ZYTIGA® (abiraterone acetate)
ZYTIGA - Pharmacokinetics - Influence of Food

SUMMARY

- Janssen cannot recommend any practices, procedures, or dosing modifications that deviate from product labeling and are not approved by the regulatory agencies.
- High inter- and intra-patient variability in abiraterone pharmacokinetics (PK) have been reported in the published literature.[1] To control the potentially large differences in abiraterone systemic exposure deriving from interday differences in dietary intake, abiraterone acetate has been administered in a fasting state in phase 3 studies.[2-5]
- In a phase 1, dose-escalation study of abiraterone acetate in patients with chemotherapy-naïve castration-resistant prostate cancer (CRPC), abiraterone exposure was 4.4 times higher after administration with high-fat food than after fasting in patients who received abiraterone acetate 1,000 mg (P=0.49).[6] In another phase 1, dose-escalation study of abiraterone acetate in patients with chemotherapy-naïve CRPC (N=33), administration of a meal (800 to 1,000 calorie breakfast) was associated with higher abiraterone exposure than after fasting.[7]
- In an open-label, repeat dosing study in patients with metastatic CRPC (mCRPC) (N=25), administration of abiraterone acetate with low-fat meals and in a modified fasting state resulted in minimal difference in systemic exposure to abiraterone. In contrast, dosing with high-fat meals resulted in an approximate 2-fold increase in the area under the plasma concentration-time curve (AUC) compared with dosing in a modified fasting state. No adverse events (AEs) meeting the primary endpoint criteria occurred in either group. The most common AEs considered to be related to abiraterone acetate treatment were hot flush (20%), hypokalemia (16%), and fatigue (12%).[8]
- In a pooled PK analysis of 3 phase 1 studies, 1 phase 1b study, and 2 phase 3 studies that included healthy subjects and patients with mCRPC with and without prior chemotherapy (N=359), administration of abiraterone acetate 1,000 mg resulted in similar exposure regardless of prior chemotherapy status. The final model predicted that when healthy subjects were administered abiraterone acetate with a low- or high-fat meal, the bioavailability would be 3.8 times and 7.6 times higher, respectively, than abiraterone acetate taken under a fasting state.[9]
- A phase 1 study determined that the systemic exposure to abiraterone acetate 500 mg once daily with a continental breakfast did not meet the criteria for bioequivalence compared to abiraterone acetate 1,000 mg administered in a fasted state due to the large variability in pharmacokinetics of abiraterone within and between patients. Due to the large variability in abiraterone exposure, the intake of abiraterone acetate with food could not be advised.[10]
- In a phase 2 study evaluating the PK of a reduced-dose regimen in patients with progressive CRPC (N=72), administration of abiraterone acetate 250 mg once daily in combination with a low-fat breakfast (LOW arm) had similar effects on prostate-specific antigen (PSA) levels compared with abiraterone acetate 1,000 mg once daily while fasting (STD arm). However, the average abiraterone trough concentrations were significantly higher in the STD arm than the LOW arm (P<0.001).[11]

BACKGROUND

Wide inter- and intra-patient variability in abiraterone PK have been reported in the published literature due to a multitude of factors, with potential for excess toxicity or sub-therapeutic levels inducing resistance and limiting therapeutic efficacy.[1] Variability in absorption dependent upon food intake has been observed, including increased abiraterone exposure in subjects taking high-fat meals compared with low-fat meals. Because fat content and composition of meals are variable and cannot be well controlled in an outpatient setting, current recommendations are to take abiraterone acetate on an empty stomach.[12] To control this variation in dietary intake and minimize variability in bioavailability, abiraterone acetate has been administered in a fasting state in phase 3 studies.[2-5]

CLINICAL DATA

PHASE 1 STUDIES

Attard et al (2008)[6] evaluated the food (high-fat food vs overnight fast) effect on the PK of two single doses of abiraterone acetate capsules in men with chemotherapy-naïve castration-resistant prostate cancer (N=21). In patients who received abiraterone acetate 1,000 mg, abiraterone exposure was 4.4 times higher after administration with high-fat food than after fasting (*P*=0.49). Absorption was extended when abiraterone was taken with food, but no significant increase in the maximum concentration of abiraterone (C_{max}) was observed.

Ryan et al (2010)[7] evaluated the PK of abiraterone acetate in escalating doses of 250, 500, 750, and 1000 mg with fasted (overnight fast) or fed (800 to 1000 calorie breakfast) cohorts in patients with chemotherapy-naïve CRPC (N=33).

Results

Pharmacokinetics

- Administration of abiraterone acetate with a meal was associated with increased abiraterone exposure. See Table: Pharmacokinetics of Abiraterone during Fasted and Fed Conditions in Patients with CRPC.

Pharmacokinetics of Abiraterone during Fasted and Fed Conditions in Patients with CRPC[7]

Parameters	Abiraterone Acetate Dosing							
	250 mg		500 mg		750 mg		1000 mg	
	Fasted (n=3)	Fed (n=3)	Fasted (n=6)	Fed (n=3)	Fasted (n=3)	Fed (n=3)	Fasted (n=6)	Fed (n=6)
Mean C_{max}, nM/L	283	421	331	676	290	1552	510	2194
Mean $AUC_{0-\infty}$, nM/L·h	1411	1387	1781	3840	1665	9359	3478	14404

Abbreviations: $AUC_{0-\infty}$, area under the curve from time of dosing extrapolated to infinity; C_{max}, maximum concentration.

Safety

- In the overall study population, the most frequent adverse events were fatigue, hypertension, headache, nausea, and diarrhea.
- In the overall study population, grade 3 AEs included hypertension (n=4), hypokalemia (n=2), constipation (n=1), diarrhea (n=1), muscular weakness (n=1), and arthralgia (n=1).

Chi et al (2015)[8] investigated the short-term safety and PK profile of continuous dosing of abiraterone acetate in fasting and fed conditions in healthy subjects (study 1, n=36) and in patients with mCRPC (study 2, n=25).

Study Design/Methods

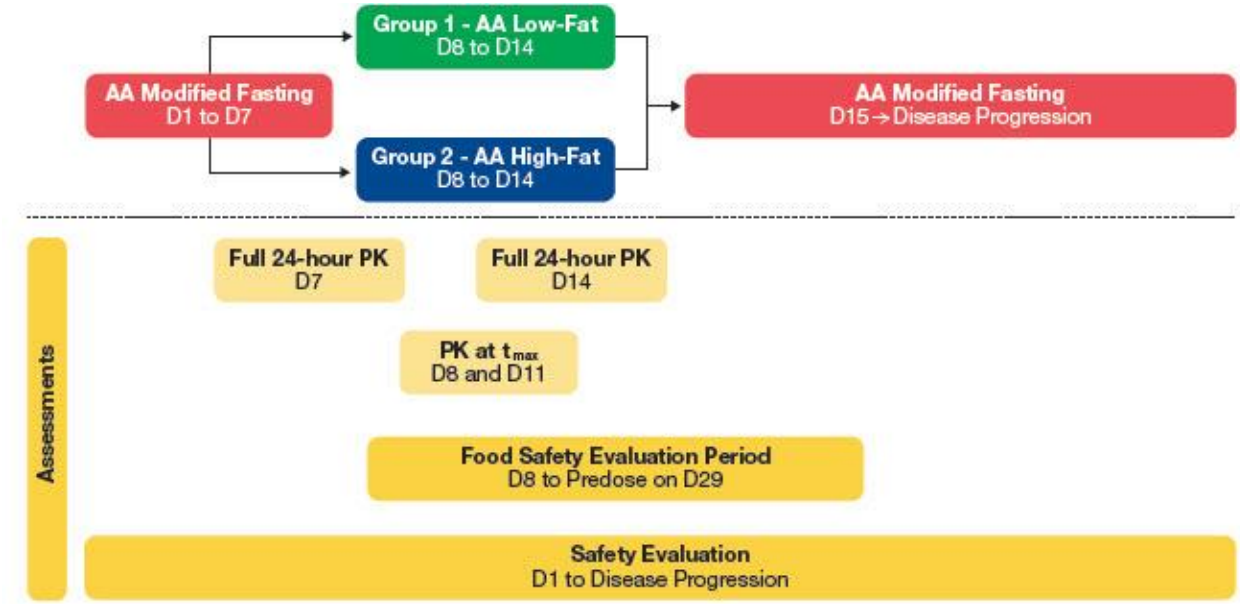
Study 1

- Phase 1, randomized, open-label, single-dose, crossover, multicenter study in healthy subjects
- Subjects included healthy males aged 18 to 55 years with a body mass index (BMI) ranging from 18 to 32 kg/m^2.
- Healthy subjects received abiraterone acetate 1,000 mg once daily with a high-fat meal (826.3 calories, 56.5% from fat), low-fat meal (298.7 calories, 7.3% from fat), or in the fasted state (overnight ≥10 hours). In the fed state, abiraterone acetate was administered approximately 30 minutes after food.
- The study evaluated the PK of abiraterone and its metabolites, as well as safety.

Study 2

- Open-label, multicenter study in patients with mCRPC
- All patients received abiraterone acetate 1,000 mg orally once daily and prednisone 5 mg orally twice daily. See Figure: Study Design.
  - On days 1-7, treatment was administered in the modified fasting state (no food for ≥2 hours before and ≥1 hour after dosing).
  - On days 8-14, treatment was administered within 0.5 hours after a standardized low-fat (group 1; n=6) or high-fat (group 2; n=18) meal.
  - From day 15 onward, treatment was administered in the modified fasting state until disease progression.
- Serial 24-hour PK sampling was conducted on days 7 and 14 (for intrasubject comparison of fasting versus fed state) and on days 8 and 11 at 2 hours post-dose.
- Safety was assessed with laboratory testing and clinical evaluations.
- **Primary endpoints:** proportion of patients with grade ≥3 AEs of special interest OR grade ≥3 serious AEs due to treatment during food safety evaluation period (day 8 to predose on day 29)

Study Design[8]



Abbreviations: AA, abiraterone acetate; D, day; PK, pharmacokinetics; t_{max}, time to maximum concentration.

Results

Patient Characteristics in Study 1

- Median age: 37 years (range, 25-53 years)
- Median weight: 80.9 kg (range, 64.1-100.8 kg)
- Median BMI: 26.8 kg/m^2 (range, 20.6-31.7 kg/m^2)

Patient Characteristics in Study 2

- Median age: 70 years (range, 55-91 years)
- Median weight: 88 kg (range, 67-128 kg)
- Mean BMI: 29.4 kg/m^2 (range, 21.6-41.4 kg/m^2)
- Median PSA: 87.0 µg/L (range, 7.1-770.0 µg/L)
- Eastern Cooperative Oncology Group (ECOG) performance status score: 0 (64%) or 1 (36%)

Pharmacokinetics

Study 1

- In healthy males, the mean C_{max} and AUC for abiraterone increased by approximately 17- and 10-fold, respectively, with a high-fat meal (826.3 calories); and by 7- and 5-fold, respectively with a low-fat meal (298.7 calories).
  - The geometric mean C_{max} of abiraterone after fasting, a low-fat meal, or high-fat meal was 70.7 ng/mL, 513 ng/mL, and 1190 ng/mL, respectively.
  - The geometric mean $AUC_{0-\infty}$ of abiraterone after fasting, a low-fat meal, or a high-fat meal was 421 ng·h/mL, 1942 ng·h/mL, and 4077 ng·h/mL, respectively.

Study 2

- In group 1, dosing with low-fat meals and in fasting state resulted in minimal difference in exposure to abiraterone. See Table: Pharmacokinetics of Abiraterone After Low-Fat and High-Fat Meal Compared with Fasting State.
- In group 2, administration of abiraterone acetate with high-fat meals resulted in an approximate 2-fold increase in AUC compared with administration in fasting state.
- A subgroup analysis of day 7 PK data demonstrated that the abiraterone geometric mean AUC_{0-24h} appeared to be higher by approximately 74% when the first meal consumed was at least 2 hours before compared with exposure when the first meal was at least 1 hour after administration of abiraterone and prednisone (1466 vs 843 ng·h/mL).

Pharmacokinetics of Abiraterone After Low-Fat and High-Fat Meal Compared with Fasting State in Patients with mCRPC[8]

Parameter	Treatment Period	n	Geometric Mean (CV%)[a]	Ratio (D14/D7), %	90% CI, %
Group 1 – Low-Fat Meal					
C_{max} (ng/mL)	Day 7 (fasting)	6	196 (71)	-	-
	Day 14 (low-fat)	6	265 (71)	135	95.79-190.79
AUC_{0-24h} (ng·h/mL)	Day 7 (fasting)	6	1185 (90)	-	-
	Day 14 (low-fat)	6	1264 (65)	107	66.48-171.13
Group 2 – High-Fat Meal					
C_{max} (ng/mL)	Day 7 (fasting)	18	196 (85)	-	-
	Day 14 (high-fat)	18	342 (70)	174	120.55-250.58
AUC_{0-24h} (ng·h/mL)	Day 7 (fasting)	18	973 (58)	-	-
	Day 14 (high-fat)	18	1992 (34)	205	161.72-259.12

Abbreviations: AUC_{0-24h}, area under the plasma concentration-time curve from time 0-24 hours after dosing; CI, confidence interval; C_{max}, maximum plasma concentration; CV, coefficient of variation; D, day.
[a]CV% is calculated as (standard deviation/arithmetic mean)×100.

Safety

- No AEs meeting the primary endpoint criteria occurred in either group.
- All treatment-emergent AEs (TEAEs) were grade ≤3 in severity and were similar across patients in groups 1 and 2 who received abiraterone acetate in fasting or fed state.
- Grade 3 TEAEs included hypertension, hypokalemia, hypocalcemia, and vomiting (1 each in 3 patients) and were not considered treatment-related.
- The most common AEs considered to be related to abiraterone acetate included hot flush (20%), hypokalemia (16%), and fatigue (12%).

POOLED ANALYSIS OF REPEAT DOSING AND SINGLE-DOSE STUDIES

Stuyckens et al (2014)[9] evaluated similarities and differences in the PK of abiraterone in patients with mCRPC with or without prior chemotherapy and healthy subjects (N=359). The influence of covariates on the PK of abiraterone was also assessed.

Study Design/Methods

- The total analysis dataset included pooled data from 3 phase 1 studies (COU-AA-008, -009, and -014), 1 phase 1b study (COU-AA-006), and 2 phase 3 studies (COU-AA-301 and -302). See Table: Overview of Studies Included in the Population PK Analysis.
- Concentrations of abiraterone in the collected plasma samples were determined by validated liquid chromatography tandem mass spectrometry.
- External validations were performed separately.

Overview of Studies Included in the Population PK Analysis[9]

Study	Dosing	Design	Population	Food	PK Sampling
COU-AA-008	Single dose 250 mg, 500 mg, 750 mg, 1,000 mg	Phase 1, dose-escalation study Open	Healthy men N=8 (1,000 mg)	Overnight fast	Intensive 0-96 hours
COU-AA-009	Single dose 1,000 mg	Phase 1, food effect study Randomized crossover (3-arm)	Healthy men N=36	Overnight fast, low-fat meal, high-fat meal	Intensive 0-96 hours
COU-AA-014	Single dose 1,000 mg	Phase 1, relative bioavailability study Randomized crossover (4-arm) 3 tablet formulations: clinical commercial site, 1 commercial site, 2 (1 repeated)	Healthy men N=18	Overnight fast	Intensive 0-96 hours
COU-AA-006	Multiple dose 1,000 mg/day[a]	Phase 1b QT/QTc study Open	Patients with mCRPC who received prior chemotherapy N=33	Modified fast[b]	Intensive 0-24 hours days 1, 8, 28; predose days 6, 7
COU-AA-301	Multiple dose 1,000 mg/day[a]	Phase 3 safety and efficacy study Randomized, placebo controlled, double blind (subsample)	Patients with mCRPC who received prior chemotherapy N=161 (with PK samples)	Modified fast[b]	Sparse cycle 1: day 1 predose +2 samples 0.5-4 hours; cycle 2: day 1; cycle 5: day 1 predose +1 sample 0-3 hours
COU-AA-302	Multiple dose 1,000 mg/day[a]	Phase 3 safety and efficacy study Randomized, placebo controlled, double blind (subsample)	Chemotherapy -naïve patients with mCRPC N=103 (with PK samples)	Modified fast[b]	Sparse cycles 1, 2, and 5 on day 1 predose +1 sample 1-5 hours

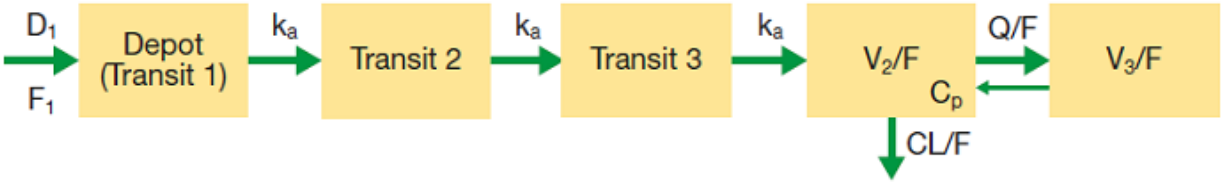
Abbreviations: AA, abiraterone acetate; mCRPC, metastatic castration-resistant prostate cancer; PK, pharmacokinetic; QTc, corrected QT interval.
[a]AA was coadministered with prednisone 5 mg twice daily.
[b]AA was taken at least 1 hour before a meal or 2 hours after a meal.

Results

Pharmacokinetics

- The full dataset consisted of 4627 samples from 359 subjects (3415 samples from 95 patients for model development and 1212 samples from 264 patients for model evaluation).
- A 2-compartment model with 3 transit compartments following sequential zero-first order kinetics was used to characterize absorption of abiraterone. Specific relative bioavailability (F1) factors were attributed to each of the 4 food conditions. See Figure: Schematic of the Population PK Model of Abiraterone.

Schematic of the Population PK Model of Abiraterone



Abbreviations: CL/F, apparent clearance; Cp, plasma abiraterone concentration; D_1, duration of zero-order input; F_1, relative bioavailability; k_a, first-order absorption rate constant; PK, pharmacokinetic; Q/F, apparent intercompartmental clearance; V_2/F, apparent volume of the central compartment; V_3/F, apparent volume of the peripheral compartment.

- The population PK parameter estimates are presented in Table: Parameter Estimates of the final Model in Chemotherapy-Pretreated and Chemotherapy-Naïve Patients with mCRPC.
- Absorption-related parameters were affected by food intake and fat content. The duration of absorption and bioavailability increased when abiraterone acetate was taken with a low- or high-fat meal in healthy subjects.
  - The final model predicted that when healthy subjects were administered abiraterone acetate with a low- or high-fat meal, the bioavailability would be 3.8 times and 7.6 times higher, respectively, than abiraterone acetate taken under a fasted state.
- The apparent clearance (CL/F) for abiraterone was extensive, with a lower CL/F in patients with mCRPC (1550 L/h) than in healthy subjects (2240 L/h).
- The PK of abiraterone was similar in both populations of patients with mCRPC. There was relatively high between- and within-patient variability.
- Health status (healthy vs mCRPC patients) was the most significant covariate to affect the PK of abiraterone, which was confirmed by a comparison of post hoc values for CL/F and estimated exposures between patients and healthy subjects.
- The PK and exposure of abiraterone were similar between chemotherapy-pretreated and chemotherapy-naïve patients.

Parameter Estimates of the Final Model in Chemotherapy-Pretreated and Chemotherapy-Naïve Patients With mCRPC[9]

Parameter	Chemotherapy-Pretreated Patients (Final Model 1)		All mCRPC Patients (Final Model 2)	
	Estimated Value (%SEM)	Interindividual Variability (%SEM)	Estimated Value (%SEM)	Interindividual Variability (%SEM)
CL/F, L/h				
Healthy subjects	2240 (14.6)	30.3 (24.4)	2240 (5.71)	28.2 (23.2)
mCRPC patients	1505 (34.1)[a]	30.3 (24.4)	1550 (15.9)[a]	28.2 (23.2)
V_2/F, L	5630 (12.5)	-	5620 (10.5)	-
V_3/F, L	17,400 (10.6)	-	17,400 (8.39)	-
Q/F, L/h	1350 (11.8)	-	1360 (9.93)	-
F_1, %				
Fasting	100[b]	53.9 (28.0)	100[b]	53.6 (30.2)
Fasting 2 h before to 1 h after dosing[c]	114 (11.8)	63.1 (15.8)	124 (12.1)	61.1 (14.3)
Low-fat meal[c]	382 (12.4)	34.6 (31.0)	380 (8.97)	34.2 (30.7)
High-fat meal[c]	758 (10.8)	33.9 (47.4)	754 (7.20)	33.6 (47.4)
k_a, h^{-1}				
Fasting	1.90 (7.05)	34.6 (23.0)	1.89 (7.14)	34.5 (21.1)
Fasting 2 h before to 1 h after dosing	1[b] (-)	57.1 (17.2)	1.91 (5.50)	58.8 (17.2)
Low-fat meal	1.85 (9.03)	30.1 (33.3)	1.91 (5.50)	31.6 (25.2)
High-fat meal	1[b] (-)	44.5 (29.8)	1.91 (5.50)	45.6 (28.2)
D_1, h				
Fasting	0.27 (33.3)	118 (29.0)	0.267 (13.7)	119 (23.5)
Fasting 2 h before to 1 h after dosing	1[b] (-)	130 (33.8)	0.267 (13.7)	144 (15.6)
Low-fat meal	1.35 (7.85)	36.1 (44.6)	1.37 (7.07)	34.8 (49.4)
High-fat meal	1.23 (7.77)	60.1 (23.3)	1.24 (7.60)	59.7 (23.5)
Residual variability in healthy subjects (%CV)	60.1 (9.4)	-	60.2 (9.36)	-
Residual variability in patients (%CV)	69.9 (10.3)	-	71.3 (8.86)	-

Abbreviations: CL/F, apparent clearance; CV, coefficient of variation; D_1, duration of zero-order input; F_1, bioavailability; k_a, first-order absorption rate constant; mCRPC, metastatic castration-resistant prostate cancer; Q/F, intercompartmental clearance; SEM, standard error of mean; V_2/F, apparent volume of the central compartment; V_3/F, apparent volume of the peripheral compartment.
[a]SEM of the shift in CL/F.
[b]Fixed parameter.
[c]Relative to F_1 in fasted condition (100%).

Inoue et al (2015)[13] evaluated the effects of food timing on single, oral doses of abiraterone acetate 1,000 mg in healthy Japanese (N=22) and Caucasian (N=23) subjects under fasted (at least 10 hours overnight) and three different modified fasting conditions.

Study Design/Methods

- Randomized, four-way crossover study
- The study included healthy men with a median age of 28 years and mean BMI of 23.85 kg/m^2.
- Subjects received abiraterone acetate 1,000 mg under four conditions including, overnight fasting (at least 10 hours) followed by a medium-fat meal (chicken katsu, white rice, mandarin oranges) containing 12 grams of fat and about 412 calories: 4 hours post-dose (group A), 1 hour and 4 hours post-dose (group B), 2 hours pre-dose and 4 hours post-dose (group C), or 2 hours pre-dose and 2 hours post-dose (group D).

- The 90% CI for the geometric mean ratios of C_{max}, AUC_{last} and AUC_{∞} were used to evaluate the PK effects of food on abiraterone in these subjects.

Results

Pharmacokinetics

- A 7 to 7.5-fold increase in abiraterone exposure was observed when abiraterone was administered 2 hours after a meal (groups C and D) versus the fasted state (groups A).
- There was approximately a 4.4 to 4.8-fold increase in abiraterone exposure in subjects receiving abiraterone 2 hours after a meal (groups C and D) versus group B.

Safety

- The AEs reported include headache (n=2), viral upper respiratory tract infection (n=2), migraine (n=1), arthropod bite (n=1), tendon rupture (n=1), fatigue (n=1), and costochondritis (n=1).
- There were no serious AEs or deaths reported and none of the AEs led to discontinuation of abiraterone acetate.

ALTERNATIVE DOSING STUDIES

Lubberman et al (2019)[10] evaluated the PK of abiraterone acetate 1,000 mg daily (fasting) followed by 500 mg with a continental breakfast in a crossover study in patients with mCRPC (N=14).

Study Design/Methods

- Phase 1, multicenter, randomized, crossover study
- Patients received abiraterone acetate 1,000 mg daily in a fasted state, followed by 500 mg daily for 14 days taken with a continental breakfast.
- Abiraterone plasma exposure was measured after both periods of 14 days.
- **Outcomes measured:** bioequivalence of a reduced dose of abiraterone acetate with a continental breakfast compared to abiraterone acetate 1,000 mg daily (fasting).
    - Bioequivalence was determined when the 90% CI of the geometric mean ratio (GMR) of the $AUC_{0\text{-}24h}$, C_{max}, and C_{trough} was within the bioequivalence threshold of 0.80 and 1.25.

Results

Patient Characteristics

- Median age: 70 years (range, 64-93)
- Median BMI: 29 kg/m^2 (range, 21-37)
- ECOG performance status: 0 (50%) or 1 (50%)
- Median PSA: 17 ng/mL (range, 0.2-93)

Pharmacokinetics

- A total of 12 patients were eligible for PK analysis.
- GMR for fed/fasted $AUC_{0\text{-}24h}$ was 0.88 (90% CI, 0.73-1.07), GMR C_{max} was 1.03 (90% CI, 0.79-1.34) and the GMR C_{trough} was 0.81 (90% CI, 0.60-1.10). The 90% confidence intervals did not meet the bioequivalence criteria.
- When abiraterone was taken fasted compared to fed, the inter-patient variability (CV%) for $AUC_{0\text{-}24h}$, C_{max}, and C_{trough} was 65% vs 57%, 55% vs 57%, and 72% vs 75%, respectively.

Szmulewitz et al (2018)[11] investigated the PK of a reduced-dose (250 mg) regimen of abiraterone acetate in combination with a low-fat breakfast in patients with progressive CRPC (N=72).

Study Design/Methods

- Phase 2, randomized, international study
- Patients received either 250 mg abiraterone acetate orally once daily with a low-fat breakfast (LOW arm, n=36) or 1,000 mg abiraterone acetate orally once daily while fasting (STD arm, n=36); all patients received prednisone 5 mg orally twice daily.
- PSA was assessed monthly; PK samples were collected on day 8 and monthly for the first 4 months.
- **Primary endpoint:** log change in serum PSA as a (nonclinically validated) biomarker for efficacy from baseline to week 12 using a noninferiority design
- **Secondary endpoints:** comparison of PK, PSA response rate (defined as a ≥50% reduction in PSA after 12 weeks of therapy), change in androgen levels, progression-free survival (PFS), and safety

Results

- Baseline characteristics were well balanced between arms, though the LOW arm had a higher percentage of patients who self-identified as African American (31% vs 14% in the STD arm).
- Noninferiority for the primary endpoint at 12 weeks was established.
  - Mean log change in PSA at 12 weeks (LOW vs STD, respectively): −1.59 vs −1.19
- There were higher drug concentrations (trough and C_{max}) and higher PK variability in the STD arm compared with the LOW arm (P<0.001 and P=0.012, respectively). There was no clear association within this study between drug concentration and efficacy.
- The PSA response rate was 58% in the LOW arm vs 50% in STD arm, and the median PFS was 8.6 months in both arms (P=0.38). Androgen levels decreased similarly in both arms.
- Overall, AEs were consistent with prior studies and observed in ≥15% of patients in either arm, though there were numerically more patients with grade 3 or higher events in the LOW arm (32.4% vs 17.6%; P=0.26).

THERAPEUTIC DRUG MONITORING STUDIES

Arasaratnam et al (2019)[1] examined the PK of abiraterone acetate and its metabolites abiraterone and Δ(4)-abiraterone (D4A), and potential contributing factors of variability in patients with mCRPC (N=22). Drug trough levels (DTL) were obtained. Thirteen patients received abiraterone acetate in the fasted state and had a mean abiraterone DTL of 12.1 ng/mL. Nine patients received abiraterone acetate in the fed state (defined as administration 30 minutes before a meal) and had a DTL of 11.1 ng/mL (P=0.8). The cohort demonstrated high inter- and intra-patient variability in both abiraterone and D4A with increase in abiraterone exposure in the fasting state compared to the fed state. The overall safety results reported that 6 (27%) patients had grade 1 or 2 hypertension, 2 (9.1%) developed grade 1 hypokalemia, and 7 (32%) had evidence of grade 1 peripheral edema.

Groenland et al (2020)[14] prospectively evaluated TDM of abiraterone acetate with food to determine clinical applicability and sufficient abiraterone acetate exposure to achieve efficacy without additional toxicity (N=32).

Study Design/Methods

- Patients received abiraterone acetate 1,000 mg once daily in a modified fasting state with PK-sampling at 4, 8, and 12 weeks after start of treatment and 12 weeks thereafter.
- PK-guided interventions were recommended if the C_{min} was <8.4 ng/mL with acceptable toxicity. Abiraterone acetate was administered concomitantly with a light meal or a snack (bread, yoghurt, or fruit, but not with food high in fat); dose increments of abiraterone acetate were recommended to 1,250 mg and 1,500 mg if exposure remained below the target.
- **Primary outcome**: 50% reduction in patients with C_{min} <8.4 ng/mL

- **Secondary outcome**: determine the feasibility, tolerability and efficacy of TDM of abiraterone with a food intervention in clinical practice and to achieve a physician adherence >90%.

Results

- A total of 194 samples were collected with a median number of samples per patient of 6 (range, 1-13).
- Twenty patients (63%) had a C_{min} <8.4 ng/mL at some time during treatment. These patients generally had more prior lines of therapy, worse World Health Organization performance status, and higher baseline PSA levels compared with patients with C_{min} ≥8.4 In these patients, the C_{min} increased from 6.9 ng/mL to 27 ng/mL (P<0.001) and additional toxicities were not observed. The interventions resulted in adequate exposure (≥8.4 ng/mL) in 16 (84%) patients.
- After PK-guided interventions, abiraterone acetate exposure was adequate in 28 (87.5%) patients.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 18 May 2023. Summarized in this response are relevant data from prospective studies.

REFERENCES

1. Arasaratnam M, Crumbaker M, Bhatnager A, et al. Inter- and intra-patient variability in pharmacokinetics of abiraterone acetate in metastatic prostate cancer. *Cancer Chemother Pharmacol*. 2019;84:139-146.
2. Acharya M, Bernard A, Griffin T, et al. A phase 1 study to determine the effect of food on the pharmacokinetics of abiraterone acetate (AA) in healthy male subjects. Poster presented at: The American Association of Pharmaceutical Scientists (AAPS) 2011 Annual Meeting; Washington, DC. 2011.
3. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med*. 2011;364(21):1995-2005.
4. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013;368(2):138-148.
5. Fizazi K, Tran NP, Fein L, et al. Abiraterone plus prednisone in metastatic castration-sensitive prostate cancer. *N Engl J Med*. 2017;377(4):352-360.
6. Attard G, Reid AH, Yap TA. Phase I clinical trial of a selective inhibitor of CYP17, abiraterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J Clin Oncol*. 2008;26(28):4563-4571.
7. Ryan CJ, Smith MR, Fong L, et al. Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J Clin Oncol*. 2010;28(9):1481-1488.
8. Chi KN, Spratlin J, Kollmannsberger C, et al. Food effects on abiraterone pharmacokinetics in healthy subjects and patients with metastatic castration-resistant prostate cancer. *J Clin Pharmacol*. 2015;55(12):1406-1414.
9. Stuyckens K, Saad F, Xu XS, et al. Population pharmacokinetic analysis of abiraterone in chemotherapy-naive and docetaxel-treated patients with metastatic castration-resistant prostate cancer. *Clin Pharmacokinet*. 2014;53(12):1149-1160.
10. Lubberman FJE Benoist GE, Gerritsen W, et al. A prospective phase 1 multicenter randomized cross-over pharmacokinetic study to determine the effect of food on abiraterone pharmacokinetics. *Cancer Chemother Pharmacol*. 2019;84:1179-1185.
11. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone in castration-resistant prostate cancer. *J Clin Oncol*. 2018;36(14):1389-1395.
12. Bryce A, CJ Ryan. Development and clinical utility of abiraterone acetate as an androgen synthesis inhibitor. *Clin Pharmacol Ther*. 2012;91(1):101-108.

13. Inoue K, Shishido A, Vaccaro N, et al. Pharmacokinetics of abiraterone in healthy Japanese men: dose-proportionality and effect of food timing. *Cancer Chemother Pharmacol*. 2015;75(1):49-58.

14. Groenland SL, van Nuland M, Bergman AM, et al. Concomitant intake of abiraterone acetate and food to increase pharmacokinetic exposure: real life data from a therapeutic drug monitoring program. *Eur J Cancer*. 2020;130:32-38.