ERRATUM

Erratum to: Phase 1 study of darolutamide (ODM-201), a new-generation androgen receptor antagonist, in Japanese patients with metastatic castration-resistant prostate cancer

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The author would like to correct the errors in the publication of the original article. The corrected details are given below for your reading. The original article was corrected.

Affiliation of Masanobu Yasuda should be: Clinical Statistics, Bayer Yakuhin, Osaka, Japan.

In abstract, second sentence of the method sections should read as:

In the single-dose period (≈ 1 week), darolutamide was administered at 300 mg (Cohort 1) or 600 mg (Cohort 2) on day -5 (fasting state) and day -2 (fed condition).

The introduction section should read as:

The global incidence of prostate cancer (PC) is approximately 1.1 million new cases per year, which accounts for

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15% of all cancer cases in men [1], including Japanese men [2]. Based on the most recent estimates for Japan, there were 73,145 PC diagnoses in 2012 (incidence rate, 117.0 per 100,000) and 11,507 PC-related deaths in 2014 (mortality rate, 18.9 per 100,000) [3]. In Japan, PC is among the most common cancer types in men and the sixth highest cause of cancer-related death [2, 4].

Initially, PC is an androgen-dependent disease and will respond to androgen deprivation therapy (ADT); however, almost all patients become resistant to ADT over time and develop castration-resistant PC [5], defined as increasing prostate-specific antigen (PSA) levels despite castrate levels of testosterone or the progression of preexisting disease with or without metastases. Patients who have PC that has progressed to advanced metastatic disease with castration resistance have a poor prognosis, with median survival times historically in the range of 1–2 years, although longer durations extending to ~ 3 years have been reported in recent clinical trials [6–9].

Androgen receptor (AR) antagonists are nonsteroidal antiandrogen agents that bind to ARs and inhibit the androgen-induced activation of these receptors, which ultimately inhibits tumor growth and proliferation. These agents have demonstrated efficacy in patients with metastatic castration-resistant PC (mCRPC) [10–12].

Darolutamide (formerly ODM-201) is a new-generation nonsteroidal AR antagonist with a unique molecular structure. It comprises a mixture of 2 diastereomers, (*S,R*)-darolutamide (ORM-16497) and (*S,S*)-darolutamide (ORM-16555), which interconvert via the major metabolite keto-darolutamide (ORM-15341) preferentially to (*S,S*)-darolutamide; all three compounds show similar pharmacologic activity [13–15]. In preclinical trials, darolutamide demonstrated higher binding affinity compared with other AR antagonists (such as bicalutamide and enzalutamide), an antiproliferative effect and tumor growth inhibition in

AR-overexpressing cells, and activity against AR mutants linked to drug resistance. In addition, darolutamide is different from other new-generation nonsteroidal AR antagonists with respect to its negligible blood–brain barrier penetration [14–16]. In early-phase clinical trials with Western mCRPC patients, darolutamide has shown a good safety profile and significant reductions in PSA levels [13, 17–19].

The aim of this phase 1 trial was to assess the safety and tolerability, pharmacokinetics (PK), and antitumor activity of darolutamide in Japanese patients with mCRPC (ClinicalTrials.gov identifier: NCT02363855).

In method, the first sentence of the second paragraph of the “Trial design” section should read as:

In the single-dose period, darolutamide was administered in the fasting state on day –5 and after a usual Japanese breakfast (fed condition) on day –2 as two 150-mg tablets (300-mg dose; Cohort 1) or as four 150-mg tablets (600-mg dose; Cohort 2).

In method section, first paragraph of “Antitumor efficacy assessments” section should read as:

Antitumor efficacy was assessed by PSA response, which is defined as percentage change of PSA at week 12 from baseline; tumor response was defined in accordance with the recommendations of the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) [20] and Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 [21]. Blood samples for PSA levels were collected at screening, once during the single-dose period (predose on day –5 or day –6; mean defined the baseline value), at three time points during the multiple-dose period (weeks 4, 8, and 12), at the end of treatment, and at the follow-up. For patients with a PSA decline from baseline at week 12, PSA progression was defined as the date of documented PSA increase $\geq 25\%$ and absolute increase ≥ 2 ng/mL above the nadir, which was to be confirmed by a second value obtained ≥ 3 weeks later. For patients without a PSA decline from baseline at week 12, PSA progression was defined as the date of documented PSA increase $\geq 25\%$ along with an absolute increase from baseline ≥ 2 ng/mL, which was to be confirmed by a second value obtained ≥ 3 weeks later.

In method section, “Safety and tolerability” section should read as:

Safety evaluations were performed until week 12 and included results of physical examinations, 12-lead electrocardiogram (ECG), Holter ECG, vital signs (blood pressure, pulse rate, and body temperature), body weight, adverse events (AEs), and laboratory examinations. All AEs were

graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03 (NCI CTCAE v4.03). Laboratory examinations were performed at screening; predose on day –5 or day –6, day –2, and day 1; at day 7 before breakfast; at each subsequent visit during the multiple-dose period; at the end of treatment; and at the follow-up/discontinuation.

The Table 1 should be:

Table 1 Demographics and patient characteristics

	Cohort 1 300 mg BID <i>n</i> = 3	Cohort 2 600 mg BID <i>n</i> = 6	Total <i>N</i> = 9
Median (range) age, years	68.0 (67–73)	73.0 (64–83)	70.0 (64–83)
Mean (SD) age	69.3 (3.2)	73.7 (7.6)	72.2 (6.6)
Median (range) weight, kg	61.9 (59–69)	58.9 (53–77)	61.9 (53–77)
Median (range) height, cm	165.5 (163–170)	158.7 (152–170)	162.8 (152–170)
Median (range) body mass index, kg/m ²	23.4 (20–25)	23.0 (21–28)	23.2 (20–28)
Median (range) PSA, µg/L	61 (39–290)	32 (5–260)	39 (5–290)
Mean (SD) PSA	130 (139)	99 (118)	109 (117)
ECOG PS, <i>n</i> (%) ^a			
0	2 (66.7)	4 (66.7)	6 (66.7)
1	1 (33.3)	2 (33.3)	3 (33.3)
EOD at screening, <i>n</i> (%) ^b			
0	1 (33.3)	0	1 (11.1)
1	0	0	0
2	1 (33.3)	2 (33.3)	3 (33.3)
3	1 (33.3)	4 (66.7)	5 (55.6)
4	0	0	0
Prior therapy, <i>n</i> (%)			
Chemo- therapy/ hormonal	1 (33.3)/3 (100.0)	0 (0)/6 (100.0)	1 (11.1)/9 (100.0)
Docetaxel	2 (66.7)	2 (33.3)	–
Abiraterone	2 (66.7)	3 (50.0)	–
Enzalutamide	3 (100.0)	3 (50.0)	–

BID twice daily, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EOD* extent of disease, *PSA* prostate-specific antigen

^aECOG PS: 0 = fully active; 1 = restricted active; 2 = ambulatory and capable of all self-care; 3 = capable of limited self-care; 4 = completely disabled

^bEOD (bone scan findings/evaluation of bone metastases): 0 = normal or abnormal because of benign bone disease; 1 = < 6 metastatic sites; 2 = 6–20 metastatic sites; 3 = > 20 lesions but not a superscan; 4 = superscan (i.e., $> 75\%$ of the ribs, vertebrae, and pelvic bones)

The Table 2 should be:

Table 2 Summary of darolutamide pharmacokinetic parameters for the single-dose period (fasting and fed conditions)

Parameter	Dose (mg)	n	Day – 5 (fasting)	Day – 2 (fed)
			Geom mean (CV%)	Geom mean (CV%)
AUC, $\mu\text{g}\cdot\text{h/mL}$	300	2	24.2 (36.7)	45.5 (23.7)
	600	4	19.0 (34.8)	63.5 (28.9)
AUC(0– t_{last}), $\mu\text{g}\cdot\text{h/mL}$	300	3	15.7 (69.6)	39.0 (20.1)
	600	6	22.0 (41.4)	55.6 (24.0)
AUC(0– $t_{\text{last}})/D$, h/L	300	3	0.052 (69.6)	0.130 (20.1)
	600	6	0.037 (41.4)	0.093 (24.0)
AUC/D, h/L	300	2	0.081 (36.7)	0.152 (23.7)
	600	4	0.032 (34.8)	0.106 (28.9)
AUC(0–12), $\mu\text{g}\cdot\text{h/mL}$	300	3	8.1 (84.8)	20.4 (15.3)
	600	6	10.8 (38.9)	25.1 (15.3)
AUC (0–12)/D, h/L	300	3	0.027 (84.8)	0.068 (15.3)
	600	6	0.018 (38.9)	0.042 (15.3)
C_{max} , $\mu\text{g/mL}$	300	3	1.05 (92.9)	2.59 (7.57)
	600	6	1.26 (41.3)	3.50 (12.1)
C_{max}/D , 1/L	300	3	0.004 (92.9)	0.009 (7.57)
	600	6	0.002 (41.3)	0.006 (12.1)
$t_{1/2}$, h	300	2	15.2 (2.84)	14.8 (16.4)
	600	4	10.1 (21.2)	14.1 (36.7)
t_{max} , h	300	3	3.05 ^a (2.95–4.97 ^b)	4.92 ^a (2.98–8.00 ^b)
	600	6	4.85 ^a (3.05–4.92 ^b)	6.29 ^a (4.93–7.90 ^b)

AUC area under the concentration versus time curve, AUC(0– t_{last}) AUC from time 0 to time of last data point, C_{max} maximum observed drug concentration, CV% geometric coefficient of variation, D dose-normalized, $t_{1/2}$ half-life, t_{max} time to reach C_{max}

^aMedian

^bRange

The Table 3 should be:

Table 3 Summary of darolutamide pharmacokinetic parameters for multiple-dose period (day 7)

Parameter	Dose, BID (mg)	n	Geom mean (CV%)
AUC _{tau} (0–12) _{md} , $\mu\text{g}\cdot\text{h/mL}$	300	3	44.4 (18.2)
	600	6	58.7 (26.9)
AUC _{tau} (0–12)/D _{md} , h/L	300	3	0.148 (18.2)
	600	6	0.098 (26.9)
$C_{\text{max,md}}$, $\mu\text{g/mL}$	300	3	4.60 (10.3)
	600	6	5.80 (22.0)
$C_{\text{max}}/D_{\text{md}}$, 1/L	300	3	0.0153 (10.3)
	600	6	0.0097 (22.0)
R_A AUC	300	3	2.18 (26.0)
	600	6	2.34 (27.8)
$R_A C_{\text{max}}$	300	3	1.78 (17.8)
	600	6	1.66 (24.6)
R_{LIN}	300	2	0.910 (4.56)
	600	4	0.961 (13.9)
$t_{\text{max,md}}$, h ^a	300	3	4.98 (3.00–8.10)
	600	6	5.48 (2.87–10.9)

AUC area under the concentration versus time curve, C_{max} maximum observed drug concentration, CV geometric coefficient of variation, D dose-normalized, md multiple dose, R_A accumulation ratio, R_{LIN} mean linearity factor, t_{max} time to reach C_{max}

^aMedian (range)

The Discussion section should read as:

This dose-escalating phase 1 study was the first clinical study to evaluate safety and PK of darolutamide in Japanese patients with mCRPC. Darolutamide administered as a single 300- or 600-mg once-daily dose (with and without food) or as multiple doses of 300 mg BID or 600 mg BID for a

median treatment duration of 84 days (range 31–328) was well tolerated in this heavily treated population, and overall toxicities were consistent with the known safety profile of darolutamide in a previously reported phase 1 trial in a Western study population [13, 17].

Our results show that there are no remarkable differences in PK parameters between Japanese and Western patients with mCRPC [13, 17]. For example, Western patients in the ARAFOR study who were administered a single dose of darolutamide 600 mg had $C_{\max}$ and AUC_{0-48} values approximately twofold greater in the fed versus fasted state compared with 2.8- and 2.5-fold greater in Japanese patients, and fed-state $t_{\max}$ values of 4.0 versus 6.3 h, respectively [17]. Similar PK results were also observed in the ARADES study in which Western patients received a daily dose of 200–1800 mg of darolutamide. On day 1, median $t_{\max}$ values were 3.0–5.1 and 1.5–5.0 h for darolutamide and keto-darolutamide, respectively. At steady state, mean half-life of darolutamide was 15.8 h, independent of dose, and 10.0 h for keto-darolutamide [13]. Thus, there is no need for dose adjustment of darolutamide based on Japanese ethnicity. Similar to the Western patient studies, a significant food effect was observed on the bioavailability of darolutamide in that absorption was slower in the fasted condition, and AUC and $C_{\max}$ were increased twofold along with a prolongation of $t_{\max}$ under fed conditions. As the current Japanese PK data support the PK findings observed in previous Western patient population studies, these collective absorption and exposure data suggest that darolutamide should be taken with food. Finally, $C_{\max}$ and $AUC(0-t_{\text{last}})$ of darolutamide increased by dose, while the accumulation ratios for darolutamide calculated from $C_{\max}$ ($R_A C_{\max}$) and AUC ($R_A AUC$), as well as the R_{LIN} of PK after repeated administration of 300 and 600 mg, were comparable for the two tested doses, suggesting that the PK of each dose was linear over time.

All patients in this study had received prior systemic treatment for mCRPC, which likely affected the observed efficacy of darolutamide. A complete response or partial response was not reported at either dose level; however, seven patients had a history of extensive anticancer treatment that included new AR antagonist agents (abiraterone and enzalutamide) and/or chemotherapy (docetaxel and cabazitaxel). Similarly, only 1 patient achieved a PSA response (patient had a PSA decline $\geq 50\%$ from baseline at week 12), which is not unexpected, considering that all patients had received previous therapy for mCRPC.

Similar to previous early-phase clinical studies in mainly Western patients, most AEs were Grade 1–2 [13, 17], and drug-related TEAEs included vomiting, headache, decreased appetite, increased amylase, and pyrexia. Only 1 serious TEAE (Grade 3 nausea) was considered drug related. All laboratory toxicities were considered unrelated

to darolutamide treatment except for amylase increase in one patient (600 mg BID). ECG findings were not clinically significant, and darolutamide had no observed effect on FSH, LH, testosterone, or DHT concentrations. Overall, a dose-dependent increase in the frequency or severity of AEs was not observed. Our results confirmed that darolutamide has a favorable toxicity profile in Japanese mCRPC patients.

A limitation of the study is that any prior systemic anticancer therapy was allowed, confounding evaluation of efficacy in this heavily pretreated patient population; it is not known whether the main objectives of the study (ie, safety and PK assessments) were affected by pretreatment. Additionally, with only three and six patients having received darolutamide 300 and 600 mg, respectively, the sample sizes were too small to reliably demonstrate dose proportionality.

The funding section should read as:

Funding Bayer Yakuhin, Ltd. sponsored the study.

The References section should read as:

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