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A randomized, open-label, multi-center, active-controlled phase II study comparing abiraterone acetate tablets (II), an improved formulation, versus originator abiraterone acetate in patients with metastatic castration-resistant prostate cancer

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Abstract

Background Abiraterone is a 17α-hydroxylase/C17-20 lyase inhibitor used for the treatment of metastatic castration-resistant prostate cancer (CRPC). This multi-center, randomized, open-label, active-controlled phase II study compared the pharmacodynamics (PD), pharmacokinetics (PK), and safety of abiraterone acetate tablets (II) (AAT[II]), a new formulation of abiraterone acetate, and ZYTIGA®, the originator abiraterone acetate (OAA), in patients with metastatic CRPC.

Methods Patients were randomized 1:1 to receive 300 mg AAT(II) daily plus 5 mg prednisone twice daily or 1000 mg OAA daily plus 5 mg prednisone twice daily for 84 days. The primary endpoint was the serum testosterone level (rounded-up) on Day 9 and/or Day 10. Absolute testosterone concentration, prostate-specific antigen (PSA) concentration, steady-state PK of abiraterone, and safety were also evaluated.

Results Sixty-nine patients were enrolled in the study, with 35 assigned to AAT(II) and 34 to OAA. The least squares (LS) mean (standard error) of serum testosterone concentration (rounded-up) on Day 9 and/or Day 10 were 1.075 (0.034) and 1.000 (0.034) in the AAT(II) and OAA groups, respectively. The geometric mean ratio (AAT[II] vs. OAA) was 1.053 (90% confidence interval [CI], 0.998 to 1.110) and the LS mean difference was 0.075 (95% CI, -0.021 to 0.171). The 90% CI fell within the 80.0% to 125.0% equivalence limits, suggesting equivalent PD effect of the two formulations. AAT(II) also exhibited high testosterone inhibition rate (> 90% at all visits) and PSA-50 rate (> 65% on Days 56

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and 84), which were comparable to that of OAA. AAT(II) also demonstrated an improved safety profile with lower incidence of adverse events compared to OAA.

Conclusions AAT(II) at 300 mg plus prednisone demonstrated equivalent PD as OAA at 1000 mg plus prednisone in reducing serum testosterone on Day 9 and/or Day 10, and the effect was maintained up to the end of the study. Compared to OAA, AAT(II) was given at a much lower dosage and was not affected by food consumption. AAT(II) was well tolerated, and no new safety issues were found.

Trial registration ClinicalTrials.gov, NCT04862091.

Keywords Castration-resistant prostate cancer, Abiraterone acetate, CYP17 inhibitor, Testosterone, Prostate-specific antigen

Background

Prostatic carcinogenesis is stimulated by the male sex hormone, testosterone [1–3]. Endocrine therapies that reduce the production of testosterone or block the effect of testosterone are standard treatments for prostate cancer that does not respond to surgery or radiotherapy [4, 5]. However, castration-resistant prostate cancer (CRPC) can progress despite in a low testosterone environment [6]. The increased activity of 17α-hydroxylase/C17-20 lyase (CYP17) in the tumor stimulates the synthesis of androgens in prostate cancer cells, leading to the progression of CRPC [7].

Abiraterone, an androgen biosynthesis inhibitor, reduces androgen production by inhibiting CYP17 [8]. The originator abiraterone acetate (OAA, ZYTIGA®) in combination with prednisone was approved by the FDA for the treatment of metastatic CRPC in 2011 [9]. However, OAA was found to have low solubility and permeability, as well as high intra-individual variability, and pharmacokinetics (PK) of OAA was highly affected by food consumption [10, 11]. Abiraterone maximum concentration (C_{max}) and area under the curve from zero to infinity ($AUC_{0\text{-inf}}$) were approximately 7- and 5-fold higher, respectively, when OAA was administered with a low-fat meal, and approximately 17- and 10-fold higher, respectively, when OAA was administered with a high-fat meal; therefore, OAA needs to be taken under modified fasting conditions (fast for 2 h before dosing and 1 h after dosing) [12, 13]. The median treatment duration in patients with metastatic castration-sensitive prostate cancer was around 24 months [14]. Strict diet restrictions can significantly lower the convenience of drug administration, thus reducing treatment compliance and quality of life. Moreover, the elderly population accounts for a large proportion of advanced prostate cancer patients, which makes them more susceptible to irregular dosing due to memory loss. This can increase the risk of adverse reactions and negatively impact efficacy.

Abiraterone acetate tablet (II) (AAT[II]) is a new and improved formulation developed using nanocrystal technology. Salcaprozate sodium is added to enhance the absorption of abiraterone, improve oral bioavailability, and reduce the food effect. Currently, three phase I studies of AAT(II) have been completed, in which AAT(II) showed linear PK characteristics and good safety and tolerability in healthy subjects, as well as smaller food effect compared to OAA [15]. After oral administration of AAT(II) with a high-fat meal, the C_{max} and AUC of abiraterone were only 2.2 times and 2.0 times higher than those under fasting conditions. Moreover, the C_{max} and AUC after OAA under modified fasting conditions were 5.9 times and 4.3 times higher than those of AAT(II) after a high-fat meal. The bioavailability of 300 mg AAT(II) was equivalent to that of 1000 mg OAA, and the PK characteristics of prednisone were not affected by the absorption enhancer [15]. With the administration of AAT(II) less restricted by diet, it can potentially improve patient compliance, thus therapeutic efficacy.

This phase II study aimed to investigate whether the pharmacodynamics (PD) of AAT(II) 300 mg plus prednisone is equivalent to that of OAA 1000 mg plus prednisone in patients with metastatic CRPC through the assessment of serum testosterone concentrations on Day 9 and/or Day 10. The absolute testosterone concentration, prostate-specific antigen (PSA) concentration, steady-state PK characteristics, and safety were also compared between the two formulations.

Methods

Patients

Eligible patients were males aged 18 years or older, had histologically or cytologically diagnosed prostate adenocarcinoma with metastatic lesions confirmed by computed tomography, magnetic resonance imaging, or bone scan, and had a castrate level of serum testosterone of < 50 mg/dL or 1.7 nmol/L at screening. Patients who had not undergone bilateral orchidectomy were required to receive ongoing gonadotropin-releasing hormone agonist or antagonist therapy throughout the study. Progression of prostate cancer was confirmed by biochemistry evidence of increasing PSA per standard guidelines or radiographic evidence based on Response Evaluation Criteria

in Solid Tumors v1.1 [16, 17]. Full eligibility criteria are available in the study protocol (Additional file 1: Study protocol).

Study design and interventions

This was a multi-center, randomized, open-label, active-controlled phase II study conducted at 35 sites in China from April 23, 2021, to January 6, 2022 (ClinicalTrials.gov, NCT04862091). Eligible patients were randomized (1:1) to receive either AAT(II) plus prednisone (AAT[II] group) or OAA plus prednisone (OAA group) by the site investigators using a centralized interactive web-response system with a block size of 4. The AAT(II) and OAA tablets were identical in appearance and packaging. Patients, investigators, and the study team were blinded to the treatment allocation. Patients in the AAT(II) group orally received AAT(II) 300 mg once daily and prednisone 5 mg twice daily under modified fasting conditions. Patients in the OAA group orally received OAA 1000 mg once daily and prednisone 5 mg twice daily under modified fasting conditions. Treatment was continued for 84 days.

Twelve patients from each group participated in a 24-h serial PK blood sampling on Day 9. These patients, designated for the 24-h PK analyses, were required to take the drugs under fasting conditions at least 1 h before taking a meal from Day 1 to Day 10; otherwise, medications were administrated under modified fasting conditions.

Endpoints and assessments

The primary endpoint was serum testosterone concentration (rounded-up) on Day 9 and/or Day 10. Blood samples were collected in the morning of Day 9 and/or Day 10 after treatment to assay the testosterone concentration. If the serum testosterone concentration was available on both days, the mean value was included in the analysis. Testosterone concentrations of <1 ng/dL (0.03 mmol/L) were rounded up to 1 ng/dL in the analysis.

Secondary endpoints included absolute testosterone concentration, testosterone inhibition rate, PSA concentration, and PSA-50 response rate. Testosterone inhibition rate was defined as the percentage of patients with a serum testosterone concentration of ≤ 1 ng/dL. PSA-50 response rate was defined as the percentage of patients with $\geq 50\%$ reduction in total serum PSA level from baseline. Blood samples for serum testosterone and PSA determination were collected on Day 9 and/or Day 10 (only assessed for testosterone), Days 28, 56, and 84. PK endpoints were steady-state minimum concentration of abiraterone and PK parameters of abiraterone. Blood samples were collected on Days 9 and/or Day 10, 28, 56, and 84 to assess the plasma concentration of abiraterone. For patients designated for the 24-h PK analyses, blood samples were collected on Day 9 at pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post-dose for the assessment of other PK parameters. Safety was assessed by adverse events (AEs), laboratory tests, vital signs, physical examination, and 12-lead electrocardiogram (ECG). AEs were monitored throughout the study and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (v5.0). Laboratory tests followed the same schedule as testosterone assessments. Vital signs were evaluated on Days 8, 9/10, 28, 56, and 84. Physical examinations were performed on Days 28, 56, and 84. 12-lead ECG was performed on Day 84 or upon treatment discontinuation/withdrawal.

Statistical analysis

The geometric mean ratio of serum testosterone concentration in AAT(II) group to OAA group was assumed to be 0.95 to 1.05 using 90% confidence interval (CI) of equivalence as the bioequivalence evaluation standard. Based on the existing literature, the coefficient of variation was assumed to be 25% [18]. With two one-sided tests at 0.05 level and 80% power, 27 patients were needed in each group. Considering the potential dropout, the total sample size was determined to be 60 patients.

All randomized metastatic CRPC patients who received at least one dose of study treatment were included in the PD analysis as randomized. The least squares (LS) mean and standard error (SE) of the testosterone concentration were calculated and compared with the one-way analysis of variance (ANOVA) model. PD of AAT(II) was considered equivalent to that of OAA if the 90% CI of the geometric mean ratio of serum testosterone concentration (rounded-up) on Day 9 and/or Day 10 in AAT(II) to OAA fell within the range of 80.0–125.0%. One-way ANOVA and 90% CI of geometric mean ratios were used for comparing absolute testosterone concentration between groups, while 95% CI of between-group difference was calculated for treatment comparison of PSA levels. Testosterone inhibition rate and PSA-50 response rate were analyzed using the Chi-square test/Fisher's exact test. PK was assessed in all randomized and treated patients who had at least one post-administration blood concentration data or PK parameter. Steady-state minimum concentration of abiraterone was summarized descriptively. PK parameters included time to maximum concentration at steady state ($T_{max,ss}$), maximum concentration at steady state ($C_{max,ss}$), area under the curve within the dosing interval at steady state ($AUC_{0-\tau}$), minimum concentration at steady state ($C_{min,ss}$), and mean blood drug concentration during the dosing interval at steady state ($C_{av,ss}$). ANOVA was performed on the natural logarithm transformed C_{max} and AUC, with group as the fixed effect to calculate the 90% CI of the geometric mean ratio. Randomized and treated patients who had

post-administration safety assessments were included in the safety analysis as treated. Safety data was summarized using descriptive statistics.

The PK analysis was conducted using the WinNonlin software (v8.1 or higher). Other analyses were conducted using SAS (v9.4 or higher).

Results

Patients

Between April 16, 2021, and September 26, 2021, 93 patients were screened. Sixty-nine patients were eligible and enrolled in the study with 35 randomized to the AAT(II) group and 34 to the OAA group (Additional file 2: Figure S1). All 69 patients received study treatment, and 65 patients completed the study. Two patients in the AAT(II) group withdrew from the study, and 2 patients in the OAA group discontinued the study due to serious AE ($n = 1$) and disease progression ($n = 1$). The mean (standard deviation [SD]) age and body mass index were 71.0 (7.1) years and 24.4 (3.3) kg/m^2. At baseline, the mean serum testosterone concentration was slightly higher in the AAT(II) group (11.3 ng/dL in AAT[II] vs. 9.5 ng/dL in OAA), and the mean PSA concentration was higher in the OAA group (119.5 ng/mL vs. 435.7 ng/mL). Demographics and disease characteristics were generally balanced between groups (Table 1).

PD

A total of 68 patients (AAT[II], $n = 34$; OAA, $n = 34$) were included in the PD analysis. One patient in the AAT(II) group was excluded because the patient did not meet the diagnosis for metastatic CRPC. The LS mean (SE) of serum testosterone concentration (rounded-up) on Day 9 and/or Day 10 were 1.075 (0.034) and 1.000 (0.034) in the AAT(II) and OAA groups, respectively (Table 2). The geometric mean ratio of serum testosterone in AAT(II) to OAA was 1.053 (90% CI, 0.998 to 1.110), suggesting that the PD of AAT(II) 300 mg was considered equivalent to that of OAA 1000 mg on Day 9 and/or Day 10, as the 90% CI was within the limits of 80.0–125.0%. This was also supported by the LS mean difference of 0.075 (95% CI, − 0.021 to 0.171), where no significant difference was observed in serum testosterone level between groups. Consistent with the primary endpoint, the mean serum testosterone concentrations (rounded-up) on Days 28, 56, and 84 were comparable between the AAT(II) and

Table 1 Demographics and baseline characteristics

	AAT(II) (*N* = 34)	OAA (*N* = 34)	Total (*N* = 68)
Age (year)	71.4 (6.4)	70.6 (7.9)	71.0 (7.1)
Height (cm)	166.9 (7.8)	166.9 (5.8)	166.9 (6.8)
Weight (kg)	69.1 (14.3)	67.5 (11.6)	68.3 (12.9)
BMI (kg/m^2)	24.6 (3.5)	24.1 (3.3)	24.4 (3.3)
ECOG performance status, n (%)			
0	7 (20.6)	12 (35.3)	19 (27.9)
1	27 (79.4)	22 (64.7)	49 (72.1)
Serum testosterone level (ng/dL)	11.3 (10.5)	9.5 (4.3)	10.4 (8.0)
PSA concentration (ng/mL)	119.5 (225.4)	435.7 (1423.0)	277.6 (1023.6)
Course of disease (month)[a]	30.9 (29.0)	28.4 (26.8)	29.6 (27.7)
Gleason score	8.3 (1.0)	8.3 (1.1)	8.3 (1.0)
Metastatic organ sites, n (%)			
1	18 (52.9)	22 (64,7)	40 (58.8)
2	11 (32.4)	7 (20.6)	18 (26.5)
3	1 (2.9)	3 (8.8)	4 (5.9)
≥ 4	4 (11.8)	2 (5.9)	6 (8.8)
Medical history, n (%)			
Hypertension	12 (35.3)	10 (29.4)	22 (32.4)
Aortic atherosclerosis	3 (8.8)	1 (2.9)	4 (5.9)
Alanine aminotransferase increased	1 (2.9)	1 (2.9)	2 (2.9)
Aspartate aminotransferase increased	1 (2.9)	0	1 (1.5)

Data are mean (SD) unless otherwise specified

AAT(II) Abiraterone acetate tablets (II), *OAA* Originator abiraterone acetate, *BMI* Body mass index, *ECOG* Eastern Cooperative Oncology Group, *PSA* prostate-specific antigen, *SD* Standard deviation

[a] Course of disease (month) = (Date of signed informed consent – Date of first pathological diagnosis + 1) × 12/365.25

Table 2 Serum testosterone concentrations (rounded-up values) and equivalence analysis

	LS mean (SE) of serum testosterone concentration, ng/dL[a]		AAT(II) vs. OAA GMR (90% CI)	AAT(II) vs. OAA LS mean difference (95% CI)
	AAT(II) (*N* = 34)	OAA (*N* = 34)		
Day 9 and/or Day 10	1.075 (0.034)	1.000 (0.034)	1.053 (0.998, 1.110)	0.075 (– 0.021, 0.171)
Day 28	1.020 (0.014)	1.000 (0.013)	1.015 (0.991, 1.041)	0.020 (– 0.018, 0.058)
Day 56	1.028 (0.020)	1.000 (0.019)	1.020 (0.987, 1.054)	0.028 (– 0.027, 0.083)
Day 84	1.064 (0.037)	1.000 (0.037)	1.042 (0.988, 1.100)	0.064 (– 0.041, 0.169)

AAT(II) Abiraterone acetate tablets (II), *OAA* Originator abiraterone acetate, *LS* Least squares, *SE* Standard error, *CI* Confidence interval, *GMR* Geometric mean ratio

[a] Values < 1 ng/dL were rounded up to 1 ng/dL

OAA groups, and the 90% CI of geometric mean ratios were within the limits of 80.0–125.0% at all timepoints (Fig. 1, Table 2). Additionally, there were no apparent differences observed in absolute testosterone concentration or testosterone inhibition rate between the two groups at any timepoints (Additional file 2: Table S1).

PSA level and PSA-50 response rate showed no statistically significant difference between AAT(II) and OAA groups on Days 28, 56, and 84 (Figs. 2 and 3, Additional file 2: Table S2 and S3). On Days 56 and 84, the PSA-50 response rate in the AAT(II) group exceeded 65% and was numerically higher than that of OAA (65.6% vs. 57.6% on Day 56 and 71.9% vs. 67.7% on Day 84).

PK

The $C_{min,ss}$ of abiraterone among patients treated with AAT(II) was lower than that in the OAA group at all visit days (Additional file 2: Table S4). The mean (SD) $C_{max,ss}$ was 164.69 (104.18) and 187.17 (119.01) for AAT(II) and OAA, respectively (Additional file 2: Table S5). The $t_{1/2}$ and $T_{max,ss}$ were comparable between groups. The mean (SD) $t_{1/2}$ was 10.02 (2.12) hours in the AAT(II) group and 11.89 (3.47) hours in the OAA group. The median $T_{max,ss}$ were 1.50 and 1.88 h, respectively. The geometric mean ratio of natural logarithm transformed C_{max}, $AUC_{0\text{-}\tau}$, and $AUC_{0\text{-}inf,ss}$ (AAT[II] vs. OAA) were 89.75% (90% CI, 53.15% to 151.55%), 56.32% (90% CI, 37.35% to 84.92%), and 52.65% (90% CI, 35.70% to 77.65%) (Additional file 2: Table S6).

Safety

A total of 69 patients were included in the safety analysis set. One patient randomized to the AAT(II) group had mistakenly taken OAA and was included in the OAA group for safety analysis. Thus, in the safety analysis set, the AAT(II) group and the OAA group contain 34 and 35 patients, respectively. A summary of AEs in the study is presented in Table 3. Treatment-emergent adverse events (TEAEs) were reported by fewer patients in AAT(II) than in OAA (26 [76.5%] vs. 30 [85.7%]). The AAT(II) group

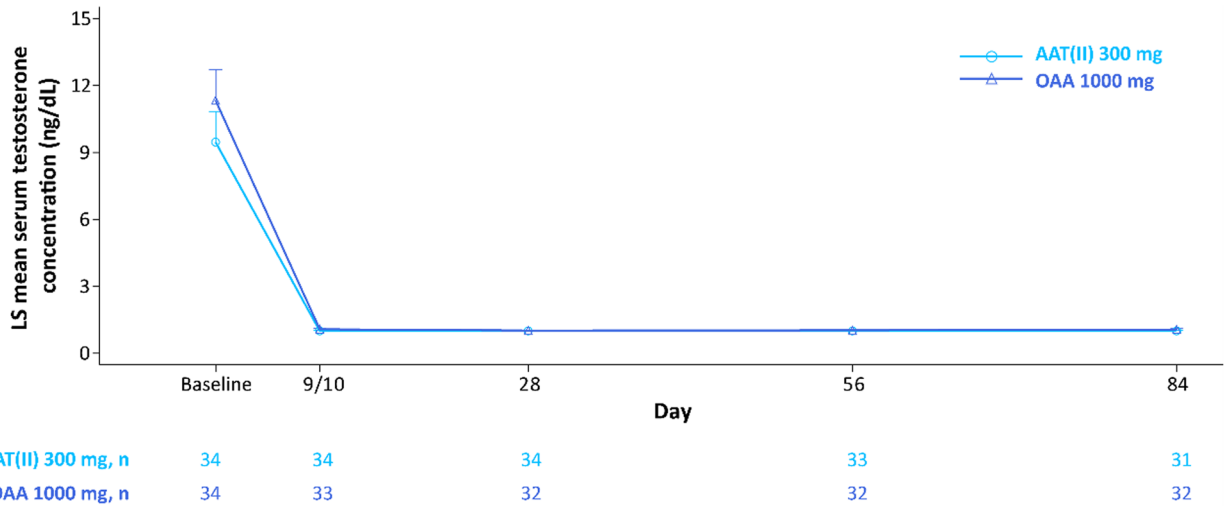

Fig. 1 Serum testosterone concentration on Days 9 and/or 10, 28, 56, and 84. Vertical bars represent standard error. AAT(II), abiraterone acetate tablets (II); OAA, originator abiraterone acetate; LS, least squares

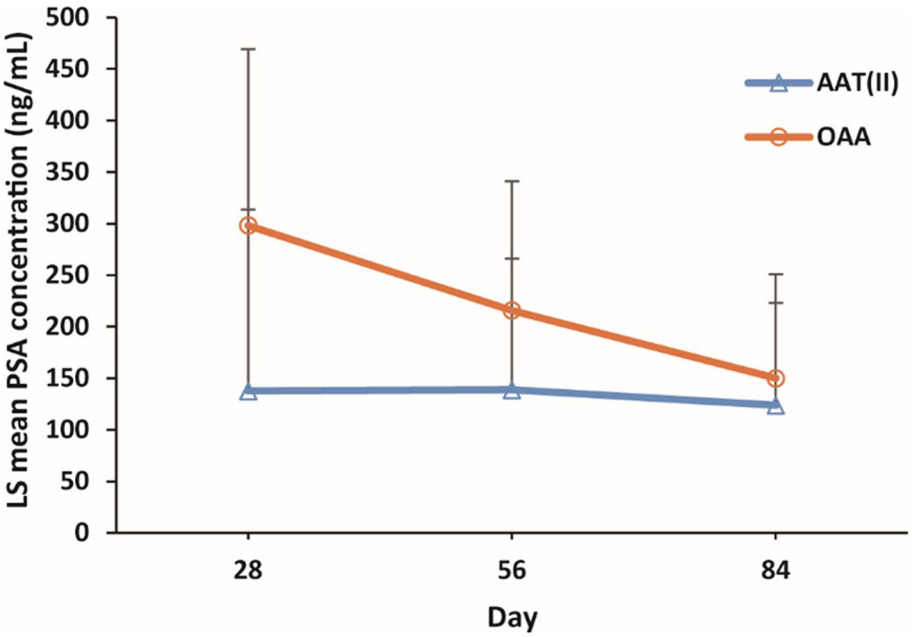

Fig. 2 PSA concentration on Days 28, 56, and 84. Vertical bars represent standard error. AAT(II), abiraterone acetate tablets (II); OAA, originator abiraterone acetate; LS, least squares; PSA, prostate-specific antigen

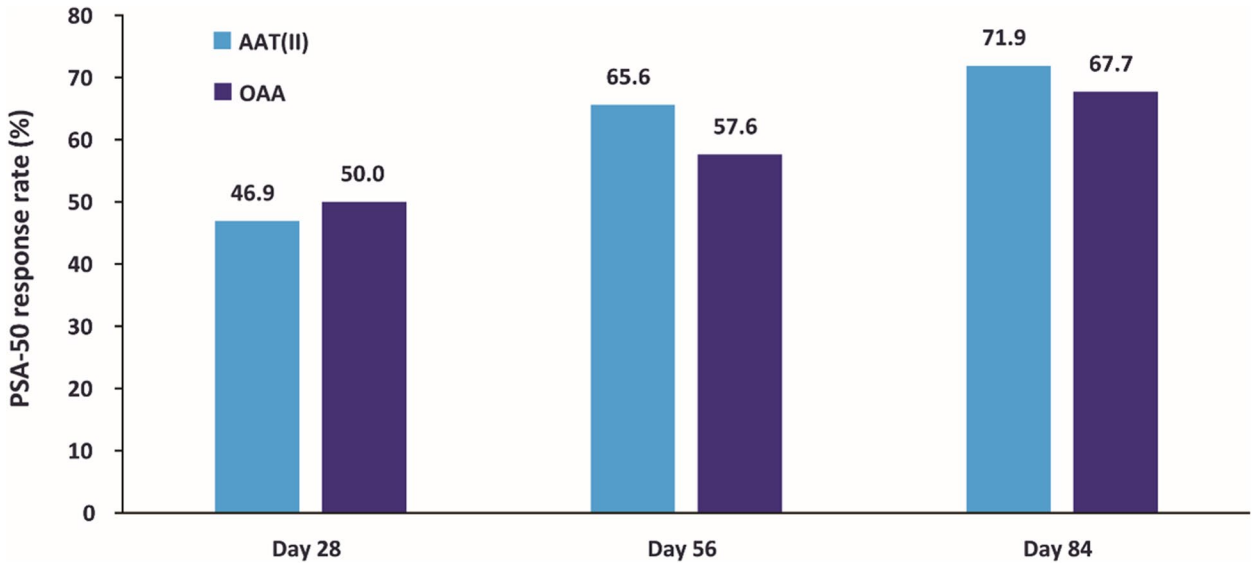

Fig. 3 PSA-50 response rate on Days 28, 56, and 84. PSA-50 response rate was defined as the percentage of patients with ≥ 50% reduction in total serum PSA level from baseline. AAT(II), abiraterone acetate tablets (II); OAA, originator abiraterone acetate; PSA, prostate-specific antigen

also had fewer patients experienced grade ≥ 3 TEAEs (3 [8.8%] vs. 8 [22.9%]) and SAEs (1 [2.9%] vs. 4 [11.4%]). Eighteen (52.9%) and 19 (54.3%) patients in the AAT(II) and OAA groups experienced treatment-related adverse events (TRAEs), with lower percentage of patients reported grade ≥ 3 TRAEs in the AAT(II) group (2 [5.9%] vs. 5 [14.3%]). Compared to OAA, there were no new safety issues identified with AAT(II) and no TEAE led to withdrawal or death.

The most common TEAEs were increased alanine aminotransferase, increased blood alkaline phosphatase, increased aspartate aminotransferase, urinary tract infection, and anemia. The incidence of common TEAEs was generally lower in the AAT(II) group.

Table 3 Treatment-emergent adverse events (TEAEs)

	AAT(II) (*N* = 34)	OAA (*N* = 35)
TEAEs	26 (76.5)	30 (85.7)
Grade ≥ 3 TEAEs	3 (8.8)	8 (22.9)
SAEs	1 (2.9)	4 (11.4)
TEAEs leading to treatment interruption or discontinuation	2 (5.9)	3 (8.6)
TEAEs leading to withdrawal	0	1 (2.9)
TEAEs leading to death	0	1 (2.9)
TRAEs	18 (52.9)	19 (54.3)
Grade ≥ 3 TRAEs	2 (5.9)	5 (14.3)
Treatment-related SAEs	1 (2.9)	1 (2.9)
TRAEs leading to treatment interruption or discontinuation	1 (2.9)	1 (2.9)
TRAEs leading to withdrawal	0	0
TRAEs leading to death	0	0
Most common TEAEs[a]		
Alanine aminotransferase increased	6 (17.6)	7 (20.0)
Blood alkaline phosphatase increased	6 (17.6)	4 (11.4)
Aspartate aminotransferase increased	5 (14.7)	8 (22.9)
Urinary tract infection	5 (14.7)	7 (20.0)
Anemia	4 (11.8)	9 (25.7)
Hypertriglyceridemia	3 (8.8)	5 (14.3)
Hypercholesterolemia	2 (5.9)	4 (11.4)
Blood glucose increased	1 (2.9)	4 (11.4)

Data are n (%)

AAT(II), Abiraterone acetate tablets (II), *OAA* Originator abiraterone acetate, *TEAE* Treatment-emergent adverse event, *SAE* Serious adverse event, *TRAE* Treatment-related adverse event

[a] Most common TEAEs are TEAEs that occurred in ≥ 10% of patients in either group

Discussion

In this phase II study, AAT(II) 300 mg plus prednisone demonstrated therapeutic equivalence as OAA 1000 mg plus prednisone in lowering serum testosterone on Day 9 and/or Day 10. Therapeutic equivalence was achieved at all assessment timepoints and sustained up to the end of the follow-up period. On Day 84, the absolute testosterone concentration was 0.387 and 0.247 ng/dL in AAT(II) and OAA, respectively. These data compared favourably to the early-stage study of OAA, in which patients treated with the originator abiraterone plus prednisone had a mean serum testosterone concentration of 0.5 ng/dL on Day 84 [19]. The testosterone inhibition rate exceeded 90% in both treatment groups with no statistically significant difference observed, further supporting the efficacy equivalence between AAT(II) and OAA. The two formulations also showed no difference in PSA reduction. The PSA-50 response rate with AAT(II) was either comparable to or higher than that with OAA.

YONSA® is another formulation of abiraterone acetate with a fine particle design (AAFP) to increase the dissolution rate of abiraterone. The high testosterone inhibition rate in this study was consistent with the results from the phase II study of AAFP, in which the testosterone inhibition rate ranged 90.9% to 100% at each timepoint [18]. These findings further support the therapeutic effect of AAT(II) in testosterone reduction and inhibition, with a recommended daily dosage (300 mg) that is further reduced compared to OAA (1000 mg) and AAFP (500 mg). Although the mean post-baseline PSA concentrations in this study were higher than that in the phase II study of AAFP (< 60 ng/mL at all follow-up visits), the PSA-50 rate was comparable between the two studies [18].

In this study, steady-state minimum concentration of abiraterone and other PK parameters indicated that the exposure to abiraterone was lower in the AAT(II) group compared to the OAA group. Similar results were also reported in the subgroup analysis of YONSA®, where the C_{min}, C_{max}, and $AUC_{0\text{-}t}$ were 47.1%, 43.7% and 56.0% of that of OAA [18]. As abiraterone has a high occupancy and long-lasting affinity with CYP17 A1 receptor, it can produce sustained inhibition of testosterone despite a lower systemic exposure [20]. Another study also showed that there is no clear dose–response relationship between abiraterone trough concentration and PSA response

rate [21]. Anyhow, the difference in PK exposure did not affect the therapeutic equivalence between AAT(II) and OAA in this study [15, 22].

AAT(II) was well tolerated with an acceptable safety profile. Patients treated with AAT(II) experienced fewer grade ≥3 TEAEs, grade ≥3 TRAEs, and SAEs compared to OAA-treated patients. In the AAT(II) group, there were no grade ≥3 hypertension, hypokalemia, or fluid retention, which are common AEs resulting from CYP17 inhibition. The lower incidence of TEAEs might be associated with the lower daily dosage of abiraterone in AAT(II) (300 mg) than in OAA (1000 mg). The relationship between AEs and abiraterone dosage can be further explored in future studies. There were no new safety issues identified. TEAEs in the AAT(II) and OAA groups were of the same category and were consistent with those reported in previous OAA studies. Compared to AAFP, the TEAE incidence rates were similar between the two improved formulations, but the proportion of patients experiencing grade 3 or higher TEAEs were lower with AAT(II) (16.7% in the AAFP study vs. 8.8% in this study) [18]. The common TEAEs in the two studies were of the same type with comparable incidence rates.

One limitation of this study is that surrogate markers (testosterone and PSA concentrations) were used to compare the PD of the two abiraterone formulations. The limited size and follow-up time of the phase II study did not allow for assessments like patient survival, disease progression, and long-term safety. Therefore, these outcomes need to be further investigated in future studies. Since the study was conducted in China, most patients were Han Chinese, which limited the generalizability of the study results. Although this was an open-label study, the PD and PK endpoints were determined through laboratory tests to minimize investigator bias.

Conclusions

Therapeutic equivalence between AAT(II) 300 mg plus prednisone and OAA 1000 mg plus prednisone was confirmed by Day 9 and/or Day 10 serum testosterone concentration in metastatic CRPC patients. The PD effects in reducing serum testosterone and PSA were maintained up to Day 84. Compared to OAA, AAT(II) was given at a much lower dosage and was not affected by food consumption. AAT(II) was well tolerated and showed an improved safety profile than OAA with fewer TEAEs.

Abbreviations

AAT (II)	Abiraterone acetate tablets (II)
AE	Adverse event
ANOVA	Analysis of variance
CI	Confidence interval
CRPC	Castration-resistant prostate cancer
CYP17	17α-Hydroxylase/C17-20 lyase
ECG	Electrocardiogram
LS	Least squares
OAA	Originator abiraterone acetate
PD	Pharmacodynamics
PK	Pharmacokinetics
PSA	Prostate-specific antigen
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
TEAE	Treatment-emergent adverse event
TRAE	Treatment-related adverse event

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12916-025-04053-7.

Additional file 1. Study protocol

Additional file 2: Supplementary tables and figure. Table S1. Absolute testosterone concentrations and equivalence analysis. Table S2. PSA concentrations. Table S3. PSA-50 response rate. Table S4. Steady-state minimum concentrations of abiraterone. Table S5. Abiraterone acetate tabletpharmacokinetics parameters. Table S6. Exposure to abiraterone after administration of AATand OAA. Figure S1. Trial profile

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Authors' contributions

DWY and XLL were responsible for the conception and design of the study and its supervision; XLL, TD, XC, BW, HC, JW, DXY, HXG, JL, HBH, TWF, LZC, XPZ, XPZ, XY, JLW, ZQX, WZY, CHH, JXL, LG, BF, QLW, XFC, YDZ, BKS, BZ, YW, HL and GQC recruited the patients, provided and interpreted clinical and diagnostic data; XLL, HW, QW made substantial contributions to acquisition, analysis and interpretation of data. XLL drafted the work and substantively revised it. All authors have approved the final manuscript and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Data availability

The data that support the findings of this study may be requested 24 months after study completion. Qualified researchers should submit a proposal to the corresponding author outlining the reasons for requiring the data. The leading clinical site and sponsor will check whether the request is subject to any intellectual property restriction. The use of data must also comply with the requirements of the Human Genetics Resources Administration of China and other country- or region-specific regulations. A signed data access agreement with the sponsor is required before accessing shared data.

Declarations

Ethics approval and consent to participate

The protocol and all amendments were approved by the Ethical Committee of Fudan University Shanghai Cancer Center (2012228–15 - 2101 A). The study was conducted according to the Declaration of Helsinki, Guidelines for Good Clinical Practice, and the local laws and regulations. All patients provided written informed consent.

Consent for publication

Not applicable.

Competing interests
Bin Zheng and Guoqiang Chen received research grants from Hengrui; Huan Wang and Quanren Wang are employees of Hengrui. The other authors declare no conflicts of interest.

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