Name of Sponsor/Company: Astellas Pharma Global Development, Inc. (APGD)		
Name of Finished Product: Xtandi®		
Name of Active Ingredient: Enzalutamide		

SYNOPSIS

Title of Study: A Phase 2 Study Determining Safety and Tolerability of Enzalutamide (Formerly MDV3100) in Combination with Abiraterone Acetate in Bone Metastatic Castration-resistant Prostate Cancer Patients

Coordinating Investigator: [redacted]

Study Center: 1 center in the United States

Publication Based on the Study: Efstathiou E, Titus MA, Wen S, SanMiguel A, Hoang A, De Haas-Amatsaleh A, et al. Enzalutamide (ENZA) in Combination with Abiraterone Acetate in Bone Metastatic Castration-resistant Prostate Cancer Patients (mCRPC). Eur Urol. 2018. Will update with volume/issue/pg upon publication

Study Period: Primary analysis data cut-off point 30 Aug 2015; The end-of-study follow-up data are presented in the current clinical study report (CSR).

Study Initiation Date (Date of First Enrollment): 09 Jul 2012

Study Completion Date (Date of Last Evaluation): 04 Jan 2018

Phase of Development: 2

Objectives: The primary objective of the study was to explore the safety and tolerability of enzalutamide in combination with abiraterone acetate plus prednisone. The secondary objectives of the study were to explore the effect of enzalutamide in combination with abiraterone acetate plus prednisone on androgen receptor (AR) signaling and androgen levels and to explore the antitumor activity of enzalutamide in combination with abiraterone acetate plus prednisone as assessed by serum prostate-specific antigen (PSA), imaging of soft tissue and bone metastases and markers of bone metabolism. The exploratory objective was to measure predose concentrations of abiraterone acetate on days 4 and 29 (optional).

Methodology: This was an open-label study to determine the safety and tolerability of enzalutamide at 160 mg once daily in combination with abiraterone acetate (from here on only called “abiraterone”) at 1000 mg once daily plus prednisone at 5 mg twice daily until disease progression in castration-resistant prostate cancer (CRPC) subjects with bone metastases by clinical evaluations at protocol specified intervals. Disease progression was defined as a composite endpoint consisting of clinical deterioration, radiographic progression or PSA progression according to the Prostate Cancer Clinical Trials Working Group 2 (PCWG2) criteria.

The following assessments of prostate cancer status were collected during the course of the study: soft tissue disease on computed tomography (CT) scan or on magnetic resonance imaging (MRI), bone disease on radionuclide bone scans and PSA. The evaluations also included the determination of the progression-free survival and measurements of markers of the bone metabolism. In addition, the study determined androgen and androgen precursor levels in bone marrow aspirate and blood by liquid chromatography mass spectrometry. Furthermore, the modulation of AR receptor signaling and its expression and subcellular localization in bone marrow biopsies and the presence of known and assessable splice variants and cytochrome P450 (CYP) 17 expression in epithelial and host compartment of the cancer were assessed. Tumor tissue was collected to determine AR signaling and candidate pathways that might be part of a signaling network implicated in therapy resistance. Archival tumor tissue samples were collected to allow for tumor profiling.

Throughout the study, safety and tolerability were assessed by recording of adverse events (AEs), monitoring of vital signs, safety laboratory evaluations, physical examinations, 12-lead electrocardiograms (ECGs), imaging (multigated acquisition scan) and assessment of Eastern Cooperative Oncology Group performance status. The occurrence of an AE or toxicity, where continued administration of study drug was deemed to be not in the subject's best interest by the investigator and/or the sponsor, resulted in the removal of the subject from therapy. For the duration of the study, all subjects were to maintain androgen deprivation with a gonadotropin releasing hormone (GnRH) agonist or antagonist or orchiectomy.

Pharmacokinetic blood samples for determination of plasma concentrations of abiraterone acetate were collected predose on days 4 and 29. In addition, pharmakokinetic blood samples for determination of plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 were collected predose on day 29.

The study drug was to be administered until disease progression (a composite endpoint, consisting of clinical deterioration, radiographic progression or PSA progression according to the PCWG2 criteria).

Subjects were excluded from the study if 1 of the study drugs (enzalutamide, abiraterone or prednisone) was discontinued. All subjects discontinuing the study drugs for any reason were to have a safety follow-up visit 30 days after their last dose of study drug or prior to initiation of subsequent anti-neoplastic therapy for prostate cancer, whichever occurred first.

Number of Patients (Planned, Enrolled and Analyzed): Sixty men were planned to receive doses of the study drug. Sixty men were enrolled into the study. All 60 subjects (100%) received at least 1 dose of any study drug (enzalutamide, abiraterone and prednisone) and were included in the Safety Analysis Set (SAF). The Plasma Evaluable Set and the Biomarker Evaluable Set (BES) included between 37 subjects (61.7%) and 52 subjects (86.7%) who had available results for the baseline and end-of-treatment (ET) assessments of the respective parameters. Seventeen subjects (28.3%) for whom at least 1 pharmacokinetic predose concentration was available were included in the Pharmacokinetic Analysis Set. All efficacy and safety analyses were performed on the SAF.

Diagnosis and Main Criteria for Inclusion: Subjects were men with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features and presence of metastatic disease to the bone at the screening visit. The subjects had ongoing androgen deprivation therapy with a GnRH analog or orchiectomy (i.e., surgical or medical castration).

Test Product, Dose and Mode of Administration, Batch Numbers: Enzalutamide, 160 mg (4 capsules 40 mg each), given orally once daily with/without food, from batch numbers CLR77222-001, CLR77222-002, CLR77222-003, CLR77222-004, CLR77222-005 and CLR77222-006; abiraterone, 1000 mg (4 tablets 250 mg each), given orally at least 2 hours before a meal or 1 hour after a meal; prednisone, 5 mg, given orally twice daily.

Duration of Treatment: All subjects were treated until disease progression.

Reference Product, Dose and Mode of Administration, Batch Numbers: None.

Criteria for Evaluation:

Efficacy: The effect of enzalutamide on blood and bone marrow testosterone and androgen precursors such as cortisol, androstenedione, pregnenolone and progesterone; the modulation of AR signaling and its subcellular localization in bone marrow biopsies; the presence of known and assessable splice variants and CYP17 expression in epithelial and host compartment of the cancer; antitumor activity as assessed based on PSA results, CT/MRI (Response Evaluation Criteria in Solid Tumors [RECIST] 1.1) and bone scan results (PCWG2 criteria), progression-free survival and markers of bone metabolism (urine N-telopeptide and bone specific alkaline phosphatase).

Safety: AEs, clinical laboratory test results (hematology, biochemistry and parameters of coagulation), vital sign measurements (blood pressure, pulse rate and body temperature), physical examinations and 12-lead ECG results.

Pharmacokinetics: Predose concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 on day 29 and of abiraterone on days 4 and 29.

Statistical Methods:

Efficacy: Efficacy analysis was conducted on secondary variables and was reported for the SAF.

Androgens, androgen receptor signaling, androgen precursors and other associated metabolites:

For each biomarker (testosterone, cortisol, androstenedione, pregnenolone and progesterone), descriptive statistics were provided for baseline, week 9, change from baseline and percent change from baseline. Summaries of change and percent change from baseline to ET were presented for BES subjects who had an ET assessment of the corresponding biomarker parameter sample. Baseline and postbaseline biomarker results were also presented graphically using waterfall plots. Biomarker results collected at baseline and at week 9 were compared using the paired t-test or the Wilcoxon signed rank test. For each biomarker,

summaries of baseline, postbaseline, change from baseline and percent change from baseline were also presented by PSA response category, where PSA response was defined as at least 50% reduction (improvement) in PSA from baseline to week 9 in the SAF. The correlation between each biomarker and the PSA level at baseline and at week 9 was estimated using Spearman's method.

Antitumor Activity:

- PSA: Baseline, postbaseline, change from baseline and percent change from baseline values of PSA measurements were summarized descriptively. The best PSA response was the largest decline in PSA, expressed as the percentage change from baseline that occurred at any time point after treatment start and was presented for the following time intervals: over the first 12 weeks of treatment, up to and including the ET visit and up to and including the end of study visit. The number (%) of subjects with a ≥ 30%, ≥ 50% and ≥ 90% decline and with the largest decline from baseline as well as undetectable values in PSA blood concentration were tabulated per visit over time (as appropriate) and as nadir.
- CT/MRI and bone scan: The number (%) of subjects with tumor identification results (i.e., target, non-target, new, bone) and lesion location (e.g., bone, breast, colorectal, kidney, etc.) was summarized. The overall objective response assessment was based on RECIST version 1.1 for soft tissue lesion on CT/MRI and the PCWG2 guidelines for bone lesions on bone scans. Time Point Response for target and non-target lesions (RECIST), RECIST Overall Time Point Response, Time Point Response for bone lesions (PCWG2) and the Overall Time Point Response were determined. The numbers (%) of subjects for the above variables were tabulated per visit over time. Also the numbers (%) of subjects with the best overall response per RECIST 1.1, during the entire investigational period was summarized. In addition to that, the numbers (%) subjects with objective response (complete response [CR] or partial response [PR]) were summarized.
- Progression-free survival and time to study discontinuation: Subjects without radiologic disease progression or clinical disease progression or PSA progression or death were censored at the last known date to be alive and progression free. Time to study drug discontinuation was calculated as the number of days from start of the study drug to the date of last dose of the study drug using the SAF and subjects still on study drug as of the data cutoff date were right censored. The Kaplan-Meier method was used to draw the survival curves for both parameters. Also, the median, 25% and 75% percentile of survival time was tabulated, including the corresponding 95% confidence interval (CI) using a robust non-parametric method (Brookmeyer and Crowley). The number of events and subjects at risk over time (at visit dates) was also tabulated.
- Markers of Bone Metabolism: Baseline, postbaseline, change from baseline and percent change from baseline values in bone specific alkaline phosphatase (µg/L) and in urine N-telopeptides (nmol BCE/mmol creatinine) were summarized descriptively.

Safety:

Adverse event: All summaries of AEs, unless otherwise stated, included treatment-emergent adverse events (TEAEs) only. AEs were coded by system organ class (SOC) and preferred term using MedDRA version 12.0 and graded using National Cancer Institute's Common Terminology Criteria for Adverse Events version 4.03. Descriptive statistics were tabulated for the AEs. The number and percentage of subjects with AEs were presented by MedDRA SOC and preferred term.

Clinical laboratory: Severity of each clinical laboratory parameter was calculated using the NCI CTCAE version 4.03. Quantitative clinical laboratory variables (i.e., hematology, biochemistry, coagulation and liver function tests) were summarized descriptively by visit. Additionally, a within-subject change from baseline was summarized for each postbaseline visit. Each quantitative laboratory result was classified as low (L), normal (N) or high (H) at each visit according to the laboratory supplied reference ranges. The incidence (and percentage) of subjects with these classifications was presented in shift tables from baseline to each particular postbaseline visit by laboratory parameter and visit. Clinically significant values in liver function test and their shift from baseline were summarized.

Vital signs were summarized descriptively by visit. Additionally, a within-subject change from baseline was summarized by visit. Figures of the mean change from baseline over time by visit were prepared for all vital signs. Each vital signs result was classified as L, N or H at each visit according to the vital signs reference ranges. Shift tables indicating shifts between baseline and postbaseline measurements by visit were presented.

Physical examination findings were only listed within the medical history or AE listings as appropriate.

12-Lead ECG: Baseline, postbaseline and their changes from baseline in ECG values were to be presented using descriptive statistics. Also overall ECG interpretation (i.e., normal, abnormal-not clinically significant and abnormal-clinically significant) as reported by the investigator was tabulated by visit. Shift tables indicating shifts between baseline and postdose measurements were presented by visit. A listing of all ECG outcomes was presented. A separate listing of subjects with CTCAE grade 3 or 4 based on prolonged corrected QT interval (QTc; i.e., QTc > 0.5 second), life-threatening signs or symptoms (e.g., arrhythmia, chronic heart failure, hypotension, shock, syncope, torsade de pointes) was also provided.

Pharmacokinetics: Individual and mean predose plasma concentrations of enzalutamide and its metabolites MDPC0001 and MDPC0002 at day 29 were summarized using descriptive statistics. Plasma concentrations of abiraterone at day 4 and day 29 were listed by subject.

Summary of Results/Conclusions:

Population:

A total of 60 subjects were enrolled, 11 (18.3%) of whom remained on study as of the primary data cutoff date (30 Aug 2015); 49 subjects (81.7%) discontinued treatment; 13

subjects (21.7%) had completed the 30-day safety follow-up visit before 30 Aug 2015. Of the 11 subjects who continued treatment, the remainder mainly discontinued treatment due to other reasons (7 subjects [11.7%]) and disease progression (3 subjects [5.0%]). Other reasons included rolling over into Study 9785-CL-0123 (4 subjects).

The demographics, other baseline characteristics and baseline disease history were reported in the primary analysis CSR.

Efficacy/Pharmacokinetic Results:

Androgen, Androgen Receptor Signaling, Androgen Precursors and Other Associated Metabolites

The bone marrow and plasma summaries of androgen and androgen precursor results and assessments of AR intensity and splice variants are available in the primary CSR.

Antitumor Activity

All 60 subjects were evaluable for PSA analysis (i.e., they had had a baseline assessment and at least 1 postbaseline assessment). Over the first 12 weeks, the median percent largest decline from baseline in PSA was −80.8%. Similar results were obtained for the time periods up to and including the ET visit and up to and including the end of study visit, showing that the main PSA decline occurred within the first 12 weeks of treatment. Over the entire study period, 52 of 60 subjects (86.7%) had a ≥ 30% reduction in PSA from baseline, 46 of 60 subjects (76.7%) had a ≥ 50% reduction and 30 of 60 subjects (50.0%) had a ≥ 90% reduction. At week 5, 49 of 59 subjects (83.1%) had a ≥ 30% reduction in PSA from baseline, 42 of 59 (71.2%) had a ≥ 50% reduction and 11 of 59 (18.6%) had a ≥ 90% reduction. Similar results were observed at week 13, except that the percentage of subjects who had a ≥ 90% reduction in PSA had more than doubled (24 of 52 subjects [46.2%]) compared to week 5. Additionally, similar results were seen at weeks 61, 109, 157 and 205.

The Best Overall Response incorporated both the RECIST Overall Time Point Response assessment for soft tissue lesions by CT/MRI and the response assessment of bone lesion according to PCWG2. At the ET visit, 52 subjects had results for the Best Overall Response. Therefore, of the 60 subjects in the study, 3 (5.0%) had PR, 21 (35.0%) had progressive disease (PD) and 28 (46.7%) had non-CR and non-PD. There was 1 subject (1.7%) with CR (bone lesion response) at week 157; otherwise, Best Overall Response per RECIST 1.1 did not change since primary analysis and a summary is available in the primary CSR.

In the Kaplan-Meier analysis, the median progression-free survival time was 251 days (95% CI: 147.0, 337.0).

Mean and median urine N-telopeptide increased during the treatment. The mean (SD) and median percent increase from baseline to week 9 was 71.93% (150.87%) and 37.7%. At the ET visit, the mean (SD) and median percent increase from baseline was 69.16% (82.95%) and 75.9%. The variability among subjects was high; therefore these results should be treated with caution. A notable decline in bone-specific alkaline phosphatase had occurred

by week 13 (mean [SD] percent decrease from baseline of −14.82 % [39.750] and median percent decrease of −11.11%). This decline continued thereafter until week 37.

In the Kaplan-Meier analysis, the median time to study discontinuation was 307.5 days (95% CI: 196.0, 477.0).

Pharmacokinetics

The mean (SD) plasma concentrations for enzalutamide, M1 and M2 metabolites are available in the primary CSR.

Safety Results:

Adverse Events

By the last evaluation data cutoff date (26 Feb 2018), all 60 subjects (100%) in the SAF reported at least 1 TEAE. Of these, 56 (93.3%) had enzalutamide-related TEAEs, 58 (96.7%) had abiraterone-related TEAEs and 16 (26.7%) had prednisone-related TEAEs. A total of 9 subjects (15.0%) reported serious TEAEs; these events were abiraterone-related in 2 subjects (3.3%) (femur fracture and urosepsis). None of the serious TEAEs were related to enzalutamide or prednisone. Three subjects (5.0%) discontinued treatment with enzalutamide due to TEAEs. None of these events were related to any of the study drugs. One subject (1.7%) experienced 2 abiraterone-related TEAEs (alanine aminotransferase [ALT] increased and aspartate aminotransferase [AST] increased) resulting in discontinuation of abiraterone only. The subject was not immediately withdrawn from the study and continued treatment with enzalutamide and prednisone (which was considered a protocol deviation). No deaths were reported as of the data cutoff date.

The most frequently reported TEAEs (in > 20 subjects [35%]) were fatigue (43 subjects [71.7%]), hyperglycemia (41 subjects [68.3%]), blood alkaline phosphatase increased (32 subjects [53.3%]), hot flush (27 subjects [45.0%]), AST increased (22 subjects [36.7%]) and anemia (21 subjects [35.0%]).

The most frequently reported enzalutamide-related TEAEs (in ≥ 25% of subjects) were fatigue (35 subjects [58.3%]), hot flush (23 subjects [38.3%]), hypertension (18 subjects [30.0%]), AST increased (17 subjects [28.3%] each) and ALT increased (15 subjects [25.0%]). The most frequently reported abiraterone-related TEAEs (in ≥ 25% of subjects) were hot flush (26 subjects [43.3%]), fatigue (20 subjects [33.3%]), AST increased (17 subjects [28.3%]), ALT increased (16 subjects [26.7%]) and hypertension (14 subjects [23.3%]). The most frequently reported prednisone-related TEAEs (in ≥ 5% of subjects) were hyperglycemia (5 subjects [8.3%]), AST increased (4 subjects [6.7%]), ALT increased and white blood cell count decreased (3 subjects [5.0%] each).

No subject experienced TEAEs with a NCI CTCAE grade of 4 or 5. The most frequently reported grade 3 TEAEs (in ≥ 5% of subjects) were hypertension (10 subjects [16.7%]), ALT increased (7 subjects [11.7%]), blood alkaline phosphatase increased and arthralgia (3 subjects [5.0%] each).

Clinical Laboratory Evaluations

No clinically relevant changes or trends were observed in mean hematology test results and most subjects had hematological parameters within the normal range, including hemoglobin, platelets and white blood cell counts. NCI CTCAE grade 4 hematology results were only seen in 5 subjects during the 30-day Safety Follow-Up Visit. A worsening of 2 grades compared to baseline occurred in > 1 subject in platelets below normal (ET visit only) and hemoglobin below normal (ET visit and 30-day Safety Follow-up visit). The most common TEAEs (in ≥ 10% of subjects) reported for hematology parameters were white blood cell count decreased, platelet count decreased, neutrophil count decreased and lymphocyte count decreased.

No clinically relevant changes or trends were observed in mean biochemistry test results and most subjects had biochemistry parameters within the normal range. NCI CTCAE grade 4 biochemistry results were experienced by 2 subjects (ALT above normal at an unscheduled visit and creatinine above normal at week 109). A worsening of ≥ 2 grades at the ET visit compared to baseline occurred in 2 subjects for potassium below normal and phosphate below normal, and in 1 subject for alkaline phosphatase above normal (grade 1 to grade 3), AST above normal (grade 0 to grade 3) and ALT above normal (grade 0 to grade 3) and bilirubin above normal; a worsening of ≥ 2 grades at the 30-day Safety Follow-up visit compared to baseline occurred in 1 subject in glucose above normal (1 subject, grade 0 to grade 2). The most common TEAEs (in ≥ 10.0% of subjects) reported for biochemistry parameters were blood alkaline phosphatase increased, AST increased, ALT increased, blood bilirubin increased and blood magnesium decreased.

Abnormal liver function test: An increase in AST or ALT from ≤ 3 x the upper limit of normal (ULN) at baseline to > 3 x ULN postbaseline occurred in 1 subject for AST and ALT at the ET visit and in no subjects at the 30-day Safety Follow-up Visit. Twelve subjects had TEAEs classified as potential drug-induced liver injury cases.

No clinically relevant changes or trends were observed in mean coagulation test results. No subjects had NCI CTCAE grade 4 coagulation results. At the ET visit, 2 subjects had a worsening in coagulation parameters at week 9 compared to baseline; no subjects had a worsening in coagulation parameters at the 30-Day Safety Follow-Up visit compared to baseline. TEAEs for coagulation parameters were reported for activated partial thromboplastin time prolonged (8 subjects [13.3%]; in 1 subject assessed as related to all 3 study drugs) and international normalized ratio (1 subject [1.7%]; unrelated).

Vital Signs and Electrocardiogram

No clinically relevant changes or trends were observed in mean vital sign results (systolic and diastolic blood pressure, pulse rate and temperature) or weight. No clinically significant ECGs were reported.

CONCLUSIONS:

This was an open-label study to determine the safety and tolerability of enzalutamide in combination with abiraterone plus prednisone in CRPC subjects with bone metastases. The

study also aimed to explore the effect of this study drug combination on AR signaling and androgen levels and to explore antitumor activity, as assessed by serum PSA, imaging of soft tissue and bone metastases and markers of bone metabolism.

A total of 60 male subjects were enrolled, of these 11 (18.3%) remained on study as of the primary data cutoff date (30 Aug 2015). Of the 11 subjects who continued treatment, the remainder mainly discontinued treatment due to other reasons (7 subjects [11.7%]) and disease progression (3 subjects [5.0%]). Other reasons included rolling over into Study 9785-CL-0123 (4 subjects).

Clinical efficacy of enzalutamide in combination with abiraterone and prednisone was noted both radiographically and by PSA response. At the ET visit, 52 subjects had results for the Best Overall Response. Therefore, of the 60 subjects in the study, 3 (5.0%) had PR, 21 (35.0%) had PD and 28 (46.7%) had non-CR and non-PD. There was 1 subject (1.7%) with CR (bone lesion response) at week 157. Over the entire study period, 52 subjects (86.7%) had a ≥ 30% reduction in PSA from baseline and 30 subjects (50.0%) had a ≥ 90% reduction. The median progression-free survival time was 251 days (approximately 8.4 months).

Assessments of bone marrow and blood androgen/androgen precursors at baseline and week 9 were consistent with the feedback response expected from this combination of study drugs, namely decreased cortisol and decreased androgens.

The mean (SD) enzalutamide plasma concentration at day 29 was 11.05 (3.311) µg/mL and the mean (SD) plasma concentrations of the M1 and M2 metabolites at day 29 were 3.45 (2.397) µg/mL and 9.36 (2.754) µg/mL, respectively. However, it could not be confirmed whether all samples were drawn predose, which affects the interpretation of these results.

The combination of enzalutamide with abiraterone plus prednisone appears to be safe and well tolerated. The most frequently reported TEAEs (in > 20 subjects [35%]) were hyperglycemia, fatigue, blood alkaline phosphatase increased, hot flush, AST increased and anemia. A total of 28 subjects (46.7%) experienced 66 TEAEs assessed as NCI CTCAE grade 3. The most frequently reported grade 3 TEAEs were hypertension, ALT increased, blood alkaline phosphatase increased and arthralgia. No subjects experienced grade 4 or 5 TEAEs. No drug-related TEAEs led to discontinuation of enzalutamide and no subjects experienced NCI CTCAE grade 4 or 5 TEAEs. Only 2 subjects experienced serious TEAEs that were considered related to abiraterone (femur fracture and urosepsis). The results for clinical laboratory evaluations, vital signs and ECGs revealed no clinically relevant trends.

The overall favorable safety profile of enzalutamide with abiraterone plus prednisone in conjunction with the anti-tumor activity noted suggests a positive benefit-risk assessment for this combination of drugs in CRPC patients with bone metastases.

Date of Report: 26 Nov 2018