

**Division of Clinical Evaluation and Pharmacology and Toxicology
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research
Food and Drug Administration**

**Cellular, Tissue and Gene Therapies Advisory Committee Meeting
March 29, 2007**

Clinical Briefing Document

**PROVENGE[®] (Sipuleucel T)
BLA # 125197**

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

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1 EXECUTIVE SUMMARY

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 criteria, clinical progression 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, but survival data were collected as part of the safety evaluation. 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 APC 8015 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.

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 prolonged 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. 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]. 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).

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 none in APC-Placebo treated subjects in D9901 and D9902A.

The sponsor subsequently submitted summarized results for CVA events observed in all the 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 compared with controls. Although these differences did not reach statistical significance, the increased CVA frequency in APC8015 treated subjects is a potential safety concern.

Table 1: Combined Summary of Efficacy, D9901 and D9902A

Study	<u>Median Time to Progression</u>		<u>Median Survival (months)</u>	
	<u>(weeks)</u>		APC8015	APC Placebo
	APC8015	APC Placebo		
D9901	11.0	9.1 (p = 0.085)	25.9	21.4 (p = 0.012)
D9902A	10.9	9.9 (p = 0.72)	19.0	15.7 (p = 0.33)

Conclusions: Neither study D9901 nor study D9902A met any study objectives (Table 1). 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 difficult to estimate the type I error of this survival analysis. 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.

The submitted data tend to support a finding of clinically meaningful increased survival, but doubts remain about the persuasiveness of the efficacy data. Additional discussion and advice from the Cellular, Tissue and Gene Therapy Advisory Committee are sought regarding the persuasiveness of these data, and the potential safety signal of increased CVA events in APC8015 treated subjects.

2 BACKGROUND

2.1 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 (1).

Initial primary treatment modalities for subjects with localized prostate cancer include expectant management (watchful waiting), surgery, radiation therapy, brachytherapy, cryotherapy (2). 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 (3). One of the most important prognostic factors is the histologic grading of prostate cancer, Gleason score (4). 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 (5-7)

- 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 (8).

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 (5).

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 was approved based on the results from a randomized, multi-center global clinical trial 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 (5;9).

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 (10).

2.2 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 (11). 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 (12).

- 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 (13).
- 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 (14).
- 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 (15).

2.3 Proposed indication

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

2.4 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.
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 ≤ 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 and less. 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

Date	Milestone Description	Outcome
24 NOV 2004	D9901 and 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.
10 Aug 2006	Clinical section of BLA submitted electronically	

2.5 Data submitted

Results of two randomized, double-blind, placebo-controlled phase 3 trials: D9901 and D9902A as well as summaries of additional preclinical, phase 1 and 2 studies were submitted in support of this BLA. The efficacy claim relies mainly on a single trial D9901 since only the results from this randomized study demonstrated a survival difference.

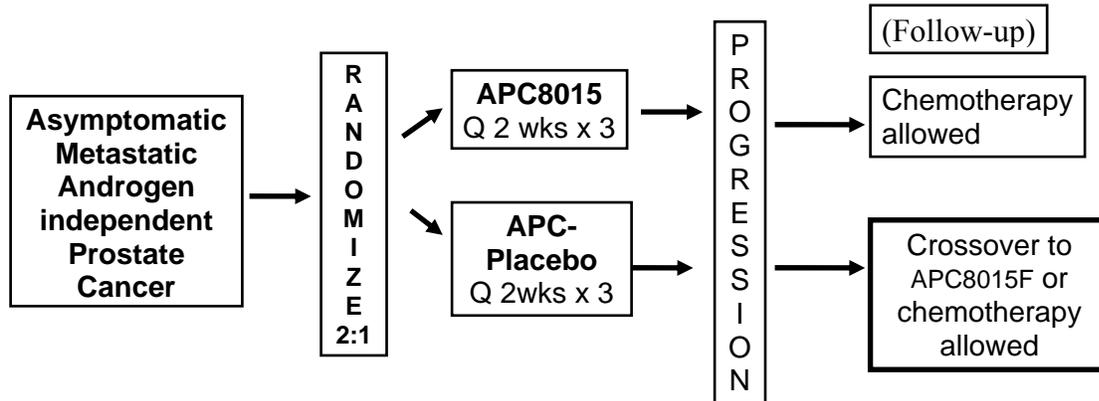
3 ANALYSES OF EFFICACY

3.1 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.

3.2 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 3.2.D). The study design is outlined in Figure 1:

Figure 1: D9901 and D9902A study design

During the study, hormonal Tx 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 statistical analytical plan was later revised before the final analyses to change the efficacy endpoints as described in section 3.3.3.B.

A. Primary and secondary objectives

- **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. D9901 was also analyzed independently.);
 - 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.

B. 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 3.2.E.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.

C. Randomization and blinding

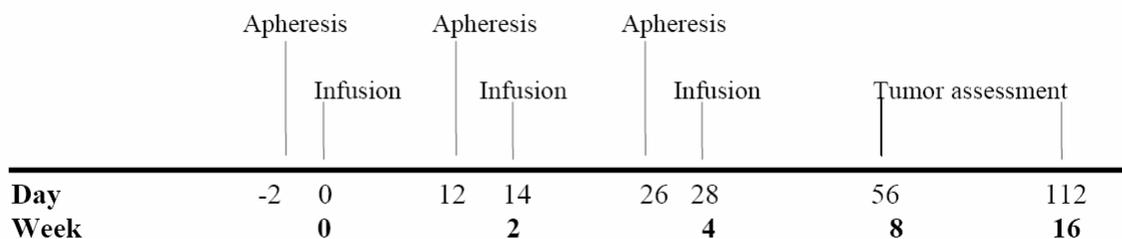
Patients were randomized 2:1 to APC8015 and to APC-Placebo. Two strata were used in the randomization: bisphosphonate use and study center. The randomization was performed by the sponsor’s contract organization. Both studies were blinded to the sponsor’s clinical personnel, investigators and patients. This blinding was maintained throughout the trial. However, the sponsor’s manufacturing personnel were not blinded.

D. 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



E. 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

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

iii. PSA progression was not used as a study endpoint. .

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

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

o 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, tumor staging (bone, MRT or CT scans) was performed at baseline, weeks 8, 16, 24, and 32, and every 12 weeks thereafter until disease progression. 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.

o 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.

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 (4-8-00) 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 (no date provided) clarified inclusion criteria to allow prior palliative radiation therapy (RT) and to exclude prior strontium therapy.

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 survival analysis: “As supporting analyses, estimates of survival rate and progression free frequencies at three, six, nine, twelve and eighteen, twenty four and thirty six months and every six months thereafter, and median survival will be provided based on the Kaplan-Meier curves.”

3.3 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.

3.3.1 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-

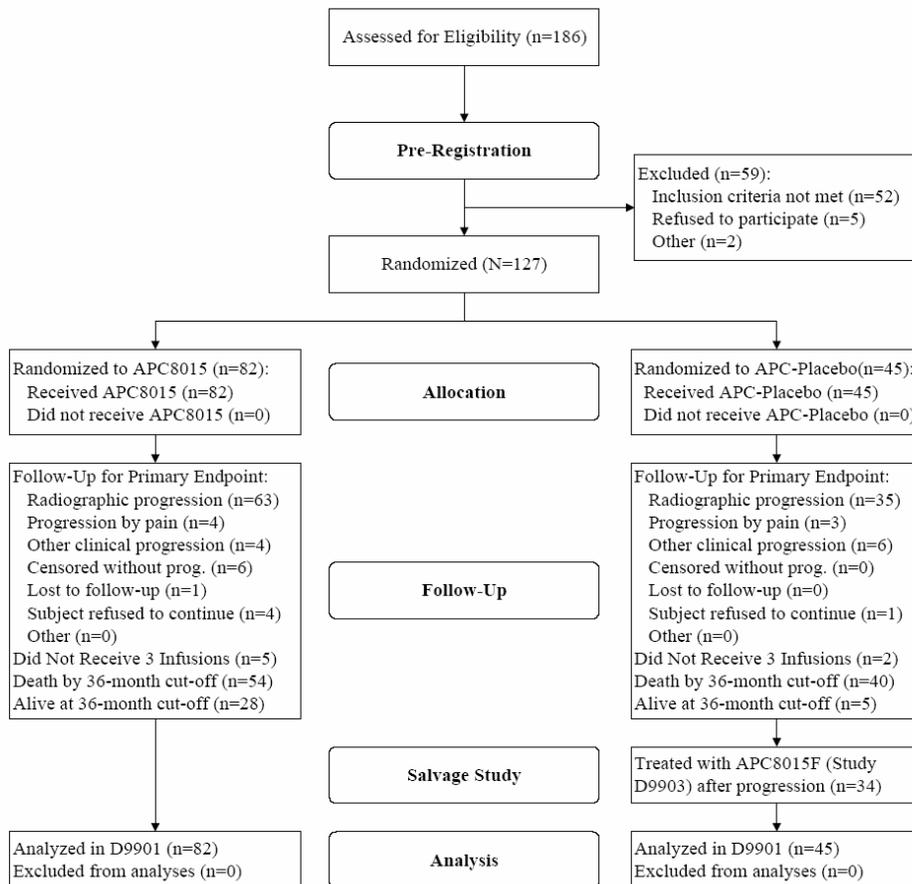
specified efficacy endpoints. Therefore, D9902A was insufficient in sample size to detect any difference in any of the pre-specified endpoints.

3.3.2 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 4 below.

Table 4: 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 5 summarizes Gleason score distributions.

Table 5: 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 6 shows the disease distribution between the two arms in study subjects. All subjects except on 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 6: Disease location and distribution D9901

Localization of Disease	APC 8015 # (%)	APC Control # (%)
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		
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 7 lists the prior treatment regimens the study subject had received prior to the study. There were no imbalances seen between the two arms.

- 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.

Table 7: Prior treatment regimen D9901

Regimen	APC 8015 N = 82	APC- Placebo N = 45
Hormone Therapies, n (%)		
Castration	5 (6.1)	3 (6.6)
Combined androgen blockade	76 (93)	42 (93)
Unknown	1 (1.2)	0 (0.0)
Prior Chemotherapy	7 (8.5)	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)

C. Study conduct

- Clinical study sites:** Nineteen clinical study sites were involved in study D9901 across the United States. Two sites, sites 14 and 69, enrolled 27% of all subjects. FDA Bioresearch Monitoring (BIMO) Program inspections did not reveal significant study conduct deviation or violations. Removal of the results obtained from these two sites did not change the magnitude and direction of the survival difference between the two arms.
- Randomization Errors:** Study center and bisphosphonate were used 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 versa. 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 8: Protocol violations D9901

Deviations	APC8015	APC placebo
	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 $\geq 50\%$ 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)

There were 6 (8%) more patients in APC8015 arm who 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.

- **Exposure:** The number of leukaphereses and infusions for D9901 study subjects are summarized in Table 9. In the ITT population, 95.3% and 94.5% of patients underwent 3 or more leukapheresis and 3 infusions respectively.

Table 9: Leukaphereses and infusions D9901

Treatment	APC8015 (n = 82)	APC-Placebo (n = 45)	Total (N = 127)
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.

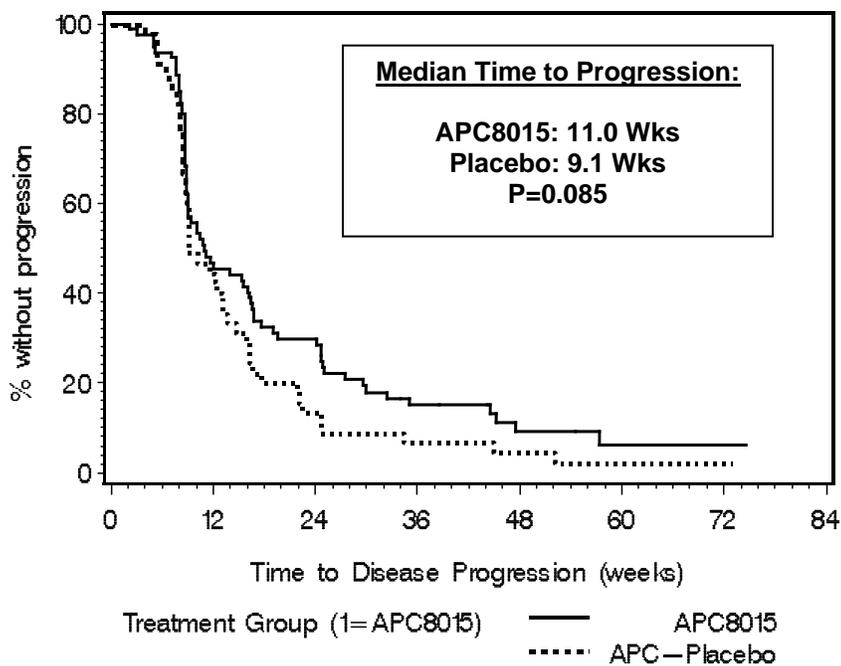
- **Study blinding**

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 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 10.

Table 10: Summary of Progression Events D9901

Progression Event	APC8015 (N = 82)	APC-Placebo (N = 45)	Total (N = 127)
Objective Disease Progression Observed	71 (86.6)	44 (97.8)	115 (90.6)
Radiological progression	63 (76.8)	35 (77.8)	98 (77.2)
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	6 (7.3)	0 (0.0)	6 (4.7)

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 ≤ 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 closed the ongoing 2nd study D9902 in March 2003 prior to its reaching accrual objectives and initiated a new study 9902B to enroll patients with a Gleason score ≤ 7 .

E. Revision of primary efficacy endpoint results

In the June 2002 analysis after unblinding of the locked database, 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. 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 (16). 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 subjects were primarily responsible for lowering p-value to 0.052.

This 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. 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. 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.

In sum, D9901 failed to demonstrate an APC8015 treatment effect on the primary endpoint in delaying the time to disease progression.

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 d) the response rate and duration of response; see summary below:

Table 11: Summary of Secondary Endpoint Results

Endpoint	APC 8015 N =82	APC-Placebo N =45	P-value (Log-Rank)
Median Time to Pain Progression (pooled with data from D9902A)	33.9 weeks	32.7 weeks	0.719
Median Time to Clinical Progression	10.7 weeks	9.1 weeks	0.061
Median Time to Treatment failure	11 weeks	10 weeks	0.124
Response Rate	0	0	N/A

G. PSA response:

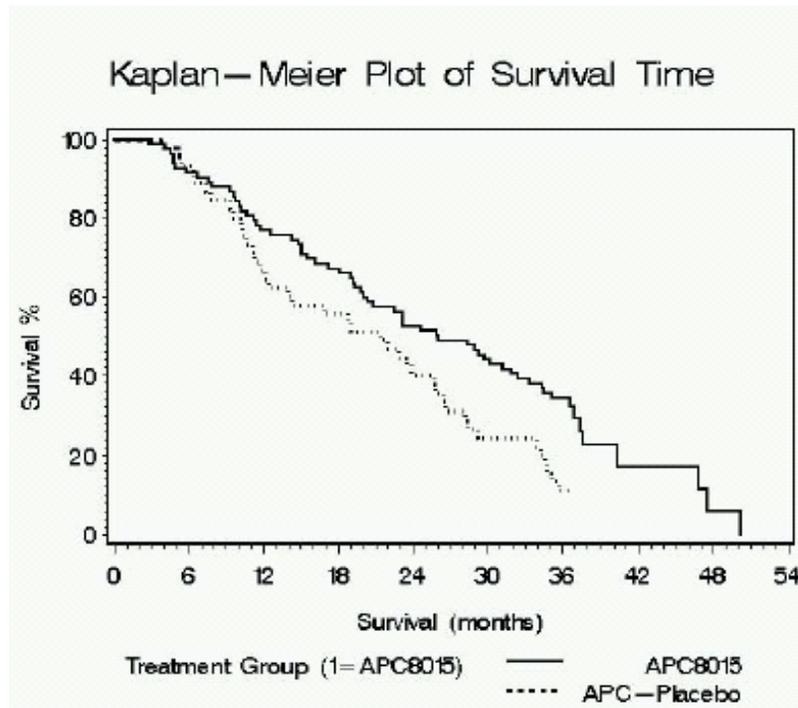
Although PSA was not used as an indicator of disease progression, the protocol and statistical analysis plan stipulated that biochemical responses would be analyzed. In the ITT population, 9 subjects (7.1% [9 of 127]) experienced a PSA reduction from baseline of at least 25% at one or more visits. Of these, 7 were treated with APC8015 and 2 treated with APC-Placebo.

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.” and a primary method of survival analysis was not pre specified in the protocol. A three-year survival analysis was performed as part of the safety monitoring plan.

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. The tail of the APC8015 included 8 additional death events after 36 months. There were no data available for APC-placebo arm after 36 months. As shown in Table 12, 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 12: 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	0.011 Log-rank

*All subjects were followed for 36 months or until death

From available data

As shown in Table 13, 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 APC-8015-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 13.

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 13: Death Events Analysis D9901

Death Events	APC8015# (%)	APC Placebo # (%)
Total death events reported in CSR 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 APC 8015 and infused fresh. 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 14 summarizes chemotherapy use reported following disease progression:

Table 14 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)

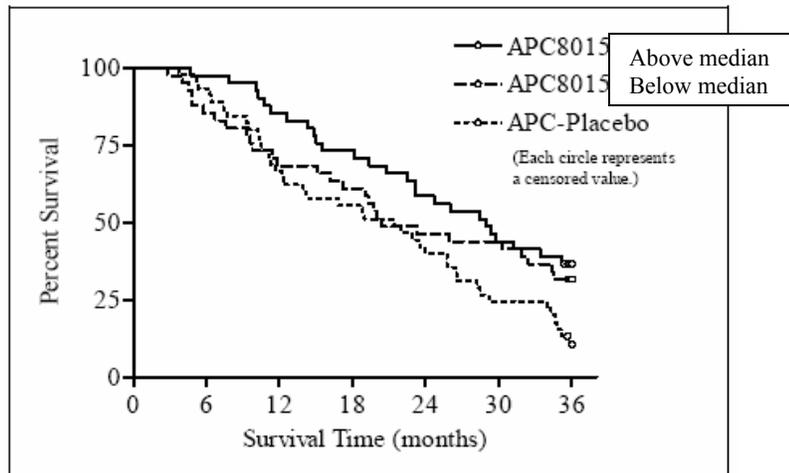
Information on chemotherapy use following progression was available in 96% of the patients in study D9901. According to the information provided, more subjects in APC-Placebo arm received chemotherapy than APC8015. Since docetaxel is the only therapy known to improve survival, an analysis of taxane use 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.

Survival result summary: A review of the data submitted, including sensitivity analyses and review of death events, 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 it difficult to estimate the persuasiveness of the submitted survival results 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. Kaplan Meier survival was analyzed by 3 groups: patients who received placebo and those who received APC8015 whose CD54 upregulation ratio was below the median and those who received APC8015 whose CD54 upregulation were at or above the median (Figure 6):

Figure 6: CD54 Intensity and survival D9901



These results were not statistically significant. There was no information on the cell counts or other characteristics in the placebo group. The study was not designed to provide confirmative evidence for relationship between survival and cell dose. See statistical review for a more detailed analysis.

- 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 15 shows that the stimulation index was higher when PA2024 was used as an antigen.

Table 15: 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 definite immune response. However the results were inconclusive because of the following limitations:

- 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 because the ITT population was not used for analyses. 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, and 125 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 10.9 weeks and 9.9 weeks, respectively. The 1.0-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.

Although a survival comparison analysis was not pre-specified, a 3-year survival analysis of D9901 was performed as part of the safety follow up. 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 ($p = 0.012$) 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, interpretation of this survival difference should be made with caution. The lack of a pre-specified primary method for survival analyses renders it difficult to estimate the type I error of this survival analysis. Thus, it is difficult to estimate the persuasiveness of the submitted survival results. The small size of the study makes it more likely that this finding could have occurred by chance. Consequently, the confidence on this survival evidence for the efficacy claim must be weighed against above-mentioned caveats of the *post hoc* nature for the survival analyses.

3.3.3 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 16 shows that one major protocol violation each occurred in APC8015 arm and in APC-Placebo arm.

Table 16: Protocol violations D9902A

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

- **Study Agent Exposure and Treatment compliance**

Table 17 shows the number of leukapheresis and infusions for D9902A study subjects. 90.6% and 86.3% of ITT population underwent 3 or more leukapheresis and 3 infusions, respectively. The treatment compliance was good.

Table 17: 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 19 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 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 18 shows the demographic and baseline characteristics of D9902A subjects.

Table 18: 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 19 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. 51.2%). 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 19: 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 20 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 20: 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)
1-5	19 (31.1)	11 (34.4)
6-10	6 (9.8)	2 (6.3)
> 10	31 (50.8)	12 (37.5)

Table 21 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.

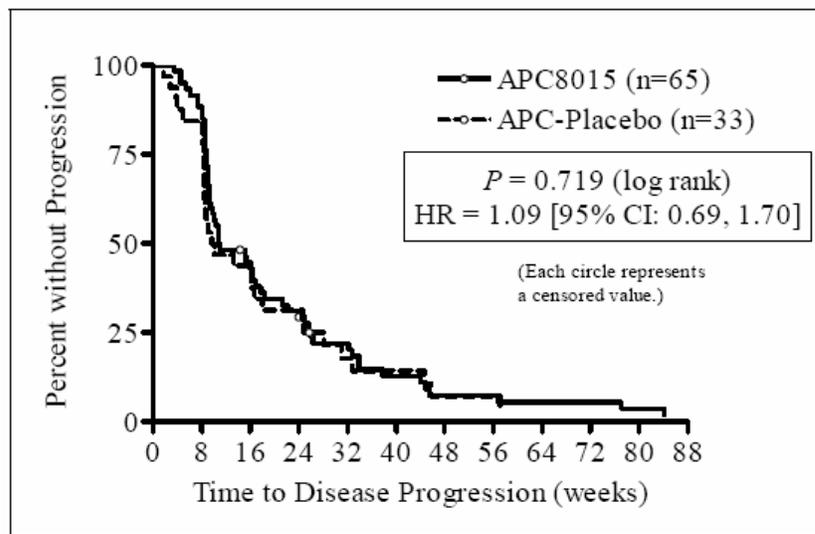
Table 21: Prior treatment regimen D9902A

Prior Treatment	APC 8015 N = 65	APC- Placebo N = 33
Hormone Therapies:	n (%)	n (%)
Castration	9 (14%)	3 (9%)

Prior Treatment	APC 8015 N = 65	APC- Placebo N = 33
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:

Figure 7: 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

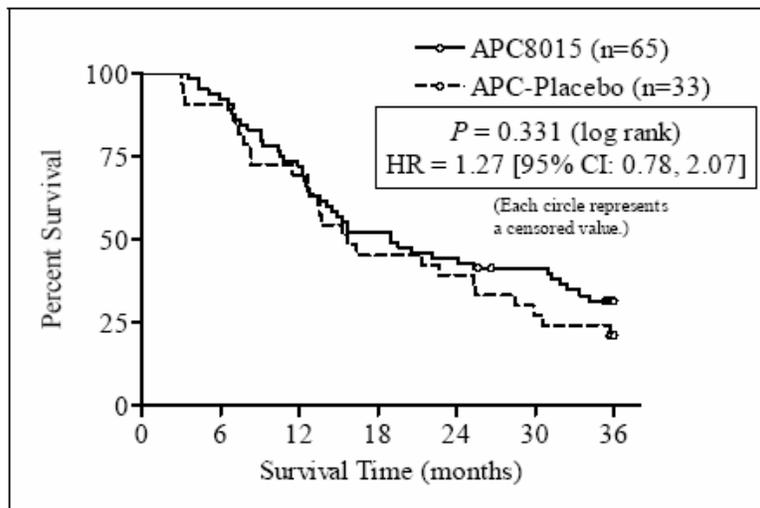
Out of 98 subjects randomized, 89 developed disease progression. 73 subjects were documented to have disease progression based on the imaging studies. 16 subjects had clinical events of disease progression (Table 22).

Table 22: Summary of Disease Progression D9902A

Objective Disease Progression Status Reason	APC8015 (N = 65)	APC- Placebo (N = 33)	Total (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 8: 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).

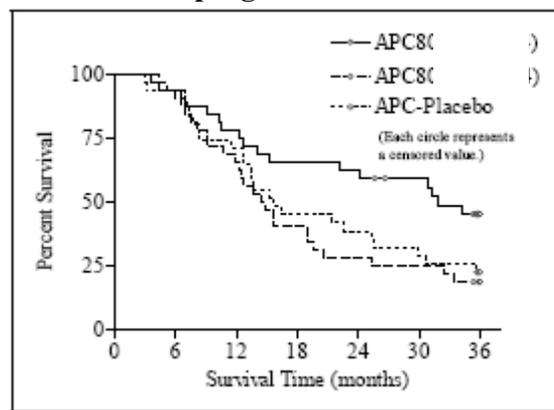
f. Results of Tertiary Endpoints

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.

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 8), appeared to have increased survival compared to those subjects below the median. CD54 expression was not measured in the APC-Placebo cells.

Figure 8: 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. However, an exploratory analysis suggest that CD54 up regulation ratio may correlate with survival

3.4 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 23).

Table 23: Combined Summary of Efficacy, D9901 and 9902A

Study	<u>Median Time to Progression</u> (weeks)		<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, the assessment must take into consideration of these factors in determining whether the trials had provided 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 (17).

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* and it is difficult to estimate the true type I error rate for the survival effect with APC8015 treatment observed in D9901.

4 REVIEW OF SAFETY

4.1 Overview of Safety

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 and analyzed for this briefing document. 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. Additional overall safety information will be submitted by the applicant at the end of March 2007 for the 4 month BLA safety update.

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, 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. This increased CVA frequency is discussed further in detailed in 4.3.C.

4.2 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 24 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 24: Infusion Exposure (D9901 and D9902A)

Infusions	APC8015		APC-Placebo	
	N = 147		N = 78	
	#	%	#	%
4	1	0.7	0	0
3	130	88.4	71	91
2	11	7.5	4	5.1
1	5	3.4	3	3.8

4.3 Findings

A. Deaths

Table 25 lists all death events occurred in two trials.

Table 25: Death analyses (D9901 and D9902A)

Cause of Death	APC8015 N = 107		APC-Placebo N = 66	
	# 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
TIA	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 4.3.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 (53/147) 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 26 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 26: SAE Frequency and Distribution (≥ 1%)

SAE	APC8015 N = 147		APC- Placebo 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	0	0
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. Sponsor's analysis of CVA Events:

CVA events were reported more frequently in APC8015 treated subjects compared to APC-Placebo treated subjects (see section 4.3 A and 4.3B) 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. 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 2.3 regulatory history 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 APC815.

There were no CVA events reported in the 213 subjects from any of the Phase 1 and Phase 2 studies (updated safety database for these trials are to be submitted at the end of March 2007). Table 28 below summarizes the CVA analyses results from the combined phase 3 studies (D9901, D9902A, D9902B, and P-11):

Table 27: 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 28: Onset of CVA Events (completed studies)^a

Study	CVA's N	Days from first infusion		Days from last infusion	
		Median	Range	Median	Range
APC8015	12	167	(26, 859)	139.5	(7, 830)
APC-Placebo	5	541	(235, 895)	323.0	(208, 707)

a: P-11, D9901 and D9902A

There appeared to be a trend towards a closer temporal relationship between the time of the event and the study treatment in the APC8015 treated group. 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 Canadian 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 29 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 29: 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

AE	APC8015		APC-Placebo	
	N = 146		N = 75	
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
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, this document reported the summary results for CVA events observed in D9902B the sponsor submitted. Quality of the data was adequate from these randomized studies.

F. Additional Submissions, Including Safety Update

The applicant plans to submit additional safety information in their update in March 2007. Additional overall safety analyses to include data from other controlled and uncontrolled trials will be performed.

G. 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.

H. Special Population

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.

4.4 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.

The sponsor subsequently submitted a summary of CVA events observed in all the phase 3 trials including p-11 and ongoing D9902B. 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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