2. SYNOPSIS

Sponsor/company Orion Corporation Orion Pharma	**Individual study table referring to a specific part of the dossier** **Volume:** **Page**	(for National Competent Authority use only)
Finished product: Not applicable		
Active ingredient: ODM-201		

Study code: 3104001/EN3386-201

Study title: Safety and pharmacokinetics of ODM-201 in patients with castrate resistant prostate cancer: open, non-randomised, uncontrolled, multicentre, multiple dose escalation study with a randomised phase II expansion component.

Investigators and study centres: A total of 23 centres in Europe and USA took part in this study. The study coordinating investigator was Karim Fizazi, Institut Gustave Roussy, 114 Rue Edouart Vaillant, 94805 Villejuif Cedex, France.

Development phase: I/II	**Study period:** 28 Mar 2011 – 09 Jul 2013

Objectives: The primary objective of the phase I component was to evaluate the safety and tolerability of ODM-201 including dose limiting toxicities (DLTs) and the maximum tolerated dose (MTD), if possible.

The primary objective of the phase II component was to evaluate efficacy and safety of ODM-201 at 3 dose levels.

The secondary objectives of the phase I component were to evaluate the pharmacokinetic (PK) profile of ODM-201 (by using the sum of ORM-16497 and ORM-16555 diastereomer concentrations) and its major metabolite ORM-15341 after single and multiple dose administrations in the fed condition at different dose levels. For both phases, preliminary antitumour activity of ODM-201 was evaluated by prostate specific antigen (PSA), soft tissue and bone lesions, circulating tumour cell (CTC) counts, Eastern Cooperative Oncology Group (ECOG) performance status, and the time on treatment. In addition, the doses of ODM-201 for further clinical studies were to be defined.

The exploratory objectives of the study were to evaluate the effects of ODM-201 on the concentration of serum bone markers. Circulating metabolites in plasma and excreted metabolites in urine of ODM-201 were to be screened and, if possible, characterised.

Methodology: The study was an open, uncontrolled, multicentre, phase I/II inter-subject dose escalation safety study with single and multiple dose PK. The phase I component was a non-randomised dose-escalation and the phase II component was a randomised, expansion component at 3 dose levels. The study duration for each patient was 14-18 weeks, including a screening period (maximum 14 days), 12-week treatment period (during which 7 visits and one telephone call were carried out), and a 4-week post-treatment period for patients who did not continue into the 3104002 extension study. During the phase I dose escalation component the treatment period consisted of an initial 28-day (4-week) treatment period and if the patient did not experience a DLT they could continue receiving treatment at the same or a previously studied lower dose level for a further 8 weeks. In the phase II expansion component each patient received treatment for 12 weeks at one of the 3 defined dose levels unless they experienced an intolerable adverse event (AE) or disease progression was seen. After the 12-week treatment period, patients could continue in the open extension study 3104002. Results of this extension study will be reported separately.

Sample size:

Phase I: Approximately 24 chemotherapy-naive or post-chemotherapy patients with metastatic progressive castrate resistant prostate cancer (CRPC) were planned to be enrolled in the phase I dose escalation component of the study. The sample size was based on a rule-based 3+3 design.

Phase II: The phase II expansion component of the study included 3 dose levels**.** A total of approximately 105

additional patients with progressive CRPC (35 patients per expansion cohort) were planned to be enrolled and treated at 1 of the 3 dose level**s** for up to 12 weeks. Patients were stratified by prior treatment to 3 groups per dose level: 9 chemotherapy-naive patients with no prior therapy with a CYP17 inhibitor (chemo-/CYP17i-naïve subgroup), 9 post-chemotherapy patients with no prior therapy with a CYP17 inhibitor (post-chemo/CYP17i-naïve subgroup), and 17 patients with prior therapy with a CYP17 inhibitor (post-CYP17i subgroup) (of which at least 8 had to be post-chemotherapy patients). The sample size was based on the assumption that the true PSA response rate was 0.70, so 8 evaluable patients per dose per subpopulation would provide 80% confidence to rule out the possibility that the PSA response rate was lower than 0.55. The phase II expansion at the 2 lowest dose levels started while the phase I dose escalation was still ongoing. The 3rd and highest dose level for the phase II expansion component was selected after completion of the phase I dose escalation component.

In total, approximately 130 patients were to be enrolled in the study. The actual enrolment was as follows:

Phase I: 24 enrolled patients (100 mg b.i.d. 4 patients, 200 mg b.i.d. 7 patients, 300 mg b.i.d. 3 patients, 500 mg b.i.d. 4 patients, 700 mg b.i.d. 3 patients, 900 mg b.i.d. 3 patients).

Phase II: 110 randomised and treated patients (100 mg b.i.d. 38 patients, 200 mg b.i.d. 37 patients, 700 mg b.i.d. 35 patients).

Diagnosis and main criteria for inclusion: Male patients aged 18 years or older with histologically confirmed adenocarcinoma of the prostate fulfilling all of the inclusion criteria and none of the exclusion criteria, for whom written informed consent (IC) was obtained. The chemotherapy-naive or post-chemotherapy patients had to be receiving androgen deprivation therapy (ADT) with a luteinising hormone-releasing hormone (LHRH) analogue or orchiectomy. All patients had to have received prior treatment with antiandrogen, and have progressive disease despite the therapy and a life expectancy at least 3 months.

Investigational product, dose and mode of administration, batch numbers: ODM-201 was provided as 100 mg in size 0 hard gelatine capsules for oral administration. In phase I, the ODM-201 starting dose was 100 mg twice daily (b.i.d.), with dose increases to 200, 300, 500, 700 and 900 mg b.i.d. In phase II, the doses were 100 mg, 200 mg and 700 mg b.i.d. Batch numbers were: 002873, 002962, 003310, 004324, 005176, 005451, 005499, 005709, 005833, 006268, and 006359.

Duration of treatment: In the phase I component, patients who did not experience any DLTs within 24 hours after the first dose administration could continue to receive 2 daily oral doses of ODM-201 for 28 days in the absence of any DLTs. After 28 days the patients who did not experience any DLTs could continue study treatment at the same dose level (or the previous lower dose level) until 12 weeks in the absence of disease progression or DLTs. In the phase II component the duration of treatment was 12 weeks in the absence of disease progression or intolerable AEs. In both components, those patients who had stable disease after 12 weeks and met the inclusion and exclusion criteria of the extension study 3104002 could continue treatment in that study if approved by the investigator.

Reference product, dose and mode of administration, batch numbers: No reference product was used in this study.

Variables and methods of assessments:

Assessment of PK variables: The following single dose PK parameters were derived in the phase I dose escalation component from the concentration-time data of ODM-201 (sum of ORM-16497 and ORM-16555), and active metabolites ORM-15341, ORM-16497 and ORM-16555, after the first dose administrations of ODM-201 at fed state:

C_{max}	Plasma peak concentration
t_{max}	Time to reach the peak concentration
AUC_t	Area under the concentration-time curve from time zero to the last sample with a quantifiable concentration
AUC_∞	Area under the concentration-time curve from time zero to infinity
λ_z	Terminal elimination rate constant
$t_{½}$	Terminal elimination half-life

The following PK parameters for ODM-201 (sum of ORM-16497 and ORM-16555), and active metabolites

ORM-15341, ORM-16497 and ORM-16555, were calculated after multiple-dosing on day 7: C_{max}, t_{max}, AUC_t, AUC_∞, $t_{½}$, and Cav_{md} (average concentration in plasma after multiple dosing).

In the phase II expansion component, samples for the determination of concentrations of ORM-16497, ORM-16555 and ORM-15341 were collected on day 28 and week 12 in the morning after dosing at the same time as the PSA sample**.**

Metabolite screening: Blood and urine samples were collected for metabolite screening during the phase I dose escalation component. Blood samples were collected on day 1 pre-dose, and at 3 and 12 hours after study treatment administration, as well as on day 7 pre-dose, and at 2 and 8 hours after study treatment administration. Total urine was collected on day 1 between 0-12 hours and on day 7 between 0-8 hours. Excreted metabolites were screened from urine.

Assessments of pharmacodynamic variables: Blood samples were collected for determination of serum testosterone, luteinising hormone (LH), follicle-stimulating hormone (FSH) and dihydrotestosterone (DHT) concentrations.

Assessment of efficacy variables:

- Assessment of PSA: Blood samples were collected for determination of the serum total PSA concentration.
- Assessment of soft tissue and bone:
  - Soft tissue: Chest, abdomen and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) were performed. Changes in lesions were evaluated.
  - Bone scan: Radionuclide bone scan was performed. Changes in the lesions were evaluated.
- Performance status: ECOG performance status was assessed. Changes from baseline were evaluated.
- Assessment of treatment response: Treatment response was assessed at week 12 separately for PSA, soft tissue lesions (CT/MRI), bone lesions (scan), and the patient's performance status.
- Circulating tumour cells (CTC): Blood sample**s** for CTC counts were collected. The number of CTCs per 7.5 mL of blood were evaluated.

Assessment of exploratory markers:

- Bone markers: Blood samples were collected for analysis of bone markers. The concentrations of serum bone-specific alkaline phosphatase (BAP) and type I procollagen N-terminal propeptide (PINP) were analysed.
- Serum serine peptidase inhibitor (SPINK1) and chromogranin A (CgA): Blood samples were collected for determination of SPINK1 and CgA during the phase II expansion component.
- TMPRSS2-ERG gene fusion and SPINK1 in the archival tumour tissue: Transmembrane protease, serine 2 encoding gene (TMPRSS2) and Est Related Gene (ERG) gene rearrangement (TMPRSS2-ERG) status were analysed using the sections cut from archival tumour tissue samples, if available. Expression level of SPINK1 was studied by immunohistochemistry (IHC) analysis using the archival tumour tissue samples, if available.
- AR gene amplification: AR gene amplification status (copy number) and the coding DNA sequence of AR gene from CTCs was analysed, if possible.
- Explorative samples for metabolomics: The PK spare blood samples collected for metabolite screening in the phase I dose escalation component could be used for explorative purposes (protein and biochemical metabolite related proof-of-mechanism studies).

Pharmacogenomic (PG) assessments: A blood sample for DNA extraction was taken from patients who had signed the PG IC. The objective of pharmacogenomic research was to study genetic polymorphisms and mutations that may relate to safety, efficacy, pharmacodynamics, absorption, distribution, metabolism or excretion of ODM-201.

Assessment of safety: Safety was assessed by AEs, vital signs, centrally read 12-lead electrocardiogram (ECG) and Holter ECG (the latter only in the Phase I component in the 700 mg and 900 mg b.i.d. dose level cohorts)**,** oral or tympanic temperature, physical examination and laboratory safety assessments.

Statistical methods:

Evaluation of PK: The PK variables were summarised using descriptive statistics.

Evaluation of pharmacodynamics: The actual values and the changes from baseline for hormone concentrations were summarised using descriptive statistics.

Evaluation of PSA: The percentage change in serum concentration of PSA from baseline at 12 weeks and maximum percentage change from baseline at any time were summarised using descriptive statistics by dose cohort and subpopulation. The proportion of patients achieving a decline in PSA ≥ 90%, ≥ 50% and ≥ 30% was analysed and tabulated. The serum PSA concentration was summarised using descriptive statistics at every time point.

Evaluation of soft tissue and bone response: The frequency of responders according to the modified Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 criteria of soft lesions was evaluated by dose cohort for phase I and dose level and by prior treatment for phase II. The changes from baseline in the number of lesions seen on the bone scan was reported as "no new lesions" or "new lesions" by the dose level. Progression in bone was defined by the appearance of at least 2 or more lesions compared to a prior scan.

Evaluation of performance status: The ECOG performance status and the changes from baseline were reported with frequency tables by dose cohort for phase I and by dose level and prior treatment for phase II.

Evaluation of treatment response: Treatment response was summarised descriptively by dose cohort for phase I and by dose level and prior treatment for phase II.

Evaluation of CTCs: The CTC counts and changes in CTC counts from baseline were reported descriptively by dose cohort for phase I and by dose level and prior treatment for phase II. The frequencies of patients with CTC count ≥ 5/7.5 mL blood (unfavourable) or <5/7.5 mL blood (favourable) were shown. The proportion of patients achieving a decline ≥ 30% and ≥ 50% in CTC counts was analysed and tabulated.

Evaluation of exploratory markers: Exploratory markers were analysed separately and the results will be reported in a separate report.

Metabolomics: At the time of the writing of this report no analyses have been performed. If metabolomic analyses are done in the future, the results will be reported in a separate report.

Evaluation of PG: At the time of the writing of this report PG analyses were not performed, If PG analyses are done in the future, the results will be reported in a separate report.

Evaluation of safety: AEs were displayed in frequency tables by dose levels and other stratifying variables. The number and proportion (%) of patients having each AE was given.

The actual values and corresponding changes from baseline for supine heart rate (HR) and blood pressure (BP), and for 12-lead ECG and Holter ECG variables were summarised using descriptive statistics. The number of patients with QTc interval prolongation was tabulated.

Oral or tympanic temperature was tabulated.

The frequencies of normal and abnormal physical examination findings were summarised.

Laboratory safety variables were summarised using descriptive statistics, with the absolute values and the changes from baseline shown.

Summary-Conclusions

Demography and other baseline characteristics:

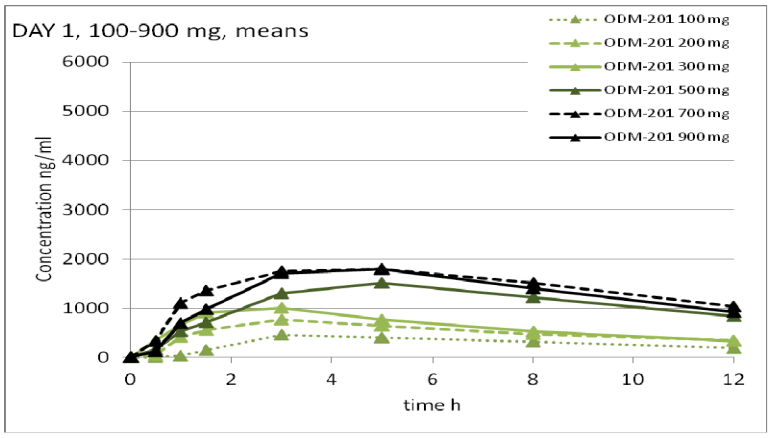
Phase I dose escalation component: The median age of the patients was 69.0 years (range 57 to 82 years), with the largest proportion of patients being in the 65 to 74 years age category (41.7%). Overall 91.7% of patients were Caucasian. The majority of patients (70.8%) were classified at ECOG stage 0 at baseline i.e. fully active, with 29.2% classed as ECOG stage 1. A total of 37.5% patients had CTC counts ≥ 5 cells/7.5 mL of blood and the median baseline PSA was 27.4 ng/mL, with values ranging from 3 to 651 ng/mL. The mean time from first diagnosis of prostate cancer to the start of study treatment was 86.7 months (i.e. approximately 7 years). The median Gleason score at diagnosis was 7.0, with 62.5% of patients categorised as having a medium Gleason score (i.e. between 5 and 7) and 29.2% categorised as having a high Gleason score (i.e. between 8 and 10) (no patients had a low Gleason score at baseline).

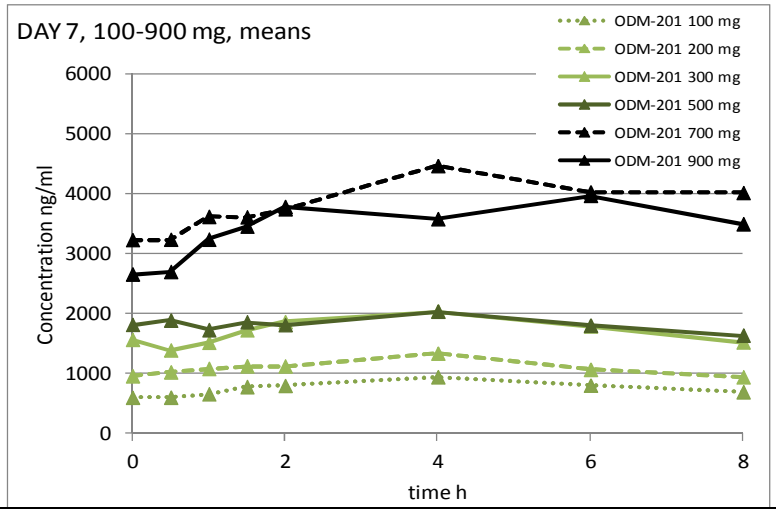
The majority of patients did not have distant metastases at diagnosis (70.8% classed as M0). At screening, disease localisation was in bone only in 25.0% of patients, in bone and soft tissue in 37.5% of patients, and in soft tissue only in 33.3% of patients (note one patient did not have metastases recorded at baseline but bone metastases were noted in the patient's medical history). One patient had visceral disease at baseline.

Phase II expansion component: The median age of the patients was 69.5 years (range 53 to 89 years), with the largest proportion of patients being in the 65 to 74 years age category (44.5%). Overall 96.4% of patients were Caucasian. Equal numbers of patients (50.0%) were classified at ECOG stage 0 (fully active) or 1 (restricted). Similar numbers of patients had CTC counts <5 cells/7.5 mL of blood (47.3%) and ≥ 5 cells/7.5mL of blood (43.6%). The median baseline PSA was 111.4 ng/mL, with values ranging from 4 to 5000 ng/mL. The mean time from first diagnosis of prostate cancer to the start of study treatment was 78.1 months i.e. 6.5 years (range 11 to 228 months. The median Gleason score at diagnosis was 8.0, with 2.7% of patients categorised as having a low Gleason score (between 2 and 4) at baseline, 42.7% categorised as having a medium score (between 5 and 7) and 48.2% having a high score (between 8 and 10). Approximately half of the patients did not have distant metastases at diagnosis (54.5% classed as M0). At screening, disease localisation was in bone only in 39.1% of patients, in bone and soft tissue in 50.0% of patients, and in soft tissue only in 10.9% of patients. A total of 23.6% patients had visceral disease at baseline.

Pharmacokinetic results:

The oral dose of ODM-201 was absorbed rapidly when administered after a breakfast, and the median t_{max} for ODM-201 ranged between 2-5 hours after a single dose. After repeated dosing, maximum concentrations (C_{max}) as well as the AUC_t values for ODM-201 on day 7 were approximately 2 to 2.5 times higher than on day 1 (see figures below).





Steady-state plasma concentrations were reached by 7 days of repeated dosing. Over the dose range 100 mg to 700 mg, the day 1 exposure (AUC_t and C_{max}) after a single dose appeared to increase in a near dose-related manner. At the 900 mg dose there was no increase in ODM-201 exposure (AUC_t) or C_{max} after a single dose compared to the 700 mg dose. After repeated dosing, steady-state concentrations for ODM-201 were similar after the 900 mg dose compared to the 700 mg dose. The 12-hour mean proportions of diastereomers ORM-16497 and ORM-16555 for AUC_t were approximately 0.25 and 0.75 respectively on day 1 after single dosing and approximately 0.15 and 0.85 respectively on day 7 after repeated dosing. Concentrations of the active metabolite ORM-15341 were higher than concentrations of ODM-201 and the mean metabolite to parent ratio was 1.6-2.4. Maximum metabolite concentrations were reached in 1.5 – 5 hours (medians) after administration.

The mean elimination half-life of ODM-201 was 5.1 to 8.7 hours after a single dose and approximately 10-30 hours after multiple dosing at steady-state. The mean elimination half-life of the metabolite ORM-15341 was similar to that of ODM-201, being 4.9 to 8.0 hours after a single dose and 7.3 to 12.5 hours after multiple dosing. After b.i.d. dosing of 100 mg, 200 mg and 700 mg in the Phase II component, the steady state concentrations for ODM-201 seemed to be at similar levels to those observed in the phase I component.

In the LC-MS metabolite profiling, 4 circulating and 11 urinary metabolites of ODM-201 were found, with the main metabolic pathway being oxidation to ORM-15341. Other less abundant biotransformation products included N-glucuronidation, hydroxylation or N-oxidation, and N-dealkylation pathways. The metabolite to parent ratios were similar between dose levels and between single and repeated dosing.

Pharmacodynamic results:

No clinically significant changes in measured serum hormone levels were seen during the study. Mean testosterone levels at baseline were 0.52 nmol/L in all patients (phase I and II components combined) (note: castration level is defined as <1.7 nmol/L), with testosterone levels remaining low throughout the whole study period. No clinically significant changes were seen in LH, FSH and DHT levels.

Efficacy results:

Unless otherwise specified, the efficacy results below are presented for the 100 mg, 200 mg and 70 mg b.i.d. dose groups from the combined phase I and II components of the study.

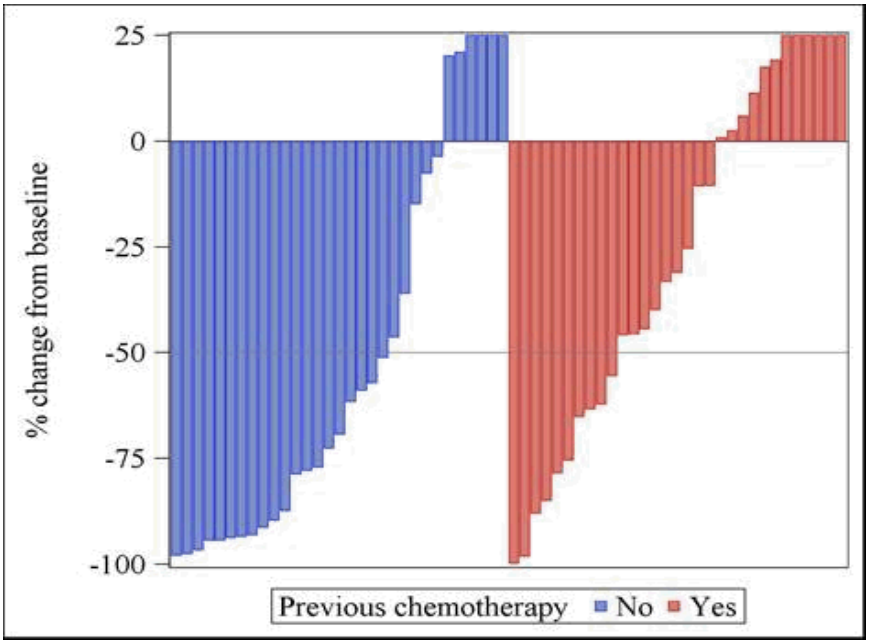
Serum PSA (PP population):

The decrease from baseline in serum PSA response at week 12 in the combined phase I+II components by selected doses and by subgroups (PP population) is shown below:

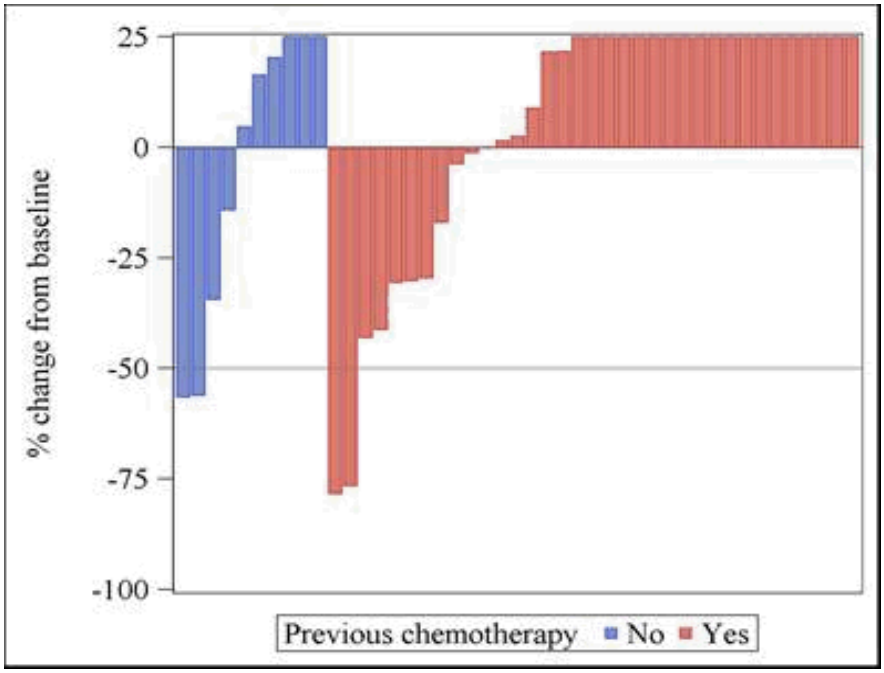
	100 mg b.i.d. (N=37)	200 mg b.i.d. (N=38)	700 mg b.i.d. (N=33)
All patients, N	37	38	33
≥ 50% decrease from baseline, n (%)	10 (27.0)	13 (34.2)	11 (33.3)
Chemo-/CYP17i-naïve subgroup, N	11	13	7
≥ 50% decrease from baseline, n (%)	5 (45.5)	9 (69.2)	6 (85.7)
Post-chemo/CYP17i-naïve subgroup, N	11	9	11
≥ 50% decrease from baseline, n (%)	5 (45.5)	1 (11.1)	4 (36.4)
Post-CYP17i subgroup, N	15	16	15
≥ 30% decrease from baseline, n (%)	4 (26.7)	4 (25.0)	1 (6.7)

A dose-related response was seen in the chemo-/CYP17i-naïve subgroup, with a higher percentage of patients in the 700 mg b.i.d. dose group achieving a decline in PSA ≥ 50% compared to the lower dose groups.

ODM-201 had a greater effect on reducing serum PSA in CYP17i-naïve patients (see figures below).



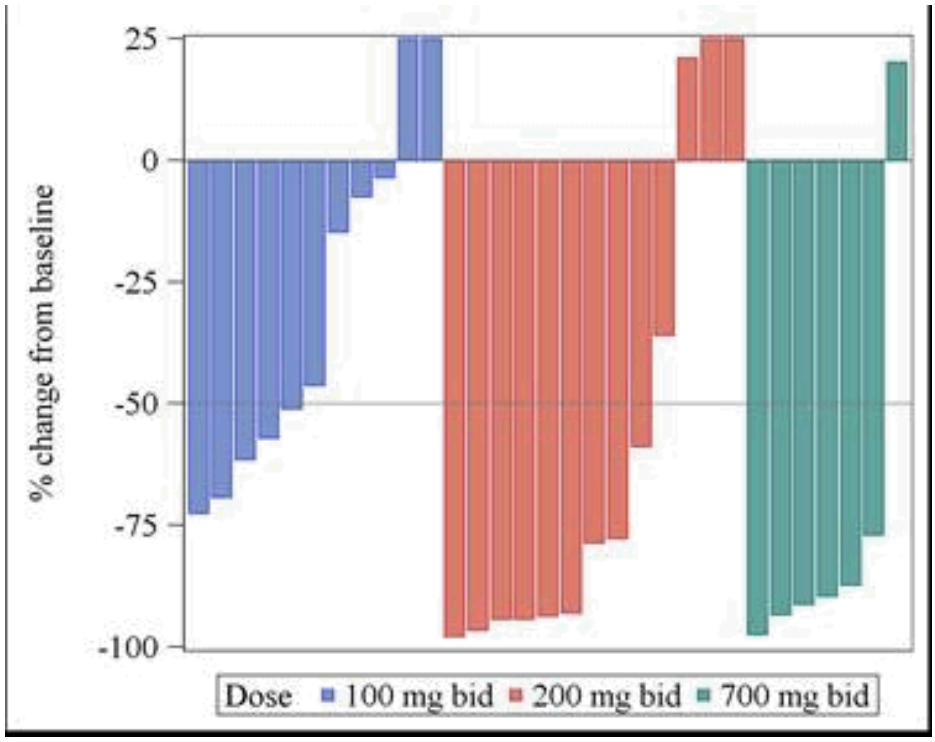
PSA waterfall plot of percentage change from baseline at week 12 by prior chemotherapy use (phase I + II) - CYP17i-naïve patients (PP population)



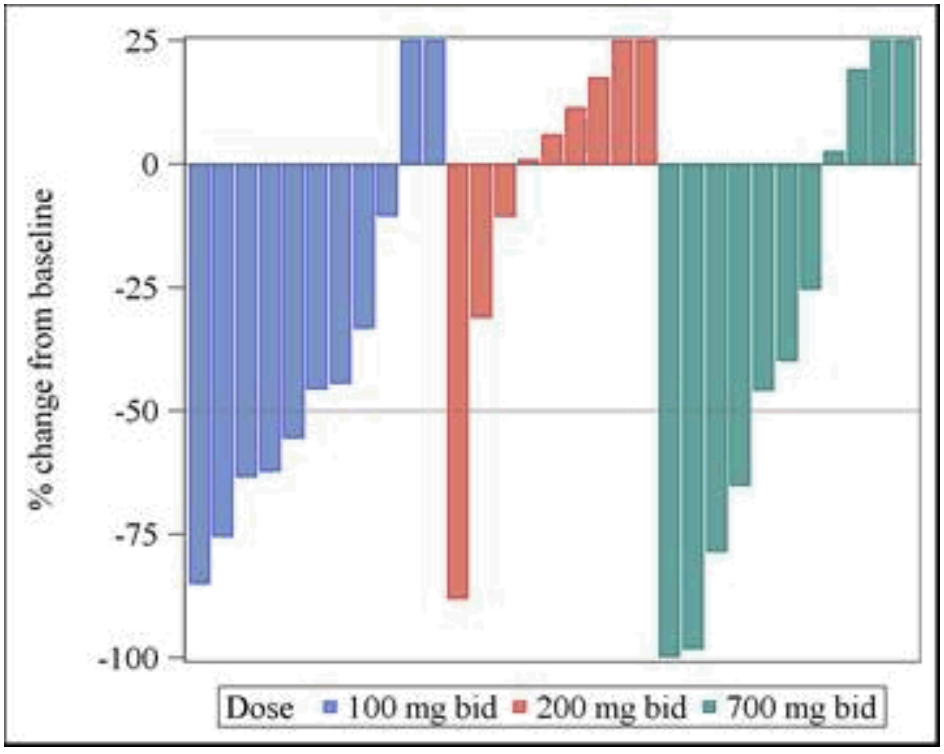
PSA waterfall plot of percentage change from baseline at week 12 by prior chemotherapy use (phase I + II) – post-CYP17i patients (PP population)

Note: PSA change on the above figures are truncated at 25% for display purposes

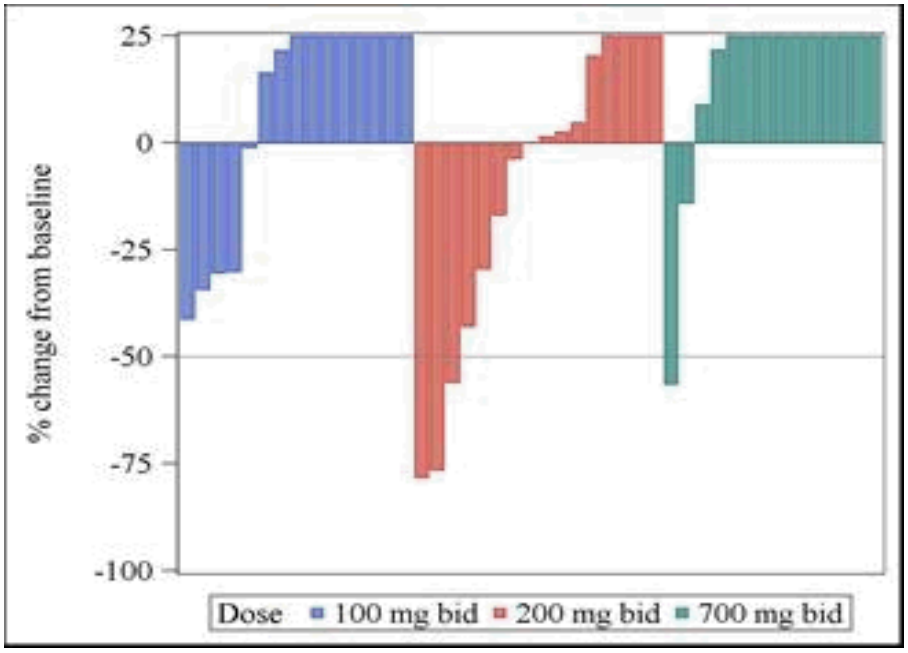
Waterfall plots showing the percentage change in serum concentration of PSA from baseline to week 12 in the PP population for the phase I and II components combined for the 100 mg b.i.d., 200 mg b.i.d. and 700 mg b.i.d dose groups are provided below for each of the 3 subgroups by dose.



PSA waterfall plot of percentage change from baseline at week 12 by dose (phase I + II) – chemo-/CYP17i-naïve subgroup (PP population)



PSA waterfall plot of percentage change from baseline at week 12 by dose (phase I + II) – post-chemo/CYP17i-naïve subgroup (PP population)



PSA waterfall plot of percentage change from baseline at week 12 by dose (phase I + II) – post-CYP17i subgroup (PP population)

Note: PSA change on all the above figures are truncated at 25% for display purposes

Soft tissue response (evaluable population):

The soft tissue response at week 12 in the combined phase I+II components by selected doses and by subgroup (PP population) is shown below:

	100 mg b.i.d. (N=37)	200 mg b.i.d. (N=38)	700 mg b.i.d. (N=33)
All patients, N	29	28	16
Overall RECIST response - CR+PR, n (%)	2 (6.9)	6 (21.4)	2 (12.5)
Overall RECIST response - SD, n (%)	16 (55.2)	12 (42.9)	10 (62.5)
Overall RECIST response - PD, n (%)	11 (37.9)	10 (35.7)	4 (25.0)
Chemo-/CYP17i-naïve subgroup, N	8	9	2
Overall RECIST response - CR+PR, n (%)	1 (12.5)	4 (44.4)	1 (50.0)
Overall RECIST response - SD, n (%)	7 (87.5)	2 (22.2)	1 (50.0)
Overall RECIST response - PD, n (%)	0	3 (33.3)	0
Post-chemo/CYP17i-naïve subgroup, N	8	7	5
Overall RECIST response - CR+PR, n (%)	1 (12.5)	0	1 (20.0)
Overall RECIST response - SD, n (%)	4 (50.0)	3 (42.9)	3 (60.0)
Overall RECIST response - PD, n (%)	3 (37.5)	4 (57.1)	1 (20.0)
Post-CYP17i subgroup, N	13	12	9
Overall RECIST response - CR+PR, n (%)	0	2 (16.7)	0
Overall RECIST response - SD, n (%)	5 (38.5)	7 (58.3)	6 (66.7)
Overall RECIST response - PD, n (%)	8 (61.5)	3 (25.0)	3 (33.3)

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease

The 1 CR was seen in the 100 mg b.i.d dose group, but most of the PRs were seen in the higher dose groups (6 in the 200 mg b.i.d dose group and 2 in the 700 mg b.i.d. dose group compared to 2 in the 100 mg b.i.d. dose group). As expected, most of the responses were seen in the chemo-/CYP17i-naïve subgroup (1 CR and 5 PRs).

Bone response (evaluable population with bone metastases at baseline): In the chemo-/CYP17i-naïve subgroup in the 100 mg dose group, 90.0% were stable/no change and 10.0% progressed, in the 200 mg dose group 70.0% were stable/no change and 30.0% progressed, and in the 700 mg dose group, 83.3% were stable/no change and 16.7% progressed. In the post-chemo/CYP17i-naïve subgroup, in the 100 mg dose group, 55.6% were stable/no change and 44.4% progressed, in the 200 mg dose group, 57.1% were stable/no change and 42.9% progressed, and in the 700 mg dose group, 20.0% improved, 50.0% were stable/no change, and 30.0% progressed. In the post-CYP17i subgroup, in the 100 mg dose group, 45.5% were stable/no change and 54.5% progressed, in the 200 mg dose group, 57.1% were stable/no change and 42.9% progressed, and in the 700 mg dose group, 54.5% were stable/no change and 45.5% progressed. Thus the best responses were seen in the 700 mg b.i.d. post chemo/CYP17i-naïve subgroup.

Performance status (evaluable population): Across all dose groups the majority of patients were stable in ECOG performance status during the study. Two patients (both in the post-CYP17i subgroup) had a worsening in ECOG of 3 or more points.

Clinical progression (evaluable population): Across all dose groups, 25 patients (21.4%) clinically progressed by week 12. The most common reason for clinical progression was worsening of pain/increased use of analgesics, which was reported in 17 patients (14.5%). Only 2 patients (5.6%) had clinical progression in the chemo-/CYP17i-naïve subgroup. The majority of the cases of clinical progression occurred in the post-CYP17i subgroup (14 patients, 29.8%), followed by the post-chemo-/CYP17i-naïve subgroup (9 patients, 26.5%).

CTCs (evaluable population): Across all dose groups, 25 patients (62.5%) achieved a decline of ≥ 30% in CTC counts and 23 patients (57.5%) achieved a decline of ≥ 50% CTC counts during the study. The majority of the cases of a decline occurred in the chemo-/CYP17i-naïve subgroup (≥ 30%: 12 patients, 92.3%; ≥ 50%: 11 patients, 84.6%). The smallest number of patients with a decline occurred in the post-CYP17i subgroup (2 patients, 15.4%, in both categories). Comparison of the percentage change from baseline to week 12 in the PP population for the phase I and II components combined, split by CYP17i-naïve or post-CYP17i patients, clearly show a better response in CYP17i-naïve patients compared to patients who have received previous CYP17i treatment. Overall 17 patients (35.4%) improved from unfavourable (CTC count of ≥ 5) at baseline to favourable (CTC count <5) at week 12. However, 9 patients (15.3%) converted from favourable at baseline to unfavourable at week 12. The remaining patients maintained either favourable counts during the study (45 patients, 76.3%) or maintained unfavourable counts (23 patients, 47.9%). All the cases of a change from unfavourable to favourable during the study were seen in the chemo-/CYP17i-naïve or the post-chemo/CYP17i-naïve subgroup (8 patients, 53.3% and 9 patients, 60.0%, respectively). No changes to a favourable CTC count were seen in the post-CYP17i subgroup.

Safety results:

Safety information presented in this section is from the 12-week treatment period only. Long-term safety data from the extension study will be presented separately at a later date. No DLTs were seen in the phase I dose escalation component of the study at any of the dose levels (a DLT was defined as: at least possibly related Grade ≥ 3 toxicity, excluding haematological toxicities, nausea, vomiting and diarrhoea; at least possibly related Grade ≥ 3 nausea, vomiting and diarrhoea uncontrolled with antiemetic and/or anti-diarrheal therapy; at least possibly related Grade ≥ 3 haematological toxicity lasting for ≥ 7 days; or at least possibly related Grade ≥ 4 thrombocytopenia and neutropenia). In the combined phase I and phase II components of the study (all dose levels), a total of 117 patients (87.3%) reported at least 1 AE during the treatment period. The most common AEs reported during the study treatment period by patient were fatigue (17.9%), back pain (11.9%), constipation (11.9%), and nausea (10.4%). No dose-related trends were noted for the occurrence of any AEs. A total of 38 patients (28.4%) had AEs that were considered related by the investigator to the study treatment. The most common drug-related AEs by patient were fatigue (8.2%), hot flush (5.2%) and diarrhoea (3.7%). Thirteen patients (9.7%) reported serious adverse events (SAEs) during the treatment period, 2 patients died, and 5 patients withdrew from the study due to AEs (one event each). None of these events were considered related to the study treatment. The majority of AEs were classified as Grade 1 (in 101 patients), with 17 patients (12.7%) reporting Grade 3 or above AEs. The only Grade 3 AEs reported in more than 1 patient were anaemia (3 patients), and general physical health deterioration (2 patients). A similar pattern of AEs was seen in each of the subgroups (chemo-/CYP17i-naïve subgroup, post-chemo/CYP17i-naïve subgroup, and post-CYP17i subgroup) with the exception of fatigue, which was seen at a lower incidence in the chemo-/CYP17i-

naïve subgroup.

No clinically significant acute or chronic changes from baseline were noted in the safety laboratory parameters and no clinically significant differences were seen between the dose groups. No clinically significant dose-related acute or chronic changes were seen in vital signs or ECG parameters. No effects on antrioventricular (AV) conduction and no signs of proarrhythmic tendency were observed in the analysis of the pre- and post-treatment Holter recordings from 6 patients treated with 700 or 900 mg b.i.d. ODM-201 in the phase I dose escalation component.

Conclusions:

No DLTs were seen in the first 28-day cycle of the phase I dose escalation component of the study. The AE profile observed in this 12-week study reflects the AE profile that is expected in a population of patients with advanced prostate cancer. Most AEs were Grade 1-2 and assessed by the investigators as not related to the study treatment. No dose-related trends were noted in the AE profile. No clinically significant changes in laboratory tests, vital signs or ECG parameters were seen.

ODM-201 was absorbed rapidly when administered after a light breakfast. Over the dose range of 100 mg to 700 mg after a single dose, exposure appeared to increase in a near linear manner and at the 900 mg dose there was no increase in exposure compared to the 700 mg dose. The main metabolic pathway in human was oxidation to ORM-15341 and the metabolite-to-parent ratios were consistent between dose levels and between single and repeated dosing.

Significant anticancer activity was seen in the study at all dose levels and in all sub-populations, as evaluated by PSA, CTC counts, and soft and bone lesion imaging. Patients in the chemo /CYP17i-naïve group responded best to the treatment, with the 700 mg b.i.d. dose being most efficacious.

The results of this study suggest that ODM-201 is a safe and efficacious treatment for patients with castration-resistant prostate cancer. The results also suggest that the 700 mg b.i.d dose is as safe and tolerable as the 100 mg bid or 200 mg b.i.d. dose levels, but is more efficacious than these lower doses in patients who are naive to treatment with chemotherapy or CYP17i. The recommend dose for further studies will be decided based on results from this study and the ongoing 3104003 study.

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