Phase I/II, multi-center, open label study to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and anti-tumor activity of ASP9521 in patients with metastatic castrate-resistant prostate cancer

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The overall objective of this phase I/II three-part study is to evaluate the benefit of 12 weeks once daily dosing with ASP9521 in a population of patients with metastatic castrate resistant prostate cancer (CRPC) who have failed one or more lines...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON38103

Source
ToetsingOnline

Brief title
9521-CL-0002 (798/118)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym
Prostate cancer, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma
Source(s) of monetary or material Support: Astellas Pharma Global Development - Europe

Intervention

Keyword: ASP9521, metastatic castrate-resistant prostate cancer

Outcome measures

Primary outcome

Efficacy Variables:

•The proportion of patients with a decline from baseline in PSA blood

concentrations of >=50% after 12 weeks of once daily dosing with ASP9521.

Secondary outcome

Efficacy Variables

• RECIST objective response rate.

• Overall survival (OS).

• Progression-free survival (PFS).

• Time to clinical progression (TCP).

• Time to PSA progression (TPP).

• Time to radiographic progression (TRP).

• CTC counts and CTC conversion rates.

Study description

Background summary

Worldwide, prostate cancer ranks third in cancer incidence and sixth in cancer mortality in men. Prostate cancer is the most common cancer in men in Europe, with about 190,000 new cases every year [Parkin et al, 2005; Boyle and Ferlay, 2005]. About 80,000 deaths a year result from this cancer in Europe [Ferlay et al, 2001]. Localized prostate cancer is the most commonly diagnosed stage. The choice of treatment (active monitoring, radical prostatectomy, or any type of radiotherapy) is based on factors such as tumor characteristics and the patient*s life expectancy. At diagnosis, prostate cancer can also be locally advanced or metastatic and therefore already spread beyond the prostate bed and/or to distant sites such as bone.
Prostate-specific antigen (PSA) is a glycoprotein that is expressed by both normal and neoplastic prostate tissue. PSA is consistently expressed in prostate cancer. The absolute value of serum PSA is useful for determining the extent of prostate cancer and assessing the response to prostate cancer treatment. Newer prognostic markers are also being explored. For example, preliminary data suggest that, in patients with metastatic prostate cancer, the number of circulating tumor cells (CTC) correlates with survival [Scher et al, 2009].
Prostate cancer growth is dependent on androgens, and depleting or blocking androgen action has been a mainstay of treatment for over 6 decades. Hormonal therapies include gonadotropin-releasing hormone (GnRH) analogues, androgen receptor antagonists, ketoconazole, and estrogenic compounds. Tumors that progress despite castrate levels of testosterone in the blood are considered castration-resistant. In clinical practice, treatment of advanced prostate cancer is therefore limited by the development of resistance to anti androgen therapies. Most patients receive two or more hormonal manipulations and are then offered chemotherapy as they continue to progress (European Association of Urology [EAU] Guidelines, 2010). Despite the early sensitivity of prostate cancer to hormonal strategies, castration-resistant progression generally represents a transition to the lethal variant of the illness, and most patients ultimately succumb to this disease. Currently, the median survival of castration-resistant disease is approximately 12 months [Petrylak et al, 2004; Pienta and Bradley, 2006]. Non-hormonal treatments of castrate-resistant prostate cancer (CRPC) including the anti-mitotic docetaxel have been shown to extend median survival in patients with advanced prostate cancer that is no longer responsive to hormone therapy [Picus and Schultz, 1999]. Furthermore, it has been shown that the effectiveness of docetaxel in survival and disease progression can be improved when administered concomitantly with prednisone [Tannock et al, 2004]. However, current guidelines recommend the use of docetaxel for limited periods and the treatment can have serious side effects.
Results of clinical investigations and studies on the molecular profiles of progressing prostate cancer show that the androgen receptor remains functional and that the tumors should respond to strategies directed at the androgen receptor signaling axis. The most powerful intracellular intraprostatic androgen, dihydrotestosterone (DHT), is formed through the standard steroidogenic pathway in which blood-derived testosterone and several blood derived adrenal steroids are involved. DHT can also be formed by a pathway that

uses progesterone as the primary substrate (the *backdoor pathway*) [Pienta and Bradley, 2006]. In the standard steroidogenesis pathway, the testes provide the major source of androgens, particularly testosterone. However, CRPC can utilize alternative pathways when testosterone and other androgens are not available from the circulation. Hence, in addition to GnRH agonists/antagonists, testosterone synthesis interfering agents, such as 17β-hydroxysteroid dehydrogenase type 5 (17βHSD5) inhibitors, are expected to reduce testosterone concentration in prostate cancer tissue and suppress the growth of prostate cancer cells.

Study objective

The overall objective of this phase I/II three-part study is to evaluate the benefit of 12 weeks once daily dosing with ASP9521 in a population of patients with metastatic castrate resistant prostate cancer (CRPC) who have failed one or more lines of hormonal treatment/androgen deprivation therapy (stratified as chemotherapy-naïve or post chemotherapy), after first establishing the safety and pharmacokinetics (PK) of ASP9521 from assessments of single and short term (4 weeks) multiple dose escalation, and to determine an optimal dose of ASP9521.

Part I - Dose Escalation
Primary Objective:
• To evaluate the safety and tolerability of ASP9521.
Secondary Objectives:
• To determine the maximum tolerated dose (MTD), if possible.
• To evaluate prostate specific antigen (PSA) decline of >=50% from baseline after 12 weeks of daily dosing with ASP9521.
• To evaluate the PK of ASP9521 following single and multiple dose administration.
• To evaluate the pharmacodynamics (PD) of ASP9521.

Part II - Expanded Dose Assessment using Combined Data Parts I+II
Primary Objective:
• To evaluate PSA decline of >=50% from baseline after 12 weeks of daily dosing with ASP9521.
Secondary Objectives:
• To evaluate the safety and tolerability of ASP9521.
• To evaluate the PK of ASP9521 following multiple dose administration.
• To evaluate the efficacy of ASP9521.
Other Objectives:
• To evaluate the PD effect of ASP9521.
• To evaluate the effect of ASP9521 on pain palliation.
• To evaluate pharmacogenetics.

Part III - Food Effect at Assumed Optimal Dose
Primary Objective:
• To evaluate the PK of single doses of ASP9521 under fed and fasted conditions.

Secondary Objectives:
• To evaluate the PD effect of single doses of ASP9521 under fed and fasted conditions.
• To evaluate the safety and tolerability of single doses of ASP9521 under fed and fasted conditions.
• To evaluate the efficacy of ASP9521.

Study design

Part I
Part I will be an open label, standard oncology 3+3 design, first in man (FIM), ascending dose evaluation of ASP9521 after a single dosing period and a 4-week (28-day) multiple daily dosing period separated by a wash out period.
Dose-limiting toxicity (DLT) will be assessed by the Dose Escalation and Expansion Committee (DEEC) after the 28-day dosing period, and depending on the DLT up to 5 cohorts of 3 to 6 patients (i.e., 5 dose levels and therefore 4 dose escalation steps) are planned per patient group of chemotherapy-naïve and post-chemotherapy patients. If possible the MTD of ASP9521 will be established. The planned doses are 30, 100, 300, 600 and 1200 mg/day. Escalation to higher doses will only be done if lower doses are adequately tolerable, as assessed by the incidence of DLT. Additional doses, intermediate to those stated above, may be assessed at the discretion of the DEEC. Each dose of ASP9521 will be administered in the morning. On the days that PK blood and urine samples are taken, the patient will fast overnight for 10 hours prior to dosing, then for a further 2 hours after dosing. The length of the fasting period will be adjusted once the results of the Part III evaluation of food on exposure to ASP9521 are known. Within a patient there will be no increase or reduction of a dose. Enrolment in every dose will be staggered; the first patient will be enrolled separately, followed by the remaining patients in that dose 3 days later. The length of the wash out period between the single and multiple dosing periods for the first dose group will be set to 10 days. The length of the wash out period for the following doses may be reduced depending on the accumulated PK data from previous cohorts.
During the 28 day dosing period patients will be continually monitored for safety, blood samples will be collected for PK assessments, and patients will be monitored for clinical benefit, including measurement of PSA levels. Based on safety data from the 28-day dosing the DEEC will decide whether to escalate or reduce the dose for the second cohort of patients, or to enroll a further 3 patients to continue on the current dose level. The same procedures will be repeated for each subsequent cohort of patients. Patients will not be enrolled to the next dosing cohort until the safety and tolerability of the previous cohort has been established. The dose escalation decision tree is shown in Section V.
Following the 28-day multiple dosing period, patients will continue to receive ASP9521 for up to 12 weeks. During this period, patients will continue to be monitored for safety and clinical benefit of the drug. The effect of multiple dosing on PK will be assessed. Evaluations of disease status will include

abdominopelvic computed tomography (CT)/magnetic resonance imaging (MRI) and bone scan, as well as measurements of PSA and CTC. Patients who have clinical benefit at 12 weeks may continue to receive this dose of ASP9521 at the discretion of the investigator until objective or clinical disease progression, or occurrence of an unacceptable toxicity. All patients will have a safety follow up visit 30 days after their last dose of study drug, which is their end of study visit (ESV).

Part II
Part II will be an open label, 12-week multiple dosing expansion of Part I, in which patients will be recruited to doses found in Part I to be well tolerated and demonstrating clinical benefit (at least one third of patients [at the discretion of the DEEC], with a decline in plasma PSA concentrations >=50% from baseline at that dose level, and based on the PSA response rate at adjacent doses).
It is expected that at most, 3 dose levels will be expanded in this way. Up to 24 patients (chemotherapy-naïve and post chemotherapy) may be recruited per dose level to receive 12 weeks treatment. This will be an expansion of up to 30 patients including those already dosed in Part I.
If possible, one dose level, the assumed optimal dose, will be expanded further to include up to 84 additional patients. This will be an expansion to 90 patients including those already dosed in Part I. This assumed optimal dose is likely to be the MTD, but a lower dose could be selected by the DEEC after review of all available safety and efficacy data. Caution will be taken expanding lower doses which might be less efficacious. Consideration will be given to: (a) a dose being the first dose with any PSA signal; (b) the number of patients within a dose cohort showing a PSA response; (c) PSA responders in one or both patient populations; and (d) any safety consideration and potential other considerations.
For each of the doses administered for 12 weeks in Part II, only one dose will be open for enrollment at one time. Patients will take their dose of ASP9521 in the morning. On the days that PK blood and urine samples are taken, the patient will fast overnight for 10 hours prior to dosing, then for a further 2 hours after dosing. The length of the fasting period will be adjusted once the results of the Part III evaluation of food on exposure to ASP9521 are known. Patients will be monitored for safety and clinical benefit of the drug, as well as evaluations of disease status as done in Part I. The effect of multiple dosing in PK will be assessed.
As in Part I, patients who have clinical benefit at 12 weeks may continue to receive ASP9521 at the discretion of the investigator until objective or clinical disease progression, or occurrence of an unacceptable toxicity. All patients will have a safety follow up visit 30 days after their last dose of study drug, which is their ESV.

Part III
Part III will be an open label, single dose, evaluation of the effect of food compared with fasting on the PK of ASP9521 at the assumed optimal dose

established in Parts I and II. Part III will be conducted as soon as the assumed optimal dose is confirmed from Parts I and II data. Furthermore, based on the PK profile (t*) established in Parts I and II, it will be decided whether to conduct Part III as a crossover or parallel group design. If Part III is conducted in a crossover design 24 patients (chemotherapy-naïve and post chemotherapy) will be randomized (1:1) on Day 1 to receive the single dose of ASP9521 under fasted conditions (Period 1) followed by fed conditions (Period 2), or under fed conditions (Period 1) followed by fasted conditions (Period 2). There will be a wash out period after each single dose of ASP9521. The length of the wash-out period will depend upon the PK profile (t*) of ASP9521 established in Parts I and II.
If the parallel group design is selected 48 patients will be randomized (1:1) on Day 1 to receive the single dose of ASP9521 either under fasted conditions (24 patients) or after a high fat breakfast (24 patients). Dosing will be followed by a wash out period. The length of the wash out period will depend upon the PK profile (t*) of ASP9521 established in Parts I and II.
Prior to the dosing on Day 1 all patients will have fasted overnight (only water allowed). For fasted conditions patients will administer the single dose of ASP9521 in the morning after the overnight fast and will not be allowed food until at least 4 hours after dosing. For fed conditions, patients will administer ASP9521 30 minutes after the start and up to 5 minutes after the completion of the high fat breakfast. Further meals will not be allowed until at least 4 hours after dosing.
Patients in Part III may continue to take ASP9521 for up to 12 weeks. During this period, patients will continue to be monitored for safety and clinical benefit of the drug, as well as evaluations of disease status as done in Part I. The effect of multiple dosing in PK will be assessed. As in Parts I and II, patients who have clinical benefit at 12 weeks may continue to receive ASP9521 at the discretion of the investigator until objective or clinical disease progression, or occurrence of an unacceptable toxicity. All patients will have a safety follow up visit 30 days after their last dose of study drug, which is their ESV.

Intervention

Part I will be an open label, standard oncology 3+3 design, first in man (FIM), ascending dose evaluation of ASP9521 after a single dosing period and a 4-week (28-day) multiple daily dosing period separated by a wash out period.

Part II will be an open label, 12-week multiple dosing expansion of Part I, in which patients will be recruited to doses found in Part I to be well tolerated and demonstrating clinical benefit (at least one third of patients [at the discretion of the DEEC], with a decline in plasma PSA concentrations >=50% from baseline at that dose level, and based on the PSA response rate at adjacent doses).

Part III will be an open label, single dose, evaluation of the effect of food

compared with fasting on the PK of ASP9521 at the assumed optimal dose established in Parts I and II. Part III will be conducted as soon as the assumed optimal dose is confirmed from Parts I and II data. Furthermore, based on the PK profile (t*) established in Parts I and II, it will be decided whether to conduct Part III as a crossover or parallel group design.

Study burden and risks

This is a new research study and the study drug has not been used in any humans before.
Previous tests (animal tests) have indicated potential effects of slight decreases in blood pressure and heart rate. Other findings also showed changes in lipid levels.

The study is undertaken in patients that pertain to the intended target population for the drug. There is a chance that the patients experience personal benefit from taking part in the treatment with ASP9521, and that it may relieve or improve their illness. The information that is collected will hopefully improve the treatment of other individuals with prostate cancer.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approved written informed consent and privacy language as per national regulations must be obtained from the patient or legally authorized representative prior to any study-related procedures.
2. Male aged 18 years or older. Female sexual partners of male participants in the study must be non-fertile, i.e., surgically sterilized or must practice an adequate contraceptive method to prevent pregnancies. Adequate contraceptive methods are defined as: sexual abstinence from the day of partner*s dosing until 3 months after the last dose; the use of a condom in addition to having their partner use another acceptable method (oral or injectable hormonal contraceptives, contraceptive patch, intra-uterine devices, vaginal hormonal rings, or sterilization by surgery, a vaginal diaphragm or cervical caps) during the study and for up to 3 months after the last dose; patient*s sexual partner is of non child bearing potential i.e., post-menopausal, surgically sterilized (e.g., tubal ligation), or hysterectomy in medical history.
3. Histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
4. Metastatic disease documented by 2 or more bone lesions on bone scan or by soft tissue disease observed by CT/MRI.
5. Ongoing androgen deprivation with LHRH agonist/antagonist therapy or bilateral orchiectomy. For patients who have not had an orchiectomy, there must be a plan to maintain effective LHRH agonist/antagonist therapy for the duration of the study.
6. Serum testosterone <1.7 nmol/L (50 ng/dL) at screening.
7. Patients receiving bisphosphonate or other approved bone targeting therapy must have been on stable doses for at least 4 weeks prior to screening.
8. Progressive disease at study entry defined as one or more of the following 3 criteria occurring in the setting of castrate levels of testosterone:
* PSA progression defined by a minimum of 2 rising PSA levels with an interval of >1 week between each determination. The PSA value at screening should be >2 ng/mL.
* Soft tissue disease progression defined by RECIST. Measurable disease is not required for entry. Lymph nodes >20 mm are considered measurable disease.
* Bone disease progression defined by at least 2 new lesions on bone scan.
9. Life expectancy of >6 months, according to the investigator*s judgment.
The following inclusion criteria must be fulfilled by chemotherapy-naïve patients:
10. Eastern Cooperative Oncology Group (ECOG) scores of 0 to 1.
11. Asymptomatic or controlled symptomatic patients with metastatic CRPC who have failed one or more lines of hormonal treatment/androgen deprivation therapy but have not received chemotherapy or have refused chemotherapy.
12. No prior chemotherapy for prostate cancer

13. Antiandrogen withdrawal patients receiving an anti-androgen as part of primary androgen ablation must demonstrate disease progression following discontinuation of anti-androgen (>4 weeks since last flutamide dose or >6 weeks since last bicalutamide or nilutamide dose).
The following inclusion criteria must be fulfilled by post chemotherapy patients:
14. ECOG scores of 0 to 2.
15. No more than 2 prior regimens of chemotherapy for prostate cancer, of which one is docetaxel-based to have been administered at least 4 weeks prior to screening.

Exclusion criteria

1. Concomitant treatment with the following is prohibited according to stratification as chemotherapy naïve or post-chemotherapy patients:
Chemotherapy-naïve patients:
* All chemotherapeutic agents.
* All biologic agents (except for sipuleucel T [Provenge®]), or other agents with anti-tumor activity against prostate cancer, including 5 alpha reductase inhibitors, androgens (e.g., testosterone), cytoproterone acetate and all other progestational agents, estrogens, and flutamide within 4 weeks prior to day of first dose of ASP9521.
* Treatment with estramustine.
* Bicalutamide or nilutamide within 6 weeks prior to day of first dose of ASP9521.
* Ketoconazole for treatment of prostate cancer.
* Treatment with abiraterone.
Post-chemotherapy patients:
* All biologic agents (except for sipuleucel T [Provenge®]), or other agents with anti-tumor activity against prostate cancer, including 5 alpha reductase inhibitors, androgens (e.g., testosterone), progestational agents, estrogens, flutamide within 4 weeks prior to day of first dose of ASP9521.
* Bicalutamide or nilutamide within 6 weeks prior to day of first dose of ASP9521.
* Ketoconazole for treatment of prostate cancer.
* Treatment with abiraterone.
2. Use of herbal products that may have hormonal anti prostate cancer activity and/or are known to decrease PSA levels or Prednisolone > 10 mg (or an equivalent) for the treatment of prostate cancer within 4 weeks of day of first dose of ASP9521, or plans to initiate the above within the study period.
3. Radiation therapy for treatment of the prostate within 3 months prior to screening.
4. Radiation therapy for the treatment of metastases within 3 weeks (if single fraction of radiotherapy then within 2 weeks) and radionuclide therapy for the treatment of metastases within 4 weeks prior to screening.
5. Major surgery within 2 months prior to screening.
6. Known or suspected intracerebral disease or brain metastasis.
7. History of another malignancy within the previous 5 years other than curatively treated non-melanomatous skin cancer.
8. Gastrointestinal disorder affecting absorption (e.g., gastrectomy or active peptic ulcer disease).
9. Any of the following significant ophthalmological abnormalities:

a. Abnormal intraocular pressure (IOP).
b. Abnormal fundus, like age-related macular degeneration (AMD) or other retinal damage
10. Significant cardiovascular disease including:
* Myocardial infarction within 6 months prior to screening.
* Uncontrolled angina within 3 months prior to screening.
* Congestive heart failure New York Heart Association (NYHA) class 3 or 4, or patients with a history of congestive heart failure NYHA class 3 or 4 in the past, unless a screening echocardiogram or multigated acquisition scan (MUGA) performed within 3 months results in a left ventricular ejection fraction that is >45%.
* History of clinically significant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, torsades de pointes).
* History of Mobitz II second degree or third degree heart block without a permanent pacemaker in place.
* Uncontrolled hypertension as indicated by a resting systolic BP >170 mmHg or diastolic BP >105 mmHg at screening.
11. Concurrent disease or any clinically significant abnormality following the investigator*s review of the pre-study physical examination, 12-lead ECG and clinical laboratory tests, which in the judgment of the investigator would interfere with the patient*s participation in this study or evaluation of study results.
12. Absolute neutrophil count <1,500/µL, platelet count <100,000/µL, and hemoglobin <5.6 mmol/L (9 g/dL) at screening; (NOTE: patients must not have received any growth factors or blood transfusions within 7 days of the hematologic laboratory values obtained at screening).
13. Total bilirubin >1.5 times the upper limit of normal (ULN) at screening. This will not apply to patients with Gilbert*s syndrome (persistent or recurrent hyperbilirubinemia that is predominantly uncongugated in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with the sponsor.
14. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times ULN or >5 times ULN in the presence of liver metastases at screening.
15. Creatinine >177 µmol/L (2 mg/dL) at screening.
16. Known or suspected hypersensitivity to ASP9521, or any components of the formulation used.
17. Use of an investigational agent within 4 weeks prior to treatment allocation or a period required by local regulation, whichever is longer.
18. Prior use, or participation in a clinical study, of an investigational agent that blocks androgen synthesis or targets the androgen receptor (like MDV3100 and TAK700).

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ASP9521
Generic name:	NA

Ethics review

Approved WMO Date:	07-07-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-11-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-05-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-06-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2012

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-08-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-023382-22-NL
ClinicalTrials.gov	NCT01352208
CCMO	NL34756.042.11