EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 June 2013
EMA/440011/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

PROVENGE

Common name: Autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T)

Procedure No. EMEA/H/C/002513/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

AEs	Adverse Events
AIPC	Androgen independent prostate cancer
ADPC	Androgen dependent prostate cancer
ANC	Absolute neutrophil count
APC(s)	Antigen presenting cell(s)
APH	Apheresis component, also referred to as leukapheresis component
CHMP	Committee for Medicinal Products for Human Use
CMML	Chronic myelomonocytic leukaemia
COI	Chain of Identity
COP	Copenhagen rats
COPs	Critical operating parameters
CR	Complete response
CSR	Clinical study report
CT	Computed tomography
CTL	Cytotoxic T lymphocyte
CTCAE	Common Terminology Criteria for Adverse Events
DC(s)	Dendritic cell(s)
DNA	Deoxyribonucleic acid
cDNA	coding DNA
DOR	Duration of Response
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
ED50	Effective Dose 50
EDQM	European Department for the Quality of Medicines
ELISA	Enzyme-linked immunosorbent assay
ELISPOT	Enzyme-linked immunosorbent spot
EMA	European Medicines Agency
EU	European Union
FBS	Fetal Bovine Serum
FDA	Food and Drug Administration
FP	Final product
FPRC	Final Product Reference Control
GC	Gas Chromatography
GCP	Good clinical practices
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HCP	Host Cell Protein
HIV	Human immunodeficiency virus
HRPC	Hormone refractory prostate cancer
HR	Hazard ratio
ICH	International Conference on Harmonization
IFN-γ	Interferon gamma

IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IPC	In-process control
ITT	Intent to treat
IV	Intravenous
LDH	Lactate dehydrogenase
LR	Lactated Ringer's Injection, USP
MAA	Marketing Authorisation Application
mAIPC	Metastatic Androgen Independant Prostate Cancer
mADPC	Metastatic Androgen Dependent Prostate Cancer
MCB	Master Cell Bank
mCRPC	Metastatic Castrate resistant prostate cancer
MHC	Major Histocompatibility Complex
mHRPC	Metastatic hormone refractory prostate cancer
MMD	Maximum manufactoring Dose
MLR	Mixed lymphocyte reaction
MTD	Maximum Tolerated Dose
MVB	Master Virus Bank
N/A	Not Applicable
NCI CTCAE	National Cancer Institute's Common Terminology Criteria for Adverse Events
NE	Not Estimable
NS	"Normal Saline", 0.9% Sodium Chloride Solution for Injection
NK	Natural killer cells
OS	Overall survival
PA2024	Recombinant fusion protein composed of PAP fused to GM-CSF
PA	Prostate antigen
PAP	Prostatic acid phosphatase
PBMCs	Peripheral blood mononuclear cells
PFS	Progression free survival
Ph. Eur.	European Pharmacopeia
PK	Pharmacokinetic
PPI	Pain intensity
PR	Partial response
PSA	Prostate-specific antigen
PSADT	PSA doubling time
PAP-GM-CSF	Prostatic acid phosphatase fused with granulocyte-macrophage colony-stimulating factor
RBC(s)	Red blood cell(s)
SAE	Serious adverse event
SAWP	Scientific Advice Working Party
SmPC	Summary of Product Characteristics
TDRP	Time to onset of disease-related pain
TNC	Total nucleated cells
TSE	Transmissible spongiform encephalopathy

ULN	Upper limit of normal
USP	United States Pharmacopeia
UV	Ultra Violet spectroscopy
VAS	Visual Analog Scale
WBC(s)	White blood cell(s)

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Dendreon UK LTD submitted on 30 December 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Provenge, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 17 February 2011.

The applicant applied for the following indication: Provenge is indicated for first line treatment of metastatic castrate resistant prostate cancer in male adults.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The applicant indicated that autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T) was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision EMA/809925 on the granting of a class waiver.

New active Substance status

The applicant requested the active substance autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T) contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 March 2008. The Scientific Advice pertained to quality, and clinical aspects of the dossier.

Licensing status

Provenge has been given a Marketing Authorisation in USA on 29 April 2010.

1.2. Manufacturers

Manufacturer of the active substance

PharmaCell
Oxfordlaan 70
NL-6229 EV, Maastricht
The Netherlands

Manufacturer responsible for batch release

PharmaCell
Oxfordlaan 70
NL-6229 EV, Maastricht
The Netherlands

1.3. Steps taken for the assessment of the product

The CAT (Co)-Rapporteurs, the CHMP coordinators and PRAC (Co)-Rapporteurs appointed by the CHMP:

Rapporteur: Egbert Flory	Co-Rapporteur: Nicolas Ferry
CHMP Coordinator: Jan Muller Berghaus	CHMP Coordinator: Pierre Demolis
PRAC Rapporteur: Brigitte Keller-Stanislawski	PRAC Co-Rapporteur: Isabelle Robine

- The application was received by the EMA on 30 December 2011.
- The procedure started on 25 January 2012.
- The Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on 18 April 2012. The Co-Rapporteur's first Assessment Report was circulated to all CAT and CHMP members on 13 April 2012.
- During the meeting on 17-18 May 2012, the CAT agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 May 2012.
- The applicant submitted the responses to the CAT consolidated List of Questions on 15 October 2012.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 21 November 2012.
- During the CAT meeting on 6-7 December 2012, the CAT agreed on a list of outstanding issues to be addressed in writing by the applicant.
- During a meeting of a SAG-Oncology on 7 February 2013, experts were convened to address questions raised by the CAT and CHMP.
- The applicant submitted the responses to the CAT List of Outstanding Issues on 15 February 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding issues to all CHMP members on 28 February 2013.

- During the PRAC meeting on 4-7 March 2013, the PRAC agreed on a PRAC RMP Advice and assessment overview.
- During the CAT meeting on 14-15 March 2013, the CAT agreed on a second list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- During a meeting of a Biostatistics Working Party on 22 March, experts were convened to address questions raised by the CAT and CHMP.
- The applicant submitted the responses to the CAT second List of Outstanding Issues on 26 April 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the second List of Outstanding issues to all CHMP members on 8 May 2013.
- During the PRAC meeting on 13-16 May 2013, the PRAC agreed on a PRAC RMP Advice and assessment overview.
- During the CAT meeting on 23-24 May 2013, outstanding issues were addressed by the applicant during an oral explanation before the CAT.
- During the meeting on 20-21 June 2013, the CAT, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Provenge on 21 June 2013.
- During the meeting on 24-27 June 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Provenge.

2. Scientific discussion

2.1. Introduction

Problem Statement

Prostate cancer is the most common cancer and the second leading cause of cancer deaths among males in most Western countries. Prostate cancer-related deaths occur as a result of complications of metastatic disease. In 2008, 393,793 European men were diagnosed with prostate cancer and over 94,350 patients were lost to the disease. In 2010, prostate cancer was the most common solid tumour malignancy in men in the United States, expected to account for over 217,730 new cases and 32,050 deaths (Jemal 2010). While records for Southeast Asia/Oceania and South American show more than 28,000 and 84,000 new cases, respectively, the death rates are much higher (more than 19,000 and 29,000, respectively).

Metastatic prostate cancer may be found at primary diagnosis or may develop after treatment for localised disease. Metastatic disease refers to tumour that has spread beyond the prostate to regional pelvic lymph nodes or distantly to other sites, most often bone. Because of widespread PSA screening in many countries over the last 20 years, most patients currently diagnosed with prostate cancer have no evidence of metastases. However, between 5 and 35%, exhibit cancer dissemination at diagnosis, mostly to the bones and lymph nodes, with the highest incidence in non-Western countries (Ferlay 2008). Metastatic androgen dependent (hormone naïve) prostate cancer (mADPC) is a non-curable and lethal disease with a median survival of approximately 4 to 5 years in recent experiences (Millikan 2008): approximately 40 months in patients with bulky (more than 2 lesions) bone dissemination and 80 months in those with low-volume dissemination (fewer than 2 bone lesions or lymph node metastases). Bilateral orchiectomy or medical castration with luteinizing hormone–releasing hormone (LHRH) agonists are the recommended initial treatments for metastatic prostate cancer (ASCO 2007), achieving temporary tumor control or regression in 80 to 85% of patients (Crawford 1989, Schellhammer 1997, Scher 1993, Small 1995). A peripheral anti-androgen, such as flutamide or bicalutamide, is commonly used during the first days or weeks following the first injection of an LHRH agonist in order to counter the initial testosterone flare, but Phase 3 trials have failed to demonstrate a clinically relevant survival benefit with continuous complete androgen blockade (ADT plus anti-androgen) when compared to ADT alone (Caubet 1997, Eisenberger 1998, PCTCG 1995). Despite hormonal therapy, most patients with disease recurrence will progress within 12 to 18 months.

Castrate-resistant prostate cancer (CRPC) is defined by disease progression despite androgen depletion therapy and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of pre-existing disease, and/or the appearance of new metastases. Three agents have demonstrated a survival advantage and are approved for the treatment of castration-resistant prostate cancer: docetaxel with prednisone as front-line chemotherapy; cabazitaxel with prednisone following docetaxel; and abiraterone acetate with prednisone or prednisolone (a hormonal therapy that blocks androgen synthesis).

Based on the results of 2 randomised controlled trials, it is currently recommended that for men with clinical or biochemical evidence of progression and evidence of metastases, treatment with

docetaxel 75 mg/m^2 administered intravenously every 3 weeks with 5 mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation and quality of life. A randomized study in metastatic castration-resistant prostate cancer comparing docetaxel administered every 3 weeks to docetaxel weekly and to mitoxantrone demonstrated a 2.4 months survival benefit for docetaxel every 3 weeks (Tannock, 2004). Once patients progress on docetaxel, cabazitaxel is approved as second-line chemotherapy with a 2.4 month survival advantage over mitoxantrone plus prednisone (de Bono, 2010). Abiraterone acetate, an oral inhibitor of androgen biosynthesis, has recently been approved, in combination with prednisone, for patients with metastatic castration resistant prostate cancer who have previously received docetaxel after demonstrating a 3.9 month survival advantage over placebo (de Bono, 2011). Abiraterone is also indicated with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

More recently, enzalutamide (an oral androgen receptor signalling inhibitor) has shown a survival advantage in patients with metastatic castration-resistant prostate cancer who have previously received docetaxel (Howard, 2012).

Treatment options for symptomatic bone disease are radiation or radionuclide agents and bisphosphonates or the RANK ligand inhibitor, denosumab.

About the product

Provenge (sipuleucel-T) is an autologous active cellular immunotherapy product that is designed to stimulate an immune response to prostate cancer. Provenge differs from classical dendritic cell (DC) products by short time culture of whole peripheral blood mononuclear cells (PBMC). The PBMCs are cultured *ex vivo* with a recombinant fusion protein consisting of prostatic acid phosphatase (PAP) which is fused to GM-CSF. The PBMCs are exposed for a short duration to the PAP-GM-CSF fusion protein. This results in targeting of PAP-GM-CSF to PBMC antigen-presenting cells expressing the GM-CSF receptor, which then undergo activation and initial maturation *ex vivo*. Cell activation/maturation results in CD54 up-regulation which is used in combination with the number of CD54+ cells as a surrogate potency assay.

Provenge contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF fusion protein, suspended in Lactated Ringer's Injection, USP, in a total volume of 250 mL in a sealed, patient-specific infusion bag.

The proposed mechanism of action for sipuleucel-T is the induction of an immune response to the target antigen, PAP. In humans, PAP is one of the major proteins secreted by prostate columnar epithelium secretory cells following puberty. PAP protein has been determined to be approximately 0.5 mg/g wet weight of prostate tissue (Yam 1974, Goldfarb 1986) and approximately 1 mg/mL in seminal fluid (Ronnberg 1981). In healthy individuals, PAP serum levels are low, whereas levels are significantly elevated in many metastatic prostate cancers. While PAP expression is relatively specific to the prostate, it has been reported to be expressed in other normal tissues and malignancies. PAP is highly expressed in both normal and malignant prostate.

The indication initially applied for was: “Provenge is indicated for first line treatment of metastatic castrate resistant prostate cancer in male adults.”

The proposed recommended course of treatment is 3 doses of Provenge at approximately 2 week intervals (range in controlled clinical trials was 1 - 15 weeks). Each dose of Provenge is preceded by a standard leukapheresis procedure approximately 3 days prior to the scheduled infusion date.

2.2. Quality aspects

2.2.1. Introduction

Provenge is an autologous active cellular immunotherapy, which consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs), activated with PAP-GM-CSF.

The finished product is a cell dispersion for infusion containing a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF and formulated with Lactated Ringer’s solution (LR) in a final volume of 250mL. It is supplied in a sealed patient-specific infusion bag. For each lot of Provenge, the subject undergoes apheresis, and the harvested PBMCs are used to manufacture the product.

Provenge is solely intended for autologous use via intravenous infusion. The recommended course of treatment is 3 complete doses of Provenge, each prepared and administered via intravenous infusion at approximately 2-week intervals.

The applicant received CHMP scientific advice (EMEA/CHMP/SAWP/485163/2007, EMA/CHMP/SAWP/343464/2011) regarding quality aspects. Quality questions at the time of CHMP advice were especially related to the influence of cells not expressing CD54. Other questions related to the validation of the flow cytometry method and specifications.

2.2.2. Active Substance

The active substance (also referred to as Sipuleucel-T) consists of autologous PBMCs, including APCs that have been activated *ex vivo* with the recombinant fusion protein PA2024. The fusion protein is composed of prostatic acid phosphatase (PAP) fused to granulocyte-macrophage colony-stimulating factor (GM-CSF). While GM-CSF activates APCs and enhances cell viability, PAP represents the target antigen. PAP uptake into APCs is followed by intracellular processing and presentation of PAP-derived peptides on Major Histocompatibility Complex (MHC) molecules to T cells.

Other mononuclear cell types found in the product include: T cells, B cells, Natural Killer (NK) cells, and APCs (including monocytes and dendritic cells (DCs)). Activated APCs are contained within the CD54+ cell population, which includes monocyte-derived APCs and DCs. DCs (the most effective APCs) represent a small percentage of all cells. CD54 expression is used to assess product potency of Provenge by measuring the number of CD54+ cells, and CD54 upregulation during *ex vivo* culture.

Manufacture

The active substance is manufactured according to GMP by PharmaCell BV, Maastricht, Netherlands.

The applicant provided a comprehensive description of the manufacturing process. The manufacturing process is continuous, with no temporal breakpoints between the active substance and finished product manufacturing.

Apheresis: Provenge is manufactured from a patient's own peripheral blood cells obtained via apheresis (APH). The APH is considered a cellular starting material. Apheresis collection sites are required to be approved or registered by their governing Health Authority for conducting apheresis collections. They are qualified by Dendreon following on-site audits and are trained in procedures specific to Dendreon products. Each lot of APH is assigned a chain of identity (COI) number, which uniquely identifies the product throughout manufacturing and shipment to the infusion center. Incoming apheresis testing is acceptable. The APH is transported from the apheresis centre to the manufacturing facility. Data (time and temperature) support apheresis shelf life at the specified transport conditions.

The manufacturing process involves several concentration and separation steps using proprietary separation solutions and devices to reduce certain cell types. The resulting population is then incubated with the fusion protein PA2024 under specified conditions (temperature and time), to activate the antigen presenting cells. Following incubation with the antigen, the cells are aseptically harvested, washed, suspended in lactated ringers, and packed for delivery to the infusion centre.

At the infusion center, the product is held, pending disposition by the Qualified Person. The infusion procedure is not initiated until a final product disposition form documenting, the release approval of the product, has been received.

One batch of Provenge is obtained from the patient's cells collected by apheresis and contains a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF. Since the manufacturing process is continuous, a batch of active substance cannot be defined.

The recommended course of treatment is 3 complete doses of Provenge, each prepared from a fresh leukapheresis and administered via intravenous infusion at approximately 2-week intervals. Therefore, 3 lots of new finished product material are generated for each patient.

Manufacture of Placebo and Salvage Product (APC8015F)

The placebo is an autologous cell product consisting of fresh PBMCs, including non-activated APCs, which have been incubated in media without exogenous antigen. The preparation of placebo is as follows: PBMCs are isolated from leukapheresis cells by several concentration and separation steps, after which a portion of the PBMCs are incubated in medium in the absence of the PA2024 antigen. The culture medium does not contain serum or exogenous cytokines.

The cells are then washed, suspended in lactated ringers, placed in a refrigerated package, and transported to the clinical trial site for infusion. The remaining processed PBMCs are cryopreserved (in a standard cryoprotectant system) and used later to generate the salvage product (APC8015F).

While Provenge is prepared from fresh APH, APC8015F is prepared from cryopreserved PBMCs collected during the subject's participation in the control arm of study D9901, D9902A, or D9902B. Quiescent PBMCs, prepared by concentration and separation steps, and frozen during the preparation of placebo control, are thawed and washed to remove cryoprotectant. Using a manufacturing process essentially identical to that of Provenge, the washed PBMCs are cultured *ex vivo* with PA2024. The incubated cells are then washed, suspended in LR, placed in a refrigerated package, and transported to the clinical trial site for infusion.

Upon request the applicant presented new data related to the manufacturing and release of placebo. Release specifications for viability were identical for placebo, APC8015F, and sipuleucel-T. It was also confirmed that after storage and transportation placebo and Provenge are highly comparable concerning this quality attribute.

Control of Materials

The active substance manufacturing process utilizes non-animal, non-human derived raw materials, with the exception of cell culture medium, and a recombinant protein (PA2024).

The cell culture medium incorporates three components of human or animal origin: human serum albumin, human transferrin and sheep wool cholesterol.

PAP-GM-CSF Fusion protein (PA2024)

PA2024 is a fusion glycoprotein consisting of a prostatic acid phosphatase (PAP) linked to granulocyte-macrophage colony-stimulating factor (GM-CSF) by a glycine-serine dipeptide. Five potential N-glycosylation sites and one potential O-linked glycosylation site have been identified. The molecular mass of the PA2024 is approximately 132 kDa because it exists in solution as a dimer. Biological activity of fusion protein has determined by measuring the bioactivity of GM-CSF using an in vitro TF-1 cell-proliferation based assay.

It is loaded onto the peripheral blood mononuclear cells during the manufacture of Provenge in order to be taken up by APCs, and to start the differentiation of monocytes into immature DCs. After intracellular processing antigenic PAP epitopes are being presented by APCs to T cells in an MHC-restricted manner. Only minute amounts of intact PA2024 are ultimately administered to patients, resembling molecules that were neither taken up by APC nor were removed during the following cell washing steps.

The name and address of the manufacturer responsible for manufacturing and release of bulk PA2024 were provided. PA2024 fusion protein (PAP-GM-CSF) is recombinantly expressed in insect cells: PA2024 is produced by a baculovirus expression vector system, which requires Sf21 host cells derived from the pupal ovarian tissue of Spodoptera frugiperda (fall armyworm). The Sf21 cells are transiently infected with baculovirus particles carrying a cDNA construct for fusion protein.

The upstream manufacturing process for bulk PA2024 involves 3 general stages: cell bank vial thaw and expansion; baculovirus stock creation and expansion; harvest and clarification of PA2024. As part of the downstream process, PA2024 product is captured, further purified (by a series of chromatographic steps), filtered, filled and stored as a buffered solution under demonstrated suitable conditions.

The manufacturing of bulk PA2024 has comprehensively been described, and characterization studies were extensive and sufficient. In process controls have been clearly specified for each step. Critical parameters were identified and considered acceptable and sufficient.

The process validation includes analysis of an appropriate number of consecutive runs manufactured using the same scale and the same facility that is proposed for commercial material. The bulk PA2024 manufacturing process is controlled by operational parameters and performance parameters (including critical parameters). All critical parameters were within the acceptance criteria for the validation runs. The results for operational control parameters and performance parameters are also provided, and further confirm the consistency of the process.

The raw materials and reagents used in the bulk PA2024 manufacturing process are summarized in the dossier. For non-compendial materials, a brief summary of specification (test parameters and acceptance criteria) was presented.

The cell substrate was derived from Sf21 cell line. A two-tiered cell banking system was historically established. The Master Cell Bank (MCB) 1 was prepared by Dendreon from a Sf21 seed stock that was adapted to serum-free medium. The MCB 2 was created from MCB 1 to replace it and ensure a sufficient supply of MCB vials for future.

The recombinant baculovirus was created by transfecting the plasmid PA2024-pBP8, which contained the gene of interest, with viral DNA using lipofection. One clone was selected to establish the PAP-GM-CSF3 Molecular Immunology (MI) Seed Stock. This MI seed stock was then used to prepare a two-tiered virus banking system: Master Virus Bank (MVB) 1 and MVB 2. The MVB 1 was prepared in 1996 and was thereafter replaced in 2000 by MVB 2.

MCB 2 and MVB 2 were tested at release and are controlled by in-process controls (IPCs) when used for a production campaign. They were both used to produce clinical material. Comparability exercises were performed to demonstrate that fusion protein PA2024 manufactured from MCB 1/MCB 2 and MVB 1/MVB 2 are comparable. Results are not discussed in the report since clinical and commercial batches are only manufactured from MCB 2 and MVB 2.

PA2024 has been characterized structurally by spectroscopic, electrophoretic and chromatographic assays. PA2024 is a fusion glycoprotein consisting of a prostatic acid phosphatase linked to granulocyte-macrophage colony-stimulating factor by a glycine-serine dipeptide. Five potential N-glycosylation sites and one potential O-linked glycosylation site have been identified. The molecular mass of the fusion protein is approximately 132 kDa because it exists in solution as a dimer. Biological activity of fusion protein has been determined by measuring the bioactivity of GM-CSF. An in vitro TF-1 cell-proliferation based assay was used.

All product-related variants have been considered as product-related impurities. Several methods are employed in routine release testing to control the purity/impurity profile of bulk PA2024.

HCP removal has been demonstrated during process validation.

The panel of test methods to be applied for bulk PA2024 release specification include tests for identity, purity/impurity profile, biological activity, protein content (UV), safety (bioburden, endotoxins) and physicochemical parameters (appearance (colour, clarity and visible particles) and pH of solution). All methods used to release bulk PA2024 for in-process, final release, or

stability specifications are either compendial or have been validated in accordance with ICH Q2A. The batch analyses shows consistent PA2024 quality with respect to the parameters tested.

Real time, long term stability data was provided and justified the shelf life for the bulk PA2024 when stored at the specified storage condition.

During the evaluation procedure it has been observed that the currently established stability acceptance criteria for the product related substance should be tightened to reflect the maximum observed value during stability studies for bulk PA2024 and vialed PA2024. It is therefore recommended to reassess the acceptance criteria for the product-related substance once end-to end cumulative stability study is concluded.

There is no further modification of bulk PA2024 to produce vialed PA2024. The vialed PA2024 formulation is identical to that of bulk PA2024. The name and address of the manufacturer of PA2024 vials were provided.

The vialed PA2024 manufacturing process consists of thawing and pooling the bulk PA2024, followed by sterilization by means of filtration before aseptic filling. The filtered bulk is stored into a receiving vessel prior to filling. After filling, a 100% visual inspection is performed, prior to labelling and packaging. No reprocessing is claimed. The manufacturing process and associated process controls have been described. The in-process controls are considered sufficient.

The validation of the vialed PA2024 manufacturing process is based on the analysis of multiple batches manufactured in 2010. The validation studies included the control of in-process controls, as well as operation parameters. The results met the acceptance criteria. The results at release comply with the established specification and demonstrated the consistency of the purity/impurity profile at the beginning, middle and end of the process.

The vialed PA2024 specifications (release and shelf-life) mainly derive from the specifications established for bulk PA2024. It includes: appearance, pH, identity, concentration, purity/impurity profile, biological activity and endotoxins. Additional testing for volume in container (only at release), sub-visible particulate, sterility and container closure integrity (at shelf-life).

Analytical methods for testing bulk and vialed PA2024 were performed identically, except for small differences in instrumentation and materials at their respective testing site. Test method differences were summarised and considered acceptable.

Real time, long term stability data were provided and support the vialed PA2024 shelf life when stored at the specified storage condition.

Control of critical steps and intermediates

Critical and non-critical process operating parameters and in-process controls are defined. Controls are considered appropriate to yield product with consistent quality.

Provenge manufacturing process has no isolated intermediates. All in-process testing is performed concurrently with subsequent manufacturing steps. Post-concentration/separation process fractions and Culture Pool however, have been identified as critical intermediates for which specifications have been established in order to ensure that the process is appropriately controlled.

Process Validation

Process validation studies at the manufacturing site (PharmaCell) were conducted using apheresis components obtained from healthy donors. These validation lots are included in the lots manufactured by PharmaCell for comparability purposes. All in-process and final product acceptance criteria were met.

The applicant has demonstrated through appropriate studies that healthy donor APH is a suitable model for prostate cancer patient APH and can be used to validate the manufacturing process for Provenge. Aseptic process validation and shipping validation were performed successfully. For further details see the discussion on the third major objection.

Manufacturing process development

The manufacturing process was designed to obtain an enriched population of APCs from peripheral blood mononuclear cells to present PAP antigen, without purifying DCs. The process underwent several changes between 2002 and 2006, during the phase 3 studies, most of these changes occurred in 2006, during the pivotal study D9902B. Data from stability, comparability, and functional performance studies showed that the process changes had no observable impact on final product quality.

Characterisation

Cellular composition

The cell composition of Provenge closely reflects the Apheresis (APH) cell composition. Surface markers have been studied to analyse final product cell composition. Data from lots manufactured for clinical studies D9902B and P-11, including all treatment weeks, show that the main population is constituted by T cells, followed by APCs. In comparison, B cells and NK cells are minor components of the total nucleated cells (TNC).

Cell composition has also been profiled across the manufacturing process: at the apheresis, post-concentration/separation, process fractions and final product stages.

Functional characteristics

The biologic function of Provenge is to activate the immune system and in particular to stimulate a T cell immune response against PAP, an antigen expressed in prostate adenocarcinoma, thanks to APCs, which incorporate PA2024 and are activated, becoming antigen-loaded APCs capable of presenting PAP epitopes to T cells upon reinfusion. Therefore APC activation, antigen uptake, and processing are essential for the critical functional attributes of Provenge and these functions have been evaluated as part of the product characterization. In addition, because the product contains a variety of mononuclear cell types, Provenge was further characterized to determine which cell populations contribute to the functional activity of the product. In addition to studies performed using APH obtained from healthy donors, selected experiments were repeated using cells obtained from clinical trial subjects.

APC Activation during Ex vivo Culture

Effective T cell stimulation by APCs involves 1) increased expression of antigen presentation, costimulatory, and adhesion molecules, 2) antigen uptake and processing, to present antigen-

derived peptides in the context of surface major histocompatibility complex (MHC) molecules, and 3) changes in the ability to produce cytokines.

Up-regulation of immune activation molecules such as CD54 after *ex vivo* culture with PA2024 has been analysed. The CD54 marker is of special interest since CD54 upregulation during Provenge manufacture in association with the large CD54+ cell number was selected as a surrogate potency marker. The data presented suggested that monocytes, the main CD54 expression cell population in Provenge, mature during cell culture towards APCs.

Experiments of PA2024 uptake show a good correlation between CD54 expression and PA2024 uptake, and demonstrate that PA2024 is taken up by monocytes and blood derived dendritic cells.

Lymphocyte proliferation assays demonstrate an increased T cell stimulatory activity in final product compared to post-concentration/separation process fractions, and antigen presentation assays show that cells which have taken up PA2024 can process and present the antigen.

Experiments performed to assess the role of GM-CSF show that the GM-CSF moiety of PA2024 is involved in maintenance of cell viability, in CD54 upregulation and in T cell stimulatory activity.

Comparison of cytokines profiles induced by GM-CSF or PA2024 during *ex vivo* culture shows greater amounts of APC and T cell-associated cytokines detected after culture with PA2024. Measurement of T cell activation markers, at the different treatment weeks, show an increased expression of some markers at week 2 following incubation with PA2024.

Overall, these studies show that, during *ex vivo* culture, cells upregulate molecules associated with antigen presentation, costimulatory activity, and cell-cell adhesion; take up, process and present PA2024; acquire the ability to secrete key cytokines; and become activated PAP-presenting APCs.

Immunological activity of cell sub-population in Provenge

These studies characterize the cell populations in sipuleucel-T, along with the ability of those cell populations to process and present antigen to PAP-specific T cell hybridomas. The data presented show that $CD54^{+}$ cells are responsible for T cell stimulation and for PAP antigen presentation, with no presentation by T cells and B cells, and very low levels by NK cells. Overall, these studies demonstrate that the population of cells primarily responsible for the processing and presentation of PAP epitopes is identified by the CD54 cell surface marker. The studies show that these cells include both CD14+ APCs and dendritic cells.

Priming of T cells and immune responses

PA2024 antigen specific immune responses were detected in Provenge products (at the pre-culture step) manufactured at week 2 and week 4. Induction of a PAP-specific immune response is less evident but is shown for some patients at weeks 2 and 4. Some responses to PAP were similar in Provenge and placebo products and did not increase with treatment weeks in Provenge products. Moreover, analyses of the T cell response in peripheral blood from D9902B patients indicate a PA2024-specific T cell response after treatment with sipuleucel-T. A humoral (IgM+IgG) response is detected against both PA2024 and PAP in sipuleucel-T treated patients.

Characterisation using cells from prostate cancer patients

Selected experiments have been performed to confirm results using cells obtained from clinical trial subjects. Provenge manufactured from prostate cancer patient's cells contains APCs that are CD54+ and that take up PA2024 antigen and present it, similarly to sipuleucel-T from healthy donors.

CD54 expression as a surrogate measure of potency

The in vitro assays mimicking the biologic functions of Provenge and therefore relevant for characterizing product potency take several days to complete, so a more rapid measure for potency is required for product release testing. Furthermore, the lack of T cell activation in Week 0 cells precludes the measurement of T cell activation markers as lot release assays for all products. In place of these assays, a flow cytometry assay for CD54 expression and upregulation has been developed for lot release testing to evaluate Provenge potency.

CD54, chosen as surrogate marker of APC potency, is based on the measure of two parameters: CD54 upregulation and the number of $CD54^+$ cells.

CD54 upregulation provides a measure of APC activation. The number of $CD54^+$ cells provides a measure of APC quantity. Characterization studies have shown that CD54 expression correlates with antigen uptake and costimulatory activity.

The relationship of CD54 upregulation with functional activity was shown for healthy donor lots. Upregulation is determined by comparing the number of CD54 molecules on the surface of large CD54+ cells before and after *ex vivo* culture with PA2024. The potency result is expressed as the ratio of these values, i.e., as CD54 upregulation, instead of as activity units.

The relationship of CD54+ cell number with functional activity in vitro has been shown using the PAP-specific antigen presentation assay for healthy donors. These results show that PAP-specific antigen presentation activity increases as the number of CD54+ cells increases. The relationship of the number of CD54+ cells with in vitro functional activity has also been shown in cells from prostate cancer patients using the lymphocyte proliferation assay.

In addition, the statistical analysis of patient overall survival (OS) and potency parameters has shown a correlation between survival and CD54 expression. However, because the correlation between OS and cumulative upregulation is not as strong as the one between OS and cumulative CD54+ cell count, and in order to further address the relevance of the potency specification based on the lots manufactured at the Pharmacell site and therefore to address the potential risk of having sub-potent lots, the MAH will revise the CD54 upregulation acceptance criterion, based on data from patient batches manufactured in Europe, when sufficient data will be available. Quality and clinical data obtained from patient batches should be considered to justify the potency specification. This issue is addressed as part of the RMP. (For further details on the MO on potency see also the discussion section).

Impurities

Non-viable cells, RBCs, platelets and granulocytes are considered as product-related impurities. The residual amount of RBCs and granulocytes is not considered to bear a special risk for the recipients. The issue raised on activated platelets has been solved and this aspect is discussed later in the report. Amounts were compared with cell counts during routine transfusion.

Process-related impurities consisting of PA2024, concentration/separation process solutions and cell culture medium are reduced to low levels by the manufacturing process.

Comparability

The applicant transferred the US manufacturing process to PharmaCell in Europe. To assess comparability between the commercial manufacturing process and the manufacturing process used in phase 3 clinical trials, the applicant followed a similar approach to the one originally employed for comparing various US sites. This approach was based on statistical equivalence testing between lots from phase 3 clinical studies and lots manufactured at PharmaCell. All in-process and final product test results met the established acceptance criteria.

In response to a major objection on comparability raised during the procedure, the applicant has provided additional data to satisfactorily resolve the objection. However, in order to further optimise the antigen presentation assay and to ensure that it is suitable for its intended purpose in the comparability exercise the applicant is recommended to implement acceptance criteria for viability of hybridoma and reference standard and to improve selection of the reference standard in order to decrease variability of the reference standard.

2.2.3. Finished Medicinal Product

The finished product is a cell dispersion for infusion containing a minimum of 50 million autologous CD54+ cells activated with PAP-GM-CSF and it is formulated with Lactated Ringer's solution in a final volume of 250 mL, and supplied in a sealed patient-specific infusion bag.

Provenge is shipped directly to the infusing provider in a cardboard shipping box with a special insulated polyurethane container and gel packs, designed to maintain the appropriate transportation and storage temperature (2 - 8°C) of Provenge until infusion.

Table 1: Provenge composition

Component	Quantity per Unit	Role of Component
Autologous mononuclear cells, including APCs loaded with recombinant prostate antigen	To contain ≥ 50 x 10^6 $CD54^+$ cells	Active
Lactated Ringer's Injection, USP	qs to 250 mL	Excipient
Infusion bag, sterile, 300 mL	One	Container/Closure

Pharmaceutical Development

Sipuleucel-T has no defined chemical properties. Instead, it has been characterized on a cellular level by flow cytometry analysis using monoclonal antibodies against different cell surface antigens, and with functional assays for antigen presentation and other immunological activities. The key cellular characteristics for sipuleucel-T are viability and potency. Potency is expressed as the number of APCs (large CD54+ cells) and the activation of these cells measured by the

increase in the cell surface expression of CD54. This increase, which is referred to as CD54 upregulation, is a surrogate measurement of the ability of the product to present antigen to T cells.

Lactated Ringer's Injection, USP, is used to formulate the final product. However, as some components of the LR do not fulfil Ph. Eur. requirements the applicant was requested to seek an alternative source of LR formulated with Ph. Eur. compliant material.

The fixed delivery volume of 250 mL ensures consistency in the duration of infusion, as well as in the packaging, cooling rate, and product temperature control within the validated range of 2-8°C.

Container closure system

Provenge container closure system consists of the immediate packaging (final product bag) and the secondary packaging, which consists of a shipment bag (leak-proof, tamper-evident polypropylene pouch), insulated polyurethane container (which protects the product from physical stresses, and cools and maintains the product within the validated temperature range of 2 to 8°C with gel packs), and the shipping package (cardboard box).

Manufacture of the product

The finished product is manufactured and released in the European Union by PharmaCell BV.

Because the manufacturing is continuous, there is no isolated active substance with separate product testing and control parameters. Final product manufacturing process is limited to final formulation of the cells in LR, and packaging in an infusion bag.

Each dose of sipuleucel-T contains all the cells that can be prepared from the patient's standard apheresis component, therefore the cell concentration is variable. The applicant has shown that there is no negative impact of cell concentration onto product quality (viability, phenotype and potency) and stability.

Product specification

The final product testing specification for sipuleucel-T consists of the following parameters: identity, viability, potency, and microbial safety (endotoxin content, microbial contamination, sterility and mycoplasma).

The specification is based on manufacturing data from Phase 3 clinical studies, characterization of the product and manufacturing process.

The identity test evaluates the presence of the PA2024 antigen in the final product but does not include the cellular component.

CD54 has been chosen as surrogate marker of APC potency, which is based on the measure of two parameters: CD54 upregulation and the number of $CD54^+$ cells. For further details on the potency assay see also characterization and the section dealing with the discussion of the major objections raised during the evaluation procedure.

Specifications for the number of non-CD54 cells (such as T, B, NK cells) have not been set. This is considered acceptable, taking into consideration that non-CD54 cells had either no or only a minimal effect on product potency. As regards to RBCs, platelets and granulocytes, it is agreed that they do not need to be included in the specification.

The analytical methods are suitable for the measurement of the proposed test parameters. The validation of analytical procedures has been described and all validation parameters studied met the predetermined acceptance criteria.

Batch analysis data were presented from lots produced for Phase 3 clinical studies conducted in the United States and Canada, the open label Phase 2 study P09-1, commercial manufacture in the US, and the process validation and comparability studies at the contract manufacturer PharmaCell. The lots from PharmaCell met all in-process and final product specifications. Safety and identity results conformed to specification except the sterility test for 5 lots for commercial Provenge.

Therefore, in order to further address the microbiological safety of Provenge and improve the overall risk profile of the product prior to its administration, the applicant has implemented routine mycoplasma testing on every lot. In addition, given the short shelf-life of the product, the applicant has been requested to investigate and implement a rapid microbial detection method as an in-process control for release of Provenge (RMP Measure).

Stability of the product

Overall the stability data provided from both the US manufacturing sites and EU site support the proposed storage conditions and shelf life. Stability data also support a shelf life of 3 hours at room temperature after the removal of the bag from its insulated container.

In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Adventitious agents

The cells used in Provenge are autologous. Only cholesterol, derived from sheep wool, human serum albumin and human transferrin are used during the *ex vivo* culture.

Patient's apheresis, cell culture medium, and PA2024 antigen are all raw materials which contain materials of biological origin. The viral safety of this product mainly relies on the quality of the starting materials, the recombinant protein PA2024 and biological products used in the production process. The microbiological safety of this product was also assessed.

The patient undergoes testing for blood borne pathogens in compliance with the requirements of annex II of EU Directive 2006/17/EC.

The cell culture medium is manufactured using three components that are of human or animal origin: human serum albumin, cholesterol, and human transferrin. The documentation provided for the cholesterol derived from sheep wool is satisfactory. Human serum albumin is medicinal product for which there is a marketing authorisation and batch release certificate. Human transferrin is in compliance Guideline on plasma-derived medicinal products

(EMA/CHMP/BWP/706271/2010). Moreover, in order to improve the viral safety of the human transferrin regarding the small non-enveloped viruses, the applicant is recommended to gamma irradiate human transferrin or to switch to a recombinant transferrin.

Regarding PA2024 fusion protein is produced in an insect ell expression system. Foetal bovine serum (FBS) is used during the Sf21 MCB 1 production. FBS was obtained from the US, prior to the EDQM certification scheme. The development of MCB 2 was done in serum- and protein-free medium. Cell /virus banks and PA2024 bulk are well characterized.

Regarding the viral clearance capacity of the process, data provided on a panel of model viruses showed that the purification process of PA2024 is efficient for removal and inactivation of viruses (however log viral reduction are lower for small non enveloped viruses). The company has provided a risk assessment relating to the presence of residual particles of baculovirus which is satisfactory. Regarding the microbiological safety, in process controls and method validation are well described and validated.

Overall TSE compliance has been satisfactorily addressed. The safety testing strategy proposed is appropriate and in compliance with the ICH Q 5A (R1).

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The following discussion focuses on the four major quality objections raised during the evaluation procedure. In addition, there were a number of other quality concerns raised. Overall, these were satisfactorily resolved by the applicant with the responses to the List of Questions (LoQ) and the two Lists of Outstanding Issues (LoOIs) as described for some above. The evaluation of the responses to some quality concerns resulted in recommendations for the further development of the product.

1. Potency assay

The first major objection was raised on the use of CD54 as surrogate marker for potency, which is based on CD54+ upregulation and number of CD54 expressing cells. It was questioned whether the acceptance criteria set by the company are relevant and also able to detect subpotent batches. In addition, also technical aspects related to the flow cytometry data in support of CD54 expression and upregulation needed to be substantiated. In their response the applicant presented Kaplan-Meier curves showing a correlation between overall survival (OS) and CD54 upregulation, therefore demonstrating that the potency assay can be considered to be robust and to correlate to clinical efficacy. The technical issues related to the flow cytometry were clarified and the remaining points were linked to the acceptance criteria proposed by the applicant for the potency assay. Therefore, in order to further address the relevance of the potency specification and to address the risk of having subpotent lots, the MAH will revise the CD54 upregulation acceptance criterion, based on data from patient batches manufactured in Europe, when sufficient data will be available. The potency specification should be based on (i) actual values for CD54 upregulation, and (ii) on the correlation of the latter data with the post approval clinical results (RMP measure).

2. Microbiological safety

The second major objection was related to the microbiological safety. Routine mycoplasma testing instead of the surveillance programme was considered to be required. With regard to the short shelf-life of the product, implementation of a rapid detection method for control of microbiological quality (refer to Pharm. Eur. monograph 5.1.6.) was considered mandatory. The applicant agreed to introduce routine mycoplasma testing. On the other hand, a rapid detection method providing results on microbial quality prior to administration of the product is not yet introduced. Final product release will be based on the interim sterility test result, applying the "negative-to-date" concept, and on the final result of the alternative method, but the applicant agreed to develop and implement an additional rapid detection method as an in-process control for microbial quality. This issue is addressed as part of the RMP.

3. Process evaluation/validation

The third major issue concerned evaluation and validation. Firstly the shelf life extension of the apheresis was questioned. In their response the applicant provided a comparison with a reference data set consisting of sipuleucel-T batches stored at established APH storage temperature range which revealed no significant differences. Secondly, it was requested to stratify validation data according to treatment week. The applicant presented comprehensive data showing that the cell type composition was similar for lots manufactured at week 0, week 2 and week 4 and therefore data do not need to be stratified for process evaluation and validation. The applicant also provided satisfactory justification to other points raised such as the choice of the number of lots presented for characterization of cell composition, and the selection of the lots, produced on the EU site, for process validation. In summary, missing information on results of process monitoring parameters was acceptable, considering that results of in-process tests, final product tests and validation limit tests comply with acceptance criteria for the validation lots, and that satisfactory results of additional process parameters have been provided.

4. Comparability between the product manufactured for the final commercial process (EU site) and the one used for phase 3 trials

In the fourth major concern the applicant was asked to show comparability between the product manufactured for the final commercial process (EU site) and the one used for phase 3 trials.

To resolve this major objection the applicant has provided additional data to demonstrate that: a) cells from healthy donors are a suitable model of prostate cancer patients for sipuleucel-T manufacturing; b) TNC and CD54+ yields are comparable between various manufacturing sites in the US versus the EU, and that data derived from healthy individuals from the US are comparable to EU healthy individual products; c) equivalence limits for TNC and %CD54+ cells parameters were sufficiently justified; d) batches manufactured at Pharmacell present antigen to PAP-specific T cell hybridoma.

Overall, the major objection related to comparability between the product manufactured for the final commercial process (EU site) and the one used for phase 3 trials was resolved. However, in order to further optimise the antigen presentation assay and to ensure that is suitable for its intended purpose in the comparability exercise the applicant is recommended to implement acceptance criteria for viability of hybridoma and FPRC used in the sipuleucel-T Antigen

Presentation Assay, and to improve selection of FPRC, in order to decrease variability between FPRC from different donors.

A safety concern raised during the evaluation procedure was related to the levels of activated platelets in Provenge, since a high amount of platelets may cause thrombotic risk in patients. Furthermore the applicant was requested to test coagulation factors and justify their levels with regards to thromboembolic risk. The range of platelet content in sipuleucel-T final product was presented for patients with thromboembolic events and shows that the platelet content in lots infused to those patients was below the platelet number in commercial platelet concentrates. These data do not suggest a correlation between sipuleucel-T final product platelet content and thromboembolic events. However, data regarding the platelet content of apheresis product and concentration/separation process fractions will be collected and monitored as part of the sipuleucel-T process monitoring program (PMP). The applicant is also requested to measure coagulation factors in a sufficient number of sipuleucel-T final product batches. This is addressed in the RMP.

In conclusion the quality outstanding major objections and other concerns raised during the evaluation procedure are considered resolved with some remaining quality issues identified for further investigation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The CAT has identified the following RMP measures necessary to address the identified quality developments issues that may have a potential impact on the safe and effective use of the medicinal product:

- In order to further address the relevance of the potency specification based on the lots manufactured at the Pharmacell site and therefore to address the potential risk of having subpotent lots, the MAH will review the CD54 upregulation acceptance criterion, based on quality and clinical data from patient batches manufactured in Europe, when sufficient data will be available.
- In order to further address the microbiological safety of Provenge and therefore improve the overall risk profile of the product prior to its administration, the MAH will develop and implement an additional rapid detection method as an in-process control for microbial quality.
- The range of platelet content in sipuleucel-T final product was presented for patients with thromboembolic events and shows that the platelet content in lots infused to those patients was below the platelet number in commercial platelet concentrates. These data do not suggest a correlation between sipuleucel-T final product platelet content and thromboembolic events. Furthermore, data regarding the platelet content of apheresis product and concentration/separation process fractions will be collected and monitored as part of the sipuleucel-T process monitoring program (PMP). The applicant is requested to measure coagulation factors in a sufficient number of sipuleucel-T final product batches.

The CHMP endorse the CAT assessment regarding the conclusions on the chemical, pharmaceutical and biological aspects as described above.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CAT recommends the following points for investigation:

- To gamma irradiate human transferrin or to switch to a recombinant transferrin, to improve the viral safety.
- To reassess the proposed acceptance criteria for the product related substance (soluble aggregates, disulphide stabilised dimer) once the end-to-end cumulative stability study is ended.
- To implement acceptance criteria for viability of hybridoma and Final Product Reference Control (FPRC) used in the sipuleucel-T Antigen Presentation Assay, and to improve selection of FPRC, in order to decrease variability between FPRC.

The CHMP endorse the CAT assessment regarding the recommendations for future quality development as described above.

2.3. Non-clinical aspects

2.3.1. Introduction

Provenge (sipuleucel-T) consists of autologous peripheral blood mononuclear cells (PBMCs), including antigen presenting cells (APCs) that have been activated *ex vivo* with a recombinant fusion protein, PA2024, composed of prostatic acid phosphatase (PAP) and granulocyte-macrophage colony-stimulating factor (GM-CSF). The aim of sipuleucel-T is to break immunological tolerance towards PAP, a self-antigen which is primarily expressed in prostate epithelial cells and prostate cancer cells and to induce an immune response that translates into clinical efficacy.

The non-clinical data includes studies investigating the pharmacological properties of sipuleucel-T, rodent surrogate products and human or rodent PAP protein. The pharmacological studies address the induction of prostate-specific inflammation, immunogenicity of PAP-proteins, the generation of PAP-specific and HLA-DR1-restricted T cell hybridomas, an *in vivo* efficacy model, the induction of immune responses to PAP autologous protein, and PAP expression in human tissues. Safety aspects such as induction of autoimmunity have also been included in these studies.

Animal models using species-specific variations of the human cell therapy product have been used. The equivalent of sipuleucel-T has been prepared from rat APCs loaded with PAP•GM-CSF fusion proteins composed of rat or human PAP (rPAP and hPAP, respectively) fused to the rat or murine GM-CSF homologues (rPAP•rGM–CSF and hPAP•mGM-CSF, respectively). The immunogenicity and anti-tumour properties of these surrogate products were evaluated in rats and mice.

Further pharmacological studies comprised analyses of PAP protein and messenger RNA (mRNA) expression in both normal and malignant human tissues, establishment of T cell hybridomas able

to detect presentation of PAP epitopes, ability of rat APCs loaded with rPAP•rGM-CSF fusion protein to stimulate prostate specific inflammation, and the ability of antigen loaded APCs to protect against tumour challenge in mice.

Conventional pharmacokinetic and toxicity studies including reproductive toxicity, mutagenicity, and carcinogenicity have not been submitted by the applicant.

All pharmacological experiments were proof of concept studies that were non-GLP compliant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Table 2: Overview of primary pharmacodynamic studies

Type of Study	Study Number	Objectives	Species / Strain	Product(s) examined	Method of Administration
Proof of concept	TR 30511	Assess rat immune responses to recombinant PAP derived from human or from rat	Rat /Copenhagen or Wistar	hPAP: 200 µg or 7.5 µg rPAP: 200 µg or 10 µg rPAP + hPAP: 100 µg each Ovalbumin: 200 µg or 20 µg hPAP•mGM-CSF: unknown rPAP•rGM-CSF: crude cell lysate	Subcutaneous Footpad Intraperitoneal
Proof of concept	TR 30508	Determine if fusion of hPAP to mGM-CSF would enhance immune responses to hPAP	Mouse / DBA/2	hPAP•mGM–CSF: 220 µg or 50 µg hPAP: 40 µg or 50 µg	Intraperitoneal Intravenous
Proof of concept and characterisation	TR 30509	Establish PAP specific, HLA-DR1 restricted murine T cell hybridomas and determine the PAP epitopes to which they respond	Mouse / C57Bl/6, B10.M/J [TG]Dr1N3	hPAP•hGM-CSF: 20 µg	Subcutaneous
Proof of concept and Immunopathology	TR 30507	Define conditions under which immunity results in prostate specific inflammation Determine degree to which inflammation is restricted to the prostate	Rats / Copenhagen or Wistar	hPAP: 7.5 µg rPAP: 10 µg rPAP•rGM-CSF: 200 µg Ovalbumin: 20 µg or 200 µg rPAP•rGM-CSF loaded spleen derived APCs: various Ovalbumin loaded spleen derived APCs: various	Intraperitoneal Subcutaneous Intravenous
Proof of concept	TR 30510	Determine whether immunizations with hPAP•hGM-CSF loaded APCs protect against challenge with PAP expressing tumor	C57Bl/6 Mouse	hPAP•hGM-CSF loaded spleen derived mouse APCs 2.5×10^5 cells/mouse	Intraperitoneal

Induction of prostate-specific inflammation (study TR30507)

Study TR30507 was performed to study the induction of prostate-specific immunity in rats. Various modes of PAP-based immunisation and boosting were explored in rats to evaluate immunogenicity and to test the specificity of the response. Normal male Copenhagen or Wistar rats were immunised and boosted with derivatives of PAP (including hPAP, rPAP, rPAP•rGM-CSF, and hPAP•mGM-CSF) administered either alone or as part of a cellular vaccines consisting in either dendritic cells obtained from syngeneic antigen-naïve rat spleens (spDCs) or cultured spleen cells (Cx-Sp-cells) pulsed with rPAP•rGM-CSF. Three series of experiments were performed: Series #1, protein prime (day 0) and protein boost (day 7 and 21); Series #2, cellular prime (day 0) and cellular boost (day 14 and 28); Series #3: cellular prime (day 0) and protein or cellular boosts (day 7 and 14). Two weeks after the conclusion of the immunisations the rats were euthanized and their prostates were examined histologically. In series #2 and #3, arrays of vital organs were also analysed histologically to determine potential cross-reactive autoimmunity.

Series #1: protein prime and protein boost

Five groups of 4 Wistar rats were included in series #1. All rats received 7.5 µg hPAP+10 µg rPAP/CFA (SC) at day 0 except in the control group (group 1) where 20 µg Ova/CFA (SC) was administered. At day 7 and 21, the four groups received respectively Ova/IFA (fp) (group 1), hPAP/IFA (fp) (group 2), rPAP/IFA (fp) (group 3), hPAP•mGM-CSF (IP) (group 4), rPAP•rGM-CSF (IP) (group 5). Histopathological examinations were made on day 35, 2 rats per group were sacrificed for *ex vivo* T cell proliferation and antibody assays. The remaining 2 rats per group (10 in total) were submitted for sacrifice, necropsy, prostate collection, processing, and hematoxylin and eosin staining. There were no significant histopathological changes in the prostate of animals in the control group and animals immunised with hPAP/rPAP in CFA/IFA only (groups 2 and 3). In rats boosted with GM-CSF-fusion proteins there was induction of mild prostate inflammation. One out of 2 animals boosted with hPAP•mGM-CSF (group 4) developed a grade 1 (minimal) multifocal lymphocytic interstitial inflammation of the prostate. Two out of 2 animals that received 2 boosts with rPAP•rGM-CSF (group 5) developed a grade 1 multifocal lymphocytic interstitial inflammation of the prostate.

Series #2: Cellular prime and cellular boost

Copenhagen male rats, 10 weeks old, were immunised with three separate intravenous (IV) infusions of enriched dendritic cells from syngeneic antigen-naïve rat spleens (spDC) that were pulsed overnight with rPAP•rGM-CSF fusion protein. Cellular immunisations took place on days 0, 14, and 28. Unimmunised syngeneic rats (age- and sex-matched) were used as controls. For the primary immunisation, the enriched splenic dendritic cells suspended in PBS (2.5 mL) were injected IV at 0.5 mL/rat (1.56×10^7 cells/rat). 9.5×10^6 cells per rat were used for the second injection, and 6.2×10^6 cells per rat were used for the third injection. On day 42, 4 rats from the control (unimmunised) and 4 rats from the treated (spDC + rPAP•rGM-CSF) groups were submitted for sacrifice, necropsies, tissue collection and processing. Collected tissues from each rat included brain, lung, heart, liver, kidney, colon, and prostate (dorsal and ventral lobes). Prostatitis was observed in all treated animals. Severity was graded as minimal, mild, and moderate in 1/4, 2/4 and 1/4 animals, respectively. The prostatic lesions consisted of a mixed inflammatory infiltration composed of plasma cells, mononuclear cells, lymphocytes, and fewer

neutrophils within the interstitium of the prostate. In the most heavily affected rat, there was some perivascular accumulation of plasma cells, mononuclear cells and lymphocytes, while the neutrophils were scattered throughout the interstitium. Neutrophils and lymphocytes in some areas were marginated in small interstitial vessels. There was some extension of the inflammatory cells into the periprostatic adventitia. In the other 3 treated rats, the inflammation was milder, and consisted of a scattered admix of plasma cells, lymphocytes, mononuclear cells and neutrophils rather than small foci; additionally, there was not a significant perivascular component.

Series #3: Cellular prime and protein or cellular boosts

Eighteen naive Copenhagen male rats, 10 weeks old, were divided into 6 groups of 3 rats each. Half (9) of these rats received primary immunisations of rPAP•rGMCSF-pulsed cultured spleen cells IV (rPAP•rGM-CSF-Cx-sp-cells), followed by boosting with further cellular immunisations, or with fusion protein rPAP•rGM-CSF alone administered either IV or SC. Control rats (9) were immunised with Ova-pulsed cultured spleen cells IV (Ova-Cx-sp-cells) and received a booster immunisation with either Ova alone (IV or SC) or Ova-cellular boosts at day 7 and 14. All animals were surveyed for induction of prostatitis as well as histological changes in a broader array of other tissues. Prostate pathology in control animals (Ova/spleen cell-immunized or saline injected), never exceeded grade 1 inflammation. Cellular immunisation with rPAP•rGM-CSF-loaded spleen cells (x 3), led to prostatitis in 1/3 rats. Single rPAP•rGM-CSF-cellular immunization followed by protein boosting IV led to consistent prostatitis induction with 3/3 rats developing grade 2 or higher inflammation. Single cellular immunization followed by SC boosting led to 2/3 rats developing grade 3 prostatitis. The rPAP•rGM-CSF immunized groups and saline immunized controls rats were also surveyed for histopathological changes in other tissues (brain, lung, heart, thymus, liver, spleen, kidney, epididymis, testes). No treatment-correlated significant pathology in organs other than prostate was observed in any animal. Trace inflammation in the epididymis was observed in 3 of 3 saline treated animals and mild inflammation was noted in 4 of 9 rPAP•rGM-CSF immunized animals. This interstitial inflammation was composed of neutrophils and a few eosinophils. There were no significant findings in the brain, heart, liver, spleen, kidneys, or testes. Hemorrhage in the lungs was most likely the result of the euthanasia procedure. The minimal thymic inflammation observed in 3 treated animals may be background lesions or may possibly be treatment-related.

Immunogenicity of hPAP•mGM-CSF fusion proteins (study TR30508)

Study TR30508 was conducted to address whether the mGM-CSF moiety of the hPAP•mGM-CSF antigen would affect the immunogenicity of hPAP in mice. Because the use of adjuvants such as CFA is not appropriate in humans, fusion of hPAP to murine GM-CSF is evaluated as a potential mechanism for targeting PAP to APCs as well as augmentation of APC development, survival and activation. DBA/2 mice, 8-10 weeks old, were immunised using different treatment regimens according to the type of immune response investigated. In series #1 studying antibody responses, animals were immunised twice with the same dose of protein (hPAP (IP) 40 µg; hPAP/CFA (IP) 40 µg; hPAP•mGM-CSF (IP) 220 µg; hPAP•mGM-CSF (IV) 220 µg) on Days 0 and 20. They were assessed for anti-hPAP or anti-BSA humoral responses on days 12, 20 and 25 by ELISA. In series #2 studying proliferative responses, animals were immunised 3 times with the same amount of protein (hPAP/CFA (IP) 50 µg; hPAP•mGM-CSF (IP) 50 µg) on days 0, 14, and 20. On day 54, spleens were removed and splenocytes were cultured. Proliferative response to

anti-hPAP was assessed by incubating cells (10^6, 5.10^6, $2.5.10^5$, $1.25.10^5$ splenocytes/well) with hPAP for 4 days, and then measuring the incorporation of 3H-thymidine added for a further 24 hour period to the cultures.

Anti-hPAP specific antibody titers were either not detectable or extremely low 12 days after the first immunization for all immunization regimens. However when anti-hPAP titers were assessed 20 days after the first immunization, the animal immunized IP with hPAP•mGM-CSF had titers as great as those of the animals immunized with either hPAP or hPAP formulated in CFA. The animal immunized IV with hPAP•mGM-CSF had the lowest reported anti-hPAP-specific titers. After boosting, the animal that received hPAP•mGM-CSF IP had greater anti-hPAP specific antibody responses than animals that received hPAP alone or hPAP formulated in CFA. Sera from the animal immunized IV with hPAP•mGM-CSF was not assayed for anti-hPAP antibodies at this time-point. Proliferative responses were higher in the hPAP/CFA immunized animal than the animal immunized with hPAP•mGM-CSF IP.

Generation of PAP-specific, HLA-DR1-restricted hybridomas (study TR30509)

The objective of study TR30509 was to demonstrate that PAP can be taken up, processed and presented to a T-cell hybridoma in the context of a human HLA-DRβ101 molecule. B10.M/J [TG] Dr1N3 transgenic mice (expressing human HLA-DRβ101) were immunised subcutaneously (SC) at the base of the tail with 20 µg of PA2024 in Complete Freund's Adjuvant (CFA). One week later, mice were sacrificed and the inguinal and para-aortic lymph nodes were harvested. Lymph node cells were cultured with 20 µg/mL PA2024. Recombinant human IL-2 (10 µg/mL) was added to the cultures after 3 days. After a further 3 days of culture, cells were harvested and fused to the TCR negative BW5147 fusion partner. Fused cells were plated out in 96-well plates. Growth positive wells were screened for antigen specificity. The hybridomas generated were then assayed for: antigen specificity and HLA-DR1 restriction; ability to respond to antigen presented by HLA-DR1+ APCs; peptide specificity mapped by measuring IL-2 production in response to culture with an HLA-DR1+ murine B cell line pulsed with a panel of 94 overlapping peptides spanning the hPAP sequence. Two different T-cell hybridoma clones with specificity for PAP and presented in the context of HLA-DR1 were identified: Papillon and Paperino. All the APCs tested presented antigen in a dose dependent manner. Sequences of PAP epitopes recognized by each hybridoma could be determined and comparison to the corresponding murine PAP sequence showed a single amino acid difference for the specific Paperino epitope, and less than 50% homology for the Papillon specific epitope.

Impairment of tumour growth by pre-immunization with hPAP•hGM-CSF pulsed antigen presenting cells (study TR30510)

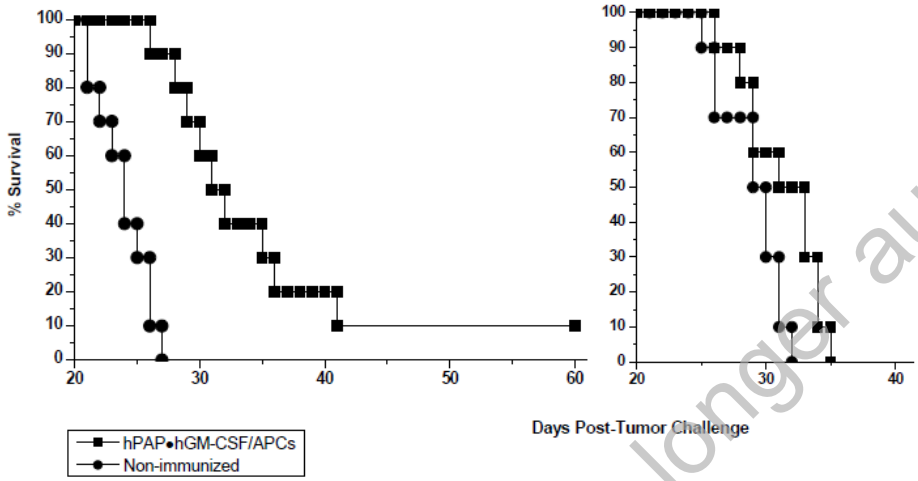
Study TR30510 aimed at studying *in vivo* the anti-tumour immunological activity of hPAP•hGM-CSF fusion protein loaded APCs. A mouse model was developed where normal immunocompetent mice were immunised with hPAP•hGM-CSF pulsed APCs, then challenged with tumours expressing human PAP. The cDNAs encoding full length hPAP or human HER2/neu were transfected into the tumorigenic mouse lymphoma cell line EL-4 to generate the EL4-hPAP and EL4-hHER2 tumour cell lines. These cells were then used in tumour challenge studies after immunization with hPAP•hGM-CSF pulsed APCs. C57BL/6 mice (10/group) were immunized IP three times, once every other week, with $2.5.10^5$ hPAP•hGM-CSF loaded splenocytes-derived APCs. The mice were rested for 2 weeks and then challenged IP with 10^5 EL4-hPAP or EL4-hHER2

cells. Their survival was evaluated for up to 60 days after tumour challenge. Non-immunised animals served as controls. Immunization with hPAP•hGM-CSF loaded APCs did not cause obvious untoward effect. Following EL4-hPAP tumour challenge, immunized mice survived longer than control non-immunized mice. In contrast, survival time of control non-immunized and immunized mice challenged with EL4-hHER2 cells was similar (Figure 1).

Figure 1: Survival after tumour challenge of mice pre-immunized with hPAP•hGM-CSF loaded APCs

A – challenge with EL4-hPAP cells

B – challenge with EL4-hHER2 cells



Induction of immune response to autologous protein with PAP-based immunization (study TR30511)

Study TR30511 was performed to assess rat immune responses to recombinant PAP derived from human or from rat. Rats were immunised with either rPAP or hPAP or both together and antibody and proliferative T-cell responses were measured. Three experiments were done utilising male Copenhagen or Wistar rats. The goal was to determine whether immunity specific to recombinant rPAP could be elicited to a similar extent as with recombinant hPAP, which is a xenoantigen for rats. In all experiments, rats (2 to 4 per group) were primed by immunising subcutaneously (SC) at the base of the tail with antigen immersed at 50% final concentration in Complete Freund's Adjuvant (CFA). Rats were boosted on day 8 and day 22 with antigen immersed in Incomplete Freund's Adjuvant (IFA) in the footpads (fp), or in some cases, with antigen alone intraperitoneally (IP). At day 32, or later, rats were sacrificed, serum was harvested for antibody titers determined by ELISA, and spleen or draining lymph node cells were analyzed for immune responses by T cell proliferation assays (^{3}H-thymidine incorporation).

Sera from rats immunised with chicken ovalbumin (Ova) showed essentially no reactivity against different PAP species, but showed good reactivity against Ova protein. Immunisation with rPAP, hPAP, or the combination resulted in high levels of IgG antibodies directed against rPAP. Cross-reactivity to rPAP detected in sera from animals immunised with hPAP was attributed to the high degree of sequence conservation between rPAP and hPAP mature proteins. Sera from rats immunised with rPAP, hPAP, or the combination reacted with baculovirus-derived hPAP. When testing the reaction against native human PAP, the highest antibody titers were obtained with the administration of antigens that included baculovirus-derived hPAP. In terms of cellular response,

lymph Node Cells (LNC) from rats immunized with Ova proliferated in response to Ova, but not to PAP proteins. LNC from rats immunized with rPAP proliferated dose-dependently in response to rPAP. Response to baculovirus-derived hPAP was seen in some rats, but was more variable between experiments. LNC from rats immunized with hPAP proliferated in response to both rPAP and hPAP. Response to native human PAP obtained from two sources was also observed.

Secondary pharmacodynamic studies

Comparative expression of PAP in normal vs. malignant tissues (study TR30548)

The aim of study TR30548 was to define which tissues in addition to prostate express PAP to better evaluate and predict cross-reactivity and potential therapeutic expansion. Immunohistochemistry (IHC) study of human tissue samples, quantitative polymerase chain reaction (qPCR) study of an array of human tissue RNA samples, and *in silico* analysis of PAP mRNA distribution in human tissues) were performed.

- IHC study of human tissue samples

IHC was performed on a set of human malignant and corresponding normal tissues using two different anti-PAP antibodies: a mouse monoclonal antibody (mAb) and a rabbit polyclonal antibody (pAb). In a first phase, it was demonstrated that staining was limited to prostate tissue (normal and malignant) at low antibody concentrations. In addition, pre-incubation of antibodies with PA2024 completely eliminated staining thus showing specificity of the antibodies. In a second phase, a limited number of malignant and corresponding normal tissues were used (n= 10 and 2/tissue, respectively). The results showed: nearly identical staining between both antibodies in all tissue samples; prominent staining in prostate tissue samples, either malignant or normal; weak staining, relative to prostate, in 2-3/10 ovarian, lung and colon carcinoma samples; staining in a subset of pancreatic islet cells, colonic neuroendocrine cells, and skin (squamous epithelium and adnexal structures).

- PAP mRNA expression in human tissue samples

PAP mRNA expression level was quantified by means of qPCR in a set of 11 tumour and corresponding normal human tissues. In normal and tumour tissues, PAP mRNA expression levels were maximal in the prostate samples. PAP mRNA expression level in prostate tumour sample was 2.4-fold that found in normal prostate sample. In non-prostate tissues, the highest PAP mRNA levels were reached in normal bladder and malignant cervix; they reached approximately 2% of PAP mRNA expression level in normal prostate. PAP mRNA expression levels in other tissue samples, either normal or malignant, remained below 0.56% of PAP mRNA expression level in normal prostate (normal kidney).

Table 3: Relative values of PAP mRNA expression and % of normal prostate expression

Tissue	Normal tissue		Tumor tissue	
	mRNA expression value	% of normal prostate	mRNA expression value	% of normal prostate
Breast	4	0.07	7	0.13
Bladder	115	2.08	12	0.22
Cervix	12	0.22	116	2.09
Colon	4	0.07	6	0.11
Kidney	31	0.56	11	0.19
Liver	1	0.02	2	0.04
Lung	8	0.14	24	0.43
Ovary	8	0.14	22	0.39
Pancreas	16	0.28	5	0.09
Prostate	5525	100.00	13264	240.07
Testes	12	0.22	11	0.19

Note: Tissue with the lowest PAP mRNA level is set to a value of 1, in this case normal liver, and all other values are indexed to this level

- *In silico* analysis of PAP mRNA distribution in human tissues

The National Cancer Institute's Cancer Genome Anatomy Project (CGAP) was utilised for Expressed Sequence Tag (EST) and Serial Analysis of Gene Expression (SAGE) virtual northern analysis of PAP expression in several tissues. The PAP gene was found in cDNA librairies from several normal and/or malignant tissue types. EST data suggested a hierarchical tissue distribution of PAP mRNA expression: prostate > prostate cancer >> mammary gland cancer > normal salivary gland > normal ovary > normal pancreatic islet cells > colon cancer > normal skin (Table 4).

Table 4: PAP-specific EST transcripts per 200,000

	Normal		Cancer	
Tissues	ESTs / 200,000	% of normal prostate	ESTs / 200,000	% of normal prostate
all tissues	22.2	2.9	19.5	2.5
Colon	0		5.7	0.7
mammary gland	0		69.4	9.1
Muscle	53.3	7.0	0	
Ovary	16.7	2.2	0	
Pancreas	0		0	
pancreatic islet	11.8	1.5	0	
Prostate	765.9	100.0	489.7	63.9
salivary gland	77.6	10.1	0	
Skin	3.7	0.5	0	

Safety pharmacology programme

The general battery of safety pharmacology studies as outlined in the International Conference of Harmonization (ICH) guidelines were not submitted by the applicant. Non-clinical safety data were collected as part of the pharmacodynamic studies (see section on primary pharmacodynamic studies), particularly in study TR30507 which was conducted in rats to assess

the induction of prostate specific inflammation. Safety aspects were also collected in study TR30510 which was conducted in mice to assess the ability of pre-immunisation with hPAP•hGM-CSF pulsed APCs to impair tumour growth. Although all mice in the treated group showed prolonged survival, no obvious adverse effects were observed during treatment (IP once every other week for a total of 3 infusions).

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted by the applicant (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

No conventional ADME studies were submitted by the applicant (see discussion on non-clinical aspects).

2.3.4. Toxicology

The general battery of non-clinical toxicology studies were not submitted by the applicant. No genotoxicity, reproductive toxicity, mutagenicity and carcinogenicity studies were provided (see discussion on non-clinical aspects).

2.3.5. Ecotoxicity / environmental risk assessment

No Environmental Risk Assessment (ERA) was provided by the applicant (see discussion on non-clinical aspects).

2.3.6. Discussion on non-clinical aspects

Prostatitis experiments were performed in rats to demonstrate the induction of prostate-specific immunity. Normal male rats were immunised and boosted with derivatives of PAP including human PAP, rat PAP, and fusions proteins rPAP•rGM-CSF, hPAP•murineGM-CSF. Since recombinant antigens were used, these immunisations were not directly comparable to the clinical setting where antigen-loaded APC were used. In a further series of prostatitis experiments, cell-based immunization or combinations of cell-based plus rPAP•rGM-CSF fusion protein (for boosting) were applied to mimic the clinical regimen. However, splenic rat cells were loaded with PAP antigens instead of peripheral blood mononuclear cells and the manufacturing processes for the cellular products differed from the sipuleucel-T process. Optimal dose and schedule for the cells or the rPAP•rGM-CSF fusion protein was not evaluated. The ideal amount of fusion protein to be loaded onto cells was not determined, either. Anti-PAP immune responses were not measured in any of the prostatitis experiments thus it was not possible to establish a direct correlation between specific anti PAP immune responses and prostatitis.

With respect to PAP immunogenicity, two separate study reports were presented. The purpose of the first study (Report TR30508) was to assess the immunogenicity of human PAP when fused to murine GM-CSF. Humoral and cellular anti PAP responses were observed. Since mice were immunised with human PAP, however, the experiments were not suitable to demonstrate that breaking immune tolerance towards self-PAP was feasible. In the second study (report TR

30511), the humoral and cellular immune responses in rats towards rat PAP was studied. The data showed that T cell immunity directed to self-PAP in rats could be accomplished. However, the protein-based immunisation did not resemble the cell-based approach in the clinic.

Two T cell hybridomas were generated and comprehensively characterised to show that human PAP can be taken up by antigen-presenting cells, followed by presentation of PAP epitopes on human HLA molecules. The antigenic peptides recognised by the hybridomas were identified by using a panel overlapping peptides that spanned the whole PAP sequence. The hybridomas also recognised the PAP epitopes on human APC, demonstrating proof of the most important prerequisite for inducing an efficient T cell response, i.e. MHC-restricted antigen presentation to T cells.

The murine C57BL/6 EL4 T cell lymphoma expressing human PAP was selected to establish an in vivo tumour model. Mice were immunised with hPAP•hGM-CSF loaded cells derived from spleens, followed by challenge with the EL4 tumour cells. However, the model was of limited relevance since it was different from the clinical setting since a foreign (human) instead of the self-antigen was used, prophylactic instead of therapeutic vaccination was done, and lymphoma instead of prostate tumour cells were used.

The applicant was asked to substantiate whether proof-of-concept has been sufficiently demonstrated taking into account the lack of proper dose finding experiments, the differences between non-clinical study regimen and the clinical treatment regimen, and the lack of evaluation of the relationship between immune response and activity. It was agreed that the cell dose is apparently not limited by toxicity. The highest feasible dose obtained e.g. from rat spleens was used in animal proof-of-concept studies. Moreover, in the clinical setting the single dose could not be further increased (leukapheresis is already used) even if non-clinical studies would indicate that this was beneficial. Concerning the differences between the animal and the human regimen it was acknowledged that it might be difficult to replicate all aspects in a small animal model. Although at the time of performing the proof of principle studies, spleen cells were used instead of PBMCs, it was acknowledged that the ability to break tolerance towards a self-antigen was an important result. As regards the endpoints, it was agreed that often prophylactic models have to be used due to the rapid growth kinetics of e.g. mouse tumours. This prevents the establishment of an effective anti-tumour immunity ahead of fatal tumour growth. It was acknowledged that the use of appropriate (prostate) tumour models was difficult if not impossible since such models were not available at the time of performing the non-clinical studies.

Several experiments were also performed to identify which tissues in addition to prostate express PAP. Predominant expression of PAP gene and protein was found in normal and malignant prostate tissue. Expression in non-prostate tissue was also demonstrated but occurred at much lower levels, notably in pancreatic islet cells, bladder, kidney, skin, and colon. The likelihood of auto-immune reactions in non-prostatic tissues expressing PAP cannot be excluded in the clinical setting and there was no robust non-clinical data to assess the risk of auto-immune reactions in non-prostatic tissues. However, more than 2,000 patients have already been treated with Provenge and human experience is much more relevant to address the issue of potential auto-immune reactions than an additional animal study. This safety concern is also addressed in the Risk Management Plan.

Conventional safety pharmacology studies were not submitted by the applicant. Two non-GLP studies were presented as part of the primary pharmacodynamics studies done in rats to assess the induction of prostate-specific inflammation. Since sufficient clinical safety data are available from clinical trials and post-marketing experience in the USA, no dedicated non-clinical safety pharmacology studies with sipuleucel-T are deemed necessary at this stage.

Since the final product consists of activated PBMCs, no conventional ADME studies were submitted in line with the CHMP guideline on human CBMP (EMA/CHMP/410869/2006). Data on distribution and trafficking of cells would have been useful to know whether cells distribute to the prostate or non-prostate tissues expressing PAP antigen or to their draining lymph node. However, in view of the available clinical efficacy and safety data, such a study would not add relevant clinical information at this stage. Conventional toxicological studies as outlined in Annex I to Directive 2001/83/EC were also not submitted.

In line with Annex I, part IV of Directive 2001/83/EC applied to ATMP, a risk-based approach discussion was provided by the applicant to further justify the extent of non-clinical data provided in the dossier and particularly the lack of pharmacokinetic and toxicity studies. The submitted risk-based approach discussion profiled unwanted immunogenicity, treatment failure, disease transmission, and toxicity as potential risks associated with the manufacture and administration of sipuleucel-T. The risk profiling based on risk-risk factor relationships adequately justified the extent of non-clinical data based on the risks listed above. However, the approach was considered limited since it did not cover identified main risks such as acute infusion reactions and infections or potential risks such as cerebrovascular events, cardiovascular disorders, autoimmune diseases and new cancers. Nevertheless, these risks are adequately addressed in the RMP. In addition, non-clinical toxicology or pharmacokinetic studies are not expected to bring additional relevant information at this stage. Therefore, the non-clinical package was considered acceptable.

The absence of genotoxicity, mutagenicity and carcinogenicity studies was considered acceptable taking into account the nature of sipuleucel-T. No such effects are expected to be associated with Provenge. Conventional reproductive and development toxicity studies were not considered relevant given the nature and the intended clinical use of this autologous cell therapy product.

A justification for not performing an environmental risk assessment (ERA) was provided in line with guideline on the environmental risk assessment of the medicinal products for human use (EMEA/CHMP/SWP/4447/00). Provenge consists in PBMCs activated *ex vivo* with recombinant PA2024. The recombinant fusion protein (PAP2024) consists of prostatic acid phosphatase (PAP), a naturally occurring antigen expressed in both healthy human prostate and in prostate adenocarcinoma, linked to granulocyte-macrophage colony-stimulating factor (GM-CSF), a naturally occurring immune cell activator expressed by multiple human cell types. During *ex vivo* culture with PAP-GM-CSF, activated antigen presenting cells take up and process the recombinant target antigen into peptides that are then presented to T cells. The activated cells are suspended in Lactated Ringer's Injection, USP. Biohazard (i.e. human tissue or cells) liquid waste is disposed of according to standard operating procedures involving decontamination of the material with potassium hydroxide and solid waste is deactivated using an autoclave. Therefore, the applicant considered and the CAT confirmed that Provenge is not expected to pose a risk for the environmental due to the specific nature of its constituents and adequate measures

will be in place for the correct disposal. The justification for not submitting an ERA was considered acceptable by the CAT.

The CHMP endorse the CAT discussion on the non-clinical aspects as described above.

2.3.7. Conclusion on the non-clinical aspects

Although the pharmacology studies presented some deficiencies, the pharmacological data were considered sufficient to establish a proof-of-concept for treatment of patients with Provenge in the proposed indication.

Conventional safety pharmacology, pharmacokinetics, toxicology, genotoxicity, carcinogenicity, mutagenicity, and reproductive toxicity studies were not submitted. This was considered acceptable.

Since considerable clinical experience is now available on the efficacy and safety of sipuleucel-T in the proposed indication, no additional studies in animals are needed.

The CHMP endorse the CAT conclusions on the non-clinical aspects as described above.

2.4. Clinical aspects

2.4.1. Introduction

The clinical data consist of 14 clinical trials conducted in the United States and Canada. One phase 2 study (Study D9906) was conducted in Japan.

Three phase I and II pharmacology studies (ACT 9610, ACT9702 and D9801) were conducted with immunotherapy products (APC8015F and APC8026) that are similar to sipuleucel-T but not identical.

Three randomised, double-blind, "placebo-leukapheresis" controlled studies were part of the application: one pivotal study D9902B and two supportive studies D9901, and D9902A.

The applicant received CHMP scientific advice (EMEA/CHMP/SAWP/485163/2007, EMA/CHMP/SAWP/343464/2011) regarding the clinical development programme. The CHMP opinion was that Progression Free Survival (PFS) and Overall Survival (OS) were preferred as primary endpoints over Time-To-Progression (TTP) in the pivotal study, and that the timing of the imaging studies did not allow proper assessment of TTP within the first 8 weeks. It was pointed out that docetaxel with prednisone was the reference treatment in the claimed indication. It was acknowledged that the question of when to start chemotherapy was not completely solved, that docetaxel should be conservatively used, and "only in the setting when chemotherapy is truly required, i.e. usually in the case of symptomatic disease" and that there was a "window of opportunity for immunotherapy for patients with asymptomatic AIPC". With regard to the (now supportive) study D9901, the CHMP underlined that the post-hoc corrections of the results on the primary endpoint TTP were not robust, and raised concerns that the post hoc significant results on OS (unplanned statistical comparison) were unlikely to support the indication and should be interpreted with caution.

One key issue raised by the CHMP was related to the inclusion of placebo patients to receive a salvage immunotherapy at the point of objective disease progression and its potential to interfere with the assessment of the primary endpoint, overall survival. In the Scientific advice, the CHMP also requested that the applicant takes into account in their statistical analysis the change in inclusion criteria (removal of Gleason sum ≤7 as eligibility criteria) that was made part way through study D9902B.

GCP

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Table 5: Tabular overview of clinical studies

Study Phase	Protocol No	Country	Indication*	Study Status
Phase 3	D9902B	USA	mCRPC	Complete
	D9902A	USA	mCRPC	Complete
	D9901	USA	mCRPC	Complete
	P-11	USA	ADPC	Ongoing Enrolment complete
Phase 1/2	P09-1	USA	mCRPC	Ongoing Enrolment complete
	ACT9610	USA	mCRPC	Completed
	ACT9702	USA	mCRPC	Completed
	D9906	Japan	mCRPC	Completed
	D9905	USA	Non-metastatic Prostate cancer	Completed
	D9903	USA	mCRPC	Completed
	PB01	USA	mCRPC	Completed
	D9801	USA	mCRPC	Completed
	P07-1	USA	Early stage prostate cancer	Ongoing
	P07-2	USA	mCRPC	Ongoing

*mCRPC = metastatic castration resistant prostate cancer, ADPC = androgen dependent prostate cancer

2.4.2. Pharmacokinetics

Formal pharmacokinetic absorption, distribution, metabolism and excretion (ADME) studies were not submitted by the applicant.

2.4.3. Pharmacodynamics

Mechanism of action

The intended mechanism of action for sipuleucel-T is the induction of an immune response to the target antigen, PA2024. Pharmacodynamic analyses from the Phase 1 and Phase 2 clinical trials focused on the cellular and humoral immune responses to sipuleucel-T and related products at various cell doses and dosing intervals. Supportive data were obtained from subjects treated with

the proposed commercial dose in randomized, placebo-controlled phase 3 studies D9902B, D9901, and P-11.

Primary and Secondary pharmacology

Table 6: Overview of phase I and phase II clinical pharmacology studies

Study	Diagnosis of Subjects	Study Objectives	Test Product	Subjects	Duration of Treatment Doses
ACT 9610	Metastatic CRPC	• Safety • Immune response • Tumor response	Sipuleucel-T	12	Weeks 0, 4, 8, and a booster at Week 24 Phase 1: 0.2 x 10^9 cells/m^2 or 0.6 x 10^9 cells/m^2 or 1.2 x 10^9 cells/m^2 Phase 2: 1.2 x 10^9 cells/m^2
	Non-metastatic CRPC			19	
ACT 9702	Metastatic CRPC	• Safety • Immune response • Tumor response	Sipuleucel-T	13	Weeks 0 and 4 plus s.c. antigen injections at Weeks 8, 12 and 16 APC8015 dose per infusion: MMD ~1.2 x 10^9 cells/m^2
				21	Weeks 0 and 2 plus s.c. antigen injections at Weeks 4, 8 and 12 APC8015 dose per infusion: MMD ~1.2 x 10^9 cells/m^2
D9801	Metastatic CRPC	• Safety • Immune response	APC8026 [a]	15	Weeks 0, 2, 4, and 16 3 dose levels: 1 x 10^9 cells/m^2;2.5 x 10^9 cells/m^2;4 x 10^9 cells/m^2

[a] APC8026 is an autologous active cellular immunotherapy product consisting of PAP-displaying APCs prepared using a single concentration/separation step.

Study ACT 9610

This study was an open label phase I and II trial conducted in a total of 31 subjects and designed to determine the maximum tolerated dose (MTD) of sipuleucel-T in men with advanced CRPC. All subjects were assessed for the humoral and cellular responses to PA2024, PAP and GM-CSF. The maximum manufacturing dose (MMD) i.e., all cells manufactured from one leukapheresis for an individual subject, was achieved before the MTD so the MMD was used in the phase II arm of this study and for subsequent studies.

A positive T cell proliferation response was defined as a stimulation index (SI) of ≥ 5.0, ≥ 10.0, and ≥ 15.0. Stimulation index was defined as the median count per minute (CPM) at a given antigen concentration divided by the median CPM for the control. Positive antibody responses were defined as ≥ 4-, 8-, and 16-fold increases in antibody titre relative to baseline. Results are presented in Table 7 and Table 8. The kinetics of the immune response suggested that at least 2 (and likely 3) doses resulted in the maximal T cell response to the target antigen, peaking at approximately 12 weeks after the first dose.

Table 7: Summary of T cell proliferation data for all phase 1 and phase 2 subjects (N = 31)[a]

	PA2024	Human PAP	GM-CSF	Junction Peptide	Influenza
Subjects with pre-existing responses at Week 0	8/31 (26%)	4/31 (13%)	10/30 (33%)	4/12 (33%)	20/27 (74%)
Subjects with a ≥ 5-fold increase in SI following treatment	30/31 (97%)	13/31 (42%)	15/28 (54%)	17/23 (74%)	13/30 (43%)
Subjects with a ≥ 10-fold increase in SI following treatment	28/31 (90%)	8/31 (26%)	9/28 (32%)	11/23 (48%)	8/30 (27%)
Subjects with a ≥ 15-fold increase in SI following treatment	25/31 (81%)	4/31 (13%)	6/28 (21%)	8/23 (35%)	7/30 (23%)

[a] Response data was not obtained for all subjects. SI = stimulation index. Stimulation index was calculated as the median count per minute (CPM) at a given antigen concentration divided by the median CPM for the control. The data presented reflect the maximum increase in SI that occurred at any follow-up time-point, and at any in vitro antigen concentration, tested during the study.

Table 8: Summary of antibody response data for all phase 1 and phase 2 subjects (N=34)[a]

	PA2024	Human PAP	GM-CSF	KLH
Subjects with a ≥ 4-fold increase in antibody titer following treatment relative to baseline	22/30 (73%)	12/30 (40%)	18/29 (62%)	2/5 (40%)
Subjects with a ≥ 8-fold increase in antibody titer following treatment relative to baseline	22/30 (73%)	11/30 (37%)	17/29 (59%)	1/5 (20%)
Subjects with a ≥ 16-fold increase in antibody titer following treatment relative to baseline	20/30 (67%)	9/30 (30%)	14/29 (48%)	0/5 (0%)

[a] Response data were not obtained for all subjects. The cut-off value used to define a positive response post treatment for PA2024, Human PAP, and GM-CSF was a reciprocal titer of 80. A value of 10 was used for Week 0 reciprocal antibody titer values that were undetectable in order to facilitate a response definition.

Study ACT 9702

This was an open-label, phase I and II trial designed to determine the safety and immunogenicity of 2 doses of sipuleucel-T (given during Weeks 0 and 4 in Phase I and during Weeks 0 and 2 in Phase II) followed by increasing doses of PA2024 administered subcutaneously (given during Weeks 8, 12, and 16 in Phase I, and during Weeks 4, 8, and 12 in Phase II). Immunologic responses to sipuleucel-T were monitored by both cellular and humoral assays against PA2024, PAP, and GM-CSF; cellular responses to junction peptide and influenza were also monitored. The

pattern and magnitude of the immune responses were similar to those observed in Study ACT 9610 at both the cellular and humoral level and did not result in significant toxicity. The humoral and cellular immune responses were similar between the 2 cohorts, suggesting that the efficacy for the Week 0 and Week 4 sipuleucel-T dosing schedule would be comparable to that of the Week 0 and Week 2 dosing schedule. Subcutaneous PA2024 dosing following 2 doses of sipuleucel-T produced only a modest increased immune response (data not shown). Based on the lack of augmentation of the cellular immune response after PA2024 injections, a regimen without protein boosters, was chosen for phase III studies.

Study D9801

This was open-label, dose-escalation, phase I study designed to define an MTD of the related cell product APC8026 in men with CRPC. APC8026 employed the same recombinant antigen (PA2024) and PBMC starting materials as sipuleucel-T, but used a modified manufacturing method. The APC8026 final product had a higher TNC and a higher percentage of APCs than sipuleucel-T. Subjects received APC8026 in Weeks 0, 2, and 4; subjects whose disease had not progressed by Week 16 received a booster infusion of APC8026. Immune monitoring samples were obtained at Baseline and Weeks 2, 4, 8, 12, 16, 20, 24, and every 24 weeks thereafter until disease progression. Immune responses to APC8026 were monitored by both cellular and humoral assays against PA2024, PAP, GM-CSF, and the junction peptide. Fifteen subjects were enrolled and 8 subjects were evaluable for immune responses. The pattern and magnitude of the immune responses were similar to those observed in studies ACT9610 and ACT9702. The humoral and cellular immune responses were similar between studies ACT9610, ACT9702, and D9801.

Immune Response

Study D9902B

Study D9902B was a randomised, multicentre, placebo-controlled, parallel group phase 3 trial in men with symptomatic or minimally symptomatic, metastatic, androgen independent prostatic adenocarcinoma. The method and the results for immune response evaluation are presented below. Efficacy and safety results are presented in the relevant sections of this report under clinical efficacy and clinical safety, respectively.

Evaluation of the immune response focused on humoral and cellular responses specific for the immunizing antigen (PA2024). Serum and Peripheral blood mononuclear cell (PBMCs) were obtained at baseline, and at weeks 6, 14, and 26 during the regular, scheduled visits and at the 2-month post-progression follow-up (PPFU) visit for subjects who experienced objective disease progression prior to Week 26. PBMC and serum samples were cryopreserved and all samples from a single individual were evaluated in the same assay.

Humoral responses to PA2024, PAP, and GM-CSF were assessed by enzyme-linked immunosorbent assay (ELISA) in cryopreserved subject serum. The antibody titre was defined as the reciprocal of the serum dilution that yielded an optical density equivalent to assay background.

Cellular responses to PA2024 and PAP were assessed by interferon gamma (IFNγ) enzyme linked immunosorbent spot (ELISPOT) assays, as well as T cell proliferation assays incorporating tritiated-thymidine (3H-thymidine). ELISPOT data were presented as the median of triplicates

with background (PBMCs incubated with media) IFNγ spots subtracted. The degree of proliferation was expressed as a stimulation index (SI), defined as the ratio of 3H-thymidine incorporation due to antigen stimulation, compared to 3H-thymidine incorporation due to media alone.

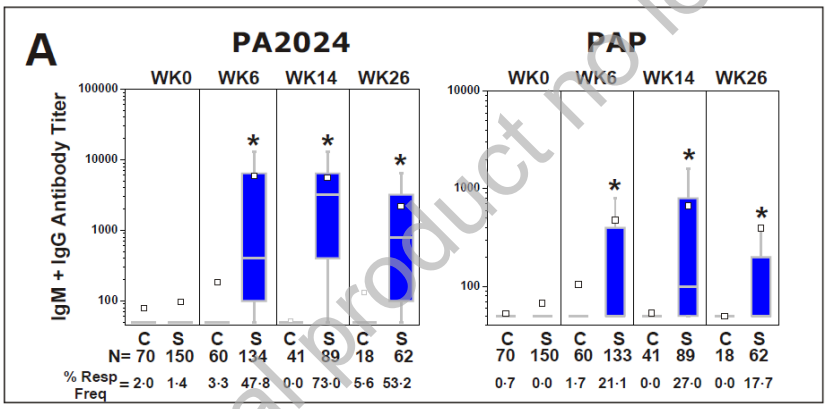
Positive responses for each assay were defined as follows:

- Proliferation: SI > 12 for PA2024, > 8 for PAP.
- IFNγ ELISPOT (per $3x10^5$ PBMC): >10 spots for PA2024, > 40 spots for PAP.
- ELISA titer: > 400 for both anti-PA2024 and anti-PAP antibodies.

Treatment induced GM-CSF neutralization was assessed by measuring the degree of inhibition of the GM-CSF-dependant cell line, TF-1. GM-CSF neutralization activity was reported as the change from baseline according to the following formula: % change in neutralization = (baseline neutralization – sample neutralization)/baseline neutralization.

A total of 237 subjects (sipuleucel-T: 160, placebo: 77) were evaluated for immune response. Only the sipuleucel-T group exhibited anti-PAP, anti-PA2024 and anti-GM-CSF-specific antibody responses post-treatment, and the responses persisted in the Provenge group, implying immunological durability, or memory.

Figure 2: Humoral Responses to PA2024 and PAP, Study D9902B

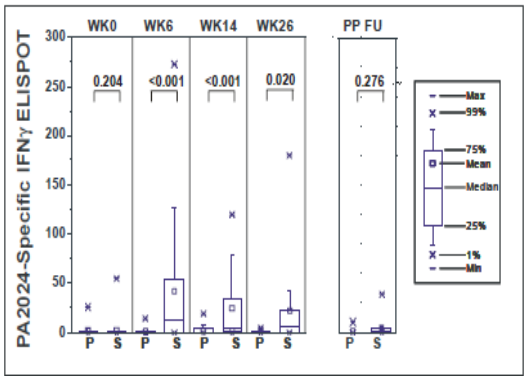


C = Placebo subjects, S= Sipuleucel-T subjects

Only Provenge treated subjects exhibited anti-PA2024 IFNY ELISPOT responses after treatment (Figure 3) and displayed appreciable PA2024-specific proliferative T cell responses post-treatment (Table 9). Their proliferative responses were greatest at Week 6 and were maintained at Week 14 and Week 26. In contrast, placebo subjects generally exhibited very low PA2024-specific proliferative responses at all timepoints.

Figure 3: PA2024-specific IFNγ ELISPOT responses and PAP-specific IFNγ ELISPOT responses in the placebo and sipuleucel-T groups

PA2024-Specific IFN γ ELISPOT Responses



PAP-Specific IFN γ ELISPOT Responses

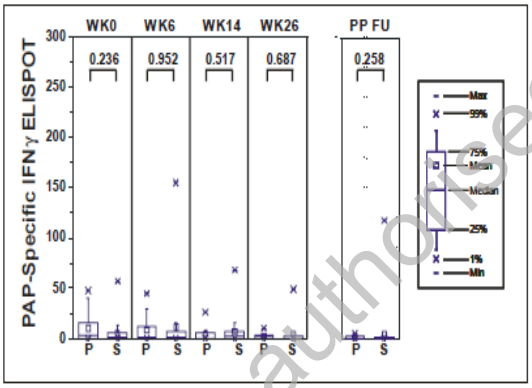


Table 9: Proliferation responses against PA2024 before (Week 0) and after (Weeks 6, 14, or 26) treatment with sipuleucel-T or placebo

Antigen	Time Point	Sipuleucel-T Proliferation Responses			Placebo Proliferation Responses			P-value*
		N	Mean SI (SE)	Min, Max	N	Mean SI (SE)	Min, Max	
PA2024	Week 0	55	7.4 (4.5)	0.2, 247.0	28	2.9 (0.9)	0.3, 21.0	0.533
	Week 6	63	121.6 (65.9)	0.4, 4160.0	33	2.3 (0.6)	0.2, 20.4	< 0.001
	Week 14	42	33.9 (7.9)	0.7, 258.7	21	1.4 (0.2)	0.1, 4.5	< 0.001
	Week 26	33	61.5 (23.4)	0.2, 681.1	8	4.4 (2.6)	0.3, 21.4	0.009

* P values are from a mixed model ANOVA of log-transformed median SI values

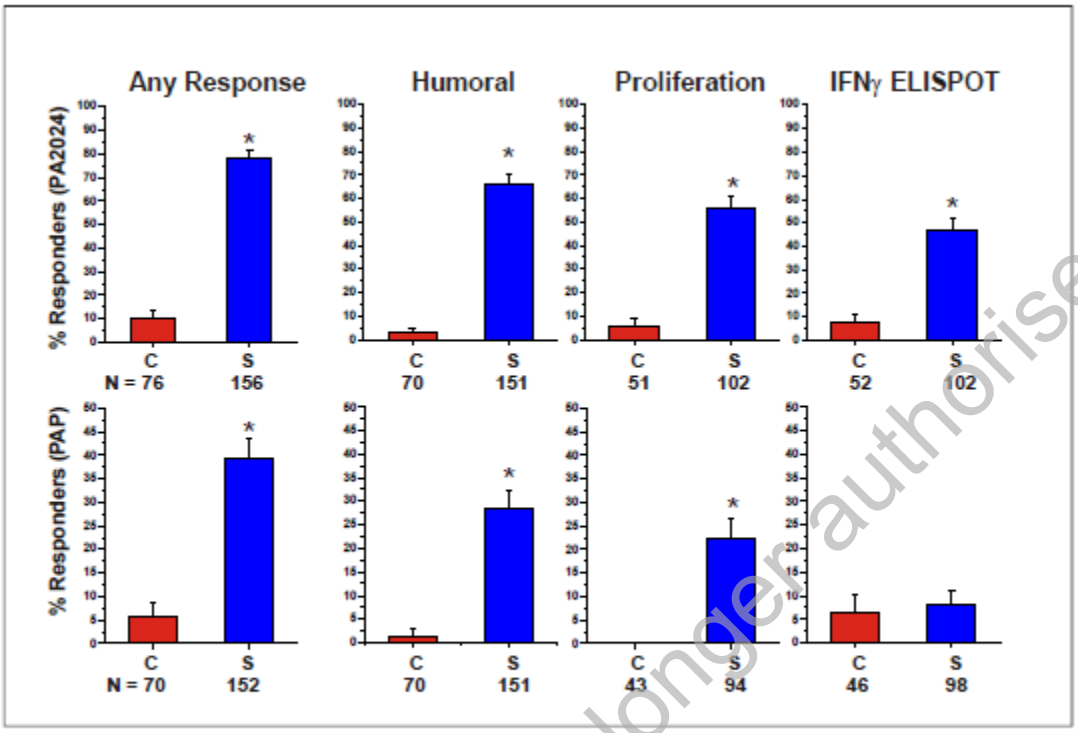
SI = stimulation index. Source: 2.7.2 Summary of Clinical Pharmacology Studies, Post-Text Table 10.0

Positive immune responses to PA2024 and/or PAP in any post-baseline immune response assay were observed in 78.8% (123/156) of sipuleucel-T subjects compared with 13.2% (10/76) of control subjects. An immune response to PA2024 was observed in 78.2% (122/156) of sipuleucel-T subjects vs. 10.5% (8/76) of control subjects. A response to PAP was observed in 39.5% (60/152) of sipuleucel-T subjects vs. 5.7% (4/70) of control subjects.

Sipuleucel-T treatment elicited PA2024- and/or PAP-specific cellular responses in a majority of subjects (60% [61/102] T cell proliferation; 48% [49/102] IFN-γ ELISPOT). This contrasted with the low rate of positive responses detected in control subjects: 6% (3/51) for T cell proliferation and 13% [7/52] for IFN-γ ELISPOT. PA2024-specific T cell proliferation and IFN-γ ELISPOT were significantly greater in the sipuleucel-T group at all post-baseline time points ($P < 0.05$), and significantly more sipuleucel-T subjects responded to each assay.

Sipuleucel-T treatment generated PA2024- and/or PAP-specific humoral responses in a majority of subjects (68%; 102/151), compared with only 3% (2/70) of control subjects.

Figure 4: Immune response rates, study D9902B



S = sipuleucel-T, C = placebo
Immune responses were determined at baseline (week 0) and weeks 6, 14, and 26 following the first product infusion in a subset of patients enrolled in IMPACT. The percent (SE) of subjects with positive responses to antigen-specific antibody (ELISA), memory IFNγ ELISPOT, and T-cell proliferation are summarized.
*P < 0.01 for sipuleucel-T versus placebo.

A total of 60 subjects (sipuleucel-T: 44, placebo: 16) were evaluated for neutralizing GM-CSF antibody responses. Fifty of these subjects were chosen randomly, and the remaining 10 subjects were chosen because they had the highest anti-GM-CSF titers among the evaluated subjects. Ten subjects in the Provenge group exhibited anti-GM-CSF antibody titers (9 subjects at Week 6, 3 subjects at Week 14 and 1 subject at Week 26) and 1 subject in the placebo group exhibited an anti-GM-CSF antibody titer (at Week 14). One subject in the Provenge group exhibited neutralizing activity at all timepoints evaluated. For the 10 subjects treated with Provenge in whom GM-CSF neutralization activity was observed, there was no obvious evidence of effect on neutrophil counts.

The relationship between overall survival (OS) and immune responses in the D9902B trial was explored by analyzing immune responses to PA2024 and PAP in any of three immune response assays (ELISA, IFN-γ ELISPOT, or T cell proliferation).

Table 10: Correlation of post-baseline PA2024- and PAP-specific immune responses by assay, study D9902B Sipuleucel-T subjects with immune response data

Assay	N[a]	Spearman Correlation (p-value)
ELISA[b]	331	0.581 (< 0.001)
ELISPOT	171	0.452 (< 0.001)
Cellular Proliferation[b]	162	0.470 (< 0.001)

Source: Day 120 Response Post-Text Table 103

[a] Sample size for each assay is the number of paired (PA2024 and PAP) results measured post-baseline. Subjects may have contributed 1, 2 or 3 paired results, depending on how many post-baseline immune response results were available for each assay.

[b] For ELISA, correlation is based upon natural logarithm of the titers; for cellular proliferation, correlation is based upon natural logarithm of the stimulation index (SI).

Table 11: Study D9902B: PA2024-specific immune responses (week 6, 14, 26) and their correlation with Overall Survival (OS)

Response		Time Point		
		Week 6	Week 14	Week 26
ELISA	N	134	89	62
	p-value	**0.079**	0.744	0.610
	HR	0.994	0.997	0.992
	(95 % CI)	(0.987, 1.001)	(0.982, 1.013)	(0.963, 1.022)
Proliferation	N	63	42	33
	p-value	0.712	**0.057**	0.874
	HR	1.055	0.569	0.959
	(95 % CI)	(0.794, 1.401)	(0.318, 1.017)	(0.569, 1.614)
ELISPOT	N	63	42	32
	p-value	0.824	0.885	**0.049**
	HR	1.004	1.004	0.867
	(95 % CI)	(0.973, 1.035)	(0.948, 1.063	(0.752, 1.000)

The presence of a positive immune response to either PA2024, PAP, or both PA2024 and PAP in at least one of the three immune response assays, were each assessed for relationship with OS in Cox regression models (Figure 5**Error! Reference source not found.**, Table 12).

Figure 5: Correlation between OS and immune responses, study D9902B

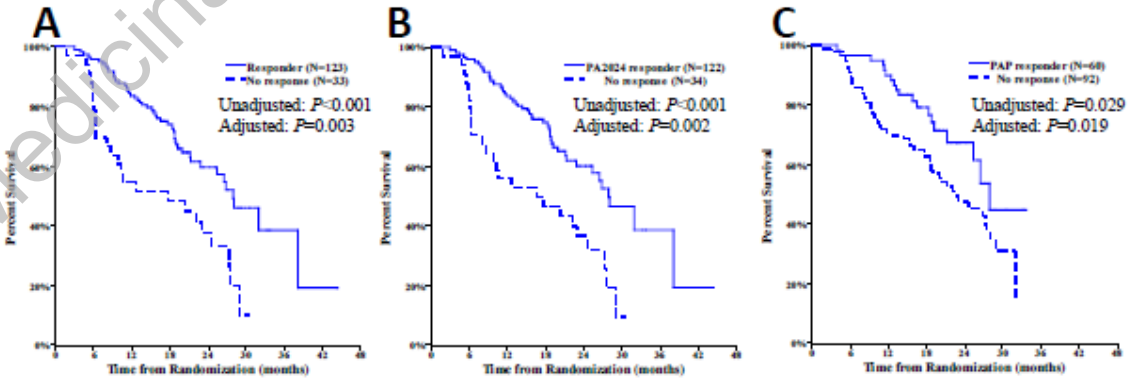


Table 12: Analyses of correlation between OS and cell product parameters, Sipuleucel-T subjects who received at least one infusion (N = 330)

Cell Product Parameter	N	p-value[1]	Hazard Ratio (95% CI)[1]
Cumulative Upregulation	330	0.123	0.751 (0.521, 1.081)
Cumulative TNC ($x10^9$)	330	0.008	0.688 (0.522, 0.906)
Cumulative CD54 Cell Count ($x10^9$)	330	0.016	0.777 (0.633, 0.954)

Program: t_OS_CMCbyCum_All.sas (Run: July 20, 2009: 16:50)

Reference Listing 16.2.6.3 and Listing 16.2.6.13
CI = Confidence Interval, ln = Natural Logarithm.
Hazard Ratios are per unit increase
[1] From 3 Cox regression models: Each cell product parameter [Cumulative Upregulation (ln), Cumulative TNC (ln), and Cumulative CD54 Cell Count (ln)] incorporated as an additional independent variable in the primary model with PSA (ln), and LDH (ln) as the common independent variables; all stratified by randomization strata.

Immune response across clinical trials

Figure 6: Immune response compared across clinical trials: Stimulation index for the proliferative response to PA2024. Pre-treatment (white bars) versus post-treatment (shaded bars)

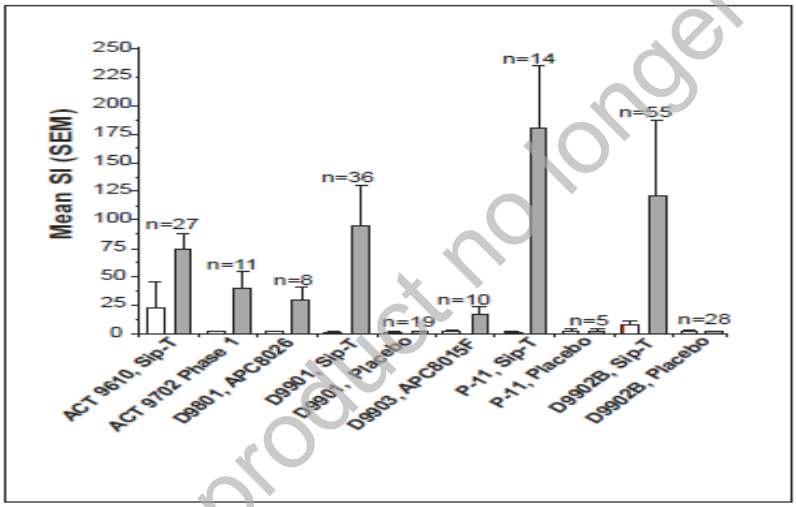


Table 13: Immune response rates comparison across clinical trials: subjects with a ≥16 fold increase in antibody response after treatment

Table 22: Immune Response Comparison Across All Clinical Trials: Subjects with a ≥ 16 fold Increase in Antibody Response After Treatment

Antigen	ACT 9610 N = 30[a] n (%)	ACT 9702 N = 29 n (%)	D9801 (APC8026) N = 15 n (%)	D9901 N=30[b] n (%)	D9901 (Placebo) N = 17[c] n (%)	D9903 (APC8015F) N = 7 n (%)	D9902B N = 147 n (%)	D9902B (Placebo) N = 69 n (%)
PA2024	20 (67)	25 (86)	11 (73)	27 (90)	1 (6)	2 (29)	92 (63)	1 (1.4)
PAP	9 (30)	2 (7)	0 (0)	2 (7)	0 (0)	0 (0)	39 (27)[d]	1 (1.4)[d]
GM-CSF	14 (48)	18 (62)	10 (67)	14 (47)	0 (0)	0 (0)	4 (3)	0 (0)

Subjects were treated with sipuleucel T unless otherwise noted (D9801: APC8026; D9901: Placebo; D9903: APC8015F; D9902B: Placebo)

[a] N = 29 for GM-CSF antigen.

[b] N = 29 for PAP antigen.

[c] N = 18 for GM-CSF antigen.

[d] The PAP used in the D9902B assay was recombinant human PAP expressed in insect cells (PAP). The PAP used in all the other assays was obtained from seminal fluid.

Sources: Post-Text Table 3.0

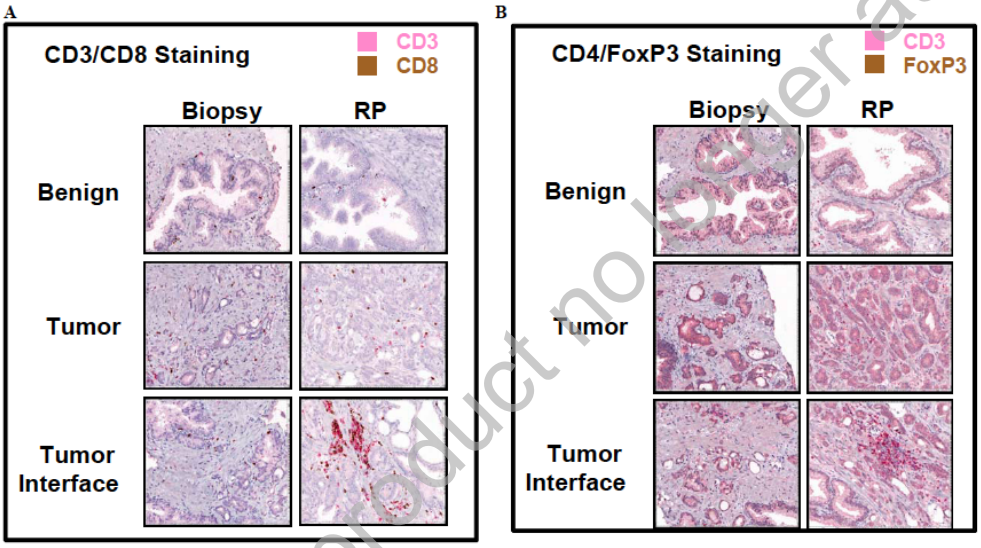
Immunohistochemistry analysis

Study P07-1

In this study, subjects with localized prostate cancer receive 3 infusions of sipuleucel-T at approximately 2 week intervals beginning approximately 6 – 7 weeks prior to a scheduled radical prostatectomy (RP). Immunohistochemistry (IHC) using antibodies to the T cell markers CD3, CD4, CD8 and FoxP3 is performed on fixed tissue from prostate biopsies obtained before treatment and then on the RP specimens. Image analysis software quantified the frequency of stained cells in benign tissue, tumor tissue, and the tumor interface. Of 42 patients enrolled, 38 received all 3 pre-RP infusions and were completely evaluable by IHC.

Figure 7 shows representative IHC micrographs that show changes in T cell infiltration (Panel A CD3/CD8; Panel B CD4/FoxP3) at the interface of tumor and normal prostate tissue prior to treatment (Biopsy) and post-treatment (RP).

Figure 7: Immunohistochemistry Analysis

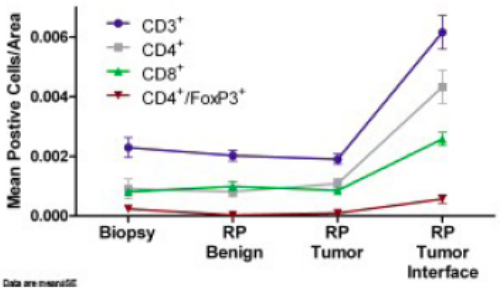


RP (radical prostatectomy, i.e. sample analysed after sipuleucel-T treatment; biopsy represents a sample taken before sipuleucel-T treatment.

Quantitative analysis is presented below in Figure 8.

Figure 8: Quantitative analysis

	Pairwise Comparison of RP Tumour Interface (P value)		
	vs Biopsy	vs Benign RP	vs Tumor RP
$CD3^+$	0.0001	0.0001	0.0001
$CD3^+/CD4^+$	0.0001	0.0001	0.0001
$CD3^+/CD8^+$	0.0001	0.0001	0.0001
$CD3^+/CD4^+/FoxP3^+$	0.004	0.0002	0.0003



2.4.4. Discussion on clinical pharmacology

Provenge is an autologous cellular immunotherapy designed to induce an immune response targeted against prostatic acid phosphatase (PAP), an antigen expressed in most prostate cancers. Peripheral blood mononuclear cells collected from the patients are cultured with PAP-GM-CSF, a fusion protein consisting of PAP linked to granulocyte-macrophage colony-stimulating factor (GM-CSF) an immune cell activator. During *ex vivo* culture with PAP-GM-CSF, activated APCs (antigen presenting cells) take up and process the recombinant target antigen into peptides that are then presented to T cells. Given the nature of the product and in accordance with the CHMP guideline on human cell-based medicinal products (EMA/CHMP/410869/2006), conventional pharmacokinetic (PK) analyses were not submitted by the applicant. Provenge metabolism and distribution are not expected to differ from normal leucocytes and the absence of PK studies is acceptable.

The mechanism of action for sipuleucel-T consists of induction of an immune response to the target antigen, PA2024. Pharmacodynamic analyses from the Phase 1 and Phase 2 clinical trials focused on the cellular and humoral immune responses to sipuleucel-T and related products at various cell doses and dosing intervals. Immune responses in patients were evaluated by *ex vivo* analyses such as ELISPOT and T cell proliferation after re-stimulation with PA2024, PAP, or GM-CSF. Anti-PA2024 responses were induced, whereas re-stimulation with the PAP antigen alone resulted in no or non-significant responses. This in principle was the case for all clinical studies where immune-monitoring was done. Similarly, humoral anti PA2024 responses were higher than PAP responses.

Exploratory analyses were performed to investigate the relationship between immune responses and overall survival in pivotal clinical study D9902B. A positive association between overall survival and the individual immune response measurement was observed. The strongest correlation was observed at week 6 for PA2024-specific ELISA, at Week 14 for PA2024-specific proliferation and at Week 26 for PA2024-specific ELISPOT. These analyses suggested that overall survival is associated with an immune response to sipuleucel-T. However, a correlation between a specific PAP T cell immune response and survival was not shown. Insufficient PAP-specific T cell responses were detectable in the peripheral blood of patients by ELISPOT analyses in pivotal clinical study D9902B. The assumption that the absence of increased T cell responses in the periphery might be due to the migration of T cells to the tumour tissue was further substantiated by IHC data. Increased numbers of T cells were detected at the interface of tumour and surrounding tissue. Induction of T cells was also shown by *in vitro* analyses during the manufacture of sipuleucel-T (data not shown). Anti-PAP specific T cells were especially increased in week 4 products.

Overall, sufficient data were provided to show that cellular anti-PAP T cell immune responses were induced. Although it was not directly shown that CD8 T cells are cytotoxic, it was observed that such cells infiltrate the tumour.

The studies suggested that 3 doses of cell product were sufficient to induce cellular and humoral responses to the target antigen. In addition, humoral and cellular responses were similar between the three studies, thus supporting a 2-weekly dosing scheme. The final product CD54+ cell count acceptance criterion of $\geq 50 \times 10^6$ cells was based on a retrospective statistical analysis of phase 3 clinical manufacturing data (data not shown) which was considered acceptable.

In study D9902B, antibody (IgM and IgG) responses against both PAP GM-CSF and the PAP antigens were observed in the Provenge group through the follow up period. In addition, T cell proliferative and γIFN ELISPOT responses to PAP and PAP-GM-CSF were observed in cells collected from peripheral blood of patients through the follow up period in the Provenge treatment group. Neutralising antibody responses to GM-CSF were reported in 10 out of 60 patients and were transient. Since production of GM-CSF neutralizing antibodies may lead to possible interference with subsequent GM-CSF adjuvant treatment, development of such antibodies has been included in the Risk Management Plan (RMP) as a potential risk and is considered adequately addressed (see also clinical safety).

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of Provenge is considered to have been adequately characterised and there are no relevant concerns or uncertainties.

Provenge is an autologous cellular therapy. The nature of Provenge is such that conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination are not applicable.

The CHMP endorse the CAT assessment regarding the conclusions on the clinical pharmacology as described above.

2.5. Clinical efficacy

The applicant submitted data from three phase III, multicentre, randomised, placebo-controlled studies in men with advanced metastatic castrate resistant prostate cancer (CRPC).

Table 14: Overview of phase III studies

Study	Diagnosis of Subjects	Study Objectives	Test Product	Subjects randomized	Duration of Treatment
D9901	Asymptomatic, metastatic, CRPC	• Safety • Survival • TTP • TDRP • Response rate and duration of response • Immune response	Sipuleucel-T/ placebo	127 (82:45)	Weeks 0, 2, 4
D9902A	Asymptomatic, metastatic, CRPC	• Safety • Survival • TTP • TDRP • Response rate and duration of response	Sipuleucel-T/ placebo	98 (65:33)	Weeks 0, 2, 4
D9902B IMPACT pivotal	Asymptomatic or minimally symptomatic, metastatic, CRPC	• Safety • Survival • TTP	Sipuleucel-T/ placebo	512 (341: 171)	Weeks 0, 2, 4

2.5.1. Dose response studies

These included studies ACT9610, ACT 9702 and D9801 already described in the clinical pharmacology section.

2.5.2. Main study

D9902B (IMPACT)

This was a randomised, multicentre, placebo-controlled, parallel group phase 3 trial in men with symptomatic or minimally symptomatic, metastatic, androgen independent prostatic adenocarcinoma.

Methods

Study Participants

Approximately 500 patients with metastatic CRPC and presenting with the following main eligibility criteria (as per final protocol of 3 January 2008 following amendment 8) were planned to be randomised into the study. Inclusion/Exclusion criteria were amended during the study (See section 'Conduct of Study').

Key inclusion criteria

- Men ≥ 18 years of age with asymptomatic or minimally symptomatic, metastatic CRPC (Asymptomatic/minimally symptomatic disease defined as not requiring regular use of opioid analgesics and pain on a visual analogue scale of 3 or less);
- Written informed consent obtained prior to the initiation of study procedures;
- Histologically documented adenocarcinoma of the prostate;
- Metastatic disease as evidenced by soft tissue lesions on baseline computed tomography (CT) scan of the abdomen and pelvis, and/or bony metastases on baseline bone scan. Subjects whose metastatic disease was detectable only on chest CT scan were not eligible;
- Castrate resistant prostate cancer. Subjects must have had current or historical evidence of disease progression concomitant with surgical or medical castration, as demonstrated by PSA progression OR progression of measurable disease OR progression of non-measurable disease
- Serum PSA ≥ 5.0 ng/mL;
- Castrate level of testosterone (< 50 ng/dL) achieved via medical or surgical castration;
- Life expectancy of at least 6 months;
- Adequate hematologic, renal, and liver function;
- ECOG Performance Status of 0 or 1;
- Negative serology tests for HIV 1 and 2, HTLV-1, HBV and HCV.

Key exclusion criteria

- The presence of lung, liver, or known brain metastases, malignant pleural effusions, or malignant ascites;
- A requirement for treatment with opioid analgesics for any reason within 21 days prior to registration;
- Average weekly pain score of 4 or more as reported on the 10-point Visual Analog Scale (VAS) on the Registration Pain Log;
- Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2;
- Use of non-steroidal antiandrogens (e.g., flutamide, nilutamide, or bicalutamide) within 6 weeks of registration;
- Treatment with chemotherapy within 6 months of registration;
- Subjects who received more than 2 chemotherapy regimens at any time prior to registration are excluded;
- Treatment with chemotherapy ≥ 3 months prior to registration is allowed provided that all of the following criteria are met:
    - The post-chemotherapy PSA is ≥ the pre-chemotherapy PSA or the nadir PSA achieved during chemotherapy
    - The post-chemotherapy bone scan is not improved in comparison to the prechemotherapy bone scan.
    - For subjects with nodal disease followed by CT or other imaging modality, the post-chemotherapy imaging study must not show a decrease in the size or number of pathologically enlarged lymph nodes in comparison to the pre-chemotherapy imaging study.
- Initiation or discontinuation of bisphosphonate therapy within 28 days prior to registration. Subjects taking bisphosphonate medication must not have their dosing regimen altered until objective disease progression is independently confirmed;
- Treatment with any of the following medications or interventions within 28 days of registration:
    - Systemic corticosteroids. Use of inhaled, intranasal, and topical steroids is acceptable.
    - External beam radiation therapy or surgery.
    - PC-SPES (or PC-SPEC) or saw palmetto.
    - Megestrol acetate (Megace), diethyl stilbestrol (DES), or cyproterone acetate.
    - Ketoconazole.
    - 5-α-reductase inhibitors (e.g., finasteride [Proscar], dutasteride [Avodart]).
    - High dose calcitriol [1,25(OH)2VitD] (i.e., > 7.0 µg/week).
    - Any other systemic therapy for prostate cancer (except for medical castration).

- Treatment with any investigational vaccine within 2 years of registration or treatment with any other investigational product within 28 days of registration;
- Participation in any previous study involving sipuleucel-T, regardless whether the subject received sipuleucel-T or placebo;
- Pathologic long-bone fractures, imminent pathologic long-bone fracture (cortical erosion on radiography > 50%) or spinal cord compression;
- Paget's disease of bone;
- A history of stage III or greater cancer, excluding prostate cancer. Basal or squamous cell skin cancers must have been adequately treated and the subject must be disease free at the time of registration. Subjects with a history of stage I or II cancer must have been adequately treated and been disease-free for ≥ 3 years at the time of registration;
- A requirement for systemic immunosuppressive therapy for any reason;
- Any infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5°F or 38.1°C) within 1 week prior to registration;
- A known allergy, intolerance, or medical contraindication to receiving the contrast dye required for the protocol-specified CT imaging;
- Any medical intervention or other condition which, in the opinion of the Principal Investigator or the Dendreon Medical Monitor, could compromise adherence with study requirements or otherwise compromise the study's objectives.

Treatments

Sipuleucel-T arm

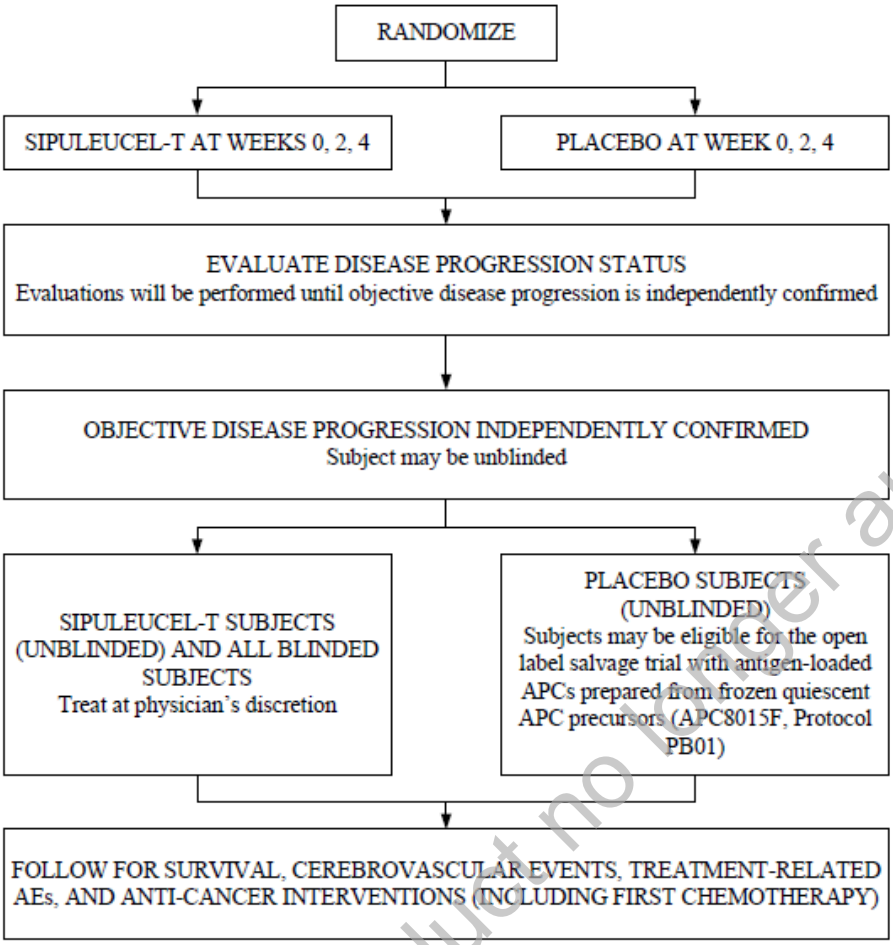
Sipuleucel-T (APC8015) consisted of autologous PBMCs including APCs which had been activated *in vitro* with a recombinant fusion protein PA2024, which comprises the tumor antigen PAP linked to the immune cell activator GM-CSF. Administered treatment was all of the nucleated cells that could be prepared from a 1.5- to 2.0- blood volume mononuclear cell leukapheresis product. A minimum dose of approximately 3×10^6 CD54+ cells was selected. Sipuleucel-T was prepared on an individual basis, each product with a unique lot number. For subjects randomized to sipuleucel-T, three infusions of sipuleucel-T were to be given at approximately Weeks 0, 2, and 4. (See also section 2.2.2 Active substance)

Placebo arm

Subjects randomized to placebo received autologous quiescent APCs held at 2°C to 8°C and not loaded with PA2024 antigen intravenously at a dose approximately one-third of the quiescent APCs prepared from a single leukapheresis procedure. Three infusions of placebo were to be given at approximately weeks 0, 2, and 4. The remaining two-thirds were cryopreserved to be used in a salvage study. Salvage therapy (APC8015F) consisted of cells that were activated the same way (i.e. with the recombinant PAP-GM-CSF-fusion protein) as sipuleucel-T prepared from unfrozen cells. (See also section 2.2.2 Active substance)

Both sipuleucel-T and placebo were formulated in 250 mL of Lactated Ringer's Injection, USP.

Figure 9: Study design protocol D9902B



Objectives

The objectives as per final protocol (following amendment 8 of 3 January 2008) are detailed below. Objectives were amended during the study (for further details see section 'Conduct of Study').

The primary efficacy objective was to assess the efficacy of sipuleucel-T in prolonging survival of subjects with metastatic androgen independent prostate cancer.

The secondary efficacy objective was to assess the efficacy of sipuleucel-T in delaying time to objective disease progression in subjects with metastatic androgen independent prostate cancer.

The tertiary efficacy objective consisted in assessing the effect of sipuleucel-T in delaying the time to clinical progression, increasing the PSADT (PSA doubling time) and generating an immune response.

The safety objective was to compare AEs, laboratory evaluations, and vital sign measurements between the 2 treatment groups.

Outcomes / endpoints

The endpoints as per final protocol (following amendment 8 of 3 January 2008) are detailed below. Endpoints were amended during the study (for further details see section 'Conduct of Study').

Primary Efficacy Endpoint: Overall survival (OS)

OS was defined as the time interval from the date of randomization to the date of death due to any cause. Subjects alive as well as subjects prematurely discontinued from the study at the time of analysis were censored in the analysis at the day of their last documented study evaluation date or contact date, whichever is later.

Secondary Efficacy Endpoint: Time to objective disease progression (TODP)

It corresponded to the time from randomization to achieving objective disease progression, as determined by the IRRC for the study. Subjects who had not demonstrated objective disease progression prior to the data cut-off date were censored at the time of their last imaging visit date obtained per protocol, unless they died prior to attaining objective disease progression in which case they were considered to be competing events. Subjects who were lost to follow-up, withdrew consent, or discontinued follow-up prior to confirmed objective disease progression were censored at the date of their last imaging visit date.

Tertiary Efficacy Endpoints:

- Time to clinical progression (TCP):

Time from randomisation to clinical disease progression defined as the first occurrence of either of the following:

- Objective disease progression,
- Development of one of the following clinically significant disease-related events:
    - Spinal cord or nerve root compression, if not confirmed by serial imaging studies;
    - Pathologic fracture, if not confirmed by serial imaging studies;
    - Metastatic disease in an anatomy for which no baseline scan was available for comparison to allow documentation of interval change on serial imaging studies;
    - Progressive disease in an anatomy for which there was a baseline imaging assessment but serial imaging was not performed;
    - A clinical indication for radiation therapy;
    - At least 2 of the following clinical signs or symptoms in comparison to baseline: An increase in ECOG performance status of $\geq$ 1 grade, progressive anaemia, $\geq$ 10% non intentional weight loss, new urinary outflow obstruction attributable to cancer.
- Prostate specific antigen (PSA) doubling time (PSADT)

- Immune response to PA2024

Sample size

The original sample size calculation (based on the co-primary endpoints time to objective disease progression and time to disease related pain) resulted in 275 subjects (183 sipuleucel-T, 92 placebo) to be included into the trial.

Following the change of the primary endpoint to overall survival, new sample size estimation took place. Approximately 500 subjects were to be enrolled and randomized in a 2:1 ratio to receive sipuleucel-T or placebo. The final survival analysis was to be performed when approximately 304 death events had been observed. This sample size would be sufficient to detect a HR for death of 0.69 (sipuleucel-T versus placebo) using the 2-sided log rank test with 88% power for the final analysis at an overall significance level of 0.05. The power calculation was based on Freedman's method.

Randomisation

Subjects were allocated to either the sipuleucel-T or placebo arm using Pocock and Simons' minimization method (Pocock 1975), following a 2:1 ratio. The allocation process was designed to minimize the degree of imbalance between the 2 treatment groups for primary Gleason grade (≤ 3, ≥ 4), the number of bone metastases (0 – 5, 6 – 10, >10), and bisphosphonate use (yes, no) across treatment groups. Imbalance between treatment groups was assessed using the deterministic variance method.

Clusters of study centres were formed during the enrolment process as part of the allocation process. Centers were assigned to 1 of 3 clusters based on their projected enrolment and the chronological order of when the first subject was pre-registered. The expected sample size for each cluster was between 167 and 174 subjects based on the planned total sample size for the study. The previously mentioned minimization procedure was then used to allocate subjects in a 2:1 ratio (sipuleucel-T: placebo) within a cluster.

Blinding (masking)

As both sipuleucel-T and placebo were formulated in 250 mL of Lactated Ringer's Injection, USP, the active treatment and control products were similar in appearance and had identical packaging. With the exception of manufacturing and quality assurance/quality control personnel, persons involved (patients, investigators, other clinical study centre and firm personnel) were blinded to treatment assignment. Personnel at the manufacturing centres were aware of subjects' treatment assignments to maintain the chain of product identity and to ensure subject safety.

Statistical methods

The primary efficacy parameter, overall survival (OS) defined as time from randomization to death due to any cause was analysed for the ITT population. The primary analysis of overall survival used Wald's test (2-sided) for treatment effect based on a stratified Cox regression model with treatment, adjusted for 2 baseline covariates [PSA (ln) and LDH (ln)], stratified by

the randomization factors mentioned above. To describe the treatment effect the HR for treatment and the corresponding 2-sided 95% confidence interval (CI) for the HR, using the placebo arm as the denominator, were generated. Survival curves for both treatment groups were estimated by means of the Kaplan-Meier method. To account for an interim analysis conducted when 247 death events had been observed, an alpha spending function of the O'Brien-Fleming type was applied. The type I error to be applied was 0.019 at interim and 0.043 at the final analysis.

For other time to event endpoints (e.g. time to objective disease progression) similar Cox-regression models as for the primary analyses were applied. A Cox regression model with cumulative CD54 up-regulation ratio as covariate was used to assess a possible impact of CD54 up-regulation on OS in subjects receiving sipuleucel-T.

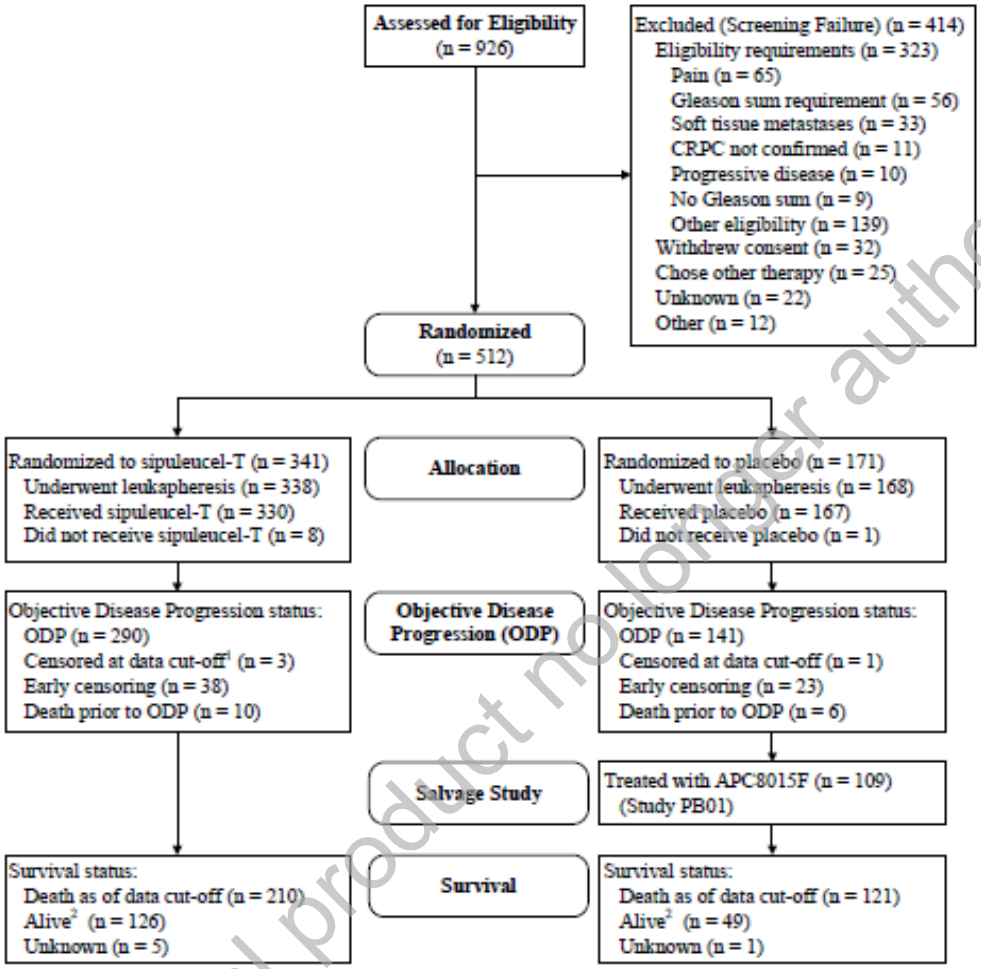
Regarding PSA doubling time (PSADT), the population PSA time slope (or PSA velocity) for each treatment arm was computed based on a mixed effects model with all log transformed PSA measurements from baseline until the institution of other systemic anticancer therapy. Fixed effects included stratification factors, time (as a continuous variable), treatment, and treatment by time interaction. Subjects were considered as a random effect. The p-value associated with the treatment by time interaction effect was used to evaluate the difference between treatments in PSADT. The estimated PSADT and its 2-sided 95% CI for each treatment arm were computed by the estimated population slope for PSA (ln).

Subgroup analyses for the primary endpoint based on baseline covariates were planned.

Results

Participant flow

Figure 10: Study D9902B – Participants flow



[1] The data cut-off date was 18 JAN 2009.
[2] Last contact occurred after beginning of survival sweep (12 JAN 2009).

Recruitment

The study took place at 75 centres in Canada and the US. The first patient was enrolled on 29 August 2003 and the last patient was enrolled on 09 November 2007. The database lock (and unblinding) was on 6 April 2009 after 331 deaths had been observed. Data cut-off date for the interim analysis was 28 May 2008. The efficacy and safety analyses were based on the data cut-off on 18 January 2009 (date of 331st death).

According to the summary of demographics and baseline characteristics, 39.6% of all patients were enrolled before amendment 7 (see below).

Conduct of the study

The originator protocol of study D9902B was D9902 (dated 21 May 2003). Protocol D9902 was conducted in 2 parts: Part A (D9902A) included subjects enrolled in the original protocol through Amendment 4 (12 March 2001). D9902A included subjects with asymptomatic, metastatic androgen independent prostate cancer, regardless of Gleason score. Part B (D9902B) commenced two years later with Amendment 5 (21 May 2003) and initially included subjects with Gleason Sum ≤ 7 malignancies only. Beginning with Amendment 7 (11 October 2005), subjects were enrolled in D9902B regardless of Gleason Sum, and minimally symptomatic subjects, in addition to asymptomatic subjects, were eligible for enrolment. Beginning with Amendment 8 (20 November 2007), all cerebrovascular events occurring throughout the study (regardless of causality) had to be reported.

The protocol for study D9902B was amended three times:

Amendment 6 (dated 29 April 2004) introduced the following changes (amongst others):

- Modification of in-/exclusion criteria: inclusion of patients with prior record of Gleason sum ≥ 8
- Removal of tertiary endpoints regarding the use of analgesics
- Introduction of the possibility of an interim analysis
- Amendment 7 (dated 11 October 2005) introduced the following changes (amongst others):
- Upgrading overall survival to be the primary endpoint,
- Downgrading of time to objective disease progression to the secondary endpoint,
- Deletion of the endpoints time to disease related pain, tumor response rate, duration of response, and skeletal morbidity rate
- Added tertiary endpoints of PSADT and immune response to PA2024,
- Widening of the population by inclusion of subjects with Gleason sum > 7,
- Changed subject population to include minimally symptomatic subjects,
- Increase in sample size from 275 subjects to approximately 450 to 550 subjects (in order to observe 360 deaths).
- Clarification that following 180 deaths an interim analysis should take place
- Change of the analysis model (Cox PHR) for the primary and secondary endpoints
- Amendment 8 (dated 3 January 2008):
- The changes implemented by amendment 8 were mostly about statistical issues (e.g. change of the alpha spending function to account for the interim analysis, number of deaths at interim and final analysis, sample size).

Table 15: Study D9902B - Amended endpoints

	Initial	APR 2004	OCT 2005
Primary endpoints	TDP	TDP	Overall survival
	Time to disease-related pain	Time to disease-related pain	
Secondary endpoints	Survival	Survival	Objective TDP
	Time to first use of opioid analgesics	Time to first use of opioid analgesics	
Tertiary endpoints	Time to clinical progression	Time to clinical progression	Time to clinical progression, revised
	Objective response rate	Objective response rate	PSADT
	Response rate in measurable /evaluable lesions	Response rate in measurable /evaluable lesions	Immune response to PA2024
	Duration of response	Duration of response	
	Skeletal morbidity rate	Skeletal morbidity rate	
	Proportion of patients requiring opioid analgesics in the first 24 weeks after randomization		
	Time to first increase in analgesic use after randomization		

Baseline data

Table 16: Study D9902B - Demographic and baseline characteristics, ITT population

	SIPULEUCEL-T (n = 341)	Placebo (n = 171)	Total (N=512)
Age, median years (min, max)	72 (49, 91)	70 (40, 89)	71 (40, 91)
Race, Caucasian (%)	89.4	91.2	90.0
ECOG status, 0 (%)	82.1	81.3	81.8
Gleason sum, ≤ 7 (%)	75.4	75.4	75.4
Weight, median kgs (min, max)	88 (53, 175)	86 (60, 136)	87 (53, 175)
Time from diagnosis to randomization, median years (min, max)	7.1 (0.8, 24.5)	7.1 (0.9, 21.5)	7.1 (0.8, 24.5)
Disease localization			
Bone only (%)	50.7	43.3	48.2
Soft tissue only (%)	7.0	8.2	7.4
Bone and soft tissue (%)	41.9	48.5	44.1

Regarding pain status, the average pain score was >0 for 164 patients in the sipuleucel-T group and 81 patients in the placebo group (=245/512=48%) and average pain score was =0 for 174 patients in the sipuleucel-T group and 90 patients in the placebo group.

Table 17: Study D9902B - Summary of baseline stratification factors, ITT population

	Sipuleucel-T (N=341)	Placebo (N=171)	Total (N=512)
Primary Gleason Grade			
<= 3	144 (42.2%)	71 (41.5%)	215 (42.0%)
>= 4	197 (57.8%)	100 (58.5%)	297 (58.0%)
Number of Bone Metastases			
0 - 5	146 (42.8%)	73 (42.7%)	219 (42.8%)
6 - 10	49 (14.4%)	25 (14.6%)	74 (14.5%)
> 10	146 (42.8%)	73 (42.7%)	219 (42.8%)
Bisphosphonate Use			
Yes	164 (48.1%)	82 (48.0%)	246 (48.0%)
No	177 (51.9%)	89 (52.0%)	266 (52.0%)

Table 18: Study D9902B - Baseline laboratory parameter, ITT population

	Normal Range	SIPULEUCEL-T (n = 341)	Placebo (n = 171)	Total (N = 512)
Serum PSA, median ng/mL	≤ 2.7 to ≤ 7.2	51.7	47.2	50.1
Serum PAP, median U/L	0.1 – 1.2	2.7	3.2	2.9
Alkaline phosphatase, median U/L	31 – 131	99.0	109.0	103.0
LDH, median U/L	53 – 234	194.0	193.0	194
Hemoglobin, median g/dL	12.5 – 18.1	12.9	12.7	12.8
White blood cell count, median x 10^3/µL	3.8 – 10.7	6.2	6.0	6.1
Total absolute neutrophil count, median x 10^3/µL	1.96 – 7.23	4.0	4.1	4.0

Table 19: Study D9902B - Prior prostate cancer therapy, ITT population

	SIPULEUCEL-T (n = 341)	Placebo (n = 171)	Total (N = 512)
Hormone therapy received, n (%)	341 (100.0)	171 (100.0)	512 (100.0)
Combined androgen blockade, n (%)	279 (81.8)	141 (82.5)	420 (82.0)
Orchiectomy, n (%)	32 (9.4)	13 (7.6)	45 (8.8)
Chemotherapy, n (%)	67 (19.6)	26 (15.2)	93 (18.2)
Docetaxel, n (%)	53 (15.5)	21 (12.3)	74 (14.5)
Radical prostatectomy, n (%)	121 (35.5)	59 (34.5)	180 (35.2)
Radiotherapy (to the prostate bed), n (%)	185 (54.3)	91 (53.2)	276 (53.9)

Table 20: Study D9902B - Summary of leukaphereses and product infusions, ITT

	Sipuleucel-T (N = 341)	Placebo (N = 171)	Total (N = 512)
Number of Leukaphereses, n (%)			
0 leukaphereses	3 (0.9)	3 (1.8)	6 (1.2)
1 leukapheresis	3 (0.9)	3 (1.8)	6 (1.2)
2 leukaphereses	11 (3.2)	3 (1.8)	14 (2.7)
3 leukaphereses	214 (62.8)	126 (73.7)	340 (66.4)
> 3 leukaphereses	110 (32.3)	36 (21.1)	146 (28.5)
Number of Infusions, n (%)			
0 infusions[1]	11 (3.2)	4 (2.3)	15 (2.9)
1 infusion	6 (1.8)	6 (3.5)	12 (2.3)
2 infusions	11 (3.2)	2 (1.2)	13 (2.5)
3 infusions	313 (91.8)	159 (93.0)	472 (92.2)

[1] Includes subjects who did not undergo leukapheresis.

Table 21: Study D9902B - Baseline demographics and prior treatment by age in Study D9902B

	Sipuleucel-T		Placebo		Total	
	<65 years N=77	≥65 years N=264	< 65 years N=49	≥65 years N=122	<65years N=126	≥65 years N=386
Age, median years	60	74	61	74	60	74
Race, Caucasian (%)	83.1%	91.3%	91.8%	91.0%	86.5%	91.2%
ECOG Status, 0 (%)	94.8%	78.4%	85.7%	79.5%	91.3%	78.8%
Gleason Sum, ≤7 (%)	72.7%	76.1%	71.4%	77.0%	72.2%	76.4%
Weight, median kg	92.5	87.3	88.6	85.5	90.7	86.4
Time from Diagnosis to Randomization, median yrs	5.4	8.1	4.9	8.1	5.1	8.1
Disease Localization,						
Bone Only (%)	49.4%	51.1%	44.9%	42.6%	47.6%	48.4%
Soft Tissue Only (%)	7.8%	6.8%	6.1%	9.0%	7.1%	7.5%
Bone and Soft Tissue (%)	42.9%	41.7%	49.0%	48.4%	45.2%	43.8%
Missing (%)	0.0%	0.4%	0.0%	0.0%	0.0%	0.3%
Number of Bone Metastases						
0-5 (%)	44.2%	42.4%	44.9%	41.8%	44.4%	42.2%
6-10 (%)	14.3%	14.4%	22.4%	11.5%	17.5%	13.5%
>10 (%)	41.6%	43.2%	32.7%	46.7%	38.1%	44.3%
Serum PSA, median ng/mL	36.4	58.7	36.8	50.8	36.6	54.9
Alkaline Phosphatase, median U/L	95.0	100.0	111.0	107.5	106.0	101.0
LDH, median U/L	193.0	194.0	196.0	191.5	194.0	194.0
Hemoglobin, median g/dL	13.2	12.7	13.2	12.6	13.2	12.7
Chemotherapy, yes (%)	23.4%	18.6%	16.3%	14.8%	20.6%	17.4%
Docetaxel, yes (%)	20.8%	14.0%	12.2%	12.3%	17.5%	13.5%
Radical Prostatectomy, yes (%)	37.7%	34.8%	49.0%	28.7%	42.1%	32.9%
Radiotherapy, yes (%)	55.8%	53.8%	44.9%	56.6%	51.6%	54.7%
Bisphosphonate Use, yes (%)	46.8%	48.5%	46.9%	48.4%	46.8%	48.4%
Baseline pain status, no pain (%)	53.2%	50.4%	57.1%	50.8%	54.8%	50.5%

Numbers analysed

The ITT population included all randomized subjects (n = 512; 341 subjects in the sipuleucel-T arm and 171 subjects in the placebo arm) and the safety population included all subjects who underwent at least 1 leukapheresis (n = 506).

Outcomes and estimation

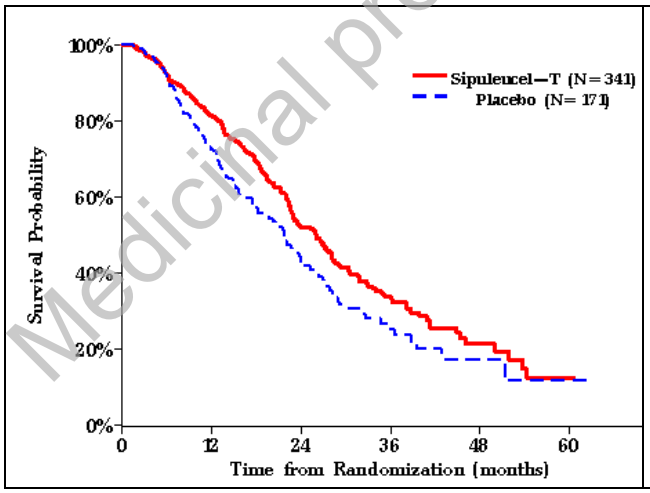
At the time of the primary analysis 210/341 (61.6%) of patients in the sipuleucel-T group and 121/171 (70.8%) patients in the placebo group had died. The results of the primary analysis are summarised below.

Primary endpoint: Overall Survival (OS)

Table 22: Study D9902B - Primary analysis of OS (ITT)

	SIPULEUCEL-T (n = 341)	Placebo (n = 171)
Censored, n (%)	131 (38.4)	50 (29.2)
Censored prior to survival sweep1, n (%)	5 (1.5)	1 (0.6)
Events, n (%)	210 (61.6)	121 (70.8)
Median Survival Time (Months; 95% CI)	25.8 (22.8, 27.7)	21.7 (17.7, 23.8)
Median Follow-Up Time (Months)		
Observed	20.6	19.3
Estimated	33.7	35.9
Primary Model		
p-value	0.032	
Hazard Ratio (95% CI)	0.775 (0.614, 0.979)	
Unadjusted Analysis		
p-value	0.023	
Hazard Ratio (95% CI)	0.766 (0.608, 0.965)	

Table 23: Study D9902B - Primary Analysis of OS and patients at risk and Kaplan-Meier (KM) survival estimates (ITT)



# at Risk	0 Months	12 Months	24 Months	36 Months	48 Months	60 Months
Sipuleucel-T	341	274	129	49	14	1
Placebo	171	123	55	19	4	1

Treatment	12 Months	24 Months	36 Months	48 Months
Sipuleucel-T	81.1	52.1	31.7	20.5
Placebo	72.4	41.2	23.0	16.0

Source: Post-Text Table 14.2.5

Table 24: Study D9902B - Sensitivity analyses of the primary endpoint

	HR	95% CI	P value	% reduction
Primary OS analysis				
Primary OS analysis (Cox model)	0.775	[0.614, 0.979]	P = 0.032	22.5%
OS without adjusting for baseline PSA and LDH (HR Cox regression Model)	0.766	[0.608, 0.965]	p= 0.023 stratified log-rank test	23.4%
OS without adjusting for baseline PSA and LDH (HR Cox regression Model)	0.771	(0.616, 0.964)	P = 0.022 unstratified log-rank test	
OS without imputing missing baseline covariates	0.764	[0.605, 0.964]	P = 0.023	23.6%
OS at 304 deaths				
OS at 304 deaths With/Without adjusting for Baseline PSA and LDH	0.770 /0.763	[0.605, 0.982] / [0.600, 0.971]	P = 0.035 /P= 0.027	23.0%
OS with modified efficacy populations				
OS Excluding Eligibility Deviations	0.770	[0.605, 0.980]	P = 0.033	
Excluding Major Eligibility Deviations 2	0.788	[0.622, 0.997]	P = 0.048	
Received At Least One Infusion	0.756	[0.598, 0.956]	P = 0.020	
Received All Three Infusions	0.763	[0.598, 0.972]	P = 0.029	
Prostate cancer specific survival				
prostate cancer specific survival	0.772	[0.606, 0.984]	P = 0.036	

Secondary endpoint: Time to objective disease progression (TODP)

Of the 512 subjects randomized, 431 subjects (84.2%) contributed a progression event (290 of 341 subjects (85.0%) randomized to sipuleucel-T and 141 of 171 subjects (82.5%) randomized to placebo). No significant delay from randomization to objective disease progression in the sipuleucel-T arm compared with the placebo arm was observed (HR = 0.951 [95% CI: 0.773, 1.169]; P = 0.628, log rank). The estimated median time to disease progression was 14.6 weeks in the sipuleucel-T arm compared with 14.4 weeks in the placebo arm. (Progression of unmeasurable lesions also counted as "event").

Figure 11: Study D9902B - Time to objective disease progression, ITT population

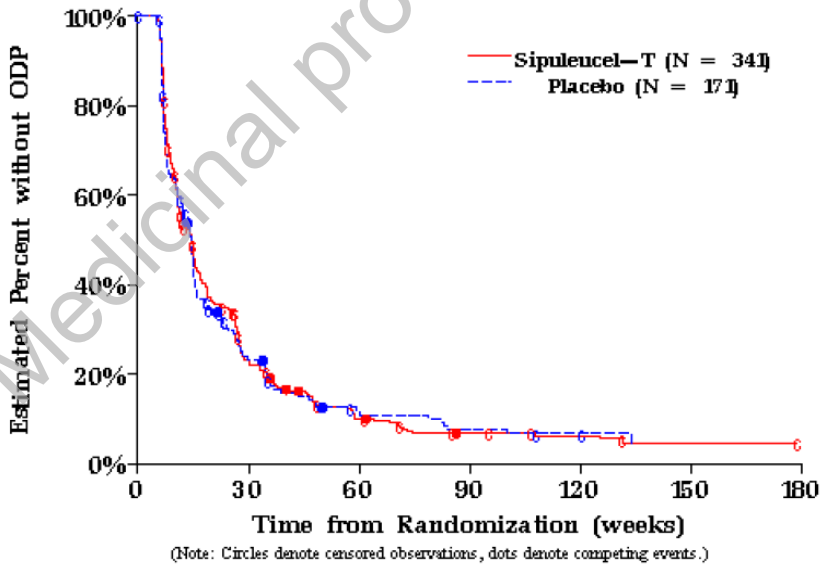


Table 25: Study D9902B - Summary of objective disease progression and duration of follow-up (ITT)

	Sipuleucel-T (N=341)	Placebo (N=171)	Total (N=512)
Subjects with ODP prior to data cutoff, n (%)	290 (85.0)	141 (82.5)	431 (84.2)
Anticancer therapy prior to ODP, n (%)	18 (5.3)	9 (5.3)	27 (5.3)
Missing 2 scan visits prior to ODP, n (%)	5 (1.5)	4 (2.3)	9 (1.8)
Distribution of Time to Event for Subjects Who Did Experience ODP, n (%)			
<= 8 weeks	94 (27.6)	55 (32.2)	149 (29.1)
8 < weeks <= 16	90 (26.4)	43 (25.1)	133 (26.0)
16 < weeks <= 24	25 (7.3)	11 (6.4)	36 (7.0)
24 < weeks <= 36	46 (13.5)	18 (10.5)	64 (12.5)
36 < weeks <= 48	16 (4.7)	4 (2.3)	20 (3.9)
> 48 weeks	19 (5.6)	10 (5.8)	29 (5.7)

ODP = Objective Disease Progression

Tertiary endpoint: Time to clinical progression (TCP)

HR for time to clinical progression was 0.917 [95% CI: 0.749, 1.123]; P = 0.398, log rank test. A summary of clinically significant disease prior to objective disease progression is provided below.

Table 26: Study D9902B - Summary of clinically significant disease-specific events prior to objective disease progression (ITT)

Summary of Clinically Significant Disease Specific Events Prior to Objective Disease Progression
Intent-to-Treat Subjects

	Sipuleucel-T (N=341) n (%)	Placebo (N=171) n (%)	Total (N=512) n (%)
Any Clinically Significant Disease-specific Event [1]	86 (25.2)	54 (31.6)	140 (27.3)
1. Spinal cord or nerve root compression	5 (1.5)	2 (1.2)	7 (1.4)
2. Pathologic fracture	3 (0.9)	2 (1.2)	5 (1.0)
3. Development of a clinical indication for beam radiation	20 (5.9)	14 (8.2)	34 (6.6)
4. Development of metastatic disease in an anatomy for which no baseline scan is available for comparison to allow documentation of interval change on serial imaging studies	4 (1.2)	2 (1.2)	6 (1.2)
5. Progressive disease in an anatomy for which there is a baseline imaging assessment but serial imaging has not been performed	2 (0.6)	3 (1.8)	5 (1.0)
6. An increase in ECOG performance status of at least 1 grade	50 (14.7)	38 (22.2)	88 (17.2)
7. Progressive anemia	16 (4.7)	5 (2.9)	21 (4.1)
8. >= 10% weight loss from baseline	5 (1.5)	5 (2.9)	10 (2.0)
9. New urinary outflow obstruction	9 (2.6)	5 (2.9)	14 (2.7)

Note: Includes only event reported prior to objective disease progression [1] Patients with multiple events only counted once.

Tertiary endpoint: PSA doubling time (PSADT)

Table 27: Study D9902B - Analysis of PSA doubling time, ITT population

Method	N (Sipuleucel-T/Placebo)	Estimated PSA (ln) Slope (Sipuleucel-T/Placebo)	Estimated PSADT (weeks) (Sipuleucel-T/Placebo)	p-value (F-test for Unequal Slopes)
Mixed model without adjusting for baseline PSA (ln)	340/171	0.039/0.041	17.6/17.0	0.721
Mixed model adjusted for baseline PSA (ln)	340/171	0.042/0.042	16.5/16.7	0.927
Mixed model adjusted for pre-study PSA (ln) slope	206/103	0.043/0.043	16.2/16.3	0.954

Ln = natural logarithm, All PSA values reported after prohibitive medications administered were deleted from the analysis, Mixed Model Analyses incorporated stratification variables.

Table 28: Study D9902B - Summary of PSA reduction from baseline, ITT population

PSA Reduction from Baseline	Sipuleucel-T (N=341)	Placebo (N=171)
>= 50% (2 or more visits at least 4 weeks apart)	8 (2.35%)	2 (1.17%)
>= 50% (1 visit)	1 (0.29%)	1 (0.58%)
>= 25% and < 50% (2 or more visits)	3 (0.88%)	1 (0.58%)
>= 25% and < 50% (1 visit)	8 (2.35%)	6 (3.51%)
Subjects with no response	291 (85.34%)	143 (83.63%)
Subjects without any postbaseline PSA visits	30 (8.80%)	18 (10.53%)

All PSA values reported after prohibitive medications administered were deleted from the analysis. Note: A subject was counted in the numerator of only 1 of the 4 PSA reduction categories (largest PSA reduction and then the most visits)

Tertiary endpoint: Immune response

Results are presented in the clinical pharmacology section.

Ancillary analyses

Progression-Free Survival (PFS)

Table 29: Study D9902B - Analysis of Progression Free Survival (PFS), ITT population

		Sipuleucel-T (N = 341)	Placebo (N = 171)
Censored, n (%)		41 (12.0)	24 (14.0)
Events, n (%)		300 (88.0)	147 (86.0)
Death Prior to ODP, n (%)[1]		10 (2.9)	6 (3.5)
Time To Event Quartile Estimates in Weeks (95% CI)[2]	25th Percentile	7.6 (7.1, 8.1)	7.1 (6.9, 8.0)
	50th Percentile	14.3 (11.1, 15.3)	14.1 (11.7, 15.0)
	75th Percentile	27.6 (26.6, 30.4)	26.9 (19.6, 34.7)
Time To Event in Weeks (Including Censored Values):	Min, Max	0.0, 178.7	0.0, 133.7
Time To Event in Weeks (Excluding Censored Values):	Min, Max	5.3, 131.7	5.6, 133.7
p-value[3]	0.533		
Hazard Ratio (95% CI)[3]	0.938 (0.766, 1.149)		

CI=confidence interval, NE=Not estimable, ITT=Intent-to-Treat, ODP=Objective Disease Progression
[1] Percentage calculation used ITT population as denominator
[2] From the Kaplan-Meier method
[3] P-Value was obtained from log-rank test and hazard ration was obtained from a Cox-regression model with treatment as the independent variable. Both were stratified by randomisation strata.

Post-randomisation treatment

Table 30: Study D9902B - Summary of all anticancer interventions (excluding APC8015F salvage treatment) after randomisation, ITT Population

	Sipuleucel-T (N = 341) n (%)	Placebo (N = 171) n (%)	Total (N = 512) n (%)
Any Anticancer Intervention[1]	279 (81.8)	125 (73.1)	404 (78.9)
Any Chemotherapy	223 (65.4)	92 (53.8)	315 (61.5)
Docetaxel	195 (57.2)	86 (50.3)	281 (54.9)
Any Chemotherapy Other Than Docetaxel	28 (8.2)	6 (3.5)	34 (6.6)
Hormone Therapy (excluding medical castration)	42 (12.3)	15 (8.8)	57 (11.1)
Radiation Therapy (e.g., external beam, radioisotopes)	72 (21.1)	45 (26.3)	117 (22.9)
Surgical Intervention	5 (1.5)	4 (2.3)	9 (1.8)
Other[2]	48 (14.1)	16 (9.4)	64 (12.5)

Note: All events that occurred after randomisation and prior to the cut-off date were included. Percentage calculation was based on intent-to-treat population.
[1] Patients with multiple anticancer interventions were only counted once.
[2] The most common types of 'Other' anticancer interventions were investigational therapies, steroid medications and secondary hormonal therapies.

A summary of the post randomisation treatment (apart from salvage immunotherapy) by age (< 65 versus ≥ 65) showed a trend for a higher rate of use of any anti-cancer intervention (84.9% vs. 76.9%) and docetaxel (61.1% vs. 52.8%) in younger subjects compared to older subjects. A similar trend was also observed in placebo arm subjects with respect to salvage use (69.4% in subjects < 65 years of age compared to 61.5% of subjects ≥ 65 years of age). Docetaxel use was less common in the sipuleucel-T arm compared to placebo in younger subjects (58.4% vs. 65.3%); while the opposite was observed in older subjects (56.8% vs. 44.3%).

Table 31: Study D9902B - Baseline characteristics of the four subgroups (Provenge +/- Docetaxel, Placebo +/- Docetaxel)

	Docetaxel		No Docetaxel	
	Provenge (N=195)	Placebo (N=86)	Provenge (N=146)	Placebo (N=85)
Age, median years (min, max)	70 (49, 88)	69 (53, 87)	74 (49, 91)	73 (40, 89)
Race, Caucasian (%)	89.7	91.9	89.0	90.6
ECOG status, 0 (%)	82.6	86.0	81.5	76.5
Gleason sum ≤ 7, (%)	75.4	73.3	75.3	77.6
Weight, median kgs (min, max)	90 (66, 159)	88 (65, 128)	86 (53, 175)	85 (60, 136)
Time from diag. to randomization, median years (min, max)	6.7 (0.8, 22,6)	7.4 (1.0, 16.6)	7.7 (0.8, 24,5)	6.5 (0.9, 21.5)
Disease localization, (%)				
Bone only	48.5	39.5	54.1	47.1
Soft tissue only	7.2	8.2	6.9	8.2
Bone and soft tissue	44.3	52.3	39.0	44.7
Primary Gleason Grade ≤ 3, (%)	43.1	38.4	41.1	44.7
Bone Metastases, (%)				
0 – 5	46.2	44.2	38.4	41.2
6 – 10	13.8	18.6	15.1	10.6
> 10	40.0	37.2	46.6	48.2
Bisphosphonate Use, (%)	49.7	51.2	45.9	44.7
Serum PSA, median ng/mL(min, max)	50 (5, 8005)	36 (6, 3745)	61 (5, 2370)	55 (7, 1519)
Serum PAP, median U/L (min, max)	2.6 (0.6, 466)	3.4 (0.6, 93)	2.8 (0.6, 433)	2.8 (0.6, 147)
Alkaline phosphatase, median U/L LDH, median U/L (min, max) Hemoglobin,	96 (38, 2031) 193 (115, 598)	104 (46, 607) 194 (101, 654)	103 (18, 2396) 196 (84, 637)	120 (43, 2813) 192 (131, 1662)
median g/dL (min, max)	13 (8, 18)	13 (9, 15)	13 (9, 16)	13 (9, 15)
Prior Orchiectomy, (%)	8.2	5.8	11.0	9.4
Prior Chemotherapy, (%)	11.3	9.3	30.8	21.2
Prior Docetaxel, (%)	7.2	4.7	26.7	20.0
Prior Radical prostatectomy, (%)	37.4	34.9	32.9	34.1
Prior Radiotherapy, (%)	53.3	55.8	55.5	50.6

A number of sensitivity analyses were conducted by the applicant to analyze the post-randomisation treatment effect of anticancer interventions.

Table 32: Study D9902B - Analyses to assess the impact of docetaxel on OS

Analysis	Effect	HR (95%-CI)
Primary analysis	Treatment	0.775 (0.614, 0.979)
Subjects censored at time of docetaxel initiation	Treatment	0.649 (0.469, 0.898)
Docetaxel as time dependent covariate	Treatment	0.777 (0.615, 0.981)
	Docetaxel	0.880 (0.692, 1.119)
Docetaxel and salvage treatment as time dependent covariates	Treatment	0.753 (0.538, 1.053)
	Docetaxel	0.882 (0.693, 1.123)
	Salvage treatment	0.950 (0.641, 1.408)

Time to non-study treatment interventions post-randomisation

Among subjects who received docetaxel at any time following randomisation, the median time from randomisation to post-treatment docetaxel use was 7.2 months (range 1.3 to 49.5 months) in the sipuleucel-T arm and 9.6 months (range 1.0 to 36.5 months) in the placebo arm.

An analysis of the time to docetaxel use for all randomised subjects was performed using the Kaplan-Meier method, where initiation of docetaxel was considered an event and subjects without docetaxel use were censored at their last study assessment. The estimated median time from randomisation to post-treatment docetaxel use was 12.3 months in the sipuleucel-T arm and 13.9 months in the placebo arm. The estimated HR for docetaxel use between the 2 groups (Sipuleucel-T vs. placebo) was 1.205 (95% CI: 0.934, 1.553; P = 0.150, log rank test).

In order to explore the sipuleucel-T treatment effect in the absence of docetaxel, an analysis was performed in which subjects in both treatment arms with known docetaxel use were censored at the time of docetaxel initiation.

Figure 12: Study D9902B - Kaplan-Meier estimate of OS by treatment arm with and without censoring at the time of docetaxel initiation

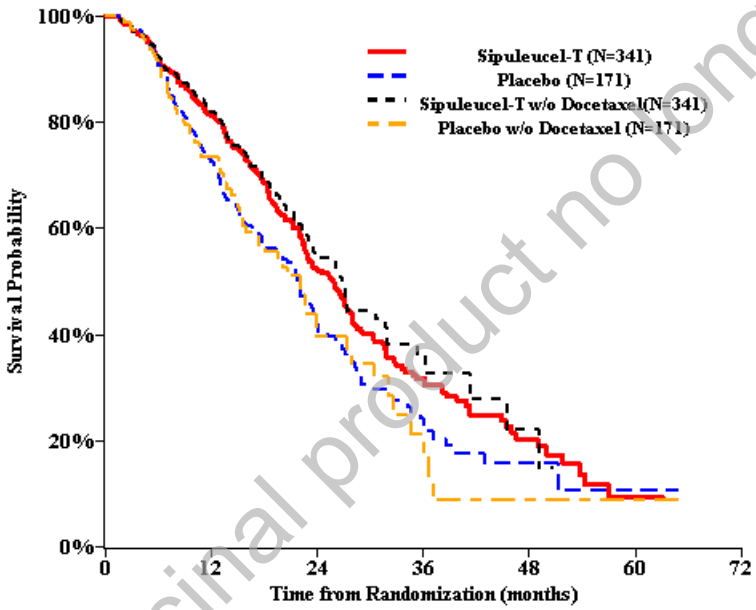
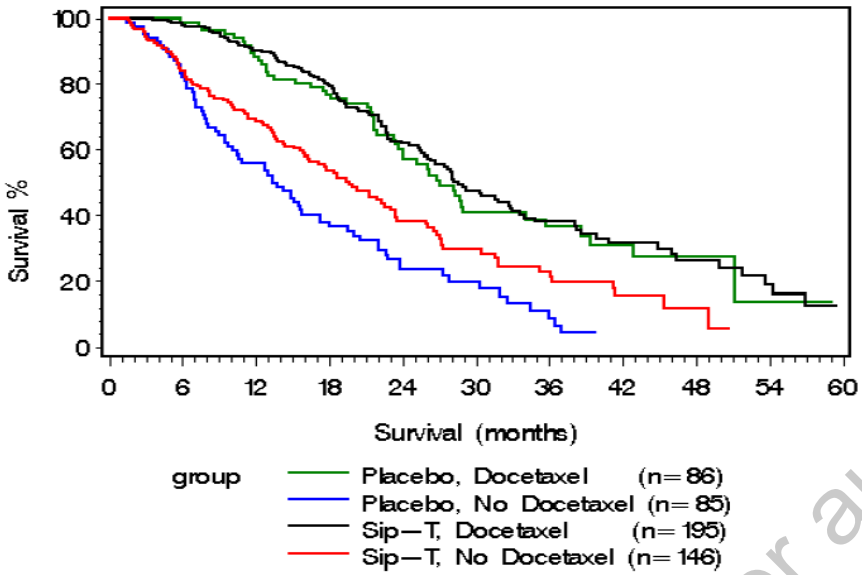


Table 33: Study D9902B - Overall survival according to treatment and docetaxel use

	Provenge		Placebo		
Docetaxel	N	Median OS	N	Median OS	HR (95%-CI)
Yes	195	28.5	86	27.1	0.936 (0.661, 1.325)
No	146	19.6	85	13.6	0.677 (0.491, 0.934)

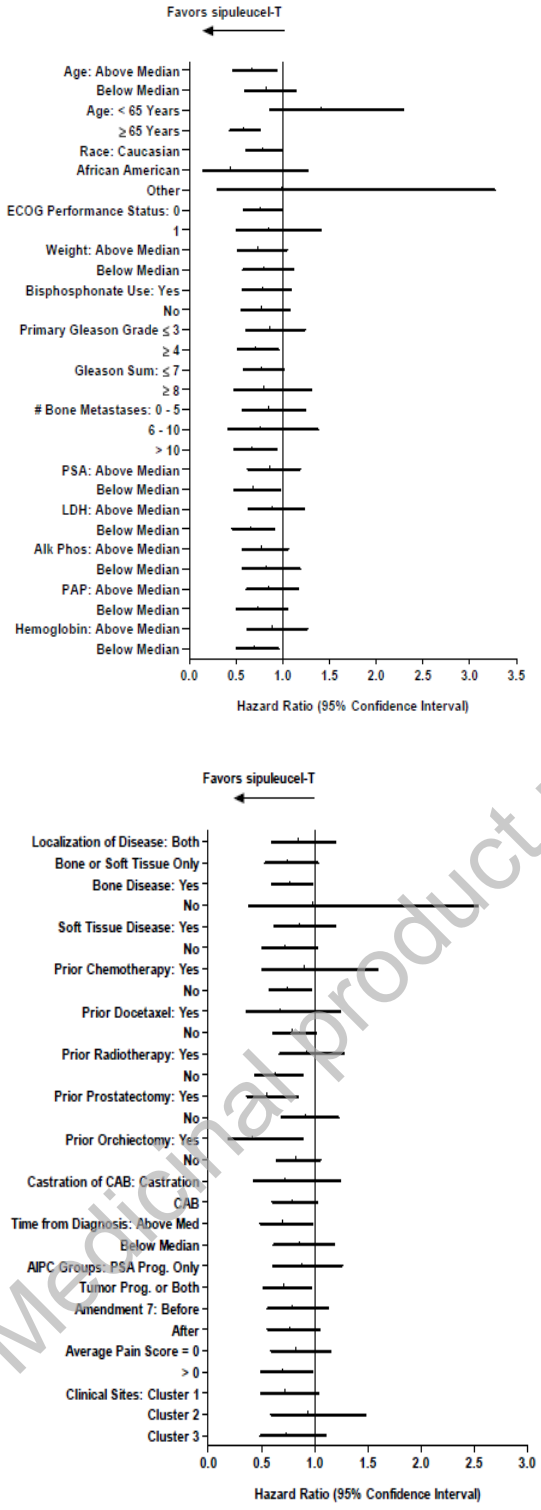
Figure 13: Study D9902B – Overall Survival by docetaxel subgroup (non-randomised)



Subgroups analysis

Subgroup analyses of overall survival by baseline covariates

Figure 14: Study D9902B - Subgroups analyses of the primary endpoint based on 27 baseline covariates



Subgroup by age quartiles

Table 34: Study D9902B - Subgroup analysis of OS by age quartiles in study D9902B (ITT)

Subgroup	Sipuleucel-T/Placebo	Median Survival Time [a] Sipuleucel-T/Placebo	Hazard Ratio (95% CI) [b]
	(n = 512)		
≤ 65	87 / 53	25.8 / 28.3	1.249 (0.792, 1.970)
66-71	80 / 43	31.5 / 17.3	0.468 (0.290, 0.757)
72-77	89 / 41	23.4 / 22.1	0.617 (0.386, 0.985)
> 77	85 / 34	18.6 / 15.0	0.700 (0.428, 1.144)

[a] Time units is in months. The median survival time was obtained using the Kaplan-Meier method.
[b] From a Cox regression model with treatment, subgroup and treatment subgroup interaction term as factors, adjusted for baseline PSA (ln) and LDH (ln), stratified by randomisation strata. All ITT patients were included in the model.

Subgroup by baseline PSA quartile

Table 35: Study D9902B – Median OS by PSA quartiles

Baseline PSA, ng/mL	PSA Q1 ≤ 22.1 (n = 128)	PSA Q2 > 22.1 to 50.1 (n = 128)	PSA Q3 > 50.1 to 134.1 (n = 128)	PSA Q4 > 134.1 (n = 128)
Median OS, months:				
Sipuleucel-T	41.3	27.1	20.4	18.4
Placebo	28.3	20.1	15.0	15.6
Difference, months	13.0	7. 1	5.4	2.8
HR (95% CI)	0.52 (0.31, 0.88)	0.69 (0.43, 1.09)	0.82 (0.53, 1.26)	0.85 (0.55, 1.32)

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 36: Summary of Efficacy for trial D9902B

Title: A Randomized, Double Blind, Placebo-Controlled Phase 3 Trial of Immunotherapy with Autologous Antigen Presenting Cells Loaded with PA2024 (Provenge, Sipuleucel-T) in Men with Metastatic Androgen Independent Prostatic Adenocarcinoma		
Study identifier	D9902B	
Design	randomized, parallel-group, placebo-controlled, double blind	
	Duration of main phase: Duration of run-in phase: Duration of extension phase:	Until disease progression or death Not applicable Not applicable
Hypothesis	Superiority of Sipuleucel-T over placebo with regard to overall survival	
Treatments groups	Sipuleucel-T	Sipuleucel-T, autologous PBMCs, including APCs loaded with PA2024 antigen. 3 infusions wks 0, 2, 4.
	Placebo	autologous quiescent APCs not loaded with PA2024 antigen, 3 infusions wks 0, 2, 4.

Endpoints and definitions	Primary: Overall survival	OS	Overall Survival: time from randomization to death from any course
	Secondary: Time to obj.disease progression	TODP	Time to objective disease progression: Time from randomisation to objective disease progression as determined by the IRRC
	Tertiary: Time to clin.progress	TCP	Time to clinical progression: Time from randomisation to clinical progression defined as: Objective disease progression Clinically relevant disease related events
	Tertiary: Prostate specific antigen (PSA) doubling time	PSADT	Estimated PSADT (weeks) with mixed effects model
Database lock	06 April 2009		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	ITT population at database cut-off (18 January 2009)		
Descriptive statistics and estimate variability	Treatment group	Sipuleucel-T	Placebo
	Number of subject	N = 341	N = 171
	Median OS (months)	25.8	21.7
	95% - CI	22.8 – 27.7	17.7 – 23.8
Effect estimate per comparison	Primary: Overall survival	Comparison groups	Sipuleucel-T vs. placebo
		HR	0.775
		95%-CI	0.614 – 0.979
		P-value	0.032
	Secondary: Time to objective disease progression	Comparison groups	Sipuleucel-T vs. placebo
		HR	0.951
		95%-CI	0.773 – 1.169
		P-value	0.628
	Tertiary: Time to clinical progression	Comparison groups	Sipuleucel-T vs. placebo
		HR	0.917
		95%-CI	0.749 – 1.123
		P-value	0.398
	Tertiary endpoint PSADT	Comparison groups	Sipuleucel-T vs. placebo
		Estimated PSADT (weeks) with mixed effects model	17.6/17.0

		P-value (F-test for unequal slopes)	0.721

Analysis performed across trials (pooled analyses and meta-analysis)

Overall Survival - Integrated data analysis

The integrated analyses of the overall survival data from the 3 studies were performed according to the abbreviated analysis plan (2008). The analysis plan was finalised prior to the interim analysis and unblinding of Study D9902B. Because Studies D9901 and D9902A did not follow subjects beyond 36 months, an estimate of treatment effect over 36 months based on pooled data was included in the analysis.

Table 37: Summary statistics for OS, integrated studies D9902B, D9901, and D9902A (ITT Population)

	Sipuleucel-T (N = 488)	Placebo (N = 249)
Censored, n (%)	180 (36.9)	62 (24.9)
Events, n (%)	308 (63.1)	187 (75.1)
Median Survival (months; 95% CI)	25.4 (22.7, 27.7)	21.5 (17.6, 23.5)
Primary Model[a]		
p-value	< 0.001	
Hazard Ratio (95% CI)	0.735 (0.613, 0.882)	
Unadjusted Analyses[b]		
p-value	< 0.001	
Hazard Ratio (95% CI)	0.734 (0.612, 0.881)	

[a] From a Cox regression model with treatment, PSA (ln) and LDH (ln) as the independent variables, stratified by study.
[b] P-Value was obtained from log-rank test and HR was obtained from an unadjusted Cox regression model, stratified by study.

Table 38

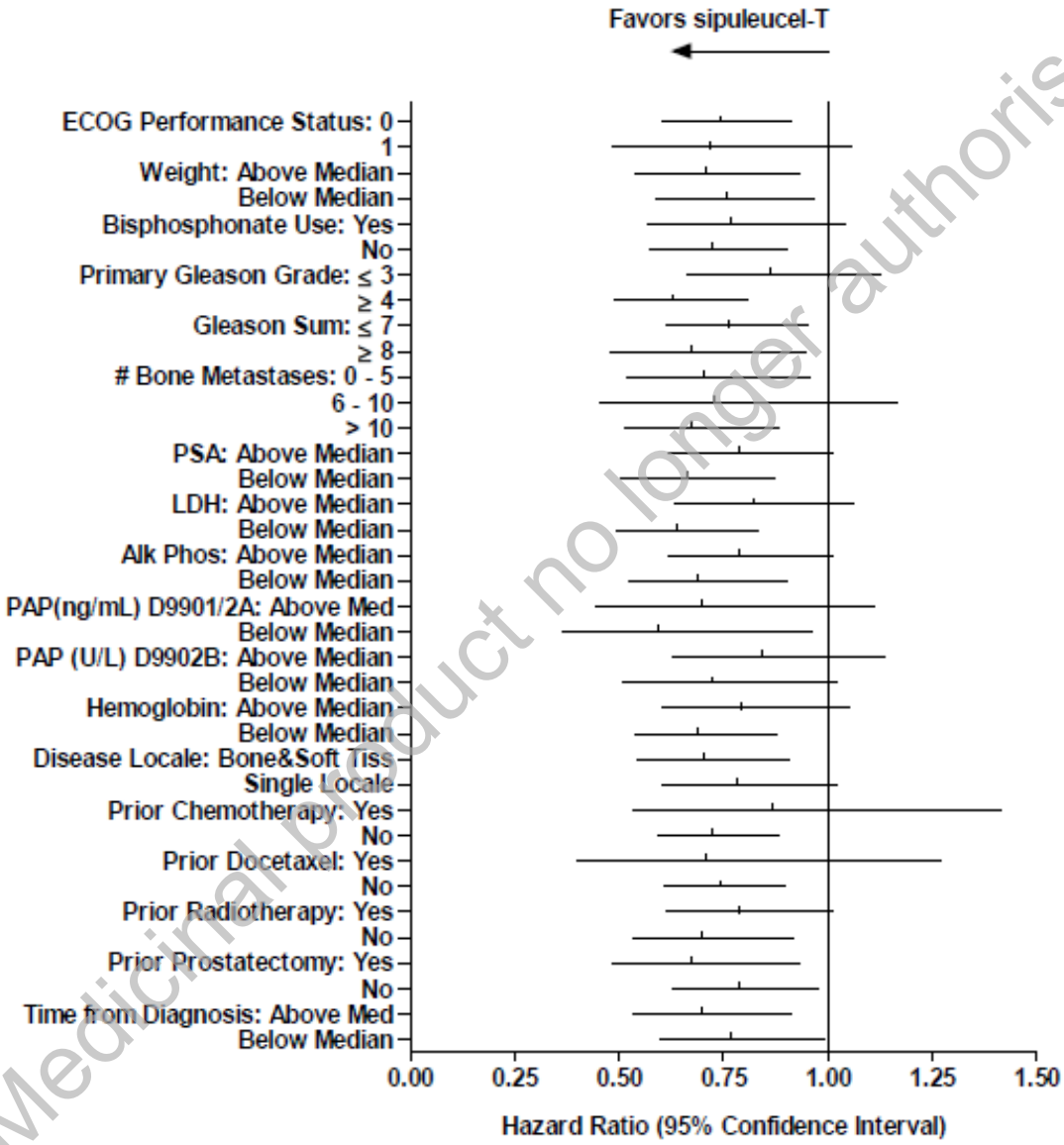
: Kaplan Meier Survival rate estimates, integrated Studies D9902B, D9901, and D9902A (ITT Population)

Treatment	12 Months	24 Months	36 Months
Sipuleucel-T	79.2	51.3	32.5
Placebo	71.0	40.9	19.7

Overall, 495 subjects (67.2%) had death events, with a median follow-up time of 36 months. The HR for treatment, based on the Cox PHR model with treatment group, baseline PSA (ln), and baseline LDH (ln) as the independent variables, stratified by study was 0.735 (95% CI: 0.613, 0.882), indicating a 26.5% reduction in the risk of death for subjects randomized to sipuleucel-T compared with placebo. The median survival time for subjects randomized to sipuleucel-T was

3.9 months longer than that for subjects randomized to placebo (median survival times of 25.4 months and 21.5 months, respectively). Excluding subjects with missing baseline covariates of either PSA or LDH from analysis, the corresponding HR for the treatment effect was 0.721 (95% CI: 0.600, 0.867).

Figure 15: Survival consistency in study subpopulations, integrated Studies (D9902B, D9901, and D9902A) (ITT Population)



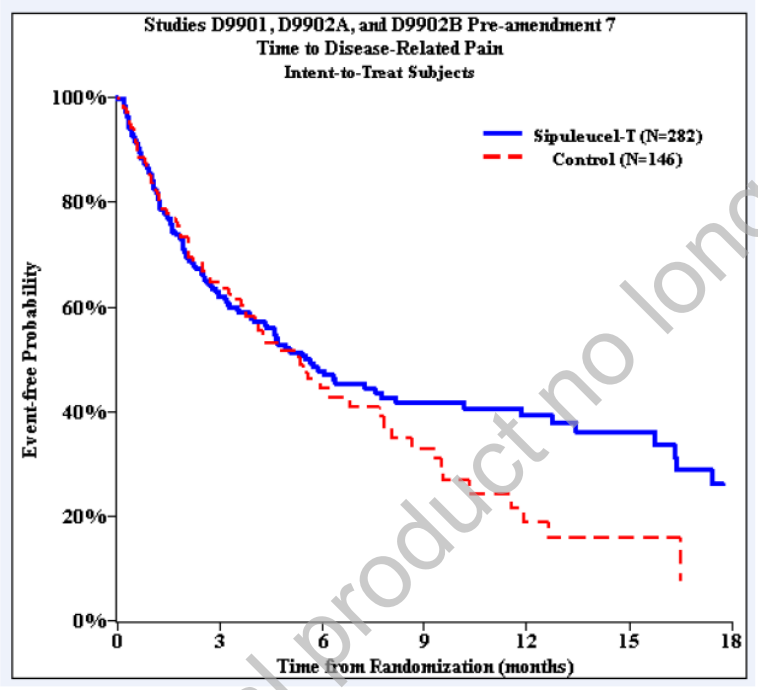
Note: Baseline PAP data could not be integrated due to the different, non-convertible units used for Study D9902B and Studies D9901 and D9902A.

Time to disease-related pain – Integrated data analysis

Table 39: Summary of disease progression and pain status by treatment arm in the Pooled Data (ITT Population)

Patient Disposition	Sipuleucel-T, n (%) (N = 282)	Placebo, n (%) (N = 146)
Pain and disease progression	125 (44.3)	69 (47.3)
Disease progression only	118 (41.8)	63 (43.2)
Pain only	12 (4.3)	6 (4.1)
No pain or disease progression	27 (9.6)	8 (5.5)

Figure 16: Time to disease related pain in studies D9901, D9902A and D9902B, pre-amendment 7



Supportive studies

Supportive studies included only asymptomatic patients and were conducted between 2000 and 2005.

Study D9901

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).

Table 40: Summary of efficacy for trial D9901

Title: A Randomized, Double blind, Placebo Controlled Trial of Immunotherapy with Autologous Antigen-Loaded Dendritic Cells (Provenge (APC8015)) for Asymptomatic, Metastatic, Hormone-Refractory Prostate Cancer					
Study identifier	D9901				
Design	<u>A Multicenter, Randomized, Double blind, Placebo Controlled Phase III</u>				
	Duration of main phase:		Study treatment until disease progression. Survival follow-up for 36 months		
	Duration of Run-in phase:		Not applicable		
	Duration of Extension phase:		Salvage extension upon progression for patients randomized in the control arm		
Hypothesis	Superiority				
Treatments groups	Intervention		APC8015, until disease progression, n= 82		
	Control, Placebo		APC-Placebo, until disease progression, n=45		
Endpoints and definitions	Primary endpoint	TDP	Time to disease progression		
	Secondary endpoints		Time to onset of disease-related pain		
			Response rate and duration of response		
			Time to clinical progression		
			Time to treatment failure		
			Incidence of ≥ Grade 3 treatment-related AEs		
	Additional endpoint		Survival		
Database lock	30 Apr 2002 (for primary analysis)				
<u>Results and Analysis</u>					
Analysis description	Primary Analysis				
Analysis population and time point description	Intent to treat				
Effect estimate per comparison	Primary endpoint TDP	Comparison groups:	APC8015 vs. APC-Pbo		
		Log rank test	Median TDP (weeks)		
		P-value = 0,052	11.7	10.0	
		Cox HR = 0.691 (0.473, 1.010)	(9.1,16.6)	(8.7,13.1)	
	Secondary endpoint: time to onset of disease-related pain	Comparison groups:	APC8015 vs. APC-Pbo		
		Log rank test	*(pooled analysis with dataset D9902A due to power considerations – results not presented)*		
		P-value = 0,210			
		Cox HR = 0.68 (0.37, 1.25)			
	Secondary endpoint: Objective TDP confirmed by imaging	Comparison groups:	APC8015 vs. APC-Pbo		
		Log rank test	Median time to event (weeks)		
		P-value = 0.183	15.4	11.6	
		Cox HR = 0.76 (0.50, 1.15)	(10.0, 17.6)	(9.1, 16.3)	

	Secondary endpoint: response rate / duration of response	No subjects experienced a tumor response, based on centralized radiological review.		
	Secondary endpoint: time to clinical progression	Comparison groups	APC8015 vs. APC-Pbo	
		Log rank test	Median time to event (weeks)	
		P-value = 0,061	10.7	9.1
		Cox HR = 0.69 (0.48, 1.02)	(8.9, 15.6)	(8.3, 13.0)
	Secondary endpoint: time to treatment failure	Comparison groups:	APC8015 vs. APC-Pbo	
		Log rank test	Median time to event (weeks)	
		P-value = 0,124	11.0	10.0
		Cox HR = 0.75 (0.52, 1.09)	(9.1, 16.3)	(8.7, 13.1)
	Additional endpoint: Survival	Comparison groups:	APC8015 vs. APC-Pbo	
		Log rank test	Median time to death (months)	
		P-value = 0,010	25.9	21.4
		Cox HR = 0.586 (0.388, 0.884)	(20.0,32.4)	(12.3,25.8)
Analysis description	Interim analyses : Two planned interim analyses were performed. Sensitivity analyses : Sensitivity analyses were performed. Subgroup / Interaction analyses: Additional analyses using the Cox proportional hazards model were performed to investigate the potential influence of prognostic factors, other than the treatment effect. Twenty-one potential prognostic factors were identified. Treatment effect on survival remained significant at the 0.05 level in the corresponding 21 Cox PH models (treatment and the factor as co variables). Based on the literature, 8 of the factors were considered of interest and their effect thoroughly explored with: - Cox PH model with treatment, the co-variable and an interaction term (treatment*co variable) - Same models, with categorization of continuous variables (mainly median split) - Multivariate analysis: 9 prognostic factors, backward stepwise selection method (entry p=0.05, removal p=0.10,LR test), resulting in a final model with 5 prognostic factors (LDH (Ln), PSA (Ln), localization of disease, number of bone metastases, body weight (lbs)) + treatment effect. Adjusted treatment HR=0.46 (p=0.002, Wald's test)			
Additional results	Overall survival 36-month survival (%): 34% Provenge (28/82) ; 11% Control (APC-Pbo) (5/45)			

Comparison of use of chemotherapy during long-term follow-up

Only the type of chemotherapy and the date of initiation were collected in this trial. No data on the dose or duration of chemotherapy are available.

Table 41: Study D9901 - Chemotherapy use following therapy

Chemotherapy	APC8015 (n = 78)	APC-Placebo (n = 41)	p-value (Fisher's Exact)
Docetaxel	29 (37.2%)	20 (48.8%)	0.244
Chemotherapy other than taxanes	34 (43.6%)	13 (31.7%)	0.240
Taxane-based chemotherapy	34 (43.6%)	22 (53.7%)	0.337
Any chemotherapy[a]	43 (54.4%)	27 (62.8%)	0.445

[a] For any chemotherapy, APC8015 (n=79) and APC-Placebo (n=43)

Study D9902A

Study D9902 was originally designed with the same sample size calculations and analysis plan as its companion study, D9901. The entry criteria were amended after 98 subjects had been enrolled. The portion of the study that was identical to D9901 and under which the first 98 subjects (65 sipuleucel-T, 33 placebo) were enrolled was designated D9902A and the portion of the study under which new subjects were enrolled was designated D9902B. Study D9902A was similar in design to the other studies, but enrollment was terminated prior to completion of accrual.

Table 42: Summary of efficacy for trial D9902A

Title: A Randomized, Double blind, Placebo Controlled Trial of Immunotherapy with Autologous Antigen-Loaded Dendritic Cells (Provenge (APC8015)) for Asymptomatic, Metastatic, Hormone-Refractory Prostate Cancer			
Study identifier	D9902A		
Design	A Multicenter, Randomized, Double blind, Placebo Controlled Phase III		
	Duration of main phase:		Study treatment until disease progression. Survival follow-up for 36 months
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Salvage extension upon progression for patients randomized in the control arm
Hypothesis	Superiority		
Treatments groups	Intervention		APC8015, until disease progression, n= 65
	Control, Placebo		APC-Placebo, until disease progression, n=33
Endpoints and definitions	Primary endpoint	TDP	Time to disease progression
	Secondary endpoints		Overall survival
			Time to objective disease progression
	Tertiary endpoints		Response rate and duration of response
			Time to onset of disease-related pain
			TDP adjusted on CPC and interaction CPC*treatment
	Safety endpoints		Incidence of ≥ Grade 3 treatment-related AEs
			Incidence of laboratory abnormalities

<table>
<tr><td colspan="5">Results and Analysis</td></tr>
<tr><td>Analysis description</td><td colspan="4">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="4">Intent to treat</td></tr>
<tr><td rowspan="15">Effect estimate per comparison</td><td rowspan="4">Primary endpoint: TDP</td><td>Comparison groups:</td><td colspan="2">APC8015 vs. APC-Pbo</td></tr>
<tr><td>Log rank test</td><td colspan="2">Median TDP (weeks)</td></tr>
<tr><td>P-value = 0,719</td><td>10.9</td><td>9.9</td></tr>
<tr><td>Cox HR = 0.921 (0.588, 1.443)</td><td>(9.3, 17.7)</td><td>(8.4, 18.0)</td></tr>
<tr><td rowspan="4">Secondary endpoint: Survival Cut-off at 36 months after randomization (N=96)+ 2 late enrollers</td><td>Comparison groups:</td><td colspan="2">APC8015 vs. APC-Pbo</td></tr>
<tr><td>Log rank test</td><td colspan="2">Median time to death (months)</td></tr>
<tr><td>P-value = 0,331</td><td>19.0</td><td>15.7</td></tr>
<tr><td>Cox HR = 0.786 (0.484, 1.278)</td><td>(13.6,31.9)</td><td>(12.8,25.4)</td></tr>
<tr><td rowspan="4">Secondary endpoint: Objective TDP confirmed by imaging</td><td>Comparison groups:</td><td colspan="2">APC8015 vs. APC-Pbo</td></tr>
<tr><td>Log rank test</td><td colspan="2">Median time to event (weeks)</td></tr>
<tr><td>P-value = 0.538</td><td>15.3</td><td>16.1</td></tr>
<tr><td>Cox HR = 0.86 (0.52, 1.40)</td><td>(10.0, 25.0)</td><td>(8.6, 24.9)</td></tr>
<tr><td rowspan="4">Tertiary endpoint: Time to onset of disease-related pain</td><td>Comparison groups:</td><td colspan="2">APC8015 vs. APC-Pbo</td></tr>
<tr><td>Log rank test</td><td colspan="2" rowspan="3">(pooled analysis with dataset D9902A due to power considerations – results not presented)</td></tr>
<tr><td>P=0.376</td></tr>
<tr><td>Cox HR = 1.41 (0.66, 3.04)</td></tr>
<tr><td rowspan="6"></td><td>Tertiary endpoint: response rate / duration of response</td><td colspan="3">Only one subject experienced a tumor response, based on centralized radiological review : partial response at W16, that lasted through W32 on bone scan assessment</td></tr>
<tr><td rowspan="4">Tertiary endpoint: time to clinical progression</td><td>Comparison groups</td><td colspan="2">APC8015 vs. APC-Pbo</td></tr>
<tr><td>Log rank test</td><td colspan="2">Median time to event (weeks)</td></tr>
<tr><td>P-value = 0,061</td><td>10.7</td><td>9.1</td></tr>
<tr><td>Cox HR = 0.69 (0.48, 1.02)</td><td>(8.9, 15.6)</td><td>(8.3, 13.0)</td></tr>
<tr><td>Tertiary endpoint: TDP adjusted on CPC and interaction CPC*treatment</td><td colspan="3">Interaction of CPC with the treatment was tested with a Cox PH model with an interaction term: the interaction parameter was significant at 0.10 level (Wald's test p=0.0771). This was attributed to an "outlier" CPC, with only 5 patients. Excluding this CPC from the analysis, the interaction test was not significant.</td></tr>
<tr><td>Analysis description</td><td colspan="4">Interim analyses
An interim analysis of survival was conducted when the 96th subject enrolled reached his 30 Month visit.
Subgroup / Interaction analyses:
As the main efficacy results were not significant, no further analyses (subgroups, etc.) are presented.
Other:
The final multivariate Cox survival prognosis model identified in study D9901 was applied to D9902A data set. Three factors previously identified were not significant among this external sample: localization of disease, number of bone metastases and body weight. PSA, lesion count and treatment (HR treatment = 0.52, p=0.023 Wald's test) remained significant.</td></tr>
</table>

Additional results	Overall Survival: 36-month survival (%): 32% (21/65) Provenge; 21% (7/33) Control (APC-Pbo)

Study P10-3 (PROCEED)

Study P10-3 is an observational study conducted in the US (registry). The applicant provided preliminary real world survival data from this ongoing registry.

Table 43: Survival rate estimate at time points in the US registry study P10-3

Survival rate estimate at time	**Sipuleucel-T** **Pivotal trial (ITT)**	**Sipuleucel-T** **US Registry Study P10-3**	**Placebo** **Pivotal trial (ITT)**
3 months	97.6 (96.0, 99.3)	97.3 (96.3, 98.4)	97.6 (95.4, 99.9)
6 months	92.0 (89.1, 94.9)	91.7 (89.8, 93.7)	90.6 (86.2, 95.0)
9 months	87.0 (83.4, 90.6)	85.6 (82.8, 88.5)	80.6 (74.6, 86.5)
12 months	81.1 (76.9, 85.3)	79.2 (75.3, 83.1)	72.4 (65.6, 79.1)

2.5.3. Discussion on clinical efficacy

Design and conduct of phase III clinical studies

The pivotal efficacy study D9902B was conducted between 2003 and January 2009 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. The inclusion criteria were amended several times during the course of the study, e.g. inclusion of patients with Gleason sum ›7, minimally symptomatic subjects (instead of only asymptomatic), and changes in eligibility criteria with regard to prior chemotherapy. The study design was initially planned with time to objective disease progression as the primary endpoint. However, the protocol was changed in 2007 to specify overall survival as the primary endpoint and time to objective disease progression as the secondary endpoint. Notwithstanding the issues of multiples amendment of eligibility criteria and efficacy criteria during the course of the study, the statistical methods applied were in general considered acceptable. Regarding concomitant treatment, the use of biphosphonate was allowed in the study. Since patients were stratified according to biphosphonate use, and dose was to be unchanged until progression, this was considered acceptable. After progression, the first anticancer intervention and the first chemotherapy were recorded and data on any subsequent anticancer intervention or PSA were lacking.

Efficacy data and additional analyses

The SAG pointed out that in case of disagreement between OS and PFS, the evidence of efficacy should be particularly convincing and ideally corroborated by other secondary endpoints, which was not the case in the pivotal study (see additional expert consultation). Similarly, the BSWP pointed out that the level of statistical evidence for the pivotal trial was not considered to be compelling. The CAT acknowledged that the reason for the dissociation between the overall survival results and other outcome measures remains unclear and that corroborative evidence from secondary endpoints was lacking in the pivotal trial. However, the CAT concluded that the observed results in terms of OS were considered sufficiently convincing in view of the consistent efficacy results observed across different trials. In the pivotal study D9902B median survival in the Provenge group was 4.1 months longer than in the placebo group translating into a statistically significant hazard ratio [HR] of 0.775 [95% CI: 0.614, 0.979], p = 0.032. A difference in OS was also observed in Study D9901 (HR = 0.586 [95% CI: 0.388, 0.884]; p = 0.010), while a trend toward improvement was observed in Study D9902A (HR = 0.786 [95% CI: 0.484, 1.278]; p = 0.331). Thus, the consistent efficacy results observed across trials were considered to provide compelling evidence of efficacy.

Due to the apparent shorter-than expected survival in patients >65 years treated in the placebo arm, the possibility of depletion of mononuclear cells leading to a detrimental effect on survival among the elderly patients in this group was investigated. The number of removed MNC was considered small, i.e. 1.5 to 2.0 litre leukapheresis procedure removed a median of 7.6×10^9 lymphocytes in study D9902B, equivalent to approximately 0.1% to 1.5% of the total body pool of lymphocytes). Safety data from the integrated analysis were also not consistent with a higher incidence of infection or higher grade infection in the placebo group. The results of the additional analysis performed by the applicant on blood counts at weeks 6, 14 and 26 after randomisation by treatment group, age and number of leukapheresis could not confirm this hypothesis. In addition, subgroup analysis by age quartile showed no increasingly positive OS effect (i.e. progressively lower HRs) with increasing age as would be expected if there was an adverse consequence of age-related effects, e.g. lymphodepletion.

Current clinical metrics of progression especially when assessed in bone are considered inadequate which may be a plausible explanation for the discrepancy as also expressed by the SAG (see additional expert consultation). In addition, immune responses to vaccines may require time to develop, and the lack of differences in progression could result from delayed antitumour responses occurring after e.g. PSA or radiologic progression.

The lack of demonstrated therapeutic benefit in secondary endpoints was not of concern per se considering that OS is the most reliably measured endpoint. In addition, the increase in median survival of 4.1 months with a 22.5% reduction in risk of death is considered clinically meaningful.

However, there were uncertainties on whether the observed difference in terms of OS resulted from a true and clinically relevant effect of Provenge due to the design of the study. Particularly, the CAT investigated whether the survival difference between the two arms could be attributable to subsequent therapies considering that the use of non-study anti-cancer treatment interventions was reported more frequently in the sipuleucel-T group. Abiraterone acetate, enzalutamide, and cabazitaxel were only available in clinical trials during study D9902B conduct and the number of trials that were conducted at the same time was limited. Therefore the

likelihood that these treatments influenced the observed sipuleucel-T treatment effect is negligible. The main therapy that could have contributed to the OS difference was docetaxel (see also additional expert consultation).

In order to assess the impact of subsequent docetaxel therapy on the estimated sipuleucel-T treatment effect, the applicant performed several subgroup analysis and simulations with different assumptions on the probability and timing of such subsequent therapies. A typical pattern of survival curves was present in study D9902B (Figure 13, Survival by docetaxel subgroup), most notably the feature of close survival curves for later line docetaxel use (regardless of initial placebo or sipuleucel-T) and separating curves for non-docetaxel use. However, the relevance of this analysis is very limited showing comparison of non-randomized groups. The between-arm comparisons are invalid due to the use of a post-randomisation outcome to define the subgroups and therefore the Kaplan-Meier estimates by subsequent docetaxel use should be interpreted with caution.

The applicant also performed two Cox-regression analyses including docetaxel as time dependent covariate. In general, correction methods based on including treatment as a time dependent covariate are likely biased, especially if switching is strongly related to underlying prognosis which may be the case in this trial because in general only subjects in sufficiently good condition could receive docetaxel.

The SAG and BSWP expressed doubts on whether the observed effect in terms of OS was a true finding due to a number of uncertainties and potential biases (see also additional expert consultation). Although the weaknesses of the data are acknowledged, the CAT considered that the difference in proportion of patients treated with docetaxel and the difference in time to start of docetaxel were too small to have a large impact on the comparison between the sipuleucel-T and the placebo groups in terms of OS. In particular, taking into account the expected OS improvement for docetaxel of 2.4 months in this patient population, the imbalance of 6.9% more patients in the sipuleucel-T treatment group who received post-randomization docetaxel in Study D9902B, and the short difference in terms of docetaxel treatment initiation after progression, are considered unlikely to explain the observed sipuleucel-T treatment effect to any significant extent. Even assuming differential patient selection for post-progression treatment with docetaxel, with factors associated with a larger docetaxel effect favouring the sipuleucel-T group, one would have to assume large interactions and very unequal distribution of favourable prognostic factors in order to have a significant impact on the overall conclusions. Such interaction and imbalance are considered unrealistic and incompatible with the consistent effect observed across trials. Thus, the efficacy of sipuleucel-T can be considered established despite the remaining uncertainties.

The SAG also highlighted the uncertainties and potential biases due to long post-progression survival period and uncertainties about the balance in post-progression therapies, and the incompleteness of the data to assess heterogeneity of the populations at progression in terms of disease burden and PSA (see also additional expert consultation). Although the uncertainties are acknowledged, the CAT considered that any imbalance in post-progression therapies would not have a large impact on the observed results (as already described for docetaxel, the effect associated with any such post-progression treatments on OS would be limited). Furthermore, major imbalances in the populations at progression in terms of prognostic factors and factors associated with post-progression treatment effect would not be expected and in any case would

not be expected to have a major impact on the effect of post-progression therapies on OS. Thus, although the uncertainties are acknowledged, these factors cannot explain the large difference in OS associated with sipuleucel-T.

In addition, there is supportive evidence from study D9901 in which a difference in OS was also observed (4.5 months) despite more frequent use of docetaxel in the placebo arm (48.8% of patients in the placebo group versus 37.2% in the Provenge group).

Although based on indirect comparisons, the results observed with Provenge were similar to data obtained in the pivotal trial of abiraterone (COU-AA-302) for OS (hazard ratio [HR] = 0.79; 95% CI, 0.66 – 0.96; P < 0.0151) (ASCO 2013).

Additional efficacy data will become available from an ongoing phase 3 randomised, study evaluating Provenge versus placebo in patients with non-metastatic prostate cancer who experience PSA elevation following radical prostatectomy (Study P-11, NCT00779402). This study could provide additional useful supportive data on efficacy of Provenge as measured by overall survival.

The final clinical study report will be provided by 31 December 2020.

In addition, the applicant will modify the protocol of observational study P12-1 (A Registry of Sipuleucel-T therapy in men with advanced prostate cancer; NCT01306890) to collect follow-up efficacy data for mCRPC patients in the context of currently available treatment options. Patients will receive either Provenge alone, Provenge plus other available treatments or only other available treatments (=no Provenge).

Study P12-1 is currently planned to evaluate characteristics predictive of a positive imaging study for distant metastases in patients with castrate-resistant prostate cancer. It will enrol 2000 non-metastatic CRPC patients over approximately 2 years who are evaluated at baseline and every 6 months thereafter for development of mCRPC. Approximately 1400 patients are expected to be diagnosed with mCRPC during the study and will then be followed in the metastatic arm of the study, i.e. patients will be treated for mCRPC at the investigator's discretion and will be followed for anticancer therapies and survival. The applicant will provide annual updates on progress on recruitment, the number of patients who developed metastasis, baseline characteristics of patients according to further treatment, and follow-up on efficacy parameters per treatment groups (e.g., including PSA progression, PSA progression-free survival, time to next line therapy, and overall survival). The amended protocol of the study will be submitted within 1 month of authorisation. The final study report is expected by 31 December 2019.

The exploratory analysis of overall survival by PSA quartile showed that patients in the lowest quartile PSA group had improved estimated median survival times. The benefit of Provenge appeared to decrease with increasing baseline PSA. The results are consistent with the mode of action of Provenge and the effectiveness of the patients' immunological responses showing a more robust and effective immune reaction in early disease stages with low cancer burden. Although exploratory, the results by PSA quartile were considered relevant to the prescribers and thus included in section 5.1 of the SmPC.

Additional expert consultation

The view of scientific advisory group (SAG) Oncology was sought on the interpretation of results of the pivotal study through six questions related to the observed contrasting effect of Provenge on the main endpoints, the potential impact of subsequent therapy on the OS results and the patient population that could benefit from Provenge. The SAG expressed doubts on whether the observed effect in terms of OS was a true finding due to a number of uncertainties and potential biases, in particular, the lower proportion of patients treated with docetaxel and a delayed treatment with docetaxel for the placebo group, a long post-progression survival period and uncertainties about the balance in post-progression therapies, and the incompleteness of the data to assess heterogeneity of the populations at progression in terms of disease burden and PSA. As regards plausible explanations for the observed discrepancy between OS and PFS, the SAG noted that difficulty in adjudicating progression based on bone imaging might have contributed. In addition, agreement between OS and PFS might potentially not be expected by sipuleucel-T being an immune modulatory agent but supportive mechanistic findings were partly missing. Importantly, in case of disagreement between these endpoints, the evidence of efficacy should be particularly convincing and ideally corroborated by other secondary endpoints. Such evidence was not observed in the pivotal study. Regarding a potential detrimental effect of the leukapheresis procedure on OS results in the placebo arm, the SAG agreed that the harvesting of mononuclear cells was unlikely to have adversely affected the outcome in the control group, also based on the current experience with healthy donors for allotransplantation.

As regards to the contrasting effect observed in the pre-planned subgroups over and under 65 years of age, the SAG considered that the apparent detrimental effect based on the point estimate of the hazard ratio associated with the younger age subgroup should be interpreted with caution and, although an interaction with age cannot be ruled out, the observed difference was most likely due to chance.

In relation to the question whether the relatively high proportion of patients having received previous chemotherapy (18%) in the pivotal study could affect the application of overall results to a first-line setting, this was not considered to constitute a major issue to draw conclusions in this setting.

Regarding potential extrapolation of efficacy data from patients without visceral metastasis to patients with visceral metastasis, the SAG was uncertain about the potential biological difference of different metastatic cancer cells and noted that the activity of Provenge in patients with visceral involvement is unknown since this population was excluded from the trial. Based on these uncertainties, it was considered not possible to extrapolate any efficacy results from a population with bone and soft tissue metastasis only to a population with visceral involvement.

The Biostatistics Working Party (BSWP) was consulted on the potential impact of post-randomisation interventions on OS results in the pivotal trial. Particularly the BSWP was enquired whether the design of the pivotal study with regard to the use of post-randomisation interventions could have biased the study results in terms of OS and whether it could be excluded that the use of docetaxel and other salvage therapy after objective disease progression had a relevant impact on the observed OS effect. The view of the BSWP was also sought on whether the strength of statistical evidence for an effect on OS associated with sipuleucel-T was convincing for an application based on a single pivotal trial.

As for the first question, the BSWP considered that the design of the pivotal study could be biased due to use of post-randomisation interventions, in particular docetaxel, because it was applied 1.6 months later and to less patients in the placebo arm (57% versus 50%), which may have put the placebo arm at an overall disadvantage.

Regarding the strength of statistical evidence, the level of statistical evidence (p=0.032 in the primary analysis, adjusted for the interim analysis to p=0.043) was not considered to be compelling and the 95%-confidence interval of the hazard ratio (0.614, 0.979) was close to 1.

The CAT considered the advice received from the SAG and BSWP (see above).

2.5.4. Conclusions on the clinical efficacy

The efficacy of Provenge has been assessed in a comprehensive development program in the target indication, i.e. patients with metastatic, castrate resistant prostate cancer in male adults.

An improvement of overall survival was observed in the pivotal study D9902B (HR=0.775 [95% CI: 0.614, 0.979], p=0.032). Median survival was 4.1 months longer in subjects who received Provenge than in subjects who received placebo. This survival difference is considered statistically significant and clinically meaningful.

On the basis of the submitted data, the argumentation put forward by the applicant, the SAG and BSWP experts, the CAT concludes that the clinical efficacy has been established.

Additional supportive efficacy data may become available from the following studies:

- Study P-11, a randomised, double-blind trial evaluating Provenge versus placebo in patients with non-metastatic prostate cancer who experience PSA elevation following radical prostatectomy;
- Study P12-1 to evaluate characteristics predictive of a positive imaging study for distant metastases in patients with castrate-resistant prostate cancer.

The CHMP endorse the CAT conclusion on clinical efficacy as described above.

2.6. Clinical safety

Patient exposure

Safety data were collected from four phase 3, randomised, controlled trials (RCTs). In addition, safety information from eight open-label uncontrolled phase 1 and 2 studies, two salvage studies and two compassionate use cases were presented (Table 44). Safety data from clinical trials were integrated or grouped by study type:

- Integrated safety data from four phase 3 double-blind, placebo-controlled studies (D9902B, D9901, D9902A, P-11), cut-off: January 2009.
- Safety data from phase 1/2 studies (7 completed phase 1/2 studies, 3 ongoing studies, 2 compassionate use cases)

Table 44: Summary of clinical studies that provided safety data

Study	Number of Subjects in safety population[1)] Test product(s) and dosage regimen	Study Population	Cut-off date
Phase 3 studies **Integrated safety analysis – cut off January 2009**			
D9902B Phase 3 Randomized (2:1) Double-blind Placebo-controlled Multicentre (completed)	**N = 506** Subject exposure - Sipuleucel-T: 330 - Placebo: 167 Treatment : Sipuleucel-T (APC8015) or Placebo[2)] 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD[3)] Minimum dose: 20 x 10^6 CD54+ cells	Asymptomatic or minimally symptomatic mCRPC[4)]	18 JAN 2009
D9901 Phase 3 Randomized (2:1) Double-blind Placebo-controlled Multicentre (completed)	**N = 127** Subject exposure: - Sipuleucel-T: 82 - Placebo: 45 Treatment : Sipuleucel-T (APC8015) or Placebo 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD Minimum dose: 3 x 10^6 CD54+ cells	Asymptomatic mCRPC	09 SEP 2004
D9902A Phase 3 Randomized (2:1) Double-blind Placebo-controlled Multicentre (completed)	**N = 96** Subject exposure: - Sipuleucel-T: 64 - Placebo: 31 Treatment : Sipuleucel-T (APC8015) or Placebo 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD Minimum dose: 3 x 10^6 CD54+ cells	Asymptomatic mCRPC	12 MAY 2005
P-11 Phase 3 Randomized (2:1) Double-blind Placebo-controlled Multicentre (ongoing)	**N = 175** Subject exposure: - Sipuleucel-T: 113 - Placebo: 59 Treatment : Sipuleucel-T (APC8015) or Placebo 3 intravenous infusions at weeks 0 – 2 – 4 1 optional booster within 3 months of biochemical failure (PSA $\geq$3 ng/ml) APC8015 dose per infusion: MMD Minimum dose: 3 x 10^6 CD54+ cells (prior to 12/2003) 20 x 10^6 CD54+ cells (after 12/2003)	Non-metastatic ADPC[5)] with PSA progression following radical prostatectomy	23 JAN 2009
Phase 1 and Phase 2 studies			
ACT 9610 Phase 1/2 Open label Uncontrolled Dose escalation Single centre (completed)	**N = 31 (Phase 1: 12, Phase 2: 19)** Subject exposure: Sipuleucel-T: 31 0.2 x 10^9 cells/m^2: 3 0.6 x 10^9 cells/m^2: 3 1.2 x 10^9 cells/m^2: 25 Treatment : Sipuleucel-T (APC8015) 4 intravenous infusions at weeks 0 – 4 – 8 – 24 (Phase 1: 0.2 x 10^9 cells/m^2 or 0.6 x 10^9 cells/m^2 or 1.2 x 10^9 cells/m^2 ; Phase 2: 1.2 x 10^9 cells/m^2)	Phase 1: mCRPC Phase 2: non-metastatic CRPC with evidence of disease progression	28 OCT 1999
D9905 Phase 2 Open label Uncontrolled (completed)	**N = 19** Subject exposure: Sipuleucel-T: 19 Treatment : Sipuleucel-T (APC8015) 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD (~1.2 x 10^9 cells/m^2)	Non-metastatic prostate cancer with PSA progression after definitive local therapy	17 JUN 2004
D9906 Phase 1 Open label	**N = 18** Subject exposure: Sipuleucel-T: 18 0.6 x 10^9 cells/m^2 : 3	Japanese men with mCRPC	31 JAN 2002

Uncontrolled (completed)	all cells from standard (7L) leukapheresis: 12 all cells from prolonged (10L) leukapheresis: 3 Treatment : Sipuleucel-T (APC8015) 3 intravenous infusions at weeks 0 – 2 – 4 3 dose levels (see above)		
ACT 9702 Phase 1/2 Open label Uncontrolled Dose escalation (completed)	**N = 34 (Phase 1: 13, Phase 2: 21)** Subject exposure: Sipuleucel-T: 34 Treatment : Sipuleucel-T (APC8015) *Phase 1:* 2 intravenous infusions at weeks 0 – 4 APC8015 dose per infusion: MMD (~1.2 x 10^9 cells/m^2) 3 subcutaneous PA2024 antigen injections at weeks 8 – 12 – 16 PA2024 dose levels: 0.3, 0.6, or 1 mg *Phase 2:* 2 intravenous infusions at weeks 0 – 2 APC8015 dose per infusion: MMD (~1.2 x 10^9 cells/m^2) 3 subcutaneous PA2024 antigen injections at weeks 4 – 8 – 12 PA2024 dose: 1 mg	mCRPC with evidence of disease progression	21 MAR 2001
P09-1 Phase 2 Open label Uncontrolled Multicentre (ongoing)	**N = 98**[1a)] Subject exposure: Sipuleucel-T: 98 Treatment : Sipuleucel-T (APC8015) 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD Minimum dose: 20 x 10^6 CD54+ cells	mCRPC with evidence of disease progression	10 AUG 2011
P07-1 Phase 2 Open label Uncontrolled Multicentre (ongoing)	**N = 15** Subject exposure: Sipuleucel-T: 15 Treatment : Sipuleucel-T (APC8015) 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD Minimum dose: 20 x 10^6 CD54+ cells If randomized, 1 booster infusion at 12 weeks following radical prostatectomy	Histologically confirmed localized prostate cancer without prior radical prostatectomy	21 DEC 2010
D9801 Phase 1 Open label Uncontrolled (completed)	**N = 15** Subject exposure: APC8026: 15 Treatment: APC8026[7)] 4 intravenous infusions at weeks 0 – 2 – 4 – 16 3 dose levels: 1 x 10^9 cells/m^2;2.5 x 10^9 cells/m^2 ;4 x 10^9 cells/m^2	Advanced CRPC	01 JUN 1999
P07-2 Phase 2 Randomized (1:1:1) Single-blind Uncontrolled Dose ranging study Multicentre (ongoing)	**N = 71** Subject exposure: - Sipuleucel-T: 23 - other: 47 (product with 5 µg/mL or 2 µg/mL PA2024) Treatment: Sipuleucel-T (APC8015) 3 intravenous infusions at weeks 0 – 2 – 4 APC8015 dose per infusion: MMD Minimum dose: 20 x 10^6 CD54+ cells Different PA2024 antigen concentrations (10, 5, or 2 µg/mL)	Asymptomatic or minimally symptomatic metastatic androgen independent prostate cancer	21 DEC 2010
Salvage studies			
PB01 Salvage study Phase 2 Open label Uncontrolled Multicentre (completed)	**N = 113** Subject exposure: APC8015F: 109 Treatment: APC8015F[6)] 3 intravenous infusions at weeks 0 – 2 – 4 Minimum dose: 3 x 10^6 CD54+ cells	mCRPC with objective disease progression in placebo group of Study D9902B	08 JUN 2009
D9903 Salvage study Phase 2	**N = 56** Subject exposure: APC8015F: 56 Treatment: APC8015F	mCRPC with objective disease	19 OCT 2004

Open label Uncontrolled Multicentre (completed)	3 intravenous infusions at weeks 0 – 2 – 4 Minimum dose: 3 x 10^6 CD54+ cells	progression in placebo group of Study D9901 or D9902A	

1): Safety population defined as subjects who underwent at least 1 leukapheresis procedure
1a: Safety population of study P09-1 comprised subjects who received at least 1 infusion of Sipuleucel-T
2): Autologous quiescent APCs not loaded with PA2024 antigen with a dose corresponding to about one third of the quiescent APCs prepared from a single leukapheresis procedure (Studies D9902A, D9902B, D9901) or to the total nucleated cell harvest from a single leukapheresis procedure (Study P-11)
3): Maximum manufacturable dose (maximum that could be prepared from single leukapheresis)
4): Metastatic castrate-resistant prostate cancer
5): Androgen-dependent prostate cancer
6): Prepared from cryopreserved autologous PBMCs that have been thawed and activated with PA2024
7): APC8026 was produced using a single separation step versus 2-step separation for APC8015

Information on all adverse events (AEs) was collected until disease progression in study D9902B, through week 16 (study day 112) in Studies D9901 and D9902A, and until the biochemical failure endpoint defined as PSA $\geq$3ng/ml was met (median time approximately 15 – 18 months) in study P-11. Thereafter, information on cerebrovascular events (CVEs), AEs considered to be related to study treatment, and deaths was collected. In the completed phase 1 and 2 studies, AEs were collected at regularly scheduled study visits, or whenever they occurred, until disease progression.

In total, 1207 subjects with prostate cancer who underwent at least one leukapheresis procedure were included in the safety population. Among them, 1193 received at least one subsequent treatment: 829 subjects were treated with Provenge, 137 subjects with placebo alone, 165 with placebo followed by APC8015F, 15 with APC8026 and 47 with the variant of Provenge manufactured with 2 or 5 µg/mL of the antigen PA2024. Among 1193 subjects, 165 received infusions of more than one product type. Specifically, these patients initially received placebo (studies D9902B, D9901, or D9902A) and were subsequently treated with APC8015F (salvage studies PB01 or D9903, respectively). There were 1358 product-type exposures. In terms of number of infusions, a total of 4018 infusions have been administered to subjects in the safety population: 2455 infusions of Provenge, 910 infusions of placebo, 470 infusions of APC8015F, 47 infusions of APC8026, and 136 infusions of variants of sipuleucel-T with different concentrations of antigen PA2024.

A total of 904 subjects (Provenge, N = 601; placebo, N = 303) were included in the safety population of the four randomised phase 3 studies ('integrated safety data') and 2677 infusions were administered (Provenge, N=1767; Placebo, N=910).

Table 45: Summary of subject demographics and baseline characteristics, integrated phase 3 studies (D9902B, D9901, D9902A, P-11), Safety Population

	Sipuleucel-T (N=601)	**Placebo (N=303)**
Age (years):		
- Mean	69.8	69.4
- Median	70	69
- Range	47 – 91	40 – 89
Age Categories, n(%):		
- 40 – 49	6 (1.0)	4 (1.3)
- 50 – 59	75 (12.5)	36 (11.9)
- 60 – 69	197 (32.8)	115 (38.0)
- 70 – 74	131 (21.8)	59 (19.5)
- 75 - 79	112 (18.6)	53 (17.5)
- 80 – 84	60 (10.0)	24 (7.9)

- 85 – 89	19 (3.2)	12 (4.0)
- ≥ 90	1 (0.2)	0 (0.0)
Ethnicity:		
- Caucasian	540 (89.9)	279 (92.1)
- African American	40 (6.7)	12 (4.0)
- Asian	2 (0.3)	2 (0.7)
- Hispanic	14 (2.3)	8 (2.6)
- Other	4 (0.7)	0 (0.0)
- Unknown	1 (0.2)	2 (0.7)
ECOG Performance Status, n(%):		
- 0	495/596 (83.1)	254/302 (84.1)
- 1	101/596 (16.9)	48/302 (15.9)
Gleason Sum, n(%):		
- < 6	102/578 (17.6)	44/294 (15.0)
- 7	325/578 (56.2)	170/294 (57.8)
- > 8	151/578 (26.1)	80/294 (27.2)
Time from Diagnosis to Randomization (Years):		
Mean	7.2	6.9
Median	6.5	6.5
Range	0.8 – 24.5	0.9 – 21.5
Time Categories (Years):		
0 – 5	222 (36.9)	109 (36.0)
6 – 10	245 (40.8)	129 (42.6)
11 – 15	99 (16.5)	56 (18.5)
16 – 20	30 (5.0)	8 (2.6)
21 – 25	5 (0.8)	1 (0.3)

Exposure to leukapheresis procedure and treatment

The study subjects were scheduled to undergo a series of three standard 1.5 to 2.0 blood volume leukapheresis procedures (at approximately weeks 0, 2, and 4) to harvest peripheral blood mononuclear cells, each followed 2 to 3 days later by infusion of the autologous cell-based investigational or control product. Prior mobilisation with a colony-stimulating factor was not performed. In some instances, additional leukaphereses were needed to produce a product suitable for infusion. The treatment schedule is detailed in Table 44.

The majority of subjects participating in the phase 3 studies underwent three leukaphereses and received 3 infusions (Table 46). Approximately 73% of subjects in the Provenge group received each infusion from a single leukapheresis procedure. 25.4% of patients treated with Provenge required more than 3 leukapheresis procedures in order to receive 3 infusions.

Table 46: Leukaphereses and infusions, integrated phase 3 studies, Safety Population

	Sipuleucel-T	**Placebo**	**Total**
1 leukapheresis	9 (1.5)	4 (1.3)	13 (1.4)
2 leukaphereses	21 (3.5)	6 (2.0)	27 (3.0)
3 leukaphereses	389 (64.7)	220 (72.6)	609 (67.4)
4 leukaphereses	148 (24.6)	61 (20.1)	209 (23.1)
5 or more leukaphereses	34 (5.7)	12 (4.0)	46 (5.1)
Number of infusions			
0 infusions	12 (2.0)	1 (0.3)	13 (1.4)
1 infusion	14 (2.3)	7 (2.3)	21 (2.3)
2 infusions	21 (3.5)	8 (2.6)	29 (3.2)
3 infusions	554 (92.2)	287 (94.7)	841 (93.0)

Booster infusion[a]	49 (8.2)	26 (8.0)	75 (8.3)

a: Subjects enrolled in Study P-11 were eligible for a booster infusion of randomized treatment (Sip-T or PBO) following biochemical failure. Subjects that had received only 1 or 2 infusions may have received a booster infusion following biochemical failure.

Table 47: Listing of reasons for not having received the full regimen of 3 infusions

Reason	Sipuleucel-T	Placebo
▪ Leukapheresis product did not meet quality standards	18	3
▪ Venous access problem	1	1
▪ Leukapheresis associated adverse event	1	1
▪ Treatment associated adverse event	9	5
▪ Disease progression prior to infusion	8	4
▪ Subject refused	6	2
▪ Other:		
- Diagnosis of intercurrent plasmacytic leukaemia	1	
- Diagnosis of pre-existing cutaneous T cell lymphoma	1	
- Epidural abscess prior to infusion	1	
- Transport failure	1	
Total	**47**	**16**

D9901: 2 additional subjects in Sipuleucel-T group received only 200 mL of first infusion due to treatment related AEs.
Source: Listings 16.2.5.1, 16.2.5.2, 16.2.5.3, 16.2.5.4, 16.2.7.1

Table 48: Summary of time between product infusions, Integrated Phase 3 Studies, Safety Population

Time	Sipuleucel-T (N = 601) Median (range)	Placebo (N = 303) Median (range)
Infusion 1 to infusion 2, days	14 (7, 84)	14 (8, 55)
Infusion 2 to infusion 3, days	14 (7, 105)	14 (7, 44)
Infusion 1 to infusion 3, days	28 (21, 119)	28 (22, 69)

Table 49: Summary of cumulative cell doses administered to subjects who received at least 1 Infusion, Integrated Phase 3 Studies (D9902B, D9901, D9902A, P-11)

		Sipuleucel-T (N=589)	**Placebo (N=302)**
CD54+ Cell Count (x10^9)	N	588[1)]	301[1)]
	Mean	2.183	1.019
	Median	1.877	0.879
	Q1 – Q3	1.292 - 2.879	0.523 - 1.315
	Min – Max	0.108 - 8.600	0.003 - 6.988
CD54 Upregulation Ratio	N	588	301
	Mean	27.652	2.594
	Median	26.959	2.683
	Q1 – Q3	21.730 - 33.618	2.394 - 2.861
	Min – Max	2.900 - 69.648	0.623 - 4.060
TNC[2)] Count (x10^9)	N	588	300
	Mean	10.893	3.532
	Median	9.831	3.384
	Q1 – Q3	6.971 - 13.668	2.299 - 4.624
	Min – Max	0.843 - 35.974	0.093 - 8.626

1): 2 subjects from study P-11 were excluded.
Subject P11011-011 was randomized to the Sipuleucel-T arm, but received 2 placebo infusions and 1 Sipuleucel-T infusion. Subject P11015-003 was randomized to placebo, but received 3 Sipuleucel-T infusions and 1 placebo booster infusion.
2): Total nucleated cell count

Table 50: CD54 Up-regulation by product and infusion for subjects who received at least 1 Infusion, Study D9902B

Infusion	**Summary Statistics**	**Sipuleucel-T** (N=330)	**Placebo** (N=167)
1	N	330	167
	Mean	6.84	0.85
	Geometric Mean (95% Confidence Interval)	6.43 (6.21, 6.66)	0.83 (0.79, 0.87)
	Median	6.53	0.86
	Minimum, Maximum	2.53 – 16.38	0.14 – 1.27
2	N	324	161
	Mean	11.62	0.86
	Geometric Mean (95% Confidence Interval)	10.79 (10.39, 11.22)	0.85 (0.8, 0.89)
	Median	11.20	0.87
	Minimum, Maximum	2.66 – 27.40	0.14 – 1.28
3	N	313	159
	Mean	11.87	0.86
	Geometric Mean (95% Confidence Interval)	11 (10.6, 11.42)	0.85 (0.8, 0.89)
	Median	11.38	0.85
	Minimum, Maximum	2.73 – 36.22	0.45 – 1.71

Sipuleucel-T: Infusion 2 vs 1: $p < 0.001$; Infusion 3 vs 1: $p < 0.001$; Infusion 2 vs 3: $p = 0.404$
Placebo: no significant differences
Examining CD54 upregulation by infusion, shows a significantly higher median value for the second and third infusion compared to the first application for the Sipuleucel-T group. In contrast, downregulation/loss of CD54 is observed for the control group.

Adverse events

A total of 882 subjects among 904 (97.6%) reported AEs in the integrated safety data (Table 51).

Table 51: Incidence of adverse events by NCI CTCAE[1)] toxicity grade, integrated phase 3 studies (D9902B, D9901, D9902A, P-11) - Safety Population

Toxicity Grade[a]	**Sipuleucel-T (N = 601) n (%)**	**Placebo (N = 303) n (%)**	**Total (N = 904) n (%)**
Any Adverse Event	591 (98.3)	291 (96.0)	882 (97.6)
Grade 1	137 (22.8)	74 (24.4)	211 (23.3)
Grade 2	268 (44.6)	120 (39.6)	388 (42.9)
Grade 3	142 (23.6)	76 (25.1)	218 (24.1)
Grade 4	24 (4.0)	10 (3.3)	34 (3.8)
Grade 5	20 (3.3)	11 (3.6)	31 (3.4)

1): National Cancer Institute's Common Terminology Criteria for Adverse Events
NCI Toxicity Grade: 1 = Mild; 2 = Moderate; 3 = Severe; 4 = Life-threatening; 5 = Fatal.
Subjects were counted only once under the maximum severity grade experienced for each preferred term.

Table 52: Most commonly reported adverse events by preferred term (decreased frequency), Safety Population, Integrated Phase 3 Studies (C9902B, D9901, D9902A, P-11)

Preferred Term	**Sipuleucel-T**	**Placebo**
	(N = 601)	**(N = 303)**
	n (%)	**n (%)**
Any Adverse Event	591 (98.3)	291 (96.0)
Chills	319 (53.1)	33 (10.9)
Fatigue	247 (41.1)	105 (34.7)
Pyrexia	188 (31.3)	29 (9.6)
Back Pain	178 (29.6)	87 (28.7)
Nausea	129 (21.5)	45 (14.9)
Arthralgia	118 (19.6)	62 (20.5)
Headache	109 (18.1)	20 (6.6)
Citrate Toxicity	89 (14.8)	43 (14.2)
Paraesthesia	85 (14.1)	43 (14.2)
Vomiting	80 (13.3)	23 (7.6)
Anaemia	75 (12.5)	34 (11.2)
Constipation	74 (12.3)	40 (13.2)
Pain	74 (12.3)	20 (6.6)
Paraesthesia Oral	74 (12.3)	43 (14.2)
Pain in Extremity	73 (12.1)	40 (13.2)
Dizziness	71 (11.8)	34 (11.2)
Myalgia	71 (11.8)	17 (5.6)
Asthenia	65 (10.8)	20 (6.6)

Diarrhoea	60 (10.0)	34 (11.2)
Influenza Like Illness	58 (9.7)	11 (3.6)
Musculoskeletal Pain	54 (9.0)	31 (10.2)
Dyspnoea	52 (8.7)	14 (4.6)
Oedema Peripheral	50 (8.3)	31 (10.2)
Hot Flush	49 (8.2)	29 (9.6)
Haematuria	46 (7.7)	18 (5.9)
Muscle Spasms	46 (7.7)	17 (5.6)
Hypertension	45 (7.5)	14 (4.6)
Anorexia	39 (6.5)	33 (10.9)
Bone Pain	38 (6.3)	22 (7.3)
Upper Respiratory Tract Infection	38 (6.3)	18 (5.9)
Insomnia	37 (6.2)	22 (7.3)
Musculoskeletal Chest Pain	36 (6.0)	23 (7.6)
Cough	35 (5.8)	17 (5.6)
Neck Pain	34 (5.7)	14 (4.6)
Weight Decreased	34 (5.7)	24 (7.9)
Urinary Tract Infection	33 (5.5)	18 (5.9)
Rash	31 (5.2)	10 (3.3)
Hyperhidrosis	30 (5.0)	3 (1.0)
Tremor	30 (5.0)	9 (3.0)
Hypoaesthesia	29 (4.8)	9 (3.0)
Abdominal pain	28 (4.7)	9 (3.0)
Groin pain	27 (4.5)	8 (2.6)
Decreased appetite	26 (4.3)	13 (4.3)
Urinary retention	26 (4.3)	14 (4.6)
Feeling cold	24 (4.0)	1 (0.3)
Hypotension	24 (4.0)	11 (3.6)
Nasopharyngitis	23 (3.8)	10 (3.3)
Anxiety	22 (3.7)	18 (5.9)
Depression	22 (3.7)	17 (5.6)
Hydronephrosis	18 (3.0)	14 (4.6)
Contusion	16 (2.7)	17 (5.6)
Dyspepsia	15 (2.5)	13 (4.3)
Haematoma	15 (2.5)	5 (1.7)
Hypoaesthesia oral	15 (2.5)	4 (1.3)
Infusion related reaction	15 (2.5)	2 (0.7)
Somnolence	15 (2.5)	7 (2.3)

Note: Subjects with multiple occurrences of the same event are counted only once in the incidence for that particular event.

Events in bold occurred at least twice as frequently in the sipuleucel-T group compared with the placebo group.

Time of onset

Adverse events occurring ≤ 1 day following a leukapheresis procedure in ≥5% of subjects in either treatment group were well balanced between treatment groups. Adverse reactions that were reported most commonly ≤ 1 day following a leukapheresis procedure in the sipuleucel-T

group included citrate toxicity (14.6%), oral paraesthesia (12.0%), and paraesthesia (11.1%). Additional adverse reactions that were seen commonly ≤ 1 day following a leukapheresis procedure included fatigue (5.5%), muscle spasm (4.0%), chills (3.0%), dizziness (2.8%), and anaemia (2.8%). The majority of AEs occurring ≤ 1 day following a leukapheresis procedure were Grade 1 or Grade 2. Grade 3 paraesthesia, fatigue, and dizziness were each reported by 1 subject in the sipuleucel-T group, and Grade 3 chills was reported by 2 subjects in the sipuleucel-T group. The majority of AEs occurring ≤1 day following leukapheresis in ≥5% of subject had a duration of ≤ 2 days. However, the majority of fatigue AEs with onset ≤1 day following leukapheresis had a duration > 2 days: 2 subjects in the sipuleucel-T group and 2 placebo subjects had fatigue AEs lasting 2 to 14 days, while 7 subjects in the sipuleucel-T group and 5 placebo subjects had fatigue AEs lasting > 14 Days.

Overall, 625 subjects (69.1%) developed an AE within 1 day of an infusion: 477 subjects (79.4%) in the sipuleucel-T group compared with 148 subjects (48.8%) in the placebo group. The AEs observed in ≥5% of subjects in the sipuleucel-T group within 1 day of infusion were chills, pyrexia, fatigue, headache, nausea, myalgia, influenza like illness, vomiting, pain, and arthralgia. The majority of these events were Grade 1 or 2 in severity. Most events were of short duration (i.e., resolved in ≤2 days). However, in both treatment groups, the duration of most fatigue, pain, and arthralgia events was 2 to 14 days.

In general, most events occurred ≤1 day or >14 days after infusion in both treatment groups. Adverse events that occurred > 14 days following infusion of sipuleucel-T in ≥ 5% of subjects were similar between treatment arms.

Occurrence of adverse events by infusion number

In general, the percentages of AEs were higher after the second infusion compared with the first and third infusion. In some cases, a slightly higher percentage of AEs were reported after the third infusion compared with previous infusions. Subjects in Study P-11 were eligible for a booster infusion at the time of biochemical failure. In some instances, the percentages of AEs reported after the booster infusion appeared slightly increased compared to the first 3 infusions, but the estimates for the booster infusion may be less precise because of the smaller sample size.

Occurrence of adverse events in relation to cell product parameters

The dose of sipuleucel-T given to each subject is based on the maximum manufacturable dose from the leukapheresis material provided by the subject. Three key product parameters define that dose: total nucleated cell count (TNC), $CD54^+$ cell count, and CD54 upregulation. A review of the incidence of AEs in subjects randomized to sipuleucel-T based on product parameters was performed. Analyses evaluated the incidence of AEs based on cell dose received, above versus below the median. In general, for $CD54^+$ cell count and TNC count, those AEs that appear to be ADRs to sipuleucel-T occurred in similar percentages of subjects who received above and below the median or in slightly higher percentages of subjects who received above the median. Hyperhidrosis was reported more frequently (≥ 2-fold) in those subjects who received above the median TNCs, but this difference was not seen based on $CD54^+$ cell count. For CD54 upregulation, there was no trend in ADRs between above the median and below the median. An

analysis evaluating the incidence of AEs based on cumulative $CD54^+$ cell count by quartiles showed no signal for increased incidence of AEs within the upper quartile.

Table 53: Incidence of ADRs to Sipuleucel-T by Preferred Term and Quartiles of Cumulative CD54+ Cell Count, Integrated Phase 3 Studies, Safety Population

Preferred Term	≤ Q1 (N = 148) n (%)	> Q1 to ≤ Q2 (N = 147) n (%)	>Q2 to ≤ Q3 (N = 147) n (%)	> Q3 (N = 147) n (%)
Any Adverse Event	145 (98.0)	143 (97.3)	147 (100.0)	147 (100.0)
Arthralgia	31 (20.9)	32 (21.8)	25 (17.0)	30 (20.4)
Asthenia	18 (12.2)	12 (8.2)	16 (10.9)	18 (12.2)
Catheter Sepsis	1 (0.7)	0 (0.0)	1 (0.7)	2 (1.4)
Chills	78 (52.7)	79 (53.7)	84 (57.1)	78 (53.1)
Citrate Toxicity	27 (18.2)	16 (10.9)	18 (12.2)	25 (17.0)
Dizziness	19 (12.8)	20 (13.6)	21 (14.3)	11 (7.5)
Dyspnoea	10 (6.8)	9 (6.1)	17 (11.6)	16 (10.9)
Fatigue	57 (38.5)	69 (46.9)	58 (39.5)	61 (41.5)
Headache	26 (17.6)	26 (17.7)	29 (19.7)	28 (19.0)
Hyperhidrosis	5 (3.4)	7 (4.8)	11 (7.5)	5 (3.4)
Hypertension	11 (7.4)	6 (4.1)	18 (12.2)	10 (6.8)
Influenza-Like Illness	9 (6.1)	13 (8.8)	19 (12.9)	16 (10.9)
Muscle Spasms	10 (6.8)	12 (8.2)	13 (8.8)	11 (7.5)
Myalgia	16 (10.8)	16 (10.9)	25 (17.0)	14 (9.5)
Nausea	38 (25.7)	26 (17.7)	27 (18.4)	36 (24.5)
Pain	18 (12.2)	21 (14.3)	19 (12.9)	16 (10.9)
Paraesthesia	18 (12.2)	25 (17.0)	20 (13.6)	22 (15.0)
Paraesthesia Oral	18 (12.2)	15 (10.2)	24 (16.3)	17 (11.6)
Pyrexia	49 (33.1)	42 (28.6)	51 (34.7)	45 (30.6)
Rash	6 (4.1)	11 (7.5)	9 (6.1)	5 (3.4)
Tremor	6 (4.1)	8 (5.4)	5 (3.4)	11 (7.5)
Vomiting	23 (15.5)	19 (12.9)	16 (10.9)	21 (14.3)

Note: Subjects with multiple occurrences of the same event are counted only once for that particular event.

Adverse events of interest

Based on the nature of the product, its mechanism of action and mode of administration, the following adverse events have been identified as potential risks associated with Provenge: acute infusion reactions due to cytokine release; thrombosis, thromboembolic events, vascular occlusion; cerebrovascular events; autoimmune reactivity; infections; new primary cancers; receipt of allogenic cells.

- **Acute infusion reactions due to cytokine release**

In the integrated phase 3 studies, 82.1% of subjects in the safety population (742 of 904 subjects) developed a potential acute infusion reaction AE (530 (88.2%) in the Provenge group and 212 (70.0%) in the placebo group). The most common acute infusion reactions included chills, fatigue, pyrexia, nausea, and arthralgia. Overall, 57.0% of subjects in the safety population (515 of 904 subjects) developed a potential acute infusion reaction AE within 1 day of infusion (71.2% of subjects in the sipuleucel-T group and 28.7% of subjects in the placebo group). The most common events (≥ 20% of subjects in either treatment group) that occurred within a day of infusion were reported more frequently in the sipuleucel-T group compared with the placebo group, including chills (49.9% vs. 5.3%), pyrexia (24.3% vs. 2.0%), and fatigue (21.0% vs. 14.2%).

Twenty-one of 601 subjects (3.5%) in the sipuleucel-T group compared with 0 of 303 subjects (0%) in the placebo group experienced a Grade 3-5 acute infusion reaction within 1 day of infusion. Seven of 601 subjects (1.2%) in the sipuleucel-T group compared with 0 of 303 subjects (0%) in the placebo group were hospitalized within 1 day of infusion for management of acute infusion reactions. The incidence of severe reactions was greater following the second infusion (2.1% vs. 0.8% following the first infusion), and decreased to 1.3% following the third infusion.

In addition, there were 3 subjects (0.5% of 601) who experienced cardiac arrhythmias within 1 day of sipuleucel-T infusion: 2 cases of atrial fibrillation considered as not related to study product by the investigator and one case of ventricular tachycardia on the day of his first infusion of sipuleucel-T, which lasted 1 minute and was considered not serious.

No Grade 4 or 5 acute infusion reactions were reported in patients in the Provenge group.

Hypertension has been identified as a potential ADR and as an acute infusion reaction. There was an increase in the percentage of subjects in the sipuleucel-T group compared with the placebo group who reported either term (10.0% vs. 6.3%, respectively). With the exception of 3 hypertension events in the sipuleucel-T group, these events were grade 1 or 2 in severity. Of subjects with hypertension AEs within 1 day of sipuleucel-T infusion, the AEs for 82.8% (24 of 29 subjects) resolved within 2 days; of subjects with blood pressure increased AEs within 1 day of sipuleucel-T infusion, the AEs for 81.3% (13 of 16 subjects) resolved within 2 days.

Respiratory reactions

There were a total of 90 subjects (15.0%) in the sipuleucel-T group and 24 subjects (7.9%) in the placebo group who experienced at least 1 respiratory reaction. The most common reported AE in the sipuleucel-T group was dyspnoea, which was reported in 8.7% of subjects compared with 4.6% of subjects in the placebo group. A total of 5.7% of subjects in the sipuleucel-T group experienced at least 1 respiratory AE within 1 day of infusion. Respiratory events that appeared temporally related to sipuleucel-T (i.e., < 1 day of infusion) included dyspnoea, hypoxia, cyanosis, oxygen saturation decreased, wheezing, and bronchospasm. Dyspnoea occurred in 2.7% of subjects in the sipuleucel-T group within 1 day of infusion; the other AEs occurred in less than 1% of subjects in the sipuleucel-T group. Events that occurred 2 or more days after infusion appeared balanced between the treatment groups.

Overall, the majority of the events were Grade 1 or Grade 2 (10.4%). 17 (2.8%) of the 601 subjects in the sipuleucel-T group and 3 (1.0%) of the 303 subjects in the placebo group reported at least one severe (Grade 3) respiratory adverse event. Grade 3 events in the sipuleucel-T group included dyspnoea (1.8%), hypoxia (0.5%), cyanosis (0.2%), bronchospasm (0.2%), and drug hypersensitivity (0.2%). Grade 3 events in the placebo group included dyspnoea (1.0%). There were no Grade 4 or Grade 5 respiratory events. There were 32 subjects (5.3%) in the sipuleucel-T group who experienced respiratory events and were subsequently rechallenged with 1 or more infusions. Twenty-seven of these subjects (84.4% of the 32 subjects) did not experience a subsequent respiratory AE upon rechallenge; 5 subjects (15.6% of 32 subjects) did experience a respiratory event upon rechallenge; 4 subjects had a recurrence of dyspnoea (0.8%) and 1 had a recurrence of hypoxia (0.2%). Of the 90 subjects in the sipuleucel-T group who reported at least 1 respiratory AE, 37 subjects (41.1%) had a pre-existing pulmonary condition.

Serious adverse events for respiratory events were reported in a total of 9 subjects (1.0%). Dyspnoea was reported as an SAE in 6 subjects (1.0%) in the sipuleucel-T group and 1 subject (0.3%) in the placebo group. Hypoxia was reported as an SAE in 2 subjects (0.3%) in the sipuleucel-T group and no subjects in the placebo group. There were 2 respiratory events that resulted in discontinuation of study treatment or withdrawal from the study: an event of Grade 3 hypoxia, and one event of dyspnoea.

Anaphylactic reactions

The incidence of adverse events in the Anaphylactic Reaction SMQ was 31.1% in the sipuleucel-T group compared to 22.8% in the placebo group. In the majority of subjects in both treatment arms, the AEs were mild (Grade 1) or moderate (Grade 2) in intensity. At least one Grade 3-5 adverse event was reported in 22 (3.7%) of the subjects in the verum group and in 7 (2.3%) of the subjects in the placebo group. In both treatment arms, dyspnoea, cough, rash, hypotension, pruritus, and flushing were the most commonly reported AEs within the Anaphylactic Reaction SMQ (reported in $\geq$ 1% of subjects), but the incidence of each of these events was lower in the placebo arm. In the verum group, further AEs occurring in $\geq$ 1% of subjects were chest discomfort, urticaria, and wheezing. These Anaphylactic Reaction SMQ adverse events were either temporally related to the infusions occurring within the day of infusion or even more events were reported > 4 days post infusion. Fewer events occurred 2-4 days post-infusion.

Evaluation of the most commonly reported AEs in the Anaphylactic Reaction SMQ (i.e., dyspnoea, cough, rash, hypotension, chest discomfort, pruritus, flushing, urticaria, and wheezing) by age group (< 65 years; $\geq$ 65 years to < 75 years; and $\geq$ 75 years) revealed increases in the incidence of dyspnoea and chest discomfort with increasing age in the sipuleucel-T treatment arm. An increase in the incidence of dyspnoea with increasing age was also observed in the placebo group.

The percentage of subjects who experienced at least one Grade 3-5 AE in the Anaphylactic Reaction SMQ increased with increasing age, both in verum and placebo group. This increase was largely due to more reports of Grade 3-5 dyspnoea in the older age groups ($\geq$ 65 years to <75 years and $\geq$ 75 years) than in the younger age group (<65 years).

- **Infections**

Overall, 27.5% of subjects (249 of 904 subjects) in the safety population of Studies D9902B, D9901, D9902A, and P-11 developed infection AEs during the course of the study (27.5% of subjects in the sipuleucel-T group and 27.7% of subjects in the placebo group), with similar percentages of subjects in both treatment groups experiencing events within 1 week of their final product infusion (15.3% of subjects in the sipuleucel-T group compared with 14.5% of subjects in the placebo group). The majority of subjects who developed an infection had an event that was Grade 1 or Grade 2 in severity (83.9%, 208 of 248 subjects). Overall, 4.4% of subjects (40 of 904) developed an infection AE ≥ Grade 3 (30 subjects in the sipuleucel-T group and 10 subjects in the placebo group). The most frequently occurring serious infections in the Provenge group were catheter sepsis (0.7%), staphylococcal bacteraemia (0.7%), sepsis (0.7%), staphylococcal sepsis (0.5%), and pneumonia (0.5%).

Venous Catheters used for the Leukapheresis Procedures and Administration of Infusions

Indwelling central venous catheter information was not collected on CRFs for Studies D9901, D9902A, and P-11. In Study D9902B, central venous catheter insertion (yes/no) information was collected, but no dates of insertion or removal were collected. The review identified 25 subjects (18 subjects in the sipuleucel-T group and 7 subjects in the placebo group) who reported infection AEs and who also had a confirmed indwelling central venous catheter at the time of the event. Nine of the 25 subjects noted above were found to have had a product sterility failure. An additional 11 cases of sterility failure were identified but no associated infection AEs were reported. The estimate of catheter related infections is 3.0% (27 of 904 subjects) in the safety population, 3.2% [19 of 601 subjects] in the sipuleucel-T group and 2.6% [8 of 303 subjects] in the placebo group. Based on this analysis, there does not appear to be an increased rate of catheter-related infections in subjects randomized to sipuleucel-T.

The Preparation, storage, and administration of Sipuleucel-T

There is a theoretical risk of introducing contamination to the product during the manufacturing process of sipuleucel-T. However, the majority of the product sterility failures identified have been related to a contaminated incoming leukapheresis product. Current review of the data indicates that 3 subjects had product that passed in-process sterility testing at release that was later found to be contaminated post-infusion (note that final sterility results are available 5–12 days post-infusion). All subjects had central venous catheters and 2 of the subjects experienced AEs as a result. Subject 92024-1142 experienced an SAE of Grade 4 catheter bacteremia following his 2nd infusion. He went on to receive his third infusion of sipuleucel-T. One subject experienced a Grade 2 AE of bacterial infection following his 2nd infusion. The infection was treated with dicloxacillin. He went on to receive his third infusion of placebo after a 1-week delay. In both cases, the incoming leukapheresis product was determined to be contaminated following release of product for infusion.

- **New primary cancers**

After excluding events related to metastatic prostate cancer, non-melanoma skin cancers, and benign tumors including meningiomas, a total of 20 subjects out of 904 (2.2%) reported new primary cancers in Studies D9902B, D9901, D9902A, and P-11, with 15 subjects in the sipuleucel-T group (2.5%) and 5 subjects in the placebo group (1.7%) reporting new primary

cancers. Bladder cancer was reported in 1 subject in each treatment group, esophageal cancer was reported in 2 subjects in the sipuleucel-T group, and chronic myelomonocytic leukemia (CMML) was reported in 2 subjects in the sipuleucel-T treatment group; no other new primary cancer events were reported in more than 1 subject. In the 2 subjects with CMML, 1 subject had evidence suggestive of pre-existing CMML, and pre-existing abnormal myelopoiesis could not be ruled out in the other subject. Based on a review of outcomes of these events as well as cause of death information, 10 of these events were fatal, including 7 in the sipuleucel-T group (1.2%) and 3 in the placebo group (1.0%). The time to reported onset of these malignancies was similar in the 2 treatment groups. One event of new primary cancer (pancreatic cancer) was reported post-marketing.

- **Autoimmune reactivity**

A MedDRA term search was conducted to identify event terms indicative of potential autoimmune signs, symptoms, or disease states. Overall, 16.7% of subjects (151 of 904 subjects) in the safety population of Studies D9902B, D9901, D9902A, and P-11 experienced an event that was captured in this list of potential autoimmune disorder terms, 16.0% of subjects (96 of 601 subjects) in the sipuleucel-T group and 18.2% of subjects (55 of 303 subjects) in the placebo group. The majority of events were Grade 1 or Grade 2 in intensity. The occurrence of these reported terms appeared balanced between treatment arms. There was no evidence of a specific type of event occurring in greater frequency in the sipuleucel-T group. A review of the events was performed and 8 events were identified as having a potential autoimmune etiology: ulcerative colitis, pernicious anemia, myositis, and myasthenia gravis were observed in 1 subject each in the sipuleucel-T group, and ulcerative colitis, keratoconjunctivitis sicca, prostatitis, and scleroderma were observed in 1 subject each in the placebo group.

Table 54: Cumulative product parameters in sipuleucel-T subjects experiencing adverse events of potentially autoimmune etiology

			Cumulative Product Parameter		
Protocol	Subject	Preferred Term	CD 54 Upregulation	CD54+ Cell Count ($x10^9$)	TNC Count ($x10^9$)
D9902A	9261-131	Pernicious Anemia	32.8	0.4	2.4
D9902B	92116-0847	Myasthenia Gravis	32.7	1.5	6.1
D9902B	92122-0435	Crohn's Disease	36.2	3.4	14.1
P11	P11006-004	Basedow's Disease	23.2	2.1	7.9
P11	P11008-004	Colitis Ulcerative	38.2	2.3	9.8
D9902B, D9901, D9902A and P11	All sipuleucel-T Subjects	Median	26.9	1.9	9.8
		Q1-Q3	21.7-33.6	1.3-2.9	7.0-13.7

Immunological data

Within study D9902B, humoral and cellular immune responses were assessed before (Week 0) and after (Weeks 6, 14, or 26) administration of sipuleucel-T or placebo. A total of 512 subjects were enrolled in the trial and samples from 237 subjects were evaluable for immune responses. Results from study D9902B are presented under 2.3.2 pharmacology.

GM-CSF neutralizing antibody activity was also assessed in 60 subjects in Study D9902B (44 in the sipuleucel-T arm and 16 in the placebo arm) prior to unblinding. GM-CSF neutralizing activity was present in a number of subjects prior to initiation of therapy. To determine whether an increase in anti-GM-CSF neutralizing activity was a consequence of sipuleucel-T treatment, the relative increase in neutralizing activity was compared before (Week 0) and after (Weeks 6, 14 or 26) treatment. Subjects with 20% or greater increases in anti-GM-CSF neutralizing activity after treatment were considered to have treatment-related neutralizing activity. Treatment-related anti-GM-CSF neutralizing activity was observed for 10 of 44 evaluated subjects in the sipuleucel-T arm (22.7%) and for 1 of 16 evaluated subjects in the placebo arm (6.3%). The presence of treatment-related neutralizing activity was generally transient, decreasing to baseline by the Week 26 time point for all subjects assessed, except for one subject treated with sipuleucel-T. Absolute neutrophil count (ANC) levels were examined for the 10 subjects treated with sipuleucel-T for whom transient treatment-related neutralizing activity was observed. There was no clear evidence for an association between the presence of anti-GM-CSF neutralizing antibodies and ANC levels.

- **Thrombosis, thromboembolic events, vascular occlusion, cerebrovascular events**

In the 4 randomized, controlled clinical studies, the safety analysis set includes 601 subjects in the sipuleucel-T treatment group and 303 subjects in the placebo group. Events of MI (event terms of myocardial infarction and acute myocardial infarction) occurred in 0.8% of subjects in the sipuleucel-T group and in 0.3% of subjects in the placebo group. Additionally, events of acute coronary syndrome and unstable angina each occurred in 0.0% of subjects in the sipuleucel-T group and each occurred in 0.3% in the placebo group. These trials did not specifically exclude patients with a history of MI or other cardiovascular disorders.

A history of myocardial infarction (or known coronary artery disease), stroke or pulmonary embolism was not an exclusion criterion for the clinical studies.

Table 55: Summary of the history of myocardial infarction, stroke or pulmonary embolism, safety population (D9902B)

History	Sipuleucel-T (N=338) n (%)	Placebo (N=168) n (%)	Total (N=506) n (%)
Any Subject Reporting Any History	85 (25.1)	42 (25.0)	127 (25.1)
Myocardial Infarction	67 (19.8)	32 (19.0)	99 (19.6)
Stroke	22 (6.5)	12 (7.1)	34 (6.7)
Pulmonary Embolism	8 (2.4)	4 (2.4)	12 (2.4)

Asymptomatic PE was detected by routine imaging in further sipuleucel-T recipients. Two of them had a history of DVT, and one a hypercoagulable state with elevated D-Dimer level. In 2 of the patients, all 3 sipuleucel-T products administered showed a CD54 upregulation above the median, and in 1 patient, the 2nd and 3rd infusion product had CD54 above the median. In the subject with elevated D-Dimer level, PE was diagnosed 5 days after his 1st (and only) sipuleucel-T infusion.

As of 29 January 2013, about 7,298 patients have been treated commercially in the US. From post-marketing surveillance, 24 reports of myocardial infarction have been received, giving an

overall reporting rate of about 0.3%. From the ongoing post approval registry study PROCEED an analysis of 1,094 patients who have had at least 28 days of follow up following the first infusion reported that 22 patients have encountered thrombotic or cardiac related SAEs.

In the 4 randomized controlled clinical studies, 14 subjects (2.3%) in the sipuleucel-T group versus 8 subjects (2.6%) in the control group experienced a cerebrovascular accident and 5 (0.8%) versus 1 (0.3%) a TIA, and 3 (0.5%) versus 1 (0.3%) a subdural haematoma. In addition, 4 sipuleucel-T recipients (0.7%) experienced an intracranial or cerebral haemorrhage, including one associated with a glioblastoma and one with an aneurysm. Cerebral infarction and lacunar infarction were each diagnosed in 2 subjects in the sipuleucel-T group (0.3%). Overall, excluding TIAs, 3.5% of subjects in the verum group versus 2.6% in the control group experienced a cerebrovascular event. In the sipuleucel-T groups, ischaemic events occurred within a few days after the last infusion (range 2-1328 days; median 71.5 days; n=16), whereas thereafter, the haemorrhagic events predominated (range 8-830 days; median 245.5 days; n=4).

Of the subjects who experienced a CVE, 38.1% of subjects in the sipuleucel-T group had a fatal event compared with 25.0% of subjects in the placebo group. The incidence rate of fatal CVEs was 0.763 per 100 person-years (95% CI: 0.329, 1.503) in the sipuleucel-T group and 0.370 per 100 person-years (95% CI: 0.045, 1.337) in the placebo group.

Platelet content

The content of free platelets in the sipuleucel-T final product has been analysed for 163 subjects receiving sipuleucel-T in Study D9902B, representing 465 of the 967 sipuleucel-T lots that passed final product release specifications. The median platelet content for all infusions was 1.75 x 10^{10}, with an estimated platelet activation of about 63%. Available final product platelet data were also analysed for commercial Provenge lots and the median final platelet count across >12,000 commercial lots was 1.05 x 10^{10}. In both cases, the platelet content is 20-30 fold below the platelet content in a standard single platelet concentrate (2-3 x 10^{11}). The median platelet content in the lots associated with ischaemic heart disease or thromboembolic events was 1.1 x 10^{10}, and the maximum platelet count was 2.6 x 10^{10}. In the 4 RCTs, events of myocardial infarction occurred in 0.8% of the 601 subjects in the sipuleucel-T group, and in 0.3% of the 303 subjects in the placebo group. These trials did not specifically exclude patients with a history of MI or other cardiovascular disorders.

The median platelet content in the commercial Provenge lots associated with myocardial infarction was 1.0 x 10^{10}, and the maximum platelet content was 2.9 x 10^{10}, both below the platelet content in a standard platelet concentrate infusion of 2-3 x 10^{11} platelets. However, the maximal amount of platelets infused with sipuleucel-T batches was 1.5 x 10^{11} in Study D9902B and peaked at 2.3 x 10^{11} in commercial lots.

Use of opioid analgesics to treat adverse events

Based on a blinded medical review of opioid use in studies D9901, D9902A, D9902B, and P-11, opioid use for each subject and specific World Health Organization Drug Dictionary (WHODRUG) preferred terms was classified into 1 of 4 categories:

- Cancer-related pain.

  Represents opioid use for which a reason other than cancer-related pain could not be readily determined. Excludes use of opioids taken for 1-2 days for nonspecific pain that was not associated with an infusion reaction.
- Infusion reaction treatment/prophylaxis.

  Represents opioid use for symptoms consistent with an infusion reaction (chills, rigors, headache) or for prophylaxis of infusion reaction symptoms. In general, this category of opioid use represents 1 day of use of intravenous meperidine/pethidine (Demerol) on the day of an infusion.
- Procedure-related pain.

  Represents opioid use for which the indication was related to surgery or a procedure (e.g., sedation, catheter placement, surgery/procedure-related pain).

  In general, opioid use in this category was of short duration.
- Other pain, which represents opioid use for any other reason (e.g., cough, pain due to injury or accident).

Table 56: Incidence of opioid analgesic use by reason for use, Safety analysis set (D9901, D9902A, D9902B, P-11)

	Sipuleucel-T (N=601)	Placebo (N=303)
Reason for Use[a]	**n (%)**	**n (%)**
Any opioid	286 (47.6)	122 (40.3)
Cancer-related pain	157 (26.1)	90 (29.7)
Infusion-related/prophylaxis	129 (21.5)	6 (2.0)
Procedure-related[b]	45 (7.5)	25 (8.3)
Other[c]	57 (9.5)	24 (7.9)

[a] Subjects were counted once for each unique reason for use cited.

[b] Opioid use for which the indication was related to surgery or a procedure (e.g., sedation, catheter placement, surgery/procedure-related pain).

[c] Opioid use for any other reason (e.g., cough, pain due to injury or accident).

Table 57: Duration of opioid use (days) by reason for use category, Safety analysis set (D9901, D9902A, D9902B, P-11)

Reason for Use	Statistic	Sipuleucel-T (N=601)	Placebo (N=303)
Cancer-related pain	N	138	88
	Mean (Standard Error)	31.6 (4.5)	47.9 (8.5)
	Median	13	18
	Minimum - Maximum	2 - 308	2 - 379
Infusion-related/prophylaxis	N	278	12
	Mean (Standard Error)	1.1 (0.1)	1.0 (0.0)
	Median	1	1
	Minimum - Maximum	1 - 15	1 – 1
Procedure-related pain[a]	N	73	48
	Mean (Standard Error)	6.5 (2.1)	4.5 (2.2)
	Median	1	1
	Minimum - Maximum	1 - 113	1 – 83
Other[b]	N	80	37
	Mean (Standard Error)	22.4 (8.5)	4.6 (2.4)
	Median	1	1
	Minimum - Maximum	1 - 419	1 – 88

Note: Each opioid medication record with a defined start and stop date is summarized in the duration (days).

[a] Opioid use for which the indication was related to surgery or a procedure (e.g., sedation, catheter placement, surgery/procedure-related pain).

[b] Opioid use for any other reason (e.g., cough, pain due to injury or accident).

Dosing data for pethidine within the infusion reaction treatment/prophlaxis category were summarised.

Table 58: Summary of pethidine dose (milligrams) used for treatement/prophylaxis of infusion reactions, Safety analysis set (D9901, D9902A, D9902B, P-11)

Statistic	Sipuleucel-T (N=601)	Placebo (N=303)
N	276	19
Mean (Standard Error)	29.8 (1.1)	29.2 (4.2)
Median	25	25
Minimum - Maximum	3 - 175	13 - 100

Note 1: One subject each in the Sipuleucel-T group (1 record) and Placebo group (2 records) had an undefined dose and are not included in the summary

Note 2: The majority of administrations were intravenous for a single use; however, all routes, including oral, subcutaneous, and intramuscular, were summarized

Adverse drug reactions

Based on causality assessment considering comparative incidence in clinical trials and time of onset, the following adverse events are considered adverse reactions for Provenge and the leukapheresis procedure.

Table 59: Adverse reactions from clinical studies and post-marketing reports

	Sipuleucel-T (N=601) n (%)
System Organ Class Preferred Term	
Infections and infestations	
Bacteraemia	3 (0.5)
Staphylococcal bacteraemia	4 (0.7)
Sepsis	4 (0.7)
Catheter sepsis	4 (0.7)
Catheter site infection	2 (0.3)
Catheter related infection	1 (0.2)
Blood and lymphatic system disorders	
Anaemia	75 (12.5)
Eosinophilia	2 (0.3)
Thrombocytopenia	7 (1.2)
Nervous system disorders	
Headache	109 (18.1)
Paraesthesia	85 (14.1)
Paraesthesia oral	74 (12.3)
Dizziness	71 (11.8)
Tremor	30 (5.0)
Hypoaesthesia	29 (4.8)
Cerebrovascular accident	12 (2.0)
Spinal cord compression	10 (1.7)
Transient ischaemic attack	6 (1.0)
Syncope	11 (1.8)
Cerebral infarction	2 (0.3)
Cardiac disorders	
Atrial fibrillation	8 (1.3)
Myocardial infarction	3 (0.5)
Acute myocardial infarction	2 (0.3)
Myocardial ischaemia	2 (0.3)
Vascular disorders	
Hypertension	45 (7.5)
Hypotension	24 (4)
Respiratory, thoracic, and mediastinal disorders	
Dyspnoea	52 (8.7)
Wheezing	8 (1.3)
Hypoxia	7 (1.2)
Bronchospasm	2 (0.3)
Gastrointestinal disorders	
Nausea	129 (21.5)
Vomiting	80 (13.3)
Abdominal pain	28 (4.7)
Skin and subcutaneous tissue disorders	
Rash	31 (5.2)
Hyperhidrosis	30 (5.0)
Pruritus	16 (2.7)

Urticaria	9 (1.5)
Musculoskeletal and connective tissue disorders	
Arthralgia	118 (19.6)
Myalgia	71 (11.8)
Muscle spasms	46 (7.7)
Renal and urinary disorders	
Haematuria	46 (7.7)
General disorders and administration site conditions	
Chills	319 (53.1)
Fatigue	247 (41.1)
Pyrexia	188 (31.3)
Pain	74 (12.3)
Asthenia	65 (10.8)
Influenza-like illness	58 (9.7)
Chest discomfort	16 (2.7)
Infusion site reaction	1 (0.2)
Injury, poisoning and procedural complications	
Citrate toxicity	89 (14.8)

Serious adverse event / deaths / other significant events

Serious adverse events

Table 60: Serious adverse events by system organ class, Integrated phase 3 studies, Safety population

System Organ Class	Sipuleucel-T (N = 601) n (%)	Placebo (N = 303) n (%)	Total (N = 904) n (%)
Any Serious Adverse Events	144 (24.0)	76 (25.1)	220 (24.3)
Nervous System Disorders	35 (5.8)	10 (3.3)	45 (5.0)
Infections And Infestations	28 (4.7)	12 (4.0)	40 (4.4)
Cardiac Disorders	23 (3.8)	16 (5.3)	39 (4.3)
General Disorders And Administration Site Conditions	23 (3.8)	3 (1.0)	26 (2.9)
Musculoskeletal And Connective Tissue Disorders	21 (3.5)	6 (2.0)	27 (3.0)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)	20 (3.3)	12 (4.0)	32 (3.5)
Respiratory, Thoracic And Mediastinal Disorders	17 (2.8)	7 (2.3)	24 (2.7)
Gastrointestinal Disorders	11 (1.8)	10 (3.3)	21 (2.3)
Injury, Poisoning And Procedural Complications	11 (1.8)	5 (1.7)	16 (1.8)
Renal And Urinary Disorders	11 (1.8)	18 (5.9)	29 (3.2)
Vascular Disorders	11 (1.8)	9 (3.0)	20 (2.2)
Metabolism And Nutrition Disorders	9 (1.5)	6 (2.0)	15 (1.7)
Blood And Lymphatic System Disorders	6 (1.0)	3 (1.0)	9 (1.0)
Skin And Subcutaneous Tissue Disorders	5 (0.8)	0 (0.0)	5 (0.6)

Investigations	3 (0.5)	2 (0.7)	5 (0.6)
Eye Disorders	2 (0.3)	0 (0.0)	2 (0.2)
Hepatobiliary Disorders	1 (0.2)	1 (0.3)	2 (0.2)

The following SAEs occurred in 5 or more subjects in the sipuleucel-T group or the placebo group: cerebrovascular accident (1.8% vs. 2.0%), pyrexia (1.7% vs. 0.3%), spinal cord compression (1.2% vs. 0.7%), chills (1.0% vs. 0.0%), dehydration (1.0% vs. 1.3%), dyspnoea (1.0% vs. 0.3%), atrial fibrillation (0.8% vs. 0.7%), and TIA (0.8% vs. 0.3%). With the exception of pyrexia and chills, most SAEs occurred more than 14 days after the last product infusion.

In the sipuleucel-T group, the SAEs that occurred within 1 day of infusion included pyrexia in 7 subjects (1.2%), chills in 4 subjects (0.7%), and atrial fibrillation, catheter sepsis, haematuria, hypertension, hypoxia, infusion related reaction and nausea in 2 subjects each (0.3%). In the sipuleucel-T group, SAEs that occurred in 1 subject each (0.2%) within 1 day of infusion included adverse drug reaction, anaemia, back pain, catheter bacteraemia, chest wall pain, dehydration, headache, myalgia, myositis, paraesthesia, procedural hypotension, sinus tachycardia, syncope, transaminases increased, and vomiting.

There were 4 subjects in the sipuleucel-T group compared with 2 subjects in the placebo group with pulmonary embolism events that were reported as SAEs (0.7% vs. 0.7%, respectively). The total number of subjects with pulmonary embolism events in the sipuleucel-T group was 4 subjects (0.7%) compared with 3 subjects (1.0%) in the placebo group. Overall there were 3 subjects (0.5%) in the sipuleucel-T group who reported deep vein thrombosis, all of which occurred > 14 days after infusion, compared with 6 subjects (2.0%) in the placebo group, of which 3 (1.0%) occurred 4 to 14 days after infusion and 3 (1.0%) occurred > 14 days after infusion. Overall, there did not appear to be a difference in the incidence of non-neurologic venous vascular events between the treatment groups.

Serious Adverse events from phase 1 and phase 2 studies

In the completed phase 1 and 2 studies, 67 of 269 subjects (24.9%) reported non-fatal SAEs comprising 75 PTs. The SAEs in a majority of these subjects (58 of 67 subjects; 86.6%) were judged by the Investigator to be unrelated to study treatment. Nine subjects had SAEs that included 12 PTs considered related to treatment.

In the ongoing phase 2 studies, SAEs have been reported for 13 subjects in study P09-1 (two were considered as possibly or probably related to study treatment), 2 subjects in study P07-1 (1 considered as possibly or probably related to study treatment) and 12 subjects in study P07-2 (2 considered as possibly or probably related to study treatment).

Deaths

Table 61: Summary of Deaths in Randomized Studies, Integrated Phase 3 Studies, Safety Population

	Sipuleucel-T (N=601) n (%)	Placebo (N=303) n (%)	Total (N=904) n (%)
Number of Subjects Who Died Prior to Data Cut-off	320 (53.2)	187 (61.7)	507 (56.1)
Number of Subjects Who Died Within 30 Days of Last Infusion	3 (0.5)	1 (0.3)	4 (0.4)
Distribution of Time to Death From Initial Product Infusion			
No First Infusion	7 (1.2)	0 (0.0)	7 (0.8)
0-3 months	9 (1.5)	7 (2.3)	16 (1.8)
> 3-6 months	30 (5.0)	16 (5.3)	46 (5.1)
> 6-12 months	62 (10.3)	49 (16.2)	111 (12.3)
> 12-24 months	119 (19.8)	69 (22.8)	188 (20.8)
> 24-36 months	64 (10.6)	40 (13.2)	104 (11.5)
> 36 months	29 (4.8)	6 (2.0)	35 (3.9)
Cause of Death[a]			
Disease Progression	240 (39.9)	151 (49.8)	391 (43.3)
Disease Progression Plus Additional Cause	18 (3.0)	9 (3.0)	27 (3.0)
Infection	4 (0.7)	1 (0.3)	6 (0.7)
Adverse Event	0 (0.0)	2 (0.7)	2 (0.2)
Cardiac Events	9 (1.5)	7 (2.3)	16 (1.8)
New Primary Cancer	6 (1.0)	1 (0.3)	6 (0.7)
Cerebrovascular Accident	8 (1.3)	2 (0.7)	10 (1.1)
Other	33 (5.5)	15 (5.0)	48 (5.3)
Not attainable or unknown	28 (4.7)	11 (3.6)	37 (4.1)
Subdural hematoma	2 (0.3)	0 (0.0)	2 (0.2)
Postoperative complications following leg fracture	1 (0.2)	0 (0.0)	1 (0.1)
Suicide	1 (0.2)	0 (0.0)	1 (0.1)
Brain aneurysm	1 (0.2)	0 (0.0)	1 (0.1)
Aspiration	0 (0.0)	1 (0.3)	1 (0.1)
Severe colitis neutropenia	0 (0.0)	1 (0.3)	1 (0.1)
Scleroderma	0 (0.0)	1 (0.3)	1 (0.1)
Respiratory failure	0 (0.0)	1 (0.3)	1 (0.1)
Unknown	20 (3.3)	9 (3.0)	29 3.2)

Note: In Study D9902B, multiple causes of death may have been selected whereas Studies D9901, D9902A, and P-11 allowed only 1 cause to be selected.

Since the time of that analysis (January 2009), an additional 18 deaths were reported in Study D9902B.

Deaths from phase 1 and phase 2 studies

Overall, a total of 25 deaths were reported during the completed Phase 1 and 2 studies of sipuleucel-T, APC8015F, or APC8026, the majority of which were attributed to disease progression. No deaths were attributed to sipuleucel-T, APC8015F, or APC8026. In addition, as of the data cut-off date for the study P09-1 interim safety report, 4 deaths were reported and 20 deaths were reported in Study P07-2 as of the data cut-off date for the 2010 annual report.

Laboratory findings

Haematology

The percentage of subjects in the Provenge group with clinically significant decreases in haemoglobin and clinically significant decreases in WBC count was 2.5% and 0.0% respectively versus 1.6% and 1.2% in the placebo group.

21.8% of subjects in the sipuleucel-T group had elevated eosinophil counts (eosinophilia) between weeks 0 – 14 compared with 2.8% of subjects in the placebo group. The eosinophilia in the sipuleucel-T group appeared to be transient, with only 5.5% of subjects noted to have eosinophilia after Week 14. There was one SAE of eosinophilia reported (study P-11).

In the sipuleucel-T group, 6.0% of subjects had elevated lymphocyte counts between Weeks 0 – 14 compared with 2.0% of subjects in the placebo group, while 11.8% of subjects in the sipuleucel-T group had low lymphocyte counts between Weeks 0 –14 compared with 16.0% of subjects in the placebo group.

Blood counts in the pivotal study

Haematology parameters evaluated by a central lab were at baseline, week 6, week 14 and week 26 and entered into the clinical database. The WBC, ANC, ALC and AMC for each performed leukapheresis procedure were not available because the first protocol-specified post-baseline haematology was drawn at week 6, after all leukapheresis were completed in the majority of subjects.

The proportion of subjects with National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 3 or 4 low WBC and ANC was low and the majority occurred after chemotherapy administration for progressive disease. While the proportion of subjects with grade 3 low ALC was numerically higher in older subjects relative to younger subjects this occurred across both treatment groups, in those undergoing ≤3 and >3 leukaphereses, and the percentages were driven by a small number of subjects. In the majority of cases grade 3 low ALC was transient and it was not associated with severe infection in any subject.

Table 62: Proportion of subjects with treatment-emergent WBC, ANC, ALC or AMC below lower limit of normal at weeks 6, 14 and 26 by age <65 versus ≥65 and by number of leukapheresis in study D9902B safety population

	Age < 65 Years				Age ≥ 65 Years			
	Sipuleucel-T		Placebo		Sipuleucel-T		Placebo	
Parameter < LLN Study Period	≤ 3 leuk (N = 48)	> 3 leuk (N = 28)	≤ 3 leuk (N =32)	> 3 leuk (N = 16)	≤ 3 leuk (N =180)	> 3 leuk (N = 82)	≤ 3 leuk (N =100)	> 3 leuk (N = 20)
WBC								
Week 6	1/39 (2.6)	2/20 (10.0)	1/29 (3.4)	3/14 (21.4)	4/151 (2.6)	1/58 (1.7)	5/79 (6.3)	0/14 (0.0)
Week 14	1/30 (3.3)	1/17 (5.9)	2/17 (11.8)	2/8 (25.0)	6/107 (5.6)	6/50 (12.0)	4/60 (6.7)	0/9 (0.0)
Week 26	4/25 (16.0)	1/9 (11.1)	1/14 (7.1)	1/7 (14.3)	7/95 (7.4)	7/44 (15.9)	3/41 (7.3)	1/9 (11.1)
Week 6, 14, or 26	5/42 (11.9)	4/27 (14.8)	2/29 (6.9)	4/15 (26.7)	15/160 (9.4)	11/71 (15.5)	8/88 (9.1)	1/17 (5.9)
ANC								
Week 6	0/38 (0.0)	0/20 (0.0)	0/30 (0.0)	1/14 (7.1)	4/154 (2.6)	0/63 (0.0)	4/83 (4.8)	1/15 (6.7)
Week 14	1/30 (3.3)	0/17 (0.0)	2/18 (11.1)	0/7 (0.0)	3/111 (2.7)	3/53 (5.7)	1/63 (1.6)	0/10 (0.0)
Week 26	3/24 (12.5)	0/9 (0.0)	0/14 (0.0)	0/7 (0.0)	5/99 (5.1)	3/47 (6.4)	2/44 (4.5)	1/9 (11.1)
Week 6, 14, or 26	4/42 (9.5)	0/27 (0.0)	2/30 (6.7)	1/15 (6.7)	12/163 (7.4)	5/77 (6.5)	5/92 (5.4)	2/19 (10.5)
ALC								
Week 6	1/38 (2.6)	3/19 (15.8)	4/31 (12.9)	0/14 (0.0)	7/143 (4.9)	9/59 (15.3)	8/80 (10.0)	3/15 (20.0)
Week 14	2/31 (6.5)	3/17 (17.6)	1/18 (5.6)	0/8 (0.0)	6/104 (5.8)	3/51 (5.9)	10/60 (16.7)	0/8 (0.0)
Week 26	3/25 (12.0)	2/9 (22.2)	2/16 (12.5)	1/7 (14.3)	12/96 (12.5)	8/44 (18.2)	5/42 (11.9)	2/9 (22.2)
Week 6, 14, or 26	4/42 (9.5)	7/26 (26.9)	5/31 (16.1)	1/15 (6.7)	19/152 (12.5)	15/72 (20.8)	18/88 (20.5)	4/17 (23.5)

	Age < 65 Years				Age ≥ 65 Years			
	Sipuleucel-T		Placebo		Sipuleucel-T		Placebo	
Parameter < LLN Study Period	≤ 3 leuk (N = 48)	> 3 leuk (N = 28)	≤ 3 leuk (N =32)	> 3 leuk (N = 16)	≤ 3 leuk (N =180)	> 3 leuk (N = 82)	≤ 3 leuk (N =100)	> 3 leuk (N = 20)
AMC								
Week 6	1/40 (2.5)	1/20 (5.0)	0/31 (0.0)	1/15 (6.7)	2/157 (1.3)	2/64 (3.1)	1/84 (1.2)	1/15 (6.7)
Week 14	0/32 (0.0)	2/17 (11.8)	2/18 (11.1)	0/8 (0.0)	2/112 (1.8)	2/55 (3.6)	2/63 (3.2)	1/10 (10.0)
Week 26	2/26 (7.7)	0/9 (0.0)	1/15 (6.7)	0/8 (0.0)	2/101 (2.0)	2/47 (4.3)	0/44 (0.0)	2/9 (22.2)
Week 6, 14, or 26	3/44 (6.8)	3/27 (11.1)	2/31 (6.5)	1/16 (6.3)	6/166 (3.6)	5/78 (6.4)	3/93 (3.2)	3/19 (15.8)

WBC = white blood cell count, ANC = absolute neutrophil count, ALC, absolute lymphocyte count, AMC = absolute monocyte count, Denominators for the percentages are based on the number of patients with both a baseline result >LLN and at least one post-baseline result

Chemistry

In the control group, there was a higher percentage of subjects with increases in alkaline phosphatase (5.0% vs. 3.4%) and creatinine (0.9% vs. 0.2%), and decreases in sodium (2.1% vs. 0.3%).

There was a greater percentage of subjects in the sipuleucel-T group compared with the placebo group who had an elevated total protein value between Weeks 0 – 14 (14.0% vs. 2.0%). After Week 14, there was a lower percentage of subjects with an elevated total protein value (7.4% in the sipuleucel-T group compared with 0.0% in the placebo group). Only 0.7% of subjects in the sipuleucel-T group had elevated albumin levels between Weeks 0 – 14, so this finding of elevated total protein in the sipuleucel-T group is likely due to an increase in serum globulin levels.

Laboratory findings from phase 1 and phase 2 studies

In study D9906, there was no apparent development of anaemia, leukopenia, or thrombocytopenia following treatment with sipuleucel-T. The most consistent hematologic change that occurred was transient eosinophilia. Based on an upper limit of normal of 600 eosinophils/µL, 13 of 18 subjects developed eosinophilia (72.2%), all of which were transient

cases. Most subjects had peak levels of eosinophil counts at approximately Day 20 to 40, followed by a return to baseline levels. There were no cases of eosinophilia noted in subjects treated at Dose Level 1. The highest eosinophil level reported was 3,200/µL in Subject AP018 at Day 36, which then decreased back to the normal range by Day 67. There were 11 reported AEs of elevated eosinophil counts (61.1%), but there were no reported clinical consequences related to eosinophilia. In some of these cases, mild lymphocytosis was noted in association with eosinophilia.

Safety in special populations

Intrinsic factors

Safety data for studies D9902B, D9901, D9902A, and P-11 were summarised by age, race, gender, and ECOG performance status. Since all subjects enrolled in the phase III studies were male and 90.6% were Caucasian the results summarised by gender and race are not shown.

Table 63: Incidence of potential ADRs to Provenge observed in subjects < 65 years of age and ≥ 65 years of age by preferred term in the integrated phase 3 studies (safety population)

Preferred Term	Provenge		Placebo	
	Age < 65 (N = 163) n (%)	Age ≥ 65 (N = 438) n (%)	Age < 65 (N = 89) n (%)	Age ≥ 65 (N = 214) n (%)
Any Adverse Event	159 (97.5)	432 (98.6)	86 (96.6)	205 (95.8)
Arthralgia	32 (19.6)	86 (19.6)	16 (18.0)	46 (21.5)
Asthenia	17 (10.4)	48 (11.0)	2 (2.2)	18 (8.4)
Catheter Sepsis	2 (1.2)	2 (0.5)	0 (0.0)	0 (0.0)
Chills	88 (54.0)	231 (52.7)	8 (9.0)	25 (11.7)
Citrate Toxicity	24 (14.7)	65 (14.8)	14 (15.7)	29 (13.6)
Dizziness	20 (12.3)	51 (11.6)	7 (7.9)	27 (12.6)
Dyspnoea	8 (4.9)	44 (10.0)	3 (3.4)	11 (5.1)
Fatigue	66 (40.5)	181 (41.3)	24 (27.0)	81 (37.9)
Headache	39 (23.9)	70 (16.0)	5 (5.6)	15 (7.0)
Hyperhidrosis	12 (7.4)	18 (4.1)	0 (0.0)	3 (1.4)
Hypertension	11 (6.7)	34 (7.8)	5 (5.6)	9 (4.2)
Influenza-Like Illness	20 (12.3)	38 (8.7)	6 (6.7)	5 (2.3)
Muscle Spasms	9 (5.5)	37 (8.4)	6 (6.7)	11 (5.1)
Myalgia	25 (15.3)	46 (10.5)	5 (5.6)	12 (5.6)
Nausea	29 (17.8)	100 (22.8)	8 (9.0)	37 (17.3)
Pain	26 (16.0)	48 (11.0)	5 (5.6)	15 (7.0)
Paraesthesia	25 (15.3)	60 (13.7)	15 (16.9)	28 (13.1)
Paraesthesia Oral	33 (20.2)	41 (9.4)	18 (20.2)	25 (11.7)
Pyrexia	64 (39.3)	124 (28.3)	5 (5.6)	24 (11.2)
Rash	5 (3.1)	26 (5.9)	4 (4.5)	6 (2.8)
Tremor	9 (5.5)	21 (4.8)	3 (3.4)	6 (2.8)
Vomiting	16 (9.8)	64 (14.6)	2 (2.2)	21 (9.8)

Note: Subjects with multiple occurrences of the same event are counted only once for that particular event.

Table 64: Incidence of potential ADRs to Provenge observed in subjects with ECOG performance status 0 versus 1 in the integrated phase 3 studies (safety population)

Preferred Term	Sipuleucel-T		Placebo	
	ECOG = 0 (N = 495) n (%)	ECOG = 1 (N = 101) n (%)	ECOG = 0 (N = 254) n (%)	ECOG = 1 (N = 48) n (%)
Any Adverse Event	485 (98.0)	101 (100.0)	246 (96.9)	45 (93.8)
Arthralgia	90 (18.2)	27 (26.7)	53 (20.9)	9 (18.8)
Asthenia	48 (9.7)	16 (15.8)	14 (5.5)	6 (12.5)
Catheter Sepsis	3 (0.6)	1 (1.0)	0 (0.0)	0 (0.0)
Chills	264 (53.3)	52 (51.5)	30 (11.8)	3 (6.3)
Citrate Toxicity	71 (14.3)	17 (16.8)	32 (12.6)	11 (22.9)
Dizziness	59 (11.9)	12 (11.9)	33 (13.0)	1 (2.1)
Dyspnoea	40 (8.1)	12 (11.9)	10 (3.9)	4 (8.3)
Fatigue	197 (39.8)	48 (47.5)	88 (34.6)	17 (35.4)
Headache	93 (18.8)	14 (13.9)	18 (7.1)	2 (4.2)
Hyperhidrosis	27 (5.5)	3 (3.0)	3 (1.2)	0 (0.0)
Hypertension	36 (7.3)	8 (7.9)	13 (5.1)	1 (2.1)
Influenza-Like Illness	46 (9.3)	11 (10.9)	10 (3.9)	1 (2.1)
Muscle Spasms	34 (6.9)	12 (11.9)	14 (5.5)	3 (6.3)
Myalgia	60 (12.1)	10 (9.9)	14 (5.5)	3 (6.3)
Nausea	100 (20.2)	28 (27.7)	36 (14.2)	9 (18.8)
Pain	66 (13.3)	8 (7.9)	11 (4.3)	9 (18.8)
Paraesthesia	72 (14.5)	12 (11.9)	36 (14.2)	7 (14.6)
Paraesthesia Oral	64 (12.9)	8 (7.9)	40 (15.7)	3 (6.3)
Pyrexia	164 (33.1)	23 (22.8)	23 (9.1)	6 (12.5)
Rash	27 (5.5)	4 (4.0)	7 (2.8)	3 (6.3)
Tremor	25 (5.1)	4 (4.0)	6 (2.4)	3 (6.3)
Vomiting	62 (12.5)	18 (17.8)	18 (7.1)	5 (10.4)

Extrinsic factors

Concomitant medications

An analysis of the use of concomitant medications following study registration was performed in studies D9902B, D9901, D9902A, and P-11. Medications used at a clinically meaningful higher frequency by subjects in the Provenge group compared with the placebo group included glucocorticoids (11.0% vs. 7.6%), H2-receptor antagonists (10.3% vs. 4.6%), pethidine hydrochloride (20.0% vs. 3.6%), and other antiemetics (4.8% vs. 1.0%).

Bisphosphonate use

In the Provenge group, a similar proportion of subjects taking bisphosphonates at registration reported AEs compared to those subjects not taking bisphosphonates at registration (98.9% vs. 98.1%, respectively). In both treatment groups, for subjects taking bisphosphonates at registration compared to those who were not, there was a higher incidence of back pain (34.1% vs. 27.7% in the sipuleucel-T group and 35.6% vs. 25.9% in the placebo group), anaemia

(19.0% vs. 9.7% in the sipuleucel-T group and 16.1% vs. 9.3% in the placebo group), musculoskeletal pain (15.1% vs. 6.4% in the sipuleucel-T group and 17.2% vs. 7.4% in the placebo group), and bone pain (11.7% vs. 4.0% in the sipuleucel-T group and 12.6% vs. 5.1% in the placebo group), which may reflect a greater amount of metastatic disease in the bones at baseline in these subjects.

Safety related to drug-drug interactions and other interactions

There has been no report of drug interactions associated with the administration of Provenge.

Discontinuation due to adverse events

Information about AEs that led to discontinuation of treatment was collected in study D9902B but was not systematically collected in studies D9901, D9902A, and P-11. In study D9902B, 5 subjects out of 338 (1.5%) in the sipuleucel-T group did not receive all infusions of study product due to AEs, 4 (1.2%) of these subjects had events classified as treatment-related and 1 subject (0.3%) had a leukapheresis-related AE. For 3 subjects, the events that led to discontinuation of treatment were considered adverse drug reactions. Specifically, 1 subject developed chills and headache, 1 subject developed chills, and 1 subject developed nausea.

In study D9903, 2 subjects (1.8%, 2 of 109 subjects) included in the safety population discontinued the study due to an AE. One subject developed Grade 1 vomiting and Grade 2 chills, hyperhidrosis, and nausea after the second infusion of APC8015F. Another subject developed Grade 4 spinal cord compression, 33 days after receiving the second infusion of APC8015F. Both subjects did not receive the third infusion. Data regarding AEs leading to premature termination of study treatment are not summarised for ongoing studies P07-1 and P07-2.

Post marketing experience

Provenge was approved by the FDA in the United States on 29 April 2010. As of 29 July 2011, approximately 1759 patients had received at least 1 infusion of Provenge and 459 safety reports had been received, 169 of which had been classified as SAE reports. Since the authorisation, four Periodic Safety Reports (PSURs) have been submitted to the FDA and there have been no AEs added to the United States prescribing information during this period.

Individual AE terms with a reporting rate ≥ 1% include chills, pyrexia, fatigue, nausea, back pain, anaemia, haematuria, pain, culture positive, vomiting, and asthenia.

As a post-authorisation requirement, the applicant is conducting a post-marketing study based on a registry design to assess the risk of cerebrovascular events in 1,500 patients with prostate cancer who receive sipuleucel-T. The study (P10-3) was initiated in January 2011 and is currently enrolling subjects. As of 29 July 2011, 28 subjects have been enrolled.

Two cases of administration of Provenge to the wrong recipient have been reported in the US.

2.6.1. Discussion on clinical safety

Patient exposure

Safety assessment was primarily based on safety data from four phase 3, randomized, controlled trials. Three of the four studies (D9902A, D9902B, and D9901) were conducted in men with asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer which is the indication applied for. One study (P-11) was performed in men with non-metastatic androgen-dependent prostate cancer. Additional safety data were provided from 10 phase 1/phase 2 studies and 2 compassionate use cases. Overall, the magnitude of the safety population is considered adequate for the indication sought. A total of 589 subjects received at least one sipuleucel-T infusion in the 4 randomised phase 3 studies, including 476 mCRPC patients.

A higher proportion of subjects in the sipuleucel-T group (27.0%) than in the control group (18.2%) required more leukaphereses than the number of infusions administered. The proportion of subjects requiring at least 2 leukaphereses more than the number of infusions administered was twice as high in the sipuleucel-T group. 25.4% of patients treated with Provenge required more than 3 leukapheresis procedures in order to receive 3 infusions. In post-marketing experience of greater than 5,000 patients treated, this incidence is approximately 19%.

In addition, 18 of 47 subjects (38.3%) in the sipuleucel-T group versus 3 of 16 (18.8%) in the control group did not receive the full allocated regimen of 3 infusions because of quality defects of the leukapheresis product. The applicant argues that the reason for this discrepancy were more defined acceptance and release criteria for sipuleucel-T, for which quality specifications had to be met for apheresis yield, in-process intermediate, and final product, respectively. Several patients who did not receive any or only incomplete sipuleucel-T treatment because of product quality failure had pre-leukapheresis white blood cell counts outside the normal range (mostly leukocytopenia). The study protocols required adequate haematological parameters for patient inclusion, but no upper or lower acceptance limits for blood cell counts were specified with regard to the leukapheresis procedure. As yield and composition of the leukapheresis harvest depend upon pre-procedure white blood cell counts, it may be necessary to define pre-donation cell count limits for patients in order to obtain a product with the specified quality parameters. Moreover, the dose spacing ranges were significantly wider for the sipuleucel-T group, which, according to the applicant, was attributable to the fact that repeat leukaphereses had to be performed in a small number of patients due product quality failures. Wider ranges were particularly observed between infusions 2 and 3, and between infusions 1 and 3, respectively. Prior to the first leukapheresis procedure, a complete blood count (CBC) test should be performed and be within ranges acceptable for the local facility. Additional CBC tests may be performed in accordance with local requirements.

Consistent with the known effects of leukapheresis, evidence of citrate toxicity was observed in 14.5% of subjects in the randomized Phase 3 studies, and occurred at a similar frequency in subjects who received sipuleucel-T compared with subjects who received placebo.

In some cases, the patient may be unable to receive a scheduled infusion of Provenge. This may be due to release criteria not being met during manufacturing, the expiration time being exceeded, or the patient being unable to meet the scheduled infusion time. In such cases, the patient may need to undergo an additional leukapheresis procedure if the treatment is to be

continued. Patients should be advised of this possibility prior to initiating treatment. It is recommended that the minimum interval between leukapheresis procedures should not be less than 2 weeks.

Adverse events

The most commonly observed adverse reactions were symptoms of chills, fatigue, pyrexia, nausea, arthralgia, headache, and vomiting. Overall, the treatment arms were balanced with respect to AEs occurring at each toxicity grade.

Adverse events of interest

Acute infusion reactions were frequently observed in the four randomised phase 3 studies. Overall, 71.2% of subjects in the sipuleucel-T group versus 28.7% of subjects in the placebo group experienced a potential acute infusion reaction adverse event within 1 day of infusion. These included but were not limited to fever, chills, respiratory events (dyspnoea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. To mitigate such reactions, premedication, consisting of paracetamol and an antihistamine was administered in clinical studies prior to infusion.

An additional analysis using the Anaphylactic Reaction SMQ showed a higher incidence of adverse events in the sipuleucel-T group (31.1%) compared to placebo (22.8%), as well as grades 3-5 adverse events (3.7% versus 2.3%). The most commonly observed events were dyspnoea, cough, rash, hypotension, chest discomfort, pruritus, flushing, urticaria, and wheezing. Increased frequencies of these AEs were also noted with increasing age. In the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed. Provenge must be administered under the supervision of a physician experienced in the medical treatment of prostate cancer and in an environment where availability of resuscitation equipment must be ensured.

Regarding the use of opioid analgesics to treat adverse events, the percentage of who required opioid use for prevention/treatment of infusion reaction AES was much higher in the sipuleucel group (23.8% in the 3 mCRPC phase 3 trials, and 21.5% in the 4 phase 3 trials) versus 2.0 % and 2.4 % in the placebo group respectively. The more frequent requirement of concomitant opioid use in patients treated with Provenge compared to placebo for treatment/prophylaxis of infusion-related AEs is reflected in the product information.

Overall, 27.5% of sipuleucel-T subjects in the 4 randomised studies developed infection AEs versus 27.7% of subjects in the placebo group. The majority of subjects (83.9%) who developed an infection had an event of severity Grade 1 or 2. A higher proportion of subjects reported upper respiratory tract infections >14 days post infusion in both groups. Leukapheresis or catheter related infections were observed in both groups, leading to sepsis or infection SAEs in 7 out of 601 (1.2%) of subjects in the Sipuleucel-T group. Indwelling central venous catheter (CVC) information was collected in Study D9902B, in which 23.0% of the subjects required an indwelling central venous catheter. Overall, there did not appear to be an increased rate of catheter-related infections in subjects randomized to sipuleucel-T. There is a theoretical risk of introducing contamination to the product during the manufacturing process of sipuleucel-T. However, the majority of the product sterility failures identified have been related to a

contaminated incoming leukapheresis product. To reduce the risk of catheter-related infections, CVCs should be considered only for patients with poor peripheral venous access. These patients should be closely monitored for signs and symptoms of infection. In addition, Provenge should be delayed in patients with active systemic infection until resolution.

In a total of 20 out of 904 (2.2%) subjects, other cancers were detected, 15 subjects in the Sipuleucel-T group (2.5%) versus 5 subjects in the control group (1.7%). The frequency of new primary cancers was slightly higher in sipuleucel-T recipients compared to placebo patients. However, this cannot be regarded as a signal given that prostate cancer is associated with a risk of additional primary cancers.

PAP expression has been shown in extra-prostatic tissues, including bladder, kidney, pancreatic islets, muscle, and salivary glands. Further, the PAP expression level is relatively lower in cancerous versus healthy prostate cells corresponding inversely to prostate cancer progression. Thus, a PAP directed immune response may be associated with adverse inflammatory or cell destructive processes in adjacent normal prostate tissue. A total of 8 events (5 in the sipuleucel-T group and 3 in the placebo) were identified as autoimmune AEs. Four of the 5 subjects with an autoimmune AE in the sipuleucel-T group had cumulative CD54 up-regulation values clearly above the group median, and 2 subjects also above the 3rd quartile. Based on the available data, a possible exacerbation or aggravation through sipuleucel-T treatment could not be ruled out in the reported cases, in particular ulcerative colitis, Morbus Crohn, Myasthenia gravis, and Basedow disease in which CD54 expression has been shown to play a role.

Up-regulation of CD54 on antigen presenting cells and binding to its integrin receptor LFA-1 (lymphocyte function associated antigen-1) on lymphocytes in the peripheral blood mononuclear cell population in the leukapheresis product may lead to cell aggregation and clumping with an associated risk of vessel obliteration and embolism following product infusion. In addition, evidence suggests an important role for an interaction between CD54 and the plasma protein fibrinogen. This interaction has been shown to promote bridging of monocytes and platelets to vascular endothelium, and may add to a potential risk of vascular occlusion.

Cerebrovascular and cerebral haemorrhagic events occurred in 21 (3.5%) of subjects in the active treatment group versus 8 (2.6%) in the control group. Among the latter were included 1 subject who experienced the event after receiving APC8015F. Ischaemic stroke events occurred mainly within a few days after the last infusion (range 2 – 1328 days; median 71.5 days; n=16), whereas thereafter, haemorrhagic events predominated (range 8 - 830 days; median 245.5 days; n=4). Therefore, Provenge should be used with caution in patients with a history of stroke after careful consideration of the potential risk-benefit on an individual basis.

Thrombo-embolic events and events of myocardial ischaemia, particularly in patients with a history of such events or with predisposing risk factors were also reported. Therefore, Provenge should also be used with caution in patients with a history of cardiovascular disorders (including prior myocardial infarction, angina pectoris, vascular occlusive disease, or those at risk for cardiac ischaemia), after careful consideration of the potential risk-benefit on an individual basis. In controlled clinical trials, myocardial infarctions were observed in 0.8% of patients in the Provenge group compared with 0.3% of patients in the control group. Based on the available data, there was no evidence for a link between platelet content and cardiac ischaemic or arterial thrombo-embolic events. The transfusion of a large amount of activated platelets in non-

thrombopenic patients who are at risk of thrombosis due to their condition could potentially result in an increase in cardiac ischaemic or arterial thrombo-embolic events. Therefore, the applicant is requested to perform a study to investigate the potential influence of administration of Provenge on coagulation parameters (P13-2) as a pharmacovigilance activity. The final clinical study report will be submitted by 31 December 2018. The applicant should also provide update on the data collected as part of the PSURs. The applicant will also measure coagulation factors in a sufficient number of sipuleucel-T final product batches (see conclusion on quality aspects).

In addition, a disease registry to assess the risk of cerebrovascular events, myocardial ischemia/infarction and the other identified and potential risks associated with the use of Provenge should be put in place in Europe.

Provenge contains approximately 800 mg sodium and approximately 45 mg potassium per infusion. Therefore, the content in sodium and potassium per infusion should be taken into account if administered in patients with cardiovascular diseases and/or renal impairment and/or on a controlled potassium and/or sodium diet. Hyperkalaemia should be corrected prior to Provenge administration.

Patients with cardiac or pulmonary conditions should be closely monitored. Furthermore, adequate risk management measures must be taken by the applicant to measure coagulation factors, quantify activated thrombocytes and monitor occurrence of related AEs (please see RMP).

Production of GM-CSF neutralizing antibodies detectable up to 26 weeks may lead to possible interference with subsequent GM-CSF adjuvant treatment. Considering that more than 20% of patients examined displayed neutralizing antibodies following treatment with Provenge and given the large sequence homology between GM-CSF and G-CSF there is a hypothetical risk of cross-reactivity of neutralizing GM-CSF antibodies with G-CSF.

There are no reports of overdose of sipuleucel-T. Clinical trial data indicate that infusions with the MMD of cells from a single leukapheresis procedure have been well tolerated, indicating that overdose is unlikely.

SAEs and deaths

Overall, 24.3% of subjects in the randomized Phase 3 studies developed an SAE; 24.0% of subjects in the sipuleucel-T group and 25.1% of subjects in the placebo group. In general, occurrence of serious adverse events was balanced between the treatment groups, with the exception of pyrexia, dyspnoea, spinal cord compression, chills, and transient ischaemic attack. In the three RCTs in the mCRPC setting, about two thirds of sipuleucel-T recipients died prior to data cut-off, including 3 subjects who died within 30 days of the last product infusion. In the majority of subjects, the death was attributed to disease progression. The 3 early deaths occurred 15, 21, and 23 days after the last sipuleucel-T infusion. They were due to disease progression (n=2) and CVA (n=1).

Serious adverse events were reported by 24% of sipuleucel-T recipients and 25.1% of subjects in the control group. In both sipuleucel-T and control group, SAEs occurred most frequently >14 days post infusion. The most common SAEs in the sipuleucel-T group were fever and chills (mostly within 1 day of infusion), dehydration, dyspnoea, spinal cord compression, and cerebrovascular accidents.

Laboratory findings

There were relatively few reports of clinically significant changes in hematology or chemistry laboratory values. A slightly larger percentage of subjects in the sipuleucel-T group reported clinically significant decreases in hemoglobin compared to placebo while in the placebo group higher percentages of patients compared to sipuleucel-T group reported decreases in sodium, and increases in alkaline phosphatase and creatinine. Cases of anaemia and thrombocytopenia have been reported in the clinical studies as well as in post-marketing experience. A higher percentage of subjects in the sipuleucel-T treatment group than in the control group showed transiently elevated eosinophil counts between weeks 0 and 14. In 5.5%, eosinophilia persisted until after week 14. One subject developed an atypical myositis SAE. Lymphocyte counts were elevated in 6.0% of subjects in the verum group versus 2% in the control group between weeks 0 and 14. Lymphocyte counts were low in 11.8% of sipuleucel-T recipients compared with 16% of subjects in the control group.

Special population

The AE profile observed in subjects < 65 years of age and those subjects ≥ 65 years of age was comparable. None of the differences observed were considered to be clinically important. Therefore, based on these results, older men do not appear to be at greater risk for developing AEs compared to younger men.

Immunocompromised patients and patients taking systemic immunosuppressive therapy were excluded from the sipuleucel studies. Since no data are available for these patients, Provenge should be used with caution in these populations after careful consideration of the potential risk-benefit on an individiual basis.

Patients with positive serology tests for human immunodeficiency virus [HIV] 1 and 2, human T cell lymphotropic virus [HTLV] 1, and hepatitis B and C were excluded from controlled clinical trials. Thus, no data are available for these patients.

No clinical data on the safety of the use of sipuleucel-T during pregnancy or breast-feeding are available since only males have been exposed to Provenge.

Safety related to drug-drug interactions and other interactions

There have been no reports of drug interactions associated with the administration of sipuleucel-T. Medications used at a clinically meaningful higher frequency by subjects in the sipuleucel-T group compared with the placebo group included glucocorticoids (11.0% vs. 7.6%), H2-receptor antagonists (10.3% vs. 4.6%), pethidine hydrochloride (20.0% vs. 3.6%), and other antiemetics (4.8% vs. 1.0%). In both treatment groups, for subjects taking bisphosphonates at registration compared to those who were not, there was a higher incidence of back pain, anaemia, musculoskeletal pain and bone pain which most likely is a reflection of a greater amount of metastatic disease in the bones at baseline in these subjects. The risks and benefits of vaccinating patients during the course of treatment with Provenge have not been studied. Therefore, vaccinations with live attenuated or inactivated vaccines whilst receiving Provenge should be carefully considered.

Cases of administration to the wrong recipient have been reported in the post-marketing phase. Provenge is intended solely for autologous use and should under no circumstances be

administered to other patients. Prior to infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the Provenge bag and on the Final Product Disposition Notification form.

Additionally, there is the small possibility/risk of transmitting infectious viruses to a patient if he is not the intended recipient of the product. Hence it is important that the procedures for handling and administering the product are precisely followed. It is strongly recommended that upon completion of each Provenge infusion, the patient specific label on the infusion bag, which contains the patient name, product name, and chain of identity (COI) product lot number, is removed and adhered to the patient file in order to maintain a link between the patient and the lot of the product.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety evaluation of Provenge was based on data from 601 prostate cancer patients in four randomised, controlled clinical trials (3 studies in metastatic castrate resistant prostate cancer and 1 study in androgen dependent prostate cancer) and post-marketing surveillance.

Overall, the leukapheresis procedure and Provenge infusion were well tolerated. The most commonly observed adverse reactions were symptoms of chills, fatigue, pyrexia, nausea, arthralgia, headache, and vomiting. In general, the treatment arms were balanced with respect to AEs occurring at each toxicity grade

The main identified risks included acute infusion reactions, toxicities (e.g., citrate toxicity) associated with the leukapheresis procedure and infections (principally associated with catheters). Cerebrovascular events, thrombo-embolic events, myocardial ischaemia, aggravation of autoimmune diseases, and new cancers present potential risks which need to be carefully monitored as part of the routine pharmacovigilance activities on this product.

Based on the safety available, the CAT considers the following measures necessary to address issues related to safety:

- Disease registry in European Union to assess the risk of cerebrovascular events, myocardial ischemia/infarction and the other identified and potential risks associated with the use of Provenge (Annex II condition).

- Provide data from the registry in place in the United States.

The CHMP endorse the CAT conclusion on clinical safety as described above.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CAT considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CAT received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 4 the PRAC considers by consensus that the risk management system for Sipuleucel-T (Provenge) for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer in male adults was acceptable provided an updated risk management plan and satisfactory responses to the minor remaining points. These points were adequately addressed by the applicant by providing the Risk Management Plan version 6.2.

This advice is based on the following content of the Risk Management Plan:

Safety concerns

The applicant identified the following safety concerns in the RMP:

Summary of safety concerns	
Important identified risks	Acute infusion reactions Adverse reactions to leukapheresis Infections Chain of Identity (COI) failure
Important potential risks	Cerebrovascular events Autoimmune events Malignancies Myocardial ischemia/infarction Embolic and thrombotic events Development of neutralising antibodies to GM-CSF Administration of expired product
Missing information	Information in patient populations excluded from clinical trials: • Patients with visceral metastases (liver, lung, brain) • Patients who are taking immunosuppressant therapies(including corticosteroids). Additional missing information: • Vaccination status of patients • Patients with moderate or severe mCRPC • Patients receiving opioid analgesics • Patients with modifications/initiation of bisphosphonate therapy

Pharmacovigilance plan

Measures in the Pharmacovigilance development plan

Activity / Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**	**Date for submission of interim or final reports**
Observational US-based registry (PROCEED, P10-3)	Quantify the risk of CVEs	Cerebrovascular events	Ongoing	• Interim data submitted in each PSUR • Final report: 30 September 2016
Proposed post-approval study (P13-2)	Describe coagulation parameters in mCRPC subjects and evaluate coagulation parameters over time in subjects treated with sipuleucel-T	Embolic and thrombotic events	Planned	• Protocol submitted to EMA within 9 months post sipuleucel-T approval in EU • Study initiation to begin within 12 months after PRAC agreement to final protocol • Updates in PSURs • Study completion within 2.5 years post study initiation • Final CSR: 31 December 2018
Measure coagulation factors in a sufficient number of sipuleucel-T final product batches in patients enrolled in study P13-2	Further address the potential impact of coagulation factors on patient safety	Embolic and thrombotic events	Planned	• P13-2 study initiation to begin within 12 months after PRAC agreement to final protocol. • Submission of evaluation report upon completion of enrolment: 30 June 2018
EU Registry study to (P13-1)	Evaluate the risk of ischemic stroke or myocardial infarction (MI) following treatment with Provenge	Cerebrovascular events, Myocardial ischaemia/infarction	Planned	• Protocol and statistical plan submitted to EMA within 6 months post Provenge approval in EU • Study initiation within 18 months after Provenge approval in EU • Updates in PSURs • Final report: 31 December 2018
Phase 2 study of concurrent versus sequential administration of abiraterone acetate plus prednisone in men with mCRPC (P11-3)	To evaluate the ability to manufacture sipuleucel-T when administered concurrently with abiraterone acetate plus prednisone, and to assess immune response, safety and efficacy with concurrent or sequential administration of sipuleucel-T and abiraterone acetate plus prednisone, in men with metastatic castrate resistant prostate cancer.	Patients who are taking immunosuppressant therapies (including corticosteroids).	Ongoing	• Final study report: 30 September 2017

Re-evaluate the CD54 up-regulation acceptance criterion, based on quality and clinical data from patient batches manufactured in Europe, when sufficient data is available.	Further address the relevance of the potency specification based on the lots manufactured at the Pharmacell site, and therefore to address the potential risk of having subpotent lots.	Potential risk of Sub-potent lots	Planned	• Updates in PSURs as needed until completion • The reevaluation of CD54 upregulation criterion completed by 31 December 2013.
Investigate and implement a rapid microbial detection method for release of sipuleucel-T if suitable and robust	Additional control for microbial quality prior to administration of sipuleucel-T.	Infections	Planned	• Type II variation to be submitted: 30 September 2014

Note: the proposed table regards the updated RMP v6.2, which followed the v4 assessed by the PRAC.

Regarding the additional pharmacovigilance activities, the PRAC noted that despite the known limitations of comparisons between two different datasets, the proposal by the applicant to pool data from the US and the EU registries could be appropriate provided that the populations in both registries are comparable and that the methods of identification, recording and evaluation of cases CVE and MI are the same. This would be particularly important for cases with MI as these cases are captured passively in the US registry and actively in the EU registry.

The PRAC also noted the lack of details with regard to the study design and statistical analysis and therefore advised if pooling of data was deemed not appropriate due to heterogeneity of data or discrepancies of the study methodology concerning identification, collection and analysis of data the applicant should commit to extend the EU registry.

Risk minimisation measures

Safety Concern	**Proposed Risk Minimisation Activities (routine and additional)**
Important identified risks	
Acute infusion reactions	Section 4.2 of the proposed SmPC: 'Provenge must be administered under the supervision of a physician experienced in the medical treatment of prostate cancer and in an environment where availability of resuscitation equipment must be ensured.' 'To minimize potential acute infusion reactions such as chills and/or fever, it is recommended that patients be pre-medicated orally with paracetamol and an antihistamine approximately 30 minutes prior to administration of Provenge.' Section 4.4 of the proposed SmPC: 'Acute infusion reactions (reported within 1 day of infusion) included, but were not limited to, fever, chills, respiratory events (dyspnoea, hypoxia, and bronchospasm), nausea, vomiting, fatigue, hypertension, and tachycardia. In

Safety Concern	Proposed Risk Minimisation Activities (routine and additional)
	the event of an acute infusion reaction, the infusion rate may be decreased, or the infusion stopped, depending on the severity of the reaction. Appropriate medical therapy should be administered as needed. In controlled clinical trials, 23.8% of patients in the Provenge group required opioids (a single dose of pethidine) on the day of infusion for infusion reactions (see sections 4.2 and 4.8). Table 1 in the proposed SmPC lists a number of acute infusion reactions, including chills, fatigue, pyrexia, arthralgia, myalgia, hypertension, hypotension, syncope, and dyspnoea. Section 4.8 of the proposed SmPC: 'Acute infusion reactions In controlled clinical trials, 71.2% of patients in the Provenge group developed an acute infusion reaction. The most common reactions (≥ 20%) were chills, fever, and fatigue. In 95.1% of patients reporting acute infusion reactions, the events were mild or moderate. Fevers and chills generally resolved within 2 days (71.9% and 89.0%, respectively). In controlled clinical trials, severe (Grade 3) acute infusion reactions were reported in 3.5% of patients in the Provenge group. Reactions included chills, fever, fatigue, asthenia, dyspnoea, hypoxia, bronchospasm, dizziness, headache, hypertension, muscle ache, nausea, and vomiting. The incidence of severe reactions was greater following the second infusion (2.1% vs. 0.8% following the first infusion), and decreased to 1.3% following the third infusion. Some (1.2%) patients in the Provenge group were hospitalized within 1 day of infusion for management of acute infusion reactions. No Grade 4 or 5 acute infusion reactions were reported in patients in the Provenge group. In controlled clinical trials, 23.8% of patients in the Provenge group required opioids (a single dose of pethidine) on the day of infusion for infusion reactions compared with approximately 2.4% of patients in control group (see sections 4.2 and 4.4). In the post-marketing setting, serious acute infusion reactions involving hypotension and syncope have been reported. Some have resulted in hospitalization. Patients should be informed of the possibility of late onset reactions and instructed to contact their physician if symptoms of dyspnoea, bronchospasm, dizziness, rash, or pyrexia occur.'
Adverse reactions to leukapheresis	Section 4.8 of the proposed SmPC: 'Adverse reactions that were reported most commonly ≤ 1 day following a leukapheresis procedure in controlled clinical trials included citrate toxicity (14.5%), oral paraesthesia (12.7%), and paraesthesia (11.3%). Additional adverse reactions that were seen commonly ≤ 1 day following a leukapheresis procedure in controlled clinical trials included fatigue (5.3%), chills (3.0%), muscle spasm (3.7%), dizziness (3.3%), and anaemia (2.3%). Additionally, there have been reports of thrombocytopenia received in spontaneous post-marketing reporting that have been temporally associated

Safety Concern	Proposed Risk Minimisation Activities (routine and additional)
	with leukapheresis.' Table 1 in Section 4.8 of the proposed SmPC lists a number of these reactions: citrate toxicity, paraesthesia oral, paraesthesia, muscle spasms, anaemia, and thrombocytopenia.
Infections	The majority of sipuleucel-T patients developing infections are central venous catheter users (see section 1.5.2.3). As shown below, this is addressed in the proposed SmPC. Section 4.4 of the proposed SmPC: "Infection: Patients with positive serology tests for human immunodeficiency virus [HIV] 1 and 2, human T cell lymphotropic virus [HTLV] 1, and hepatitis B and C were excluded from controlled clinical trials. No data are available for these patients. Provenge should be delayed in patients with active systemic infection until resolution. Serious infections including sepsis have been observed in patients treated with Provenge. Some serious infections and sepsis were related to the use of central venous catheters (CVCs). To reduce the risk of catheter-related infections, CVCs should be considered only for patients with poor peripheral venous access. These patients should be closely monitored for signs and symptoms of infection." Section 4.8 of the proposed SmPC: In controlled clinical trials, infection occurred in 27.5% of subjects in the Provenge group and 27.7% of subjects in the control group. Serious infections occurred in 4.7% of subjects in the Provenge group and 4.0% of subjects in the control group. The most frequently occurring serious infections in the Provenge group were catheter sepsis (0.7%), staphylococcal bacteraemia (0.7%), sepsis (0.5%), staphylococcal sepsis (0.5%), and pneumonia (0.5%). Reports of serious infection have been received in post-marketing surveillance including device-related infection, device-related sepsis, pneumonia, sepsis, bacteraemia, and urinary tract infection.' 'Catheter sepsis', 'catheter related infection', and 'catheter site infection' are listed as uncommon adverse reactions (Table 1, Section 4.8, proposed SmPC). Educational materials regarding catheter care may be provided to apheresis and infusion sites, which includes nationally accepted guidelines (PROVENGE Apheresis Catheter Care sheet). Additionally, the company performs a rapid sterility test for product release. The product is currently released using in-process sterility tests and the results of Gram stain testing. If the final results indicate a contamination post-infusion, Dendreon has a defined process for notifying treating physicians so that patients can be carefully monitored for signs of infection and treated promptly. Dendreon also plans to investigate and implement a rapid microbial detection method for release of sipuleucel-T which, if suitable and robust, will be an additional control for microbial quality prior to administration of sipuleucel T. Dendreon intends to submit a Type II variation to the Provenge MAA 12 months post-approval.
COI failure	Section 4.2 of the proposed SmPC:

Safety Concern	Proposed Risk Minimisation Activities (routine and additional)
	'It must be ensured that the APPROVED Final Product Disposition Notification form has been received from the marketing authorisation holder and the product has not expired (see section 6.6). Before infusion, it must be confirmed that the patient's identity matches the essential unique patient information on the Provenge bag and on the Final Product Disposition Notification form.' Section 6.6 of the proposed SmPC: 'What to check prior to infusion • It must be ensured that the Final Product Disposition Notification form containing the patient identifiers, expiration date and time, and the disposition status (approved for infusion or rejected) has been received from the marketing authorisation holder. • It must be ensured that the patient's identity matches the essential unique patient information on the Provenge bag and on the Final Product Disposition form.' 'After the infusion •Upon completion of the infusion, the patient specific label on the infusion bag should be removed and adhered to the patient file.' Section 6.0 of the proposed Package Leaflet: 'Each Provenge bag contains one individual infusion treatment and the container will only be opened when you are ready to receive your treatment. Your doctor or nurse will confirm that your details (name and date of birth) correspond to the details provided with the Provenge container.' In addition, product labeling is specific to an individual patient and training materials are provided to both patients and health care professionals involved with the leukapheresis and infusion procedures (see Section 5.0) The following actions also contribute to risk minimization: •Validated Enterprise Resource Planning (ERP) system that maintains COI from leukapheresis to infusion for whole course of treatment. •Training program and detailed instructions for use provided to all healthcare professionals involved in the process.
Important potential risks	
Cerebrovascular events	Section 4.4 of the proposed SmPC: 'Cerebrovascular disease In controlled clinical trials, cerebrovascular events (hemorrhagic and ischaemic strokes) were observed in 3.5% of patients in the Provenge group compared with 2.6% of patients in the control group. The clinical significance is uncertain.'
Autoimmune events	Section 4.4 of the proposed SmPC" 'Immunocompromised patients Provenge should be used with caution in immunocompromised patients in general including patients taking systemic immunosuppressive therapy, after careful consideration of the potential risk-benefit on an individiual basis. No data are available for these patients.'

Safety Concern	Proposed Risk Minimisation Activities (routine and additional)
Malignancies	None
Myocardial Ischaemia/Infarction	Section 4.4 of the proposed SmPC: 'Cardiovascular disorders In controlled clinical trials, myocardial infarctions were observed in 0.8% of patients in the Provenge group compared with 0.3% of patients in the control group. The clinical significance is uncertain.'
Embolic and Thrombotic Events	Section 4.4 of the proposed SmPC: 'Embolic and thrombotic events Provenge should be used with caution in patients with a history of embolic and thrombotic disorders.'
Development of neutralizing antibodies to GM-CSF	None
Administration of expired product	The SmPC and product labeling provide clear instructions to not initiate infusion if the product has expired.
Missing Information	
Patients with visceral metastases	Section 4.1 of the SmPC, Therapeutic indications, states 'Provenge is indicated for treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated.' Thus patients with visceral metastases are excluded from the indication. In addition the physicians education materials cover the identification of patients suitable for treatment with Provenge.
Patients who are taking immunosuppressant therapies	Section 4.4 of the proposed SmPC: 'Immunocompromised patients Provenge should be used with caution in immunocompromised patients in general including patients taking systemic immunosuppressive therapy, after careful consideration of the potential risk-benefit on an individiual basis. No data are available for these patients.' Section 4.5 of the proposed SmPC: 'Provenge is designed to stimulate the immune system. Immunocompromised patients and patients taking systemic immunosuppressive therapy were excluded from controlled clinical trials. Concurrent use of immunosuppressive agents (such as systemic corticosteroids) may alter its efficacy and/or safety. Therefore, concurrent use of immunosuppressive agents (such as systemic corticosteroids) should be avoided during Provenge treatment. Patients should be carefully evaluated to determine whether it is medically appropriate to discontinue immunosuppressive agents prior to treatment with Provenge (see section 4.4).'
The effect of leukapheresis and sipuleucel-T treatment on vaccination status of patients	Section 4.4 of the proposed SmPC: 'Immunisations 'The risks and benefits of vaccinating patients during the course of treatment with Provenge have not been studied. Therefore, vaccinations with live attenuated or inactivated vaccines whilst receiving Provenge should be carefully considered.'
Patients with moderate or severe mCRPC	None
Patients receiving opioid analgesics	None

Safety Concern	Proposed Risk Minimisation Activities (routine and additional)
Patients with modifications/initiation of bisphosphonate therapy	None

Note: the proposed Table regards the updated RMP v6.2 ,which followed the v4 assessed by the PRAC.

The PRAC was of the opinion that the submitted data for the proposed risk minimisation activities, including the proposed additional activity for COI failure mentioned in the RMP, were not sufficient to minimise the risks of the product.

Additional risk minimisation measures

The PRAC considered that the following additional risk minimisation measures are necessary for the safe and effective use of the product:

Educational material for healthcare professionals including a Provenge treatment checklist, a Provenge Apheresis Catheter Care sheet and a training completion form in order to:

- Enable appropriate selection of patients for treatment with Provenge
- Understand the specific handling and administration requirements for Provenge

Educational material for patients and/or carers to explain:

- The leukapheresis process
- The Provenge treatment process

Patient Alert card

Provenge registration form

Final Product Disposition Notification Form

Obligation to conduct post-authorisation measures

The PRAC recommends that a study to investigate the potential influence of administration of Provenge on coagulation parameters should be a condition of the MA.

The PRAC recommends that a disease registry to assess the risk of cerebrovascular events, myocardial ischemia/infarction and the other identified and potential risks associated with the use of Provenge should be a condition of the MA.

The PRAC recommends that further efficacy data should be collected through the following studies:

- Observational study P13-1 (EU registry)

- Observational study PROCEED/P10-3 (US Registry)

- Phase II study of Provenge with concurrent versus sequential administration of abiraterone acetate plus prednisone in men with mCRPC (P11-3)

The CAT endorsed this advice with changes. These changes concerned the following elements of the Annex II:

The CAT agreed that the applicant should conduct a study to investigate the potential influence of administration of Provenge on coagulation parameters as reflected in the risk management plan. However the CAT considered that the potential risk of thromboembolic event is unlikely to be attributed solely to coagulation disorders following Provenge administration and therefore advised that this study should not be a condition to the marketing authorisation. Characterisation of this risk is adequately addressed through RMP measures.

The observational studies P13-1 and PROCEED/P10-3 as well as the proposed phase II study (P11-3) of Provenge with concurrent versus sequential administration of abiraterone acetate plus prednisone are unlikely to provide unequivocal evidence that would address the efficacy uncertainties.
Consequently, the CAT considered that follow-up efficacy data should rather be provided from studies P11 and P12-1 (see discussion on clinical efficacy) and therefore these trials should be reflected in Annex II. However, the observational studies P13-1 and PROCEED/P10-3 (registries) will further characterise the long term safety profile of Provenge and thus should be kept as Annex II conditions.

The CHMP endorse the PRAC and CAT advice on the RMP.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Data to support the efficacy of Provenge for the treatment of men with mCRPC are available from three randomised, double-blind, placebo-controlled, multi-centre phase 3 studies which enrolled 737 patients and were conducted according to GCP.

An improvement in overall survival was observed in one randomised, double-blind, placebo/plasmapheresis-controlled, pivotal phase 3 trial study D9902B including 512 patients (HR=0.775, 95%-CI 0.614, 0.979, P =0.032) in a population that included almost 20% of patients with prior chemotherapy, asymptomatic or minimally symptomatic mCRPC patients, most of them with Gleason score ≤7 and non-visceral metastasis only. Median survival in study D9902B was 4.1 months longer in subjects who received sipuleucel-T than in subjects who received placebo.

There is supportive evidence from study D9901 in which a secondary analysis revealed prolonged overall survival of same magnitude, i.e. 4.5 months (HR=0.586. 95%-CI: 0.388, 0. 884, P=0.010).

A discrepancy was observed between OS and secondary endpoints in the pivotal and the two supportive studies. This might be explained by the expected mechanism of action and by the difficulty in adjudicating progression based on bone imaging. In any case, the most clinically convincing endpoint in this setting is overall survival and the observed difference was consistent across independent trials. Thus, failure to observe a difference in secondary endpoints did not impact the clinical relevance of the findings in terms of the primary endpoint.

The concern that the observed discrepancy might be due to imbalances in post-progression treatment, particularly for docetaxel and salvage therapy in the placebo group, has been assessed through expert clinical and statistical advice (see discussion on clinical efficacy). Although the expert advice highlighted several weaknesses in the design of the pivotal study and a possible bias in the estimation of the effect associated with Provenge, the CAT considered that the observed effect was sufficiently large so that even in the presence of confounding from post-progression treatments, the efficacy can be considered established. This effect was supported by the results of independent supportive trials. Further supportive efficacy data may become available from two studies in related patient populations.

Uncertainty in the knowledge about the beneficial effects

The applicant has proposed a potency assay specification which is consistent with the data used in the pivotal clinical trial. However, to further ensure the relevance of the potency specification the applicant will re-evaluate the CD54 up-regulation acceptance criterion, based on quality and clinical data from patient batches manufactured in the E.U., when sufficient data is available as detailed in the RMP.

The pivotal study (D9902B) excluded patients with visceral metastases and therefore efficacy and safety in this population are not known. Due to uncertainties about the potential biological difference of different metastatic cancer cells, extrapolation of the activity of Provenge in patients with visceral involvement is not possible. Therefore, the indication is restricted to patients with non-visceral castrate resistant prostate cancer as reflected in section 4.1 of the SmPC.

Risks

Unfavourable effects

The total safety database is based on 1207 subjects who underwent at least one leukapheresis procedure and of these, 1193 subjects received at least one subsequent treatment in phase 1 to 3 studies. The size of the database is considered adequate to obtain a perspective on the nature and frequency of adverse events, serious adverse events and areas of concern. Overall, the leukapheresis procedure and Provenge infusions were well tolerated.

The main risks identified were acute infusion reactions, toxicities (e.g., citrate toxicity) associated with the leukapheresis procedure and infections (principally associated with catheters).

Provenge is not expected to pose a risk for the environment due to the specific nature of its constituents and adequate measures will be in place for the correct disposal.

Uncertainty in the knowledge about the unfavourable effects

PAP expression has been shown in extra-prostatic tissues, including bladder, kidney, pancreatic islets, muscle, and salivary glands although the observed expression in these tissues was about one or two orders of magnitude less than that in the prostate. Treatment with Provenge may lead to unwanted long term immunological effects in the body system. This potential risk is adequately addressed in the risk management plan.

In addition, upregulation of CD54 on antigen presenting cells and binding to its integrin receptor LFA-1 (lymphocyte function associated antigen-1) on lymphocytes in the peripheral blood mononuclear cell population in the leukapheresis product may lead to cell aggregation and clumping with an associated risk of vessel obliteration and embolism following product infusion. In addition, potential correlation between leukapheresis-related anaemia and myocardial infarction especially in patients with concurrent risk factors may be a safety concern and needs further evaluation. Cerebrovascular events, thrombo-embolic events, myocardial infarction and cardiac ischaemia are potential risks for Provenge which require particular attention as appropriately reflected in the risk management plan.

New cancers also present a potential risk for Provenge and will thus be closely monitored as part of the routine pharmacovigilance activities in the risk management plan.

Additional data will become available to further characterise the long term safety profile of Provenge through the registries (see discussion on clinical safety). Particularly, the risk of cerebrovascular events, myocardial ischemia/infarction and the other identified and potential risks associated with the use of Provenge will be followed in the disease registry in EU. In addition, data will be available from a study investigating the potential influence of administration of Provenge on coagulation parameters. The applicant will also measure coagulation factors in a sufficient number of sipuleucel-T final product batches.

Microbial safety of Provenge is ensured by final product release testing, however to improve the overall risk profile of the product prior to its administration, the applicant will develop and implement an additional rapid detection method as an in-process control for microbial quality as detailed in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

Improved overall survival of 4.1 months (p=0.03) as demonstrated in one pivotal, double blind trial with supportive data from an independently conducted second trial (4.5 months, p=0.01) is considered of great importance to the patient and clinically relevant.

In general, Provenge was well tolerated. The main identified and potential unfavourable effects include acute infusion reactions, toxicities (e.g., citrate toxicity) associated with the leukapheresis procedure, infections, thrombo-embolic events, particularly myocardial infarction and cardiac ischaemia, cerebrovascular events, aggravation of autoimmune diseases, and new

cancers. The routine and additional pharmacovigilance and risk minimisation activities as described in the RMP are considered adequate to manage these risks. Additional data will become available to further characterise the long term safety of Provenge through the registries and a phase II coagulation study.

Benefit-risk balance

The large effect in terms of OS associated with sipuleucel-T is considered to outweigh the risks identified for Provenge.

Discussion on the benefit-risk balance

Improved overall survival of 4.1 months (p=0.03) as demonstrated in one pivotal, double blind trial (D9902B) is statistically significant and clinically meaningful. Similar effects were observed in two supportive clinical trials.

Although questions have been raised about Provenge treatment effect due to possible confounding factors in the pivotal study,

- The observed difference in overall survival was large and cannot be attributed to small imbalances in post-progression therapy with docetaxel;
- Results in the pivotal study were confirmed by overall survival data from a supportive trial D9901 (4.5 months) despite more frequent use of docetaxel in the placebo arm;
- Regarding a potential detrimental effect of the leukapheresis procedure on OS results in the placebo arm, the harvesting of mononuclear cells was unlikely to have adversely affected the outcome in the control group.

Overall, taking into account:

- the above considerations on efficacy;
- that the proposed indication is restricted to patients in whom chemotherapy is not yet clinically indicated;
- that Provenge is considered less toxic than other therapies (abiraterone acetate, enzalutamide, docetaxel and cabazitaxel) that are currently approved for the treatment of patients with mCRPC;
- the potential and identified risks of Provenge are adequately addressed in the risk management plan through pharmacovigilance and risk minimisation activities;

The benefit-risk balance of Provenge in the proposed indication is considered favourable.

The CHMP endorse the CAT conclusion on Benefit Risk balance as described above.

Divergent positions are appended to this report.

4. Recommendations

Outcome

Based on the CAT review of data on quality, safety and efficacy, the CAT considers by majority decision that the risk-benefit balance of Provenge in the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated is favourable and therefore recommends the granting of the marketing authorisation.

Based on the draft CAT opinion adopted by the CHMP and the review of data on quality, safety and efficacy, the CHMP considers by majority decision that the risk-benefit balance of Provenge in the treatment of asymptomatic or minimally symptomatic metastatic (non-visceral) castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within six months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk

profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

Prior to launch of Provenge in each Member State, the Marketing Authorisation Holder (MAH) shall agree the content and format of the educational materials with the National Competent Authority. The MAH shall also agree with the National Competent Authority any requirements for prior audit of apheresis centres and training courses for healthcare professionals in the use of Provenge.

The MAH shall ensure that all healthcare professionals who are expected to prescribe or use Provenge are provided with the following items:

Summary of Product Characteristics (SmPC)

Educational material for Healthcare professionals

Provenge treatment checklists

Apheresis catheter care sheets

Educational materials for patients

Patient Alert card to record the scheduled leukapheresis and infusion dates

The educational material for healthcare professionals will include the following key elements:

- Training completion form as agreed with the national competent authority
- Selection of patients for treatment with Provenge
- Specific handling and administration requirements for Provenge
- Chain of identity requirements
- The need to provide patients with the educational material and explain the use of the patient alert card
- The existence of the EU Registry of patients treated for metastatic castrate resistant prostate cancer and how to enter patients in it.

Educational material for patients and/or carers to explain:

- The leukapheresis process
- The Provenge treatment process

The CHMP endorse the CAT conclusion on the additional risk minimisation activities.

- **Obligation to complete post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due dates
To establish and keep an observational EU-based registry of men with mCRPC to evaluate overall survival, the risk of ischemic stroke or myocardial infarction following treatment with Provenge and other identified and potential risks (observational study P13-1)	Submission of study protocol with first PSUR Interim data submitted in each PSUR Final study report by 31 December 2018
To provide data from the observational US-based registry (PROCEED, Study P10-3)	Interim data submitted in each PSUR Final study report by 30 September 2016
To submit the results from study P-11, a randomised, double-blind trial evaluating Provenge versus placebo in patients with non-metastatic prostate cancer who experience PSA elevation following radical prostatectomy	Final study report by 31 December 2020
To conduct study P12-1 to evaluate characteristics predictive of a positive imaging study for distant metastases in patients with castrate-resistant prostate cancer. The study should provide a summary of baseline patient characteristics including PSA and PSA doubling time, the number of patients who develop metastatic disease, subsequent therapies received after diagnosis of metastatic disease, and efficacy parameters following subsequent therapies, including PSA progression, PSA progression-free survival, time to next line therapy, and overall survival.	Submission of study protocol within 1 month of authorisation Update on study outcome annually Final study report by 31 December 2019

The CHMP endorse the CAT conclusion on the obligation to conduct post-authorisation measures with a modification of the milestones of study P-11.The CHMP considered that performing an interim analysis that was not initially planned in the protocol could hamper the validity of the study. Hence, this request was not supported by CHMP and was deleted from the Annex II.

Divergent positions to the majority recommendation are appended to this report.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T) is qualified as a new active substance.

The CHMP endorse the CAT conclusion on the new active substance status claim.

APPENDIX 1

Divergent positions

DIVERGENT POSITION EXPRESSED BY CHMP MEMBERS

The undersigned members of CHMP did not agree with the CHMP's opinion recommending a positive opinion of the granting of a Marketing Authorisation for Provenge.

The reasons for divergent opinion were as follows:

There are major remaining objections that preclude drawing conclusions on whether the 4.1 months difference in overall survival observed in one randomised, placebo-controlled, pivotal phase 3 trial, and the difference in overall survival observed in the two supportive, randomised, placebo-controlled trials, result from a true and clinically relevant effect of Provenge:

- This effect was neither supported by Progression Free Survival (PFS) nor by Time to disease progression results;
- In the pivotal trial, there was more frequent requirement for rescue therapies (including docetaxel) in the Provenge group;
- There is no support either from Time to pain progression nor quality of life;
- There is no observed improvement of the secondary endpoint of Prostate-Specific Antigen (PSA) doubling time;
- Improvement of time to opioid use was not robustly demonstrated;
- Statistical evaluation highlighted that an effect of Provenge cannot be excluded, however, the size of the effect and potential bias due to imbalance in post-progression therapies cannot be estimated based on the available information;
- Interpretation of the results may have been confounded by the design of the clinical trials which allowed salvage therapy with product APC8015 (sipuleucel-T prepared from cryopreserved quiescent APCs) in the placebo arm as well as use of other treatments based on a non-randomised basis.
- The additional studies proposed by the company do not add to the required data supporting the efficacy claim for the indication (treatment of asymptomatic or minimally symptomatic (non-visceral) metastatic castrate resistant prostate cancer in male adults in whom chemotherapy is not yet clinically indicated):

  a) Absence of information on the variability of concomitant treatments from US registryctive study

  b) The additional randomized controlled double blind trial study P-11 is targeting non metastatic patients with increased PSA following radical prostatectomy therefore not relevant for a tumor infiltrating medicinal product.

As a result, the efficacy of the product is not sufficiently demonstrated.

In addition, there are concerns about the safety of the product regarding the occurrence of thromboembolic events when injecting significant amounts of activated platelets in patient prone to thromboembolic events which deserve further consideration.

Based on the above, the benefit-risk balance cannot be considered as positive which precludes a positive opinion.

London, 27 June 2013

Pierre Demolis - FR

Ian Hudson - UK

Barbara Van Zwieten Boot - NL

Aikaterini Moraiti - EL

Conception Prieto Yerro - ES

Reynir Arngrimsson - IS
Statistics

Hubert Leufkens - PhV, epidemiology

Nevenka Tršinar – SI

Nela Vilceanu - RO

Agnes Gyurasics - HU

Pieter Neels - BE

Bruno Sepodes – PT

Robert James Hemmings - Medical