekly Pain and Analgesic Use log for up to an additional 4 weeks, regardless of pain status. In this log, subjects were asked to indicate their site(s) of pain and rate their pain on a scale of 0 (no pain) to 10 (pain as bad as you can imagine). Investigators were instructed to perform clinical evaluations of possible disease-related pain whenever the subject developed clinically significant pain (excluding usual pain such as minor headaches, toothaches, arthritis-related pain, or accidental injuries) or if the subject developed significant analgesic consumption to control pain. During the clinical visit, each painful site was carefully evaluated to rule out other causes for the pain. Radiographic procedures were performed as appropriate to document the site of pain.

- ii. Results: Protocol D9901 was not sufficiently powered to address the principal secondary efficacy endpoint of time to onset of disease-related pain. The applicant combined the data from both Phase 3 trials (Protocols D9901 and D9902A) for the analysis of the overall time to development of disease-related pain. The following table shows the pain progression data.

Table 15. Pain events (D9901 and D9902A pooled)

Events, n (%)	52 (35.4)	27 (34.6)	79 (35.1)
Censored, n (%)	95 (64.6)	51 (65.4)	146 (64.9)

There was no difference in the time to pain progression between two arms. Median times to pain progression were 33.9 weeks for APC8015 treated subjects and 32.7 weeks for APC-Placebo, respectively. P-value by log rank test was 0.719. It should be noted that almost 2/3 of patients were censored because there were no pain events within 4 weeks after disease progression.

b) Time to clinical progression events

Time to clinical progression was analyzed to determine the difference in the primary endpoint in cases where both subjective evidence and independently confirmable evidence of disease progression were present. For the time to clinical progression analysis, the first evidence of disease progression for each subject was used, whether based on subjective or independently confirmable evidence. Twenty-two subjects treated with APC8015 and 18 subjects treated with APC-Placebo had a clinical progression date that differed from their time to disease progression date.

There was no difference in time to clinical progression between the two arms. Median times to clinical progression were 10.7 weeks for APC8015 treated

subjects and 9.1 weeks for APC-Placebo, respectively. P-value by log rank test was 0.061.

c) Time to treatment failure

Time to treatment failure was defined as the time from randomization until any of the following occurred: disease progression, death, or withdrawal for any reason except withdrawal of consent. Initiation of other primary anticancer therapy, including radiation therapy, in the absence of study withdrawal was considered treatment failure for the purpose of this endpoint, as of the date the therapy was initiated.

There was no difference in time to clinical progression between the two arms. Median times to clinical progression were 11 weeks for APC8015 treated subjects and 10 weeks for APC-Placebo, respectively. P-value by log rank test was 0.124.

d) Response rate: There were no clinical responses seen in any of the D9901 subjects.

G. PSA response:

Although PSA was not used as an indicator of disease progression, the protocol and statistical analysis plan stipulated that biochemical responses would be analyzed. In the ITT population, 9 subjects (7.1% [9 of 127]) experienced a PSA reduction from baseline of at least 25% at one or more visits. Of these, 7 were treated with APC8015 and 2 treated with APC-Placebo (see Appendix 3 for detailed CRF review for PSA responses). Since the PSA measurement after the enrollment was not required in the protocol, the data collection was not consistent among study subjects with the majority of subjects lacking PSA serial measurement. Only four subjects (all received APC8015) experienced 50% PSA reduction at measurements at least 4 weeks apart. It is interesting to note that these subjects with PSA reduction appeared to have a longer survival times:

Subject 9123-034: Survival time 31.2 months

Subject 9125-972: Remained alive at 36 month visit

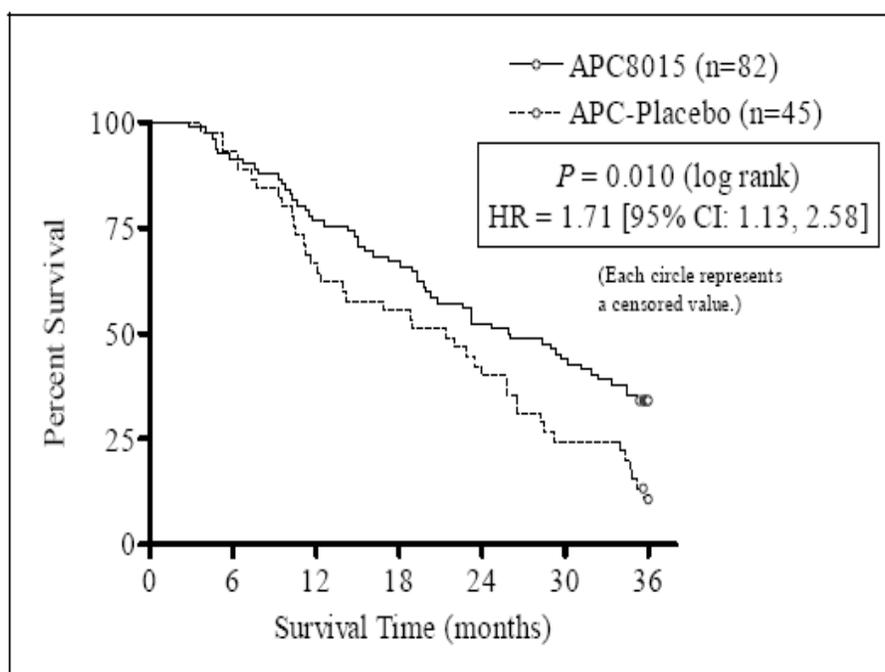
Subject 9137-100: Remained alive at 36 month visit

Subject 9169-077: Remained alive at 36 month visit

H. D9901 Survival analysis

The protocol stated that “This study is not powered to show a survival effect. However, survival data will be summarized descriptively.”

A survival difference between the two arms was observed, with an increased survival observed in APC8015 treated patients. Figure 5 depicts the Kaplan-Meier Plot for survival of D9901 subjects.

Figure 5: Kaplan-Meier Survival analysis D9901

Two curves appeared to separate at month 8 and this separation remained during the study period. As shown in Table 15, the survival rates at 36 months were 34% in APC8015 and 11% in APC-Placebo. This difference of 23% favoring APC8015 was statistically significant at p value of 0.0046 by Chi square test. The median survival times for APC8015 treated subjects and APC-placebo treated subjects were estimated to be 25.9 and 21.4 months, respectively. This difference of 4.5 months favoring APC8015 was statistically different ($p = 0.011$ by log-rank test).

Table 16: Survival Analysis D9901

Treatment	N	Deaths before 36 months*	Deaths after 36 months#	Alive at 36 months	Median Survival (months)
APC8015	82	54	8	28 (34%)	25.9
APC-Placebo	45	40	0	5 (11%)	21.4
p-value	---	--		0.0046 chi2	0.010 Log-rank

*All subjects were followed for 36 months or until death

From available data

As shown in Table 16, at the 36-month cutoff, 54 and 40 subjects died in APC8015 and APC-Placebo, respectively. Eight additional death events were reported for APC8015 after 36 months and were included in the BLA submission. No data were available after

36 months for the subjects in APC-Placebo arm. At 36 months, mortality for the APC8015 arm was 66% compared to 89% for placebo.

There were 20% fewer APC-8015 subjects who died from prostate cancer in APC (compare 63% in APC8015 to 83% in APC-Placebo). However, 13% more APC8015-treated subjects died due to causes other than prostate cancer progression (compare 18% in APC8015 to 5 % in APC-placebo). In addition, 6% more APC8015-treated subjects had unknown causes of death compared to APC-Placebo treated subjects. Thus the APC8015 arm had fewer death events and the prostate cancer specific death was lower in APC 8015 arm compared to APC-Placebo. Analysis of death events are summarized in Table 16.

Because of the small sample size of D9901 and the fact that the competing cause of the death in this patient population is common such as cardiovascular events, the determination of the cause of death is critical to ascertain whether the difference of the death events seen between APC8015 and APC-Placebo was due to the causes other than prostate cancer. To this end, FDA requested that the applicant attempt to obtain death certificates for the subjects who died during the study. The applicant obtained death certificates in 50% of death events. Even with available death certificates, it may be difficult to determine the cause of death.

Table 17: Death Events Analysis D9901

Death Events	APC8015 # (%)	APC Placebo # (%)
Total death events reported in Clinical Study Report at 36 months cutoff	54/82 (67)	40/45 (89)
Total death events listed in DEATH table	62/82 (76)	40/45 (89)
Death events attributable to the progression of prostate cancer	39/62 (63)	33/40 (83)
Death events attributable to causes other than the progression of prostate cancer	11/62 (18)	2/40 (5)
Deaths with unknown causes	12/62 (19)	5/40 (12)
Death certificate obtained	31/62 (50)	21/40 (53)
Death events attributable to the progression of prostate cancer with death certificate obtained	26/62 (42)	20/40 (50)
Death events attributable to causes other than the progression of prostate cancer with death certificate obtained	5/62 (8)	0

Other than prostate cancer, the known causes of death in the APC8015 treated patients included cerebral vascular accidents (CVA's), myocardial infarction, intracranial

hemorrhage, esophageal cancer, and glioblastoma. From above analyses, it appeared that fewer APC8015-treated subjects died from prostate cancer, and more died from other causes.

Possible confounders for survival analyses:

- **Crossover to treatment with APC8015F:** Patients in the APC placebo arm who had objective disease progression were eligible for the treatment with APC8015F. APC8015F was prepared from the frozen remaining 2/3 of apheresed PBMCs collected at the onset of the trial. These PBMCs were thawed and processed similarly as APC8015 and infused fresh. Thirty-four (34) subjects from APC placebo arm received APC8015F (75.6%). It should be noted that this “cross-over” was not a true cross-over since the APC-Placebo subjects subsequently received APC8015F, a slightly different product than APC8015.
- **Chemotherapy use on study after disease progression:** Another potential confounding factor for the survival analysis might have been the use of chemotherapy following disease progression. Table 17 summarizes chemotherapy use reported following disease progression:

Table 18: Chemotherapy Use after Disease Progression D9901

Treatment arm	ITT population	Chemo info available	Received Taxane (%)	Received any chemo (%)
APC8015	82	79	34 (43.6)	43 (54.4)
APC placebo	45	43	22 (53.7)	27 (62.8)

Information on chemotherapy use following progression was available in 96% of the patients in study D9901. According to the information provided, more subjects in APC-Placebo arm received chemotherapy than APC8015. Since docetaxel is the only therapy known to improve survival, an analysis of taxane use was also performed. A higher percentage of patients in the placebo group received taxanes than those in the APC8015 group. Because an earlier use of docetaxel in the APC8015 group could have favored the treatment group, FDA requested an analysis of timing of subsequent chemotherapy. This analysis did not suggest that increased survival in the treatment group could be attributable to earlier use of chemotherapy in general or taxanes specifically. Information on chemotherapy dosing was not obtained.

Additional death events reported after the 36-month cutoff:

Eight additional death events were reported in the data listing table (DEATH.xpt), but was not used for survival at the 36th month.

Seven subjects had survival time beyond 36 months (1080 days):

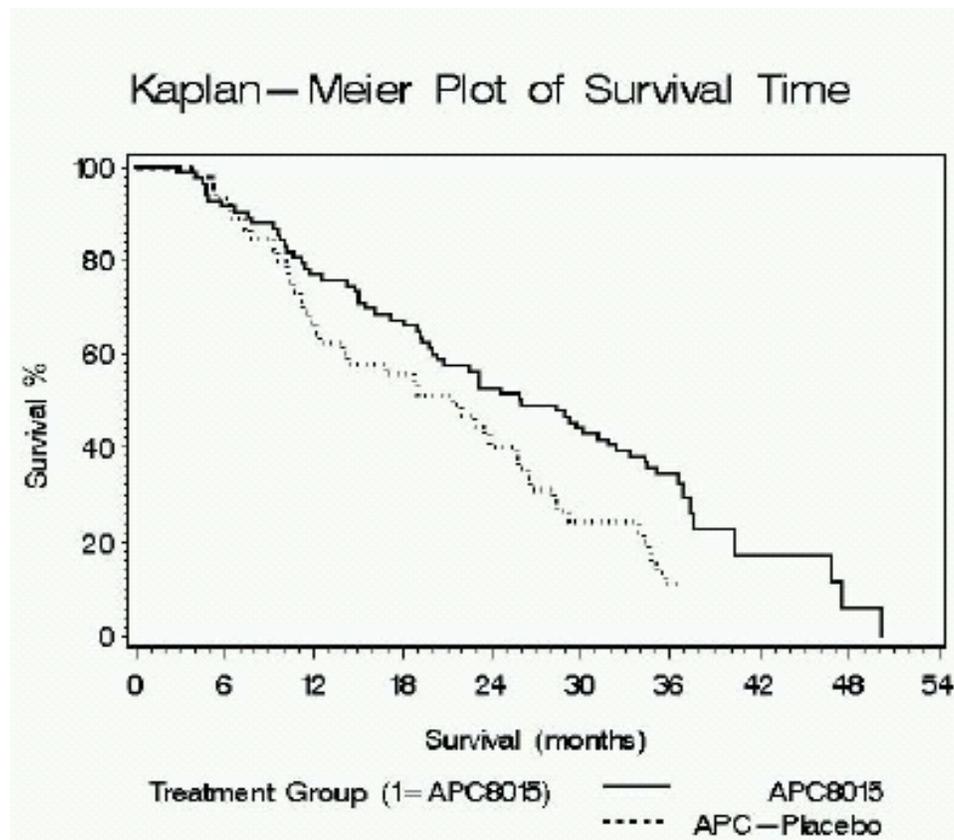
9165-059 (36 month +7 days); APC-Placebo

9168-055 (36 month +29 days); APC8015

9159-053 (36 month +58 days); APC8015
 9137-102 (36 month +51 days); APC8015
 9126-052 (36 month +137 days); APC8015
 9125-020 (36 month +38 days); APC8015
 9124-050 (36 month +439 days); APC8015

The reviewer requested further information on other death events beyond 36 months especially for APC-Placebo subjects. The sponsor replied in an email exchange on 11-29-06, stating that there were no more death data available beyond what was submitted in the BLA for D9901. The FDA’s analysis of Kaplan-Meier curve is shown below which include these additional 8 death events in the APC8015 arm that were observed beyond 36-month cut-off date.

Figure 6: D9901 Kaplan Meier survival including patients beyond 36 months



The overall curve of APC8015 is still statistically significant from the APC placebo control. P-value=0.012. The caveat of this analysis is that the absence of data beyond the 36 months in the placebo arm.

Confirmation of Death dates through review of CRFs including death certificates, dataset and study report

All death dates were confirmed including subjects with unknown causes of death.

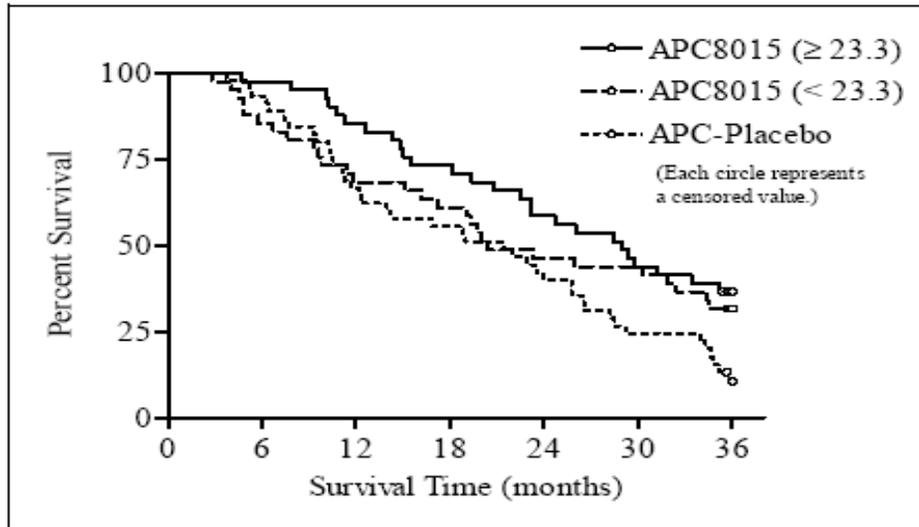
Two subjects, 9126-154 (APC8015) and 9127-054 who were lost for primary endpoint follow up, had death dates available. Subject 9126-154 withdrew his consent on 8-30-01 and multiple attempts to contact this subject were reported in the CRF to be unsuccessful. The death date was reported to be -b(6)--, a search result from social security death index (SSDI). The date last known to be alive for the other subject, 9127-054, was -b(6)-- and this patient was lost to follow-up, but the death date was reported to be September 2002 through SSDI search. Discrepancies were noted by the consultant reviewer between the reported death dates in CRF's and datasets in three patients (Appendix 1) However, the primary clinical reviewer verified that the death dates were correctly listed in the death table (dataset) used for analyses based on the death certificates.

Comparison of death dates reported to the dates in SSDI. The sponsor compared the death date recorded by the clinical study center (on the Death Summary CRF) to the date listed on the SSDI for 93 of the 94 subjects who died during the 36 month follow-up. (An SSDI death date was not available for 1 subject.) Dates were concordant for 86 of these 93 subjects (92.5%), including 1 subject for whom the SSDI listed only the year of death. Discrepancies were noted for 4 subjects treated with APC8015 and for 3 subjects treated with APC-Placebo (confirmed by BIMO inspection). The observed differences between CRF death and SSDI death dates resulted in a net change of 4 days later for subjects treated with APC8015 and 21 days later for subjects treated with APC-Placebo). Sensitivity analyses indicated that this difference did not impact the overall survival difference.

Survival result summary: A review of the data submitted, including sensitivity analyses and review of death events including CRF and death certificates, confirmed the 4.5 month difference in survival reported by the sponsor between treatment arms in study D9901 favoring APC8015 treatment. There was no apparent excess of deaths attributable to causes other than prostate cancer in the control arm. The survival difference is clinically meaningful, and compares favorably with other therapeutic options in this disease setting. However, the absence of survival as an efficacy endpoint and the lack of a pre-specified primary method for survival analysis make the analyses of the submitted survival results *post hoc* in nature and the small size of the study raises the possibility that this finding could have occurred by chance. In addition, the potential confounding effect of subsequent chemotherapy on survival cannot be ruled out.

I. Additional Exploratory Analyses

- **CD54 upregulation and relationship with survival:** Because CD54, a cell surface marker on dendritic cells, was a potency release criterion, all APC8015 subjects had CD54 expression and cell count data. The sponsor performed an exploratory analysis to correlate the CD54 upregulation with survival. Kaplan Meier survival curves from three groups of patients were shown below: subjects who received placebo, APC8015 subjects whose CD54 upregulation ratio was below the median and APC8015 subjects whose CD54 upregulation were at or above the median (Figure 7):

Figure 7: CD54 Upregulation and survival D9901 (Sponsor's)

These results were not statistically significant. The APC-Placebo cells did not undergo the same manufacturing process as APC8015. The study was not designed to provide confirmative evidence for relationship between survival and cell dose. The CD54 upregulation could simply reflect a better patient status.

• Analyses for T cell response

T cell responses were analyzed by an *in vitro* stimulation test using the following antigens

- PA2024 (PAP fused with GM-CSF) cloned in a baculovirus system and expressed in Sf21 insect cells
- Human PAP isolated from human seminal fluid
- GM-CSF
- Influenza (used as a recall antigen to assess baseline immune function)
- A 22 amino acid peptide that spans the PAP and GM-CSF

All tests were performed using fresh PBMC's. Stimulation Index (SI) was defined as the median cpm at a given antigen concentration divided by the median cpm for control (i.e., no antigen added). Data were not obtained from the ITT population because fresh samples and single laboratory testing required the shipment of fresh samples. Table 19 shows that the stimulation index was higher when PA2024 was used as an antigen.

Table 19: T cell Stimulation Index

Antigen	APC8015	APC-Placebo	p-value
Median of the Geometric Mean			
Week 0 to Week 8	n = 31	n = 16	
PA2024	16.91	1.99	0.0004
Human PAP	1.07	1.90	0.2238
Week 0 to Week 16	n = 14	n = 8	
PA2024	13.22	0.91	0.0001
Human PAP_a	0.99	0.40	0.0890

It appeared that APC8015 treatment induced a higher stimulation index compared to APC-placebo treatment. However the results were inconclusive because of the following limitations:

- The assays were performed in only a number of subjects.
- The assay the sponsor used to analyze the cellular immune response reflected the cellular proliferation after antigen stimulation. The increase observed in this assay included proliferations from all cell types tested such as T cells and mononuclear cells. Therefore, this assay results were not specific for T cell immune response.
- Although the median SI from APC8015 was significantly higher than that of APC placebo, FDA cannot make the conclusion that treatment with APC 8015 induced an increase in the cellular response. Therefore, the analyses were exploratory.

J. D9901 efficacy summary

The primary objective of study D9901 was to demonstrate a 3.7-month increase in time to disease progression in APC8015 treated patients with asymptomatic metastatic androgen independent prostate cancer over APC-Placebo. One hundred eighty six subjects were screened and 127 subjects enrolled in the study. Two subjects were lost to follow up for disease progression, and all 127 subjects were followed until 36 months or death. The study did not achieve its primary objective of prolonging time to disease progression. The median time to disease progression observed in the APC8015 and APC placebo treated subjects was 11.1 weeks and 10.0 weeks, respectively. The 1.9-week difference was not statistically significant with a p-value of 0.085 by log-rank test. The study did not achieve any of its secondary endpoints.

The survival analysis showed that the median survival times in the subjects treated with APC8015 and APC-Placebo were 25.9 and 21.4 months, respectively, a difference of 4.5 months. This difference reached statistical significance ($p = 0.010$) by log rank test. The unadjusted HR was 1.71 [95% confidence interval (CI): 1.13, 2.58]. Review of the survival data including death events and additional sensitivity analyses supported a finding of a survival difference between arms in study D9901. Some imbalances in the distribution of Gleason scores and disease locations were

noted between APC8015 and APC-Placebo arms, but sensitivity analyses did not suggest that these imbalances had impact on the overall survival results (see statistical review). Nonetheless, the lack of a pre-specified primary method for survival analyses renders it impossible to estimate the type I error of the survival result. In addition, the small size of the study makes it more likely that this finding could have occurred by chance. Thus, the submitted survival results were not persuasive for the purported treatment effect of sipuleucel T and the confidence on this survival evidence for the efficacy claim was low.

6.6 D9902A efficacy Results

A. Regulatory History

D9902 had the same trial design, endpoints and execution as D9901. Enrollment commenced 4 months after D9901 started.

In March 2003, the D9901 study results became available, demonstrating that none of the efficacy objectives were met. Consequently, the sponsor decided to terminate D9902 trial. At the time of termination, 98 subjects were enrolled already to D9902. The sponsor renamed it to be D9902A. Because of this early termination, D9902 contained an insufficient sample size and was not powered to demonstrate a difference between the two arms in either time to disease progression and survival.

D9902A primary endpoint: time to disease progression.

B. Revisions of D9902A efficacy endpoints

▪ Secondary endpoints

The secondary endpoints were initially the same as D9901 in the clinical protocol. However, in November 2004 after the analyses of D9901 overall survival demonstrating a survival difference between the two arms, the sponsor revised the secondary endpoints to be the following

- Overall survival
- The time to objective disease progression confirmed by imaging studies

▪ Tertiary endpoints

The original protocol did not have tertiary endpoints. The revised statistical analyses before unblinding the data included the following as tertiary endpoints

- The time to the development of disease-related pain in subjects treated with APC8015 versus APC-Placebo.
- The time to disease progression with treatment, cell processing center (CPC), and their interaction tested in subjects treated with APC8015 versus APC-Placebo

- The incidence of Grade 3 and greater treatment-related adverse events (AEs) in subjects treated with APC8015 versus APC-Placebo
- Response rate.

C. Study Conduct

- **Randomization Errors**

Study center and bisphosphonate were used for stratification of randomization. Eighteen (18) randomization errors occurred. The majority of errors consisted of subjects not being assigned to the randomization slots expected based on the sequence of enrollment. There were no subjects who were randomized to APC-Placebo actually received APC8015 or vice visa.

- **Protocol Deviations**

Table 20 shows that one major protocol violation each occurred in APC8015 arm and in APC-Placebo arm.

Table 20: Protocol deviations D9902A

Deviations	APC8015	APC placebo
	N = 65	N = 33
Major	1 (1.5%)	1(3 %)
Testosterone \geq 50 ng/dl	✓	✓
No metastatic diseases	✓	
Minor	17 (26.2%)	11 (33.3)

- **Study Agent Study Agent Exposure and Treatment compliance**

Table 21 shows the number of leukapheresis and infusions for D9902A study subjects. 86.3% of ITT population underwent 3 or more leukapheresis and 3 infusions, respectively. The treatment compliance was good.

Table 21: Summary of Leukaphereses and infusions, D9902A

	APC8015 (n = 65)	APC- Placebo (n = 32)	Total (N = 98)
Number of Leukaphereses, n (%)	N = 65	N = 31	N = 96
1 leukapheresis	2 (3.1)	1 (3.2)	3 (3.1)
2 leukaphereses	4 (6.2)	2 (6.5)	6 (6.3)
3 or more leukaphereses	59 (90.8)	28 (90.3)	87 (90.6)
Number of Infusions, n (%)	N= 64	N=31	N=95
1 infusion	2 (3.1)	1 (3.2)	3 (3.2)
2 infusions	7 (10.9)	3 (9.7)	10 (10.5)
3 infusions	55 (85.9)	27 (87.1)	82 (86.3)

D. Study Results

- a. Study subject disposition:** There were 27 clinical study sites involved in this study across the United States. The 1st subject was enrolled in May 2000 and the last enrollment (at early determination) was in March 2003. The study was completed for survival follow up in May 2005. All subjects from ITT population were accountable. There were three subjects who were randomized, but did not receive the study agents: one in APC8015 and two in APC-Placebo.
- b. Patient Demographic and Baseline Characteristics (Table 21)**

Table 22: Patient Demographic and Baseline Characteristics D9902A

Parameter	APC8015 (n = 65)	APC- Placebo (n = 33)	Total (N = 98)
Age (years)			
Mean	69.6	70.6	69.9
Range	(51 – 84)	(57- 87)	
Race, n (%)			
Caucasian	59 (90.8)	31 (93.9)	90 (91.8)
African American	2 (3.1)	2 (6.1)	4 (4.1)
Hispanic	1 (1.5)	0 (0.0)	1 (1.0)
Unknown	3 (4.6)	0 (0.0)	3 (3.1)
Weight, mean (lbs)	195.7	195.3	195.6
ECOG Performance Status, n (%)			
0	51 (78.5)	23 (69.7)	74 (75.5)
1	14 (21.5)	10 (30.3)	24 (24.5)
Serum PSA (ng/mL)			
Mean	153.7	177.1	161.6
Median	61.3	44.0	53.3

There were no significant imbalances between the two arms in Ethnicity, PSA, weight and ECOG performance status. The median age in this population was 70.0 years. The majority of subjects from both treatment groups had a baseline ECOG performance status of 0 (78% of subjects treated with APC8015 and 69% of subjects treated with APC-Placebo). Ethnicity of the population: 91.8% of subjects were Caucasians, 4.1% were African-American and 1.0% were Hispanic and 3.1% unknown. Therefore, caution should be exercised when extrapolating the trial data to general population of prostate cancer patients since African-American subjects were underrepresented.

Table 23 lists the distribution of Gleason Scores in study subjects. One subject in the APC8015 group was missing a baseline Gleason score. There were 17.6% more subjects in APC8015 arm who had lower Gleason score compared to APC placebo (68.7% vs. 51.5%). Placebo arm had 16.8% more subjects who had higher Gleason score (≥ 8) (31.3% vs. 48.5%). This imbalance in the Gleason Scores may create bias in the study results.

Table 23: Gleason Score distribution in D9902A study subjects

Gleason Score	APC8015 (%) (N = 65)	Placebo (%) (N = 33)
≤ 6	15 (23.4)	9 (27.3)
= 7	29 (45.3)	8 (24.2)
≥ 8	20 (31.3)	16 (48.5)

Table 23 shows the disease distribution between the two arms in study subjects. There were 13.3% more subjects in APC 8015 who had >10 bony metastasis per subject. Although these imbalances could have led to biases to the study results, the sensitivity analyses performed did not suggest that they confounded the survival results. See statistical review for details.

Table 24: Disease location and distribution D9902A

Localization of Disease	APC 8015 # (%) (N=65)	Placebo # (%) (N = 33)
Bone metastases only	31 (47.7)	10 (30.3)
Soft tissue metastasis/pelvis recurrence only	7 (10.8)	7 (21.2)
Both bone metastasis and soft tissue metastasis/pelvic recurrence	27 (41.5)	16 (48.5)
Number of bone metastases per subject	(N = 61)	(N= 32)
0	5 (8.2)	7 (21.9)

Localization of Disease	APC 8015 # (%) (N=65)	Placebo # (%) (N = 33)
1-5	19 (31.1)	11 (34.4)
6-10	6 (9.8)	2 (6.3)
> 10	31 (50.8)	12 (37.5)

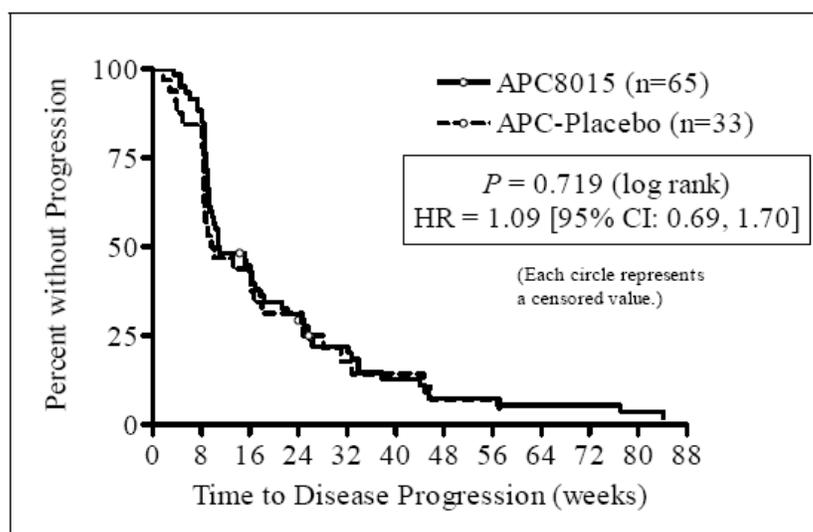
Table 25 lists the treatment regimens the study subject had received prior to the study. There were no imbalances seen between the two arms considered likely to affect results.

Table 25: Prior treatment regimen D9902A

Prior Treatment	APC 8015 N = 65	APC- Placebo N = 33
Hormone Therapies:	n (%)	n (%)
Castration	9 (14%)	3 (9%)
Combined androgen blockade	41 (63.1)	21 (63.6)
Combined androgen blockade plus other	15 (23.1)	9 (27.3)
Chemotherapy	7 (11.1)	3 (9.1)
Curative Radiotherapy	27 (42.9)	10 (30.3)
Palliative Radiotherapy	14 (22.2)	7 (21.2)
No radiotherapy received	22 (34.9)	15 (45.5)
Orchiectomy	12 (18.5)	4 (12.1)
Bisphosphonate	8 (12.3)	3 (9.1)

c. Results of Primary endpoint --- Time to Disease Progression:

The Kaplan-Meier analysis of time to disease progression for study D9902A is shown below in Figure 8:

Figure 8: Kaplan-Meier Plot for time to disease progression - D9902A

The two curves overlap each other. There was no overall statistical difference between the two curves; $p=0.719$ by log rank test. The estimated median time to disease progression was 10.9 weeks in the APC8015 arm (ranging from 3.4 weeks to 106.6) compared with 9.9 weeks in the APC- Placebo group (ranging from 1.7 weeks to 130.1).

d. Progression events

Out of 98 subjects randomized, 89 developed disease progression. 73 subjects were documented to have disease progression based on the imaging studies. 16 subjects had clinical events of disease progression (Table 26).

Table 26: Summary of Disease Progression D9902A

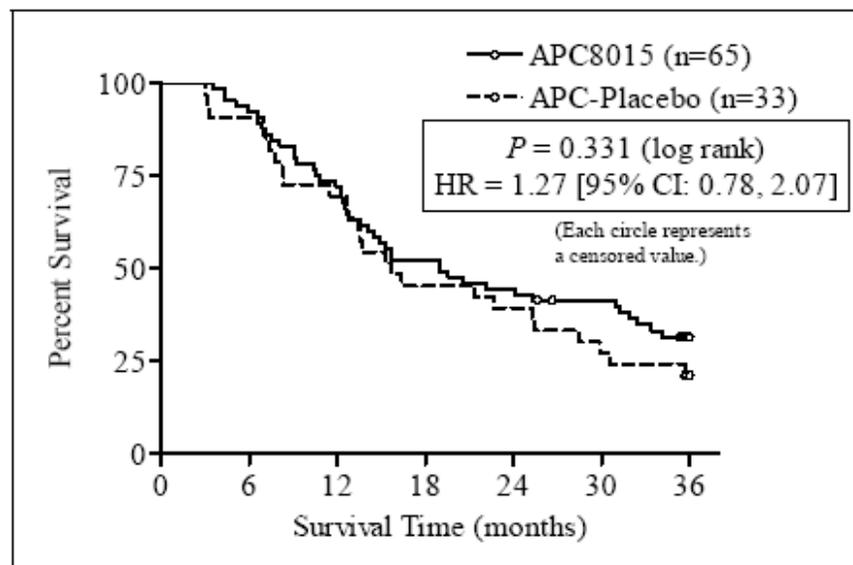
Objective Disease Progression Status	APC8015	APC-Placebo	Total
Reason	(N = 65)	(N = 33)	(N = 98)
Disease Progression Observed	58 (89.2)	31 (93.9)	89 (90.8)
Radiological progression	47 (72.3)	26 (78.8)	73 (74.5)
Clinical progression	11 (16.9)	5 (15.2)	16 (16.3)
No Disease Progression Observed	7 (10.8)	2 (6.1)	9 (9.2)
Off Study	2 (3.1)	1 (3.0)	3 (3.1)
No Follow-up After Randomization	5 (7.7)	1 (3.0)	6 (6.1)

e. Results of Secondary Endpoints

Overall Survival: As shown in the Figure 8, there was no difference of the survival curves between the two arms. The median survival time for subjects treated with APC8015 was 3.3 months longer than that for subjects treated with

APC- Placebo (median survival times of 19.0 months [95% CI: 13.6, 31.9] and 15.7 months [95% CI: 12.8, 25.4], respectively). This difference was not statistically significant ($p = 0.331$, log rank test).

Figure 9: Overall survival - D9902A



▪ Time to Objective Disease Progression

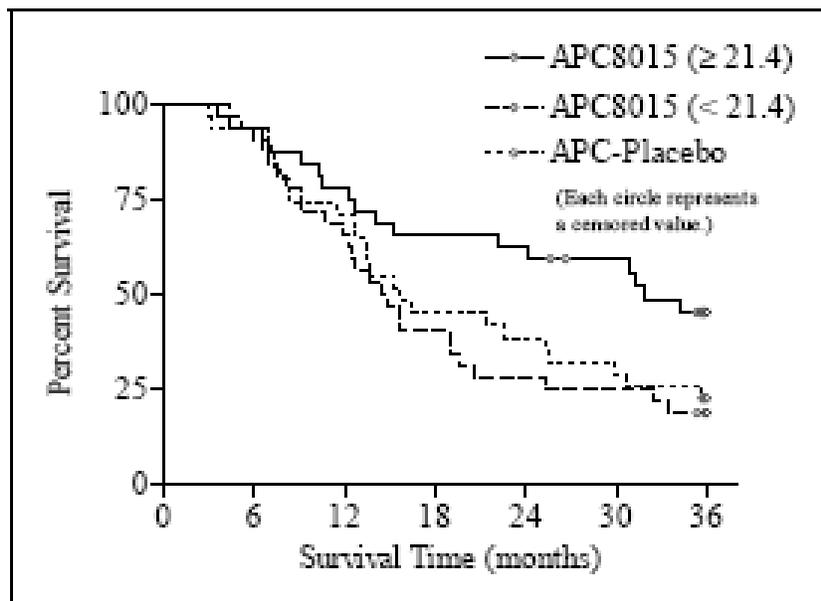
Based on the imaging-determined disease progression, the median times to objective disease progression were 15.3 for APC8015 and 16.1 weeks for APC-placebo. The difference is not statistically significant ($p = 0.538$, log rank test).

f. Results of Tertiary Endpoints

Pooled data from D9901 was used in the analysis for time to pain progression. There was no difference in the time to pain progression ($p = 0.719$). One subject experienced a partial response at Week 16 that lasted through Week 32 on bone scan assessment (see detailed CRF review in Appendix 3).

g. Exploratory analysis --- CD54 upregulation and survival

- An exploratory Kaplan Meier analysis was performed to determine whether cell counts or CD 54 upregulation ratios above or below the median correlated with survival. Subjects who had CD54 upregulation ratio at or above the median (Figure 9), appeared to have increased survival compared to those subjects below the median. The APC-Placebo cells did not undergo the same manufacturing process as APC8015.

Figure 10: CD54⁺ Upregulation vs. survival D9902A

E. Summary of D9902A efficacy

Because of the early termination, D9902A was insufficient in sample size and was not powered to demonstrate a difference in the primary endpoint of time to disease progression. After the database lock before unblinding and analysis, the sponsor revised endpoint to include overall survival as a secondary endpoint. Results from these analyses indicated that the APC8015 treatment did not improve the primary endpoint and there was no difference in the median survival time between APC 8015 and APC placebo treated subjects.

6.7 Discussion of Overall Efficacy Results

Both D9901 and D9902A shared the same trial design and execution. A total of 225 subjects were enrolled in these two trials. There was no statistical significance seen for the time to progression. The median time to progression in APC8015 arm in both study populations was approximately 10 weeks. This result was only a third of the predicted 31 weeks based on the single arm phase 2 studies, illustrating an overestimation of the effect size and inaccuracy from single arm phase 2 data.

Only D9901 showed a statistical significant survival difference --- 4.5-month increase in APC8015 arm. However, this difference must be interpreted with caution since the primary method for survival analysis was not pre-specified and the survival was not a pre-specified efficacy endpoint.

D9902A was terminated early, thus could not provide enough sample size to demonstrate a difference in time to progression or survival.

Compared to D9901, the median survival times for both arms in D9902A were shorter (Table 27).

Table 27: Combined Summary of Efficacy, D9901 and 9902A

Study	<u>Median Time to Progression</u> <u>(weeks)</u>		<u>Median Survival (months)</u>	
	APC8015	APC Placebo	APC8015 Placebo	APC
D9901	11.0	9.1	25.9	21.4
D9902A	10.9	9.9	19.0	15.7

The causes of this 6-month survival difference between two trials are not known and could be due to a number of possibilities. First, the patient baseline characteristics may be different. Secondly, post-progression chemotherapy use might have been different, which may have prolonged the survival in D9901. Third, some unidentified factors might have contributed to the difference. Lastly, the difference might have happened by chance.

Comparative analyses between two studies on the patient baseline characteristics and post progression use of chemotherapy did not reveal apparent factors that may have contributed to the shorter survival time in D9902A.

In summary, only one trial, D9901, demonstrated a survival increase in APC8015 treated subjects, the basis for this BLA claim. However, the nature of post hoc analyses rendered it difficult to estimate the true type I error for this survival difference. Accordingly, these results did not provide substantial evidence for the effectiveness of APC8015 in the targeted population.

A. Overall discussion of survival as an endpoint in cancer trials.

Overall survival is defined as the time from randomization until death from any cause, and is measured in the intent to treat (ITT) population. Survival is the most reliable cancer endpoint, and when studies can be conducted to adequately assess it, it is usually the preferred endpoint. An improvement in survival is of unquestioned clinical benefit. The endpoint is precise and easy to measure, documented by the date of death. Bias is not a factor in endpoint measurement. Overall survival almost always needs to be evaluated in randomized controlled studies. Randomized studies minimize the effect other than drug treatment, including patient selection, improved imaging techniques (which can alter tumor staging and prognosis), or improved supportive care by allowing a comparison of outcomes in patient groups where such factors should be similar. Demonstration of a statistically significant improvement in overall survival is usually considered to be clinically significant, and has often supported new drug approval (21).

B. Survival analyses in the studies submitted in this BLA.

Although the survival as discussed above is a preferred endpoint for cancer trials, the survival analyses used in this BLA submission has limitation. The survival analyses were post hoc in a small number of subjects and thus did not provide substantial evidence for sipuleucel T (APC8015) effectiveness in the study population.

7 REVIEW OF SAFETY

7.1 Overview of Safety

The safety database was mainly derived from 147 patients, 146 of whom received APC8015 and 78 patients who received APC-placebo; a total of 225 subjects in trials D9901 and D9902A. Since these studies were similar in design and eligibility, safety results were pooled and analyzed. In addition, the sponsor submitted summary safety information on the phase 1 and 2 studies as well as information on cerebrovascular accidents (CVAs) observed in D9901, D9902A and D9902B which were contained in an amendment to this BLA.

Overall, APC8015 treatment was relatively tolerated. Most APC8015 treated subjects developed Adverse Events (AEs), but most of these were grade 1 to 2 and resolved within 48 hours. Chills, fatigue pyrexia, and back pain were the most common AE's (> 25% of subjects who received APC8015). These events generally occurred within 1 day of an infusion with APC8015, were Grade 1 or 2, were managed on an outpatient basis, and had median durations of 24 to 48 hours. No deaths were reported to be related to the infusion of APC8015 and no deaths occurred within 30 days after the infusion. Twenty-four percent (23.8%) of APC8015 treated subjects developed Serious Adverse Events (SAEs) other than death, not different from 23% of APC-Placebo treated subjects. These SAEs included life-threatening adverse events, inpatient hospitalization or prolongation of existing hospitalization, or a persistent or significant disability/incapacity. However, 3.9% (18 out of 461) APC8015 treated subjects experienced CVA-related SAEs, compared to 2.6 % (6 out of 231) in APC-Placebo treated subjects in four randomized phase 3 studies (D9901, D9902A, P-11 and D9902B).

7.2 Infusion exposure

More than 88% of the subjects exposed underwent three apheresis 2 days prior to each infusion of study product and received the scheduled 3 infusions of the APC8015 or APC-Placebo every two weeks.

All subjects were followed until 36 months or death, whichever came first. Table 28 shows the number of infusions subjects received. The vast majority of subjects received 3 infusions as per protocol (88.4% in APC8015 arm and 91% in APC-Placebo arm).

Table 28: Infusion Exposure (D9901 and D9902A)

Infusions	APC8015		APC-Placebo	
	N = 147		N = 78	
	#	%	#	%
3	132	89.8	71	91
2	10	6.8	4	5.1
1	4	2.7	3	3.8
0	1	0.7	0	0

7.3 Findings

A. Deaths

Table 29 lists all death events occurred in two trials.

Table 29: Death analyses (D9901 and D9902A)

Cause of Death	APC8015		APC-Placebo	
	# Death	%	# Death	%
Disease Progression	70	65.4	51	78.5
Unknown	21	19.6	10	15.4
Other	15	14.0	5	7.7
CVA	5	4.6	0	0
CHF	2	1.9	3	4.5
Cardiac Arrest	1	0.9	0	0
Dementia	1	0.9	0	0
Glioblastoma	1	0.9	0	0
Met. Esophageal Ca	1	0.9	0	0
Orthopedic Complication	1	0.9	0	0
Renal Failure	1	0.9	0	0
Sepsis and ARDS	1	0.9	0	0
UTI	1	0.9	0	0
Small Cell Carcinoma	0	0	1	1.5
CVA	0	0	1	1.5
Infection	1	0.9	0	0

A total of 173 deaths were reported, including 9 additional deaths in APC8015 after the 36- month cutoff, accounting for 72.8% death in APC8015-treated subjects and 84.6% of APC-Placebo treated subjects. The majority of patients died from disease progression, 65.4% and 78.5% in APC015 and APC-Placebo treated subjects,

respectively. The cause of deaths was unknown in 19.6% APC8015-treated subjects and 15.4% APC-Placebo treated subjects. No deaths were reported to be related to the infusion of APC8015 and no deaths occurred within 30 days after the infusion. Five out of 147 (3.4%) of APC8015-treated subjects died from CVA compared to none in APC-placebo treated subjects. This increased frequency of CVA related death events is discussed further in detail in 7.3.C.

B. Other Serious Adverse Events

Out of a total of 1904 adverse events listed, 135 SAE events were reported in 225 patients; 96 events in APC8015, 39 events in APC Placebo. If the same SAE happened in the same patient is counted only once, a total of 118 SAE occurred; 82 such SAEs in APC 8015 and 36 events in APC- Placebo. Twenty Four per cent (35/147) of APC8015 treated subjects developed Serious Adverse Events (SAEs) other than death, compared with 23% (18/78) of APC-Placebo treated subjects. These SAEs included life-threatening adverse events, inpatient hospitalization or prolongation of existing hospitalization, and persistent or significant disability/incapacity. Table 29 shows the SAE frequency distribution. CVA events again were noted to have an increase in frequency in APC8015 subjects than APC-Placebo, 2% vs. none, respectively. The sponsor's analysis of CVA events will be discussed below.

Table 30: SAE Frequency and Distribution ($\geq 1\%$)

SAE	APC8015		APC-Placebo	
	N = 147		N = 78	
	#	%	#	%
Chills	5	3.4	0	0
Dyspnea	4	2.7	1	1.3
Pyrexia	4	2.7	0	0
Cerebrovascular accident	3	2.0	1	1.3
Dehydration	3	2.0	2	2.6
Anemia	2	1.4	1	1.3
Back pain	2	1.4	1	1.3
Catheter sepsis	2	1.4	0	0
Chest wall pain	2	1.4	0	0
Hematuria	2	1.4	2	2.6
Hypertension	2	1.4	0	0
Sepsis	2	1.4	1	1.3
Spinal cord compression	2	1.4	0	0
Urinary retention	2	1.4	3	3.8
Urinary tract infection	2	1.4	0	0

C. Analysis of CVA Events:

CVA events were reported more frequently in APC8015 treated subjects compared to APC-Placebo treated subjects (see section 7.3 A and 7.3B) in D9901 and D9902A. Because of this observation, the sponsor initiated an analysis of CVA events in all the phase 3 studies including unblended results from two additional randomized, double-blind, APC-placebo controlled phase 3 trials: P-11 and D9902B. This analysis included cerebrovascular or cerebrovascular-related AEs, SAEs, and death events that appeared in the nervous or vascular system disorders system organ classes including terms such as cerebrovascular accident, stroke, intracranial hemorrhage, TIA, lacunar infarction, and cerebral infarction. A neurologist consultant reviewed events to ascertain the pathophysiology of CVAs (ischemic vs. hemorrhagic). Based on his review of the cases, a summary of the CVA events by ischemic versus hemorrhagic etiology is also provided. Descriptive statistics (count and percent) were used to summarize AEs and SAEs by treatment group. For each comparison of interest, the odds ratio (OR) and its 2-sided 95% confidence interval (CI) are provided. Nominal 2-sided p-values were provided using Fisher's exact test.

Study P-11 was a randomized, phase 3 trial in 175 subjects with non-metastatic androgen dependent prostate cancer randomized in a 2:1 ratio to APC8015 (116 subjects) and APC-placebo (59 subjects). The treatment regimen was similar to that of D9901 and D9902 (see Appendix 6 for detail). One out of 116 (0.9%) APC8015 treated subjects developed CVA event compared to 3 of 59 (5.1%) APC-placebo treated subjects, an absolute increase of 4.2% CVA events in APC-placebo. No deaths were reported to be related to CVA events. Study D9902B enrolled 294 subjects (198 in APC8015 arm and 96 in APC-Placebo arm, 2:1 randomization) as of 11-6-2007, and remains blinded (see section 3.5 regulatory history and Appendix 6 for D9902B trial detail). An independent data monitoring committee provided the sponsor with CVA events in each arm; however, treatment code remains blinded at the subject level. Five out of 198 (2.5%) APC8015 treated subjects developed CVA event compared to 1 of 96 (1.0%) APC-placebo treated subjects, an absolute increase of 1.5% CVA events in APC8015.

There were no CVA events reported in the 213 subjects from any of the Phase 1 and Phase 2 studies. Table 30 below summarizes the CVA analyses results from the combined phase 3 studies (D9901, D9902A, D9902B, and P-11):

Table 31: Sponsor's analysis of CVA Events

Group	APC8015 n / N (%)	APC-Placebo n / N (%)	Odds Ratio (95% CI)	p- value^a
All studies ^b	18 / 461 (3.9%)	6 / 231 (2.6%)	1.52 (0.6, 3.9)	0.5
Proposed indication ^c	17 / 345 (4.9%)	3 / 172 (1.7%)	2.92 (0.84, 10)	0.092
P-11	1/116 (0.9%)	3 of 59 (5.1%)	0.16 (.02, 1.6)	0.11
In first 16 weeks	9 / 461 (2.0%)	1 / 231 (0.4%)	4.58 (0.6, 36)	0.18
Deaths attributed to CVAs	7 / 461 (1.5%)	2 / 231 (0.9%)	1.76 (0.36, 8.6)	0.725
Hemorrhagic	3 / 461 (0.6%)	1 / 231 (0.4%)	1.51 (0.156, 14.564)	1.00
Ischemic	11/461(2.4%)	5/231(2.2%)	1.10(0.38,3.22)	1.00
Unknown	4/461 (0.9%)	0/231 (0.0%)	-	0.307

a: Fisher's Exact 2- sided test b: D9901, D9902A, P-11 and D9902B c : D9901, D9902A, and D9902B

Because P-11 enrolled a different patient population (androgen dependent prostate cancer without metastatic diseases), the results of P-11 are presented separately. CVA events in the 3 studies with metastatic AIPC included 17 events in APC8015 (4.9%) treated subjects and 3 events (1.7%) in APC-Placebo treated subjects, an approximately three-fold increase in CVA events in the APC8015 treated group. CVA events that occurred prior to Week 16 were collected in a comprehensive manner; later reporting was less consistent across all studies, in particular for Investigator-assessed events that were deemed not related to study treatment. CVA events were 9/345 (2.7%) occurring in the treatment group combined across studies compared with 1/172 (1.0%) within 16 weeks of 1st infusion.

Seven patients (2%) in the APC8015 arm died from CVA events compared to 2 (1.2%) in the APC- Placebo arm (OR= 1.76 [0.36, 8.6]). Three APC8015 subjects (0.9 %,) developed hemorrhagic CVA compared to none in APC-Placebo subjects. Ten (2.9%) APC8015 subjects had ischemic strokes compared to 3 out of 172 (1.7%) APC-Placebo subjects. It appeared that more subjects had ischemic events, but conclusions about the relative risk of CVA events of ischemic versus hemorrhagic etiology could not be made because of the small number of events. The onset of CVA events in 3 completed randomized studies is summarized descriptively in the table below:

Table 32: Onset of CVA Events (completed studies)^a

	CVA's	Days from first infusion		Days from last infusion	
Study	N	Median	Range	Median	Range
	12	167	(26, 859)	139.5	(7, 830)
APC-Placebo	5	541	(235, 895)	323.0	(208, 707)

a: P-11, D9901 and D9902A

Review of CVA case summaries did not reveal a temporal association of CVA events with the administration of either APC8015 or APC-placebo (Appendix 5).

No difference were found between the APC8015 and APC-placebo subjects with respect to the rate of non-neurological vascular events such as deep venous thrombosis, pulmonary embolism, myocardial infarction and myocardial ischemia. Analyses on the risk scores for the patients with CVA's based on models described in the Framingham Study as well as in the Cardiovascular Health Studies, revealed slightly higher CVA risk scores in both models for patients with CVA's compared with no CVA's in both treatment arms, and similar risk scores between the APC8015 and APC-placebo subjects whether or not they had reported a CVA (sponsor's results).

Conclusions regarding CVA events analyses:

- Eighteen out of 461 (3.9%) subjects treated with APC8015 developed CVA events compared to 6 out of 231 (2.6%) in the APC-Placebo treated subjects, an absolute increase of 1.3% (odds ratio = 1.5).
- Seventeen out of 345 APC8015 subjects (4.9%) developed CVA events compared to 3 out of 172 (1.7%) in APC-Placebo treated subjects, a threefold increase by odds ratio (p=0.092) and an absolute increase of 2.8% in the APC8015 arm for the study population with the proposed indication of metastatic AIPC.
- Two percent (7/345) of subjects in the APC8015 arm died from CVA events compared to 1.2 % of subjects in the APC- Placebo arm (2/172), an absolute increase of 0.8% in APC8015 arm.
- Although these differences did not reach statistical significance, the increased CVA frequency is a potential safety signal.
- There appears to be an increased risk of both hemorrhagic and ischemic strokes, however the number of hemorrhagic strokes are too small to make any definite conclusions.

D. Common Adverse Event

1900 adverse events were reported in 221 patients. Table 32 shows the common toxicities (5%) that occurred in APC8015 treated subjects.

Most frequently reported AEs included chills, fatigue, and pyrexia. For AEs that occurred in $\geq 5\%$ of subjects, chills, pyrexia, dyspnea, headache, and tremors occurred significantly more frequently ($P \leq 0.05$) in subjects treated with APC8015

than in subjects treated with APC-Placebo. These events generally occurred within 1 day of an infusion with APC8015, were Grade 1 or 2, were managed on an outpatient basis, and had median durations of 24 to 48 hours.

Table 33: Frequency and Distribution of Adverse Events (>5% in APC8015 arm)

AE	APC8015		APC-Placebo	
	N = 146		N = 75	
	#	%	#	%
Chills	85	58.2	6	8.0
Fatigue	63	43.2	25	33.3
Pyrexia	48	32.9	5	6.7
Back pain	38	26.0	18	24.0
Headache	28	19.2	5	6.7
Arthralgia	26	17.8	15	20.0
Anemia	22	15.1	9	12.0
Asthenia	22	15.1	5	6.7
Nausea	22	15.1	6	8.0
Paraesthesia	19	13.0	7	9.3
Vomiting	17	11.6	2	2.7
Chest wall pain	16	11.0	5	6.7
Constipation	16	11.0	11	14.7
Dyspnea	16	11.0	2	2.7
Pain	15	10.3	8	10.7
Pain in extremity	15	10.3	12	16.0
Anorexia	14	9.6	6	8.0
Edema peripheral	14	9.6	10	13.3
Citrate toxicity	13	8.9	6	8.0
Myalgia	13	8.9	4	5.3
Tremor	13	8.9	0	0.0
Diarrhea	12	8.2	7	9.3
Dizziness	10	6.8	6	8.0
Shoulder pain	10	6.8	5	6.7
Cough	9	6.2	6	8.0
Hematuria	9	6.2	3	4.0

AE	APC8015		APC-Placebo	
	N = 146		N = 75	
Influenza like illness	9	6.2	3	4.0
Upper respiratory tract infection	9	6.2	2	2.7
Weight decreased	9	6.2	3	4.0
Feeling cold	8	5.5	1	1.3
Pallor	8	5.5	4	5.3

E. Assessment of Quality and Completeness of Data

The database reviewed here was mainly derived from two randomized studies D9901 and D9902A, a total of 225 subjects, 147 APC8015-treated, and 78 APC-Placebo treated. In addition, the summary results for CVA events observed in P-11 and D9902B were analyzed. Quality of the data was adequate from these randomized studies.

F. Drug-Drug Interactions

The cells were infused alone without any other drugs or biologics. There were no drug-drug interactions reported in the trial subjects.

7.4 Safety Summary and Conclusions

Overall, APC8015 treatment appeared to be relatively tolerated when compared to APC-Placebo. Ninety-nine percent of APC8015 treated and 93.5% of APC-Placebo treated subjects developed Adverse Events. Most AEs were grade 1 to 2 and resolved within 48 hours. Twenty-four percent of APC8015 treated subjects developed SAEs, not different from 23% of APC-Placebo treated subjects. However, CVA events appeared to occur more frequently in APC8015 treated subjects: 5.4% (8 out of 147) APC8015 treated subjects experienced CVA-related SAEs, compared to none in APC-Placebo treated subjects in D9901 and D9902A.

CVA events observed in all four phase 3 trials including p-11 and ongoing D9902B were also analyzed. Eighteen out of 461 (3.9%) subjects treated with APC8015 developed CVA events compared to 6 out of 231 (2.6%) in the APC-Placebo treated subjects overall, an absolute increase of 1.3% (odds ratio = 1.5). In the population with metastatic AIPC, 17/345 APC8015 subjects developed CVA events in D9901, D9902A and D9902B (4.9%) compared to 3 out of 172 (1.7%) in APC-Placebo treated subjects, an approximately three-fold increase in CVA's for subjects treated with APC8015 (p=0.092). Two percent (7/345) of APC8015 subjects died from CVA events compared to 1.2 % of APC-Placebo subjects (2/172), an eighty percent increase in the odds of dying

from a CVA event. This risk was not clearly confined to the thrombotic CVA's; the risk of hemorrhagic strokes may have been increased as well. Although these differences did not reach statistical significance, the increased CVA frequency is a potential safety signal.

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9 APPENDICES

9.1 Appendix 1: Consultant's review of D9901 case report forms (CRFs)

Consultant's Summary of Baseline Characteristics: Study 9901

The case report forms for 127 patients enrolled on Study 9901 were reviewed and compared with the data tables. The case reports from the placebo patients who were crossed over to active treatment (Sipuleucel-T) were not submitted for review unless an adverse event occurred. The following document is a review of the information contained within the Case Report Forms for Study 9901. Some information has been compared with the data (statistical) tables submitted by the sponsor.

Histologic Documentation and Other Cancers

All patients had pathologically documented prostate cancer which stained positive immunohistochemically for the prostate associated antigen, PAP. The following second neoplasms are noted:

- At enrollment one patient (9137-081) appeared to have a second cancer, a mass at the base of the tongue with cervical, mediastinal, and axillary nodes as well as abdominal adenopathy. He had sclerotic bone lesions consistent with prostate cancer.
- A second patient (9144-064) was noted to have right lung mass and mediastinal adenopathy which could be consistent with a lung primary. This patient had bone lesions and right inguinal adenopathy consistent with prostate cancer.
- A third patient (9121-160) on bone scan had uptake in multiple skin lesions, which is an unusual site of metastases for prostate cancer. The patient had multiple bone lesions some sclerotic in nature consistent with prostate cancer.
- A fourth patient (9169-177) who developed plasma cell leukemia at approximately one year on study had bone lesions consistent with multiple myeloma on enrollment on study. The patient also had evidence of prostate cancer with an increased PSA.

All of these patients were enrolled on the active arm.

Gleason Scores, ECOG Performance Status

Gleason scores were available for all patients and appeared to be equally distributed between the arms. The Gleason score data set was not reviewed for errors. All patients had ECOG performance status 0 – 1.

Baseline Testosterone Levels

Castrate levels of testosterone (< 50 ng/dl) were noted in 125 patients. The median testosterone in the active arm was 19 ng/dl (range: <1 -160 ng/dl) and in the placebo arm was 19 ng/dl (range: <1 – 51ng/dl). Two patients (9127-083, 9137-070) had levels greater than 50 ng/dl. Patient 9127-083 (Testosterone level -160 ng/ml) was enrolled on the active arm of the study with permission of the Dendreon clinical monitor. Patient 9137-070 on the placebo arm had a testosterone level of 51 ng/ml. On the active arm twenty-two (27%) patients had orchiectomy to reduce testosterone levels, sixty (73%) patients were on a gonadotrophic suppression (LHRH agonists). On the placebo arm eleven patients had orchiectomy, two were also on gonadotrophic suppression, and thirty-four were on gonadotrophic hormone suppression. Information on compliance with use of gonadotrophic releasing agents was not collected routinely during this study. This may account for the wide range of testosterone values observed among the enrolled patients. Testosterone level in patients with some hormonal sensitive cell would have increased / increased disease activity depending on whether compliance improved or worsened during study.

Chemotherapy, Radiotherapy

One patient (9125-072) was receiving radiation at the time of enrollment for cervical spine pain. Radiation while on study was not allowed as radiation is known to depress the immune system decreasing the potential for immunological response. On the active arm three patients (9128-081, 9168-065, 9169-123) received chemotherapy prior to enrollment. At least one patient (9169-123)

was allowed on study by the Dendron medical monitor despite six months of chemotherapy (paclitaxol, carboplatin, and estramustine) ending just two months prior to enrollment. Four patients on the placebo arm (9123-148, 9126-144, 9168-172, 9169-141) also received chemotherapy. Patient 9169-141 received two different regimens (mitozantrone for three months followed by paclitaxel for four months) with last regimen ending approximately six months prior to enrollment. One or more of these patients was enrolled with the knowledge of the Dendron medical monitor. Use of chemotherapy may diminish or abrogate responsiveness of the prostate cancers to hormonal and immunologic therapies.

Use of Systemic Steroids

Use of systemic steroids were not allowed within one year of study except for replacement hormones. Five patients on the active arm (9121-049, 9124-166, 9125-186, 9126-154, 9170-113) received a steroid therapy for periods greater than two month. These violations occurred from 20 days to six months prior to enrollment. Four of these patients were receiving ketoconazole as therapy for their metastatic prostate cancer, the fifth decadron for unclear reasons. Three other patients (9122-082, 9126-069, 9159-044) were receiving ketoconazole, however prednisone use was not reported in these patients. On the placebo arm two patients (9127-023, 9162-109) were receiving hydrocortisone along with ketoconazole for periods of two months or more within five weeks to five months of enrollment. Two other patients (9125-022, 9125-012) on the placebo arm were treated with ketoconazole without hydrocortisone according to the case report forms. Again, use of steroids could perturb the immune system and make responsiveness to immunologically modulated therapy less likely.

Laboratory Abnormalities

Hematologic, renal and hepatic function were normal in most patients enrolled on this study. One patient (9124-001) had an SGOT > 1x ULN and an SGPT > 5 x ULN. A second patient (9160-086) had an SGPT > 1 x ULN on enrollment. One patient (9169-177) noted to have multiple myeloma in addition to prostate cancer, whose creatinine was 1.5mg% (ULN) at baseline, developed renal insufficiency after the first leukopheresis. Creatinine continued to climb and the patient required dialysis within six weeks. One additional patient (9144-098) was enrolled on study with a hemoglobin reported as 12.4 gm%. After the first week of therapy the patient's hemoglobin dropped to 8.5%. Review of the record revealed that the patient was receiving transfusions on a frequent (more than once per week) due to a prostatic involvement of the bone marrow.

Prior Management of Disease:

The following table presents information on the management of disease at initial presentation based on data that the sponsor provided. A higher percentage of patients on the active arm had definitive therapy after biopsy. This may account in part for the increase in extensive soft tissue disease on the placebo arm.

Baseline Management Of Disease	Active N=82 (100%)	Placebo N=45 (100%)
Biopsy Only	18 (22)	14 (34)
Biopsy + Radiation	8 (10)	3 (7)
Biopsy + Orchiectomy	4 (5)	3 (7)

Surgery	13 (16)	8 (18)
Surgery + Radiation	20 (24)	8 (18)
Surgery + Orchiectomy	7 (9)	4 (9)
Surgery + Radiation + Orchiectomy	6 (7)	3 (7)
Other , Unknown	4 (5)	3 (7)

Antiandrogen Usage:

The following table provided information of exposure to antiandrogens (flutamine, aminogluthemide, diethylstibesterol, etc) and is based on information included in the sponsor data set and has been only cursorily checked against the CRFs.

Antiandrogen Use

Exposure	Active Arm N=82 (100%)	Placebo N=45 (100%)
No information	3 (4)	2 (4)
No exposure	1 (1)	0 (0)
One Exposure	36 (44)	21 (46)
Two Exposures	12 (15)	9 (20)
Three Exposures	8 (10)	5 (11)
Four Exposures	4 (5)	0 (0)
Five Exposure	0	0 (0)
Ketoconazole + Steroid + AA	10 (12)	5 (11)

It is NOT clear why so many patients who had one cycle of antiandrogens (in addition to LHRH agonists) did not have a second exposure to antiandrogen therapy prior to enrollment on this study. Several patients had long androgen withdrawal periods and should have been responsive to a second round of antiandrogens. Several patients who appeared to be responding to antiandrogens were discontinued and enrolled on this trial after a very brief “withdrawal” period. Whether their PSA levels were rising on antiandrogens is not clear. The PSA levels that were used to document “androgen refractoriness” have not been carefully reviewed as yet. Looking at the differences in the number of antiandrogen exposures raises questions about the heterogeneity of this study population in terms of hormone refractoriness. Differences in the survival between arms on this study and the differences between the survival in this and other studies may be explained in part by differences in prostate cancer androgen responsiveness. Tumor related hormone independence may also explain why some PSA levels* collected after the patient had been on study for some period were noted to decline. PSAs were noted to decline in five patients (9123-034, 9125-024, 9125-072, 9137-100, 9167-077) on the active arm and two (9169-072, 9169-141) on the placebo arm. Unfortunately a survival analysis looking into differences in a **truly** androgen refractory and androgen non-refractory population have not been done.

*PSA levels were not systemically collected after baseline.

Baseline Disease Characteristics:

With regard to baseline disease characteristics the sponsor's assessment and the reviewer's assessment differed for several patients. The differences in baseline characteristics are as follows:

Baseline Disease Characteristics: Active Arm

(Assessment: 0 = bone only, 1 = soft tissue only, 2 = bone and soft tissue)

Patient Number	Sponsor Disease Assessment	Reviewer Disease Assessment	Reason
9127-027	1	2	L-5 vertebrae read as degenerative progressed on follow-up scans
9127-042	2	0	CT positive for bony disease (iliac bone)
9128-026	0	2	CT shows only bony disease (in L-2)
9164-051	2	0	CT shows only bone disease
9168-065*	0	2	CT shows large pleural effusion
9169-123*	2	0	CT shows 6 cm adrenal mass ? adenoma
9169-125	2	1	CT shows only bony disease (in Rt. Ilium)
9170-147*	2	1	CT shows small Lt lung nodule
9124-001	0	NE	No CT (AP) performed to assess soft tissue
9123-007	2	NE	MRI spine; No assessment abdomen / pelvis
9160-040	0	NE	No Baseline CT of abdomen / pelvis

*Counted in the disease assessment table as min?none disease

Baseline Disease Characteristics: Placebo Arm

(0 = bone only, 1 = soft tissue only, 2 = bone and soft tissue)

Patient Number	Sponsor Disease Assessment	Reviewer Disease Assessment	Reason
9121-084	0	2	CT assessment notes enlarged prostate (see comment section)
9173-126	2	0	CT shows only a T-7 vertebral lesion
9162-109	0	NE	No CT scan done to assess soft tissue

This difference appears to be due to the fact that any patient with a CT or MRI report was assessed by the sponsor as having "soft tissue" disease even if the radiographic study was of a bony lesion. The incorrect identification of soft tissue disease sites may have also caused problems with randomization.

During the CRF review an unusual number of serious complications were noted in the placebo arm as compared to the active arm in the first eight weeks of study (first time point for disease evaluation) suggesting that the placebo population was different in some way. These complications are presented in the following table:

Complications: First Eight Weeks of Study

Complication	Active Arm (Time of Occurrence)	Placebo Arm (Time of Occurrence)
Hydronephrosis	1 (Week 4)	1 (Week 8)
Transfusion Dependence	1 (Week 1)	
Pain Progression	1 (Week 1)	4 (Week 2, 2, 4, 6)
Transfusion, Gross Hematuria	1 (Week 7)	1 (Week 4)
Renal Failure	1 (Week 2) (Probable Multiple Myeloma)	1 (Week 5) Bil. Ureteral Obstruction
Bladder Invasion		1 (Week 7)
Increased Back Pain	3 (Week 4, 8, 8)	
Cord Compression		2 (Week 6, 8)

In addition two patients on the placebo arm were noted to have bladder invasion at week 11 and week 18.5 while only one on the active arm was found to have bladder invasion at week 14.

These findings lead to the construction of a data base that contains information on all sites of disease both measurable and non-measurable. The following scheme was used to assess the extent of disease:

Soft Tissue:

CODE

- 1 Minimal: One or two nonmeasurable disease sites (small, ≤ 2 cm. nodes)
One measurable disease site ≤ 5 cm² with one or two non-measurable sites
One site of disease except prostate, bladder, or liver
- 2 Moderate: One measurable site $>5 \leq 10$ cm² with < 3 non-measurable disease
Multiple non-measurable nodes at one sites (more than small amount of disease)
- 3 Extensive: Measurable disease > 10 cm² w/without non-measurable disease
Two measurable lesions >5 and ≤ 10 cm² with ≥ 2 non-measurable sites
Prostate, bladder, or liver disease
Three or more non-measurable sites with $> one$ node visualized.

Bone:

Code:

- 1 None
- 2 Minimal: Less than six single lesions or sites unless evidence of soft tissue extension (mass effect) (2)
- 3 Moderate: Six- ten discrete sites or $< five$ sites with + indicating several lesions at one site
- 4 Extensive: $> Ten$ discrete lesions or multiple lesions at one site (X) or at more than one site (XX)

The following table contains the reviewer's assessment of the extent of disease.

Reviewer Assessment: Extent of Disease

	SOFT TISSUE					
	MINIMAL/NONE		MODERATE		EXTENSIVE	
BONE	ACTIVE N=82	PLACEBO N=45	ACTIVE N=82	PLACEBO N=45	ACTIVE N=82	PLACEBO N=45
NONE	0	0	2 (2.4%)	0	3 (3.7%)	4 (8.9%)
MINIMAL	2 (2.4%)	4 (8.9%)	2 (2.4%)	0	11 (13.4%)	9 (20.0%)
MODERATE	3 (3.7%)	2 (4.4%)	1 (1.2%)	1 (2.2%)	4 (4.9%)	5 (11.1%)
EXTENSIVE	8 (9.8%)	2 (4.4%)	1 (1.2%)	1 (2.2%)	7 (8.5%)	5 (11.1%)

Review of the table demonstrates that a higher percentage of patients in the placebo arm had extensive soft tissue disease with about an equal percentage also having some bone bony disease. According to the statistician survival is not a confounded by this factor.

Tumor Evaluations During the Course of Study

The sponsor decided to amend the study protocol so that patients who had evidence of bone disease only would not have follow-up soft tissue studies. Some patients who had measurable / non-measurable disease on abdominal /pelvic CTs at baseline did not have follow-up radiographic tests performed because the investigator did not recognize the soft tissue disease. The following is a list of patients who are not evaluable after complete baseline studies.

Active Arm- Non-Evaluable Due to Violations During Study:

The sponsor considers these patients evaluable for progression, the reviewer does not.

- 9122-082 Baseline CT – Evaluable / Measurable disease, no follow-up CT
- 9124-003 No Week 8 Studies. Patient removed from study Week 5 due to intractable pain with no radiographic confirmation.
- 9125-099 Baseline CT- Negative for disease. Next CT was done at 24 week which showed progression in the abdomen. Bone scan was unchanged. The time to progression in the abdomen is unknown.
- 9137-030 Baseline CT -Mass at base of tongue. No further CT submitted for review. Investigator read Week 8 CT as progression
- 9137-002 Baseline CT showed liver lesion 986 cm²; no follow-up CT done on this measurable lesion. (This patient is actually ineligible for study due to visceral disease.)

The reviewer considers these patients evaluable up to a certain time point.

Active Arm: Partially Evaluable Patients

- 9123-034 Appropriate radiologic and PE information was obtained so patient is evaluable from 9/18/00 until 9/18/01. Patient is not evaluable for disease status after this date (Sponsor considers patient NE)
- 9124-152 Baseline studies performed on 7/6/01. Had Week 16 studies performed (11/2/01). Refused further follow-up on 12/7/01
- 9124-161 Baseline studied performed on 7/27/01. No further bone scans performed after 4/18/02
- 9125-020 Baseline studies performed on 6/27/00. Last scans done 12/21/00 showed no progression. Patient refused to remain on study on 1/26/01. PSA noted to increase from a baseline value of 82.5 to 256.8. No CTs were done as patient was bone only disease at baseline
- 9137-100 Baseline studies performed around 4/10/01. Had bone scan only follow-up until 2/22/02 then no further radiologic follow-up reported.
- 9169-094 Baseline scans performed around 3/20/01. Last follow-up scans (bone and soft tissue reported 4/25/02
- 9169-125 Baseline scans were done around 6/6/01. A measurable bone lesion was identified on baseline CT. No follow-up CTs were performed at Week 8, Week 16. At Week 24 (12/31/01) a new lesion was identified on CT scan.

Placebo Arm: Non-Evaluable Patients

- 9124-004 No baseline CT (soft tissue assessment)
- 9128-006 No baseline CT (soft tissue assessment)
- 9121-169 No Week 8 assessment of nodes seen in mediastinum; No further radiologic assessments were performed.
- 9168-124 Baseline CT of abdomen / pelvis showed perirectal mass. No further CTs were performed.

Placebo Arm: Partially Evaluable Patients

- 9160-036 Baseline Bone scan positive for disease. Week 8 evaluation showed no progression. No further bone scans were done. (Sponsor considers non-evaluable.)

The sponsor and the reviewer disagree on the date of progression for eighteen patients in the active arm and for eight patients in the placebo arm. This is based on information from the -b(4)----- Data and from the Investigator statements in the CRF. The following table presents this data.

Difference in Progression Dates

Patient Number A Active Arm	Sponsor Progression Date	Reviewer Progression Date
9121-013	12/18/2000	13/24/2000
9121-049	5/22/2001	3/29/2000
9123-023	7/21/2000	5/22/2000
9124-050	----	8/06/2001*
9124-152	---	11/12/2001**

9124-161	---	4/18/2002***
9125-020	---	12/21/2000***
9125-027	11/28/02	10/3/2000
9137-100	----	2/22/2002***
9144-064	1/03/2002	8/06/01
9144-098	7/30/2001	7/19/01
9160-086	6/20/2001	6/11/2001
9164-062	7/30/2001	6/5/2001
9164-071	9/26/2001	7/24/2001
9169-075	5/30/2001	5/08/2001
9169-077	---	7/10/2001**
9169-123	9/24/2001	7/30/2001
9170-147	---	11/29/2002

*New Prostatic nodule on physical exam

** Censored – No further CT done

***Censored –Date of Last Bone Scan

Placebo Arm	Sponsor Progression Date	Reviewer Progression Date
9121-084	5/14/2001	5/7/2001
9121-095	4/15/2002	7/20/2001*
9124-150	8/20/2001	8/17/2001
9144-018	12/04/2001	11/13/2001
9144-066	11/12/2001	12/14/2001
9164-146	8/22/2001	7/27/2001
9170-185	1/24/2002	11/20/01**

* No CT done

** Two New Bone Lesions on CT

These differences will not be discussed further since the time to progression or progression free survival was not statistically significant.

Death Dates

Three dates came into question when the survival dates listed in the data set were compared to the CRF. For Patient 9125-010 the date of death in the table is listed as -b(6)-. In the CRF the date is listed as -b(6)-----. For Patient 9173-076 the date in the table is listed as -b(6)--, in the CRF last date of follow-up is -b(6)-----. For Patient 9160-036 date of death is -b(6)-----. Review of the CRF reveals that the correct date is -b(6)-----

Infusions

On the active arm one patient did not receive any infusions. The first infusion in one patient (9127-102) was cancelled as the patient was febrile. Two patients did not receive the third infusion, one (9126-154) for medical reasons and one (9122-082) for near anaphylactic reaction to the second infusion. Three patients (9127-027, 9144-046, 9164-131) had a one week delay in

the second infusion. No explanation has been given for this delay. In two patients (9144-098, 9160-086) the infusions were given monthly rather than every two weeks. In one patient (9196-077) the product was not infused as it appeared “not suitable for infusion”.

Cerebrovascular Accidents

The following patients were identified through CRF review to have had central nervous system events.

Active Arm

9124-001	Died one year after the last infusion from a stroke
9127-027	Had CVA one week after the third infusion. Also had an acute MI sixteen weeks into study
9144-043	Had CVA eight weeks after the third infusion
9160-039	Had a subarachnoid bleed fifteen months after the last infusion
9169-168	Intracranial bleed four months post last infusion; known hemangioma in liver
9126-154	Had leukopheresis on 7/17/01. Had a mild stroke on 7/28/01 which resolved on 8/3/01. Had one infusion on 8/16/01, discontinued study
9170-147	Had an intracranial bleed approximately 17 months after the third infusion
9170-147	Intracranial bleed fourteen weeks post last infusion secondary to Glioblastome Multiforme

Placebo Arm:

9169-073	Had a TIA followed three days later by intracranial bleed occurring twelve months after infusion
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Chemotherapy Post Study

The timing and duration of chemotherapy and or other regimens could not be assessed from the information contained in the CRFs. The investigator was only required to supply information about the first therapeutic manipulation that the patient received after disease progression was assessed.

Consultant Reviewer’s Conclusions

Issues about the study conduct include Dendreon approval of patients who did not meet eligibility criteria particularly with regard to prior steroid and chemotherapy use. One wonders how randomization was accomplished if the investigator was not aware of soft tissue disease at initiation of the study. Even more disturbing is the enrollment of good percentage of patients who may not have been refractory to antiandrogen therapy. While the number appears balanced between arms further research is needed to determine a more exact percentage of androgen refractory patients in each arm. The percentage of androgen refractory patients, if only a little worse on the placebo arm, coupled with the unfavorable (though not statistically different) increase in extensive disease on the placebo arm could have shifted the survival advantage in favor of the active arm. Since the study is small any trend is magnified.

9.2 Appendix 2: Primary Clinical reviewer's CRF review of progression dates

For subjects whose progressions dates were revised in the sponsor's re-analysis on primary endpoint --- time to progression

- **9122-082 (APC8015) CRF review --- an increase of 4 days in TTP after the change.**

Initially reported date of progression, 26 MAR 01 was based on the onset of disease-related pain reported by the investigator.

The sponsor changed that date to 3-30-01 based on the he Weekly Pain and Analgesic Use Log is the date of pain onset" (CT-33) because the protocol Section 4.2.2. states that if the date of Investigator-reported disease-related pain (on CT-14 and CT-15; 26-Mar-01) differs from the date of disease-related pain derived from the Weekly Pain and Analgesic Use Logs (CT-33; 30-Mar-01), then "the date on the Weekly Pain and Analgesic Use Log is the date of pain onset" (CT-33).

Reviewer's summary:

- CT-33 (pain progression CRF) showed a date of disease related pain on 3-30-01, but the method of determination was not marked.
- CT-15 CRF did contain the date of 3-29-01 as the onset of the pain.
- Right hip X-ray was done along with the stage scans: no changes in the lesions from the baseline, but right hip X-ray revealed new lesion (CT-15 and page 18 of 67), although the -b(4)----- source document did not state the X-ray findings.

Reviewer's conclusion:

The reviewer cannot verify the date change because of the lack of information: X-ray reading and the patient's pain log on 3-29 or 3-30-01.

- **Subject: 9124-152 (APC8015) --- This subject's time to disease progression was revised to increase by 49 days**

1. Sponsor's reason for change:

The date was changed from 18-Sep-01 (censored), the date of a protocol violation, to 6-Nov-01 (censored), the date of last physical examination.

(CORRECTION - 6 Nov-01 is the date of last radiographic scan and not the date of last physical examination)

2. CRF review:

- Registration date: Not found in the eligibility form (CT-3) was version “Rev.1/01”. In this subject’s CT-3, there was no entry heading for “registration date”. Instead, “visit date” was in place. Date of visit: 7-06-01

Date of randomization: 7-09-01

Obtained from D9901 efficacy data listing table: Table “Efficacy.xpt”

Inconsistency noted in CRF CT-3.

- Product infusion dates: 7-13-01; 7-27-01; 8-10-01
- Site of disease: Lesions (CT and bone scan 6-28-01) (page 12 of 60)
 - #1: left shoulder
 - #2 right anterior pelvis
 - #3 left anterior pelvis
 - #4 upper T-Spine
 - #5 multiple mid T-spine lesions
 - #6 lumbar spine lesions
 - #7 L-S spine lesions
 - #8 multiple left ribs
 - #9 right ribs
 - #10 left S-I joint region
 - #11 right S-I joint region
- The sponsor’s original date of progression: 18 SEP 01, reported to be the date of a protocol violation --- stopping hormone treatment.

The subject was not on hormone therapy as required by eligibility criteria (page 50 of 60).

The subject did not meet eligibility criteria.--- Protocol violation

The reviewer could not find the reason why the 18 SEP 01 was the date of a protocol violation.

- The sponsor’s CORRECTION - 6 Nov-01 was the date of last radiographic scan and not the date of last physical examination.

Week 8 and Week 16 bone scan and CTC and CTA were same as baseline. No objective disease progression (pages 28 and 29 of 60).

Reviewer’s summary:

- According to the protocol, this subject was not eligible since he did not have current hormone therapy --- protocol violation.

- The reviewer could not find the information on why the subject had a protocol violation on 18 SEP 01.
- Serial scans did not reveal objective disease progression. Last scan date was 11-06-01.

Reviewer's conclusion:

Because of violation, the TTP date is not interpretable.

- **Subject: 9125-072 (APC8015) --- This subject's time to disease progression was revised to increase by 303 days**
 - Registration date: 3-5-01
 - Product infusion dates: 3-8-01; 3-22-01; 4-5-01
 - Site of disease: bone only in T8, L2 and lower cervical spine (Baseline scan: 2-16-01, page 10 of 97). Lesions were named 1, 2 and 3, respectively.
 - The sponsor's original date of progression: 3-21-01, reported to be the date of protocol violation because the subject received radiation.
 - Details on the radiation:
 - Patient actually started radiation for T8 on 02 MAR 01, NOT 21 MAR 01, ended on 4-12-01.
 - Radiation dose: 3750 cGy, 15 fractions in 23 days.
 - Reason for radiation: back pain. XRT was originally listed "NOT used to treat adverse event", then revised in the data clarification sheet as "Yes, used to treat adverse event" (query form #8190).
 - An entry of back pain was made for adverse event, but was deleted on 3-1-05 (CT-16), no explanation.
 - No information on the T8 disease status on 02 March 01
 - New lesion on 06 July 01 (left sternum, page 30 of 97). This lesion was named #4.
 - New lesion on 18 JAN 02 (T-12), which the sponsor used to revise the final date for this subject (page 42 of 97). This lesion was named #5.

Reviewer's Summary of CRF review:

- Originally reported date of radiation (XRT) on CRF was 02 MAR 01, inconsistent with the sponsor's date of 21 MAR 01
- No information on T8 status at the time of radiation

- The sponsor revised CRF to state that XRT was used to treat adverse event
 - Radiation started on 02 MAR 01. The patient was registered on 05 MAR 01. Inconsistent with the protocol eligibility: “Prior radiation therapy and surgery are allowed except for treatment of sites of painful metastases. At last 4 weeks must have elapsed since the completion of radiation therapy or surgery and the patient must have recovered from acute side effects. STUDY CSR-D9901 Page 794 of 5814, section 5.1.9).”
- A new lesion (#4) was detected on 06 Jul 01, and another new lesion #5 was detected on 18 JAN 02. The patient was declared to have disease progression on 18 JAN 02. Since only one new lesion was noted on each of the two dates, the subject did not appear to meet the disease progression criteria according to the protocol: ““Scan Only” Bone Disease: An appearance of ≥ 2 new areas of abnormal uptake on bone scan. Increased uptake of pre-existing lesions on bone scan does not constitute progression.” However, it should be noted that the preceding protocol description did not state clearly whether ≥ 2 new areas of abnormal bone scan were those appearing simultaneously or those accumulative from the baseline.

Reviewer’s conclusion:

- Based on above inconsistencies and unclear description of tumor progression criteria, the reviewer cannot verify the sponsor’s justification in revising this subject’s date of disease progression.
- **Subject: 9164-062 (APC8015) --- This subject’s time to disease progression was revised to increase by 57 days**

1. Sponsor’s reason for change:

Following an internal audit at ---b(4)----- was notified that the disease progression date should be 5-Jun-01, not 9-Apr-01 as formerly indicated. The date was changed from 9-Apr-01 to 5-Jun-01

2. CRF review:

- Registration date: Not found in the eligibility form (CT-3) was version “Rev.1/01”. In this subject’s CT-3, there was no entry heading for “registration date”. Instead, “visit date” was in place. Date of visit: 02-09-01

Date of randomization: 02-12-01

Obtained from D9901 efficacy data listing table: Table “Efficacy.xpt”

The sponsor reported a randomization date of 02-09-01, inconsistent with the datalisting in the Table “Efficacy.xpt” .

Inconsistency noted in CRF CT-3 and the date of randomization.

- Product (APC8015) infusion dates: 2-15-01; 2-28-01; 3-15-01
- Site of disease at registration: Lesions (CTA and CTP and bone scan 2-05-01) (page 10 of 64)
 - #1: 7th antero rib
 - #2 right shoulder
 - #3 left paraortic node level of renal vein
 - #4 Aortocaval adenopathy
 - #5 other paraortic adenopathy
 - #6 right common iliac node
 - #7 right external iliac adenopathy
- The sponsor’s original date of progression: 09 Apr 01 (week 8)
 The scan was read on 03 APR 2006, No CTA.
 The radiologist note showed that lesions 3,4,5, not assessable due to the lack of CTA (page 25 of 64).
 The reviewer did not understand what “PC” meant.

Inconsistency was noted: the database was locked in June 2002, but this subject’s scan was read in April 2006.

Noticed the appearance of the source document copy for 09 Apr 01 was different from that of all other copies.

- The sponsor’s revision of the date to 5-Jun-01 (week 16).

The sponsor stated that “following an internal audit at ---b(4)----- was notified that the disease progression date should be 5-Jun-01, not 9-Apr-01 as formerly indicated”.

Review of -b(4)----- source document on 5-Jun-01 showed the increase in lesion 7 and became measurable and progression of lesion 3 (measurable lesion) (page 31 of 64).

The subject subsequently had scans at week 24, showing two new bone lesions (page 35 of 64). There was a note “based on re-read of week 8...”, but the CRF did not contain the initial reading of week 8.

Reviewer’s summary:

- Validity of the week 8 scan source document cannot be determined: Scan was performed in 2001, but re-read in 2006. No information on the initial reading.
- A variant appearance of the week 8 source document raises a question on its authenticity.
- Week 16 scan result was verified.
- The week 8 (09-Apr-01) CT scan of abdomen was not performed, but the sponsor used this date as the initial date of disease progression. It was not clear whether this date was a censored date or not.
- The protocol stated that in the situation of missing scans, the date on the latest scan showing disease progression would be the date of disease progression. Applicable to this subject, that date would be 5-Jun-01 (week 16). However, this subject did not miss the scan, but missed a study in that scan.

Reviewer's conclusion:

The reviewer cannot verify the sponsor's justification for the revision of the disease progression date because of above inconsistencies.

- **9169-141 (APC-Placebo) CRF review:**

Initial reported date of progression based on imaging was 12-Jul-01, revised to be 30-Jul-01, resulting an 18-day increase in Time to progression in this placebo subject (p-value from 0.085 to 0.088).

Reviewer's summary and conclusion: source data reviewed. Revised date of 30-Jul-01 was confirmed (week 8 scans, multiple progressions in bone and soft tissues).

- **Subject: 9170-147 (APC8015) --- This subject's time to disease progression was revised to increase by 118 days**

1. Sponsor's reason for change:

The date was changed from 1-Aug-01 (censored), the date of a protocol violation, to 27-Nov-01 (censored), the derived date of disease-related pain progression.

(CORRECTION - 27-Nov-01 is the date of last radiographic scan and not the date of disease-related pain progression)

2. CRF review:

- Registration date: Not found in the eligibility form (CT-3) was version "Rev.600". In this subject's CT-3, there was no entry heading for "registration date". Instead, "visit date" was in place. CT-3 "Rev. 600" from other subjects contained an entry heading for registration date. Date of visit:7-19-01

Date of randomization: 7-20-01

Obtained from D9901 efficacy data listing table: Table "Efficacy.xpt"

Inconsistency noted in CRF CT-3.

- Product infusion dates: 7-25-01; 8-8-01; 8-22-01
- Site of disease: Lesions (CT and bone scan 7-02-01) (page 11 of 67)
 - #1: left first rib
 - #2 S1 vertebral body
 - #3 Right iliac bone
 - #4 L5 pedicle
 - #5 Right acetabulum
 - #6 Small left lung nodule
- The sponsor's original date of progression: 01 Aug 01, reported to be the date of a protocol violation --- stopping hormone treatment.

Zoladex started on 1-20-00 and stopped 01 MAY 01 (before enrollment) (page 49 of 67) and no further treatment and the subject did not have an orchiectomy (page 50 of 67).

Inconsistency is noted here: the subject did not have current hormonal therapy as specified in the protocol eligibility criterion (section 5.1.5, Page 793 of 5814 STUDY CSR-D9901).

- The sponsor's date of 27-Nov-01 (censored), the derived date of disease-related pain progression.

The reviewer could not find any information regarding the date of disease-related pain progression.

- The sponsor's CORRECTION: 27-Nov-01 was the date of last radiographic scan and not the date of disease-related pain progression

Week 8 bone scan: same as baseline

Week 8 (9-18-01) CTA: #6 small lung nodule was noted; and another small right lung nodule was noted (#7) (page 26 of 67).

According to the protocol: According to the protocol, appearance of any new lesion on Xray, CT or MRI constituted progression. However, the subject was not declared to have tumor progression

Inconsistency was noted with what was actually observed and what was described in the protocol.

The subject's last CT and bone scan date: 27 NOV 01. Original source -b(4)---- scan document showed that all seven lesions were same as week 8 (page 33 of 67)

However, the Dendreon's own assessment showed that there were two new areas of uptake on bone scan (page 30 of 67) in T3 and thoracic spine.

Inconsistency is noted here regarding the scan results, but the sponsor stated that the results of Dendreon's own assessment were not used in the analysis. Instead, the date from --b(4)---- was used for analysis (Censored, no progression)

Reviewer's summary:

- According to the protocol, this subject was not eligible since he did not have current hormone therapy
- The subject had a new lung lesion, but was not declared as having disease progression, inconsistent with the protocol disease progression
- Inconsistencies were noted in the format of this subject's CRFs compared to other CRFs and in the interpretation of the bone scan results.

Reviewer's conclusion:

The reviewer cannot verify the sponsor's justification in revising this subject's date of disease progression.

9.3 Appendix 3: Review of Clinical and PSA responses in the submitted studies

Summary of tumor responses in subjects who received APC8015:

- **One out of 65 (1.5%) experienced a partial response (83.9% tumor area reduction) in D9902A**

Source of document: BLA submission, D9902A CRF review.

9235-015: 67 year-old man with multiple lesions as described below received three infusions of APC8015 at weeks 0, 2 and 4.

Lesions:

A. At registration:

Bone lesions:

- 1 multiple rib
 - 2 multiple bilateral humerus
 - 3 multiple bilateral femur
 - 4 right ischium lesion
 - 5 multiple patchy t-spine
 - 6 multiple patchy l-spine sites
 - 7 sternum
- Soft tissue lesions

Measurable

8 Left paraaortic nodal mass Length (cm) 5.2; Width (cm) 4.6; product of length and with (area cm²) 23.9

9 Right retrocaval node Length (cm) 3.3; Width (cm) 2.7; product of length and with (area cm²) 8.9

10 Left paraaortic node above bifurcation Length (cm) 3.7; Width (cm) 2.6; product of length and with (area cm²) 9.6

Total measurable tumor area: 42.2 cm²

Non-measurable

- 11 multiple other upper abdominal adenopathy
- 12 bilateral hydronephrosis

13 bilateral pelvic sidewall adenopathy
14 retrocrural adenopathy

B. Week 32

Bone lesions: 1-7 no changes

Soft tissue lesions
Measurable

8 Left paraaortic nodal mass Length (cm) 2; Width (cm) 1.3; product of length and with (area cm²) 2.6

9 Right retrocaval node Length (cm) 2; Width (cm) 0.9; product of length and with (area cm²) 1.8

10 Left paraaortic node above bifurcation Length (cm) 2; Width (cm) 1.2; product of length and with (area cm²) 2.4

Total measurable area: 6.8

Non-measurable lesions 11-14: same as baseline

Total tumor area reduction from registration to week 32 (last scan):

$$(42.2 - 6.8)/42.2 = 83.9\%$$

- **One out of 19 (5.3%) in a phase 2 trial (D9702) experienced a “complete response” reported by the investigators.** However, this response cannot be verified because of the lack of source document in the study report and poor data quality of the published article:

Source of document: BLA submission, abbreviated study report ACT 9702 and Published article, Prostate 60: 197–204, 2004. No CRF available for this subject.

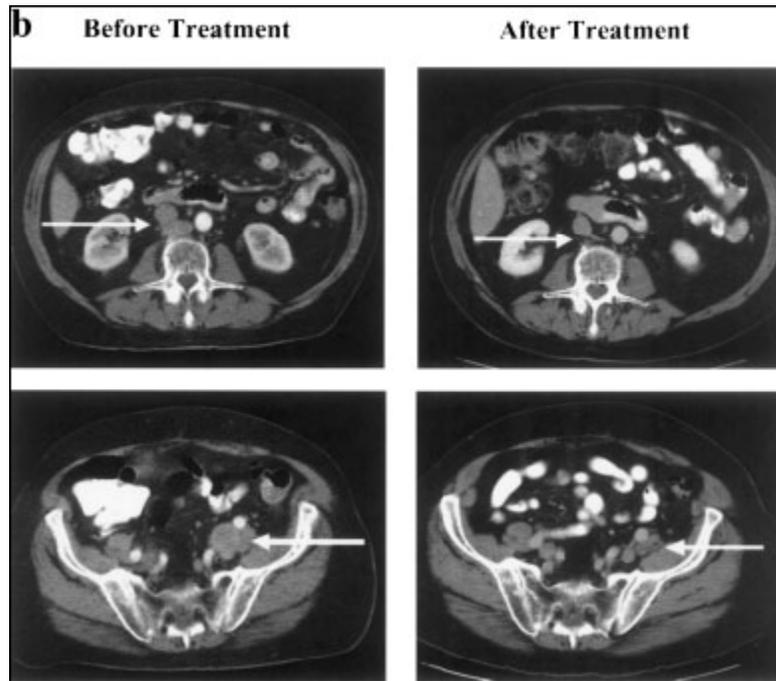
The subject 9702-22 was a 78 year-old man with metastatic prostate cancer lesions in retrocaval, para-aortic and iliac adenopathy noted on computed tomography (CT) scan of the abdomen and pelvis at baseline.

The subject received two intravenous infusions of APC8015 on week 0 and week 2. Subsequently he received three subcutaneous injections of 1.0 mg of PA2024 (0.5 mg into each thigh) at weeks 4, 8, and 12.

The study report (page 25 of 1010, STUDY CSR-D9702) described that a Complete Response (CR), verified by CT scan of the abdomen and pelvis, was reported on Study Days 244 and 300.

In the published paper, the imaging scans at registration and 22 month scans were compared. Note the discrepancy of the scan timing between the study report and the published paper (300 days vs. 22 month).

It should be noted that the CT images in the upper panels were obtained at different levels, and the images in the lower panels seemed to have a different FOV.



Summary of PSA responses in subjects who received APC8015

Definition: 50% decrease from baseline or a reference PSA level, measured at least 4 weeks apart.

D9901: 4/28 subjects (14.3%) met above definition

D9902A: 1/12 subjects (8.3%) met above definition although the result cannot be verified

Source of document: study reports, CRFs contained in the BLA submission.

D9901

Four subjects are described below:

Subject 9123-034: Baseline PSA value: 34.4 ng/mL, dropped to 1.4 ng/mL at Week 16 and remained at < 1 ng/mL through Week 68. No data available after that. On Day 25 he began treatment with cerivastatin, a hydroxymethyl glutaryl coenzyme A reductase inhibitor, which was also continued throughout the study.

There were no other medications of relevance that were started following randomization. It is unlikely, although possible, that cerivastatin could have contributed to the PSA reduction seen in this subject.

Subject 9125-072: PSA value: 21.3 ng/mL, dropped to 3.6 ng/mL at Week 16 and was 3.5 ng/mL at Week 32. No data available after that. He was on low dose prednisone (6 mg QD) and gold therapy for rheumatoid arthritis for more than 10 years prior to registration. No new medications were started while on study. At week 17, he began treatment with celecoxib. He did not initiate treatment with any other medications following randomization

Subject 9137-100: Baseline PSA value was 12.8 ng/mL, dropped to 1.2 ng/mL at Week 16 and was 4.7 ng/mL at Week 44. No data available after that.

Subject 9169-077: Baseline PSA value was 54 ng/mL. It dropped to 15.5 ng/mL at Week 16 and was 9.8 ng/mL at Week 64. Nine days prior to randomization he began treatment with low dose estrogen (1 mg QD diethylstilbestrol [DES]). Treatment with DES may have contributed to the PSA reduction seen in this subject.

D9902A:

Study report described the subject 9235-015 who had a PSA level of 568.6 ng/ml at week 0 decreased to 4.5 ng/ml at week 16 (CSR D9902A page 2589 of 4062). However, the CRF of this subject did not contain the form for week 16 PSA measurement.

9.4 Appendix 4: Clinical Reviewer's analyses of death events

TXGRP: treatment group. 1=APC 8015; 2=APC placebo

DCAUSECD: Cause of Death Code. 1= progression of prostate cancer; 3= infection; 8=other causes with comments; 9= unknown

Certificate: Death Certificate. 1= obtained.

PATNO	TXGRP	DEATHDT	DCAUSECD	Comments	Certificate
9121-013	1		.		.
9121-049	1		.		.
9121-084	2	----b(6)----	1		1
9121-091	1		.		.
9121-095	2	----b(6)----	1		1
9121-163	1	----b(6)----	1		1
9121-169	2	----b(6)----	1		1
9122-060	2	----b(6)----	1		.
9122-082	1	----b(6)----	1		1
9123-002	1	----b(6)----	1		1
9123-007	1	----b(6)----	1		1
9123-032	2	----b(6)----	1		1

PATNO	TXGRP	DEATHDT	DCAUSECD	Comments	Certificate
9123-034	1	----b(6)----	8	died of progressive metastatic esophageal carcinoma	1
9123-035	1	----b(6)----	1		1
9123-148	2	----b(6)----	9	Unknown cause	1
9124-001	1	----b(6)----	8	acute cerebrovascular accident	.
9124-003	1	----b(6)----	1		.
9124-004	2	----b(6)----	1		.
9124-021	1		.		.
9124-050	1	----b(6)----	1		.
9124-074	2	----b(6)----	8	congestive heart failure	.
9124-104	1	----b(6)----	1		1
9124-150	2	----b(6)----	1		.
9124-152	1	----b(6)----	.		.
9124-161	1		.		.
9124-166	1	----b(6)----	1		1
9124-170	1	----b(6)----	1		.
9125-009	1	----b(6)----	1		1
9125-010	1	----b(6)----	1		.
9125-012	2	----b(6)----	9	Unknown	.
9125-015	1	----b(6)----	9	unknown	.
9125-017	1	----b(6)----	1		.
9125-020	1	----b(6)----	1		.
9125-022	2	----b(6)----	1		1
9125-024	1	----b(6)----	1		.
9125-048	2	----b(6)----	1		1
9125-072	1	----b(6)----	1		.
9125-085	2	----b(6)----	1		.
9125-099	1		.		.
9125-182	1	----b(6)----	9	unknown	.
9125-186	1	----b(6)----	1		1
9126-025	1	----b(6)----	9	unknown	.
9126-033	2		.		.
9126-052	1	----b(6)----	8	urinary tract infection	.
9126-069	1	----b(6)----	9	unknown	.
9126-090	2	----b(6)----	1		.
9126-096	1		.		.
9126-144	2	----b(6)----	1		.
9126-154	1	----b(6)----	9	unknown	.
9126-178	2	----b(6)----	1		1
9127-023	2		.		.
9127-027	1	---b(6)---	1		1
9127-028	1	----b(6)----	8	stroke	1
9127-042	1	----b(6)----	1		1
9127-047	2	----b(6)----	1		1
9127-054	1	----b(6)----	9	unknown	.

PATNO	TXGRP	DEATHDT	DCAUSECD	Comments	Certificate
9127-083	1	----b(6)----	1		1
9127-122	1	----b(6)----	1		1
9127-162	2	----b(6)----	1		1
9128-006	2	----b(6)----	1		1
9128-026	1	----b(6)----	8	MI and CHF	1
9128-081	1	----b(6)----	1		1
9137-011	1	----b(6)----	9	unknown	.
9137-014	2	----b(6)----	1		.
9137-030	1	----b(6)----	1		.
9137-070	2	----b(6)----	1		.
9137-100	1		.		.
9137-102	1	----b(6)----	8	Progressive Dementia	.
9144-018	2	----b(6)----	1		1
9144-043	1	----b(6)----	9	unknown	.
9144-046	1		.		.
9144-064	1	----b(6)----	1		1
9144-066	2	----b(6)----	1		.
9144-098	1	----b(6)----	1		1
9159-044	1	----b(6)----	1		1
9159-053	1	----b(6)----	1		.
9160-036	2	----b(6)----	1		.
9160-038	2	----b(6)----	1		1
9160-039	1	----b(6)----	8	stroke	1
9160-040	1	----b(6)----	9	unknown	1
9160-086	1		.		.
9160-179	2	----b(6)----	1		.
9162-109	2	----b(6)----	1		1
9164-051	1	----b(6)----	1		.
9164-058	2	----b(6)----	1		1
9164-062	1		.		.
9164-071	1		.		.
9164-078	2		.		.
9164-129	1	----b(6)----	1		1
9164-131	1	----b(6)----	9	unknown	.
9164-145	1	----b(6)----	1		.
9164-146	2	----b(6)----	9	unknown	.
9165-059	2	----b(6)----	1		1
9168-055	1	----b(6)----	1		.
9168-065	1	----b(6)----	1		1
9168-124	2		.		.
9168-172	2	----b(6)----	1		1
9169-056	1		.		.
9169-073	2	----b(6)----	8	Stroke	.
9169-075	1	----b(6)----	1		.
9169-077	1		.		.
9169-079	1	----b(6)----	1		1
9169-089	2	----b(6)----	1		.
9169-094	1		.		.
9169-103	1	----b(6)----	8	stroke	1

PATNO	TXGRP	DEATHDT	DCAUSECD	Comments	Certificate
9169-105	2	----b(6)----	1		1
9169-115	1	----b(6)----	3	Infection	1
9169-123	1	----b(6)----	1		1
9169-125	1		.		.
9169-130	1	----b(6)----	1		1
9169-139	2	----b(6)----	1		1
9169-140	2	----b(6)----	1		1
9169-141	2	----b(6)----	1		1
9169-159	1	----b(6)----	1		1
9169-164	1		.		.
9169-168	1	----b(6)----	9	unknown	.
9169-177	1	----b(6)----	8	Refusing renal dialysis--RF	1
9170-108	2	----b(6)----	1		.
9170-113	1	----b(6)----	1		.
9170-121	1	----b(6)----	1		.
9170-142	1		.		.
9170-147	1	----b(6)----	8	CVA	.
9170-167	2	----b(6)----	9		.
9170-176	1		.		.
9170-185	2		.		.
9173-076	1		.		.
9173-126	2	----b(6)----	9		.

9.5 Appendix 5: CVA case summaries

Source of Document: BLA amendment 4

Study D9901 and Study D9902A

APC8015

9124- 001: Subject 9214- 001, enrolled in Study D9901, was 75 years old at registration. At Baseline he had metastatic prostate cancer including skull metastases. He received three infusions of APC8015, the last on 04 February 2000. At Study Week 56 (approximately Study Day 392), it was noted he had undergone a left carotid endarterectomy and was treated with aspirin, clopidogrel, and amlodipine. He progressed on Study Day 398. Low grade disseminated intravascular coagulation (DIC) was noted on the disease progression case report form (CRF). ----b(4)----- following his last infusion, he expired with the cause of death on the death summary CRF listed as acute cerebral vascular accident (CVA). --- Primary reviewer's note: complication from the left carotid endarterectomy? most likely unrelated.

9124- 050: Subject 9124- 050, enrolled in Study D9901, was 60 years old at registration. He received three infusions of APC8015, the last on 12 January 2001. Approximately 15 to 30 days after this third infusion, he experienced the adverse event of transient ischemic attack (TIA) with a duration noted as one minute. No treatment was required for this

event. He was subsequently (in February 2001) started on aspirin 325 mg daily. At the study conclusion he was alive and had not met the disease progression endpoint. Primary reviewer's note: 15 to 30 days after this third infusion. possibly related.

9127- 027: Subject 9127- 027, enrolled in Study D9901, was 68 years old at registration. He had a history of CVA in 1994 (with residual partial expressive aphasia), hypercholesterolemia, and hypertension. He was treated with aspirin, pravastatin, and nifedipine. He stopped taking aspirin for 2 months then resumed on the day of his third infusion. He received three infusions of APC8015, the last on 07 September 2000. Seven days after his third infusion he experienced 24 hours of Grade 1 slurred speech, which resolved. He had disease progression on Study Day 62. He died on Study Day 625 of disease progression. Primary reviewer's note: stopped taking aspirin for two month, prior history of CVA, CVA seven days after his third infusion but possible related.

9127- 028: Subject 9127- 028, enrolled in Study D9901, was 69 years old at registration. At Baseline, he had metastatic prostate cancer including skull metastases. He had no reported risk factors for CVA; however, his Baseline electrocardiogram (EKG) showed normal sinus rhythm with multiple premature atrial contractions. He was taking aspirin every other day. He received three infusions of APC8015, the last on 08 September 2000. He had disease progression including multiple skull metastases on Study Day 57. On Study Day 80, he started treatment with an investigational tyrosine kinase inhibitor. According to the death summary CRF, the subject had an ischemic stroke on --b(6)----- following his last infusion of APC8015. Despite being treated with tissue plasminogen activator, he expired the same day (Study Day b(6)), with the cause of death on the death certificate listed as CVA. --- Primary reviewer's note: b(6) days following his last infusion of APC8015, most likely not related.

9144- 043: Subject 9144- 043, enrolled in Study D9901, was 71 years old at registration. He received 3 doses of APC8015, the last on 27 November 2000. He developed expressive aphasia on 06 March 2001 (Study Day 124). The computed tomography (CT) scan of his brain on 06 March 2001 was negative. It was thought that the aphasia was a side effect of the narcotic analgesics he was taking for chronic low back pain. His Baseline medications included aspirin, atorvastatin, and atenolol; although the AE CRF stated that he stopped his medications 1 week prior to the event. On 13 March 2001, a magnetic resonance imaging (MRI) scan showed a subacute infarct. He was not hospitalized for this event. However, the subject was hospitalized on 25 April 2001 for increasing lethargy and aphasia, approximately 5 months after the last administration of APC8015. Multiple diagnostic studies were done and he was discharged on 01 May 2001. Discharge diagnoses included cerebrovascular insufficiency and subacute infarction in the left middle cerebral artery distribution. Primary reviewer's note: approximately 5 months after the last administration of APC8015, stopped taking cardiac meds one week prior to the event, most likely unrelated.

9144- 046: Subject 9144- 046, enrolled in Study D9901, was 79 years old at registration. He received 3 infusions of APC8015, the last on 21 December 2000. He had a history of squamous cell carcinoma of the neck that was surgically resected in 2000. He had been

taking aspirin for 3 years, but it was discontinued 10 months prior to the event. He experienced a CVA on 02 January 2002, approximately 13 months after his last infusion. While hospitalized he received a pacemaker for bradycardia and radiation treatment to his left hip. His condition resolved and he was discharged after 9 days of hospitalization. Primary reviewer's note: stopped taking aspirin 10 month prior to the event, approximately 13 months after his last infusion, surgical procedure prior to the event. Most likely unrelated.

9160- 039: Subject 9160- 039, enrolled in Study D9901, was 79 years old at registration. He had a history of atrial fibrillation and was treated with digoxin and furosemide. He received 3 infusions of APC8015, the last on 13 November 2000. He was noted to have progressive disease on approximately Study Day --b(6)----- days after his third infusion, he suffered a subarachnoid hemorrhage and expired. Primary reviewer's note: --b(6)---- after his third infusion. Possibly related.

9169- 168: Subject 9169- 168, enrolled in Study D9901, was 78 years old at registration. He had a history of hypertension, non- insulin dependent diabetes mellitus, and atrial fibrillation that was treated with warfarin sodium and digoxin. He also had deep vein thrombosis due to estrogen therapy. At Baseline, his bone scan showed greater than 10 sites of metastases including the skull. He received all three infusions of APC8015, the last on 20 September 2001. Following documented disease progression at Study Day 117, he received docetaxel on 12 February 2002 (Study Day 175). He expired -b(6)-days following his last infusion, with the cause of death attributed to intracranial hemorrhage. Primary reviewer's note: -b(6)- after his third infusion. On coumadin. most likely unrelated.

9235- 035: Subject 9235- 035, enrolled in Study D9902A, was 75 years old at registration. He had a history of hypertension. He received cytoxan 150 mg daily for 7 years, along with hydrocortisone and ketoconazole; all were discontinued 2 to 3 months prior to registration. He was taking aspirin, which was discontinued 13 days prior to the event. He received 2 doses of APC8015. Eleven days after his second infusion (Study Day 26), he was noted to have unsteady gait and dizziness. It was felt by the Investigator that he had Bell's palsy. He was also noted to have a lacunar infarct in the right caudate nucleus which could account for some left-sided findings. He also had extensive lumbar spine metastases, which may have contributed to his lower extremity weakness. He had disease progression at Study Day 37 and died on Study Day 207 of prostate cancer. Primary reviewer's note: Eleven days after his second infusion (Study Day 26). Possibly related.

9261- 008: Subject 9261- 008, enrolled in Study D9902A, was 79 years old at registration. At Baseline he had metastatic prostate cancer including skull metastases. He had a history of insulin dependent diabetes mellitus, hypercholesterolemia, hypertension, myocardial infarction in 1981 and 1987, and 5 vessel coronary bypass graft procedures in 1987. He was being treated with insuline and aspirin prn, but aspirin was not listed as a medication at the time of the event. He received 3 infusions of APC8015, the last on 13

December 2000. He met the primary study endpoint of disease progression on 01 March 2001 (Study Day 106). On 27 May 2001 (Study Day 193), he developed hemiparesis and a CT scan of the brain revealed a left sided CVA. He expired b(6) days later, on Study Day b(6), due to the CVA as noted on the death summary CRF. Primary reviewer's note: multiple risk factor for CVA. 6 months after last infusion. Most likely unrelated.

9261- 037: Subject 9261- 037, enrolled in Study D9902A, was 55 years old at registration. He had a history of hypertension. He received three infusions of APC8015, the last on 31 May 2001. He stopped atenolol four days prior to the subsequent event; it is not clear why he discontinued this medication. Nine days after his third infusion, he was noted to have a change in mental status accompanied by weakness in his right side. At the time of hospital admission on 08 June 2001, his blood pressure was 181/ 111. An MRI performed on 08 June 2001 detailed multiple findings, most notably that the subject's calvarial metastasis had extended locally to the subjacent dura, manifesting as a mass of 1.3 x 2.2 cm. Additionally, there was a large acute intraparenchymal hematoma of the left parietal lobe that was contiguous with the dural metastatic lesion, as well as a large left subdural hematoma. He was noted to have disease progression on Study Day 35 based on this event. He underwent a left parieto-occipital craniotomy for neurosurgical evacuation of the hematoma on 10 June 2001. He expired on -b(6)----- (Study Day 275) of disease progression. Primary reviewer's note: stopped high bp med 4 days prior to the event. intracranial bleeding with high blood pressure. b(6) days after the last infusion. most likely unrelated.

APC- Placebo

9121- 095: Subject 9121- 095, enrolled in Study D9901, was 75 years old at registration. He received 3 infusions of APC- Placebo, the last on 03 May 2001. He had a history of atrial flutter and fibrillation. Thirteen days prior to the event, he received paclitaxel chemotherapy for progressive prostate cancer. The week prior to this event, he was treated for tachycardia with atenolol. He experienced a CVA on 25 November 2001, which led to hospitalization, approximately 7 months after his last infusion (Study Day 235). On 27 November 2001, he developed aphasia and right arm paralysis. A CT angiogram revealed decreased blood flow through the left middle cerebral artery, consistent with an embolic CVA. He was treated with alteplase, warfarin sodium, and metoclopramide. He recovered with sequelae and was discharged to a Rehabilitation Unit 4 days after admission. Primary reviewer's note: cardiac history. approximately 7 months after his last infusion. Most likely unrelated.

9169- 073: Subject 9169- 073, enrolled in Study D9901, was 65 years old at registration. He received 3 infusions of APC- Placebo, the last on 05 April 2001. On 07 January 2002, approximately 9 months after his last infusion, he experienced an abnormal sensation in his left arm and had difficulty with appropriate response and following commands. A TIA was diagnosed. A CT scan of his head diagnosed a TIA. On 10 January 2002, he became unresponsive and developed seizures. A CT scan of his head revealed right parietal bleeding with edema. He was diagnosed with a right parietal hemorrhagic CVA and cerebral brainstem herniation. He received intensive care, but expired within b(6)

b(6) (on Study Day 307). Primary reviewer's note: b(6) months after his last infusion. Most likely unrelated.

Study D9902B (blinded at the subject level)

92025-0346: Subject 92025- 0346 was 73 years old at registration. He received 3 doses of study product (APC8015 or APC- Placebo), the last on 26 August 2004. He had a history of hypertension and hypercholesterolemia; his concomitant medications included hydrochlorothiazide, prnivil, and simvastatin. Two days after his third infusion (Study Day 30), he lost vision in his right visual field. A CT scan of the head demonstrated diffuse sclerotic calvarial metastases with a subtle 1.5 cm hypodense area in the left occipital lobe. The appearance was suggestive of a subacute infarct; although, a metastatic lesion could not be ruled out. He recovered and was placed on 325 mg of aspirin per day after 3 days of hospitalization (Study Day 33). Primary reviewer's note: CVA diagnosis was not definitive.

92036-0624: Subject 92036- 0624 was 68 years old at registration. He received 1 infusion of study product (APC8015 or APC- Placebo) on 21 October 2005. He had a history of hypertension and glaucoma; his concomitant medications included aspirin, fosinopril, and atenolol. Seven days after his first infusion, he experienced a CVA. No acute intracranial hemorrhage or midline shift was seen. Treatment with tPA was administered. Repeat scanning revealed a significant intracranial hemorrhage. A hematology consultation report stated that the subject experience several episodes of bleeding even after the tPA half- life. Platelet function tests were consistent with aspirin use. The hematologist's impression was that it was unlikely that the subject had an intrinsic coagulation problem with a normal PT and PTT prior to therapy. The subject expired on --b(6)----- (Study Day b(6)). Post-mortem, the subject was unblinded and it was determined that he had been randomized to APC- Placebo. Primary reviewer's note: -b(6)--days after his first infusion. most likely unrelated.

92057- 0712: Subject 92057- 712 was 77 years old at registration. He received 3 infusions of study product (APC8015 or APC- Placebo), the last on 22 March 2006. He had a history of CVA (2 months prior to treatment), TIAs, splenic infarct, and heparin-induced thrombocytopenia. His concomitant medications included coumadin and indomethacin. -b(6)--- days after his third infusion (Study Day 41), he had a CVA and was treated with tissue plasminogen activator (tPA). Subsequently, a CT scan of the brain revealed new areas of hemorrhage and the subject expired b(6) days following his third infusion (Study Day b(6))

Post- mortem, the subject was unblinded and it was determined that he had been randomized to APC8015. Primary reviewer's note: b(6) days after his third infusion. Prior CVA history. most likely unrelated.

92074- 0526: Subject 92074- 0526 was 69 years old at registration. He received 3 infusions of study product (APC8015 or APC- Placebo), the last on 14 July 2005. He has

a history of hypertension and SVC thrombosis; he was being treated with coumadin. Twenty- seven days after his third infusion (Study Day 97), he was admitted to the hospital for TIA where he was started on aspirin and clopidogrel. All studies were negative for sources of emboli. Three days later he was discharged in stable condition. Primary reviewer's note: 27 days after last infusion. Piror thromotic history. most likely unrelated.

92122- 0243: Subject 92122- 0243 was 59 years old at registration. He received 3 infusions of study product (APC8015 or APC- Placebo), the last on 24 March 2004. He was an ex-smoker with a history of Crohn's disease; his concomitant medications included mesalazine and aspirin. On Study Day 45, he had an obstructed left nephrostomy tube. While hospitalized, he was noted to have had a recent MI. A head CT revealed acute right partial lobe infarct and an acute left occipital lobe infarct. Workup was negative for embolic etiology, including a negative transesophageal echocardiogram. He was discharged on warfarin and oxygen. He was readmitted on Study Day 66 with a new left CVA and myocardial infarction. He was discharged home 15 days later. He met the time to disease progression and pain endpoints 8 days prior to the second event and died of prostate cancer disease progression 3 weeks after the second event, on Study Day 90.

Primary reviewer's note: b(6) days after the last infusion (?). Recent MI. Most likely unrelated.

92125- 0236: Subject 92125- 0236 was 60 years old at registration. He received 3 infusions of study product (APC8015 or APC- Placebo), the last on 26 February 2004. He had a history of stage II left salivary gland cancer (in 1999), which was treated with radiation therapy; he was not taking any concomitant medications. Microclots were noted on 3 Baseline CBC samples. He was noted to have multiple right parietal skull lesions and he received docetaxel beginning on Study Day 122. On Study Day 726, he experienced a CVA that caused his death. Primary reviewer's note: b(6) months after last infusion. Received Taxotere. Most likely unrelated.

92146- 0238: Subject 92146- 0238 was 69 years old at registration. He received 3 doses of study product (APC8015 or APC- Placebo), the last on 04 April 2004. He had a history of hypertension, bradycardia, and colitis; his concomitant medications included aspirin, metoprolol, and doxazosin. Forty- dix days after his third infusion (Study Day 88), he was admitted to the hospital with right hemiparesis due to an acute lacunar infarct in the left internal capsule. Doppler revealed plaque in the right internal carotid artery. He recovered and was discharged 2 days later on clopidogrel therapy. Primary reviewer's note: 2 months after last infusion. Possibly related.

Study P- 11

APC8015 P- 11- 14- 004: Subject P- 11- 14- 004 was 78 years old at registration. He received 3 infusions of APC8015, the last on 02 January 2003. Prior history included a right thalamic CVA one year prior to randomization, an MI (year unknown), left

ventricular hypertrophy, aortic stenosis, and dyslipidemia. He did not receive prior chemotherapy or have metastases prior to study entry. On 08 April 2004 (Study Day 614), he experienced a cerebral infarction. At the time of the cerebral infarction, he was taking aspirin, clopidogrel, and atorvastatin. An MRI of the brain revealed acute ischemic changes in the right posterior parietal region. He recovered with residual leg weakness and was released from the hospital on 12 April 2004 (Study Day 618). Primary reviewer's note: Prior CVA history. 20 months after last infusion. most likely unrelated.

APC- Placebo

P- 11- 10- 027: Subject P- 11- 10- 027 was 70 years old at registration. He received 3 infusions of APC- Placebo, the last on 25 February 2004. Following biochemical progression, he received a booster infusion of APC- Placebo on 02 September 2004 (Study Day 218). He has a history of hypercholesterolemia and hypertension; he was treated with daily aspirin. On 22 July 2005 (Study Day 541), he experienced left visual field loss due to a right occipital hemorrhagic CVA. Workup revealed right carotid and right vertebral artery stenosis. He recovered and was discharged from the hospital to a rehabilitation center on 29 December 2004; he was discharged from the hospital on 23 July 2005. Primary reviewer's note: Booster infusion of Placebo? 28 months after last infusion. Most likely unrelated.

P- 11- 11- 010: Subject P- 11- 11- 010 was 62 years old at registration. He received 3 infusions of APC- Placebo, the last on 23 July 2003. He had a history of hypertension, diabetes mellitus, and hyperlipidemia; concomitant medications included insulin, atenolol, pioglitazone, glyberide, metformin, benzapril, and amlodipine. On 25 December 2004 (Study Day 555), the subject experienced acute onset of left lateral vision changes and was diagnosed with a right pons acute CVA. A CT of the head revealed a lacunar infarct in the right caudate nucleus. A carotid ultrasound suggested moderate bilateral carotid artery stenosis. He was started on aspirin therapy. He improved neurologically and was discharged on 29 December 2005 (Study Day 559) on continuous aspirin therapy. Primary reviewer's note: multiple risk factors for CVA. 28 months after infusion. Most likely unrelated.

P- 11- 13- 017: Subject P- 11- 13- 017 was 69 years old at registration. He received 4 infusions of APC- Placebo; infusion 3 occurred on 10 April 2003 and the booster infusion of APC-Placebo occurred on 10 September 2003. He had a history of hypertension and atrial fibrillation; concomitant medications included sotalol, valsartan, HCTZ, furosemide, and doxazosin. For unknown reasons, he stopped taking aspirin prior to this event. On 17 August 2005 (Study Day 895), he experienced left hemiparesis and dysarthria. An MRI of the brain revealed acute ischemia in the basal ganglia as well as scattered white matter changes suggestive of microvascular ischemic changes. He was immediately treated with tPA upon arrival to the emergency room. He recovered and was discharged on warafin on 22 August 2005. Primary reviewer's note: Multiple CVA risk factors on multiple meds. 29 months after last infusion. Most likely unrelated.

9.6 Appendix 6: Ongoing Studies (P-11 and D9902B)

P-11 short summary

Source of documents: IND 6933 annual report (year 2006) and the sponsor email reporting the preliminary results in November 2006. I summarized the slides the sponsor.

(APC8015, Provenge) in Patients with Non-Metastatic Prostate Cancer Who Experience PSA Elevation Following Radical Prostatectomy: A Randomized, Controlled, Double-Blind Trial

Study No.	P-11 (Phase 3)
Study Title	An Autologous PAP-Loaded Dendritic Cell Vaccine (APC8015, Provenge®) in Patients with Non-Metastatic Prostate Cancer Who Experience PSA Elevation Following Radical Prostatectomy: A Randomized, Controlled, Double-Blind Trial
Patient Population	Non-metastatic prostate cancer patients with serologic (PSA) disease progression
Study Status	Closed to accrual
Objectives	<ul style="list-style-type: none"> • Primary: Time from randomization to biochemical failure (BF), PSA \geq 3.0 ng/mL (108 biochemical failure events) <ul style="list-style-type: none"> – No confirmatory PSA required – Confirmatory PSA required (\geq 2 weeks, but \leq 4 weeks following initial PSA) • Secondary endpoints <ul style="list-style-type: none"> – PSA doubling time – Time to distant failure (TTDF) – Survival (OS) – Evaluate safety of APC8015 in subjects with hormone-sensitive prostate cancer
Main Inclusion Criteria	<ul style="list-style-type: none"> • Histological diagnosis of adenocarcinoma of the prostate • Radical prostatectomy for stage T1b-T3c, N0-N1, Nx, M0 disease performed at least 3 months but no more than 10 years prior to initiation of the run-in period • Therapeutic PSA response to primary therapy was below 0.4 ng/mL • Experienced PSA relapse while not currently receiving androgen ablation therapy; if androgen ablation was given for a previous relapse, PSA must have increased to a level at least 25% above the nadir observed while on this therapy, and to an absolute level of at least 3 ng/mL • Confirmed M0; a bone scan with no evidence of osseous metastasis must be on record, dated within 6 months prior to entry into the study

- Estimated life expectancy \geq 1 year

Total number of subjects planned for inclusion	159
Total number of subjects entered into the study to date	176
	Age (mean): 64.7
	Gender: Males (100%)
	Race: Caucasian = 90.3%
	African American = 6.8%
	Asian = 0%
	Hispanic = 1.7%
	Other = 1.2%
	Unknown = 0%
Total number of subjects treated	172 treated ^a
Total number of subject who dropped out of study for any reason	67
	Reason for discontinuing:
	Refused to continue = 46
	Protocol violation = 2
	SAE = 3
	Intercurrent illness = 4
	Lost to follow-up = 2
	Progressive disease in absence of PSA failure = 2
	Death = 1
	Other = 7

a: Subjects did not enter the study (i.e. were not randomized) until after the 3-month LHRH agonist run-in period

P-11 Results:

Primary endpoint: Time to BF. No difference

[

b(4)

]

2nd endpoints

[
b(4)
]

D9902B summary

Source of document: IND 6933 annual report (year 2006) and IND 6933 amendment XXX amendment 198, revised SPA submitted to FDA on October 25, 2005.

Protocol D9902B: A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded with PA2024 (Provenge®, APC8015) in Men with Metastatic, Androgen Independent Prostatic Adenocarcinomas

Study No.	D9902B (Phase 3)^a
Study Title	A Randomized, Double Blind, Placebo Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded with PA2024 (Provenge®, APC8015) in Men with Metastatic Androgen Independent Prostatic Adenocarcinomas
Patient Population	Asymptomatic or minimally symptomatic, metastatic AIPC
Study Status	Ongoing
Primary Objective	To compare the overall survival in subjects treated with APC8015 to those treated with the control infusion (APC-Placebo)
Secondary Objective	To compare the time to objective disease progression between the 2 groups
Main Inclusion Criteria	<ul style="list-style-type: none"> • Histologically documented adenocarcinoma of the prostate • Metastatic disease as evidenced by soft tissue and/or bony metastases on imaging studies • Androgen independent prostatic adenocarcinoma. Subjects must have current or historical evidence of disease progression concomitant with surgical or medical castration, as demonstrated by PSA progression OR progression of measurable disease OR progression of non-measurable disease • Serum PSA \geq 5 ng/mL • Castration levels of testosterone (< 50 ng/mL) achieved via medical or surgical castration. Subjects receiving medical castration therapy must continue such therapy throughout the blinded portion of the study • Life expectancy of at least 6 months
Total number of subjects initially planned for inclusion	450-550
Total number of subjects entered into the study to date	358 ^b Age (mean): 70.7 Gender: Males (100%) Race: Caucasian = 93.0% African American = 3.8% Asian = 0.6% Hispanic = 2.6% Other = 0% Unknown = 0%

Total number of subjects treated	301
Total number of subjects who dropped out of study for any reason	26
	Reason for discontinuing:
	Refusal to continue = 20
	Lost to follow-up = 2
	Other = 4

a This summary reflects changes made under Amendment No. 7 to Protocol D9902B (refer to BB-IND 6933, Amendment No. 198, submitted October 11, 2005).

b Case Report Form data available for N = 313. (number as of 3-27-07)

Recent update: As of April 1, 2007, a total of 403 subjects have been randomized; there are a total 80 death events. This represents 22% (80/360) of the targeted number of death events.

SAP plan:

- Sample size consideration

Enrollment in this trial will continue until approximately 360 death events have been observed. It is estimated that approximately 450 to 550 subjects will be enrolled in order to achieve this number of death events. This sample size is sufficient to detect a hazard ratio for death of 1.45 (APC-Placebo versus APC8015) using the Cox proportional hazards model specified in Section 4.1.1 with at least 90% power using a 2-sided Wald chi-square test at a significance level of $\alpha = 0.05$. The Wald chi-square test will be used to determine if the survival distributions for APC8015 and APC-Placebo are the same (equivalent to testing if the coefficient (β_1) for the factor 'treatment group' is zero).

- Statistical methods

- Efficacy

All efficacy and safety analyses will compare APC8015 to APC-Placebo. Nominal significance levels for the interim and final analysis will be based on the Lan-DeMets implementation of the Pocock method (details in Section 4.4). No adjustment for multiple comparisons across efficacy variables will be performed.

Time-to-event variables will be analyzed using Cox regression methods for proportional hazards. Stratified Cox models will be evaluated for each time-to-event variable including treatment group and pre-specified prognostic factors. Each model will be stratified by the stratification variables defined for the adaptive randomization [primary Gleason grade (= 3 and = 4), number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no)].

A second analysis will be performed for the time-to-event variables to evaluate the impact of the stratification variables on the treatment effect. A Cox proportional hazards model (i.e., unstratified) will be evaluated for each time-to-event variable to include the stratification variables and variates defined for the stratified Cox models as terms in the model. The same nominal significance levels defined for the interim and final analysis of the stratified Cox models will apply.

The proportional hazards assumption for each Cox model will be assessed by including the interaction of each factor with survival time as a term in the model and by evaluating residual diagnostics (2).

Kaplan-Meier methods will also be used to estimate the event-free distribution for all time-to-event variables (3). Additional comparisons between the 2 treatment groups will be performed using a stratified log-rank test. The stratification variables for this test will include the stratification variables specified for the randomization.

- Time to Subject Death

Survival time for a subject is defined as the time from randomization to death due to any cause. Trial subjects alive at the end of the study or lost to follow-up will be censored from the day of their last documented on-study evaluation in the analysis. Survival time will be calculated as follows:

- a) For subjects who died:

$$\text{Survival time (days)} = [(\text{date of death}) - (\text{randomization date})] + 1$$

- b) For censored subjects:

$$\text{Survival time (days)} = [(\text{date of last study visit/contact}) - (\text{randomization date})] + 1$$

- Interim Analysis

An interim analysis is planned for this trial when approximately 180 events (deaths) been observed. When this occurs, the Independent Data Monitoring Committee (IDMC) for the trial will be provided (by an independent third party per IDMC charter) an unblinded analysis of the time to death and time to objective disease progression.

The Lan-DeMets implementation of the Pocock method will be utilized to maintain the overall significance level $\alpha = 0.05$ for the primary efficacy variable (time to subject death). The nominal significance levels for the interim (0.0310) and final analysis (0.0277) were calculated assuming a hazard ratio (APC-Placebo versus APC8015) of 1.45. Based on this assumption and an overall significance level of $\alpha = 0.05$ the study will have 90% power with 360 deaths (events).

The interim analysis will occur when 180 deaths are observed. Tables 2 and 3 present power and sample size estimates for possible hazard ratios observed for the interim analysis of the primary and secondary efficacy variables based on 180 deaths (events).

Table 2: Estimated Power for the Interim Analysis of Time to Subject Death

No. of Events	Nominal α		Hazard Ratios ^c									
			1.25	1.30	1.35	1.40	1.45	1.50	1.55	1.60	1.70	1.80
180 ^a	0.0310	% Power	25	34	43	53	61	69	76	82	90	94
		Total N ^b	389	394	400	408	413	419	424	431	440	452

^aInterim analysis will occur when 180 deaths (events) are observed assuming a HR = 1.45 for the time to subject death.

^bEstimated number of subjects enrolled. Allows for a 2% rate of subjects lost to follow up.

^cHR = (Hazard APC-Placebo) / (Hazard APC8015)

Table 3: Estimated Power for the Interim Analysis of Time to Objective Disease Progression

Nominal α		Hazard Ratios ^b							
		1.25	1.30	1.35	1.40	1.45	1.50	1.55	1.60
0.0310	% Power	47	60	72	81	88	92	95	97
	Total N	389	394	400	408	413	419	424	431
	No. of Events ^a	349	348	347	346	345	345	344	343

^aThis is an estimate of the expected number of objective disease progression events. The exact number of events for objective disease progression will not be known until the time of the interim analysis since the timing of the analysis is based on observing 180 deaths for the primary variable.

^bHR = (Hazard APC-Placebo) / (Hazard APC8015)

At the time of the interim analysis, if the observed treatment effect in the primary efficacy analysis is statistically significant (i.e., $P = 0.0310$) enrollment in the trial may be closed following consultation with the IDMC and Food and Drug Administration (FDA). Conversely, if for survival the observed hazard ratio for the treatment effect (APC-Placebo versus APC8015) is less than 0.75 (indicating no survival benefit) the IDMC and FDA will be consulted to determine if the trial should be stopped. Details are described in the IDMC charter.

The IDMC may choose to review unblinded efficacy data summaries and analyses (conducted by a third party per IDMC charter) during the course of the trial to further assess the risk/benefit ratio of APC8015.

To adjust for these possible interim IDMC analyses and to maintain the overall significance levels for the planned interim and final analyses of the primary and secondary efficacy variables, a Lan-DeMets type I spending function will be utilized. The nominal alphas and upper boundaries for possible analyses are presented in Table 4.

Table 4: Alpha Spending for Possible Interim IDMC Analyses of the Primary or Secondary Efficacy Variable

IDMC Interim Analysis	Nominal α	Upper Boundary (Symmetric)
1 st	0.0001	3.8906
2 nd	0.0001	3.8906
3 rd	0.0001	3.8906
4 th	0.0001	3.8906
↓	↓	↓
k th	0.0001	3.8906

Alpha spending will be utilized only if interim IDMC analyses occur.

Table 5 details a possible scenario where the IDMC has requested 5 interim analyses (looks) at efficacy during the course of the trial.

Table 5: Example – Possible Alpha Spending Scenario for 5 Interim IDMC Analyses of the Primary or Secondary Efficacy Variable

IDMC Interim Analysis	Nominal α	Upper Boundary (Symmetric)	Cumulative Exit Probability
1 st	0.0001	3.8906	0.00010
2 nd	0.0001	3.8906	0.00019
3 rd	0.0001	3.8906	0.00027
4 th	0.0001	3.8906	0.00034
5 th	0.0001	3.8906	0.00040

For illustrative purposes, assume that 2 of the analyses occurred before the protocol planned interim analysis (to be conducted at the 0.0310 level) and that the remaining 3 were performed after the planned interim but prior to the final planned analysis. Based on Table 5 the adjusted nominal significance level for the planned final analysis of the primary and secondary efficacy variables would be between 0.0274 and 0.0277.