Summary Basis for Regulatory Action

Date: April 29, 2010

From: Thomas Finn, PhD, Chair of the Review Committee
BLA/ STN#: 125197/0

Applicant Name: Dendreon Corporation

Date of Submission: Oct 30, 2009

PDUFA Goal Date: May 1, 2010

Proprietary Name: PROVENGE
Established (USAN) Name: sipuleucel-T

Indication: PROVENGE is indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

Recommended Action: Approval

Signatory Authorities Action:

Offices Signatory Authority:

Celia Witten, PhD, MD, Director, Office of Cellular, Tissue, and Gene Therapies
Mary Malarkey, Director, Office of Compliance and Biologics Quality

✓ **I concur with the summary review.**

□ **I concur with the summary review and include a separate review to add further analysis.**

□ **I do not concur with the summary review and include a separate review.**

Material Reviewed/ Consulted Specific documentation used in developing the SBRA

Clinical Review	04-May-2007 Peter Bross 8-May-2007 Ke Liu 28-April-2010 Chaohong Fan, Bindu George, Peter Bross 28-April-2010 Wilson Bryan
Statistical Review	18-Apr-2007 Bo-Guang Zhen 15-Apr-2010 Bo-Guang Zhen
CMC Review	03-May-2007 Keith Wonnacott, Thomas Finn, Malcolm Moos, Syed R Husain 21-Apr-2010 Thomas Finn, Malcolm Moos, Syed R Husain, Steven Oh
DMPQ Review	27-Apr-2007 Gang Wang 22-Apr-2010 Gang Wang 26-Mar-2010 Gang Wang 13-Apr-2010 Gang Wang
Pharmacology/ Toxicology Review	11-Apr-2007 Yongjie Zhou
Bioresearch Monitoring Review	24-Mar-2010 Bhanumathi Kannan
Establishment Inspection Report	23-Apr-2010 Gang Wang, Randa Melham, Thomas Finn, Steven Oh, Barbara Wilimczyk
Advisory Committee Transcript	29-Mar-2007
Advertising and Promotional Labeling Review	09-Mar-2010 Catherine Miller 14-Jan-2010 Catherine Miller 12-Feb-2010 Catherine Miller
Pharmacovigilance Review	01-Feb-2010 Faith Barash

1. Introduction

Biologics License Application (BLA) 125197 is for sipuleucel-T, which is manufactured by Dendreon Corporation. Sipuleucel-T is an autologous cellular immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.

Sipuleucel-T contains a minimum of 50 million autologous $CD54^+$ cells activated with PAP-GM-CSF and suspended in Lactated Ringer's Injection, USP for a total volume of 250 ml in a sealed, patient-specific infusion bag. The active components in sipuleucel-T are autologous antigen presenting cells and a recombinant protein, PAP-GM-CSF. PAP-GM-CSF consists of human prostatic acid phosphatase (PAP), an antigen expressed in prostate cancer tissue, linked to human granulocyte-macrophage colony-stimulating factor (GM-CSF), an immune cell activator.

This document summarizes the basis for approval for sipuleucel-T. Unique Chemistry, Manufacturing, and Control (CMC) and clinical issues were encountered during BLA review that relate to the fact that sipuleucel-T is an autologous cellular immunotherapy. All review issues have been addressed. The review team recommends approval of this BLA.

2. Background

Prostate cancer:
An estimated 27,360 patients died due to prostate cancer in the United States (US) in 2009[1]. An estimated 192,280 new cases of prostate cancer were diagnosed in 2009 in the US. Of these new cases, 20-40% will have disease progression requiring androgen deprivation therapy (ADT).[2] Most patients requiring ADT will have metastases to distant sites. For patients with castrate recurrent prostate cancer who have metastatic disease, salvage therapy options include docetaxel, secondary ADT, mitoxantrone, palliative therapy with radiation or radionucleide agents for treatment of symptomatic bone disease, and bisphosphonates for bone metastases.

Docetaxel is the only treatment proven to improve survival in patients with metastatic prostate cancer. Docetaxel was approved in 2004 for use in patients with androgen independent (hormone refractory) metastatic prostate cancer. In the pivotal Phase 3 study, median survival was 18.9 months in subjects who received docetaxel, compared to 16.5 months in subjects who received mitoxantrone.

Sipuleucel-T is a cellular immunotherapy, and thus has a different mechanism of action than docetaxel. Unlike docetaxel, which is cytotoxic, sipuleucel-T is thought to stimulate an immune response against the prostate cancer.

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[1] Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009; CA Cancer J Clin. 2009; 59(4):225-249.
[2] Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy; Nature Clinical Practice Urology 2005 Apr; 2(4):174-82.

Regulatory history:
Dendreon Corporation submitted biologics license application 125197 on November 9, 2006 to request approval of sipuleucel-T, an autologous cellular immunotherapy. A Complete Response (CR) letter was issued by FDA to Dendreon on May 8, 2007. This letter requested additional information regarding the manufacturing quality and controls and the clinical effectiveness of sipuleucel-T.

A randomized, double-blind, placebo-controlled, Phase 3 study (D9902B) with overall survival as the primary endpoint was ongoing in 2007 when the CR letter was issued. This study has been completed and confirmed the clinical effectiveness of the product. In D9902B, sipuleucel-T extended median survival of men with metastatic, castrate resistant prostate cancer by 4.1 months. The CMC issues noted in the 2007 CR letter were resolved by the sponsor in amendments to the BLA and were confirmed during a second pre-licensure inspection conducted in 2010.

3. Chemistry Manufacturing and Controls (CMC)

a) Product Quality

Product description:
To manufacture sipuleucel-T, a patient's --b(4)--------- cells are collected by standard leukapheresis and shipped to Dendreon's manufacturing facility for processing. At the manufacturing facility, the cells are put through two buoyant density gradient separations -----b(4)---------- PAP-GM-CSF, a recombinant protein which consists of human PAP linked to human GM-CSF, is then added to the cells. The GM-CSF portion of the protein helps to target the PAP protein to antigen presenting cells and activate those cells. ----b(4)----------. PAP provides the tumor specific antigen that is intended to direct the immune system to target prostate cancer. The cells are cultured in the presence of PAP-GM-CSF for 36-44 hours. After culture, the cells are washed and suspended in Lactated Ringer's Injection,USP for infusion back into the patient. Minimal residual levels of the intact PAP-GM-CSF are detectable in the final product.

The course of therapy is 3 doses, given at approximately 2 week intervals. Each leukapheresis produces one dose; therefore the patient undergoes 3 separate leukapheresis procedures. Each leukapheresis product goes through the identical manufacturing process to produce a unique lot of sipuleucel-T. If a lot fails to meet requirements for quality, the patient must undergo an additional leukapheresis to make a new lot of product. Each dose is shipped and administered fresh (without cryopreservation) within 18 hours of manufacture. The lot release testing is performed concurrently with product packaging and shipping to the infusion center. All lot release tests must meet specifications for the product to be infused and a product disposition form is sent to the infusion site to clear the lot for infusion.

Due to the autologous nature of the product, specifically patient-to-patient variability in the cellular composition and total cell number of the leukapheresis, the product has high inherent variability. The level of product variability does not extend to all lot release criteria as -b(4)--------- is very high and consistent at all stages of manufacturing. The most variable product attributes are $CD54^+$ cell number (-b(4)-----), the level of CD54 upregulation (--b(4)----------), based on lots manufactured to date. Product lot release specifications were based on a statistical analysis of historical manufacturing data and set around 3 standard deviations from the mean.

Manufacturing controls:

----b(4)---------- ----------

For sipuleucel-T, process and product controls are in place to assure cellular product quality. Adherence to process controls, including manufacturing step times is a key element in production of lots that can be shipped and infused by the 18 hour dating period. Step times were identified and established for all process steps. Adherence to these established time limits will be monitored and criteria for the generation of Exception Reports, conducting investigations, and implementing Corrective and Preventive Action plans are in place.

Lot release is based on a combination of in-process testing results as well as final product testing. The table below shows the lot release testing for sipuleucel-T.

Lot Release Specifications for sipuleucel-T

Attribute	Test Parameter	Sample	Acceptance Criteria
In-process Testing			
	--b(4)-------	--b(4)--------	-b(4)----
	---b(4)------- ----------	--b(4)---------	--b(4)---------
	--b(4)---------- ----------	----b(4)----------	--b(4)----------
	--b(4)--------- ----------	---b(4)--------	----b(4)----------

Final Product Testing			
Identity	Identity	Final Product	--b(4)----------
Potency	CD54 upregulation	Final Product/--b(4)--------	--b(4)----------
	Number of CD54+ cells	Final Product	--b(4)----------
Purity	--b(4)---------	Final Product	--b(4)----------
Safety	Endotoxin content	Final Product	--b(4)----------
	Microbial contamination	Final Product	--b(4)----------
	Sterility (--b(4)------)	Final Product	--b(4)----------

----------b(4)----------

Potency: Product potency testing is based on a measure of both the number of CD54 cells present and the level of upregulation of CD54 on the cell surface. The sponsor
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Sterility: Dendreon uses the ----b(4)---------- for sterility testing. Validation data submitted to the BLA support the use of the -b(4)------- assay with a b(4) incubation period under the conditions described in the BLA. Product lot release is based on the in-process sample test result from a b(4)-day incubation and -b(4)---- on a sample of the --b(4)--------. Based on the nature of the product, manufacturing process, and short dating period of sipuleucel-T, the final results from --b(4)------ cultures are obtained after the product has been infused into the patients. The package insert contains information on the plan for follow-up by Dendreon to the prescribing physician if the sterility results obtained after product infusion indicate microbial contamination.

Product comparability:
Dendreon manufactured product for clinical trials atb(4)different manufacturing sites. For the commercial product, Dendreon will perform all manufacturing at one facility located in Morris Plains, NJ. Dendreon performed a comparability study comparing their Seattle, WA manufacturing site used under IND and the Morris Plains, NJ site that will be used for all commercial manufacturing. Dendreon has also compared lot release testing data from the Morris Plains, NJ site to b(4) additional contract manufacturing sites used under IND. Although the range of product lots generated at each site differs, product lot averages are comparable.

Manufacturing risks:
The greatest risks associated with the manufacturing of this autologous product are 1) the risk of product mix-ups and 2) the risk of product contamination. Due to these risks there is a need to maintain strict chain of identity throughout the manufacturing and distribution process as well as the need to adhere to strict aseptic process techniques because the product cannot be sterilized.

Chain of identity of all in-process and final product manufacturing steps is maintained through the use of a human-readable barcode scanning system, lot-specific unique identifiers, and multiple patient lot identifiers. Chain of identity of QC samples is also managed through barcode scanning and unique identifiers, including a second level of identifiers used exclusively in the QC lab.

Sipuleucel-T is manufactured using aseptic procedures and ---b(4)---------- supplies for all product contact. Aseptic processing steps are carried out in ISO --b(4) ---------- within controlled ISO b(4)clean rooms. --b(4)----------. The manufacturing process is campaign based and --b(4)------- of sipuleucel-T is processed in a WS at any given time. All open manipulations of the product occur within the -b(4)- Exposure of the cells to the ISOb(4)environment inside the b(4) is minimized by the use of functionally ---b(4)----------

In addition, procedures are in place to ensure segregation and prevent cross-contamination. Infectious agent testing of patients is not required by Dendreon but may be instituted by the apheresis centers. Product labels, shipping carton labels, and the package insert are labeled accordingly. An additional label is affixed to the primary product container only in the event that Dendreon is informed that the apheresis center policy requires testing of the autologous donor for infectious disease(s) and a positive test result was reported. Product and product samples transported or handled outside the WS are sealed in primary containers and enclosed in secondary containers to mitigate the risk of cross contamination. Cleaning and change-over procedures are in place to further minimize the risk of cross-contamination.

b) CBER Lot Release

An exemption is being granted from CBER Lot Release testing, including no requirement for submission of product samples to CBER. Instead, Dendreon has agreed to a post-marketing commitment to --b(4)----------. The rationale for this decision is based on the autologous nature of the product and the short dating period of the final product. --b(4)---------- lot failure has minimal impact on the public health. The cellular product is administered fresh and has only an 18 hour shelf life. This does not allow enough time to provide samples to CBER to test the product before expiry.

c) Facilities Review/Inspection

Two pre-license inspections (PLI) were conducted to support the review and licensure of this product and the manufacturing facility. These inspections were conducted at Dendreon's manufacturing site in Morris Plains, New Jersey. The Morris Plains, NJ plant is to be the sole manufacturing site for the commercial product for the current BLA. Contract manufacturing for the --b(4)---------- is performed by Diosynth RTP Inc. Dendreon's corporate headquarters is in Seattle, WA. The Corporate Scheduling Group that oversees patient leukapheresis and infusion scheduling, monitors available manufacturing resources, and monitors real-time product delivery to infusion sites is located at Dendreon's corporate headquarters. Key personnel from the Corporate Scheduling Group were interviewed during both PLIs.

The first PLI of the Morris Plains, NJ facility was conducted February 12 – 16, 2007. The facility information for this site is:

Dendreon Corporation
220 East Hanover Ave.
Morris Plains, NJ 07950
FEI: 3005890060

The Morris Plains, NJ plant was a brand new facility designed specifically for manufacturing this type of product. All in-process and final product manufacturing is conducted at this facility. All in-process and final product testing is also performed at this facility with the exception of -b(4)------- testing which is performed by a contract testing facility. -b(4)-------- testing is performed as a quarterly surveillance program.

The 2007 PLI resulted in an issuance of a Form FDA 483 containing nine observations. The major deficiencies included inadequate process and production capacity validation in Modules -b(4)-, inadequate capability of maintaining the chain of identity to track and manage the in-process and final release samples in the QC Lab during production, and insufficient personnel with appropriate GMP training to perform the aseptic process validation, etc. The subsequent Form FDA 483 responses provided by the sponsor did not fully address all the 483 issues. The PLI was classified as a Voluntary Action Indicated (VAI). The outstanding issues from Form FDA 483 were included as an item in the CR letter issued by CBER to the sponsor on May 8, 2007.

All the inspectional issues identified in the Form FDA 483 observations have since been adequately addressed by the sponsor and all the Form FDA 483 issues are considered resolved (detailed in amendments to the BLA, submitted 5/14/2007 through 3/11/2010).

Because the last PLI was conducted almost three years ago in February 2007 and the facility had not been re-inspected since that time, CBER conducted a reinspection at the sponsor's Morris Plains, NJ facility on January 25 – 29, 2010.

The 2010 PLI focused on the systems that are used to manufacture and provide quality controls for the product. The inspection team reviewed the documents related to the quality system, facility and equipment systems, material management system, production system, packaging and labeling system, and QC laboratory control system. During the PLI, the inspection team also observed the production processes of b(4) lots of sipuleucel-T. At the conclusion of the PLI, a Form FDA 483 containing three observations was issued to the sponsor. The deficiencies identified during the inspection were insufficient Quality Assurance involvement in verifying and releasing the Workstations for change over and room clearance during production, inadequate environmental monitoring for non-viable particles within the Class --b(4) ----------, and inadequate cleaning validations in the Cleanroom. The sponsor has since satisfactorily responded to the 483 observations and all the inspectional issues are considered resolved. The inspection was classified as a VAI.

Based on the 2007 and 2010 inspections, the overall compliance status of Dendreon's Morris Plains, NJ manufacturing facility is deemed acceptable for product approval.

CBER did not perform an inspection on Diosynth, a contract manufacturer for --b(4)----------, during the current BLA review. This facility was previously inspected by the Agency on September 8-11, 2008 as part of a biannual inspection of licensed biological therapeutic drug products (FACTS Assignment # -----b(4)----). A Form FDA 483 was issued related to an --b(4)---------- procedure for an unrelated product. There are no outstanding issues related to this BLA. The facility information for this site is:

--b(4)----------.
--b(4)----------
--b(4)----------
--b(4)----------

d) Environmental Assessment

A request for a categorical exclusion from an Environmental Assessment under 21 CFR §25.31(c) was submitted to the BLA in the original submission. The sponsor believes this application meets the categorical exclusion criteria and to their knowledge no extraordinary circumstances exist. The Agency agrees with this conclusion and the requirement of an environmental assessment is not warranted.

4. Nonclinical Pharmacology/Toxicology

Due to the autologous nature of sipuleucel-T, limited preclinical studies were conducted in support of this BLA. Pharmacology studies conducted by the sponsor demonstrated that PAP is a potential immune target for prostate cancer active immunotherapy. *In vitro* studies showed that two murine T cell hybridoma cell lines that responded to both murine and human HLA-DR1^{+}APCs and recognized two HLA-DR1 restricted PAP-specific

epitopes could be established, indicating that human PAP can be taken up, processed and presented in the context of human MHC.

Immunization of mice or rats with hPAP, hPAP/b(4), rPAP or hPAP•mGM-CSF resulted in both humoral and cellular immune responses to PAP antigen. While immunization of rat with rPAP•rGM-CSF could induce prostate-specific inflammation in rats, no inflammation was observed in a limited set of normal non-prostate tissues examined. Thus, breaking of tolerance to autologous prostate tissue was shown to be possible, providing a rationale to support clinical development of sipuleucel-T. Mice immunized with hPAP•hGM-CSF loaded APCs prior to challenge with murine EL4 lymphoma transfected with the human PAP gene showed prolonged survival compared to the control groups; however, the rationale for selection of the dose level of the hPAP•hGM-CSF loaded APCs used, as well as the immunization regimen, was not provided. In this tumor challenge model, immunological endpoints associated with an anti-tumor response mediated by hPAP•hGM-CSF loaded APCs were not determined. In addition, the anti-tumor response in mice bearing established tumors prior to immunization was not evaluated with the rodent equivalent of sipuleucel-T.

In vitro analysis of PAP protein or PAP gene expression in human tissues demonstrated high expression of the PAP protein or gene in normal and malignant prostate tissue, with significantly lower expression in a limited set of non-prostate normal tissues.

Toxicology studies, as described in the International Conference on Harmonization (ICH) Safety ('S') guidelines, consisting of pharmacokinetics, acute toxicology, chronic toxicology, genotoxicity, carcinogenicity, reproductive and developmental toxicity, safety pharmacology, and immunotoxicity (http://www.ich.org/cache/compo/276-254-1.html) were not conducted due to the autologous nature of sipuleucel-T and the patient population of focus evaluated in this BLA.

5. Clinical Pharmacology

No studies of drug interactions have been performed with sipuleucel-T. Particularly, use of immunosuppressive agents given concurrently with the leukapheresis procedure or sipuleucel-T has not been studied. Sipuleucel-T is designed to stimulate the immune system, and concurrent use of immunosuppressive agents may alter the efficacy and/or safety of sipuleucel-T.

6. Clinical/ Statistical

a) Clinical Program

Results discussed in this section are based on both the clinical and statistical reviews submitted to the file.

Fourteen clinical trials of sipuleucel-T or related products have been conducted to date. Data to support the efficacy of sipuleucel-T for the treatment of men with metastatic AIPC are provided from these randomized, double-blind, placebo-controlled, multi-center Phase 3 studies (D9902B, D9901, and D9902A). These three studies enrolled 737 patients, including a total of 488 patients randomized to sipuleucel-T. Study D9902B is the pivotal trial in this submission and is supported by the results of Studies D9901 and D9902A.

Pivotal efficacy study:

Study D9902B was a randomized, double-blind, placebo-controlled, phase 3 trial in patients with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer. Eligibility criteria included metastatic disease in the soft tissue and/or bone with evidence of progression either at these sites or by serial Prostate Specific Antigen (PSA) measurements. Exclusion criteria included visceral (liver, lung, or brain) metastases, moderate to severe prostate cancer-related pain, and use of narcotics for cancer-related pain.

The study design was initially accepted under a Special Protocol Assessment (SPA) with time to objective disease progression as the primary endpoint. The protocol was later changed to specify overall survival as the primary endpoint and time to objective disease progression as the secondary endpoint. These changes were accepted by FDA under the SPA agreement.

Five hundred twelve patients with metastatic AIPC were randomized to receive either sipuleucel-T (n = 341) or placebo (n = 171). The median age was 71, and 90% of the subjects were Caucasian. Thirty-five percent of subjects had undergone radical prostatectomy, 54% had received local radiotherapy, and 82% had received combined androgen blockade. All subjects had baseline testosterone levels < 50 ng/mL. Forty-eight percent of subjects were receiving bisphosphonates, and 18% had received prior chemotherapy, including docetaxel. Eighty-two percent of subjects had an ECOG performance status of 0, 58% had primary Gleason scores of four or more ,44% had bone and soft tissue disease, 48% had bone-only disease, 7% had soft tissue-only disease, and 43% had more than ten bony metastases.

Dendreon performed a pre-specified interim analysis in May of 2008, after 247 death events had occurred. The hazard ratio and 95% confidence intervals were provided to the sponsor by the Independent Data Monitoring Committee (IDMC), as per the IDMC charter. Study enrollment was complete at the time of the interim analysis, and the interim analysis did not lead to any unblinding of treatment allocation. Therefore, study integrity was not compromised by the interim analysis.

In the final primary analysis of Study D9902B, treatment with sipuleucel-T was associated with a statistically significant improvement in overall survival, compared to a placebo control. Median survival was 4.1 months longer in subjects who received sipuleucel-T than in subjects who received placebo. The finding was supported by multiple sensitivity and subgroup analyses.

Bioresearch Monitoring, Data Quality, and Good Clinical Practices:
----Information withheld per the Privacy Act----------

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[Information withheld per the Privacy Act]

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

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

Supportive evidence of effectiveness:
Study D9901 had a design similar to D9902B, and randomized (2:1) a total of 127 patients to receive sipuleucel-T (n = 82) or control (n = 45). The primary endpoint was time to disease progression. Analysis of the primary endpoint did not reach statistical significance. A statistically significant improvement in overall survival (p = 0.01), comparing the sipuleucel-T group to the control group, was observed in Study D9901; however, the method for the analysis of overall survival was not pre-specified.

Study D9902A was similar in design to the other studies, but enrollment was terminated prior to completion of accrual. The study randomized 98 patients: 65 received sipuleucel-T; 33 received control. A trend towards improved survival was associated with sipuleucel-T, compared to control, in Study D9902A.

An integrated analysis of efficacy results from the three randomized trials supports the claim of improved survival associated with sipuleucel-T. Efficacy results of the three randomized studies in subjects with asymptomatic or minimally symptomatic, metastatic, castrate resistant prostate cancer are summarized in the table below.

Summary of Overall Survival Analysis Results

	Sipuleucel-T		Placebo		Sipuleucel-T vs. placebo	
	N	Median Survival[4]	N	Median Survival[4]	Hazard Ratio (95% CI)	p-value
D9902B (N=512)[1]	341	25.8	171	21.7	0.775 (0.614, 0.979)	0.032
D9901 (N=127)[2]	82	25.9	45	21.4	0.586 (0.388, 0.884)	0.010
D9902A (N= 98)[2]	65	19.0	33	15.7	0.786 (0.484, 1.278)	0.331
Integrated Studies (N=737)[3]	488	25.4	249	21.5	0.734 (0.612, 0.881)	0.0009

[1] Hazard Ratio (HR), confidence interval (CI), and p-value estimated according to the primary analysis methods.
[2] HR, CI, and p-value estimated based on unadjusted Cox model and log rank test as presented in the individual clinical trial report. The analysis methods for overall survival were not pre-specified.
[3] HR, CI, and p-value estimated based on Cox model with treatment as independent variable, stratified by study.
[4] Based on a Kaplan-Meier estimate (in months).

No difference between the two study arms in time to objective disease progression, progression free survival, time to clinical progression, or time to prostate-specific antigen (PSA) doubling time was observed in any of the Phase 3 studies. The reason for the dissociation between overall survival and these other outcome measures is unclear. However, overall survival is the most reliably measured and clinically meaningful of these endpoints.

Efficacy review issues:
Immune response samples were collected from only a subset of the study subjects. The sipuleucel-T group had some specific immune responses post-treatment. However, the clinical meaningfulness of these responses is unclear.

The placebo control was autologous peripheral blood mononuclear cells that had not been activated during manufacturing. Following disease progression, control group subjects had the option to receive their own autologous frozen, thawed, and activated mononuclear cells (APC8015F). These APC8015F cells were activated in the same way (i.e., with the recombinant PAP-GM-CSF fusion protein) as sipuleucel-T prepared from unfrozen cells. The review team considered the possibility that this APC8015F administration might have affected the study results. However, exploratory analyses were inconclusive with regard to the existence of a relationship between APC8015F administration and survival.

Docetaxel is the only available treatment for metastatic castration resistant prostate cancer with a known survival benefit. One concern regarding interpretation of Study D9902B was that the survival difference between the two arms might be attributable to

subsequent therapy with docetaxel. In Study D9902B, 7% more subjects in the sipuleucel-T arm received docetaxel following study treatment, compared to the placebo arm. Also, the median time from randomization to docetaxel use in the sipuleucel-T arm was shorter than in the placebo arm. Several analyses were conducted to explore the relationship between docetaxel administration and survival. These analyses were inconclusive. In Study D9901, the opposite pattern was observed: 49% of subjects in the placebo arm were treated with docetaxel following disease progression, compared with 37% of the sipuleucel-T-treated subjects. Despite differences in the patterns of subsequent docetaxel use, overall survival results were similar in the D9902B and D9901.

Regulatory standard for evidence of effectiveness:
As stated in the FDA guidance *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, the usual standard for marketing approval is two or more adequate and well-controlled studies. In the sipuleucel-T BLA, the recommendation for approval is based on only one adequate and well-controlled investigation, D9902B. As stated in the guidance on effectiveness, FDA will generally rely on a single trial only when a second trial is not ethical and/or feasible. Because D9902B provides substantial evidence of improved survival, a second study would be neither ethical nor feasible in the United States.

In addition, as stated in the guidance on providing evidence of effectiveness, the assessment of the adequacy of a single trial will consider the characteristics of that single trial and the availability of supportive evidence of efficacy. Characteristics of Study D9902B that support its use as the only primary evidence of effectiveness include that the study was relatively large (N = 512), multicenter, with results that were consistent in multiple sensitivity analyses and across numerous subgroup analyses. In the sipuleucel-T BLA, supportive evidence of efficacy comes from two Phase 3 studies, D9901 and D9902A.

In summary, D9902B, supported by the results of D9901 and D9902A, meets the regulatory standard for a single trial that provides the substantial evidence of effectiveness necessary to support a marketing approval.

Label considerations:
The review team discussed broadening the indication statement to include all patients with metastatic castrate resistant prostate cancer. After thorough consideration, the review team decided that the indication statement should be limited to such patients who are also asymptomatic or minimally symptomatic, as studied in the Phase 3 trials (i.e., D9902B, D9901, and D9902A) that provide the substantial evidence of efficacy.

b) Pediatrics

Prostate cancer does not occur in the pediatric population. Therefore, the FDA Pediatric Review Committee (PeRC) Subcommittee and the review team recommend that a pediatric waiver be granted for sipuleucel-T for the treatment of prostate cancer.

c) Other Special Populations

The BLA contains data from three randomized trials (512 subjects in Study D9902B; 127 subjects in Study D9901; and 98 subjects in Study D9902A). Data from all three randomized trials were combined. This combined data set was used for multiple subgroup analyses. Subjects randomized to sipuleucel-T showed a numerical improvement in overall survival, compared to those randomized to placebo, in all subgroups analyzed.

No subgroup analysis was conducted for gender since prostate cancer occurs only in men.

7. Safety

The safety review is based on the safety data from four randomized, placebo-controlled studies (D9901, D9902A, D9902B, and P-11). The study protocols specified that three infusions of sipuleucel-T or placebo were to be administered at approximately 2 week intervals. Each dose of sipuleucel-T required a standard leukapheresis procedure approximately three days prior to the infusion.

The safety population consisted of 904 subjects (601 sipuleucel-T; 303 control) who underwent at least one leukapheresis procedure in these four trials. The demographic and baseline disease characteristics were fairly well balanced between the two treatment groups.

The control group received autologous peripheral blood mononuclear cells that had not been activated during manufacturing. Infusion of this control is expected to cause some infusion reactions; therefore, the control was not a true placebo from a safety perspective. In addition, placebo group subjects underwent three leukaphereses, which are expected to cause some adverse events. Therefore, some adverse events that occurred in the control group were not due to the background disease but were related to the treatment procedures common to both placebo and sipuleucel-T. For example, citrate toxicity occurred in 14 – 15% of subjects in each treatment group, and was almost certainly related to the leukapheresis procedure. Other adverse events (e.g., paresthesia) that were relatively common in both treatment groups were also most likely related to the study procedures (i.e., leukapheresis and/or infusion).

Sipuleucel-T was generally well-tolerated. A total of 98.3% of subjects who received sipuleucel-T in the four ISS studies reported adverse events (AEs). The majority (67.4%) of subjects had events that were mild or moderate in severity. The most common AEs, occurring in ≥15% of subjects who received sipuleucel-T, included chills, fatigue, fever, back pain, nausea, arthralgia, and headache. Sipuleucel-T was discontinued in 1.5% of subjects due to adverse reactions. Severe (Grade 3), life-threatening (Grade 4), and fatal (Grade 5) adverse events were reported in 23.6%, 4.0%, and 3.3% of subjects who received sipuleucel-T. The most common (≥2%) Grade 3-5 adverse events reported in the sipuleucel-T group were back pain and chills.

Seventy-one percent of subjects in the sipuleucel-T group developed an acute infusion reaction, most commonly chills, fever, or fatigue. These infusion reactions generally occurred within 1 day of infusion, were mild or moderate in severity, and resolved within two days.

Serious adverse events (SAEs) include any life-threatening or fatal event, inpatient hospitalization, or persistent or significant disability. Overall, 24.0% of subjects in the sipuleucel-T group and 25.1% of subjects in the placebo group developed an SAE.

Of the 904 subjects (601 randomized to sipuleucel-T and 303 randomized to placebo) in the four ISS studies (D9902B, D9901, D9902A, and P-11), 56.1% of subjects died as of the data cut-off. The fatalities included 53.2% of the subjects in the sipuleucel-T group and 61.7% of the subjects in the placebo group. The majority of deaths were attributed to disease progression**.**

Cerebrovascular Events

Cerebrovascular event (CVE) analyses were performed for the four randomized, double-blind, placebo-controlled studies (Studies D9902B, D9901, D9902A, and P-11). CVEs were observed in 21/601 (3.5%) of subjects in the sipuleucel-T group vs. 8/303 (2.6%) of the subjects in the control group. Therefore, a safety signal of slightly increased risk of stroke was identified. The review team recommends that a postmarketing study be required to further evaluate this risk.

There was disagreement among the review team regarding the value of a planned postmarketing registry study. Because the proposed postmarketing study is not a randomized, concurrently controlled, clinical trial, it will not provide a definitive measure of the relative risk of CVE in sipuleucel-T-treated subjects compared to a placebo group. However, there was a consensus among the review team that assessing CVE risk with a clinical trial comparing sipuleucel-T-treated subjects to control subjects would not be ethical or feasible. The review team decided that, considering the existence of a safety signal for a serious and unexpected risk, a postmarketing registry study represents a reasonable strategy to further assess the risk of CVEs.

8. Advisory Committee Meeting

The original BLA for sipuleucel-T for treatment of prostate cancer was submitted in 2006. That application was based on results from Studies D9901 and D9902A. On March 29, 2007, FDA held an advisory committee meeting (Cellular, Tissue and Gene Therapies Advisory Committee, supplemented by members of the Oncology Drugs Advisory Committee and several prostate cancer specialists) to seek advice on the persuasiveness of the sipuleucel-T efficacy and safety results. In addition, several questions regarding product potency, variability, and mechanism of action were discussed.

The committee generally agreed that the data supported the proposed mechanism of action, that CD54 up-regulation was a good indicator of antigen presenting cell activation, and that the therapy has the potential to improve antigen presentation to tumor-specific T cells. Regarding the immune monitoring data, the Committee stated that more information was needed in order to 1) determine the function of antigen presenting cells in the product in stimulating T and B cell responses, 2) determine the role of PAP antigen in eliciting an immune response, and 3) evaluate host T cell activation and suppression in product function, and how that will or will not correlate with survival.

After discussions regarding the significance of the CVEs reported in the submitted studies, the committee voted unanimously (17-0) that safety had been established. The Committee recommended that postmarketing pharmacovigilance studies be performed to monitor the incidence of CVEs, with attention to the African American population and other minorities.

After additional discussion, the Committee voted 13 yes and 4 no to the question of whether there was substantial evidence that the product was effective. Despite the majority of yes votes, the majority of Committee members expressed uncertainty regarding treatment effect (increased survival) of sipuleucel-T in the intended patient population. In addition, there was a consensus that the ongoing D9902B trial must be completed; that, to confirm the survival advantage seen in D9901, the integrity of D9902B must not be compromised, and that the under-representation of the African American population should be addressed.

After complete review of the original BLA submission, the FDA determined that the efficacy result in the original application was not statistically persuasive. Therefore, the FDA issued a complete response letter requiring submission of the results of Study D9902B before licensure.

9. Other Relevant Regulatory Issues

Financial Disclosures.
Certification of financial disclosure (Form 3454) was provided by the applicant. Documentation of financial disclosure was provided for all investigators except for three sub-investigators. The applicant made multiple attempts to obtain this information and has stated that no compensation was provided by the applicant to these three sub-investigators. Two other investigators were provided compensation by the applicant for consulting, honoraria, authorship/editing, market research and advisory board participation. There is no evidence that financial conflicts influenced the study results.

10. Labeling

The package insert (PI) originally submitted to the BLA and all subsequent amendments related to the label were reviewed by all members of the BLA review team.

Multiple discussions about the PI were held between review team members and Dendreon, which resulted in multiple rounds of revisions until final agreement was reached. The most significant changes are summarized below:

- The product was described as containing 50 million autologous CD54+ cells activated with PAP-GM-CSF instead of 50 million activated CD54+ antigen presenting cells.
- PAP-GM-CSF was included in the list of active ingredients.
- Several sections were revised to add or clarify procedures and precautions regarding product receipt, storage, preparation, and infusion.
- The Product Safety Testing subsection was revised to clarify procedures related to product sterility.
- The summary of immune monitoring data was modified to include only significant observations, and to add the statement that no conclusions could be made about the clinical significance of the immune response data.
- The indication statement was limited to the population that was studied in the Phase 3 trials, i.e., men with asymptomatic or minimally symptomatic metastatic castrate resistant (hormone refractory) prostate cancer.
- Safety information was provided regarding the incidence of adverse events, severe adverse events, and serious adverse events.
- The control agent was identified as non-activated autologous peripheral blood mononuclear cells.
- The Clinical Trials section of the label was revised to emphasize Study D9902B and de-emphasize Studies D9901 and D9902A.

The Advertising and Promotional Labeling Branch reviewed, and found acceptable, the proposed name for this product. In addition to the proprietary name, the Advertising and Promotional Labeling Branch reviewed the package insert, patient labeling, and carton and container labels. Changes to container and package labels were required in order to be in full compliance with regulations. After discussions with the sponsor, all of these submissions were found to be acceptable.

After some discussion with the sponsor, the Patient Counseling Information and Patient Labeling submissions were found to be acceptable.

The sponsor will submit the label in Structured Product Labeling format after product licensure.

The proposed label provides adequate directions for the safe and effective use of sipuleucel-T in the indicated population.

11. Recommendations and Risk/ Benefit Assessment

a) Recommended Regulatory Action

The reviewers recommend approval of sipuleucel-T for the treatment of asymptomatic or minimally symptomatic, metastatic, castrate resistant (hormone refractory) prostate cancer. The recommended dose is three intravenous doses at approximately 2-week intervals.

b) Risk/ Benefit Assessment

Sipuleucel-T offers substantially improved survival to patients with a fatal disease. The risks associated with sipuleucel-T administration are minor relative to the benefit of improved survival. The quality, efficacy, and safety of this product have been thoroughly reviewed and have been determined to be acceptable for use of this product as indicated in the label.

c) Recommendation for Postmarketing Risk Management Activities

No safety issue was identified that warrants a Risk Evaluation and Mitigation Strategy (REMS). Sipuleucel-T is expected to have a favorable risk-benefit ratio when used as described in the label.

d) Recommendation for Postmarketing Activities

Product:
The nature of the product makes CBER lot release testing unfeasible and therefore the sponsor was given an exemption. The CMC review team determined that in lieu of CBER lot release testing, the sponsor should submit summary analyses and data trending of lot release testing conducted for all lots generated during a manufacturing year.
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Clinical:
The increased incidence of CVEs in sipuleucel-T-treated subjects represents a signal of a serious risk, as defined under the Food and Drug Administration Amendments Act (FDAAA) of 2007.

Therefore, the review team recommends that Dendreon be required to conduct a postmarketing study based on a registry design to assess the risk of cerebrovascular events. The registry study should enroll 1500 patients with prostate cancer who receive sipuleucel-T. Dendreon has agreed to conduct this postmarketing study and has agreed to submit the final study protocol by June 30, 2010, to complete the study by December 31, 2015, and to submit a final study report by September 30, 2016.