Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP9521		

SYNOPSIS

Title of Study: 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

Investigators: Dr. [redacted]; Dr. [redacted], Dr. [redacted], Dr. [redacted], Dr. [redacted]; Dr. [redacted]

Study Centers: [redacted], United Kingdom; [redacted], United Kingdom; [redacted], United Kingdom; [redacted], France; [redacted], Belgium

Publication (reference): none to date

Study Period: April 2011 to September 2012

Date of First Enrollment (study initiation date): 26 April 2011

Date of Last Evaluation (study completion date): 28 September 2012

Phase of Development: 1/2

Objectives: The primary objective of Part I was to evaluate the safety and tolerability of ASP9521. The secondary objectives of Part I were to determine the maximum tolerated dose (MTD), if dose-limiting toxicity (DLT) was observed; to evaluate prostate-specific antigen (PSA) decline of ≥ 50% from baseline after 12 weeks of daily dosing with ASP9521; to evaluate the pharmacokinetics of ASP9521 following single- and multiple-dose administration and to evaluate the pharmacodynamics of ASP9521.

Methodology: This was a phase I/II, multi-center, open-label, ascending single- and multiple-dose study that was planned in 3 parts (Parts I, II and III) to assess the safety, tolerability, pharmacokinetics (including food effect), pharmacodynamics and antitumor activity of oral ASP9521 in patients with metastatic CRPC (mCRPC) who had failed one or more lines of hormonal treatment/androgen deprivation therapy, with the option for patients to continue on therapy after 12 weeks (end of study was determined by disease progression of the last patient). Part I of the study was performed as described below. Parts II and III of the study were planned but not performed. The sponsor elected to discontinue the current study after analysis of the fourth dose escalation cohort (600 mg) in Part I. Analysis of the currently available data showed no effect of ASP9521 on PSA (the primary efficacy variable used in the study), no effect on circulating tumor cells (CTCs) (a biomarker known to predict overall survival [OS]) and no effect on the pattern of endocrine markers involved in the ASP9521 targeted androgen biosynthesis pathway. The sponsor concluded that, due to the lack of activity of ASP9521 observed in mCRPC patients, the current clinical study assessing ASP9521 should be terminated.

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Part I was planned as an open-label, standard oncology 3+3 design, first-in-man, ascending-dose evaluation of ASP9521 after a single dosing period and an initial multiple daily dosing period of 4 weeks (28 days) with an extension to 12 weeks. The single and multiple dosing periods were separated by a washout period. An effort was made to establish the MTD of ASP9521. Part I was conducted at phase I units. The study population consisted of postchemotherapy patients, which were patients with mCRPC who had progressed following no more than 2 prior regimens of chemotherapy for prostate cancer, of which one was docetaxel-based, at least 4 weeks prior to screening. Enrollment of chemotherapy-naïve patients was planned after obtaining an efficacy signal in the postchemotherapy patient population; however, the study was terminated before that time and therefore no chemotherapy-naïve patients were enrolled.

The DLT was assessed by the Dose Escalation and Expansion Committee (DEEC) after 4 weeks of dosing. Depending on the DLT, up to 5 cohorts of 3 to 6 patients (i.e., 5 dose levels and therefore 4 dose escalation steps) were planned. The planned doses were 30, 100, 300, 600 and 1200 mg/day. Escalation to higher doses was only done if lower doses were adequately tolerable, as assessed by the incidence of DLTs. The maximum dose allowed was 1200 mg/day. Additional doses, intermediate to those stated above, could have been assessed at the discretion of the DEEC. On the days of blood and urine pharmacokinetic sampling, the patient fasted overnight for a minimum of 10 hours or may have eaten a light breakfast a minimum of 6 hours prior to dosing, followed by a further 2-hour fast after dosing. Enrollment at every dose level was staggered; the first patient was enrolled initially, followed by the remaining patients at that dose at least 3 days later. The length of the washout period between the single and multiple dosing periods was set to 6 days.

During the 28-day dosing period, patients were continually monitored for safety, blood samples were collected for pharmacokinetic assessments and patients were monitored for clinical benefit, including measurement of PSA levels. Based on safety data and the presence/absence of DLTs from the start of single dosing until the first 28 days of continuous dosing, the DEEC decided whether to escalate or reduce the dose for the next cohort of patients and to enroll a further 3 patients to continue on the current dose level. The same procedures were repeated for each subsequent cohort of patients. Patients were not enrolled in the next dosing cohort until the safety and tolerability of the previous cohort had been established.

Following the 4 weeks of multiple dosing, patients continued to receive ASP9521 for another 8 weeks (i.e., to week 13). During this period, patients were monitored for safety and clinical benefit from the drug. The effect of multiple dosing on pharmacokinetics was assessed. Evaluations of disease status included computed tomography (CT)/magnetic resonance imaging (MRI) and bone scan, as well as measurements of PSA. Patients who had clinical benefit after 12 weeks of daily dosing could have continued to receive this dose of ASP9521 at the discretion of the investigator until objective or clinical disease progression, or occurrence of an unacceptable toxicity or any other reason leading to study discontinuation. All patients had a safety follow-up visit 30 days after their last dose of ASP9521, which was their end-of-study visit (ESV).

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Number of Patients (planned, enrolled and analyzed): In Part I, the planned sample size was 15 to 30 patients (3 to 6 patients at 5 dose levels). If chemotherapy-naïve patients had been enrolled, the sample size would have been 30 to 60 patients. A total of 14 patients were screened for Part I; 13 patients (92.9%) received treatment and 1 patient (7.1%) discontinued before receiving treatment. All 13 patients who received treatment were included in the safety, pharmacokinetic and pharmacodynamic analysis sets.

Diagnosis and Main Criteria for Inclusion: The study population consisted of male patients with mCRPC and histologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features. The study population was to consist of both postchemotherapy and chemotherapy-naïve patients; however, no chemotherapy-naïve patients were enrolled because the study was terminated before enrollment of these patients commenced. All patients maintained androgen deprivation with luteinizing hormone-releasing hormone (LHRH) agonist/antagonist or bilateral orchiectomy for the duration of the study.

Test Product, Dose and Mode of Administration, Batch Numbers: ASP9521 (10- or 100-mg tablets), from batch numbers [redacted] and [redacted] (10 mg) and [redacted] and [redacted] (100 mg), administered orally under fasting conditions as single ascending 30-, 100-, 300- and 600-mg doses per day.

Duration of Treatment (or Duration of Study, if applicable): In Part I, patients were to receive a single oral dose of ASP9521 on day –7 (single-dose period) and multiple oral doses of ASP9521 on days 1 through 85. Patients were confined to the clinical unit for a maximum period of 6 days (5 nights). The doses of ASP9521 shown to be safe and tolerable during the dose escalation were administered for up to 12 weeks or more. The length of the washout period between the single and multiple dosing periods was set to 6 days.

Reference Product, Dose and Mode of Administration, Batch Numbers: Not applicable.

Criteria for Evaluation:

Efficacy Variables

- Decline from baseline in PSA blood concentrations of ≥ 50% after 12 weeks of once daily dosing with ASP9521
- Objective response according to Response Evaluation Criteria in Solid Tumors (RECIST)
- 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

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Pharmacokinetic Variables

Plasma pharmacokinetics after single dose:

- Area under the plasma concentration time curve up to the last sampling time (AUC_{last})
- Area under the plasma concentration-time curve from time 0 to infinity (AUC_{inf})
- Area under the plasma concentration-time curve from time 0 to 24 hours (AUC_{0-24})
- Maximum concentration (C_{max})
- Time to reach Cmax (t_{max})
- Lag time (t_{lag})
- Terminal elimination half life ($t_{1/2}$)
- Apparent volume of distribution during the terminal phase after extravascular administration (V_z/F)
- Apparent clearance after extravascular administration (CL/F)

Urine pharmacokinetics after single dose:

- Total amount of drug excreted in urine to the last sampling time (Ae_{last})
- Total amount of drug excreted in urine from time 0 to infinity (Ae_{inf})
- Proportion of drug excreted in urine to the last sampling time ($Ae_{last\%}$)
- Proportion of drug excreted in urine from time 0 to infinity ($Ae_{inf\%}$)
- Renal clearance (CL_R)

Plasma pharmacokinetics after multiple dosing:

- Trough plasma concentrations (C_{trough})
- Last dose:
  - Area under the plasma concentration-time curve from time 0 to time tau over a dosing interval, where tau is the length of the dosing interval (AUC_{tau})
  - C_{max}, Ct_{rough}, t_{max}, $t_{1/2}$, V_z/F, CL/F
  - Observed accumulation ratio upon repeated dosing (R_{acc})
  - Peak trough ratio (PTR)

Urine pharmacokinetics after multiple dosing:

- Last dose:
  - Amount of drug excreted in urine during a dosing interval (tau) at steady state (Ae_{tau})
  - Proportion of drug excreted in urine during a dosing interval (tau) at steady state ($Ae_{tau\%}$)
  - CL_R

Pharmacodynamic Variables

- Decline ≥ 50% in PSA after 12 weeks of daily dosing with ASP9521
- CTC

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- Time to reach the minimum concentration (t_{min}) or t_{max}; absolute and percentage change from baseline and average concentrations for the period from day 1 to week 13 for the following biomarkers: luteinizing hormone (LH), follicle-stimulating hormone (FSH), sex hormone-binding globulin (SHBG), dehydroepiandrosterone (DHEA), DHEA-sulfate (DHEA-S), estradiol, prolactin, cortisol, corticosterone, testosterone, dihydrotestosterone (DHT), androstenedione, androstenediol (5-adiol), adrenocorticotrophin (ACTH) and, if possible, androsterone glucuronide (androsterone-G), 3-α-androstanediol-glucuronide (3-α-diol-G) and 3-β-androstanediol-glucuronide (3-β-diol-G)

Safety Variables

- Nature, frequency and severity of adverse events (AEs)
- Safety laboratory tests (biochemistry, hematology and urinalysis)
- Vital signs
- 12-lead electrocardiogram (ECG), plus additional monitoring with Holter ECG
- Physical examination (including neurological examination)
- Ophthalmological examination

Statistical Methods:

The safety analysis set (SAF) included all patients who received at least 1 dose of study drug. The SAF was used for the summary of safety and efficacy data in Part I. All safety data were listed. AE data were summarized to include the following: the number of treatment-emergent adverse events (TEAEs) and serious TEAEs; the number and percentage of patients with TEAEs, serious TEAEs and drug-related serious TEAEs; and the incidence of drug-related TEAEs, deaths, TEAEs leading to permanent discontinuation of study drug and drug-related TEAEs leading to permanent discontinuation of study drug. Clinical laboratory results, vital sign measurements, quantitative ECG measurements and Holter ECG data were summarized using descriptive statistics. Ophthalmological examination data were summarized and physical examination findings were reported as AEs. All efficacy data were presented in the data listings and summarized using descriptive statistics; no formal statistical testing was performed on these data.

The pharmacokinetic analysis set (PKAS) included all patients who received at least 1 dose of study drug and had values of concentration for a sufficient number of time points to reliably calculate at least 1 pharmacokinetic parameter. The PKAS was used for the summary and analysis of pharmacokinetic data in Part I. The pharmacokinetic data were presented in data listings, summary tables and figures. Pharmacokinetic data analysis was performed using WinNonlin software (v5.3 or higher) for plasma data and urine parameters were calculated using SAS software (v9.1 or higher). Pharmacokinetic parameters were calculated using noncompartmental analysis. In the single- and multiple-dose period in Part I, dose proportionality of AUC_{inf} (single-dose period) or AUC_{tau} (week 13 visit in the multiple-dose period) and C_{max} were examined. Treatment period effect was examined by determining the mean ratio and 90% confidence intervals (CIs) for selected pharmacokinetic parameters after steady state versus single dose.

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The pharmacodynamic analysis set (PDAS) included all patients who received at least 1 dose of study drug and had values of concentration for a sufficient number of time points to reliably calculate at least 1 pharmacodynamic variable. The PDAS was used for the summary and analysis of pharmacodynamic data in Part I. The pharmacodynamic data were presented in data listings, summary tables and figures.

Summary of Results/Conclusions:

Population:

All 13 patients who received treatment were included in the safety, pharmacokinetic and pharmacodynamic analysis sets [Table 1].

Table 1 Summary of Patient Disposition: Part I

	Number of Patients, n (%)				
Parameter	**ASP9521 30 mg (n = 3)**	**ASP9521 100 mg (n = 3)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 4)**	**Total (n = 13)**
Safety analysis set†	3 (100)	3 (100)	3 (100)	4 (100)	13 (100)
Pharmacokinetic analysis set‡	3 (100)	3 (100)	3 (100)	4 (100)	13 (100)
Pharmacodynamic analysis set§	3 (100)	3 (100)	3 (100)	4 (100)	13 (100)

† All patients who received at least 1 dose of study drug.

‡ All patients who received at least 1 dose of study drug and had values of drug concentration for a sufficient number of time points to reliably calculate at least 1 pharmacokinetic parameter and for whom the time of dosing on the day of sampling was known.

§ All patients who received at least 1 dose of study drug and had values of drug concentration for a sufficient number of time points to reliably calculate at least 1 pharmacodynamic variable.

Source: Table 12.1.1.2

Demographic characteristics were generally similar among the treatment groups [Table 2]. All patients enrolled in the study were men. The majority of patients were White (12 of 13 patients; 92.3%) and 65 years of age or older (10 of 13 patients; 76.9%).

Table 2 Summary of Demographic Characteristics (Safety Analysis Set): Part I

Parameter	**ASP9521 30 mg (n = 3)**	**ASP9521 100 mg (n = 3)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 4)**	**Total (n = 13)**
Sex					
Male, n (%)	3 (100)	3 (100)	3 (100)	4 (100)	13 (100)
Race					
White, n (%)	2 (66.7)	3 (100)	3 (100)	4 (100)	12 (92.3)
Black or African American, n (%)	1 (33.3)	–	–	–	1 (7.7)
Age (years)					
Mean (SD)	64.0 (10.82)	69.0 (9.64)	70.0 (5.29)	67.3 (8.81)	67.5 (8.02)

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Parameter	ASP9521 30 mg (n = 3)	ASP9521 100 mg (n = 3)	ASP9521 300 mg (n = 3)	ASP9521 600 mg (n = 4)	Total (n = 13)
Age group					
< 65 years	1 (33.3)	1 (33.3)	–	1 (25.0)	3 (23.1)
≥ 65 years	2 (66.7)	2 (66.7)	3 (100)	3 (75.0)	10 (76.9)
Weight (kg)					
Mean (SD)	79.13 (6.860)	78.20 (7.302)	91.67 (16.166)	73.35 (7.806)	80.03 (11.193)
Height (cm)					
Mean (SD)	170.33 (6.807)	172.77 (6.532)	172.67 (3.055)	177.0 (6.782)	173.48 (5.898)
BMI (kg/m^2)					
Mean (SD)	27.27 (0.777)	26.37 (4.128)	30.80 (6.126)	23.38 (1.617)	26.68 (4.224)

All patients who received at least 1 dose of study drug (Safety Analysis Set).
–: no data; BMI: body mass index.
Percentages were calculated against the total number of patients per treatment group, excluding missing values.
Source: Table 12.1.2.1.1

Efficacy Results:

None of the 13 patients who received treatment experienced a 50% or greater decline in PSA values by week 13 (last observation carried forward [LOCF]). For all 13 patients who received treatment, the mean PSA value at nadir (defined as the lowest value during the first 12 weeks on treatment up to and including week 13) was 386.349 µg/L, which reflected a mean change from baseline of 22.448 µg/L and a mean percent change from baseline of –5.692%. There was a small decrease in PSA values corresponding to a natural variation of PSA, which disappeared by week 13 or the LOCF if a patient discontinued before week 13.

According to the RECIST criteria, 5 of the 13 patients who received treatment were considered to have progressive disease and 2 patients had stable disease at week 13. In terms of RECIST best overall response (over the first 12 weeks of daily dosing treatment and during the entire treatment duration), 6 patients had progressive disease and 2 patients had stable disease. It should be noted that 5 of 13 patients who discontinued early from the study did not have any post baseline assessments of overall response.

Eleven of 13 patients had CTC counts ≥ 5 CTC/7.5 mL at both baseline and the ESV; the other 2 patients also had CTC counts ≥ 5 CTC/7.5 mL at baseline but did not have data collected at the ESV. No patients demonstrated conversions from CTCs ≥ 5 CTC/7.5 mL to ≤ 5 CTC/7.5 mL throughout the study period.

Pharmacokinetic Results:

The mean ASP9521 pharmacokinetic profiles were characterized by a rapid absorption; lag times were not observed. Median t_{max} was similar for the 30 and 100 mg dose levels; 2 hours and 3 hours, respectively. For the 300 and 600 mg dose levels, median t_{max} was 5 hours. Individual pharmacokinetic profiles generally showed a

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single elimination phase, although some profiles showed a short distribution/elimination phase preceding the apparent terminal elimination phase.

The graphical and statistical analyses suggested that AUC_{last} and AUC_{inf} after a single dose increased proportionally to the dose across the 30 mg to 600 mg dose range. Dose-normalized C_{max} values tended to be somewhat lower for the 300 and 600 mg dose levels compared to the 30 and 100 mg dose levels, although the ranges of the individual values overlapped. The relatively lower C_{max} values after the 300 and 600 mg doses compared to the 30 and 100 mg doses, combined with the longer median t_{max} values, suggested some degree of a dose-dependent effect on the rate of absorption. For AUC_{last} and AUC_{inf}, inter-subject variability expressed as CV% was modest for the 100, 300 and 600 mg dose levels (values ranging between 17% and 23%). For the 30 mg dose level, CV% values for AUC_{last} and AUC_{inf} were 41% and 43% respectively [Table 3]. For C_{max}, CV% was also modest, with values ranging between 10% and 19% across the dose levels.

For the 100, 300 and 600 mg doses, mean $t_{1/2}$ was similar, with mean values of 23 hours (range: 20 to 26 hours), 26 hours (range: 24 to 30 hours) and 22 hours (range: 16 to 27 hours), respectively, which was slightly lower compared to the 30 mg dose (mean: 30 hours; range: 25 to 35 hours). Mean V_z/F for the 100, 300 and 600 mg dose levels were similar (35 L, 37 L and 36 L, respectively) and also somewhat lower compared to the 30 mg dose (46 L).

As single-dose pharmacokinetic profiles were available for only 3 patients at the 30, 100 and 300 mg dose levels and for 4 patients at the 600 mg dose level, the results discussed previously must be interpreted with caution.

Based on the available trough levels during once daily dosing, steady-state conditions appeared to be reached within 1 week. However, fluctuations in trough levels were observed and the trough levels continued to increase somewhat after day 8 in some patients. Steady-state ASP9521 pharmacokinetic profiles on day 85 were only available for [redacted] in the 30 mg dose group and 2 patients in the 100 mg dose group. Therefore, no meaningful conclusions could be drawn regarding steady-state pharmacokinetics. In the patients for whom a pharmacokinetic profile was available on day 85, steady-state CL/F values were roughly in the same range as the observed values after the single dose, providing at least an indication of the absence of an obvious time-dependent effect on ASP9521 pharmacokinetics.

Table 3 Single-dose Plasma Pharmacokinetic Parameters for ASP9521 (Pharmacokinetic Analysis Set)

Parameter (unit) Statistic	**ASP9521 30 mg (n = 3)**	**ASP9521 100 mg (n = 3)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 4)**
AUC_{inf} (ng•h/mL)				
Mean	30745	98708	320369	539312
SD, CV%	13053, 43	22841, 23	61330, 19	93059, 17

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Parameter (unit) Statistic	**ASP9521 30 mg (n = 3)**	**ASP9521 100 mg (n = 3)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 4)**
AUC_{last} (ng•h/mL)				
Mean SD, CV%	29819 12257, 41	97827 22262, 23	315686 60402, 19	533423 92450, 17
C_{max} (ng/mL)				
Mean SD, CV%	913 145, 16	3148 326, 10	7033 1310, 19	13651 2439, 18
t_{max} (h)				
Median	2.00	3.02	5.02	5.02
Min-Max	1.0 – 2.2	3.0 – 4.0	3.1 – 10	3.1 – 10
$t_{1/2}$ (h)				
Mean SD, CV%	30.4 4.9, 16	23.4 2.8, 12	26.3 3.2, 12	22.2 4.6, 21
CL/F (L/h)				
Mean SD, CV%	1.11 0.48, 43	1.05 0.24, 23	0.963 0.21, 21	1.14 0.18, 16
V_z/F (L)				
Mean SD, CV%	46.3 13, 27	34.8 3.9, 11	36.5 8.1, 22	36.0 7.4, 21

All patients who received at least 1 dose of study drug and had values of concentration for a sufficient number of time points to reliably calculate at least 1 pharmacokinetic parameter (Pharmacokinetic Analysis Set).
CV: coefficient of variation; Min: minimum; Max: maximum.
Source: Table 12.4.2

The amount of ASP9521 excreted in urine unchanged after a single dose was negligible [Table 4]. The individual percent of the dose excreted in urine ($Ae_{inf\%}$) ranged between 0.08% and 0.41%. Individual CL_R values ranged between 1.2 and 2.8 mL/h. At steady state, the observed CL_R value for the patient in the 30 mg dose group (Patient [redacted] was [redacted] For the 2 patients in the 100 mg dose group (Patients [redacted] and [redacted] the values were [redacted] and [redacted] respectively.

Table 4 Single dose Urine Pharmacokinetic Parameters for ASP9521 (Pharmacokinetic Analysis Set)

Parameter Statistics	**ASP9521 30 mg (n = 3)**	**ASP9521 100 mg (n = 2)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 2)**
$Ae_{last\%}$ (%)				
Mean SD, CV%	0.193 0.12, 62	– –	0.158 0.040, 25	– –
$Ae_{inf\%}$ (%)				
Mean SD, CV%	0.241 0.16, 68	– –	0.189 0.057, 30	– –

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Parameter Statistics	**ASP9521 30 mg (n = 3)**	**ASP9521 100 mg (n = 2)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 2)**
CL_R (mL/h)				
Mean	2.16	–	1.80	–
SD, CV%	0.72, 33	–	0.54 – 30	–

All patients who received at least 1 dose of study drug and had values of concentration for a sufficient number of time points to reliably calculate at least 1 pharmacokinetic parameter (Pharmacokinetic Analysis Set).
–: no data; CV: coefficient of variation.
Source: Table 12.4.4

Pharmacodynamic Results:

For single and daily dosing, no apparent changes were observed in mean levels of endocrine markers. During daily dosing, the obtained predose levels were generally in range with baseline values for all parameters. It should be noted that between-subject variability in the endocrine marker levels was generally high.

Safety Results: During Part I, 12 of 13 patients (92.3%) reported 73 TEAEs in the overall ASP9521 group; 4 patients (100%) in the 600 mg group, 3 patients each (100%) in the 100 mg and 300 mg groups and 2 patients (66.7%) in the 30 mg group [Table 5].

During Part I, 8 of 13 patients (61.5%) in the overall ASP9521 group reported drug-related TEAEs; 4 patients (100%) in the 600 mg group, 2 patients (66.7%) in the 30 mg group and 1 patient each (33.3%) in the 100 mg and 300 mg groups.

Table 5 Incidence of Treatment-emergent Adverse Events Reported by ≥ 2 Patients Overall (Safety Analysis Set): Part I

MedDRA (v13.1) System Organ Class Preferred Term†	**Number of Patients, n (%)**				
	ASP9521 30 mg (n = 3)	**ASP9521 100 mg (n = 3)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 4)**	**ASP9521 Total (n = 13)**
Single-dose Treatment Phase					
Overall	2 (66.7)	2 (66.7)	3 (100)	2 (50.0)	9 (69.2)
Gastrointestinal disorders					
Constipation	0	0	2 (66.7)	1 (25.0)	3 (23.1)
Diarrhoea	1 (33.3)	0	1 (33.3)	0	2 (15.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Cancer pain	0	1 (33.3)	1 (33.3)	0	2 (15.4)
Multiple-dose Treatment Phase					
Overall	1 (33.3)	3 (100)	3 (100)	4 (100)	11 (84.6)
General disorders and administration site conditions					
Asthenia	1 (33.3)	2 (66.7)	2 (66.7)	0	5 (38.5)
Infections and infestations					
Rhinitis	1 (33.3)	0	1 (33.3)	0	2 (15.4)

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MedDRA (v13.1) System Organ Class Preferred Term†	Number of Patients, n (%)				
	ASP9521 30 mg (n = 3)	**ASP9521 100 mg (n = 3)**	**ASP9521 300 mg (n = 3)**	**ASP9521 600 mg (n = 4)**	**ASP9521 Total (n = 13)**
Musculoskeletal and connective tissue disorders					
Back pain	0	0	0	2 (50.0)	2 (15.4)
Bone pain	0	0	1 (33.3)	1 (25.0)	2 (15.4)
Blood and lymphatic system disorders					
Anaemia	0	1 (33.3)	1 (33.3)	0	2 (15.4)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	1 (33.3)	1 (33.3)	0	0	2 (15.4)
Whole Trial					
Overall	2 (66.7)	3 (100)	3 (100)	4 (100)	12 (92.3)
General disorders and administration site conditions					
Asthenia	1 (33.3)	2 (66.7)	2 (66.7)	0	5 (38.5)
Oedema peripheral	0	0	2 (66.7)	0	2 (15.4)
Gastrointestinal disorders					
Constipation	0	0	3 (100)	1 (25.0)	4 (30.8)
Diarrhoea	1 (33.3)	0	2 (66.7)	0	3 (23.1)
Musculoskeletal and connective tissue disorders					
Back pain	0	0	1 (33.3)	2 (50.0)	3 (23.1)
Bone pain	0	0	1 (33.3)	1 (25.0)	2 (15.4)
Infections and infestations					
Rhinitis	1 (33.3)	0	1 (33.3)	0	2 (15.4)
Metabolism and nutrition disorders					
Decreased appetite	0	0	1 (33.3)	1 (25.0)	2 (15.4)
Nervous system disorders					
Lethargy	0	0	0	2 (50.0)	2 (15.4)
Vascular disorders					
Hypertension	1 (33.3)	1 (33.3)	0	0	2 (15.4)
Blood and lymphatic system disorders					
Anaemia	0	1 (33.3)	1 (33.3)	0	2 (15.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)					
Cancer pain	0	1 (33.3)	1 (33.3)	1 (25.0)	3 (23.1)
Respiratory, thoracic and mediastinal disorders					
Dyspnoea	1 (33.3)	1 (33.3)	0	0	2 (15.4)

All patients who received at least 1 dose of study drug (Safety Analysis Set).

† Sorting order: descending in incidence of treatment-emergent adverse events in the ASP9521 total group by system organ class and decreasing order of frequency of preferred terms within each individual system organ.

Source: Table 12.6.1.2

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Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP9521		

No deaths were reported. Serious TEAEs were reported by [redacted] in the 300 mg group (bone pain) and [redacted] in the 600 mg group (cancer pain and urinary retention) and nontreatment-emergent SAEs were reported by [redacted] in the 300 mg group (pathological fracture and hypokalemia). [redacted] in the 30 mg group discontinued because of a TEAE (bone pain). None of these events were considered related to the study drug.

Overall, 12 of 13 patients (92.3%) reported TEAEs that were considered possibly or probably related to the study drug by the investigator. The TEAEs considered probably related to the study drug were cytolytic hepatitis, asthenia, anemia, hypophosphatemia, increased blood alkaline phosphatase, neutropenia, muscle spasms and diarrhea. The TEAEs considered possibly related the study drug were vision blurred, visual acuity reduced, hypertension, anemia, fatigue, stomatitis, lethargy, viral rash, hypercalcemia, lymphedema and cataract.

Of the 73 TEAEs reported, 46 TEAEs were of Grade 1 severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) criteria, 22 TEAEs were of Grade 2 severity and 5 TEAEs were of Grade 3 severity. The TEAEs of Grade 3 severity were cancer pain (2 events), muscle contracture, anemia and bone pain. It should be noted that when TEAEs were reported by NCI-CTCAE grade, the data were summarized at the maximum severity per preferred term per patient.

Overall, there were no consistent or clinically relevant changes in clinical laboratory results during the study. Treatment-emergent AEs of anemia were reported for [redacted] each in the 100 mg and 300 mg groups. The TEAE of anemia in the 100 mg group was Grade 1 in severity and probably related to study drug. The TEAE in the 300 mg group was Grade 3 in severity and possibly related to study drug. Treatment-emergent AEs of lymphopenia and neutropenia were reported by [redacted] each in the 100 mg group. The TEAE of lymphopenia was Grade 1 in severity and not related to the study drug. The TEAE of neutropenia was Grade 1 in severity and probably related to the study drug. Treatment-emergent AEs of hyperkalemia, hypocalcemia and vitamin D deficiency were reported by [redacted] each in the 300 mg group. All of these TEAEs were Grade 1 in severity and not related to the study drug. A single TEAE of hypophosphatemia was reported by [redacted] in the 100 mg group. This TEAE was Grade 2 in severity and probably related to the study drug. A single TEAE of increased blood alkaline phosphatase was reported by [redacted] in the 100 mg group. This TEAE was Grade 2 in severity and probably related to the study drug.

Overall, there were no consistent or clinically relevant changes in vital sign or weight measurements during the study. Treatment-emergent AEs of hypertension were reported for [redacted] each in the 30 mg and 100 mg groups. The TEAE in the 30 mg group was Grade 2 in severity and possibly related to study drug. The TEAE in the 100 mg group was Grade 2 in severity and not related to the study drug.

Overall, there were no consistent or clinically relevant changes in cardiac safety parameters (ECG and Holter measurements) during the study. A single TEAE of ECG QT prolonged was reported by [redacted] in the 600 mg group. This TEAE was Grade 2 in severity and not related to the study drug.

Name of Sponsor/Company: Astellas Pharma Europe B.V.		
Name of Finished Product: Not applicable		
Name of Active Ingredient: ASP9521		

Overall, there were no consistent or clinically relevant changes in physical examination, ophthalmological examination, neurological examination or Eastern Cooperative Oncology Group (ECOG) performance status findings during the study.

CONCLUSIONS:

Efficacy: ASP9521 showed no effect on PSA, the primary efficacy variable used in the study, and no effect on CTC counts.

Pharmacokinetics: ASP9521 was absorbed rapidly and no lag times were observed after a single dose. Median t_{max} values were 2 and 3 hours, respectively, for the 30 and 100 mg dose levels and 5 hours for the 300 and 600 mg dose levels. The AUC_{last} and AUC_{inf} values of ASP9521 appeared to increase dose proportionally across the 30 mg to 600 mg dose range. Dose-normalized C_{max} values were somewhat lower for the 300 and 600 mg doses compared to the 30 and 100 mg doses, but the ranges of individual values overlapped. Individual pharmacokinetic profiles generally showed a single elimination phase. Mean $t_{1/2}$ values were similar across the 100 to 600 mg dose range, with mean values ranging between 22 and 26 hours. For the 30 mg dose level, mean $t_{1/2}$ was somewhat higher (30 hours). During once daily dosing of ASP9521, steady-state conditions were generally reached within 1 week. Steady-state pharmacokinetic profiles at week 13 were only available for 3 patients, so no meaningful conclusions could be drawn regarding steady-state pharmacokinetics. Urinary excretion of unchanged ASP9521 was negligible.

Pharmacodynamics: Once daily dosing of ASP9521 did not appear to have an effect on the measured endocrine marker levels. However, it should be noted that only limited data were available and no firm conclusions could be drawn.

Safety: Overall, no safety signals were observed for ASP9521 at any dose level. There were no consistent or clinically relevant changes in clinical laboratory results, vital sign and weight measurements, cardiac safety parameters (ECG and Holter measurements), physical, ophthalmological and neurological examination findings or ECOG performance status during the study.

Date of Report: 05 September 2013