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Phase I Clinical Trial of a Selective Inhibitor of CYP17, Abiraterone Acetate, Confirms That Castration-Resistant Prostate Cancer Commonly Remains Hormone Driven

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ABSTRACT

Purpose
Studies indicate that castration-resistant prostate cancer (CRPC) remains driven by ligand-dependent androgen receptor (AR) signaling. To evaluate this, a trial of abiraterone acetate—a potent, selective, small-molecule inhibitor of cytochrome P (CYP) 17, a key enzyme in androgen synthesis—was pursued.

Patients and Methods
Chemotherapy-naïve men (n = 21) who had prostate cancer that was resistant to multiple hormonal therapies were treated in this phase I study of once-daily, continuous abiraterone acetate, which escalated through five doses (250 to 2,000 mg) in three-patient cohorts.

Results
Abiraterone acetate was well tolerated. The anticipated toxicities attributable to a syndrome of secondary mineralocorticoid excess—namely hypertension, hypokalemia, and lower-limb edema—were successfully managed with a mineralocorticoid receptor antagonist. Antitumor activity was observed at all doses; however, because of a plateau in pharmacodynamic effect, 1,000 mg was selected for cohort expansion (n = 9). Abiraterone acetate administration was associated with increased levels of adrenocorticotropic hormone and steroids upstream of CYP17 and with suppression of serum testosterone, downstream androgenic steroids, and estradiol in all patients. Declines in prostate-specific antigen ≥ 30%, 50%, and 90% were observed in 14 (66%), 12 (57%), and 6 (29%) patients, respectively, and lasted between 69 to ≥ 578 days. Radiologic regression, normalization of lactate dehydrogenase, and improved symptoms with a reduction in analgesic use were documented.

Conclusion
CYP17 blockade by abiraterone acetate is safe and has significant antitumor activity in CRPC. These data confirm that CRPC commonly remains dependent on ligand-activated AR signaling.

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INTRODUCTION

Prostate cancer is the second leading cause of cancer death in men in the western world[1,2]; this is a result of castration-resistant prostate cancer (CRPC).[3] Castration blocks gonadal testosterone generation, but androgens from nongonadal sources are postulated to drive androgen receptor (AR) signaling. This is supported by recent studies, which report high intratumoral androgens, continued AR signaling,[4] and overexpression of enzymes key to androgen synthesis, which suggests that CRPC may synthesize androgens de novo.[5-7] Despite this, currently available strategies that target the AR, such as antiandrogens, ketoconazole, estrogens, or glucocorticoids, result in modest benefit.[8-13]

Cytochrome P (CYP)17 is a microsomal enzyme that catalyzes two independently regulated steroid reactions key to androgen and estrogen biosynthesis (Fig 1A).[14-16] Congenital CYP17 deficiency does not result in adrenocortical insufficiency, as corticosterone synthesis is unaffected; CYP17 loss interrupts the negative feedback control of adrenocorticotropic hormone (ACTH), which results in high levels of ACTH and steroid precursors upstream of CYP17.[17] Abiraterone is a potent,

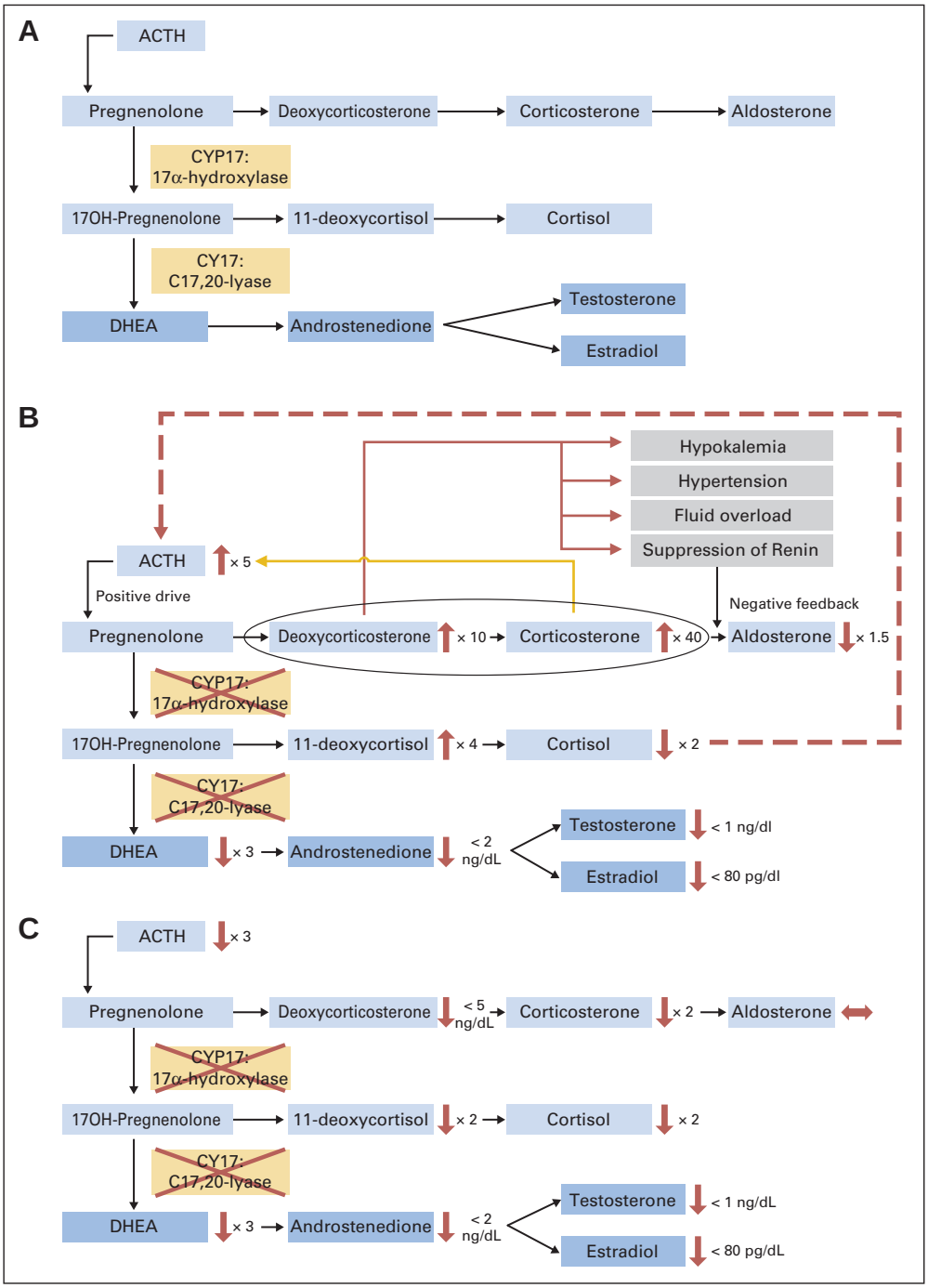

Fig 1. Physiologic consequences of treatment with abiraterone acetate. (A) Steroid biosynthesis pathway. (B) Abiraterone inhibits 17α-hydroxylase (crossed out in red), which results in a reduction in serum cortisol and a consequent increase in adrenocorticotropic hormone (ACTH) that drives the steroid biosynthesis pathway: levels of deoxycorticosterone and corticosterone increase by a median of 10- and 40-fold, respectively. Up to a four-fold increase in 11-deoxycortisol is observed, but there is complete inhibition of C17,20-lyase (crossed out in red) and significant suppression of dehydroepiandrostenedione (DHEA), androstenedione, and testosterone. (C) Addition of dexamethasone 0.5 mg/d to abiraterone acetate results in suppression of ACTH to three-fold less than baseline levels, a consequent decrease in deoxycorticosterone levels to less than the limit of sensitivity of the assay used (< 5 ng/dL), and a consequent decrease in corticosterone levels by two-fold. Similarly, 11-deoxycortisol levels decrease. Downstream steroid levels remain suppressed.

selective, and irreversible inhibitor of CYP17 (IC_{50}, 2 to 4 nmol/L),[18-20] unlike the antifungal ketoconazole, which is a less potent and competitive inhibitor of several CYP enzymes.[21-24] In preclinical toxicology studies, it reduced the weights of androgen dependent organs and had minimal side effects in other organs.[25] When administered as abiraterone acetate, it has good oral bioavailability. First-in-man studies reported that abiraterone acetate was safe when administered daily for 12 days to men with prostate cancer, and it suppressed testosterone synthesis in noncastrate patients.[26] We conducted a phase I study to define the safety, tolerability, and recommended phase II dose of abiraterone acetate when administered once daily to castrate men with CRPC.

PATIENTS AND METHODS

Patients

This was a single-center study conducted at the Royal Marsden Hospital (RMH), United Kingdom. Castrate patients who had an Eastern Cooperative Oncology Group performance status of 0 to 1, a histologic diagnosis of prostate

Table 1. Patient Characteristics

Patient No.	Dose (mg)	Age (years)	Gleason Score at Diagnosis	Previous Systemic Treatments*	Baseline PSA (ng/mL)	PSA Doubling Time Prior to Study Entry		Presence of Measurable Disease on Baseline CT Scan	Presence of Bone Metastasis on Baseline Bone Scan	*ERG* Gene Class	Baseline DHEA (ng/dL)	Baseline Androstenedione (ng/dL)	Confirmed PSA Decline (%)†	Duration of PSA Decline (days)
						Months	Days							
01	250	52	4 + 5	Dex, DES	34.2	0.5	16	No	Yes	2N	67	< 2	No	—
02	250	66	4 + 5	HDACi‡	75	1.7	53	No	Yes	Edel	172	13	≥ 90	206
03	250	68	3 + 4	—	8.8	3.7	112	Yes	No	Esplit	407	77	≥ 90	578§
04	500	72	3 + 3	Dex, DES, antiangiogenic, and pan-CDKi‡	354	2.2	66	Yes	No	Edel	221	32	≥ 75	421
05	500	77	N/A	Dex	79	1.6	49	Yes	Yes	N/A	285	46	≥ 90	427
06	500	58	4 + 4	Dex, DES	290	2.2	67	Yes	No	Edel¶	466	23	No	—
07	750	74	4 + 5	—	28.1	2.5	75	None	Yes	2N¶	437	52	No	—
08	750	69	N/A	—	36.8	2.6	78	None	Yes	Edel¶	70	16	≥ 90	451§
09	750	85	4 + 4	Dex, DES	46	2.4	73	Yes	Yes	2N	192	46	≥ 90	465§
10	1,000	62	4 + 4	Dex, DES, HDACi‡	110	12.3	375	No	Yes	N/A	524	70	≥ 50	69
11	1,000	69	3 + 3	—	34.3	11.6	354	Yes	Yes	2N	320	27	≥ 90	406§
12	1,000	75	3 + 4	Dex, DES, pamidronate	58	5.5	166	No	Yes	2N	320	43	No	—
13	2,000	60	3 + 4	Dex	39.3	2	61	No	Yes	2N¶	122	15	≥ 75	351§
14	2,000	82	3 + 3	Dex	56	5.5	166	Yes	Yes	N/A	227	34	No‖	—
15	2,000	62	4 + 5	—	35.5	22.7	81	Yes	Yes	3N¶	102	9	No	—
16	1,000	62	3 + 4	DES	75	1.1	34	No	Yes	2N	87	8	No (≥ 30)	—
17	1,000	78	5 + 3	Dex, DES	279	0.6	19	No	Yes	2N	93	19	No	—
18	1,000	72	5 + 4	panERBi‡	34.6	3	91	No	Yes	2N¶	285	51	≥ 50	70
19	1,000	72	5 + 3	—	30.2	3.5	108	No	No	2N	902	125	≥ 75	145
20	1,000	62	3 + 5	—	28.4	0.7	20	No	Yes	2N	1310	107	≥ 50‖	84
21	1,000	67	3 + 3	DES	205	1.3	41	No	Yes	2 + Esplit¶	320	50	No (≥ 30)‖	—

Abbreviations: PSA, prostate-specific antigen; CT, computed tomography; DHEA, dehydroepiandrostenedione; Dex, dexamethasone 0.5 mg daily; DES, diethylstilboestrol 1 mg/3 mg daily; HDACi, histone deacetylase inhibitor; pan-CDKi, pan–cyclin-dependent kinase inhibitor; N/A, not assessable; N, normal, characterized by twinned red (3′-*ERG*) and green (5′-*ERG*) FISH signals; panERBi, pan-ERB inhibitor.

*All patients were castrate, and all patients had previously progressed on an antiandrogen therapy.

†Evaluation of decline ≥ 50%; response of no indicates ≥ 50% decline was not achieved, and ≥ 30% decline is noted additionally.

‡Experimental agents were administered in the context of a clinical trial.

‖A ≥ 50% decline in PSA occurred on addition of dexamethasone 0.5 mg/day.

¶*ERG* gene status confirmed on castration-resistant prostate cancer sample.

§PSA and clinical responses continue.

adenocarcinoma, and progressive disease as defined by Prostate-Specific Antigen Working Group (PSAWG) criteria[27] were eligible. Patients were required to have a minimum washout period of 4 weeks after the use of prostate cancer therapy, except gonadotropin-releasing hormone agonists, and 6 weeks after stopping antiandrogens. Patients who had previously received chemotherapy or a radionuclide for their prostate cancer were excluded. Other eligibility criteria included normal serum potassium and adequate bone marrow, renal, and hepatic function. Patients were excluded if they had brain metastases or spinal cord compression, active autoimmune disease that required corticosteroid therapy, uncontrolled hypertension, a history of cardiac failure class III or IV, or a serious concurrent medical illness. The study was approved by the ethics review committees of the RMH, United Kingdom.

Study Design

This was an open-label, dose-escalation study. Capsules of abiraterone acetate powder 250 mg were administered once daily, continuously, in 28-day cycles, to fasted patients in three-patient cohorts that escalated through the preplanned doses of 250, 500, 750, 1,000 and 2,000 mg. Any drug-related grade 3 or 4 toxicity (excluding nausea, vomiting, or diarrhea controlled by standard therapies) that occurred in the first cycle—except the anticipated toxicities that related to a syndrome of secondary mineralocorticoid excess, including hypertension, hypokalemia, and fluid overload—was considered a dose-limiting toxicity (DLT). Toxicity related to elevated mineralocorticoid levels was managed with a mineralocorticoid receptor antagonist (eplerenone 50 to 200 mg/d), and treatment of dexamethasone 0.5 mg daily to suppress ACTH was only utilized if mineralocorticoid antagonism did not reverse these toxicities. Spironolactone was not utilized, as it has been reported to bind and activate the AR.[28] Cohort expansion to six patients was required if one DLT was reported. Dose escalation would stop if two DLTs were observed, and the preceding cohort would be expanded to six patients. In the absence of any DLT, a total of nine patients would be treated to complete food-effect pharmacokinetic (PK) studies.

This study also was prospectively designed to allow the addition of dexamethasone (0.5 mg daily) to abiraterone acetate in all patients at disease progression to test the hypothesis that resistance could be reversed by suppressing ACTH and by decreasing upstream androgenic steroids that could activate a mutated, promiscuous AR.[29,30] We also hypothesized that harboring the androgen-dependent *TMPRSS2-ERG* fusion gene[31,32] could indicate dependence on AR signaling and could define a tumor subgroup with a higher response rate to abiraterone acetate.

Procedures

Safety evaluations were conducted at baseline, weekly for the first two cycles, and at every cycle thereafter. All patients had a physical examination; complete blood count; clotting, serum creatinine, electrolyte, and liver function tests. An ACTH stimulation test also was performed at baseline. All

adverse events were graded according to the US National Cancer Institute common toxicity criteria, version 3.0.

For the PK analyses of patients who were treated at 250 mg, 500 mg, and 750 mg, a single dose of abiraterone acetate initially was administered 7 days before continuous dosing and after an overnight fast. Venipuncture was carried out for PK measurements at 1, 2, 4, 6, 8, 24, 48, and 72 hours postdose; on days 1, 8, and 15 of cycle 1; and on day 1 of the second and third cycles. Patients in the 1,000-mg and 2,000-mg cohorts were randomly assigned to receive two single doses of abiraterone acetate (one with high-fat content food, the other after an overnight fast) administered 5 days apart on days −7 and −3 before continuous dosing. PK analyses after both doses were done at the same time points as the lower-dose cohorts. Abiraterone levels were measured by liquid chromatography tandem mass spectrometry, using a previously published method.[33]

Prostate-specific antigen (PSA) was measured at baseline and at the end of every cycle. High-resolution computed tomography (CT) scans and bone scans were performed on all patients at baseline and every 3 months. Serum was collected for the measurement of ACTH, cortisol, deoxycorticosterone (DOC), aldosterone, corticosterone, and testosterone at baseline, weekly for the first two cycles, and at every cycle thereafter; serum also was collected at baseline and at every cycle to measure androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and estradiol. Testosterone was measured with a supersensitive assay that utilized liquid chromatography tandem mass spectrometry (Quest Diagnostics, Lyndhurst, NJ). DHEA-S, aldosterone, corticosterone, and DOC were measured by Quest Diagnostics, and ACTH, DHEA, androstenedione and estradiol, were measured by the RMH Academic Biochemistry Laboratories (London, United Kingdom). Fluorescent in situ hybridization (FISH) that used an *ERG* break-apart assay[34] was performed on sections cut from archival tumor tissue, and castration-resistant tumors were biopsied for research purposes before or after starting abiraterone acetate.

Data Analyses

PK was analyzed using a noncompartmental model with WINNonlin Software (Model 200; Scientific Consultant, Apex, NC). The food effects were assessed by a bioequivalence crossover model. Rates of PSA decline confirmed by a second reading were reported as recommended by PSAWG criteria on an intention-to-treat basis. CT scans were reported as the best result by Response Evaluation Criteria in Solid Tumors (RECIST)[35] at least 3 months after the start of treatment. For *ERG* gene status, tumors were classified into one of five groups on the basis of the observed FISH patterns, described previously[34] (Appendix Table A1).

RESULTS

Patient Characteristics

Twenty-one patients (median age, 69 years; range, 52 to 85 years) were recruited on to this study between December 13, 2005 and February 22, 2007. All patients were resistant to castration and antiandrogens. Ten (48%) of 21 patients had previously progressed on treatment with continuous steroids; nine (43%) of the 21 had previously progressed on diethylstilboestrol; and seven (33%) of these 21 patients had progressed on treatment with both (Table 1). The median baseline PSA was 46 ng/mL (range, 8.8 to 354 ng/mL). At baseline, 17 (81%) of 21 patients had bone metastasis, and eight (38%) of 21 patients had soft tissue disease (Table 1). Five patients remain on study and have an ongoing clinical response to abiraterone acetate alone; seven patients remain on the combination of dexamethasone and abiraterone acetate.

Safety and Tolerability

Dose escalation to the maximum preplanned daily dose of 2,000 mg was achieved. There were no treatment-related grade 3 or 4 toxicities in this study. A plateau of endocrine effects was reported at doses greater than 750 mg, and 1,000 mg was selected as the dose for phase II evaluation. An additional six patients were treated at 1,000 mg to complete PK/pharmacodynamic (PD) studies. Hypertension, hypokalemia, and lower-limb edema were observed in six, 10, and one patient, respectively. These side effects were controlled with eplerenone. The incidence of hypertension (one of three for 250, 500, 750, and 1,000 mg, and two of nine for 1,000 mg doses) appears similar across all doses (Table 2).

One patient in the 1,000-mg cohort who had a history of migraines developed daily grade 2 migrainous headaches after 8 weeks of treatment, which necessitated interruption of treatment. Physical examination and magnetic resonance imaging of the brain found no abnormalities. Serial serum potassium levels were less than 3 mmol/dL, which were in keeping with a syndrome of secondary mineralocorticoid excess. Dexamethasone 0.5 mg daily was initiated to

Table 2. Most Common Adverse Events of Abiraterone Acetate by Dose

	Event Grade per Dose									
	250 mg (n = 3)		500 mg (n = 3)		750 mg (n = 3)		1,000 mg (n= 9)		2,000 mg (n = 3)	
Adverse Event	1 to 2	3	1 to 2	3	1 to 2	3	1 to 2	3	1 to 2	3
Hypokalemia	0	0	0	1	2	0	5	0	2	0
Hypertension	1	0	0	0	1	0	2	0	2	0
Peripheral edema	0	0	0	0	0	0	0	0	1	0
Headache	0	0	0	0	0	0	1	0	0	0
Dyspnea/wheeze (exacerbation of baseline asthma)	0	0	0	0	0	0	1	0	0	0
Anorexia	0	0	2	0	0	0	0	0	0	0
Fatigue	0	0	0	0	1	0	1	0	0	0
Hot flushes	1	0	0	0	1	0	1	0	0	0
Testicular atrophy	0	0	1	0	0	0	0	0	0	0
ALT/AST increased	0	0	1	0	0	0	0	0	0	0
Skin rash	0	0	1	0	0	0	0	0	0	0
Dysgeusia	1	0	0	0	0	0	0	0	0	0

suppress ACTH, and the patient's headaches resolved, which allowed the recommencement of abiraterone acetate in combination with dexamethasone. The cause of headache in this patient remains unknown, but a causal relationship with abiraterone acetate could not be excluded. Another patient treated at 1,000 mg who had a history of asthma that was controlled on inhaled $\beta 2$ agonists developed an acute exacerbation of asthma that was associated with a decline in peak expiratory flow rate (PEFR), hypereosinophilia, an increase in inflammatory markers, and a seven-fold increase in PSA 7 weeks after starting abiraterone acetate. High doses of steroids were initiated. After control of the patient's symptoms, PEFR and eosinopilia normalized, and the PSA returned to the pre-exacerbation level. Subsequently, he was maintained on a combination of abiraterone acetate and dexamethasone 0.5 mg daily for 22 weeks with no recurrent increase in PSA.

No other adverse effects that required intervention were reported in this study. Grade 2 fatigue and anorexia were both reported in two patients, and three patients complained of grade 1 hot flushes. A grade 1 increase in liver transaminases was reported in one patient; this abnormality resolved without treatment interruption (Table 2).

Plasma PK

Plasma was collected from all 21 patients for PK analysis. Mean apparent clearance values ranged from 494.3 to 1,347.2 L/h. The area under the concentration-time curve (AUC) and maximum concentration (C_{max}) increased with dose but not proportionally ($r^2 = 0.186$ and 0.049, respectively; Figs 2A and 2B). Up to five-fold differences were observed in AUC and C_{max} within the 250-mg and 500-mg cohorts, and 2.5-fold variations were observed at 750-mg and 2,000-mg cohorts. In the 1,000-mg cohort, the variation reached nine-fold. The terminal half-life was relatively consistent (mean, 10.3 hours; Fig 2C). When administered with food that had high-fat content, drug exposure was significantly increased (by 4.4-fold) compared with fasting administration ($P = .049$; Fig 2D). The variability between fed patients was comparable to that observed between fasted patients. There was no significant increase in C_{max}, but absorption was significantly extended after food.

PD: Endocrine Studies

Circulating testosterone levels were in the castrate range (median, 7 ng/dL; range, < 1 to 34) at baseline in all patients, and they rapidly became undetectable (< 1 ng/dL) within 8 days at all doses

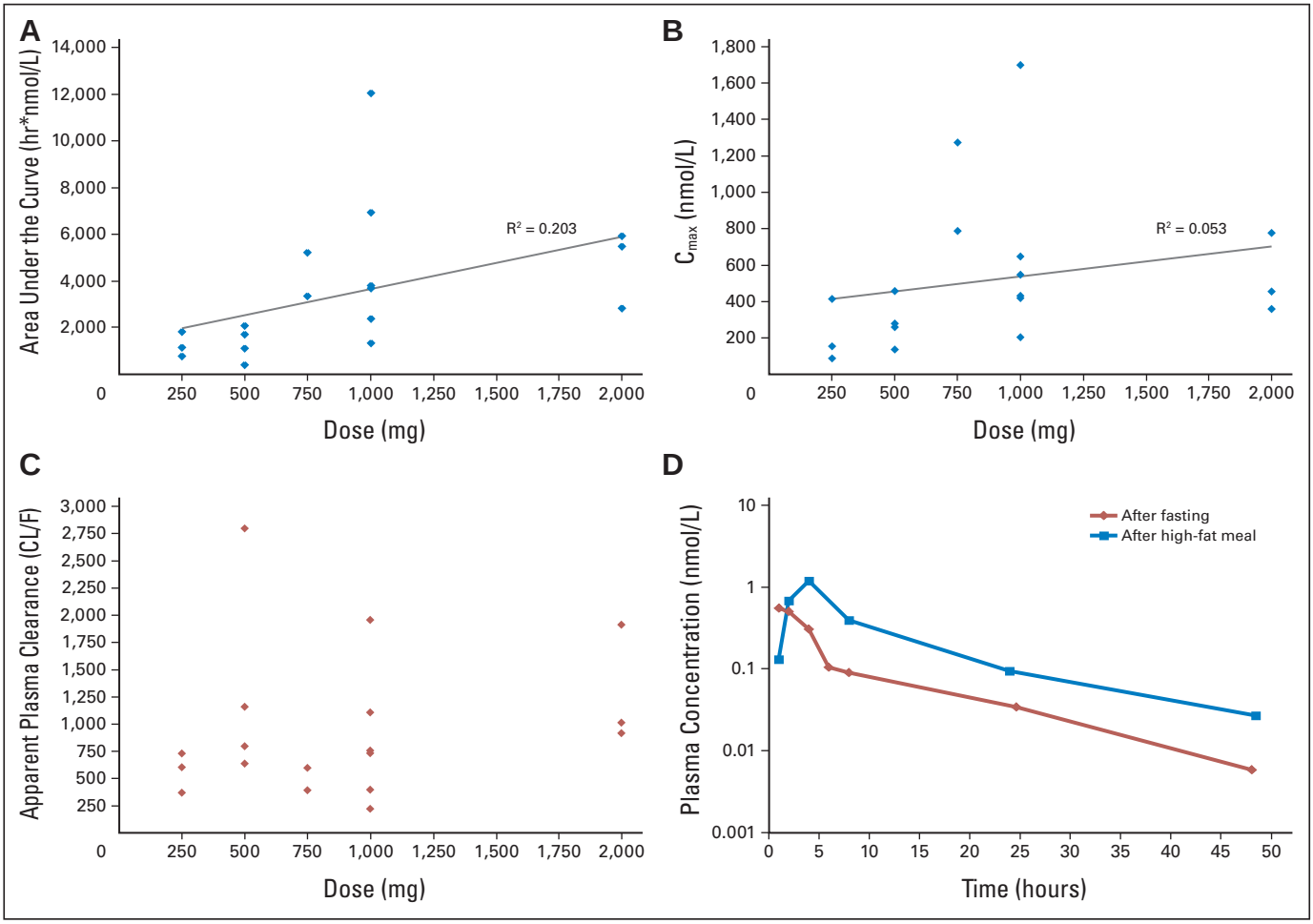

Fig 2. Pharmacokinetics of abiraterone acetate. (A) Area under the concentration-time curve versus dose in fasted patients; (B) maximum concentration (C_{max}) versus dose in fasted patients; (C) apparent plasma clearance (CL/F) in fasted patients at all doses; (D) plasma concentration versus time profile in a patient treated with abiraterone acetate 1,000 mg who fasted and received abiraterone acetate after a high-fat meal.

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