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Androgen Receptor Modulation Optimized for Response (ARMOR) Phase I and II Studies: Galeterone for the Treatment of Castration-Resistant Prostate Cancer

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ABSTRACT

Purpose: Galeterone is a selective, multitargeted agent that inhibits CYP17, antagonizes the androgen receptor (AR), and reduces AR expression in prostate cancer cells by causing an increase in AR protein degradation. These open-label phase I and II studies (Androgen Receptor Modulation Optimized for Response-1 [ARMOR1] and ARMOR2 part 1) evaluated the efficacy and safety of galeterone in patients with treatment-naive nonmetastatic or metastatic castration-resistant prostate cancer (CRPC) and established a dose for further study.

Experimental Design: In ARMOR1, 49 patients received increasing doses (650-2,600 mg) of galeterone in capsule formulation; 28 patients in ARMOR2 part 1 received increasing doses (1,700-3,400 mg) of galeterone in tablet formulation for 12 weeks. Patients were evaluated biweekly for safety and efficacy, and pharmacokinetic parameters were assessed.

Results: In ARMOR1, across all doses, 49.0% (24/49) achieved a ≥30% decline in prostate-specific antigen (PSA; PSA30) and 22.4% (11/49) demonstrated a ≥50% PSA decline (PSA50). In ARMOR2 part 1, across all doses, PSA30 was 64.0% (16/25) and PSA50 was 48.0% (12/25). In the 2,550-mg dose cohort, PSA30 was 72.7% (8/11) and PSA50 was 54.5% (6/11). Galeterone was well tolerated; the most common adverse events were fatigue, increased liver enzymes, gastrointestinal events, and pruritus. Most were mild or moderate in severity and required no action and there were no apparent mineralocorticoid excess (AME) events.

Conclusion: The efficacy and safety from ARMOR1 and ARMOR2 part 1 and the pharmacokinetic results support the galeterone tablet dose of 2,550 mg/d for further study. Galeterone was well tolerated and demonstrated pharmacodynamic changes consistent with its selective, multifunctional AR signaling inhibition.

TRANSLATIONAL RELEVANCE

Despite the recent advances in the understanding and treatment of metastatic castration-resistant prostate cancer (mCRPC), it remains a lethal disease. Androgen receptor (AR) signaling remains a primary target of therapy, as the understanding of both the disease and mechanisms of resistance expand. Galeterone, a selective, multitargeted agent, is distinct from other mCRPC therapies in that it combines the mechanisms of current agents—CYP17 inhibition and AR antagonism—with the novel mechanism of increasing AR protein degradation. These first assessments of galeterone in mCRPC identified a well-tolerated dose that resulted in clinically significant reductions in prostate specific antigen, and demonstrate the potential of this agent. *In vitro* data and results of these studies have informed future investigation of galeterone, which will include AR-related biomarker analyses.

INTRODUCTION

Despite recent advances in the treatment of castration-resistant prostate cancer (CRPC), prostate cancer remains the second most common cancer-related mortality in men in the United States (1). The development of a new generation of therapies targeting the androgen axis has been based on an expanded understanding of the molecular mechanisms of CRPC. It is now understood that in the clinical setting of castrate levels of serum testosterone, prostate tumors adapt by upregulating tissue androgens and androgen receptors (AR) in order to maintain proliferation. Tumor androgen levels remain sufficiently elevated to stimulate ARs as a result of tumor conversion of circulating adrenal androgens and de novo androgen synthesis (2–5). Additionally, prostate cancer adapts to androgen-deprivation therapy by AR gene amplification, upregulation of AR transcripts, or protein expression (6, 7). Thus, inhibition of the synthesis of nongonadal androgens and blockade of AR remain key targets in CRPC therapy.

Abiraterone and enzalutamide have improved outcomes for patients with metastatic CRPC (mCRPC). Although abiraterone and enzalutamide have been shown to improve overall survival (OS), these agents are not curative and not without safety and tolerability issues (8–11). In addition, a significant proportion of patients do not respond; and in those who do respond, therapy will eventually fail because of the development of resistance (9, 10, 12–14). A major component of resistance to second-generation AR targeting agents may be mediated by AR splice variants, such as AR-V7, which are produced in tumor cells as a result of aberrant RNA splicing of the wild-type AR transcript. The resultant truncated AR protein lacks the C-terminal domain to which androgen binds and is the primary site of action of nonsteroidal antiandrogens such as enzalutamide. Furthermore, splice variants have been shown to be constitutively active transcription factors, leading to the activation of androgen-responsive genes even at castrate levels of androgens (15, 16). Mutations in the AR may also contribute to resistance in CRPC, and AR point mutations allow activation of the receptor by nonphysiologic ligands (e.g., cortisol, progesterone, flutamide, bicalutamide) (17, 18, 19). As a result, androgen-independent, but AR-dependent, tumor growth occurs, and tumors become resistant to therapeutic agents that alter androgen production (e.g., abiraterone) or antagonize binding to the AR (e.g., bicalutamide, enzalutamide). Recent data demonstrated that patients with detectable circulating tumor cells harboring AR-V7 had inferior responses to abiraterone or enzalutamide, including inferior prostate-specific antigen (PSA) response, clinical and radiographic progression-free survival (PFS), and poor OS (12, 13).

Galeterone is a selective, multitargeted agent that disrupts androgen signaling at multiple points in the pathway. Preclinical data have shown that galeterone is a selective potent CYP17 inhibitor and a potent AR antagonist, but unlike other available agents that target androgen signaling, galeterone reduces AR expression in prostate cancer cells by causing an increase in AR protein degradation (20–26). Preclinical *in vitro* and *in vivo* data have shown that galeterone treatment in prostate cancer models resulted in a significant reduction in both full-length AR and AR-V7 splice variant levels. In addition, galeterone has been shown to have activity against AR point mutations T878A (20-25) and, in preliminary findings, to have activity in cells expressing the AR point mutation F876L (27).

This paper reports the safety and efficacy of galeterone in a phase I study, Androgen Receptor Modulation Optimized for Response (ARMOR1), and the dose-escalation component of the phase II ARMOR2 study (ARMOR2 part 1). The dose-escalation component of ARMOR2 was conducted to determine the phase II and phase III dose of a galeterone spray dry dispersion (SDD) tablet. This formulation was developed after a healthy volunteer study confirmed a significant food effect with the capsule formulation that was used in ARMOR1 (**Supplementary Data**). The SDD tablet formulation was shown in a healthy volunteer study to not be affected by food, providing similar exposure (area under the concentration-time curve [AUC]) in fed and fasted states (28). Results of this study also demonstrated equivalent serum concentrations using either 1,700 mg of the SDD tablet or 2,600 mg of the capsule, which was the highest dose studied in ARMOR1. Thus, the dose-escalation portion of ARMOR2 was conducted to evaluate the safety and tolerability of escalating doses of the SDD formulation and to determine the recommended dose for ARMOR2 part 2 and ARMOR3.

PATIENTS AND METHODS

Patients

Eligible men had histologically confirmed nonmetastatic (M0) or metastatic (M1) adenocarcinoma of the prostate, a life expectancy of >12 weeks, and progressive disease despite ongoing androgen-deprivation therapy. Patients were required to have progressive disease according to Prostate Cancer Clinical Trials Working Group 1 [PCWG1] criteria(29) in ARMOR1, or PCWG2 criteria(30) in ARMOR2 part 1, ongoing treatment with gonadotropin-releasing hormone analogs or orchiectomy (serum testosterone <50 mg/dL), and an Eastern Cooperative Oncology Group (ECOG) performance status of ≤1. ARMOR1 excluded patients who had previously received chemotherapy, ketoconazole, abiraterone, or enzalutamide. ARMOR2 part 1 permitted the enrollment of abiraterone-refractory patients, provided it had been discontinued ≥4 weeks before enrollment and that the duration of therapy was ≥6 months before PSA progression or >6 weeks with documentation of an initial response followed by PSA progression. Previous ketoconazole treatment was permitted upon agreement between the investigator and the study sponsor. Patients with nonhepatic visceral metastases and/or tumor-associated bone pain that required active pain management were excluded from ARMOR1. Patients with indeterminate lung nodules were eligible. Other exclusion criteria included any previous radium-223, strontium, or samarium therapy within 8 weeks of enrollment; radiation therapy ≤4 weeks before enrollment or completed radiotherapy in ARMOR1; or radiation therapy ≤3 weeks (≤2 weeks for single-fraction radiotherapy) in ARMOR2 part 1. Patients were excluded if they had previous treatment with investigational drugs or agents that could have interfered with the efficacy and safety assessments. Patients with abnormal laboratory test results, including serum creatinine level >1.5 times the upper limit of normal (ULN), liver function test results >1.5 x ULN, hemoglobin level ≤9.0 g/dL, platelet count ≤100 x 10^9/L, absolute neutrophil count ≤1.5 x 10^9/L, and serum potassium level <3.5 mmol/L, were ineligible, as were those with serious concurrent illnesses or conditions, including heart failure, uncontrolled hypertension, angina, active autoimmune disease, or gastrointestinal disorders or gastric bypass surgery that could have interfered with study medication absorption. Written informed consent was obtained from participants before enrollment.

Study design

ARMOR1 (NCT00959959) was a phase I, multicenter, open-label, dose-escalation study conducted in collaboration with the Department of Defense Prostate Cancer Clinical Trials Consortium, designed to assess the tolerability, safety, and efficacy of oral galeterone for chemotherapy-naive patients with CRPC. The primary goals were to find the optimal dose of galeterone with an acceptable safety profile, defined as an observed dose-limiting toxicity (DLT) rate of ≤35%, and to identify a dose for further phase II study. The dose equivalence component of ARMOR2 (i.e., part 1; NCT01709734) evaluated the pharmacokinetics (PK), safety, and efficacy of a new formulation of galeterone with improved bioavailability. A micronized powder formulation (capsule) was used in ARMOR1 and an SDD formulation was used in ARMOR2 part 1. These studies were designed and monitored in accordance with Sponsor procedures, which comply with the ethical principles of Good Clinical Practice, as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki and the US Food and Drug Administration regulations. The protocols were approved by the institutional review board of each study site.

In ARMOR1, galeterone capsules (micronized powder, 325 mg) were administered orally as (1) 650 mg in the evening, (2) 975 mg in the evening, (3) 975 mg in the morning, (4) 1,300 mg in the evening, (5) 1,950 mg in the evening, (6) 1,950 mg divided into morning and evening doses, (7) 2,600 mg in the evening, or (8) 2,600 mg divided into morning and evening doses, according to the cohort they entered. All doses were administered with a patient-selected meal, except for the 975 mg morning dose cohort, which received a high-fat, high-calorie nutritional supplement (Novasource® Renal, Nestle HealthCare Nutrition, Florham Park, NJ) in place of the meal. Enrollment target was 6 patients per dose cohort. If an acceptable safety profile was determined by the internal monitoring committee (IMC; DLT rate ≤35% or ≤2 of 6 patients in cohorts of 6 patients), subsequent dose levels and schedules were opened for enrollment. If ≥3 of 6 patients experienced DLTs, dose de-escalation was required. DLTs were defined as any study drug–related grade 3 or higher adverse event (AE; National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) considered to be possibly, probably, or definitely related to the study drug.

In ARMOR2 part 1, galeterone SDD tablets (425 mg) were administered at doses of 1,700 mg, 2,550 mg, and 3,400 mg once daily with the morning meal. Enrollment target was 6 patients per dose level. Dose escalation occurred when no clinically significant grade 2 or greater sustained AEs or serious, unexpected grade 3 or higher AEs occurred in a dose group 2 weeks after the last patient in that cohort received his first dose.

The planned treatment duration of both studies was 12 weeks, with optional extension dosing for eligible patients based on safety and tolerability during the 12-week phase. Extension dosing was continued until the patient withdrew, experienced unacceptable toxicity, the disease progressed, or the patient died.

Assessments

Safety assessments, conducted at baseline and every 2 weeks during the 12-week study and every 4 weeks during the optional extension phase, included physical examination, vital signs, electrocardiogram (ECG), serum chemistry, hematology, urinalysis, and performance status. AEs that occurred during the study and up to 30 days after the last dose of study drug were collected, coded according to Medical Dictionary of Regulatory Activities, version 12.1, and graded using CTCAE version 4.0. PSA was determined at each study visit.

In the first 4 dosing cohorts of ARMOR1, blood samples for PK analysis were obtained predose and at 4 hours on day 1. In the remaining cohorts, blood samples were obtained before (hour 0) and 1, 2, 4, and 6 hours after the first dose on day 1. At all remaining visits, if the regimen for the cohort included a morning dose, blood samples were obtained at 6 hours after their dose; for all other cohorts, blood samples were obtained at any time during the visit. In ARMOR2 part 1, blood samples for PK analyses were obtained before (hour 0) and 2, 3, 4, 5, and 6 hours after the day 1 dose, and predose on days 7, 14, 21, 28, and 84. Additional samples were obtained in consenting patients on day 1 at 8, 12, 16, and 24 hours postdose and on day 84 at 2, 3, 4, 5, 6, 8, 12, 16, and/or 24 hours postdose. Blood samples were also obtained at each study visit of ARMOR2 part 1 for determination of pregnenolone, 17-hydroxyprogesterone, deoxycorticosterone, 11-deoxycortisol, corticosterone, cortisol, dehydroepiandrosterone sulfate (DHEAS), androstenedione, and testosterone concentrations.

DATA ANALYSIS

Efficacy endpoints included the proportion of responders (PSA decrease ≥50% [PSA50] and ≥30% [PSA30]), maximal decrease in PSA from baseline to 12 weeks or PSA nadir, changes from baseline in tumor response as assessed by bone scan and computed tomography or magnetic resonance imaging using PCWG2 and Response Evaluation Criteria in Solid Tumors [RECIST] v1.1). PSA efficacy was based on the intent-to-treat population (ITT), defined as enrolled patients who received at least 1 dose of study drug. Response was based on measurable disease in both studies. Time to progression, PFS defined as the time from first dose of study drug until objective CRPC progression or death, whichever occurred first), and OS were the endpoints assessed in the ARMOR1 extension phase. Descriptive statistics were used for most variables (*n*, mean, standard deviation, median, minimum, and maximum for continuous variables and frequency and percentage for categorical variables).

RESULTS

Patients

Baseline patient and disease characteristics are presented in **Table 1**. In ARMOR1, 49 patients were enrolled in 8 cohorts, with 6 patients in each, except cohort 4, which enrolled 7 patients. Twelve patients discontinued the study before completion of 12 weeks because of treatment-emergent AEs (TEAEs; *n* = 5; nausea, chronic obstructive pulmonary disease exacerbation [event onset before dosing], elevated aspartate aminotransferase/alanine aminotransferase levels [AST/ALT; *n* = 2], acute renal failure [reversible after resolution of rhabdomyolysis, which occurred while the patient was receiving simvastatin therapy and became evident after the patient fell], disease progression [*n* = 5], or withdrawal of consent/personal choice [*n* = 2; **Table 2**]). Twenty-two of the 37 patients who completed the study were eligible for the optional extension phase, and 21 patients were dosed. Overall, all patients received 650 to 2,600 mg galeterone daily for <1 to 20 months. In ARMOR2 part 1, 28 patients were enrolled in 3 dosing cohorts, with 6 patients in the 1,700-mg cohort, 14 in the 2,550-mg cohort (abiraterone-resistant, *n* = 3), and 8 in the 3,400-mg cohort. Six patients discontinued the study before 12 weeks because of TEAEs (*n* = 4; angioedema [in an African American who was receiving the angiotensin-converting enzyme inhibitor, lisinopril], rash, weakness, and tremulousness) or disease progression (*n* = 2). All 3 patients with abiraterone-resistant disease completed the 12-week phase of the study. Nineteen of 22 patients who completed the study participated in the optional extension phase; 2 of the patients with abiraterone-resistant disease were not eligible for the extension because of disease progression **(Table 2).** Overall duration of therapy ranged from <1 month to 14 months.

Safety and tolerability

ARMOR1

Safety reviews were completed after all patients were dosed in each cohort and the IMC recommended continued escalation following review of all doses. There were 2 deaths; 1 from disease progression, and 1 from acute septic shock followed by acute metabolic acidosis and renal failure which was not related to galeterone. All patients experienced at least 1 TEAE during the 12-week phase, with most being mild or moderate in severity (91.5%) and comparable among cohorts. The majority (73%) of the AEs required no action. The most common TEAEs were fatigue (17 patients [34.7%]), increased AST level (16 patients [32.7%]), increased ALT level (15 patients [30.6%]), nausea (12 patients [24.5%]), diarrhea (11 patients [22.4%]), and pruritus (11 patients [22.4%]) **(Table 3)**. The most common treatment-related TEAEs were increased AST level (7 patients [14.3%]), nausea (5 patients [10.2%]), increased bilirubin level (4 patients [8.2%]), fatigue (4 patients [8.2%]), and diarrhea (3 patients [6.1%]). The majority of patients (85.7%) in the extension phase experienced mild or moderate TEAEs that were consistent with those reported during the treatment phase.

ARMOR2 Part 1

Galeterone tablets were well tolerated at all doses, as assessed by the IMC. Safety reviews were completed after all patients were dosed in each cohort, and the IMC recommended continued escalation. Most patients (93%) experienced at least 1 TEAE, with the majority (91%) being grade 1 or 2 in severity and comparable among cohorts. Most (72%) AEs required no intervention. There were no DLTs at any dose level. The most common TEAEs were nausea (13 patients [46.4%]), fatigue (9 patients [32.1%]), pruritus (9 patients [32.1%]), vomiting (8 patients [28.6%]), and decreased appetite (6 patients [21.4%]) **(Table 3)**. The most common treatment-related TEAEs were nausea (10 patients [35.7%]); pruritus (9 patients [32.1%]); fatigue, vomiting, and decreased appetite (6 patients [21.4%] for each); and constipation, diarrhea, increased ALT level, and dizziness (3 patients [10.7%]) for each). While edema and hypokalemia were observed, they were independent events in different patients and no combined apparent mineralocorticoid excess events were seen (**Table 4**).

Pharmacokinetics

The PK analysis plan of ARMOR1 was not designed to fully characterize the PK of galeterone. There was no consistency or dose dependence with respect to plasma concentrations and regimen. There was little or no difference in mean concentrations in the single daily doses, with only the 650-mg dose demonstrating lower mean concentrations, and the PK of the 975-mg dose was no different after the supplement, compared with a patient-selected meal. Dividing the dose did not have a significant effect on exposure (AUC).

The PK analysis plan of ARMOR2 was not designed to fully characterize the PK of galeterone. The ARMOR2 part 1 PK parameters after single doses of 1,700 mg, 2,550 mg, and 3,400 mg of the SDD tablet formulation were similar among doses. Exposure, expressed as AUC from predose to 6 hours postdose (AUC_{0-6}), was 2,646 ± 1,748 h • ng/mL, 2,684 ± 2,043 h • ng/mL, and 2,528 ± 1,529 h • ng/mL for the 1,700-mg, 2,550-mg, and 3,400-mg doses, respectively.

Efficacy endpoints

ARMOR1

The ITT population for PSA efficacy included 49 patients. Across all doses tested, 24 of 49 (49.0%) achieved a PSA30 and 11 of 49 patients (22.4%) demonstrated PSA50 **(Fig. 1A)**. During the study, one patient in the 650-mg/day group discontinued his gonadotropin-releasing hormone analog and one patient in the 975-mg/day group underwent transurethral resection of the prostate. Excluding these patients, across groups the PSA30 was 51.1% (24 of 47) and the PSA50 was 23.4% (11 of 47). An increase in response rate was observed with higher doses. At the 2,600-mg dose, 9 of 12 patients (75.0%) demonstrated a PSA30 and 5 of 12 patients (41.7%) demonstrated a PSA50. There was no difference in PSA response between groups that had divided dosing and groups that had once-daily dosing. Of the evaluable patients (those with measurable target lesions at screening or baseline who had a follow-up scan at the 14-week [final] study visit; *n* = 17), 2 patients had a partial response (PR) and 10 patients had stable disease (SD), according to RECIST. In the extension phase, disease progression ultimately occurred in 20 of the 21 patients. No consistent trends were observed in time to progression (range, 14–592 days), PFS, or OS (shortest: 189 days, cohort 3 [1,300 mg/d]) between treatment cohorts. Best overall response assessed by RECIST was SD in 13 of 17 patients (76.5%) in the extension phase; the remaining 4 patients had disease progression.

ARMOR2 Part 1

The ITT population for PSA efficacy in treatment-naïve patients included 25 patients. Three patients had received prior abiraterone treatment. Across the 3 doses in treatment-naive patients, the decline in PSA from baseline in the ITT population was ≥30% in 16 of 25 patients (64.0%) and ≥50% in 12 of 25 patients (48.0%). In the 2,550-mg dose cohort, 8 of 11 treatment-naive patients (72.7%) had a ≥30% decline in PSA from baseline and 6/11 patients (54.5%) had a ≥50% decline in PSA from baseline. In the 1,700-mg dose cohort 50% (3 of 6 patients) achieved a PSA30 and PSA50. In the 3,400-mg dose cohort, 62.5% (5 of 8 patients) achieved a PSA30 and 37.5% (3 of 8 patients) achieved a PSA50 **(Fig. 1B)**. One patient in the 2,550-mg/d group had only 1 post-baseline PSA measurement (performed at 2 weeks) and 1 patient in the 3,400-mg/day group had no post-baseline measurement of PSA. Excluding these patients, the PSA30 and PSA50 were 80% and 60% in the 2,550-mg/day group, and 71.4% and 42.9% in the 3,400-mg/d group. Of the 3 patients treated with 2,550-mg/d who had prior treatment with abiraterone; 1 patient (33%) achieved PSA30, 1 patient had a maximal percent change of –2%, and 1 patient had an increase from baseline. Of the 26 evaluable patients with measurable disease at baseline, 20 (76.9%) patients had SD and 1 patient had PR at 12 weeks.

Steroidogenic pathway markers

Galeterone resulted in overall reductions in median serum testosterone, DHEAS, and androstenedione concentrations. Median corticosterone level was increased from a median baseline of 204 ng/dL to 1,377.5 ng/dL at week 12, and cortisol and deoxycorticosterone levels were generally unchanged **(Table 5)**.

DISCUSSION

Results of ARMOR1 and ARMOR2 part 1 demonstrated that galeterone, an agent that previous studies have shown inhibits androgen production, blocks the ligand-binding domain of AR, and suppresses AR levels *in vitro*, is safe and shows promising PSA responses in patients with mCRPC. Results from phase I healthy volunteer PK studies and the PK results of ARMOR2 part 1 support a 2,550-mg/d dose of galeterone SDD tablet for use in future trials.

All doses tested had similar safety and tolerability profiles. Results of these studies demonstrate that galeterone is well tolerated in men with CRPC, with infrequent grade 3 and 4 toxicities. The most common treatment-related AEs were nausea, vomiting, fatigue, pruritus, and decreased appetite. Of these events, the vast majority (~90%) were grade 1 or 2 and did not require any intervention. Of note, there were no apparent mineralocorticoid excess AEs, supporting results of preclinical studies demonstrating the specificity of galeterone for CYP17 lyase compared with hydroxylase (19). This hypothesis is further supported by the steroidogenic marker results showing no change in deoxycorticosterone or cortisol and a small increase in corticosterone, relative to a large increase observed with abiraterone even in the absence of coadministration of steroids with galeterone (31). The reductions in testosterone are slightly less than those seen at full dose abiraterone but similar to that found in the dose escalation study(31).

Significant PSA declines were observed with all dose levels. Patients in ARMOR1 had an overall PSA30 and PSA50 of 49% and 22%, respectively, with the highest dose (2,600 mg) showing PSA30 and PSA50 of 75% and 42%, respectively. In ARMOR2 part 1, 2,550 mg of the SDD tablet formulation, the dose found to provide exposure similar to that of 2,600 mg of the capsule, resulted in greater PSA30 and PSA50 of 80% and 60%, respectively. These results are comparable to those observed in phase I and phase II trials of abiraterone and enzalutamide (8, 11, 31). Of note, these results were marginally better than the 3,400-mg (PSA30 = 71%, PSA50 = 43%) and 1,700-mg (PSA30 = 50%, PSA50 = 50%) doses.

Although ARMOR1 showed that increasing the dose resulted in a better PSA response, a phase 1 healthy volunteer PK study showed that the capsule formulation was confounded by a food effect and resulted in exposure that plateaued above 1,950 mg (Appendix) (28). The lack of a clear food effect in ARMOR1 could be attributed to the study design in that the blood sampling strategy was not optimal for assessment of PK parameters, and patient-selected meals precluded assessment of the effect of fat and calories.

ARMOR2 part 1 served as a bridging study between the original capsule formulation and the SDD tablet formulation, which was developed to have improved relative bioavailability over the capsule. In PK studies in healthy volunteers, the SDD tablet was shown to result in dose-related increases in exposure that were similar in fed and fasted states that plateaued at doses above 2,550 mg (32). Additionally, it was found that the exposure after 1,700 mg of the SDD tablet was similar to that with 2,600 mg of the original capsule formulation—the dose in ARMOR1 that resulted in the best efficacy numbers.(28) ARMOR2 part 1 evaluated increasing doses of the SDD tablet formulation starting at the 1,700-mg dose. The PK results of this study showed that there was no increase in exposure with higher doses. Although the lack of increase in exposure between the 1,700-mg and the 2,550-mg dose was not consistent with earlier PK evaluations of the SDD tablet, it could again be attributed to study design, in that the sampling strategy was not optimal for a full PK assessment. The results from the PK, safety and PSA decline data support the choice of the 2,550-mg dose for use in Phase II and III clinical studies. The phase II studies have been completed and are in follow-up, and the phase III study is planned (ARMOR3-SV). The ability of galeterone to target splice variant AR through enhanced degradation suggests that it may have potential activity in tumors expressing these resistant variants. The phase III, ARMOR3-SV study will target splice variant (AR-V7) positive tumors and is based on PSA responses seen patients with C-terminal loss in the treatment naïve cohort of ARMOR2 (33).

CONCLUSION

The efficacy and safety results from ARMOR1 and ARMOR2 part 1, and the PK results from phase I healthy volunteer studies and ARMOR2 part 1 support the recommended dose of galeterone 2550 mg daily taken with food for ARMOR2 part 2 and the phase III study (ARMOR3-SV) using the SDD tablet formulation with improved bioavailability. Galeterone is well tolerated in CRPC patients and demonstrates pharmacodynamic changes consistent with its selective multifunctional AR signaling inhibition. The analysis of galeterone is ongoing in expanded patient cohorts in ARMOR2 part 2 and plans are underway for a phase III trial (ARMOR3-SV) comparing galeterone with enzalutamide in treatment-naive patients with mCRPC whose prostate tumors express the AR-V7 splice variant.

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Table 1. Baseline characteristics

Characteristic	**ARMOR1 (*N* = 49)**	**ARMOR2 Part 1 (*N* = 28)**
Age, median (range), y	68 (47–89)	70 (48–90)
Ethnicity, *n* (%)		
White	43 (87.8)	24 (85.7)
African American or black	3 (6.1)	2 (7.1)
Asian	1 (2.0)	1 (3.6)
Other	2 (4.1)	1 (3.6)
Metastatic disease (M1), *n* (%)	25 (51.0)	24 (85.7)
Bone, *n*	25	24
Nodal, *n*	15	10
Bone and nodal, *n*	9	8
Visceral (liver and/or lung), *n*	7	1
Visceral and bone, *n*	6	1
Visceral and nodal, *n*	3	0
Soft tissue (not nodal, liver, or lung), *n*	17	11
Previous therapies, *n* (%)		
Medical and/or surgical castration	49 (100)	28 (100)
Immunotherapy	1 (2)	2 (7.1)
Radiation therapy	27 (55)	16 (57.1)
Surgery	24 (49)	12 (42.9)
Abiraterone	NA	3 (10.7)
Enzalutamide	NA	0
ECOG, *n* (%)		
0	45 (91.8)	22 (78.6)
1	4 (8.2)	5 (17.9)
Missing	0	1 (3.6)
Gleason score, median (range)[a]	7 (6–10)	8 (6–10)
PSA, median (range), ng/dL	24 (6–200.6)	17.6 (3.3–6,760)

ECOG, Eastern Cooperative Oncology Group; NA, not applicable; PSA, prostate-specific antigen.

[a] Data were missing in 2 patients in ARMOR1 and 1 patient in ARMOR 2 Part 1.

Table 2. Treatment cohorts and patient disposition

ARMOR1 – Galeterone capsules (*N* = 49)				**ARMOR2 Part 1 – Galeterone spray dry dispersion tablets (*N* = 28)**			
Dosing cohort	**Enrolled, *n***	**Completed 12-week study, *n***	**Entered extension phase, *n***	**Cohort**	**Enrolled, *n***	**Completed 12-week study, *n***	**Entered extension phase, *n***
650 mg with meal	6	3	3	1,700 mg	6	6	6
975 mg with meal	6	5	2	2,550 mg	14	11	9
1,300 mg with meal	6	5	3	3,400 mg	8	5	4
1,950 mg with meal	7	5	2				
975 mg with supplement[a]	6	4	4				
1,950 mg divided doses with meal	6	5	2[b]				
2,600 mg with meal	6	5	2				
2,600 mg divided doses with meal	6	5	3				

[a] Novasource® Renal, Nestle HealthCare Nutrition, Florham Park, New Jersey.

[b] Three patients were eligible for the extension phase, however only 2 patients were dosed with galeterone.

Table 3. Treatment-emergent adverse events occurring in >10% of patients in ARMOR1 or ARMOR2 Part 1

	ARMOR1 (N = 49)		**ARMOR2 Part 1 (N = 28)**	
Adverse event	**Grade 1 or 2, *n* (%)**	**Grade 3 or higher, *n* (%)**	**Grade 1 or 2, *n* (%)**	**Grade 3 or higher, *n* (%)**
Abdominal pain	5 (10.2)	0	1 (3.6)	0
Increased alkaline phosphatase level	7 (14.3)	0	0	0
Increased ALT level	7 (14.3)	8 (16.3)	1 (3.6)	3 (10.7)
Decreased appetite	6 (12.2)	0	6 (21.4)	0
Arthralgia	6 (12.2)	0	1 (3.6)	0
Increased AST level	13 (26.5)	3 (6.1)	1 (3.6)	1 (3.6)
Back pain	1 (2.0)	0	3 (10.7)	0
Increased bilirubin level	6 (12.2)	1 (2.0)	0	0
Constipation	5 (10.2)	0	3 (10.7)	1 (3.6)
Cough	7 (14.3)	0	3 (10.7)	0
Diarrhea	11 (22.4)	0	4 (14.3)	1 (3.6)
Dizziness	3 (6.1)	0	3 (10.7)	0
Fall	0	0	3 (10.7)	0
Fatigue	16 (32.7)	1 (2.0)	9 (32.1)	0
Nausea	12 (24.5)	0	13 (46.4)	0
Pruritus	11 (22.4)	0	9 (32.1)	0
Rash	5 (10.2)	0	0	1 (3.6)
Urinary tract infection	4 (8.2)	0	4 (14.3)	0
Vomiting	6 (12.2)	0	8 (28.6)	0
Decreased weight	5 (10.2)	0	4 (14.3)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Table 4. Summary of Potential AME Adverse Events in ARMOR1 or ARMOR2 Part 1

Number of Incidences	Adverse Event	Attribution: related/unrelated[1]
1	Grade 2 hypokalemia	1/0
3	Grade 3 hypokalemia	1/2
1	Grade 1 peripheral edema	0/1
3	Grade 2 peripheral edema	2/1

[1] All events were individual occurrences and not considered AME symptoms

Table 5. Median (range) concentrations of steroidogenic pathway markers in ARMOR2 Part 1

	Median (range)	
Steroid	**Baseline**	**Week 12**
Testosterone, ng/dL	7.5 (3–22)	2 (<1–14)
Androstenedione, ng/dL	32 (7–81)	14 (<5–34)
DHEAS, µg/dL	37.5 (<15–220)	18 (<15–105)
Corticosterone, ng/dL	204 (<20–874)	1,377.5 (97–4,375)
Deoxycorticosterone, ng/dL	<16 (<16–18)	<16 (<16–89)
Cortisol, µg/dL	14.7 (1.8–28.7)	18.1 (4.1–35)

DHEA-S, dehydroepiandrosterone sulfate.

Figure Legend

Figure 1. (A) Maximal percentage change in PSA from baseline at 12 weeks by total daily dose in treatment-naive patients in ARMOR1 (*n* = 49). Patterned data points reflect one patient who discontinued his gonadotropin-releasing hormone analog (650-mg/d group) and one patient who underwent transurethral resection of the prostate (975-mg/d group). (B) Maximal percentage change in PSA from baseline by total daily dose in evaluable treatment-naive patients in ARMOR2 Part 1 (*n* = 25). Patterned data point reflects a patient who only had 1 post-baseline PSA measurement (at 2 weeks). One patient in the 3,400-mg/day group (*n* =8) is not included in the graph because no post-baseline PSA measurements were completed. Abiraterone-refractory patients (N=3) were not included in this analysis. Reference lines: green, –50%; orange, –30%. PSA, prostate-specific antigen.*Maximal PSA values >100% increase from baseline.

Figure Legend

Figure 1. (A) Maximal percentage change in PSA from baseline at 12 weeks by total daily dose in treatment-naive patients in ARMOR1 (n = 49). Patterned data points reflect one patient who discontinued his gonadotropin-releasing hormone analog (650-mg/d group) and one patient who underwent transurethral resection of the prostate (975-mg/d group). (B) Maximal percentage change in PSA from baseline by total daily dose in evaluable treatment-naive patients in ARMOR2 Part 1 (n = 25). Patterned data point reflects a patient who only had 1 post-baseline PSA measurement (at 2 weeks). One patient in the 3,400-mg/day group (n =8) is not included in the graph because no post-baseline PSA measurements were completed. Reference lines: green, –50%; orange, –30%. PSA, prostate-specific antigen.*Maximal PSA values >100% increase from baseline.

Figure 1A.

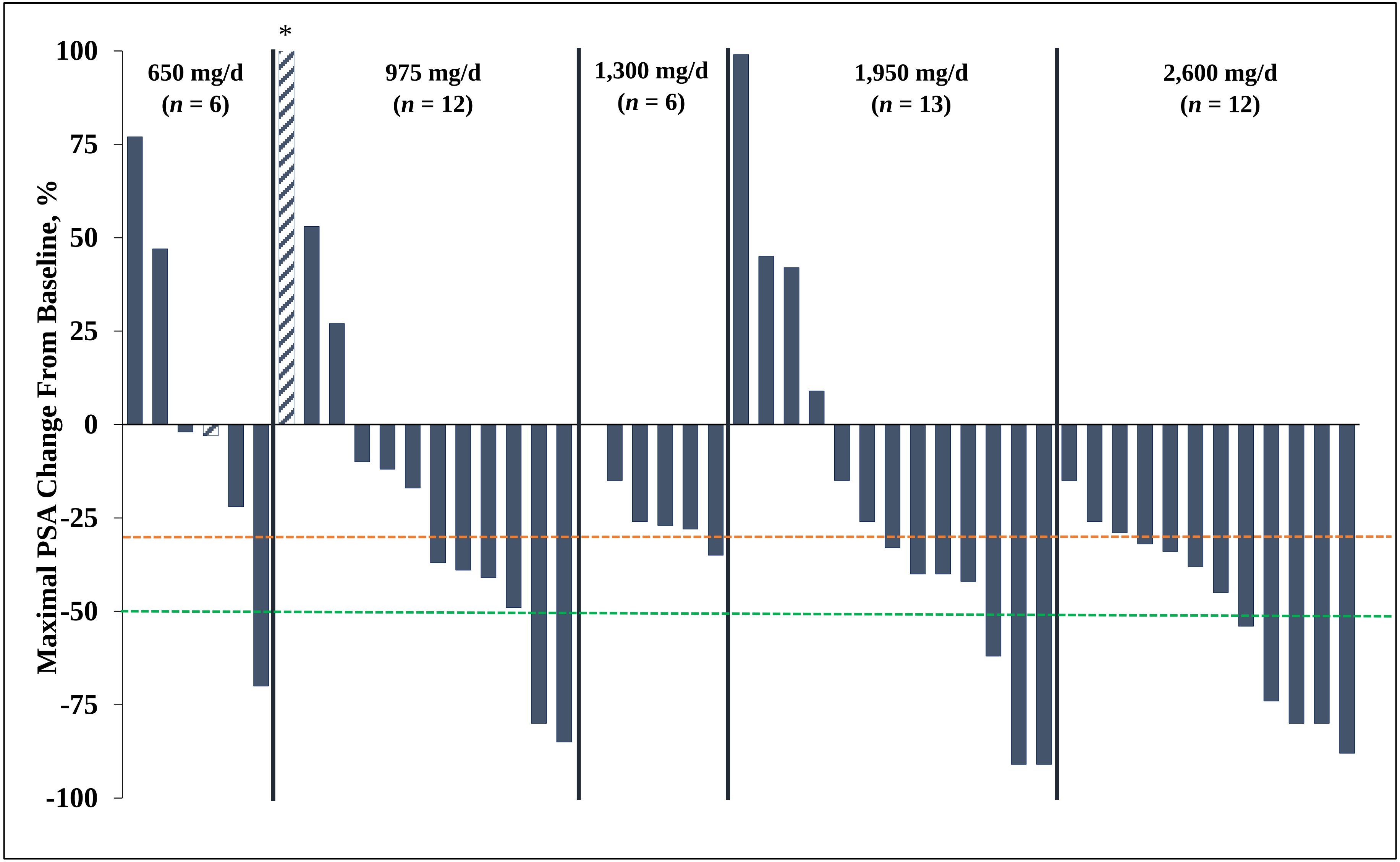
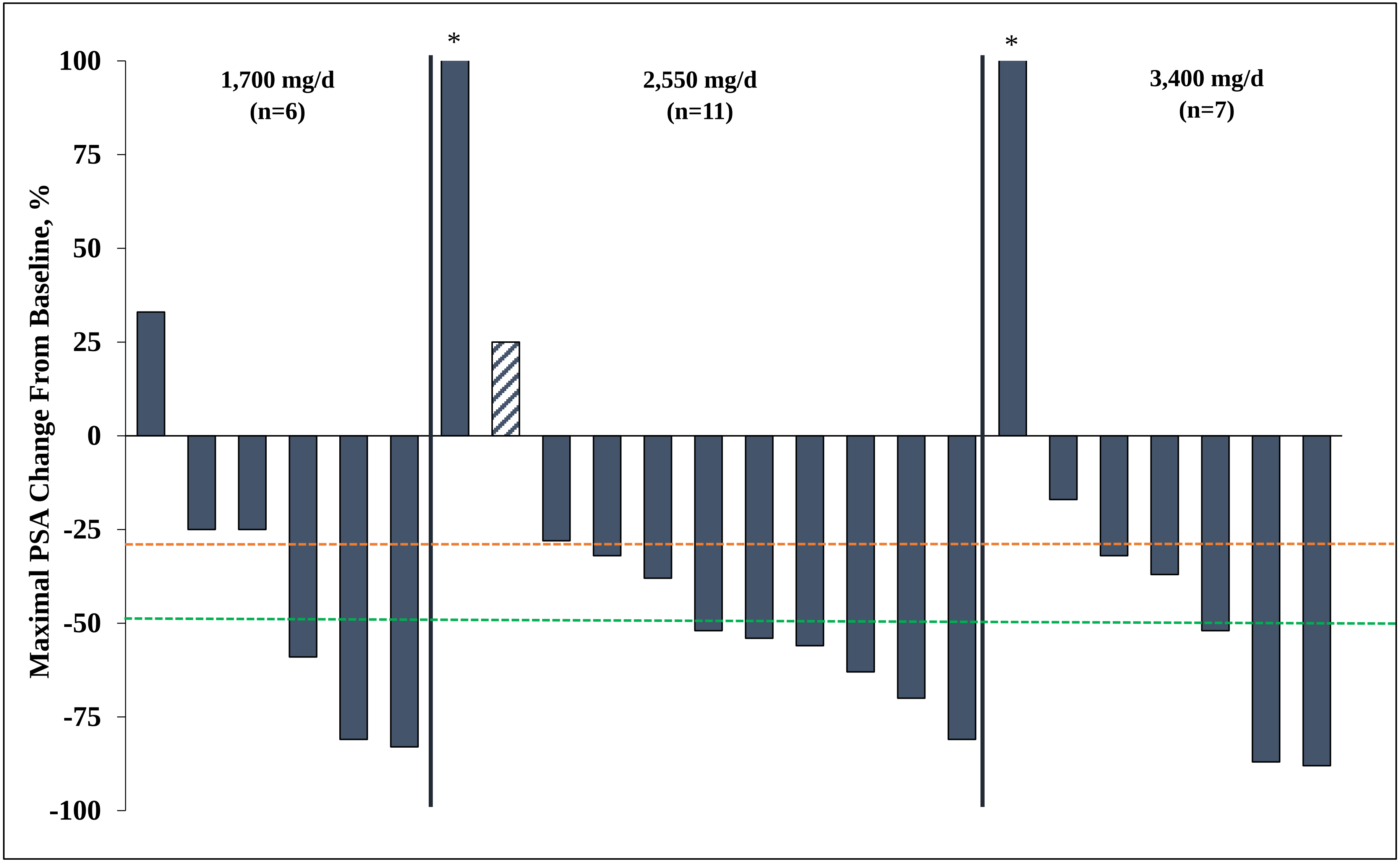

*
100
75
50
25
0
-25
-50
-75
-100
Maximal PSA Change From Baseline, %
650 mg/d
(n = 6)
975 mg/d
(n = 12)
1,300 mg/d
(n = 6)
1,950 mg/d
(n = 13)
2,600 mg/d
(n = 12)

Figure 1B.



Maximal PSA Change From Baseline, %
100
75
50
25
0
-25
-50
-75
-100
1,700 mg/d
(n=6)
2,550 mg/d
(n=11)
3,400 mg/d
(n=7)
*
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