European Medicines Agency
Evaluation of Medicines for Human Use

London, 19 November 2009
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WITHDRAWAL ASSESSMENT REPORT
FOR
Oncophage

International Nonproprietary Name:
vitespen

Procedure No. EMEA/H/C/1072

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

This should be read in conjunction with the "Question and Answer" document on the withdrawal of the application: the Assessment Report may not include all available information on the product if the CHMP assessment of the latest submitted information was still ongoing at the time of the withdrawal of the application.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Antigenics Therapeutics Ltd. submitted on 29 September 2008 an application for Marketing Authorisation to the European Medicines Agency (EMEA) through the centralised procedure for Oncophage, which was designated as an orphan medicinal product EU/3/05/270 on 11 April 2005.
Oncophage was designated as an orphan medicinal product in the following indication: Treatment of renal cell carcinoma. The calculated prevalence of this condition was 3.4 per 10,000 EU population.

The applicant applied for the following indication: as adjuvant treatment for localized renal cell carcinoma (RCC) patients at increased risk of recurrence with the following features: Primary tumour stage T1b or T2 with high-grade (3 or 4) histology with no nodal involvement. These characteristics include patients who are considered Stage I or II according to American Joint Committee on Cancer (AJCC) criteria.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier: 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 test or studies.

Information on Paediatric requirements

Pursuant to Article 7, the application included an EMEA Decision P/47/2008 for the following condition:

- Treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney)

on the granting of a class waiver.

Information relating to Orphan Market Exclusivity

Similarity
Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application contained a critical report addressing the possible similarity with authorised orphan medicinal products Nexavar (sorafenib tosylate), Torisel (temsirolimus) and Afinitor (everolimus).

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 18 March 2005. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
Oncophage has been given a Marketing Authorisation in Russia on 3 April 2008.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Ian Hudson

Co-Rapporteur: Pierre Demolis

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 29 September 2008.
- The procedure started on 22 October 2008.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 9 January 2009 . The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 January 2009.
- During the meeting on 16-19 February 2009, the CHMP 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 19 February 2009.
- An inspection at the Antigenics, Inc manufacturing site was carried out between 27-30 April 2009.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 May 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 3 June 2009.
- During the CHMP meeting on 20-23 July 2009, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The written responses to list of outstanding issues from the applicant were received on 21 September 2009.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 5 October and revised version of overview and clinical assessment on 15 October 2009.
- During the BWP meeting on 13 October 2009 quality outstanding issues were addressed by the applicant during an oral hearing before the BWP.
- During the CHMP meeting on 20 October 2009 outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 16-19 November 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Oncophage on 19 November 2009.
- The CHMP adopted a report on similarity of Oncophage with Nexavar and Torisel on 18 December 2008.
- The CHMP adopted an updated report on similarity of Oncophage with Nexavar, Torisel and Afinitor on 19 November 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Kidney cancer is the 15th most common cancer in the world with an annual incidence in the European Union of more than 58,700 new cases (Ferlay et al, 2002). Renal cell carcinoma is the most common malignant lesion of the kidney accounting for 85% of all renal neoplasms and 3% of all adult malignancies (Chow et al, 1999). Clear-cell carcinoma is the predominant histological cell type, constituting approximately 60% to 70% of renal epithelial tumours. At the time of diagnosis, most patients have localized or locally advanced disease and will undergo partial or radical nephrectomy with curative intent. Tumour size, nodal involvement, histological grade and Eastern Cooperative Oncology Group (ECOG) performance score are prognostic factors for outcome. Despite earlier detection, patients with locally advanced disease face a poor prognosis with a 5-year survival rate of approximately 50 percent due to recurrence of disease.

Currently there are no treatment options for patients post-surgery to reduce the risk of recurrence. The availability of a treatment that stimulates the immune response to residual tumour could be anticipated to reduce the rate of disease recurrence and thereby prolong recurrence-free survival. Such a treatment would fulfil an unmet need in this group of patients.

Oncophage (vitespen) solution for injection contains approximately 20 μg of autologous tumour-derived gp96 Heat Shock Protein 96-Peptide Complex (HSPPC-96) in 0.40 mL of a sucrose, potassium phosphate buffer solution. It is derived and prepared from the patient's own tumour and contains an enriched fraction of a heat shock protein-peptide complex (HSPPC-96).

Heat shock protein–peptide complexes are known to contain a broad array of peptides non-covalently bound to the heat shock protein (HSP) molecules. The peptide component of the complex is tumour-(and patient-) specific and it is thought to primarily mediate immunity, although the HSP molecules are also purported essential prerequisites for immunogenicity. Host phagocytic cells such as macrophages, dendritic cells or Langerhans cells have been shown to take up HSP-peptide complexes via the HSP receptor CD91. The cells are then thought to migrate to lymph nodes, where the complexes are processed so that the peptides chaperoned by the HSPs are re-presented to naive T cells. The T cells recognize the peptides and, as a result, undergo stimulation. Treatment with HSP-peptide complexes is said to elicit a CD8+, major histocompatibility complex (MHC) class I–restricted T- cell response. CD4+ T cells and natural killer (NK) cells are also recruited and are thought to mediate additional immunity against the tumour.

Antigenics Therapeutics Ltd. applied for a conditional marketing autorisation for Oncophage (vitespen). The application was submitted in accordance with Directive 2001/83/EC, article 8(3): complete independent application for a new active substance.

The proposed therapeutic indication was as follows:

'Oncophage is indicated for use as an adjuvant treatment for localised renal cell carcinoma (RCC) patients at increased risk of recurrence with the following features: Primary tumour stage T1b or T2 with high-grade (3 or 4) histology with no nodal involvement. These characteristics include patients who are considered Stage I or II according to American Joint Committee on Cancer (AJCC) criteria'.

Vitespen was proposed for administration by intradermal injection (ID). A standard dose of 25 μg of vitespen was suggested for all patients. This was changed to 20 μg during the assessment procedure. Injections were to be administered once per week for the initial four weeks, and then every other week thereafter until the patient's supply of vaccine was depleted.

Oncophage was granted orphan status by the European Commission on 11 April 2005 for the treatment of renal cell carcinoma. According to the conclusion of the COMP (Opinion dated 03/03/2005) the prevalence of the "condition" renal cell carcinoma is 3.4 per 10,000 individuals in the EU, at the time the application was made.

No paediatric investigation plan was submitted with the application. Oncophage is covered by a class waiver on the 'treatment of kidney and renal pelvis carcinoma (excluding nephroblastoma, nephroblastomatosis, clear cell sarcoma, mesoblastic nephroma, renal medullary carcinoma and rhabdoid tumour of the kidney)', a condition which is not applicable to children.

2.2 Quality aspects

Introduction

Oncophage (vitespen or HSPPC-96) solution for injection contains approximately 25 µg, which was revised to 20 µg of Autologous Tumour-Derived gp96 Heat Shock Protein-Peptide Complex (HSPPC-96) in 0.40 mL of a sucrose, potassium phosphate buffer solution. It is derived and prepared from the patient's own tumour that contains an enriched fraction of a heat shock protein-peptide complex (HSPPC-96).

Oncophage has been developed as an adjuvant treatment for localized renal cell carcinoma (RCC) patients. The product is administered by intradermal injection (ID) at a standard dose of 20 µg once a week for the initial four weeks, then every other week until depletion of supply.

The pharmaceutically active protein component of HSPPC-96 is described as 96 kDa heat shock protein, gp96 (also known as grp94, tumour rejection antigen 1, endoplasmin, HSP90β) complexed to peptides.
gp96 is a glycoprotein whose mRNA expression is widely distributed across normal and tumour cells and tissues. gp96 in its dimeric form acts as an ATPase. gp96 has the ability to chaperone peptides, mediate receptor uptake of protein-peptide complexes and deliver peptides into the MHC class I antigen processing pathway for presentation to T cells.
The applicant states that the peptide component of HSPPC-96 is tumour- (and patient-) specific and immunogenic.
The claimed mechanism of action is based on the product's ability to stimulate an immune response against the tumour antigens.

- Manufacture of drug substance and drug product

Manufacturer
Oncophage (HSPPC-96) drug substance and drug product are manufactured by Antigenics Inc., 3 Forbes Road, Lexington, MA 02421-7305, USA. This facility has recently been inspected by an EU Competent Authority and GMP status is pending since major deficiencies to comply with GMP were found, particularly relating to the drug product manufacture. The drug product will be imported in the EU by Penn Pharmaceutical Services Ltd., Tredegar, United Kingdom. Penn currently holds a license for importation of biological IMP (investigational medicinal products). An update of the license of Penn Pharmaceutical Services Ltd covering all activities for Oncophage (i.e. importation and release) is outstanding.

Manufacturing process and control of critical steps
A description of the drug substance manufacturing process as well as a flow chart has been provided. Briefly, the drug substance manufacturing process consists of starting material preparation (e.g. tumour homogenisation, protease inhibition) and purification by a series of two chromatographic columns and buffer exchange into the final formulation buffer. The process does not include any culture steps. A drug substance batch is obtained in a single manufacturing run from a target amount of tumour. The batch size varies according to the amount harvested and the concentration of gp-96 achieved. Although a drug substance stage has been identified, there is no long storage period at this stage (the process is presented as a continuous process).

Formulation is performed at the drug substance level, and only a dilution with the final formulation buffer and filtration is performed at the drug product level to achieve a defined target concentration of gp96. The final batch size will vary depending on the yield of drug substance. The complete manufacturing process (from tumour preparation to drug product) appears to take less than one day.

Major deficiencies concerning the manufacturing process and control of critical steps remain: The description of the manufacturing process is deficient. The in-process testing and the process control systems are inadequate as process controls and consistency of the process has not been demonstrated.

Overall: a) In the absence of reliable and robust methods and appropriately defined specifications which provide data on both components of active substance (gp-96 and peptides) or which can relate quality attributes to a clinical effect or clinical marker, the proposed process parameters are not considered satisfactory and consistency is not considered demonstrated. b) The proposed manufacturing process and quality of drug product can only be considered acceptable if they are used in clinical trials which have demonstrated an appropriate safety and efficacy profile. c) The operating parameters and ranges for drug product do not relate to the process step and the operating ranges are not sufficiently strict to ensure a consistent product. d) Process validation data has not been supplied to demonstrate consistency of drug product before and after the filtration step.

Control of starting material
The starting material is human renal cell carcinoma tumour tissue placed in labelled tubes and stored at -80°C within 30 minutes of tumour excision. The controls performed at the procurement site are defined as i) the time from excision to freezing, ii) the pathology, iii) tissue meets quality guidelines for viable tumour (i.e. appears pinkish, homogenous and firm) and iv) the biological serology tests are negative.

The tumour procurement form (TPF), Certificate of Conformance (COC) and tumour evaluation report (TER) should have been revised as requested. A bar code system to identify and track tumour material from receipt to drug product has not been validated and introduced.

Stability of the starting material during transport to Antigenics has not been demonstrated although the Applicant argues that literature and batch data support storage of starting material. This is acceptable, however, formal transport and stability studies should have been conducted and the data should have been provided. In the absence of a correlate between the potency markers and clinical effect, and an analysis of whether storage at -80^{o}C alters the peptides bound to gp-96 or peptide binding by gp-96, it may prove difficult for the Applicant to demonstrate stability of starting material.

At Antigenics, the physician-provided documents are reviewed and a test for identity (renal cell carcinoma) of the starting material is conducted. The proposed minimum starting weight of tumour has been revised in line with manufacturing process parameters. A suitable specification for gp96 content of homogenised tumour samples has been introduced. However, validation data has not been supplied for the assay. A commitment to provide justification and data to support the proposed specification is outstanding. In addition, the Applicant has not introduced a specification for bioburden of homogenised tumour samples.

The shipping studies are inadequate as data have not been supplied for the containers proposed for use for tumour starting material. Data from shipping studies for both starting material and drug product should have been supplied for the proposed commercial container, representing the full range of possible configurations and number of tubes, and the full range of temperatures proposed. The studies should have included re-icing and graphical data from thermalogs should be provided.

Process validation
Due to the autologous nature of the product, processing of multiple batches from a single patient's tumour is often impossible. As a consequence, process validation was based on the pooling of multiple patient tumours in order to make multiple replicate batches from a pooled tumour source. In the original dossier, the pooled tumours were split into three lots of starting material used in three consecutive validation runs, according to the final commercial process. The data from this study raised questions about process consistency as variability in yield and impurity levels were apparent. The Applicant has subsequently indicated that these 3 batches were not derived from truly homogenous material and performed a supplemental process validation study using human renal cell carcinoma samples to establish another common tumour homogenate.

From the data provided it is concluded that major deficiencies remain concerning the validation of the manufacturing process. In summary, in the absence of a suitable potency assay or an appropriate link between quality attributes and clinical effect/efficacy, the product/process consistency is not considered to have been demonstrated. The process has not been fully validated and demonstrated to

be robust. Drug product specifications do not include any measurement of the peptide component of active substance or a link with clinical effect, and process validation data have not demonstrated consistent binding of a peptide component to gp96. Thus the validation of the process has not been demonstrated. Whilst the difficulty in obtaining sufficient amount of human renal tumours was recognized, comprehensive process validation data from an appropriate number of batches has not been provided. Further more: a) Process validation data for drug product steps, particularly losses of active substance on filtration, has not been provided. Data demonstrating that a consistent HSPPC-96 amount is contained in drug product has not been submitted. b) The acceptability of an annual revalidation can not be determined at present as full process validation data has not been presented and many of the tests used for in-process control and product release have not been validated. c) Process validation data for drug product steps has not been submitted with data demonstrating that consistent gp-96 content is provided in filled drug product. d) The applicant has not investigated alternative detection methods with lower limits of detection to confirm the overall reduction of a specific process related impurity.

Since the process cannot be validated solely based on data generated from autologous material, it was recommended to the Applicant to perform process characterisation, validation and stability studies with a tumour model. An appropriate tumour model has not been developed and used to obtain the necessary data, nor has the absence of such a model been justified nor the necessary data provided by alternative means.

Manufacturing process development
Several improvements were introduced during manufacturing process development, leading to processes from version 1 to 6; version 6 being the commercial manufacturing process.

The material used in Phase 3 clinical trial C-100-12 Part 1 included ~643 lots manufactured according to different process versions (4, 5.1 and 5.2). Process version 6 was initiated in June 2005 to supply several clinical trials in different indications (e.g. glioblastoma), and clinical trial C-100-12 Part 2 for renal cell carcinoma (results not provided). This process includes the addition of a cocktail of protease inhibitors, change in the sterile filtration and product formulation (from PBS to S/KPO_4). Approximately 76 batches appear to have been produced with process version 6 and batch analysis data have been provided.

The batch analysis data for drug product derived from the different processes from version 4 to 6 show a clear evolution of purity level, along with an increase in activity and a decrease in residual impurity. These evolutions were also accompanied by an improvement in the yield and a decrease in the product strength. No data have been provided to analyse the binding of the tumour peptide to gp96. No data were provided on the evolution of other process related proteins which may potentially play an important role in the intended biological activity of the product. Although the data provided are rather limited, they suggest a significant evolution of the product quality of the product through the different process versions, and thus product derived from these different processes cannot be considered comparable based on quality data.

Considering the significant evolution of the product quality through the different process versions, and the analytical limitations, comparability has not been demonstrated, and thus, the pivotal clinical trial should have been performed with product obtained with the final commercial process (i.e. version 6).

Characterization
Characterisation studies have been conducted with state of the art techniques including amino acid analysis, N-terminal sequencing, molecular weight by SEC and MALDI-TOF, peptide mapping, analysis for secondary and tertiary structure by circular dichroism (CD), fluorescent and UV absorption spectroscopy, and analysis of glycosylation by MALDI-TOF.

Most characterisation studies originally presented were generated or derived from published data on gp96 from various origins (e.g. human placenta, human melanoma, mouse Meth-A), while only limited data are available on the product intended to be commercialised (i.e. gp96 complexed with a tumour peptide from renal tumour origin). Further data on glycosylation, phosphorylation, RP-HPLC,

amino acid analysis, N-terminal sequencing and charged variants have been provided for RCC-derived product. Overall the characterisation of the gp-96 component of Oncophage is considered acceptable despite uncertainties over validity of gp-96 N terminal sequence data, glycosylation and phosphorylation.

The original data provided focused on gp96 alone, due to the difficulty in analysing the attached peptides as they vary from one tumour to another, and may be separated from gp96 during sample preparation or due to the analytical method. The company has undertaken further work in an attempt to demonstrate the presence of peptides in Oncophage and identified a peptide sequence which had the potential to be used as a marker of bound peptide if a method were developed to measure it quantitatively. Subsequent studies failed to demonstrate the presence of this peptide associated with gp96 in HSPPC derived from other renal cell carcinoma material. Although the Applicant has detected peptide in drug product samples derived from RCC, the tests conducted to date (and proposed for product specifications) do not provide quantitative information which is required to demonstrate that the yield of gp-96-peptide complexes is consistent or demonstrated that this peptide(s) is relevant clinically.

Whilst preliminary data may indicate that peptides are bound to gp-96, the data is not conclusive and does not address whether peptides may be bound to co-purifying fragments of gp96. Data from animal studies may show an effect of the drug product in protecting against tumours when given prophylactically although there are several experimental inconsistencies and the relevance of the model compared with the proposed use of the product is questionable.

A tumour model has yet to be developed, although the Applicant is continuing efforts to develop a suitable model and relevant assays. In the absence of a model, quality parameters can not be linked to a clinical marker.

In conclusion major deficiencies remain concerning the characterisation of the active substance: The approach the company has taken is that normally used for a well defined protein product which would imply that all available tools and analytical techniques would be applied. However, insufficient physicochemical characterization data for the active substance have been provided. The company claims that the mechanism of action of the active substance is based on peptides complexed with gp-96 but has not provided sufficient evidence (either physicochemical or pharmacological) for the presence of peptides complexed with gp-96 in the drug product. The Applicant has not demonstrated that the peptides found in the studies conducted are bound to gp-96 rather than any co-purifying protein(s). As was recognized and discussed with the Applicant during the course of assessment, this product is a tumour extract, containing a range of protein/peptide species and thus an approach to quality aspects based more on relevant biological/immunological activity may have been advantageous.

- Specification

Drug substance
The drug substance specification (or in-process control prior to filling) is insufficient to assure a consistent quality of the product (major deficiency). Drug product was filled on the basis of total protein, rather than the amount of active substance present. Thus the doses used in clinical trials were not equivalent, raising questions about the validity of the clinical trial.

Originally, no release testing was performed on the HSPPC-96 drug substance as the process immediately moves into the production of the drug product. At the final drug substance manufacturing step, a concentrated protein fraction is produced. The protein concentration of this fraction is taken in order to determine the dilution factor for the drug product. The Bradford Protein Assay is used to determine protein concentration of drug substance.

On request specifications have been proposed for the drug substance including identity, purity and gp-96 content determined by RP-HPLC. Whilst the introduction of this test is encouraged, the test has not

been validated and suitable acceptance limits set. A quantitative test is also required to demonstrate consistent yield of gp-96-peptide complexes and thus to ensure delivery of a consistent dose of active substance to patients. The challenges to introduce such a test have been discussed during the course of the assessment.

Furthermore, tests on drug substance do not include analysis of all components of the active substance. A quantitative test to detect peptides bound to gp-96 has not been introduced and applied to validation batches or introduced for routine testing.

Drug product
Drug product specifications do not include any measurement of the peptide component of active substance or a link with clinical effect, and process validation data has not demonstrated consistent binding of a peptide component to gp96 (major deficiency). In the absence of reliable and robust methods and strictly defined product specification which address the peptide component of HSPPC-96, or can be related to a clinical effect or a clinical marker, drug product specifications can not be considered adequate. Furthermore, the Applicant has not justified the specifications for the activity and Representation assays based on the mechanism of action and clinical data.

The identity of the drug product has been controlled by Western blot analysis, and RP-HPLC is proposed for future batches. Taking into account the other tests performed (e.g. representation and activity assays), the identity of gp96 is considered sufficiently controlled, assuming suitable validation of RP-HPLC. However, these tests are not capable of discriminating between product from different tumour sources (e.g. renal carcinoma, melanoma, human/non human, patients). In other words, these tests will only confirm the gp96 identity; and the product identity (i.e. gp96 + chaperoned peptide for the correct patient) will not be assessed. In the absence of such a test, the identity of the product from procurement to administration of the drug product will rely on appropriate materials management through the different sites and the process.

The purity/impurity profile of the product is currently controlled by SDS-PAGE (Coomassie stain), although RP-HPLC is proposed for the future.

The only process related impurity is controlled using an ELISA assay, and a reduced limit/dose will be applied. Although validation data indicate that levels of the second impurity are below the assay LOD, considering the potential residual amount, this impurity should also be routinely controlled using a more sensitive assay.

According to the data provided, the product appears to only have a biological activity when present as a dimer. A size exclusion chromatography method has been used in characterisation studies to analyse the distribution of monomers, dimers and other oligomers, however this method was not applied in the specification due to the amount of material required. The only tests retained to monitor these aspects are the activity and representation assays.

Limits were proposed for an activity assay. The data provided in Module 5 indicate that there is no statistically significant relationship between this activity assay and the clinical outcomes of overall survival or recurrence-free survival. Thus the relevance of this activity assay as a potency indicator has not been demonstrated and the data do not support the proposed lower limit. This assay should have been justified as a potency assay and the limit should have been appropriately tightened.

The strength of the product was previously based on the protein content controlled by a Bradford assay prior filling. The limit proposed for this test has been revised based on both total protein and purity as determined by SDS-PAGE (or RP-HPLC). The Applicant argued that any variability in gp-96 content of batches (process versions, formulations etc) would not affect efficacy or safety. This view is not supported and outstanding issues, relating to dosing in the pivotal clinical trial, remain. In addition, aseptic filling of the diluted bulk has not been validated to show that it does not affect protein content.

Appearance, pH, sterility and endotoxin are included in the drug product specification. The Applicant states that these tests will be performed in accordance with Ph. Eur. monographs for commercial batches.

Analytical methods
The analytical methods used to test drug product have not been justified in relation to the structure and activity of drug product. The analytical methods were not sufficient as they did not address all components of the active substance. A suitable potency assay was not proposed. Validation data for all proposed drug substance and drug product release tests were not provided (major deficiency).

Reference material
Five reference standards have been established through the development of this product, using different sources of materials, processes and formulations. A lot manufactured from placenta by process version 6 is proposed to be used as both primary and working reference standard. This batch has been analysed according to current release criteria and stability is monitored. Additional tests, SEC, RP-HPLC, amino acid analysis, IEF and peptide mapping have been conducted on this reference standard. It is not clear how the reference standard is to be used to ensure the quality of product batches. Details of the proposed reference standards for use in all product release assays should have been supplied with an indication of how they will be used.

Release upon importation from a third country
The Applicant argued that release testing at the Antigenics facility, plus regulatory retains, consumes at least 5 vials of the total vials available, and that there is a finite volume of tumour starting material available for manufacturing resulting in a limited number of vials for patient treatment, and thus a full re-testing upon importation into the EU should be limited, as it would otherwise consume too much product. The Applicant proposed a reduced set of release tests to be performed at Penn to limit testing to one patient vial (removal of the re-presentation assay, sterility, and strength). Whilst the proposal for reduced batch release testing scheme is supported, the proposed specification is not adequate as it does not address quality parameters of the complete active substance (gp96 complexed to peptides) and the RP-HPLC assay has yet to be validated. An appropriately revised specification for EU batch release should have been provided.

Batch data
In conclusion, batch analysis data have been provided but reinforce questions about the sufficiency of the drug substance and drug product testing regimes and the consistency of dosing and quality parameters. Data provided indicate that purity failures may be related to proteases in starting material.

The batch data provided show that there was variability in dosing (either total protein or gp-96) in the clinical trial as batches are not consistent for strength (total protein), purity or activity. It is not possible to comment on the representation assay results because only qualitative data, based on an arbitrary pass criterion, are provided. The Applicant has supplied an analysis of activity assay and representation activity in historical batches which demonstrates a certain degree of variability in these quality parameters used as indicators of potency, raising further questions as to whether these assays can be regarded as relevant potency indicators and on the consistency of dosing in clinical trials.

These issues highlight that the Applicant is unclear of which are the key attributes of their drug product. Batch data show that purity failures exist in manufacturing version 6, raising concerns about the consistency of the process and suitability of criteria used on starting material.

Container closure system
Information on the container closure systems for the drug substance fraction (5 mL sterile polypropylene cryovial) and the drug product (2 ml crimp top vial and stopper assembly (Butyl rubber laminated with fluororesin and coated with silicone) was provided.

- Stability

Drug substance
The drug substance stability study (hold period validation) did not provide any information on the functional characteristics of the drug substance and was therefore considered deficient to support the claimed shelf-life for the drug substance (72-hour at 2ºC - 8ºC). This claim is based on 3 batches which were tested for purity and concentration [the manufacturing version used was not cited in the submission]. Considering that the batches used in the stability study are not considered representative of the final commercial process, and that the 2 tests performed have not been demonstrated to be sufficiently sensitive to detect product degradation, this "shelf-life" was not acceptable. No additional data has been supplied to support the hold period at the drug substance step. The Applicant committed to perform a study on 3 batches in cryovials. The acceptability of the data from such a study would depend on the ability to demonstrate that peptide(s) is bound to gp-96 in drug substance and drug product.

Drug product
The company's claim of a shelf life for the drug product (18 months at -80°±20°C) is not considered acceptable (major deficiency). The drug product shelf life is only supported by 2 lots that appear to be representative of the final commercial process, and that were analysed up to 18 months. Stability results do not show any significant trends in the proposed storage conditions. However, taking into account the limitations of the specification (i.e. no test available to confirm that the product really maintains association with the tumour peptide through storage), the proposed studies are not considered satisfactory. Furthermore, in-use stability studies have not been performed.
As a consequence, the drug product stability is not considered acceptable, and appropriate stability studies, in line with ICH Q5C, should have been provided. Taking into account the specificity of this product, and the limitation of the analytical tools, the samples used in this study should be drug product produced with the final commercial process (i.e. version 6), derived from appropriately justified, and documented tumour model(s) for which sufficient knowledge of the tumour peptide(s) has been acquired.
The Applicant has committed to include in its stability monitoring program at least one batch of drug product per year derived from RCC or a relevant marker tumour.

- Adventitious agent testing

Starting material
The donor selection is focused on serological qualification for HIV, hepatitis and syphilis and is in compliance with the requirements of EU Directive 2004/23/EC. The Tumour Evaluation Report has been appropriately revised to record additional and appropriate serology testing for HTLV-1 RhD, HLA, malaria, CMV, toxoplasma, EBV, Trypanosoma cruzi.
The Applicant proposed to introduce bioburden testing of tumour homogenates and presented data from batches to demonstrate that the low levels of bioburden detected in tumour homogenates results in sterile drug product.

Other biological products used during the manufacturing process
For each of the protease inhibitors in the complex (except for one) each supplier has provided a statement that no material of animal/human origin is used during the manufacturing process. However, each supplier should have addressed as well how the unintentional contamination of process material and/or equipment with extraneous material (insect, bird and animal excreta) is avoided or controlled.

Discussion on chemical, pharmaceutical and biological aspects

Major deficiencies remain relating to manufacturing process and control of critical steps; characterisation; drug substance and product specifications, process validation; analytical procedures and validation of analytical procedures; batch analyses; and stability.

The physicochemical and biological characterization data provided are not sufficient to establish the detailed structure of the active substance. The company claims that the mechanism of action of the active substance is based on peptides complexed with gp-96 but has not provided sufficient evidence (either physicochemical or pharmacological) for the presence of peptides complexed with gp-96 in the active substance and finished product. As was recognized and discussed with the Applicant during the course of assessment, this product is a tumour extract, containing a wide range of protein/peptide species and thus an approach to quality aspects based more on relevant biological/immunological activity may have been advantageous.

Since the process cannot be validated solely based on data generated from autologous material, it was recommended to perform process validation and stability studies with a well characterised tumour model. Data obtained from an appropriate tumour model have not been provided, and no alternative approach has been proposed.

It is stressed that the comparability between the different products and processes has not been established at the quality level. Considering the significant evolution of the product quality through the different process versions, and the analytical limitations, comparability has not been demonstrated, and thus, the pivotal clinical trial should have been performed with product obtained with the final commercial process (i.e. version 6).

Due to the complexities of the remaining major quality objections at Day 180, the Applicant proceeded with an oral hearing of the BWP in an effort to address the outstanding issues. Whilst the Applicant has attempted to address the major deficiencies in its written responses and at the BWP oral hearing, the necessary data has not been supplied and the key issues regarding the presence and quantification of peptides bound to gp-96 and a relevant potency assay have not been resolved. In the absence of a suitable testing regime for the complete active substance, the company has been unable to demonstrate that process parameters are sufficient, that the process is suitably validated and controlled, that product used in clinical trials is consistent despite changes in manufacturing facility, manufacturing process and formulation, and that product is stable and that active substance in drug product is adequately controlled.

In addition to outstanding GMP compliance, other minor issues relating to the starting material, manufacturing process, characterisation, control of excipients, specifications and analytical procedures, container closure systems, stability, adventitious agents testing should have been resolved prior to granting of marketing authorisation.

2.3 Non-clinical aspects

Introduction

The non-clinical development programme for vitespen was unconventional due to the nature of the active substance, i.e. an autologous human-tumour derived immunotherapeutic product. The ICH S6 (Preclinical safety evaluation of biotechnology-derived pharmaceuticals) and the Note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95) were considered primarily pertinent to the evaluation of vitespen. Moreover, the CHMP Guideline on Human Cell-Based Medicinal Products (EMEA/CHMP/410869/2006), although primarily intended for products containing viable human cells rather than cell-derived proteins, could be applied to non-viable cellular fragments derived from human cells.
The immune response to vitespen is tumour/patient specific and depends on the peptide component of vitespen. Therefore, pharmacology and toxicology studies were performed in rodents only (mice)

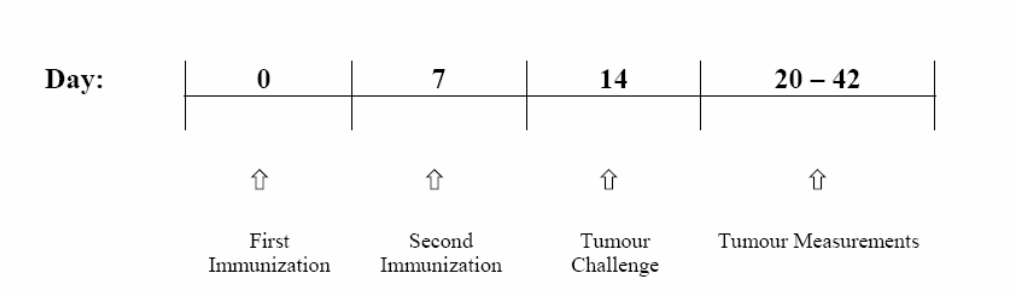
using an equivalent rodent autologous product prepared using essentially identical methodology as that employed for the human product. Non rodents were not studied because equivalent tumour models are not available for dogs or primates. Repeat-dose toxicity studies were performed in both tumour-bearing and healthy mice with the murine surrogate to detect potential toxicity in conditions mimicking the clinical settings, as well as off-target effects.
The non-clinical studies submitted were not formally performed in compliance with GLP. The applicant claimed that the syngeneic mouse tumour models are specialised models that are not readily available in GLP-compliant contract research organizations. Terminal pathology examinations of animals included in toxicity studies were performed in a GLP-compliant testing laboratory, although they were not fully GLP-compliant. According to the applicant, the studies were well-designed and conducted and reporting and data interpretation were of a standard equivalent to that achieved in many GLP-compliant laboratories.

Pharmacology

Primary pharmacodynamics

The pharmacology studies for vitespen have largely been performed in BALB/c or C57BL/6 mice immunised with 'murine surrogate' vitespen derived from their respective tumours. Two mouse tumour models were employed: the methylcholanthrene A prophylactic model and the D122 subclone of the Lewis lung carcinoma therapeutic model. Both models have been established for several decades and have been used to assess the activity of other cancer vaccine strategies (Sturmhoefel K, 1999; Mandelboim O, 1995).
The Meth A tumour line is one of many fibrosarcoma lines that was induced by injection of the carcinogen, methylcholanthrene, into the skin of BALB/c mice (Old LJ, 1962). The Meth A line is maintained by serial passage of a suspension of tumour cells in the peritoneum of naïve BALB/c mice. Injection of Meth A cells into the skin or subcutaneous space of BALB/c mice leads to progressive tumour growth at the site of injection and death of the animal within approximately 30-45 days.
The design of the studies in the Meth A model encompassed two prophylactic immunisations of mice with vitespen isolated from Meth A tumour cells on Days 0 and 7. On Day 13, the mice were shaved on the right flank and on Day 14 challenged intradermally (on the shaved flank) with 1 x 10^5 viable Meth A cells in order to assess whether immunisation with vitespen conferred protection from tumour growth (Figure 1 outlines the method). Control groups received the vehicle and, in some experiments, a positive control group received irradiated Meth A cells. Morbidity and mortality checks were performed daily and physical observations were recorded daily during the business week. Tumour measurements were performed approximately every three days. Animals were killed on approximately day 42.

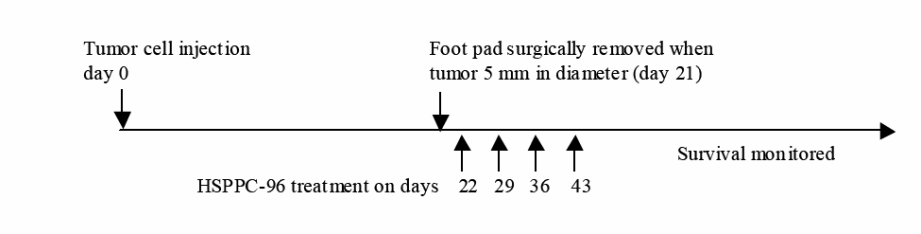
Figure 1: Schematic Representation of Prophylactic Study Design



Dunnett's test was used to determine whether differences in the mean tumour size within vitespen immunised groups and between each vitespen immunised and the buffer control groups, were significant. Fisher's exact test was used to determine whether the percentage of mice that were completely protected from tumour growth (no measurable tumour at end of study) was significantly different among groups.
D122 is a highly metastatic variant of the 3LL tumour line of low immunogenicity that arose spontaneously in the lungs of a C57BL/6 mouse (Sugiura K, 1955). The tumour line is maintained in

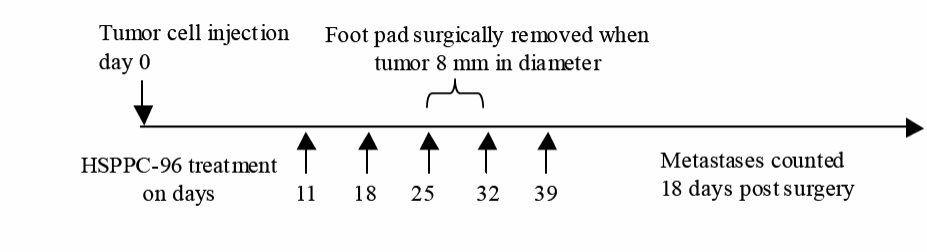
cell culture flasks. Upon injection subcutaneously or in the footpad, tumour cells metastasise spontaneously to the lungs leading to death within approximately 45 days.
The design of the 3LL-D122 therapeutic studies is shown in figures 2 and 3. In the post-operative therapy model (Figure 2), tumour cells were injected into the foot pad and allowed to grow to 5 mm diameter at which time the lower limb was amputated rendering the animals clinically disease free. During the time before surgery, tumour cells metastasise to the lungs and untreated animals die with extensive lung nodules by approximately day 45. Therefore, the goal of post-surgical treatment was to reduce or eliminate the pulmonary metastatic burden and prolong life span. In the vitespen post-operative therapy study, treatment began one day after surgery and continued for a total of four weekly injections. Survival of mice was monitored.

Figure 2: Schematic Representation of Post-operative Therapy Study Design



In the peri-operative model (Figure 3), immunisation begun before and continued after surgery. In all studies, a control group received the vehicle.

Figure 3: Schematic Representation of Peri-operative Therapy Study Design



The pharmacology studies conducted by or on behalf of the applicant using the above disease models fall into five categories listed below:

- Formulation. Two formulations have been used: the earlier studies used a phosphate buffered saline (PBS) formulation and the latter used a 9% sucrose/potassium phosphate buffer (S/KPO_4) version, which is the one intended for marketing. Studies were conducted to compare the efficacy of the two formulations.
- Manufacturing process improvements. Studies were also conducted to assess whether changes intended to improve the manufacturing process had any effects on the biological activity of vitespen.
- Evaluating dose levels. The optimal efficacious dose was estimated using the Meth A prophylactic model.
- Evaluating route of administration. The effect of route on immunogenicity was studied in three Meth A prophylactic studies.
- Tumour specificity. Three specificity studies tested the ability of vitespen derived from one tumour type to elicit protection from challenge with that same tumour type or an antigenically-distinct tumour.

Formulation

Phosphate buffered saline formulations are known to be sub-optimal for a number of reasons, particularly if intended for frozen storage. Therefore, an alternative formulation to the initial phosphate buffered saline (PBS)was developed using sucrose (S/KPO_4). Five studies were conducted in BALB/c mice using the Meth A prophylactic model to assess the impact of final product formulation on vitespen anti-tumour activity.

Only in one of the five studies was there a statistically significant difference between the two formulations, with the S/KPO_4 buffer performing better than the PBS. In three of the five studies, vitespen in either formulation demonstrated statistically significant anti-tumour activity. In the fourth study, only the S/KPO_4 formulated product was active to a significant degree, while in the fifth study, no statistically significant anti-tumour activity was demonstrated by product in either formulation, although the PBS-formulated product protected more mice from tumour challenge than the S/KPO_4 formulated product (data not shown).

Manufacturing process improvements

A total of 13 process improvement studies were undertaken to assess whether changes in the manufacturing version used to isolate vitespen from tumour tissue affected biological activity of the product. The Meth A model in BALB/c mice was used in all studies.

As demonstrated by reduction in mean tumour size relative to the control group or by complete tumour rejection, HSPPC-96 showed some activity in 10 of the 13 studies. In 9 of the 10 studies, at least one result reached statistical significance, whereas in the tenth study only a non-significant reduction in mean tumour size was observed (data not shown).

In terms of the effect of manufacturing process improvements on product activity, the applicant concluded that the manufacturing changes that were implemented over time did not deleteriously affect biological activity of the product, but rather maintained or improved product performance.

Dose level

Based on relevant literature (Srivastava et al, 1986; Chandawarkar et al, 1999), the applicant claimed that, in general, vitespen demonstrates little to no activity at a low dose, clear activity at a middle dose and little to no activity at a high dose. This pattern of activity resembles a bell shaped curve and is consistent with the dose/activity relationship of vaccines in general. The applicant conducted seven studies, five using the Meth A model and two using the 3LL-D122 model, to evaluate the optimal effective dose of vitespen.

In the five Meth A prophylactic dosing studies, vitespen demonstrated anti-tumour activity, as assessed by reduction in mean tumour volume or complete protection from tumour growth. The activity was statistically significant in three of the five studies in which the product was administered subcutaneously with optimal activity in the 10 – 70 µg range (data not shown). In the two remaining studies, vitespen was administered to mice intradermally at doses that ranged from 0.5 - 20 µg. Doses of 1, 5 and 20 µg were associated with inhibition of tumour growth but the results were not statistically different from diluent control (data not shown). Determination of the protective dose range of intradermally administered vitespen in the Meth A tumour model was examined further in the above-mentioned non-clinical studies associated with optimisation of the vitespen manufacturing process and product formulation. In these studies, a protective dose range of 3-10 µg was defined for intradermally administered vitespen (data not shown). In the two 3LL-D122-therapy studies employing the peri-operative and post operative design, respectively, vitespen was administered by subcutaneous injection. In the peri-operative model, vitespen administered at doses of 15 µg or 20 µg showed statistically significant anti-tumour activity as documented by significantly lower lung weights and number of metastatic lung nodules compared to placebo. In the post-operative model, subcutaneous injection of 10 µg and 20 µg of vitespen prolonged mean survival compared to placebo in a dose-dependent manner. Finally, the applicant claimed that doses up to 30 µg were tested in this system and no instances of immune suppression were observed (data not shown).

Route of administration

Three studies have been conducted in the Meth A model to assess the efficacy of tumour derived vitespen administered by various routes to mice before tumour challenge.

In the first study, vitespen administered by the oral and intramuscular routes did not show any activity, while the activity of intravenously and intraperitoneally administered vitespen did not reach statistical significance. Statistically significant activity was only shown for subcutaneously administered vitespen (data not shown). In the two other studies, the intradermal and subcutaneous routes of administration were tested. In one, a 5 µg dose of vitespen administered intradermally and 10 and 30 µg administered subcutaneously provided statistically significant anti-tumour protection. In the other, 10 µg and 117 µg of vitespen administered subcutaneously showed activity, compared to 0.83 µg and 8.3 µg, but not 1.7 µg and 3.3 µg, administered intradermally (data not shown).

Tumour specificity
Three studies were conducted to assess the specificity of vitespen vaccination against tumour challenge.
In the first study, specificity of vitespen vaccination was examined in the 3LL-D122 post-operative model. Activity was shown for vitespen administered subcutaneously at 20 or 30 µg when derived from parental 3LL-D122 cells or a non-metastatic variant of the 3LL-D122 cell line, but not from an unrelated melanoma cell line (or in case of a placebo injection, data not shown).
In the other two studies, specificity of vaccination was examined in the Meth A prophylactic model using vitespen derived either from Meth A cells or from an unrelated colon carcinoma line. In one study, upon intradermal administration of up to 10 µg of vitespen, there was no statistically significant difference between vitespen derived from the Meth A cell line and the unrelated colon carcinoma cell line, but no significant differences from placebo control were observed and in many cases tumours grew larger in the vitespen-treated animals compared to placebo (data not shown). In the other study, vitespen was administered at doses of 10 µg or 20 µg by subcutaneous injection and 1 µg or 2 µg by intradermal injection. Tumours in the intradermally injected mice were generally smaller compared to those in mice injected subcutaneously. Upon subcutaneous injection, only Meth A-derived vitespen showed statistically significant activity compared to placebo and also compared to the unrelated source vitespen. Upon intradermal injection, similar trends were observed, but no differences reached statistical significance (data not shown).
The specificity of vitespen vaccination was also examined in the above-mentioned non-clinical studies associated with improvement of the vitespen manufacturing process. Vitespen isolated from Meth A tumour cells protected mice better from Meth A tumour challenge compared to HSPPC-96 isolated from normal mouse organs (data not shown).

In addition to the studies described above, a review of papers from the scientific literature was submitted, which provided evidence for the mechanism of action of, the type of immune response elicited by and the efficacy of vitespen in a variety of rodent tumour models (cancers of the colon, skin, liver, lung, prostate and breast; also lymphoma).

- Secondary pharmacodynamics

No studies were submitted. (see Discussion on non-clinical aspects).

- Safety pharmacology programme

No studies were submitted (see Discussion on non-clinical aspects).

- Pharmacodynamic drug interactions

No studies were submitted. (see Discussion on non-clinical aspects).

Pharmacokinetics

No studies were submitted. (see Discussion on non-clinical aspects).

Toxicology

- Single dose toxicity

No studies were submitted. (see Discussion on non-clinical aspects).

- Repeat dose toxicity (with toxicokinetics)

The applicant conducted 5 repeat-dose toxicity studies (one of which was in two parts) using either mouse fibrosarcoma-derived or mouse Lewis Lung carcinoma (3LL-D122)-derived vitespen. Indeed, mouse tumour-derived vitespen was used as surrogate because an autologous human product is not

appropriate for use in animal studies. Of the five studies, one included tumour-bearing mice, three were conducted in non-tumour bearing mice and the bipartite study included both healthy (part A) and tumour-bearing mice (part B).
The design of the 5 repeat-dose toxicity studies submitted and the main results obtained are shown in the Table 1.

Table 1: Repeat-dose toxicity studies

Study No	Model Test article	Dose/Route Duration	Parameters evaluated Major findings
1	Prophylactic model: Healthy, naïve BALB/c mice* (5 F/ group**) Meth A fibrosarcoma-derived HSPPC-96	0, 5, 10, 30, 70 µg/ week SC route 2 weeks (dosed on days 0 and 7) Tumour induction on day 14, termination on day 45	Clinical signs, Body weight No adverse consequence of immunization on body weight was observed.
2A	Healthy, naïve BALB/c mice (5 F/group) Meth A fibrosarcoma-derived HSPPC-96	0, 10, 100 µg/ week SC route 2 weeks (dosed on days 0 and 7) Necropsy at day 80	Clinical signs, Haematology, Clinical chemistry***, Histopathology[a] - Minimal to mild inflammation of the subcutis at injection site (1/5, 2/5, 0/5 at 0, 10 and 100 µg, respectively) - Lymphoid hyperplasia: follicular hyperplasia, paracortical hyperplasia, ↑ tangible body macrophages in mesenteric lymph node (10 and 100 µg)
2B	Therapeutic Lung carcinoma 3LL-D122-bearing C57BL/6 mice (5 F/group) 3-LL-D122 fibrosarcoma-derived HSPPC-96	0, 20 µg/ week SC route 4 weeks (dosed on days 1, 8, 15, and 22) Tumour induction, footpad amputation on day 0, necropsy at day 194.	Clinical signs, Haematology, Clinical chemistry***, Histopathology[a] - ↑ mortality from disseminated pulmonary metastasis (0 µg) ⇒ no blood sample collected in this group, and only lungs were available for histopathological examination of control animals - ↑ total leukocyte count (20 µg) - ↑ peripheral blood lymphocytes (20 µg) - Moderate to marked lymphoid hyperplasia of all peripheral lymphoid organs, i.e. spleen and lymph nodes (20 µg) - Injection site: subacute minimal inflammation (1/5, 20 µg) - Liver: severe diffuse vacuolation of hepatocytes – small vacuoles consistent with possible glycogen infiltration (20 µg) - Liver: multiple minimal or mild foci of inflammation which consisted of infiltrates of approximately 5-20 mononuclear cells in each focus (20 µg) - Kidney; focal tubular degenerative changes (1/5, 20 µg) - Kidney: focal fibrosis (1/5, 20 µg)
3	Healthy, naïve BALB/c mice (5 F/group) Meth A fibrosarcoma-derived HSPPC-96	0, 10, 100 µg/ week SC route 2 weeks (dosed on days 0 and 7) Necropsy at day 14	Clinical signs, Clinical chemistry[b], Histopathology[a] Clinical chemistry values were increased for various enzymes reflective of changes in the liver and tissue degeneration. Pathology examination demonstrated evidence of **acute mouse hepatitis virus (MHV) infection** in the colon, mesenteric lymph node, and liver of all groups that accounted for the alteration in clinical chemistry parameters.

Study No	Model Test article	Dose/Route Duration	Parameters evaluated Major findings
$	Therapeutic Lung carcinoma 3LL-D122-bearing C57BL/6 mice (5 F/group) 3-LL-D122 fibrosarcoma-derived HSPPC-96	0****, 0, 20 µg/ week SC route 4 weeks (dosed on days 1, 8, 15, and 22) Tumour induction, footpad amputation on day 0, necropsy at day 40.	Clinical signs, Clinical chemistry[b], Histopathology[a] - All healthy (non tumour-bearing) control mice survived the entire study duration - All tumour-bearing controls died between days 18 and 24: no blood sample was collected in this group - 1/5 treated mice died on day 40, immediately before sacrifice - ↑ LDH (2/5 and 4/5 mice at 0**** and 20 µg, respectively) - ↑ AST and ↑ K (1/5, 20 µg) - All tumour-bearing control mice died during the course of the study of extensive metastasis of the tumour to multiple organs (lung, brain, heart, lymph node, kidney). Similar metastases to the lung, brain, and thymus were observed in treated mice (but survival increased)
5	Healthy, naïve BALB/c mice (5 F/group) Meth A fibrosarcoma-derived HSPPC-96	0, 10, 100 µg/ week SC route 2 weeks (dosed on days 0 and 7) Necropsy at day 18	Clinical signs, Clinical chemistry[b], Histopathology[a] - ↑ ALT (1/5, 4/5 and 1/5, at 0, 10 and 100 µg respectively) - ↑ AST (1/5, 4/5 and 1/5, at 0, 10 and 100 µg respectively) - ↑ LDH (1/5 and 3/5 at 0 and 10 µg respectively) - Liver: subacute inflammation (1/5, 4/5, 3/5 at 0, 10 and 100 µg respectively) - Liver: cytoplasmic vacuolation (3/5, 4/5, 5/5 at 0, 10 and 100 µg respectively)

* mice were challenged by ID injection of Meth A fibrosarcoma cells one week following the end of treatment ; ** 10 F in control group; *** planned but not performed because enough blood could not be obtained; **** group of healthy mice (treated phosphate buffered saline)

[a] tissues examined: injection sites and regional (prescapular) lymph node, mesenteric and mandibular lymph nodes, lung, thymus, spleen, brain, liver, heart and kidney

[b] serum parameters measured: Ca, P, Na, K, Cl, glucose, total protein, albumin, globulin, total bilirubin, ALT, ALP, LDH, AST, triglycerides, cholesterol, CK, BUN

- Genotoxicity

No studies were submitted. (see Discussion on non-clinical aspects).

- Carcinogenicity

No studies were submitted. (see Discussion on non-clinical aspects).

- Reproduction Toxicity

No studies were submitted. (see Discussion on non-clinical aspects).

- Toxicokinetic data

No studies were submitted. (see Discussion on non-clinical aspects).

- Local tolerance

Specific local tolerance toxicity studies were not submitted. Histopathological examination of injection sites was performed in repeat-dose toxicity studies conducted with either Meth A or 3LL-D1222 derived HSPPC-96. These examinations revealed that any local reactions were related largely to the injection procedure, and that the murine HSPPC-96 product did not cause any significant local irritation.
The local tolerability of HSPPC-96 formulations was also assessed in clinical trials involving several hundred patients, which identified injection site erythema and induration as common adverse events.

These findings were only mild to moderate in severity and were considered by the applicant an expected local reaction to intra-dermal injection of a protein vaccine product.

- Other toxicity studies

Studies on impurities
A study on the major process impurities was submitted. Based on the release limit for one of the major impurities, the 'worst case' human exposure could be about 0.0127 µg/kg/dose for a 70 Kg patient. This is many orders of magnitude lower than the lowest toxic or lethal doses reported in mice, rats and rabbits (data not shown).

Ecotoxicity/environmental risk assessment

The applicant calculated a PECsw according to the methodology detailed in the relevant guideline (Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMEA/CHMP/SWP/4447/00). Taking into consideration the default values for Fpen (0.01), WASTEinhab (200 L/inh/day) and Dilution (10), and an overestimated maximum daily dose of 25 µg, the PECsw amounted to $1.25.10^{-4}$ µg/L. This value is lower than the action limit of 0.01 µg/L.

Discussion on the non-clinical aspects

With regard to the vitespen non-clinical development programme in general, the CHMP considered that the validity of the submitted non-clinical studies was compromised because the manufacturing process was not standardised and the drug product was not sufficiently characterised. The applicant claimed that it is the presence of peptides associated with Heat Shock Protein-96 that induces the tumour specific response. However, the CHMP had doubts whether peptides remain in the final product. This questioned whether the submitted preclinical studies were meaningful and relevant to the final product.
The pharmacology of vitespen was addressed through the submission of published papers and a series of studies. In the primary pharmacology studies relevant activity was observed, albeit inconsistently, in a prophylaxis model using two weekly ID or SC doses before tumour challenge and in two therapy models using weekly SC dosing following tumour challenge. On a weight of evidence basis, the studies demonstrated pharmacodynamic activity, with 26 of the 31 submitted studies showing a positive result to some extent, although as noted above, the effect was not consistent.
The optimal efficacious dose of vitespen in the Meth A prophylactic model was observed by the Applicant to be approximately 10 µg. In a small number of studies, lower amounts of vitespen were also effective (1 – 5 µg). In the therapy studies using the 3LL-D122 model, the optimal dose was identified by the Applicant as 20 µg, although activity was also seen at 15 µg and 30 µg (the highest dose tested).
The CHMP raised a major objection with regard to the expected tumour-promoting activity of high doses of vitespen reported in the literature (Chandawarkar RY, 1999). The applicant also claimed that, in general, vitespen demonstrates little to no activity at a low dose, clear activity at a middle dose and little to no activity at a high dose. This pattern of activity resembles a bell shaped curve and is consistent with the dose/activity relationship of vaccines in general. However, the tumour-promoting activity was not observed in any of the non-clinical pharmacology studies conducted by or on behalf of the Applicant, while it has only been reported once in the literature. In light of the lack of definitive evidence, the CHMP dropped this major objection but nevertheless remained concerned about the choice of dose used clinically (see also discussion on clinical efficacy).
Tumour protection offered by vitespen vaccination was statistically significant when the product was administered intradermally or subcutaneously. Within any one route of administration, the degree of tumour protection was generally positively correlated with vitespen dose, with the caveat noted above of the inconsistent response.
Cognate vitespen elicited statistically significant anti-tumour activity, as expected, while vitespen derived from an irrelevant tumour line elicited only partial tumour immunity. A similar finding was observed in two studies in the Meth A prophylactic model. However, this was another instance where the findings were not consistent between studies.

No secondary pharmacodynamics, safety pharmacology or pharmacodynamic drug interaction studies have been submitted. This is acceptable for a product of this type.
No pharmacokinetic studies were submitted. The applicant argued that unlike treatment with small molecule pharmaceuticals, where the level and duration of drug persistence in blood and tissues correlate with the pharmacological effect, vitespen does not need to achieve any particular level in tissue, but rather to elicit a specific immune response. Moreover, vitespen is not distributed, metabolised or excreted in the conventional sense. Consistent with EU guidance for vaccine antigens, (Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines CPMP/SWP/465/95), the CHMP considered the absence of pharmacokinetic and absorption, distribution, metabolism and excretion studies acceptable.
The conventional approach of toxicity testing in two species (rodent/non-rodent) is not applicable to vitespen, as the pharmacology of the product needs to be reproduced in the animal models used and relevant disease models only exist in mouse.
The absence of single dose toxicity studies is acceptable, as is the case for vaccines in general.
Five safety studies were conducted in mice using mouse tumour-derived vitespen. One study was repeated because of an infection with mouse hepatitis virus. Because the product is autologous in nature, the question of viral contamination is less of a safety issue than for an exogenously derived material.
Over the five studies, no severe adverse signs were observed either as body-as-a-whole or at the site of injection, for both healthy and tumour-bearing mice and there were no test article-related deaths. However, these studies do not allow satisfactory assessment of the risks related to the administration of vitespen to humans due to the lack of GLP-compliance and inadequacy of study design. More specifically, the following deficiencies were pointed out:
1) The product used was prepared in phosphate-buffered saline (PBS), whereas the intended commercial formulation for vitespen uses sucrose/potassium phosphate (S/KPO4) as the vehicle. The Applicant pointed out that the comparability of the two formulations had been shown in the non-clinical primary pharmacology studies.
2) Mice were treated for up to 4 weeks, whereas the clinical regimen often involves treatment for longer than 4 weeks (in the pivotal clinical trial the median number of administrations was 12 injections given over a 20-week period). However, the conduct of longer term or chronic toxicity studies is not feasible in the relevant mouse models, as the mice usually survive for 30 days or less following foot pad amputation/metastasis formation after tumour induction.
3) Mice were treated subcutaneously, whereas the intradermal route was chosen for phase III studies. However, based on non-clinical pharmacology and clinical phase I/II data, differences in the safety profiles for vitespen administered either intradermally or subcutaneously were not expected. Intradermal administration is also difficult to achieve in mice, and only small volumes can be delivered. As higher volumes can be administered by the subcutaneous route, it is likely that higher systemic exposure to vitespen could be achieved.
4) Naïve mice were treated with vitespen doses up to 200 µg (2x100 µg/week), and tumour-bearing mice received up to 80 µg (4x20 µg/week). In general, the approach to dosage selection for toxicity studies with vaccine antigens is to administer the equivalent of one human dose per administration to the animals. However, mice received doses at least two orders of magnitude higher both per injection and cumulatively.
5) Each treatment group was composed of 5 females, although commonly 10 animals/sex/group are used. Only female mice were used because the syngeneic mouse tumour model originated in female BALB/c mice. The use of only 5 females per group was justified by the applicant due to the technical and logistical difficulties associated with the conduct of studies in such an animal model. The applicant also indicated that the group size employed in these studies was regarded as acceptable in statistical terms to enable any clear effects of vitespen treatment to be detected.
6) Not all of the study protocols for the repeated dose toxicity studies included all of the metameters that are routinely incorporated in GLP compliant regulatory toxicity study protocols in rodents. However, between the five studies conducted, clinical observations, body weights, haematologic and clinical chemistry examinations were investigated. Histopathologic examinations were performed but the list of tissues examined was more restricted than that usually expected in toxicity studies conducted for regulatory purposes. However, the applicant considered this histopathological examination adequate to detect any significant target organ toxicity of vitespen, with the possible exception of the reproductive tract tissues.

The absence of toxicokinetic data is acceptable based on similar considerations to those pertaining to pharmacokinetic data.
The absence of genotoxicity tests is acceptable in accordance with available guidance (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6)).
The absence of carcinogenicity tests is also acceptable in accordance with available guidelines (Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (ICH S6), Guideline on the need for carcinogenicity studies of pharmaceuticals (ICH S1A) and the CPMP Note for Guidance on the Preclinical Evaluation of Anticancer Medicinal Products).
No reproductive and developmental toxicity studies have been performed. A concern was raised for fear that vitespen might interfere with normal embryonic development.
Finally, no Environmental Risk Assessment is required for proteins and peptides, according to Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use, EMEA/CHMP/SWP/4447/00. However, the Applicant estimated the predicted environmental concentration in surface water (PECsw) in accordance with Phase I of the above guideline. The PECsw is above the action limit specified in the guideline so no further investigation was required.

2.4 Clinical aspects

Introduction

This was a application for conditional marketing authorisation based on a single pivotal clinical study, C-100-12.
The proposed therapeutic indication is as follows:
'Oncophage is indicated for use as an adjuvant treatment for localised renal cell carcinoma (RCC) patients at increased risk of recurrence with the following features: Primary tumour stage T1b or T2 with high-grade (3 or 4) histology with no nodal involvement; these characteristics include patients who are considered Stage I or II according to American Joint Committee on Cancer (AJCC) criteria'.
Vitespen was proposed for administration by intradermal injection (ID). A standard dose of 25 µg of vitespen was suggested for all patients. This was changed to 20 µg in the course of the assessment procedure. Injections were proposed to be administered once per week for the initial four weeks, and then every other week thereafter until the patient's supply of vaccine was depleted.
The Applicant received formal EMEA Scientific Advice in March 2005 (ref. EMEA/95035/2005) regarding the clinical development program for Oncophage in renal cell carcinoma (RCC). The Scientific Advice pertained to the design, choice of primary endpoint and statistical analysis plan of the pivotal clinical study and the adequacy of the study as designed to support a marketing authorisation application.
A paediatric class waiver for RCC was issued on 31 July 2008 - confirmation number EMEA/20/2008.
No studies in special populations, such as elderly, males/females or ethnic groups were conducted.
The development programme of Oncophage comprises studies in renal cell carcinoma but also in other indications supporting the safety profile of the medicinal product. These are tabled below:

Table 2: Summary of Ongoing and Completed Clinical Trials of vitespen

Protocol	Phase	Indication	Dose, Route of Administration	Dose Regimen	Patients Enrolled /Treated	Study Status
C-100-21	3	Stage IV metastatic melanoma	25 µg SC	Weekly x 4, then every 2 weeks until depletion	322/133	Completed
C-100-02	1/2	Melanoma	2.5, 25, 100 µg ID	Weekly x 4	36/36	Completed
C-100-06	1/2	Metastatic melanoma	5, 50 µg ID or SC	Weekly x 4	45/45	Completed
C-100-01	1	Resected pancreatic adenocarcinoma	5 µg ID	Weekly x 4	11/11	Completed
C-100-04	1/2	Gastric cancer	2.5, 15, 25, 100 µg ID	Weekly x 4	20/20	Completed
C-100-05	2	Liver metastasis from colorectal cancer	2.5, 25, 100 µg ID	Weekly x 4, then every 2 weeks until depletion	40/40	Completed
C-100-09	2	Indolent lymphoma	25 µg ID	Weekly x 4, then every 2 weeks until depletion	20/17	Completed
C-100-26	2	Resectable non-small cell lung carcinoma	25 µg SC	Weekly x 4, then every 2 weeks until depletion	10	Closed to enrollment
C-100-22 (Investigator Sponsored)	2	Malignant Melanoma	50 ID or SC	Weekly x 4, then every 2 weeks until depletion	38/27	Closed to enrollment
C-100-34 (Investigator Sponsored)	1/2	Glioma	25 µg ID	Weekly x 4, then every 2 weeks until depletion	12 in Phase 1; Phase 2 on-going	Actively enrolling patients
C-100-12 (Part I) / C-100-27 (Survival Registry to C-100-12)	**3**	**Renal cell carcinoma**	**25 µg ID**	**Weekly x 4, then every 2 weeks until depletion**	**728/300***	**C-100-12 Completed; C-100-27 Continues to follow patients**
C-100-12 (Part II)	**3**	**Renal cell carcinoma**	**25 µg ID**	**Weekly x 4, then every 2 weeks until depletion**	**17/7**	**Terminated**
C-100-03	1/2	Metastatic renal cell carcinoma	2.5, 25, 100 µg ID	Weekly x 4	38/38	Completed
C-100-07	2	Metastatic renal cell carcinoma	15, 25 µg ID	Weekly x 4, then every 2 weeks until depletion	84/72	Completed
C-100-08	2	Metastatic renal cell carcinoma	25 µg ID	Weekly x 4, then every 2 weeks until depletion	3/3	Completed
C-100-15	2	Metastatic renal cell carcinoma	25, 50 µg SC	Weekly x 4, then every 2 weeks until depletion	4/4	Completed
C-100-23	1/2	Metastatic renal cell carcinoma	50 µg ID or SC	Weekly x 4, then every 2 weeks until depletion	21/7	Closed to enrollment

GCP

GCP inspections of three investigator sites (two sites in Russia and one site in France) of the pivotal clinical trial were performed. The inspection concluded that the pivotal phase 3, randomized, open-label, international clinical trial (C-100-12) was conducted in accordance with Good Clinical Practices (GCP). During these inspections, no critical findings were observed but 17 major findings were reported, 3 of which impacted on the results.

Pharmacokinetics

No pharmacokinetic studies were submitted (see discussion on clinical pharmacology).

- Absorption

No studies were submitted (see discussion on clinical pharmacology).

- Distribution

No studies were submitted (see discussion on clinical pharmacology).

- Elimination

No studies were submitted (see discussion on clinical pharmacology).

- Dose proportionality and time dependencies

No studies were submitted (see discussion on clinical pharmacology).

- Special populations

No studies in children, elderly or ethnic groups were submitted. The effect of gender differences, weight, renal or hepatic impairment was not addressed (see discussion on clinical pharmacology).

- Pharmacokinetic interaction studies

No studies were submitted (see discussion on clinical pharmacology).

- Pharmacokinetics using human biomaterials

No studies were submitted (see discussion on clinical pharmacology).

Pharmacodynamics

No pharmacodynamic studies were submitted (see discussion on clinical pharmacology).

- Mechanism of action

No studies addressing the mechanism of action of Oncophage were submitted (see discussion on clinical pharmacology).

- Primary and Secondary pharmacology

No pharmacodynamic studies in the context of Renal Cell Cancer (RCC) were submitted. Although there are no specific guidelines for autologous vaccines, the Note for Guidance on the Clinical Evaluation of New Vaccines (EMEA/CHMP/VWP/164653/2005), which states that pharmacodynamic

studies essentially comprise the immunogenicity studies characterizing the immune response to the vaccine, may be considered of relevance. Information on HSP immune responses in man is available from the literature. Assessment of immune response post vaccination with vitespen has been explored by participating investigators in the settings of melanoma, colorectal cancer and glioblastoma multiforme. The overall design of these studies is detailed in table 3 and the immunology results are shown in table 4.

Table 3: Design of Vitespen Clinical Trials Reporting Immunological Monitoring Results

Study No.	Countries	Design / Population	Treatment Dose (µg) Regimen/ Route of Administration	Number of Subjects Randomized or Enrolled/ Treated*	Number of Subjects Evaluable for Immune Response	Type(s) of Method(s)	Study Dates/ Type of Report
C-100-05	Italy	Phase 2, open-label, nonrandomized, multicenter study in patients with liver metastatis from colorectal cancer	2.5, 25, 100 µg ID, weekly x 4, then bi-weekly x 4	40	29	ELISPOT / DTH	22 Feb 1999 to 25 March 2004 Completed/ Abbreviated Clinical Study Report
Publications	Mazzaferro V., *et al*. Vaccination with autologous tumor-derived heat-shock protein gp96 after liver resection for metastatic colorectal cancer. *Clin Cancer Res*. Aug 15 2003;9(9):3235-3245. Pilla L., *et al*. Natural killer and NK-Like T-cell activation in colorectal carcinoma patients treated with autologous tumor derived heat shock protein 96. *Cancer Res*. May 1 2005;65(9):3942-3949.						
C-100-06	Italy	Phase 1/2, open-label, nonrandomized, multicenter study in patients with metastatic melanoma	5, 50 µg ID or SC, weekly x 4, then bi-weekly until depletion	45	23	ELISPOT	22 Feb 1999 to 23 March 2004 Completed/ Full Clinical Study Report
Publications	Belli., *et al*. Vaccination of metastatic melanoma patients with autologous tumor-derived heat shock protein gp96-peptide complexes: clinical and immunologic findings. *J Clin Oncol*. Oct 15 2002;20(20):4169-4180.						
C-100-22	Italy	Phase 2, open label study of Heat Shock Protein-Peptide Complex (HSPPC-96) in combination with GM-CSF and IFN-a in subjects with stage IV resectable malignant melanoma	HSPPC-96: 25 µg SC, weekly x 4, then bi-weekly until depletion GM-CSF: 75 µg SC, the day before, the same day and the day after (day -1, 0 and +1) the first two vaccinations of the 1st and 2nd cycle. Then administered only once, along with the vaccine. IFN-a: 3 MU, SC 2 times a week x 4, starting at day 2 after each vaccine injection. During the 2nd cycle, 3 times a week during the weeks in between the vaccination weeks	38	15 total (13 could be assessed using autologous melanoma cells)	ELISPOT / DTH	March 2002 – February 2003. Investigator sponsored. Report of the trial is available through the publication (see footnote)
Publications	Pilla L., *et al*. A phase II trial of vaccination with autologous, tumor-derived heat-shock protein peptide complexes Gp96, in combination with GM-CSF and interferon-alpha in metastatic melanoma patients. *Cancer Immunol Immunother*. Aug 2006;55(8):958-968.						

C-100-34	US	Phase I/II, open label study, for patients with recurrent high-grade glioma	Phase 1: 6 Patients: HSPPC-96 25 µg ID, every 2 weeks x 4, and every 2 weeks thereafter 6 patients: HSPPC-96 25 µg ID, weekly x 4, and every 2 weeks thereafter. Phase 2: HSPPC-96 25 µg ID, weekly x 4, then bi-weekly until depletion or 52 weeks.	Phase 1: 12 patients Phase 2: still enrolling	12 (data currently available on 8 patients)	ICS / qRT-PCR	On-going. Investigator Sponsored.
Publications	Parsa A., *et al.* AANS Abstract: 2007 Apr 16: Autologous Heat Shock Protein Vaccine For Recurrent Glioma: Results of A Phase I Clinical Trial, AANS Abstract: 2007 Apr 16.						

Table 4: Immunology Results of Vitespen Clinical Trials

Study	Dose	Immunologic outcomes
Metastatic colorectal cancer (C-100-05)	2.5, 25, and 100ug	**Immunology**: 59% of evaluable patients (n = 29) showed a statistically significant increase in anti-colon carcinoma–specific immune response. 2 patients showed an increase that did not appear HLA-restricted, thus probably attributable to NK cells. Immune response was detectable after 4 vaccinations. **Publications**: Mazzaferro *et al. Clin Cancer Res* 2003(Mazzaferro, Coppa et al. 2003) Rivoltini *et al. J Immunol* 2003(Rivoltini, Castelli et al. 2003).
Advanced melanoma (C-100-06)	5 and 50ug	**Immunology**: 48% of evaluable patients (n = 23) showed a statistically significant increase in T-cell anti-melanoma–specific immune response. **Publications**: Belli *et al. JCO* 2002(Belli, Testori et al. 2002); Rivoltini *et al. J Immunol* 2003(Rivoltini, Castelli et al. 2003).
Metastatic melanoma (C-100-22, investigator-sponsored)	25ug	**Immunology** (ELISPOT): Increased T-cell reaction against autologous melanoma cells postvaccination in 7of 13 patients.Increased T-cell recognition of allogeneic HLA-A– and/or –B–compatible melanoma lines postvaccination in 4 of 15 patients. **Publications:** Pilla *et al. Cancer Immunol Immunother.* 2006(Pilla, Patuzzo et al. 2006)
Recurrent, high-grade glioma (C-100-34, investigator-sponsored)	25ug	**Immunology**: (ICS, PCR, CFSE, Phenotype): All 12 treated patients demonstrated significant tumour-specific immune response ($P < .001$) and 11 of 12 patients demonstrated CD8 T cell IFN gamma production upon restimulation with recombinant gp-96 ($p<0.01$). Additionally, the majority of patients (11/12) exhibited significant Th1 type responses as measured by multi-cytokine qPCR. The presence of an adaptive immune response and minimal residual disease was associated with survival beyond 36 weeks. **Publications:** Parsa *et al AACR-NCI-EORTC* 2007(Parsa, Crane et al. 2007)

Limited data were available for the assessment of the immunogenicity studies referred to in tables 3 and 4 through the respective publications. The work was performed and retained by the investigator laboratories, and not transferred to Antigenics; therefore immune response data were reported only in publications: In general, the currently reported data supports a high degree of specificity and very limited toxicity associated with HSPPC-96. ELISPOT and, in one study, soluble tetramers were studied: The phase I and II studies conducted with HSPPC-96 in different solid tumours employed a range of doses from 2.5 µg to 100 µg with the median number of doses ranging from 4 µg to 29 µg.
Although an immune response was observed, none of the studies were designed to correlate dose level or dose regimen with immune response. However, it was determined that an immune response can be detected after 4 vaccine administrations and at a dose as low as 5 µg. Immune response could not be correlated to safety or to the relatively restricted clinical outcomes. However, the data reported by Belli et al. showed that the 2 patients with complete responses also demonstrated a statistically significant increase in specific anti-melanoma T cells after HSPPC-96 administration. Mazzaferro et al. reported that patients with statistically significant increases in anti–colon cancer T cells reported improved disease-free survival and overall survival compared with patients who did not report a significant immune response. Additionally, Parsa et al. reported that patients with adaptive immune responses and minimal residual disease were more likely to survive beyond 9 months than patients

with significant residual disease. In patients with recurrent glioma, all patients (12/12, 100%) showed tumour-specific immune response. In all other Phase 1 and 2 studies of HSPPC-96, immunization elicited cell-based immune responses in up to half of the evaluable patients with solid tumours. Finally, there were no biochemical markers or other prognostic features identified that could serve as surrogates for a clinical effect of vitespen.

Discussion on clinical pharmacology

Oncophage (vitespen) is an autologous vaccine prepared from the individual patient's tumour and administered by intradermal injection to the same individual patient. Moreover, it is not metabolized in the conventional sense. Following intradermal administration, local dendritic cells and other antigen presenting cells are thought to take up complex of HSP96 with associated peptides and migrate to lymph nodes where naïve T cells are expected to recognize the tumour-specific peptides and, in turn, become stimulated by them. In view of the route of administration, proposed mechanism of action and autologous nature of the product, the absence of any PK data on absorption, distribution, elimination, as well as dose proportionality and time dependencies for vitespen was considered acceptable. No drug-drug interactions are expected; hence the lack of relevant studies was also acceptable.
No vitespen-specific PD assessments were made. One pharmacodynamic parameter (i.e., intended biologic effect) that can be measured in many cases with therapeutic cancer vaccines is the ability to elicit a measurable antigen-specific T-cell immune response. The analytical methods available to measure specific immune responses include ELISPOT, intracellular cytokine staining, MHC-peptide tetramer staining and CTL assays. While these assays remain labour intensive and would not be readily implemented in large clinical trials, a pilot study with a homogeneous population with detailed PD readouts would have been informative. No assessment of the immune response to vitespen in RCC was submitted. Although the term "HSPPC-96" is used for all studies where gp96 is isolated from tumours, the difference between the HSPPC-96 isolated from different tumours underlies the proposed mechanism of action (i.e. tumour-specific peptide-HSP complex presentation). As no tumour associated peptides for renal cell carcinoma were characterised for vitespen, this increases the difficulty in identifying an immune response and reduces the range of assays that can be used to detect one.
However and as noted by the Applicant, other investigators have examined the effects of vitespen in the setting of different tumours such as melanoma. The Applicant further argued that it could be qualitatively concluded from the human immunology data collected across three different tumour types (melanoma, colorectal cancer and glioma) that about 50% or more of vitespen treated patients showed a measurable specific anti-tumour T-cell response. This data provides further support towards validating the biological mechanism of action of vitespen, which appears to follow the same fundamental pathway regardless of the tumour type. The CHMP noted that the extrapolation of the PD data from studies in other tumours to RCC is not clear. This difference between the vitespen used in RCC makes any inferences from PD data performed with other tumour-derived HSPPC-96 of limited value. The lack of any PD data to guide dose finding or to demonstrate proof of principle in RCC was considered a major deficiency.

Clinical efficacy

The efficacy of vitespen vaccination has been evaluated in a single Phase III study in the adjuvant setting in patients with renal cell carcinoma (protocol C-100-12).

- Dose response studies

No dose-response studies in the claimed indication were submitted. In the early phase studies in indications other than RCC (see section on pharmacodynamics), a range of doses (2.5, 5, 25, 50 and 100 μg) all elicited evidence of cellular immunity in some immunised subjects after 4 weekly vaccinations. However, given the study designs employed, the dose could not be definitively correlated with immune response, clinical data on adverse events or change in tumour size. In the Phase III renal cell carcinoma trial, 25 μg was used as the dose for vitespen treatment based on its mid position in the dose ranges tested and absence of serious safety problems.

- Main study(ies)

C-100-12

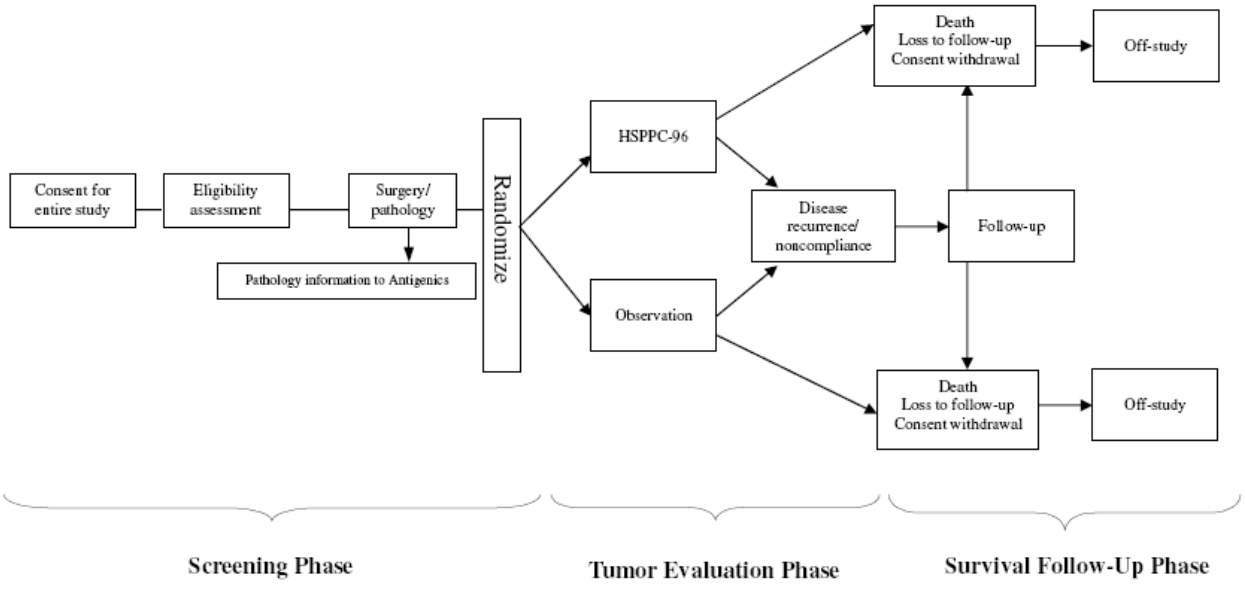
The study was designed as a randomized, open-label, controlled investigation conducted at 127 centres in North America, Europe and Russia.

METHODS

Study Participants
Adults with histologically diagnosed renal cell carcinoma, who were scheduled for or had recently undergone nephrectomy to remove the primary tumour, were enrolled if they had no evidence of residual or metastatic disease and met all other eligibility criteria.
Inclusion criteria were based on the patients' presurgical condition (at least one of tumour size ≥5 cm, macroscopic nodes, renal vein or vena cava thrombus; performance status ≤1 and life expectancy of >3 months; no previous RCC therapy; age of ≥18 years; no pregnancy; informed consent), as well as the postsurgical availability of viable tumour for vitespen production, pathological evaluation of RCC for histology type, stage and grade (histologic diagnosis of clear cell carcinoma (at least 25%) and the following TNM and Furhman grade features indicative of high risk of recurrence: AJCC Stage I with T1b (> 5cm) or AJCC Stage II with high (3-4) Furhman grade; AJCC Stage III any Furhman grade; AJCC Stage IV (no metastases) any Furhman grade), imaging evaluation of disease status (by abdominal, pelvic and chest CT scan and brain CT/MRI scan) and adequate renal, hepatic, cardiac and bone marrow function.
Exclusion criteria included metastatic disease, other treatments for RCC, other malignancies, immunodeficiency/immunosuppression, other serious medical conditions and embolisation of the renal artery prior to nephrectomy.

Treatments
Patients were to receive adjuvant treatment with vitespen or no adjuvant treatment (observation only), as there are no other adjuvant therapies available for RCC treatment. Vitespen was processed for each specific patient randomized to the vitespen arm using autologous tumour harvested during surgical resection of the kidney. All dosed patients received vitespen at weekly intervals for 4 weeks (starting about 6 to 8 weeks after surgery), and thereafter at 2-week intervals until the patient's available supply of vitespen was depleted or until recurrence of disease.
The overall study design is depicted below:

Figure 4: Pivotal study design



Objectives
The objective of the study was to show significant benefit from the administration of vitespen in the adjuvant setting.

Outcomes/endpoints
The primary efficacy endpoint in this study was Recurrence Free Survival (RFS, same as Disease Free Survival). This was defined as time from randomisation until recurrence of disease or death from any cause. Tumour evaluations (CT scans) were conducted in both the vitespen and observation arms every 3 months in the first year, every 6 months in the next two years and yearly thereafter (or at any time if clinically indicated). Assessments were made by the investigators until November 2005 when the independent Clinical Events Committee (CEC), composed of 3 board-certified radiologists and a board-certified oncologist, reviewed all available data for all randomized eligible patients. The CEC reviewers assessed the presence or absence of metastatic or residual disease at baseline, the presence or absence of recurrence and the date of recurrence. These data were utilized for the primary analysis of RFS.
The secondary endpoint was Overall Survival (OS) and subsequent to the tumour evaluation phase, all patients were followed for survival every 3 months until 6 years post-surgery, consent withdrawal or loss to follow-up. Overall survival (OS) was initially defined as the primary efficacy endpoint.

Sample size
Sample-size calculations were based on an anticipated median RFS of 6.8 years in the observation group (hazard rate 0.102) and a median RFS of 12.1 years in the vitespen group (hazard rate 0.0575). An exponential distribution was assumed. This difference was considered clinically meaningful (5-year RFS of 75% in the HSPPC-96 group *versus* 60% in the observation group). An overall 1-sided type I error probability of 0.025 was used. Based on these assumptions, a sample size of 325 eligible patients per group would have an overall power of 85%. The sample size allowed for an estimate of 15% vaccine production failures in patients randomized to receive HSPPC-96.
The following analysis sets were defined for efficacy:
- Intent-to treat (ITT): all randomised patients who were considered eligible for the study after completion of all screening procedures (also referred to as the randomised eligible analysis set). This definition was required as 90 patients were randomised in error before completion of screening procedures and therefore did not continue with study procedures.
- Full analysis set (FAS): all eligible patients who did not have metastatic or residual disease at baseline as determined by the CEC based on assessment conducted before and after randomisation.
- Evaluable patient set: patients from the FAS who received at least one vaccination (Oncophage group) or had at least one post-baseline tumour evaluation visit (both groups).

Randomisation
Patients were randomly assigned in blocks of 4 in a 1:1 ratio to receive adjuvant vitespen treatment or observation alone. The sponsor generated the randomization scheme and administered the randomization throughout the trial. Randomization was conducted with a computer generated pseudo-random number generator.
Randomization 1:1 to vitespen or observation was stratified by Fuhrman grade (low [1–2] versus high [3–4]), regional lymph node status (N0/Nx versus N+) and ECOG performance status (0 versus 1).

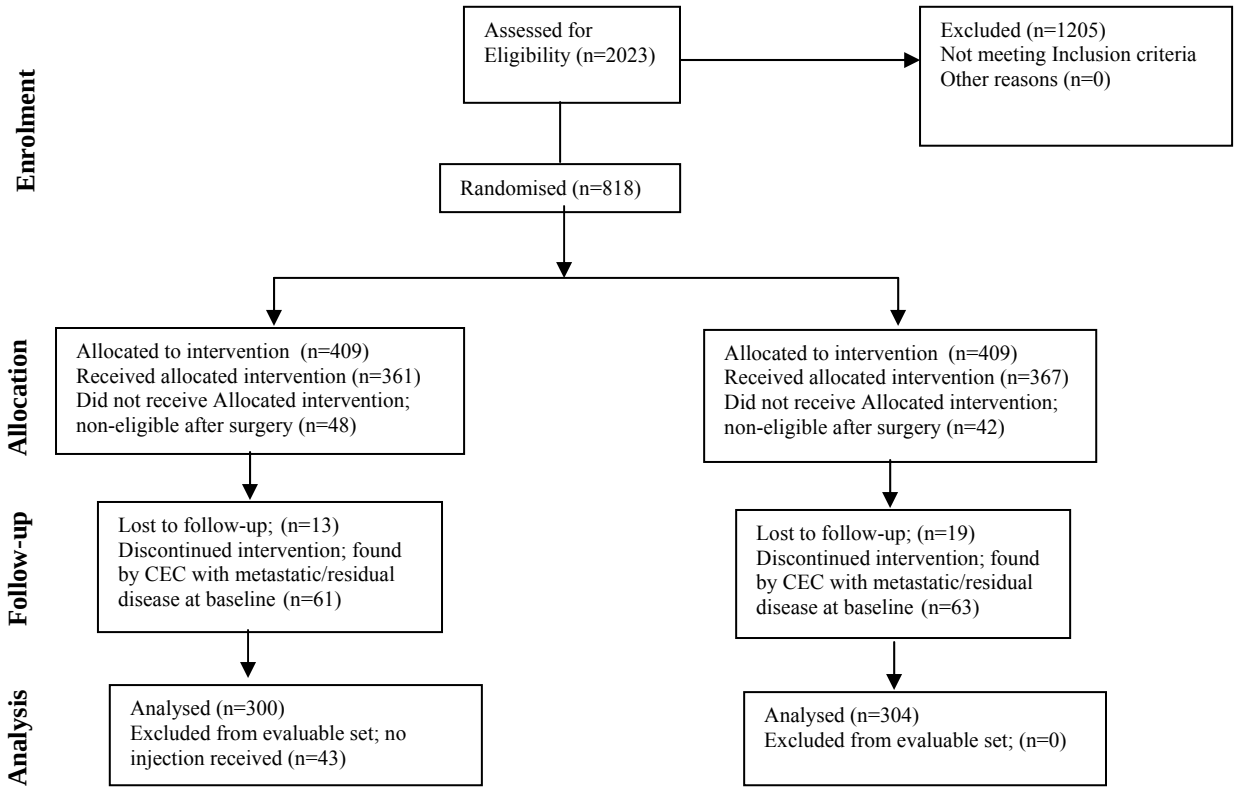
Blinding (masking)
The study was open-label.

Statistical methods
The primary efficacy analysis was 1-sided and an overall type I error probability of 0.025 was used; analyses are based on an overall 1-sided type I error probability of 0.025 unless otherwise specified. As noted in the protocol, the trial was designed for a 1-sided question because success would be manifest only if the RFS in the treatment group was significantly more favourable than RFS in the observation group. The interpretation of the results needs to also take into account the magnitude of the difference seen in the percentage of events reported and the hazard ratios, along with the 95% confidence intervals.

An interim analysis of patient data was planned when 52 events had occurred. The final analysis of data was to be conducted when 214 recurrence events had occurred. At the time of final RFS analysis, OS data were not expected to be mature; therefore, OS data collected at that time point were to be considered interim.

RESULTS

Participant flow



Recruitment

C-100-12 was initiated in February 2001 and terminated March 2007. The last dose of vitespen in the study was administered on February 27, 2007.

Conduct of the study

There were 5 amendments to the original protocol dated 15 May 2000. No patients were enrolled under the original protocol. Under Amendments 1 and 2, 70 patients were enrolled; 277 patients were enrolled under Amendment 3; and 471 patients were enrolled under Amendment 4.

The key modifications to the study protocol introduced by the amendments are outlined below:

- With agreement from the US FDA, the primary endpoint was modified by Amendment 4 from overall survival to recurrence-free survival, and overall survival became a secondary endpoint. With this modification, the sample size was decreased from 712 to 650 patients and the timing of the final analysis was modified from the occurrence of 312 deaths to the occurrence of 214 recurrence events.
- TNM stage in the original protocol required patients to have T2-4, N1 and M0, and Fuhrman grade was not specified (i.e., patients were required to have AJCC [per 1997 guidelines] stage III or IV disease with ≥1 positive regional lymph node and without distant metastasis). Amendment 1 modified the protocol to allow for the enrollment of patients with stage II disease who had Fuhrman grade 3 or 4 histopathology, stage III disease, or stage IV disease without distant metastasis. In Amendment 4, the tumour size cut-off was changed to ≥5 cm based on anticipated changes to the AJCC staging revision in 2002 for T1b disease.
- Histology of the carcinoma was not specified in the original protocol. Amendment 1 modified the protocol to specify that the histology had to show ≥25% clear cells and excluded patients with

papillary, Bellini and carcinomatoid tumours. The exclusionary clause was later dropped in Amendment 4, assuming that the requirement of clear cell carcinoma (including ≥25% clear cell) criterion would exclude these histological types of renal cancer.
- Under the original protocol, the randomization process required tumour stage and pathology eligibility before randomization but allowed for completion of the patient eligibility assessment after randomization. Thus, patients may have been randomized and later determined not to be eligible by the study site. Following Amendment 4 of the protocol, randomization was not conducted until after all screening eligibility procedures had been completed. A total of ninety patients, equally distributed between both study arms (48 vitespen and 42 observation arm), were randomised before eligibility was fully verified and were declared screening failures because of baseline disease. These patients were removed from the dataset and the remaining study group designated as the Randomized Eligible Analysis dataset, which served as the intention to treat population (n=728, see Table 7 below).
- The stratification factors in the original protocol were grade, nodal status (N0 or Nx vs. N1) and performance status. The factors remained the same; however, nodal status was modified to N0 or Nx vs. N+ with Amendment 4.
A partial hold was instituted by the FDA in September 2003 related to the potency testing of vitespen. The FDA deemed vaccine provided to patients before December 2003 as insufficiently characterized because it had not undergone the full battery of tests required for drugs used in pivotal trials. The hold was lifted in November of the same year. Stored patient samples of HSPPC-96 were eventually tested to assure potency. After the clinical hold was lifted, the FDA requested that qualified potency assays be implemented prior to release of vaccine lots for all trials of vitespen. The sponsor submitted its validation package for the qualified potency assays to the FDA in 2004 and successfully concluded discussions with the FDA on this issue in May 2005.
Patients who received ≥1 dose of vitespen were considered to be compliant with the requirements of the study. 318 of the 361 vitespen patients in the Randomized Eligible Analysis set received ≥1 dose of vitespen and 43 patients were untreated (28 vaccine production failures, 9 consent withdrawals, 2 lost to follow-up, 2 death/progression, 2 other reasons).
A planned interim analysis of patient data was conducted on 19 December 2003. The required number of events (52 under the null hypothesis) was reached in September 2003. The test for futility, although planned, was not performed. The DMC reviewed the results of the interim analysis and recommended continuing the study according to protocol.

Baseline data
Distribution of patients was balanced across geographic regions (Western Europe/Israel 207 patients, 25.3%, Russia/Poland 311 patients, 38.0% and United States/Canada 300 patients, 36.7%). Subjects were well matched in terms of demographic characteristics across geographic regions with the exception of ECOG performance. Fewer patients in Eastern Europe had an ECOG performance score of 0 compared with other regions.

Table 5: Summary of demographic characteristics and baseline performance status by geographic region, Full Analysis Set (FAS, N=604)

	North America		Western Europe		Eastern Europe	
Characteristic	**HSPPC-96 (n = 99)**	**Observation (n=101)**	**HSPPC-96 (n = 76)**	**Observation (n = 72)**	**HSPPC-96 (n = 125)**	**Observation (n = 131)**
Age, years						
Mean (SD)	57.0 (10.44)	60.1 (10.37)	60.1 (10.17)	57.8 (9.81)	57.9 (10.76)	60.4 (10.72)
Median	56.0	60.0	60.5	56.5	57.0	61.0
Min, max	34, 81	35, 86	40, 80	38, 78	29, 81	36, 83
Gender [n (%)]						
Male)	75 (75.8	64 (63.4)	54 (71.1)	47 (65.3)	60 (48.0)	72 (55.0)
Female	24 (24.2)	37 (36.6)	22 (28.9)	25 (34.7)	65 (52.0)	59 (45.0)
Race [n (%)]						
White	86 (86.9)	84 (83.2)	75 (98.7)	71 (98.6)	125 (100.0)	131 (100.0)
Hispanic	6 (6.1)	9 (8.9)	0	0	0	0
Asian/Pacific	(2.0)	4 (4.0)	1 (1.3)	1 (1.4)	0	0
Black	0	3 (3.0)	0	0	0	0
Other	5 (5.1)	1 (1.0)	0	0	0	0

Characteristic	North America		Western Europe		Eastern Europe	
	HSPPC-96 (n = 99)	Observation (n=101)	HSPPC-96 (n = 76)	Observation (n = 72)	HSPPC-96 (n = 125)	Observation (n = 131)
ECOG perf score [n (%)]						
0	91 (91.9)	89 (88.1)	68 (89.5)	66 (91.7)	72 (57.6)	83 (63.4)
1	8 (8.1)	12 (11.9)	8 (10.5)	6 (8.3)	53 (42.4)	48 (36.6)

Baseline disease characteristics for the two treatment arms are summarized in Table 6.

Table 6: Summary of baseline disease characteristics

Disease Characterisitic	Randomized Eligible		FAS		Safety	
	HSPPC-96 (n = 361)	Observation (n = 367)	HSPPC-96 (n = 300)	Observation (n = 304)	HSPPC-96 (n = 318)	Observation (n = 359)
AJCC stage						
I	8 (2.2%)	6 (1.6%)	8 (2.7%)	5 (1.6%)	6 (1.9%)	6 (1.7%)
II	131 (36.3%)	122 (33.2%)	117 (39.0%)	110 (36.2%)	110 (34.6%)	121 (33.7%)
III	202 (56.0%)	218 (59.4%)	163 (54.3%)	181 (59.5%)	185 (58.2%)	212 (59.1%)
IV	20 (5.5%)	21 (5.7%)	12 (4.0%)	8 (2.6%)	17 (5.3%)	20 (5.6%)
Tumour stage						
T1b	10 (2.8%)	6 (1.6%)	10 (3.3%)	5 (1.6%)	8 (2.5%)	6 (1.7%)
T2	135 (37.4%)	126 (34.3%)	120 (40.0%)	113 (37.2%)	114 (35.8%)	125 (34.8%)
T3	49 (13.6%)	41 (11.2%)	41 (13.7%)	36 (11.8%)	45 (14.2%)	40 (11.1%)
T3a	86 (23.8%)	94 (25.6%)	70 (23.3%)	78 (25.7%)	78 (24.5%)	90 (25.1%)
T3b	78 (21.6%)	91 (24.8%)	58 (19.3%)	67 (22.0%)	71 (22.3%)	89 (24.8%)
T3c	1 (0.3%)	5 (1.4%)	0	3 (1.0%)	1 (0.3%)	5 (1.4%)
T4	2 (0.6%)	4 (1.1%)	1 (0.3%)	2 (0.7%)	1 (0.3%)	4 (1.1%)
Lymph node status						
NX or N0	332 (92.0%)	337 (91.8%)	279 (93.0%)	290 (95.4%)	291 (91.5%)	331 (92.2%)
N+	29 (8.0%)	30 (8.2%)	21 (7.0%)	14 (4.6%)	27 (8.5%)	28 (7.8%)
Metastatic/residual disease						
No	300 (83.1%)	304 (82.8%)	300 (100%)	304 (100%)	264 (83.0%)	299 (83.3%)
Yes	61 (16.9%)	63 (17.2%)	0	0	54 (17.0%)	60 (16.7%)
Histological type						
Clear cell	361 (100%)	367 (100%)	300 (100%)	304 (100%)	318 (100%)	359 (100%)
Granular cell	68 (18.8%)	59 (16.1%)	60 (20.0%)	50 (16.4%)	58 (18.2%)	58 (16.2%)
Sarcomatoid	15 (4.2%)	10 (2.7%)	11 (3.7%)	4 (1.3%)	14 (4.4%)	10 (2.8%)
Papillary	11 (3.0%)	10 (2.7%)	9 (3.0%)	9 (3.0%)	9 (2.8%)	10 (2.8%)
Chromophobe	0	2 (0.5%)	0	2 (0.7%)	0	2 (0.6%)
Other	21 (5.8%)	27 (7.4%)	18 (6.0%)	21 (6.9%)	16 (5.0%)	27 (7.5%)
% Clear cell						
0–25%	8 (2.2%)	9 (2.5%)	7 (2.3%)	7 (2.3%)	7 (2.2%)	8 (2.2%)
>25–50%	61 (16.9%)	54 (14.7%)	48 (16.0%)	47 (15.5%)	52 (16.4%)	53 (14.8%)
>50–75%	64 (17.7%)	68 (18.5%)	49 (16.3%)	59 (19.4%)	53 (16.7%)	67 (18.7%)
>75%	227 (62.9%)	235 (64.0%)	195 (65.0%)	190 (62.5%)	205 (64.5%)	230 (64.1%)
Unknown	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.3%)	1 (0.2%)	1 (0.3%)
Nuclear grade						
Low (1, 2)	109 (30.2%)	108 (29.4%)	92 (30.7%)	94 (30.9%)	97 (30.5%)	107 (29.8%)
High (3, 4)	252 (69.8%)	259 (70.6%)	208 (69.3%)	210 (69.1%)	221 (69.5%)	252 (70.2%)

Numbers analysed

Of the total 818 randomised, 90 patients were subsequently found to be screening failures and did not continue into the study. Therefore the ITT population, on which the primary efficacy analysis was based, included 728 patients. A Full Analysis Set (FAS) of data were also analyzed. At a late point in the study the Clinical Evaluation Committee (CEC) concluded that 124 patients (61 vitespen and 63 observation arm) with metastatic or residual disease at baseline had been erroneously randomized and these patients were removed from the analysis set. The Full Analysis Set [FAS] comprised therefore 604 patients in total.

The overview of the efficacy and safety analysis sets is presented in Table 7:

Table 7: Overview of analysis sets

Analysis Sets	Overall Analysis Set	
	HSPPC-96 n (%)	**Observation n (%)**
All randomized patients	409 (100%)	409 (100%)
Randomized eligible set (ITT)	**361 (88.3%)**	**367 (89.7%)**
Reasons for exclusion from randomized eligible set		
Eligibility criteria not met[1]	48 (11.7%)	42 (10.3%)
Full analysis set	**300 (73.3%)**	**304 (74.3%)**
Reasons for exclusion from FAS		
Metastatic/residual disease at baseline	61 (14.9%)	63 (15.4%)
Evaluable patient set	**261 (63.8%)**	**299 (73.1%)**
Reasons for exclusion from evaluable set		
No injection received	36 (8.8%)	NA
No postbaseline tumour evaluation assessment	13 (3.2%)	5 (1.2%)
Safety set	**318 (77.8%)**	**359 (87.8%)**
Reasons for exclusion from safety set		
No HSPPC-96 administered/no postbaseline assessment	91 (22.2%)	50 (12.2%)
No vaccine produced	29 (7.1%)	NA
Vaccine produced but not administered	62 (15.2%)	NA

Outcomes and estimation

Primary Endpoint: Recurrence-Free Survival

The results for the primary endpoint of recurrence free survival based on CEC assessment at the time of the planned final analysis (data cut off date: November 2005) are presented in the following tables and figures.

Table 8: Recurrence Free Survival, Randomised Eligible Set (ITT, N=728)

Statistic	**HSPPC-96 (n = 361)**	**Observation (n = 367)**	**Hazard Ratio[1] (95% CI)**
RFS events	136 (37.7%)	146 (39.8%)	0.923
Censored	225 (62.3%)	221 (60.2%)	(0.729, 1.169)
Median follow-up[2] (days)	545	565	
Minimum, maximum	1, 1535	1, 1463	
Recurrence-free survival (days)			
25th percentile	200	165	
Median (95% CI)	1174 (1100, NE)	1096 (912, NE)	
75th percentile	NE	NE	
P value[3]	0.253		

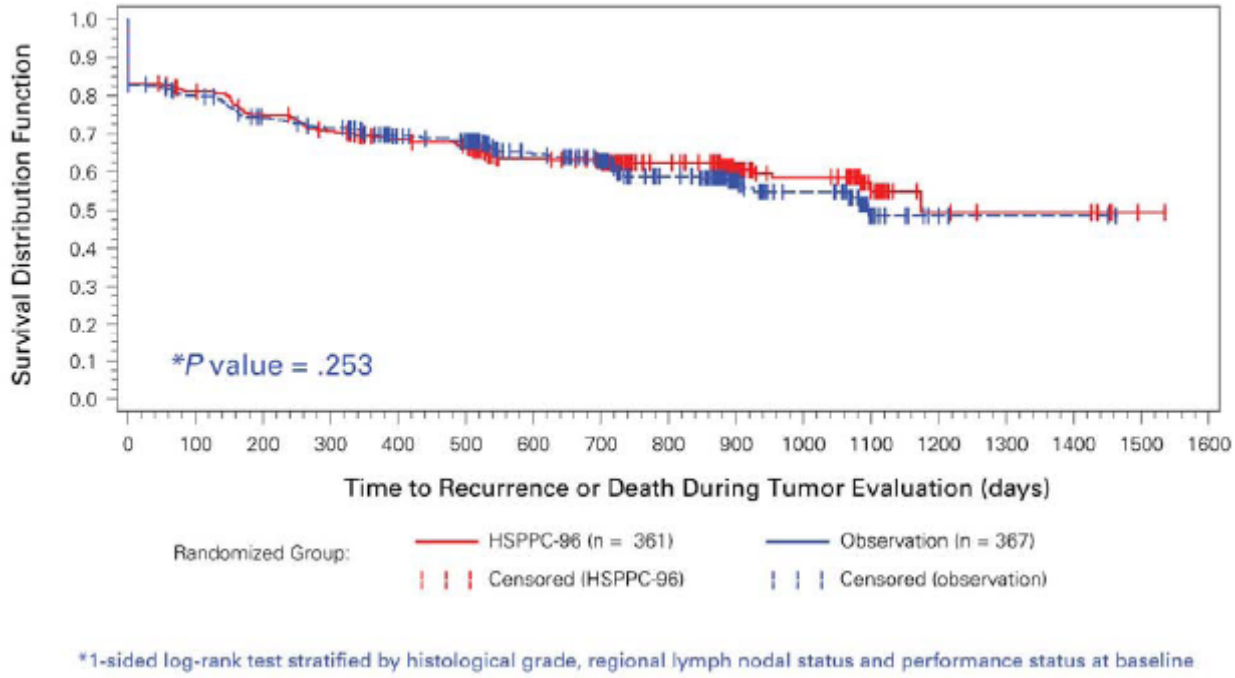
NE: not evaluable due to too few events.

1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.

2 Follow-up time for censored patients calculated using the date of last contact.

3 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status.

Figure 5: Kaplan-Meier Curve for Recurrence-Free Survival, ITT (N=728)



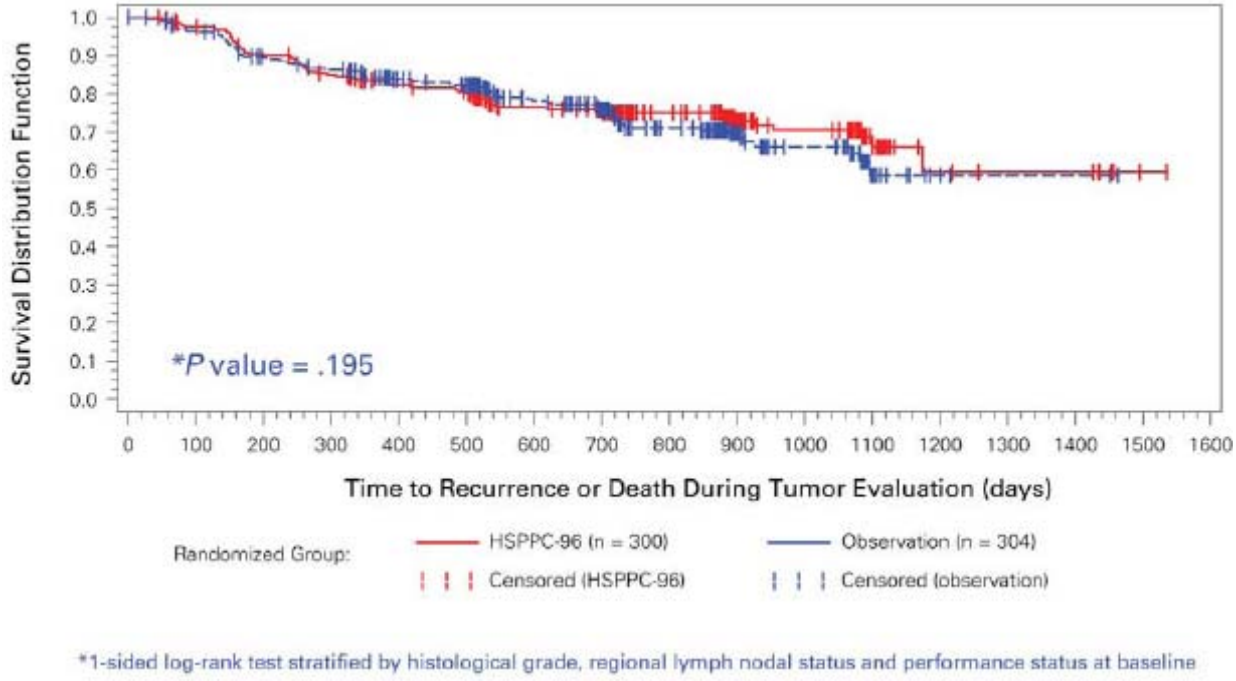
*1-sided log-rank test stratified by histological grade, regional lymph nodal status and performance status at baseline

Table 9: Recurrence Free Survival, Full Analysis Set (FAS, N=604)

Statistic	HSPPC-96 (n = 300)	Observation (n = 304)	Hazard Ratio[1] (95% CI)
RFS events	75 (25.0%)	83 (27.3%)	0.870
Censored	225 (75.0%)	221 (72.7%)	0.633, 1.196
Median follow-up[2] (days)	716.0	707.5	
Minimum, maximum	1, 1535	1, 1463	
Recurrence-free survival (days)			
25th percentile	878	716	
Median (95% CI)	NE	NE	
75th percentile	NE	NE	
P value[3]	0.195		

NE: not evaluable due to too few events.
1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.
2 Follow-up time for censored patients calculated using the date of last contact.
3 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status.

Figure 6: Kaplan-Meier Curve for Recurrence Free Survival, FAS (N=604)



*1-sided log-rank test stratified by histological grade, regional lymph nodal status and performance status at baseline

No statistically significant difference was seen between the treatment arms in terms of the median or the hazard ratio for recurrence-free survival in the ITT. This was also repeated in the analysis of the FAS and the evaluable patient population (data not shown). The analysis of the primary variable for the same population including the additional 17 months follow-up data based on investigators' assessment (data cut-off date: March 2007) confirmed the primary analysis (data not shown).

Secondary Endpoint: Overall Survival

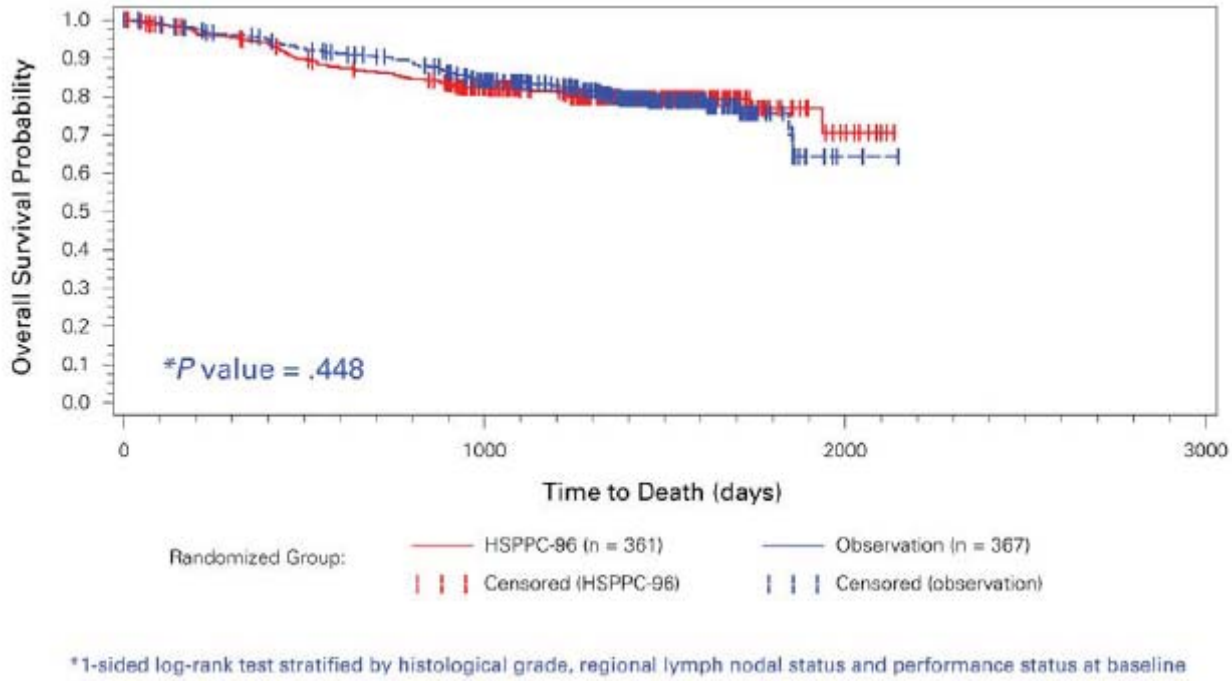
The most updated results for Overall Survival submitted initially (data cut-off date: March 2007) are presented in the following tables and figures.

Table 10: Overall Survival, Randomised Eligible Set (ITT, N = 728)

Statistic	HSPPC-96 (n = 361)	Observation (n = 367)	Hazard Ratio[1] (95% CI)
Deaths	70 (19.4%)	72 (19.6%)	0.978
Censored	291 (80.6%)	295 (80.4%)	(0.702, 1.364)
Median follow-up[2] (days)	1351	1354	
Minimum, maximum (days)	1, 2136	1, 2147	
Overall survival (days)			
25th percentile	1936	1844	
Median	NE	NE	
75th percentile	NE	NE	
P value[3]	0.448		

1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.
2 Follow-up time for surviving patients.
3 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status.

Figure 7: Kaplan-Meier curve for Overall Survival, ITT (N = 728)



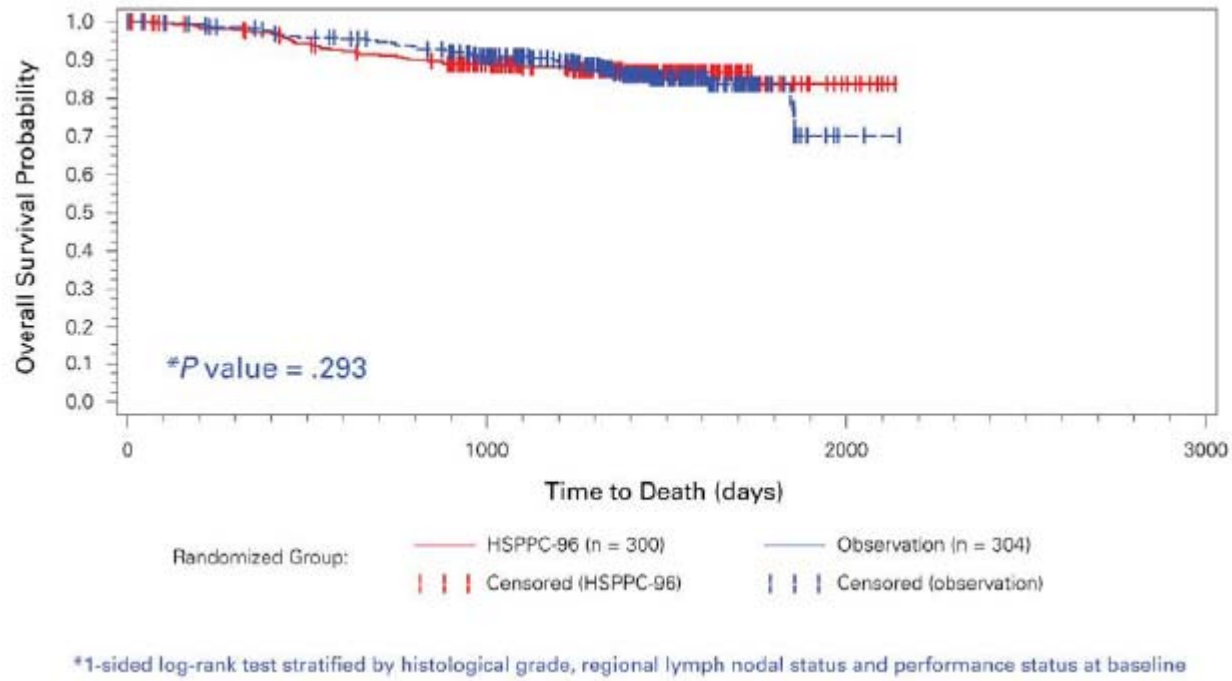
*1-sided log-rank test stratified by histological grade, regional lymph nodal status and performance status at baseline

Table 11: Overall Survival, Full Analysis Set (FAS, N=604)

Statistic	HSPPC-96 (n = 300)	Observation (n = 304)	Hazard Ratio[1] (95% CI)
Deaths	37 (12.3%)	40 (13.2%)	0.882
Censored	263 (87.7%)	264 (86.8%)	(0.561, 1.388)
Median follow-up[2] (days)	1386.5	1397	
Minimum, maximum (days)	1, 2136	1, 2147	
Overall survival (days)			
25th percentile	NE	1855	
Median	NE	NE	
75th percentile	NE	NE	
P value[3]	0.293		

1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.
2 Follow-up time for censored patients calculated using the date of last contact.
3 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status.

Figure 8: Kaplan-Meier curve for Overall Survival, FAS (N=604)



*1-sided log-rank test stratified by histological grade, regional lymph nodal status and performance status at baseline

The hazard ratios of 0.978 and 0.882 for the Randomised Eligible Set (ITT) and the Full Analysis Set (FAS), respectively, indicate a similar hazard rate in the HSPPC-96 arm compared to the observation arm. Similar results were obtained in the Evaluable Patient Analysis Set, as well as in OS analyses by stratification factors and AJCC stage (data not shown). Overall survival results were updated by the Applicant during the review using a January 2009 data cut-off for the Randomised Eligible Set (ITT), the Full Analysis Set (SET) and sub-population analyses. Results for both the ITT and the FAS at this later cut-off were not statistically significant, but showed improved hazard ratios of 0.882 and 0.813, respectively.

Ancillary analyses

In ancillary post-hoc analyses, no significant differences were observed in Overall Survival (OS) analyses by tumour stage or in Overall Survival (OS) analyses in intermediate- and high-risk patients (data not shown). Intermediate Risk patients were defined as those with tumours Stage I, Stage II, or Stage III T1, T2, T3a (Grade 1 or 2). By contrast, High Risk patients were defined as those with tumours Stage III T1, T2, T3a (High Grade), T3b, T3c or Stage IV. In the analysis of Overall Survival with data cut-off of January 2009, a significant difference was observed in intermediate risk patients (HR 0.541, 95% CI 0.303-0.967, p=0.036).
Additional Recurrence Free Survival (RFS) analyses were submitted, including RFS analysis by stratification factors, multivariable ANCOVA and Cox proportional hazards model including treatment by covariable interactions. None revealed significant differences between the vitespen arm and the observation arm (data not shown).
No significant differences were found in Recurrence Free Survival (RFS) analyses by tumour stage.

Table 12: Recurrence Free Analysis (RFS) based on CEC assessment by AJCC stage, randomized eligible analysis set (N = 728), data cut-off: November 2005

Statistic	HSPPC-96 (n = 361)	Observation (n = 367)	Hazard Ratio[1] (95% CI)
AJCC stage I/II[2], n = 267			
n	139	128	
Events	33 (23.7%)	44 (34.4%)	0.706
Censored	106 (76.3%)	84 (65.6%)	0.449, 1.111
Median follow-up[3] (days)	715	705	
Minimum, maximum	1, 1535	1, 1215	
Recurrence-free survival (days)			
25th percentile	878	542	
Median	NE	1083	
75th percentile	NE	NE	
P value[4]	.065		
AJCC stage III/IV5, n = 461			
n	222	239	
Events	103 (46.4%)	102 (42.7%)	1.062
Censored	119 (53.6%)	137 (57.3%)	0.804, 1.402
Median follow-up[3] (days)	518	521	
Minimum, maximum	1, 1457	1, 1463	
Recurrence-free survival (days)			
25th percentile	154	134	
Median	1085	1096	
75th percentile	NE	NE	
P value[4]	.335		

1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.
2 T1b (>5 cm) N0 M0 or T2 N0 M0, high-grade
3 Follow-up for recurrence-free patients.
4 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status at baseline.
5 T1-2 N1 M0, T3 N0-1 M0, T4 N0-1 M0 or any T N2 M0, any grade.

Table 13: Recurrence Free Survival (RFS) based on CEC assessment by AJCC stage, full analysis set (n = 604), data cut-off: November 2005

Statistic	HSPPC-96 (n = 300)	Observation (n = 304)	Hazard Ratio[1] (95% CI)
AJCC stage I/II[2], n = 240			
n	125	115	
Events	19 (15.2%)	31 (27.0%)	0.576
Censored	106 (84.8%)	84 (73.0%)	0.324, 1.023
Median follow-up[3] (days)	730	725	
Minimum, maximum	1, 1535	1, 1215	
Recurrence-free survival (days)			
25th percentile	NE	720	
Median	NE	NE	
75th percentile	NE	NE	
P value[4]	.028		
AJCC stage III/IV5, n = 364			
n	175	189	
Events	56 (32.0%)	52 (27.5%)	1.083
Censored	119 (68.0%)	137 (72.5%)	0.735, 1.595
Median follow-up[3] (days)	704	699	
Minimum, maximum	1, 1457	1, 1463	
Recurrence-free survival (days)			
25th percentile	506	716	
Median	1174	NE	
75th percentile	NE	NE	
P value[4]	.343		

1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.
2 T1b (>5 cm) N0 M0 or T2 N0 M0, high-grade
3 Follow-up for recurrence-free patients.
4 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status at baseline.
5 T1-2 N1 M0, T3 N0-1 M0, T4 N0-1 M0 or any T N2 M0, any grade

In the analysis with data cut-off of November 2007, the HR for AJCC stage I/II patients in the FAS deteriorated slightly (HR=0.628, 95% CI 0.366-1.080, p=0.090).
No significant differences were found in Recurrence Free Survival (RFS) analyses in high risk patients (data not shown). The Applicant claimed a significant benefit for Oncophage based on the Recurrence Free Survival analysis in Intermediate Risk Patients. This result was based on the Full Analysis Set of patients; the equivalent analysis in the Randomised Eligible Set (ITT) did not show statistically significant differences.

Table 14: Recurrence Free Survival (RFS) based on CEC analysis in intermediate-risk patients (Stage I, Stage II, or Stage III T1, T2, T3a [Grade 1 or 2]), data cut-off: November 2005

	Randomised Eligible Set (ITT, N=728)			Full Analysis Set (FAS, N=604)		
Statistic	**vitespen (n = 205)**	**Observation (n = 198)**	**HR[1] (95% CI)**	**vitespen (n = 184)**	**Observation (n = 178)**	**HR[1] (95% CI)**
RFS events	49 (23.9%)	67 (33.8%)	0.733	28 (15.2%)	47 (26.4%)	0.589
Censored	156 (76.1%)	131 (66.2%)	0.505-1.063	156 (84.8%)	131 (73.6%)	0.367- 0.944
Median follow-up[2] (days)	716	704		733	717	
(min, max)	(1, 1535)	(1, 1215)		(1, 1535)	(1, 1215)	
RFS(days)						
25th percentile	879	542		1100	725	
Median	NE	NE		NE	NE	
75th percentile	NE	NE		NE	NE	
P value[3]		0.050			.013	

1 Ratio of HSPPC-96:observation; based on Cox proportional hazards regression model stratified by nuclear grade, regional lymph node status and performance status.
2 Follow-up for recurrence-free patients.
3 Log-rank test (1-sided) stratified by nuclear grade, regional lymph node status and performance status.

In the analysis with data cut-off of November 2007, the HR for intermediate risk patients improved further (HR=0.521, 95% CI 0.333-0.815, p=0.004).

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

Not applicable.

- Clinical studies in special populations

No studies were submitted.

- Supportive study(ies)

Protocol C-100-03: Active specific immunotherapy in patients with renal cell carcinoma using autologous tumour-derived gp96 heat shock protein-peptide complex (HSPPC-96) vaccine
The feasibility of production of vitespen, safety, tolerance and anti-tumour activity were investigated in a single centre open-label phase I/II dose escalation study in patients who had undergone primary surgery for metastatic renal cell carcinoma. A total of 38 patients with metastatic renal cell carcinoma with measurable disease were enrolled and treated with 2.5, 25, or 100 µg of vitespen intradermally once weekly for 4 weeks, then biweekly until vaccine supply exhaustion. Treatment was initiated 4 to 6 weeks post nephrectomy. The study was conducted in the USA.
Vitespen production from primary renal cell tumours was feasible. Among the 37 patients who were evaluable for disease response, 3 responses (8%) were observed including 1 complete response (CR) and 2 partial responses (PR). The median time to progression was 2.9 months. Estimated median overall survival time was 15 months with a documented survival in one patient of 2.4 years.

Protocol C-100-07: A phase 2 trial of active specific immunotherapy in patients with renal cell carcinoma using autologous tumour-derived heat shock protein-peptide complex (HSPPC-96) with or without subcutaneous IL-2.
The efficacy of treatment with vitespen with or without interleukin 2 (IL-2) was investigated in a single centre non-randomised open-label study in 72 patients with renal cell cancer and measurable metastatic disease scheduled to undergo nephrectomy. The study was conducted in the USA.
Four weeks post nephrectomy, patients received vitespen intradermally at a dose of 25 µg once weekly for 4 weeks, followed by 2 biweekly doses and then varied numbers of biweekly doses according to clinical condition until exhaustion of vaccine supply. For 8 patients for whom sufficient vaccine could not be produced, the dose was reduced to 15 µg to preserve some duration of exposure to vitespen. Patients with progressive disease at week 10 also received IL-2 subcutaneously 5 days/week until

progression. Of the 72 treated patients, 35 received vitespen only and 37 received vitespen plus IL-2. Fifty-five (76%) of the 72 treated patients received ≥6 doses of vitespen, and 42 (58%) patients received ≥10 doses of vitespen. Eight (11%) patients had 15 μg vitespen produced. Two patients had second surgeries and additional vitespen production during the study. Efficacy was determined by clinical response rates.

For the 72 treated patients, 60 were evaluable for disease response. Preliminary signals of efficacy for vitespen were demonstrated in metastatic renal cell carcinoma. In the overall evaluable population, 2 (3%) patients achieved a durable complete response with vitespen therapy alone, and were alive with no evidence of disease more than 5 years after surgery. Two (3%) patients achieved partial response, one who received combination treatment with vitespen and IL-2 and one who received treatment with vitespen alone. Seven (12%) patients had confirmed stable disease and 16 (27%) patients had stable disease that was not confirmed by an additional tumour evaluation.

During vitespen–only treatment, median time to progression from first vitespen treatment among all evaluable patients was 65 days. Among evaluable patients receiving IL-2 in addition to vitespen, median time from first vitespen treatment to subsequent progression (after combination treatment initiated after first progression) was 168 days. Median time to first progression from time of surgery was 101 days for all evaluable patients.

As of the last follow-up in December 2004, 13 (18%) of the 72 treated patients were reported as alive, with an estimated median survival from time of first treatment of 1.3 years. Seven (10%) patients were alive more than 5 years after their first treatment, with the longest documented survival at 5.4 years. Of the 35 patients who received vitespen only, 9 (26%) were reported as alive, with an estimated median survival time of 1.6 years from first treatment. Of the 37 patients who received vitespen + IL-2, 4 (11%) patients were reported as alive, with an estimated median survival time of 1.3 years from first treatment. Analysis of median survival from time of surgery was similar to that of median survival from time of first treatment.

Protocol C-100-27: International Survival Follow-up of Patients Enrolled In the Renal Cell Carcinoma Evaluation of Adjuvant Oncophage Treatment in the Antigenics C-100-12 (Part I) Protocol

The C-100-27 follow-up protocol has been initiated to follow the 513 patients from the C-100-12 study for RFS and OS for an additional 3 years from data lock of that study, which occurred on 30 March 2007. These 513 patients were officially terminated from the C-100-12 protocol due to its closure. The protocol stipulates that patients will be contacted every 6 months if no disease recurrence has been reported, and every 3 months if disease has recurred. In addition, physicians will report status of disease and recurrence as patients are evaluated per standard of care.

Based on a feasibility analysis of the C-100-12 study sites and investigators' ability to participate in the survival follow-up, it is anticipated that 60 to 70 of the 98 sites with potentially eligible patients at the closure of the C-100-12 study will take part in this registry. This translates into approximately 415 of the 513 (~81%) potentially eligible patients. The aim is to enrol as many eligible patients as possible into the registry, but some level of attrition is expected.

All patients enrolled in the Antigenics C-100-12 protocol with a survival status reported as "alive" and with a reason off-study reported as "administrative study closure" will be invited to participate in the INSPIRE registry.

To be eligible, the patient must have:

1. Participated in the Antigenics C-100-12 protocol and completed the study with the last survival status reported as "alive" at their final survival time point in that study and were off study due to administrative study closure.
2. Signed an informed consent to participate in the C-100-27 survival follow-up, and be willing to receive contact from the protocol investigative study centers and/or any subsequently identified co-investigator sites and/or a team member from a company designated by the sponsor, every 6 months if no disease recurrence and every 3 months if disease has recurred.

Endpoints to be evaluated from the observational data collected will include:

1. Duration of survival, reported as date of death.
2. Disease recurrence, reported as confirmed, absent or unknown, with the date of recurrence provided by the investigator.
3. Cause of death, reported as progression of renal cell carcinoma or other disease, or unknown.

Submissions to Competent Authorities and Local Ethics Committees for Regulatory approvals are complete. Site mobilization, patient consent and enrolment have commenced in all geographic areas.

- Discussion on clinical efficacy

The absence of dose-finding studies and the resulting empirical choice of dose in the pivotal clinical trial were considered a major deficiency.
More importantly, the CHMP considered that the single pivotal clinical trial, C-100-12, did not provide sufficient evidence of efficacy for the proposed indication. For results from a single pivotal trial, particularly in a trial with an open label design, clear evidence of efficacy in terms of recurrence free survival and a strong trend in improvement in overall survival would be a minimum requirement for marketing authorisation in the requested indication.
The primary efficacy analysis for Recurrence Free Survival (RFS) failed to demonstrate superiority of the Oncophage treatment over the comparator arm in which no additional treatment was given but the patient was simply 'observed'. The failure to achieve significance was repeated in all analyses of the primary variable for additional pre-defined analysis populations. The Applicant conducted a further analysis after an additional 17-month follow-up period to allow for further maturation of the data. The analysis of the primary efficacy variable at this new data cut-off confirmed the primary analysis.
Results were similar for the secondary endpoint of Overall Survival (OS) for all populations and at both time points. Finally, a large number of pre-specified subgroup analyses were carried out without any adjustment for multiplicity. The Applicant attempted to address this point through a simulation technique and a calculation of the probability of the associated type 1 error. The Applicant further claimed statistically significant findings in terms of the primary endpoint in one subgroup only (namely intermediate risk patients) supported by near significant results for both the primary endpoint (RFS) and Overall Survival (OS) in another subgroup (namely AJCC stage I/II patients). The CHMP considered that the results of a sub-group analysis in a single open-label pivotal study are not considered sufficient evidence of efficacy to support a marketing authorisation in this sub-population, in accordance with relevant guidance (CPMP/EWP/908/99: Points to consider on multiplicity issues in clinical trials) stating that claims on subgroups are possible only after the primary objective of the clinical trial has been achieved.
In addition to the lack of demonstrated efficacy, the CHMP was concerned regarding several aspects of the conduct of the pivotal trial. The open-label study design was questioned due to the potential for introducing bias in the assessment of the primary endpoint, Recurrence Free Survival (RFS). In this respect, the use of the Clinical Events Committee (CEC) and the Data Monitoring Board to limit the introduction of bias, were appropriate. However, at the time of the updated efficacy analysis, the CEC did not assess the imaging data to determine whether recurrence of disease had occurred. Moreover, and although the Applicant claimed a high level of concordance between the opinion of the investigators and the CEC over the initial phase of the study where both were recorded, the introduction of bias due to the open-label design remained a concern overall.
The lack of standardisation of surgical procedures including the requirement for lymph node dissection was noted, but it was accepted as a consequence of the heterogeneous patient population studied and the multicentre nature of the trial. On the other, hand, the heterogeneous population included and the wide variation in treatment number received (1-109) made interpretation of the endpoints very problematic in terms of efficacy, and this applied to the group as a whole and to the exploratory sub-group analysis.
There was concern over the need for five amendments to the protocol, four of which were made during the conduct of the study including a change to the primary efficacy endpoint. Furthermore, the reason for the pre-planned interim analysis was unclear, although no changes were made to the study, which continued as planned. Although futility analysis was planned for the interim analysis, this was not conducted. The reasons for this decision were not provided.
A further problem related to the quality of the vitespen throughout the trial. It is not clear that the vitespen produced before December 2003 (the date before which the FDA considered the product as insufficiently characterised) was sufficiently similar to vitespen produced later in the trial.
In addition to the changes to the protocol, a large number of patients violated the protocol. Although over 800 patients were randomised, 258 were excluded from the evaluable patient set. These included 90 patients who were randomised but not treated, because they were found to be screening failures,

and an additional 124 patients (61 vitespen and 63 observation arm) with metastatic or residual disease at baseline that the Clinical Evaluation Committee (CEC) excluded as erroneously randomized.

Clinical safety

- Patient exposure

The database for the evaluation of the safety of vitespen includes safety information from a total of 15 Antigenics sponsored studies that treated 771 patients with various forms of cancer with vitespen. These include the pivotal C-100-12 phase III trial in the applied indication and the phase III trial in metastatic melanoma (C-100-21). The studies and the numbers of patients exposed to vitespen in the course of all studies are presented in the following table.

Table 15: Number of Patients Included in Safety Tabulations by Analysis Set across Phase and Study

	Pool of All Treated Patients by Indication			Pool of All Randomized Patients by Arm	
Phase / Study (Indication)	**RCC**	**Melanoma**	**Other**	**HSPPC-96**	**Control**
Phase 3 Completed					
C-100-12 Part 1 (Locally advanced RCC)	318			361	367
C-100-21 (Stage IV melanoma)		133		215	107
Phase 1 and 1/2 Completed					
C-100-01 (Pancreatic cancer)			10		
C-100-02 (Melanoma)		36			
C-100-03 (Metastatic RCC)	38				
C-100-04 (Gastric carcinoma)			20		
C-100-06 (Metastatic melanoma)		45			
Phase 2 Completed and Ongoing					
C-100-05 (Colorectal cancer/liver mets)			40		
C-100-07 (Metastatic RCC)	72				
C-100-08 (Metastatic RCC)	3				
C-100-09 (Indolent lymphoma)			17		
C-100-15 (Metastatic RCC)	4				
C-100-23 (Metastatic RCC)	18				
C-100-26 (NSCLC, N=10)			10		
Phase 3 Terminated					
C-100-12 Part 2 (Locally advanced RCC)	7				
TOTAL:	**460**	**214**	**97**	**576**	**474**

The number of vaccine doses administered in the 15 studies included in the safety database is presented below:

Table 16: Exposure to HSPPC-96, Pool of All Treated Patients by Indication and Overall

Exposure to HSPPC-96	HSPPC-96 Treated Patients RCC (N=460)	Melanoma (N=214)	Other (N=97)	Total (N=771)
Number of vaccines [n (%)]				
1-4	63 (14)	98 (46)	52 (54)	213 (28)
5-8	100 (22)	62 (29)	32 (33)	194 (25)
9-12	81 (18)	25 (12)	4 (4)	110 (14)
13-16	46 (10)	7 (3)	2 (2)	55 (7)
17-20	42 (9)	6 (3)	1 (1)	49 (6)
21-24	38 (8)	7 (3)	1 (1)	46 (6)
>24	90 (20)	9 (4)	5 (5)	104 (13)
Number of vaccines				
N	460	214	97	771
Mean (SD)	16.5 (15.08)	8.5 (10.94)	7.7 (8.80)	13.2 (13.96)
Median	12.0	5.0	4.0	8.0
Minimum, maximum	1, 109	1, 87	1, 59	1, 109

In the following, analyses of adverse events will focus on the two randomised trials, for which comparisons can be made against the respective control arm, ie observation only for the RCC pivotal trial C-100-12 and physician's choice for the melanoma trial C-100-21.

- Adverse events

Of relevance to the sought indication, in the pivotal trial C-100-12 the AE collection procedure was modified during the study by protocol amendments. Specifically, AEs were assessed for the vitespen arm only under the initial protocol and amendments 1 and 2, while in subsequent amendments (3, 4 and 5) AEs were collected for both vitespen and control arms for increasing time periods (with each amendment) through the vaccine administration and tumour evaluation visits.

An overview of adverse event frequencies in the two randomised phase III studies is presented below:

Table 17: Overview of Adverse Events, by Study and Study Arm (Randomized Eligible Analysis Set, ITT)

Patients With:	Study C-100-12, Part I HSPPC-96 (N=361)	Obser-vation (N=367)	Study C-100-21 HSPPC-96 (N=215)	PC (N=107)	Randomized Pool HSPPC-96 (N=576)	Control (N=474)
Any adverse event	327 (91)	265 (72)	198 (92)	91 (85)	525 (91)	356 (75)
Related adverse event[1]	221 (61)	2 (<1)	47 (22)	23 (21)	268 (47)	25 (5)
Grade 3 or 4 adverse event	79 (22)	56 (15)	151 (70)	72 (67)	230 (40)	128 (27)
Related Grade 3 or 4 AE	0 (0)	0 (0)	8 (4)	4 (4)	8 (1)	4 (<1)
Serious adverse event	109 (30)	77 (21)	119 (55)	55 (51)	228 (40)	132 (28)
Related SAE	2 (<1)	0 (0)	2 (<1)	0 (0)	4 (<1)	0 (0)
Treatment DC due to AE	19 (5)	0 (0)	4 (2)	4 (4)	23 (4)	4 (<1)
AE resulting in death	15 (4)	14 (4)	153 (71)	66 (62)	168 (29)	80 (17)

Of particular interest, the overview of adverse events in the pivotal clinical trial is presented below:

Table 18: Overview of Adverse Events, Study C-100-12 by Study Arm (Safety Analysis Set)

Patients With:	HSPPC-96[1] (n=318) n (%)	Observation (n=359) n (%)
Any adverse event	301 (95)	263 (73)
Related adverse event[2]	221 (69)	NA
Grade 3 or 4 adverse event	66 (21)	55 (15)
Related grade 3 or 4 AE	0	NA
Serious adverse event	94 (30)	76 (21)
Related SAE	2 (<1)	NA
Treatment discontinuation due to AE	19 (6)	NA
AE resulting in death	13 (4)	13 (4)

The most common adverse events in the two randomised phase III clinical studies are listed in the table below:

Table 19: Adverse Events reported in ≥5% of all vitespen patients, by Study and Study Arm (Randomized Eligible Analysis Set)

	Study C-100-12, Part I		Study C-100-21		Randomized Pool	
Patients With:	HSPPC-96 (N=361)	Obser-vation (N=367)	HSPPC-96 (N=215)	PC (N=107)	HSPPC-96 (N=576)	Control (N=474)
Malignant Neoplasm Progression	32 (9)	17 (5)	152 (71)	64 (60)	184 (32)	81 (17)
Injection Site Erythema	158 (44)	0 (0)	0 (0)	0 (0)	158 (27)	0 (0)
Injection Site Induration	153 (42)	0 (0)	0 (0)	0 (0)	153 (27)	0 (0)
Nausea	22 (6)	7 (2)	54 (25)	33 (31)	76 (13)	40 (8)
Fatigue	34 (9)	12 (3)	33 (15)	19 (18)	67 (12)	31 (7)
Back Pain	43 (12)	18 (5)	23 (11)	8 (7)	66 (11)	26 (5)
Headache	40 (11)	9 (2)	21 (10)	13 (12)	61 (11)	22 (5)
Constipation	17 (5)	7 (2)	40 (19)	13 (12)	57 (10)	20 (4)
Pyrexia	17 (5)	3 (<1)	40 (19)	17 (16)	57 (10)	20 (4)
Vomiting	12 (3)	8 (2)	37 (17)	22 (21)	49 (9)	30 (6)
Asthenia	20 (6)	6 (2)	29 (13)	15 (14)	49 (9)	21 (4)
Arthralgia	29 (8)	21 (6)	20 (9)	9 (8)	49 (9)	30 (6)
Post Procedural Pain	5 (1)	2 (<1)	41 (19)	6 (6)	46 (8)	8 (2)
Hypertension	29 (8)	9 (2)	12 (6)	0 (0)	41 (7)	9 (2)
Anorexia	7 (2)	3 (<1)	32 (15)	12 (11)	39 (7)	15 (3)
Abdominal Pain	15 (4)	15 (4)	21 (10)	8 (7)	36 (6)	23 (5)
Dyspnoea	8 (2)	10 (3)	28 (13)	9 (8)	36 (6)	19 (4)
Oedema Peripheral	10 (3)	6 (2)	25 (12)	8 (7)	35 (6)	14 (3)
Nasopharyngitis	30 (8)	5 (1)	5 (2)	1 (<1)	35 (6)	6 (1)
Anaemia	9 (2)	6 (2)	25 (12)	16 (15)	34 (6)	22 (5)
Incision Site Complication	29 (8)	14 (4)	5 (2)	2 (2)	34 (6)	16 (3)
Diarrhoea	19 (5)	7 (2)	14 (7)	10 (9)	33 (6)	17 (4)
Urinary Tract Infection	25 (7)	19 (5)	7 (3)	3 (3)	32 (6)	22 (5)
Pain In Extremity	12 (3)	10 (3)	17 (8)	13 (12)	29 (5)	23 (5)

The most commonly reported adverse events across the Pool of All Randomized Patients was malignant neoplasm progression; based on the aggressive nature of the disease under study, this event was reported more commonly in both study arms in the melanoma study C-100-21 (71% and 60% of patients in the HSPPC-96 and control arms, respectively) compared to the RCC study C-100-12, Part I (9% and 5%, respectively).
The most common adverse events in the pivotal clinical trial are listed in the following table:

Table 20: Adverse Events reported in ≥5% of all vitespen patients, Study C-100-12 by Study Arm (Safety Analysis Set)

MedDRA Preferred Term	HSPPC-96 (N=318) n (%)	Observation (N=359) n (%)
Injection-site erythema	158 (50)	0
Injection-site induration	153 (48)	0
Back pain	39 (12)	18 (5)
Headache	39 (12)	9 (3)
Fatigue	33 (10)	12 (3)
Malignant neoplasm progression	31 (10)	16 (4)
Nasopharyngitis	29 (9)	5 (1)
Arthralgia	28 (9)	21 (6)
Hypertension	28 (9)	9 (3)
Urinary tract infection	25 (8)	19 (5)
Nausea	21 (7)	7 (2)
Diarrhoea	19 (6)	7 (2)
Asthenia	18 (6)	6 (2)
Influenza	18 (6)	19 (5)
Pyrexia	17 (5)	3 (<1)
Constipation	17 (5)	7 (1)
Dizziness	17 (5)	6 (1)

In the pivotal trial (C-100-12), 91% of patients in the vitespen arm and 72% of patients in the control arm reported an adverse event. The most commonly reported adverse events in the HSPPC-96 arm were injection site reactions, including erythema (50%) and induration (48%), as well as back pain (12%), headache (12%), fatigue (10%) and malignant neoplasm progression (10%). All other events were reported in <10% of vitespen patients. The most common AEs, including headache, fatigue and pain, were reported more commonly in the active treatment arm compared to the observation arm.
Treatment-related adverse events in the randomised phase III trials are listed below:

Table 21: Treatment-related Adverse Events reported in >1% of all vitespen patients, by Study and Study Arm, (Randomized Eligible Analysis Set)

	Study C-100-12, Part I		Study C-100-21		Randomized Pool	
Patients With:	HSPPC-96 (N=361)	Obser-vation (N=367)	HSPPC-96 (N=215)	PC (N=107)	HSPPC-96 (N=576)	Control (N=474)
Injection Site Erythema	157 (43)	0 (0)	0 (0)	0 (0)	157 (27)	0 (0)
Injection Site Induration	153 (42)	0 (0)	0 (0)	0 (0)	153 (27)	0 (0)
Fatigue	21 (6)	0 (0)	8 (4)	3 (3)	29 (5)	3 (<1)
Pyrexia	5 (1)	0 (0)	11 (5)	5 (5)	16 (3)	5 (1)
Headache	9 (2)	0 (0)	6 (3)	2 (2)	15 (3)	2 (<1)
Injection Site Pain	14 (4)	0 (0)	0 (0)	0 (0)	14 (2)	0 (0)
Nausea	5 (1)	0 (0)	7 (3)	11 (10)	12 (2)	11 (2)
Rash	7 (2)	0 (0)	3 (1)	1 (<1)	10 (2)	1 (<1)
Injection Site Oedema	8 (2)	0 (0)	1 (<1)	0 (0)	9 (2)	0 (0)
Asthenia	5 (1)	0 (0)	3 (1)	1 (<1)	8 (1)	1 (<1)
Myalgia	2 (<1)	0 (0)	6 (3)	3 (3)	8 (1)	3 (<1)
Vomiting	1 (<1)	0 (0)	6 (3)	7 (7)	7 (1)	7 (1)
Arthralgia	6 (2)	0 (0)	1 (<1)	2 (2)	7 (1)	2 (<1)
Pruritus	2 (<1)	0 (0)	4 (2)	2 (2)	6 (1)	2 (<1)

Treatment-related adverse events in the pivotal trial are presented below:

Table 22: Treatment-related Adverse Events reported in >1% of all vitespen patients, Study C-100-12 (Safety Analysis Set)

MedDRA Preferred Term	HSPPC-96 (N=318) n (%)
Injection-site erythema	157 (49)
Injection-site induration	153 (48)
Fatigue	21 (7)
Injection-site pain	14 (4)
Headache	9 (3)
Injection-site oedema	8 (3)
Rash	7 (2)
Arthralgia	6 (2)
Antinuclear antibody positive	5 (2)
Asthenia	5 (2)
Erythema	5 (2)
Injection-site haemorrhage	5 (2)
Nausea	5 (2)
Pyrexia	5 (2)
Medication error[1]	4 (1)
Nasopharyngitis	4 (1)

The most commonly reported treatment-related events were injection site erythema (49%), injection site induration (48%), and fatigue (7%); all other treatment-related events were reported in <5% of patients.
With regard to severe adverse events, 66 (21%) of reported AEs were described as grade 3/4 in the active treatment arm compared to 55 (15%) in the control arm (safety analysis set, see table 18).
None of the patients in the vitespen arm experienced a vaccine-related grade 3/4 adverse event.

- Serious adverse event/deaths/other significant events

The serious adverse events reported in the two randomised trials are listed below:

Table 23: Serious Adverse Events reported in >1% of all vitespen patients, by Study and Study Arm (Randomised Eligible Analysis Set, ITT)

	Study C-100-12, Part I		Study C-100-21		Randomized Pool	
Patients With:	HSPPC-96 (N=361)	Obser-vation (N=367)	HSPPC-96 (N=215)	PC (N=107)	HSPPC-96 (N=576)	Control (N=474)
Patients with at least 1 SAEs	109 (30)	77 (21)	119 (55)	55 (51)	228 (40)	132 (28)
Malignant Neoplasm Progression	32 (9)	16 (4)	80 (37)	30 (28)	112 (19)	46 (10)
Pneumonia	4 (1)	1 (<1)	4 (2)	2 (2)	8 (1)	3 (<1)
Dehydration	0 (0)	0 (0)	8 (4)	1 (<1)	8 (1)	1 (<1)
Anaemia	2 (<1)	0 (0)	5 (2)	2 (2)	7 (1)	2 (<1)
Abdominal Pain	0 (0)	1 (<1)	7 (3)	3 (3)	7 (1)	4 (<1)
Nausea	0 (0)	1 (<1)	7 (3)	2 (2)	7 (1)	3 (<1)
Vomiting	1 (<1)	2 (<1)	6 (3)	2 (2)	7 (1)	4 (<1)
Metastases To CNS	0 (0)	0 (0)	6 (3)	5 (5)	6 (1)	5 (1)

In the pivotal study, SAEs were reported in 30.5% and 21.2% of patients in the vitespen and observation arms, respectively (Safety Analysis Set). These are listed in the following table:

Table 24: Serious Adverse Events reported in >1% of all vitespen patients, Study C-100-12 (Safety Analysis Set)

MedDRA Preferred Term	HSPPC-96 (N=318) n (%)	Observation (n = 359) n (%)
Patients with at least 1 SAEs	*97 (31)*	*76 (21)*
Malignant neoplasm progression	31 (10)	15 (4)
Angina pectoris	4 (1)	0
Pneumonia	4 (1)	1 (<1)

Only 2 SAEs were assessed as drug-related to HSPPC-96:

- autoimmune thyroiditis (thyrotoxicosis), 25 months after first study-treatment intake. Antithyroid microsomal antibodies were increased up to 57.29 U/mL (normal range: 0 to 30 U/mL)
- medication error: One patient received by error a single vial derived from and intended for another patient. No adverse event was reported in the patient administered the inappropriate medication.

In the pivotal trial, adverse events leading to death were reported in 26 patients overall, including 13 (4%) patients in the vitespen arm and 13 (4%) in the observation arm. None of the 13 deaths in the vitespen arm were assessed as treatment-related.
The most common cause of death in these 26 patients was related to progression of their underlying malignancy (8 patients and 5 patients in the vitespen and observation arms, respectively). Other events reported as leading to death included acute cardiac failure (1 and 3 patients, respectively), myocardial infarction (1 patient in each study arm), 1 patient each in the vitespen arm with paraneoplastic syndrome, sudden death, and cardiac arrest, and 1 patient each in the observation arm with sub-ileus, liver disorder (hepatopathy), cerebral infarction and pulmonary embolism.
Across all 771 patients who received vitespen in all 15 trials included in the safety assessment, 171 deaths were reported, of which 134 were related to adverse event.
The majority of these patients were enrolled in the melanoma studies (102 of the 134 deaths) with 5 deaths reported among patients treated for indications other than RCC or melanoma.
Among the 460 patients with RCC, a total of 27 patients had AEs leading to death; 13 patients in the pivotal study as mentioned above and 14 patients in the other 6 RCC (phase 1 and 2) studies which enrolled patients with metastatic disease.

- Laboraroty findings

In terms of haematological parameters, in the pivotal trial C-100-12 there were no clinically meaningful changes over time during vitespen administration and no clinically meaningful differences between the study arms for changes post-surgery (data not shown). Across all 771 patients who received vitespen, the only hematology abnormalities reported as adverse events in >1% of patients were anemia (54 of 771 patients, 7%) and thrombocytopenia (8 of 771 patients, 1%). The haematologic abnormalities reported as treatment-related adverse events were anemia and leukocytosis each reported in 1 patient (<1%, data not shown).
In terms of clinical chemistry parameters, in the pivotal trial C-100-12 there were no clinically meaningful changes over time during vitespen administration and no clinically meaningful differences between the study arms for changes post-surgery (data not shown). Across all 771 patients who received vitespen, clinical chemistry abnormalities reported as adverse events in >1% of patients were hypercalcemia (19 of 771 patients, 2%), hypokalemia (11 patients, 1%), hyperglycemia (8 patients, 1%), and hyponatremia (8 patients, 1%). There was one clinical chemistry abnormality reported as treatment-related adverse event and it occurred in <1% of patients (alanine aminotransferase increased, 1 patient, <1%).
In terms of immunological events, in the pivotal trial C-100-12 a slight increase in thyroid autoantibodies and antinuclear antibodies were seen in the treated group compared with the control group. Across all 771 patients who received vitespen, the only immunology abnormality reported as adverse event in >1% of patients was antithyroid antibody positive (8 patients, 1%). Immunological abnormalities reported as treatment related all occurred in <1% of patients and included antinuclear antibody positive (5 of 771 patients, <1%) and antithyroid antibody positive (2 patients, <1%).

- Safety in special populations

Analyses were submitted for all patients across RCC studies (N=460) and all patients exposed to vitespen in all indications (N=771) by age (<65 and ≥65 years old), sex, age and sex and, finally, race. Minor differences of doubtful clinical significance were noted (data not shown). Seven patients, all in the RCC group, were missing age at study entry and were not included in the by age analysis. There were few non-white patients in both the RCC trials (12%) and across all trials and indications (6%).

- Safety related to drug-drug interactions and other interactions

No studies were submitted.

- Discontinuation due to adverse events

In Study C-100-12, a total of 19 (6.0%) of the 318 vitespen–treated patients were reported to have discontinued treatment due to adverse events. The most common adverse event leading to treatment discontinuation was malignant neoplasm progression, reported in 7 patients (2%); all other reasons for treatment discontinuation were reported in <1% of patients. Events assessed as causally related to vitespen that led to treatment discontinuation in Study C-100-12 were reported in 3 patients, including anxiety in 1 patient and autoimmune thyroiditis in 2 patients; all other events leading to treatment discontinuation were assessed as unrelated to vitespen.
Overall, 28 (4%) of 771 vitespen-treated patients across all 15 clinical studies discontinued vitespen due to adverse events. The most common events leading to discontinuation were malignant neoplasm progression (10 patients-7 patients in the pivotal trial and 3 patients in the melanoma phase III trial) autoimmune thyroiditis and rash (each in 2 patients). All other events leading to discontinuation were reported in 1 patient each.
Treatment-related events leading to discontinuation were reported in 4 patients overall, including the 3 patients in Study C-100-12 with malignant neoplasm progression described above and 1 patient in the melanoma Study C-100-21, with anorexia, myalgia, musculoskeletal stiffness, systemic lupus erythematosus rash, tremor, rash, tinnitus and fatigue.

- Post marketing experience

Not applicable

- Discussion on clinical safety

The provided safety data derived from a pivotal phase III study conducted in patients with RCC, a melanoma phase III study and 12 phase I/II studies conducted in various indications other than RCC. Overall, 771 patients received vitespen and 474 patients were enrolled in the control arms of the 2 randomized Phase III studies.
An important shortcoming in the reporting of adverse events in both phase III trials has been that the frequency of visits in the active vitespen treatment arms was higher than that in the control arms, which could have led to over-reporting of adverse events in the vitespen treatment arms.
In the RCC Phase III trial, the majority (91%) of patients in the vitespen arm experienced at least one treatment-emergent adverse event, compared with 72% in the observation arm who had received no active treatment. Serious adverse events were reported in 30% and 21% of the vitespen and control arms respectively. Assessment of pooled data from the randomized phase III studies (576 vitespen vs. 474 controls) showed that the most commonly reported adverse event was progression of underlying neoplasm.
The CHMP raised a major objection with regards to the higher proportion of patients with malignant neoplasm progression reported in the active arms compared to the control arms. In the pivotal study, 54 patients (17%) died from RCC compared to 15% in the observation arm. A higher proportion of patients had malignant neoplasm progression reported as an adverse event (31 patients, 10%) compared to the observation arm (16 patients, 4%). Similarly, in study C-100-21, malignant neoplasm progression was reported as an AE in 96 (72.2%) patients receiving vitespen and 64 (59.8%) patients

in the Physician's Choice arm. Overall, in the randomized pool (study C-100-12 and Study C-100-21), malignant neoplasm progression regardless of relationship, was reported as an AE in 184 patients (32%) receiving HSPPC-96 and 81 (17%) of control arm.
The Applicant argued that the higher proportion of malignant neoplasm progression reported as an adverse event was a result of underreporting of progressions in the control arms. When considering the number of progression events irrespective of whether these were also reported as AEs, these were lower in the vitespen arm compared to the observation arm of the pivotal RCC trial (Randomised Eligible Analysis Set: 37.7 vs 39.8%, Full Analysis Set: 25 vs 27.3% and Safety Analysis Population: 38.7 vs 39.8%). In the metastatic melanoma phase III trial, the number of cumulative progressions in the treated population (133 patients who received at least 1 dose of vitespen and 86 patients who received at least 1 treatment of the patient's physician's choice) was equivalent in both arms (89.5% in the treated vs 88.4% in the physician's choice).
Due to uncertainties in the reporting of progressions as adverse events, the CHMP finally decided to drop the major objection with regards to potential vitespen contribution to malignant neoplasm progression.
Auto-immune disorders were also considered as another important concern. Indeed, in both phase III trials, patients from vitespen arms experienced auto-immune disorders including autoimmune thyroiditis/thyrotoxicosis and systemic lupus erythematosus. Positive auto-antibodies were also reported with a higher frequency in patients receiving study drug compared to control arm. The Applicant considered a causal relationship between vitespen and autoimmunity as unlikely and the CHMP refrained from drawing any conclusions, as the more frequent AE assessments in the active arm compared to the control arm precluded any comparison between the two. However, abnormal levels of autoantibodies, hypothyroidism, keratoconjuctivitis sicca, dry mouth and other autoimmune disorders including but not limited to thymus hypertrophy, lupus erythematosus rash and rheumatoid arthritis, had been included in the important identified and potential risks of the RMP.
The frequency of hypertension was higher in the vitespen arm, in the pivotal RCC study (9% versus 3%), in the melanoma study (6% versus 0%) and in the randomized pool comprising both studies (7 versus 2%). Once again, given that patients in the observation arm were not monitored at the same frequency as those in the active arm, no conclusion could be drawn from the provided data.
One event of medication error was reported as study-drug related SAE in study C-100-12.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

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

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

The CHMP, having considered the data submitted in the application, was of the opinion that the efficacy of the medicinal product had not been established based on the data submitted. In the absence of established efficacy, it cannot be assessed if the proposed risk minimisation activities would be adequate in reducing the risks to a sufficient level to make the benefit risk balance positive. Therefore the CHMP was of the opinion that risk minimisation activities cannot be agreed at this stage.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The physicochemical and biological characterization data provided are not sufficient to establish the detailed structure of the active substance. The Applicant claims that the mechanism of action of the active substance is based on peptides complexed with gp-96, however, did not provide sufficient

evidence (either physicochemical or pharmacological) for the presence of peptides complexed with gp-96 in the drug product.
Whilst it is acknowledged that the use of autologous starting material presents difficulties and that the Applicant attempted to address the major deficiencies, the necessary data were not supplied and the key issues regarding the presence and quantification of peptides bound to gp-96 and a relevant potency assay were not resolved. In the absence of a suitable testing regime for the complete active substance, the Applicant was unable to demonstrate that process parameters are sufficient, that the process is suitably validated and controlled, that product used in clinical trials is consistent despite changes in manufacturing facility, manufacturing process and formulation, and that product is stable and that the active substance in the drug product is adequately controlled.

Non-clinical pharmacology and toxicology

On a weight of evidence basis, the non-clinical pharmacodynamic studies demonstrated pharmacodynamic activity, with 26 of the 31 studies showing a positive result to some extent, although not consistently, so that no dose-response relationship could be established.
In the toxicology studies, no severe adverse signs were observed either as body-as-a-whole or at the site of injection, for both healthy and tumour-bearing mice and there were no test article-related deaths. However, these studies did not allow satisfactory assessment of the risks related to the administration of vitespen to humans due to the lack of GLP-compliance and inadequacy of study design.
In general, the validity of the submitted non-clinical studies was compromised because the manufacturing process was not standardised and the drug product was not sufficiently characterised.

Efficacy

The efficacy of Oncophage was determined in a single, pivotal phase III trial in RCC (C-100-12), in which 728 adult patients with localised resectable renal cell carcinoma and with no known distant metastases were randomised to receive vitespen (n= 361) or subjected to observation only (n= 367). The primary endpoint was Recurrence Free Survival (RFS), with Overall Survival (OS) serving as a secondary efficacy outcome.
The primary efficacy analysis failed to demonstrate superiority of the Oncophage treatment over the comparator arm in which no additional treatment was given but the patient was simply 'observed'. The failure to achieve significance was repeated in all analyses of the primary variable for additional pre-defined analysis populations as well as in all analyses for the secondary efficacy variable of Overall Survival. The Applicant decided to conduct a further analysis after an additional 17-month follow-up period to allow for further maturation of the data. However, at the time of the updated analysis, the independent Clinical Events Committee (CEC) was not used to assess the images to determine whether recurrence of disease had occurred. The analysis of the primary efficacy variable for the randomised eligible patient population at this new data cut-off confirmed the primary analysis. A large number of pre-specified subgroup analyses were carried out. The Applicant claimed significant findings in one post hoc subgroup only (namely patients at intermediate risk for recurrence, as defined by AJCC stage, primary tumour involvement and Fuhrman grade).

Safety

The safety database for Oncophage comprises the pivotal phase III study conducted in patients with RCC, a melanoma phase III study and 12 phase I/II studies conducted in various indications other than RCC. Overall, 771 patients received vitespen and 474 patients were enrolled in the control arms of the 2 randomized Phase III studies.
An important shortcoming in the reporting of adverse events in both phase III trials has been that the frequency of visits in the active vitespen treatment arms was higher than that in the control arms, which could have lead to over-reporting of adverse events in the vitespen treatment arms.
The most commonly reported adverse drug reactions in the pivotal trial were injection site erythema (49%), injection site induration (48%), and fatigue (7%); all other treatment-related events were reported in <5% of patients.

Malignant neoplasm progression, hypertension and other adverse events were reported more frequently in the active treatment arm compared to the control arm. However, potential over-reporting of adverse events in the active treatment arm precludes any conclusions to be made with confidence.
Autoimmune phenomena and medication errors were observed with Oncophage and identified as demonstrated or potential risks.

- User consultation

Only a pilot user testing report was submitted and the user consultation was not concluded in light of the major objections raised.

Risk-benefit assessment

In general, an application based upon a single pivotal trial can suffice for a Marketing authorisation if, according to the CHMP 'Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99)', the data from a single pivotal study are compelling, the study is well designed, the outcome is positive and the data are robust in terms of efficacy and safety. The results from the single pivotal trial did not establish the efficacy of Oncophage as an adjuvant treatment for localized renal cell carcinoma (RCC) patients at increased risk of recurrence. In addition to methodological and study conduct concerns (open label design, heterogeneous population, empirical choice of dose, variable number of administered doses, unclear comparability of product used in clinical trial and product to be marketed, change of primary endpoint in the course of the trial, poor correlation between investigators' and CEC assessment of subjects' disease status, lack of centralised histology review), the pivotal trial failed to show any statistically significant difference between the two treatment arms. The claimed observed benefit in a post-hoc defined subgroup of patients can at best be considered as hypothesis generating.
Imbalances in the reporting of adverse events between the active treatment arm and the control arm of the pivotal trial hampered the assessment of the safety profile. Finally, serious issues regarding the quality of both drug substance and drug product create major concerns about both the efficacy and the safety of Oncophage.
Overall, the benefit risk balance of Oncophage is negative.

Similarity with authorised orphan medicinal products

The CHMP is of the opinion that Oncophage is not similar to Torisel, Nexavar and Affinitor within the meaning of Article 3 of Commission Regulation (EC) No. 847/200 (See appendix 1 and 2).

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Oncophage in the adjuvant treatment of 'localised renal cell carcinoma (RCC) patients at increased risk of recurrence with the following features: Primary tumour stage T1b or T2 with high-grade (3 or 4) histology with no nodal involvement; these characteristics include patients who are considered Stage I or II according to American Joint Committee on Cancer (AJCC) criteria' was unfavourable and therefore did not recommend the granting of the conditional marketing authorisation.
In addition, the CHMP, with reference to Article 8 of Regulation EC No 141/2000, considers Oncophage not to be similar (as defined in Article 3 of Commission Regulation EC No. 847/2000) to Torisel, Nexavar and Affinitor for the same therapeutic indication.

Grounds for refusal

- The single pivotal open-label trial submitted failed its primary endpoint and it has not provided sufficient evidence of efficacy in the proposed indication. The claimed effect based on a single, post-hoc defined, subgroup analysis can only be considered as hypothesis generating. A large

number of pre-specified subgroup analyses were carried out without any adjustment for multiplicity.

- Insufficient physicochemical characterization data for the active substance have been provided. The company claims that the mechanism of action of the active substance is based on peptides complexed with gp96 but has not provided sufficient evidence (either physicochemical or pharmacological) for the presence of tumour peptides complexed with gp96 in the drug product.

- The drug substance specification (or in-process control prior to filling) is insufficient to assure a consistent quality of the product. Drug product was filled on the basis of total protein, rather than the amount of active substance present. Thus the doses used in clinical trials were not equivalent, raising questions about the validity of the clinical trial.

- Drug product specifications do not include any measurement of the peptide component of active substance or a link with clinical effect, and process validation data has not demonstrated consistent binding of a peptide component to gp96.

- The analytical methods used to test drug product have not been justified in relation to the structure and activity of drug product. The analytical methods were not sufficient as they did not address all components of the active substance. A suitable potency assay was not proposed.

- The description of the manufacturing process is deficient. There was limited in-process testing and the process control systems are inadequate. Consistency of the process has not been demonstrated and the process is not considered to be validated.

- Stability of drug product, manufactured by the proposed commercial process and facility, at the proposed temperature for the complete shelf-life has not been demonstrated.

- The validity of the non-clinical studies submitted is compromised because the manufacturing process is not standardised and the drug product is not sufficiently characterised.

- No clinical pharmacodynamic studies in Renal Cell Carcinoma were submitted to support the efficacy of the product.

- No dose-finding studies were performed.

- Due to the aforementioned concerns a satisfactory summary of product characteristics, pharmacovigilance system, risk management plan and follow-up measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

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