CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA	202-379
Submission Date:	20 December, 2010
Brand Name:	Zytiga™
Generic Name:	Abiraterone Acetate
Formulation:	250 mg immediate release tablet
OCP Reviewer:	Elimika Pfuma, PharmD, PhD
OCP Team Leader:	Jeanne Fourie Zirkelbach, PhD
Pharmacometrics Reviewer:	Nitin Mehrotra, PhD
Pharmacometrics Team Leader:	Christine Garnett, PharmD
OCP Division:	Division of Clinical Pharmacology V
ORM Division:	Division of Drug Oncology Products
Sponsor:	Centocor Ortho Biotech Inc
Submission Type; Code:	0000/1
Dosing regimen:	A single oral daily dose of 1000 mg abiraterone acetate (four 250 mg tablets) at least (b) (4) hour before or (b) (4) hours after a meal in combination with daily oral prednisone (10 mg).
Indication:	Abiraterone acetate in combination with prednisone in patients with metastatic castration resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel .

OCP Briefing was held on 25 March 2011 and was attended (either in person or by teleconference) by Aakanksha Khandelwal, Amna Ibrahim, Bahru Habtemariam, Brian P Booth, Chandrahas G Sahajwalla, Christine Garnett, Darrell Abernethy, Elimika Pfuma, Gene M Williams, Hua Lillian Zhang, Issam Zineh, Jeanne Fourie Zirkelbach, Jian Wang, Jogarao V Gobburu, Jun Yang, Katherine Fedenko, Katherine Needleman, Ke Liu, Kellie S Reynolds, Kelly Filipski, Lei K Zhang, Mehul U Mehta, Nam Atiqur Rahman, Nitin Mehrotra, Paul Kluetz, Pengfei Song, Ping Zhao, Pravin Jadhav, Qi Liu, Rosane Charlab Orbach, Safaa Burns, Sarah J Schrieber, Shiew Mei Huang, Srikanth Nallani, Susan Jenney, Yang-Min (Max)Ning, Young-Jin Moon, Young M Choi.

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1 Executive Summary

Abiraterone acetate is a pro-drug of its active metabolite abiraterone. Abiraterone is an irreversible inhibitor of 17α-hydroxylase/C17, 20-lyase (CYP17), a key enzyme in the production of androgens in the testes and adrenal glands. The proposed indication is the use of abiraterone acetate in combination with prednisone in patients with metastatic castration resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel.

A special protocol assessment agreement letter for the pivotal trial # COU-AA-301 was issued on March 28, 2008. The pivotal trial was a phase 3 multi-national, randomized, multi-center, double-blind, placebo-controlled study of abiraterone acetate and prednisone in 1195 patients with mCRPC whose disease had progressed on or after docetaxel-based chemotherapy. Patients were randomized 2:1 to receive 1000 mg of abiraterone acetate daily plus 5 mg of prednisone twice daily or placebo plus prednisone using the same dosing regimen, respectively. The primary efficacy endpoint was overall survival (OS) with a median OS of 14.8 months in the abiraterone acetate arm versus 10.9 months in the placebo arm ($P < 0.0001$) showing a hazard ratio of 0.646.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology 5 and Pharmacometrics have reviewed the information contained in NDA 202-379. This NDA is considered acceptable from a clinical pharmacology perspective.

Labeling Recommendations

Please refer to Section 3 - Detailed Labeling Recommendations.

1.2 Phase IV Requirements

1. Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inhibitor (e.g., ketoconazole) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed protocol must be submitted for review prior to trial initiation.

2. Conduct a drug-drug interaction trial to evaluate the effect of a strong CYP3A4 inducer (e.g., rifampin) on the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate. The proposed protocol must be submitted for review prior to trial initiation.

3. Conduct a trial to determine the pharmacokinetics of abiraterone after an oral dose of abiraterone acetate in individuals with severe hepatic impairment. The proposed protocol should contain the rationale for dose selection, and must be submitted for review prior to trial initiation. In the design of the trial, consider development of lower dosage strengths to allow for administration of a safe dose in patients with severe hepatic impairment.

4. Perform an *in vitro* screen to determine if abiraterone is an inhibitor of human CYP2C8. Based on results from the *in vitro* screen, a clinical drug-drug interaction trail may be needed.

1.3 Summary of Clinical Pharmacology Findings

Abiraterone acetate is a pro-drug of its active metabolite abiraterone. Abiraterone is an irreversible inhibitor of 17α-hydroxylase/C17, 20-lyase (CYP17), a key enzyme in the production of androgens in the testes and adrenal glands. CYP17 is expressed in testicular and adrenal tissues and catalyzes the conversion of pregnenolone or progesterone into dehydroepiandrosterone (DHEA) or androstenedione, respectively, which are 2 precursors of testosterone.

The proposed indication is the use of abiraterone acetate in combination with prednisone in patients with metastatic castration resistant prostate cancer (mCRPC) who have received prior chemotherapy containing docetaxel. The proposed dosing regimen is 1000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone acetate should be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

A special protocol assessment agreement letter for the pivotal trial # COU-AA-301 was issued on March 28, 2008. The pivotal trial was a phase 3 multi-national, randomized, multi-center, double-blind, placebo-controlled study of abiraterone acetate and prednisone in 1195 patients with mCRPC whose disease had progressed on or after docetaxel-based chemotherapy. Patients were randomized 2:1 to receive 1000 mg of abiraterone acetate daily plus 5 mg of prednisone twice daily or placebo plus prednisone using the same dosing regimen, respectively. The primary efficacy endpoint was overall survival (OS) with a median OS of 14.8 months in the abiraterone acetate arm versus 10.9 months in the placebo arm ($P < 0.0001$) showing a hazard ratio of 0.646.

A total of 11 completed studies were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA. The single dose studies were performed in healthy volunteers which included seven Phase 1 studies (dose escalation [COU-AA-**008**], dose proportionality [COU-AA-**016**], relative bioavailability [COU-AA-**010** and COU-AA-**014**], bioequivalence [COU-AA-**005**], food effect [COU-AA-**009**] and mass balance [COU-AA-**007**])

and two organ impairment studies (hepatic [COU-AA-**011**] and renal [COU-AA-**012]**). The multiple dose studies were performed in patients with mCRPC, and consist of two Phase 1 studies (CYP2D6 and CYP1A2 drug-drug interaction study [COU-AA-**015**] and QT/QTc interval study [COU-AA-**006]**).

In vivo, abiraterone acetate is hydrolyzed into its active metabolite abiraterone, which then undergoes further metabolism. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples. The main circulating abiraterone metabolites in human plasma are abiraterone sulphate and N-oxide abiraterone sulphate, accounting for about 43% of exposure each. CYP3A4 and SULT2A1 are the enzymes involved in the formation of N-oxide abiraterone sulphate and SULT2A1 is involved in the formation of abiraterone sulphate. Abiraterone is an inhibitor of CYP2D6*, in vivo*. The systemic exposure of dextromethorphan (CYP2D6 substrate) as assessed by the ratios of the geometric mean for Cmax and AUC, were approximately 2.8- and 2.9-fold higher, respectively, when dextromethorphan was co-administered with abiraterone acetate. Following oral administration of ^{14}C-abiraterone acetate in a human mass balance study, approximately 88% of the radioactive dose was recovered in feces and approximately 5% was recovered in urine.

Following oral administration of abiraterone acetate in mCRPC patients, the median time to reach maximum plasma abiraterone concentrations (T_{max}) is approximately 2 hours and the mean terminal half-life is approximately 12 hours. No major deviation from dose proportionality was observed in the dose range of 250 to 1000 mg. Steady state is achieved within eight days (intensive PK sampling was performed on Days 1 and 8 of Cycle 1) following once-daily dosing of 1000 mg, with approximately 2-fold higher exposure at steady state (steady state AUC) compared to when the same dose is administered as a single dose. At the dose of 1000 mg daily in patients with mCRPC, steady state mean values of Cmax were 226 ± 178 ng/mL and of AUC were 1173 ± 690 ng.hr/mL. Inter-subject variability was approximately 79% for Cmax and 64% for $AUC_{0\text{-}24h}$ after multiple day dosing. A food effect was observed with the geometric mean for abiraterone Cmax and AUC $_{0\text{-}\infty}$ increased by approximately 17- and 10-fold, respectively, when abiraterone acetate was administered with a high-fat meal.

In the dedicated hepatic impairment study (COU-AA-011), systemic exposure of abiraterone in the mild hepatic impairment cohort (Child-Pugh Classification A) was comparable to that in the normal hepatic function cohort. Based on geometric mean estimates, the Cmax was 2.7-fold higher and AUC was 3.6-fold higher in the moderate hepatic impairment cohort (Child-Pugh Classification B) compared to the normal hepatic function cohort. The mean $T_{1/2}$ was approximately 4.6 to 5.5 hours longer for the mild and moderate hepatic impairment cohorts compared to the normal hepatic function cohort. No dose adjustments are recommended for patients with mild hepatic impairment. In patients with moderate hepatic impairment, a dose reduction to 250 mg once daily is recommended to achieve abiraterone exposures similar to those in patients with normal hepatic function. Abiraterone acetate has not been studied in severe hepatic impairment and we recommend that it should be avoided in these patients. The assessment of abiraterone acetate in severe hepatic impairment will be done as a Phase IV Requirement.

In the reduced design dedicated renal impairment study (COU-AA-012), systemic exposure of

abiraterone after a single oral 1000 mg abiraterone acetate dose was comparable in subjects with end-stage renal disease (ESRD) on dialysis compared to those with normal renal function. No dose adjustments are recommended for patients with renal impairment.

There were insufficient exposure data collected in the pivotal phase 3 trial to support evidence of exposure-response for OS and safety endpoints (hepatotoxicity, hypokalemia, fluid retention/edema, hypertension). Pharmacokinetic (PK) data were available for only 161 (20%) of the patients in trial COU-AA-301. Limitations in the bioanalytical assay in earlier studies precluded pooling data across clinical trials for safety exposure-response analysis.

(b) (4)

Since efficacy at lower doses or exposures is unknown, reducing the exposures by (b) (4) (b) (4) could result in a loss of efficacy. It is important to note that both the 750 and 1000 mg doses had similar biomarker activity in study COU-AA-001 (phase 1/2 dose ranging study). The two-step dose reduction was specified in the protocol for study COU-AA-301 to manage hepatotoxicity and other toxicities. The majority of the patients (21/27) followed the step dose reduction scheme in the pivotal trial. Approximately 60% (16/27) of the patients had their dose reduced to 750 mg and did not need further dose reduction. Five patients had step dose reductions from 1000 to 750 to 500 mg. Six patients had a direct dose reduction from 1000-500 mg of which two patients subsequently resumed dosing at 1000 mg. It is not clear whether the four patients that were reduced directly to 500 mg and stayed at that dose would have tolerated 750 mg. Thus, having an option to be treated at the 750 mg dose may reduce the likelihood of experiencing hepatotoxicity while maintaining efficacy.

Signatures:

Reviewer: Elimika Pfuma, PharmD/PhD	Team Leader: J Fourie Zirkelbach, PhD
Division of Clinical Pharmacology 5	Division of Clinical Pharmacology 5
Reviewer: Nitin Mehrotra, PhD	Team Leader: Christine Garnett, PharmD
Division of Pharmacometrics	Division of Pharmacometrics

Cc: DDOP: CSO - A Tilley; MTL - K Liu; MO - Y M Ning , Safety MO - P Kluetz
DCP-5: Reviewers - E Pfuma (CP), N Mehrotra (PM)
CP TL - J Fourie Zirkelbach , PM TL - C Garnett
DDD - B Booth DD - A Rahman

2 QUESTION BASED REVIEW

2.1 GENERAL ATTRIBUTES

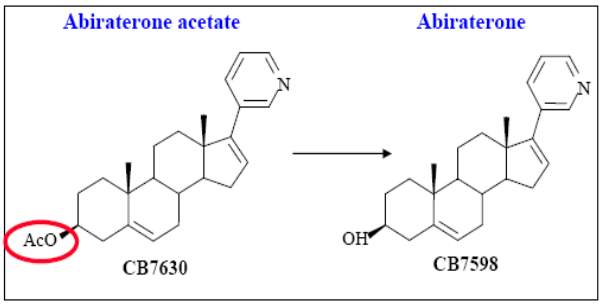
2.1.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

Abiraterone acetate has been developed as 250 mg immediate-release uncoated tablets for oral administration. It is a white to off-white oval shaped tablet debossed with 'AA250'.

Physical-chemical properties

1. **Structural formula:**

Figure 1: Structural Formula of Abiraterone Acetate and its Active Metabolite, Abiraterone

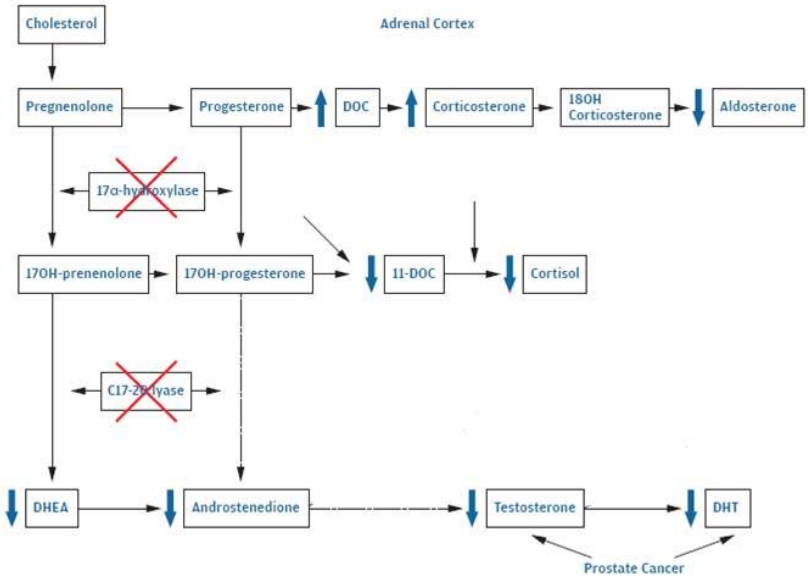


2. **Established names:** Abiraterone Acetate , CB7630
3. **Molecular Weight:** 391.6 Daltons (349.5 for abiraterone)
4. **Molecular Formula:** $C_{26}H_{33}NO_2$ ($C_{24}H_{31}NO$ for abiraterone)
5. **Partition coefficient (log P):** 5.12
6. **Dissociation Constant (pKa):** 5.19 as determined in 0.15M KCl solution
7. **Chemical Name:** 3β-acetoxy-17-(3-pyridyl)androsta-5,16-diene
8. **Melting Point Range:** 147°C to 148°C
9. **Solubility:** Abiraterone acetate is practically insoluble in aqueous media over a wide range of pH values tested (2 - 12) at 20° Celsius and slightly soluble in a 0.1 N HCl solution. Abiraterone acetate is soluble in organic solvents, particularly alcohols.

2.1.2 What are the proposed mechanisms of action and therapeutic indications?

Abiraterone acetate is a pro-drug of its active metabolite abiraterone. Abiraterone is an irreversible inhibitor of 17α-hydroxylase/C17, 20-lyase (CYP17), a key enzyme in the production of androgens in the testes and adrenal glands. CYP17 catalyzes 17α-hydroxylation of C_{21} steroids and cleavage of the C17, 20 bond of C_{21} steroids. The 17α-hydroxylation activity is a step in cortisol biosynthesis, whereas the C17, 20 bond cleavage is needed for subsequent biosynthesis of androgens. The CYP17 enzyme is expressed in testicular and adrenal tissues and catalyzes the conversion of pregnenolone or progesterone into DHEA or androstenedione, respectively, which are two precursors of testosterone.

Figure 2: Proposed Abiraterone Acetate and Abiraterone Mechanism of Action



The applicant claims that since abiraterone is a selective inhibitor of CYP17, it is expected to have improved efficacy and minimized adverse events compared to other anti-androgens due to the reduced risk of non-specific enzyme inhibition affecting the synthesis of glucocorticoids and mineralocorticoids.

The proposed indication is for abiraterone acetate in combination with prednisone in patients with metastatic castration resistant prostate cancer (mCRPC) who have received prior chemotherapy containing a (b) (4)

2.1.3 What are the proposed dosage(s) and route(s) of administration?

The applicant proposes a dosing regimen of 1000 mg of oral abiraterone acetate administered once daily at least (b) (4) hour before or (b) (4) hours after food with prednisone 10 mg daily. However, the clinical trial used prednisone 5 mg twice daily. Therefore, the dosing regimen recommended is, 1000 mg administered orally once daily in combination with prednisone 5 mg administered orally twice daily. Abiraterone acetate should be taken on an empty stomach. No food should be consumed for at least two hours before the dose of abiraterone acetate is taken and for at least one hour after the dose of abiraterone acetate is taken.

2.2 GENERAL CLINICAL PHARMACOLOGY

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

A single pivotal trial in patients with mCRPC was conducted to support the efficacy claim.

Pivotal Phase 3 Trial in Patients with mCRPC (COU-AA-301):

The pivotal trial was a phase 3 multi-national, randomized, multi-center, double-blind, placebo-controlled study of abiraterone acetate (1000 mg daily) and prednisone in patients with mCRPC whose disease had progressed on or after docetaxel-based chemotherapy. This study randomized 1195 patients 2:1 to receive abiraterone acetate plus prednisone or placebo plus prednisone, respectively. Patients received either abiraterone acetate 1000 mg or 4 placebo tablets orally once daily at least 1 hour before or 2 hours after a meal and prednisone 5 mg orally twice daily. In regions where prednisone was not available, prednisolone was provided.

The primary efficacy endpoint was overall survival and the Table 1 below shows a summary of the results based on this primary endpoint.

Table 1: Overall Survival in Patients with Metastatic CRPC (COU-AA-301)

	Abiraterone Acetate (n=797)	**Placebo (N=398)**
Deaths	333 (42%)	219 (55%)
Median Overall Survival in Months (95% CI)	14.8 (14.1, 15.4)	10.9 (10.2, 12.0)
P-value	**< 0.0001**	
Hazard Ratio (95% CI)	**0.646 (0.543, 0.768)**	

CI=confidence interval

The secondary efficacy endpoints were time to prostate specific antigen (PSA) progression, radiographic progression free survival (PFS) and response rate. The other efficacy endpoints were objective response rate, pain palliation rate, time to pain progression, time to first skeletal related event (SRE), modified PFS, circulating tumor cells (CTC) response rate and functional status.

A total of 11 completed studies were used to support the Clinical Pharmacology and Biopharmaceutics Section of the NDA.

Single dose studies in healthy volunteers:

- Seven Phase 1 studies - Dose escalation (COU-AA-**008**), dose proportionality (COU-AA-**016**), relative bioavailability (COU-AA-**010** and COU-AA-**014**), bioequivalence (COU-AA-**005**), food effect (COU-AA-**009**) and mass balance (COU-AA-**007**)
- Organ impairment studies - Hepatic (COU-AA-011) and renal (COU-AA-012)

Multiple dose studies in patients with mCRPC:

2 Phase 1 studies - Drug interaction with CYP2D6 and 1A2 substrates (COU-AA-**015**) and QT study (COU-AA-**006**).

Table 2: Overview of Clinical Pharmacology Related Studies Submitted in NDA

Study Number	**Study Description/Design**	**Subjects Evaluated Sex M/F**	**Treatment Regimen/ Duration**

Start/End Date		Age (yr): Mean (Range) Race (W/B/Ot)	Route of Administration Batch Number
Bioavailability Studies			
COU-AA-010 08 Oct 2009/ 05 Dec 2009	Phase 1, randomized, open-label, single-center, 2-period, 2 sequence crossover study designed to determine the relative bioavailability of abiraterone acetate tablets vs. abiraterone acetate liquid oral formulation in healthy adult male subjects	**Subjects evaluated:** 22 **Sex:** M **Age (yr):** 34 (20-52) **Race (W/B/Ot):** 14/7/1	Abiraterone acetate 1000 mg single dose administered orally under fasted conditions as four 250 mg tablets (Treatment A) and 1000 mg oral liquid formulations in 30 mL olive oil (Treatment B) according to the treatment sequence (AB or BA) with an approximate 7-day washout between dosing periods **Duration:** approximately 38 days to complete both study treatments. **Tablet batch #:** 9405.028 **Liquid formulation batch #:** CMLW-228/09 CR4
Comparative Bioavailability and Bioequivalence Studies			
COU-AA-005 17 Feb 2010/ 13 Apr 2010	Phase 1, single-dose, open-label, randomized, 2-way crossover study designed to determine the bioequivalence and evaluate acute toxicity of abiraterone acetate tablets (1000 mg) manufactured by clinical trial process a (b) (4) (Treatment A) vs. commercial process at Patheon, Inc. (Treatment B) in healthy adult male subjects.	**Randomized subjects**: 120 **Sex:** M **Age (yr)**: **Sequence AB**: 36 (19-55) **Sequence BA**: 34 (18-55) **Race (W/B/Ot)**: **Sequence AB**: 48/11/1 **Sequence AB**: 40/14/5	Abiraterone acetate 1000 mg single dose was administered as four 250 mg tablets orally under fasted conditions according to the treatment sequence (AB or BA) on Days 1 and 8 with an approximate 7-day washout period between each single dose treatment **Duration:** 14 days **Batch numbers:** (b) (4) **Clinical Trial (Treatment A):** 9405.008 **Patheon Commercial (Treatment B):** R0315001
Healthy Subject Pharmacokinetic and Initial Tolerability Studies			
COU-AA-008 17 Dec 2008/ 02 Apr 2009	Phase 1, open-label, dose escalation study designed to evaluate PK and safety of single dose abiraterone acetate in healthy adult male subjects.	**Subjects evaluated:** 33 **Sex:** M **Age (yr):** 37 (22-54) **Race (W/B/Ot):** 19/13/1	Single dose of abiraterone acetate 250 mg, 500 mg, 750 mg and 1000 mg (administered as 250 mg tablets) orally. **Duration:** 22 days per subject **Batch number:** 9405.008
COU-AA-016 30 Mar 2010/ 13 May 2010	Phase 1, single-dose, randomized, open-label, 4-way crossover study to evaluate the effect of dose on the PK of abiraterone in healthy adult male subjects.	**Subjects enrolled:** 32 **Subjects completed:** 27 **Sex**: M **Age (yr):** 37 (22-54) **Race (W/B/Ot):** 22/7/3	Four single doses of abiraterone acetate at 250 mg, 500 mg (2x250 mg tablets), 750 mg (3x250 mg tablets), and 1000 mg (4x250 mg tablets) orally on Study Days 1, 8, 15, and 22 according to the subject's assigned treatment sequence **Batch number:** 9405.023
COU-AA-009 19 Aug 2009/ 05 Oct 2009	Phase 1, randomized, open-label, single dose, 6-sequence, 3-period, crossover study designed to characterize the effect of a standardized high-fat meal and standardized low-fat meal on the PK of abiraterone acetate and its major metabolite(s)	**Randomized subjects:** 36 **Sex:** M **Age (yr):** 38 (25-53) **Race (W/B/Ot):** 26/10/0	Abiraterone acetate administered orally at 1000 mg with a 7-day washout between each dosing period Subjects were randomized to 1 of 6 treatment sequences (ABC, ACB, BAC, BCA, CAB, CBA): Treatment A: Abiraterone acetate tablets taken immediately after a high-fat meal. Treatment B: Abiraterone acetate tablets taken immediately after a low-fat meal. Treatment C: Abiraterone acetate tablets given in the fasted state. **Duration:** The planned total duration of participation for a single subject was 21 days. **Batch number:** 9405.028
COU-AA-007 28 Dec 2009/ 26 Jan 2010	Phase 1, open-label, single dose, mass balance study of ^{14}C labeled abiraterone acetate in healthy male Subjects	**Subjects evaluated:** 8 **Sex:** M **Age (yr):** 33(20 – 53) **Race (W/B/Ot):** 8/0/0	Each subject received a total of 3 capsules containing ^{14}C-abiraterone acetate (Lot No. 60251-09-002), for a total dose of 1000 mg abiraterone acetate (approximately 100 µCi). **Duration:** 30 days for each subject.
COU-AA-014 16 Nov 2009/ 30 Dec 2009	Phase 1, randomized, open-label, single center, single-dose, 4-period (extra-period), 6-sequence, 3-treatment crossover study designed to estimate the relative bioavailability of 3 different abiraterone acetate tablets: 250 mg tablets manufactured using	**Randomized subjects:** 18 **Sex:** M **Age (yr):** 33 (19-55) **Race (W/B/Ot):** 11/7/0	Abiraterone acetate 1000 mg, administered as 4 x 250 mg tablets under fasted conditions; there was a 7-day washout between each dosing period. Subjects were randomized to 1 of 6 treatment sequences (ABCC, ACBB, BCAA, BACC, CABB, CBAA) Duration: 28 days for a single subject **Batch number:**

	the clinical trial process (b) (4) Clinical Trial [Treatment A]), 250 mg tablets manufactured using the commercial process (b) (4) Commercial [Treatment B]), and 250 mg tablets manufactured using the commercial process at a new site (Patheon Commercial [Treatment C]) under fasted conditions in healthy adult male subjects.		(b) (4) **Clinical Trial (Treatment A):** 9405.008 (b) (4) **Commercial (Treatment B):** 9405.028 **Patheon Commercial (Treatment C):** R0315001
COU-AA-011 16 Sep 2009/ 16 Apr 2010	Phase 1, single dose, open-label PK study of abiraterone acetate in non-prostate cancer male subjects with mild or moderate hepatic impairment compared to matched control subjects with normal hepatic function.	**Subjects evaluated:** 24 **Sex:** M **Age (yr):** 53(44 - 61) **Race (W/B/Ot):** 23/1/0	Single dose of 1000 mg abiraterone acetate (4 x 250 mg tablets) given orally. **Duration:** Approximately 22 days for each subject. **Batch number:** 9405.022
COU-AA-012 20 Oct 2009 /28 Jan2010	Phase 1, single dose, open-label reduced/staged pharmacokinetic study of abiraterone acetate in non-prostate cancer male subjects with impaired renal function on stable hemodialysis compared to matched control subjects with normal renal function.	**Subjects evaluated:** 16 **Sex:** M **Age (yr):** 49(40 - 61) **Race (W/B/Ot):** 8/8/0	Single dose of abiraterone acetate 1000 mg (4 x 250 mg tablets) given orally. **Duration:** Approximately 22 days for each subject **Batch number:** 9405.022
Extrinsic Factor Pharmacokinetic Studies			
COU-AA-015 2 Feb 2010/ 12 Aug 2010	Phase 1b, open–label, multi-center, abiraterone acetate plus prednisone drug-drug interaction study with dextromethorphan (Group A) and theophylline (Group B) in subjects with mCRPC who were medically or surgically castrated and had received no more than 1 chemotherapy regimen.	Subjects enrolled and treated: 34 Sex M/F: M Age (yr): Mean (Range): Group A: 69 (44-80) Group B: 68 (55-81) Both: 69 (44-81) Race (W/B/Ot): Group A: 16/0/2 Group B: 16/0/0 Both: 32/0/2	Abiraterone acetate was supplied as 250-mg tablets **Group A:** Received multiple doses of abiraterone acetate plus prednisone (5 mg tablets) and a single dose of dextromethorphan HBr 30 mg on Cycle 1 Day -8 and on Cycle 1 Day 8 under fasting conditions. **Group B:** Received multiple doses of abiraterone acetate plus prednisone and a single dose of theophylline 100 mg on Cycle 1 Day -8 and on Cycle 1 Day 8 under fasting conditions. **Duration:** until disease progression. **Abirateratone acetate batch number:** 9405.028
Efficacy and Safety Controlled Clinical Studies			
COU-AA-301	Phase 3, randomized, double-blind, placebo-controlled, multi-national, multi-center study designed to compare the clinical benefit, safety profile, characterize PK, explore the utility of CTCs as a surrogate for clinical benefit and evaluate the effect of treatment on QoL of abiraterone acetate and prednisone/ prednisolone with placebo and prednisone/ prednisolone in men with mCRPC who had progressed on or after 1 or 2 chemotherapy regimens, at least 1 of which contained docetaxel.	**Randomized (ITT):** 1,195 **Abiraterone acetate:** 797 **Placebo:** 398 **Sex:** M **Age (yr):** 69 (39,95) **Race (W/B/Ot):** 1111/43/39 (20 Asian, 3 American Indian)	Abiraterone acetate 1000 mg (administered as four 250 mg tablets) or 4 placebo tablets orally once daily at least 1 hour before or 2 hours after a meal, and prednisone/prednisolone 5 mg orally twice daily **Duration:** until disease progression (PSA, radiographic and symptomatic) or unacceptable toxicity **Batch numbers:** 9405.008, 9405.009, 9405.010, 9405.011, 9405.012, 9405.013A, 9405.016, 9405.019, 9405.020, 9405.024, 9405.025, 9405.028, R0304001, C1641001
Efficacy and Safety Uncontrolled Clinical Studies			
COU-AA-006 6 Jun 2009	Phase 1, open-label, single-arm, multi-center, study to evaluate effects of abiraterone acetate plus prednisone on cardiac QT/QTc interval by using pharmacokinetic and time-matched ECGs in subjects with metastatic CRPC who failed gonadotrophin releasing hormone (GnRH) therapy and have a PSA ≥ 2 ng/mL, who were medically or surgically castrated, and received	**Subjects evaluated:** 33 **Sex:** M **Age (yr):** 65 (42-85) **Race (W/B/Ot):** 33/0/0	Abiraterone acetate 1000 mg administered as 4 x 250 mg tablets orally once daily at least 1 hour before or 2 hours after a meal and prednisone 5 mg orally twice daily. **Duration:** until disease progression or unacceptable toxicity **Batch numbers:** 9405.021, 9405.022, 9405.023

	no more than 1 course of chemotherapy		

2.2.2 What is the basis for selecting the response endpoints (i.e., clinical or surrogate endpoints) or biomarkers (collectively called pharmacodynamics (PD)) and how are they measured in clinical pharmacology and clinical studies?

The primary efficacy endpoint in the phase 3 protocol (COU-AA-301) was overall survival. Overall survival is an unambiguous endpoint and is generally considered as the gold standard for drug approval in Oncology. In this study, overall survival was defined as the time from randomization to death (regardless of cause). Survival time of living subjects was to be censored at the last date a subject was known to be alive or lost to follow up.

The key secondary efficacy endpoints were:

- time to PSA progression as defined in the PSA working group (PSAWG) criteria;
- radiographic PFS based on imaging studies by investigator;
- and PSA response rate defined as the proportion of patients achieving a PSA decline of at least 50% according to PSAWG criteria.

Comparisons between treatment groups for these three secondary efficacy endpoints were conducted according to Hochberg's test procedure to adjust for multiple testing. The applicant reported PSA at baseline and every 12 weeks thereafter and provided Pharmacokinetic/Pharmacodynamic (PK/PD) analyses with this endpoint. However, the clear relationship of PSA with survival or benefit is not established.

The other efficacy endpoints were:

- objective response rate according to modified RECIST criteria;
- pain palliation rate based on the Brief Symptom Inventory-Short Form (BSI-SF) worst pain intensity score;
- time to pain progression;
- time to first SRE;
- modified PFS which considers PSA progression, increase in glucocorticoid use, pain progression, a SRE or the initiation of new systemic anticancer therapy as well as radiographic progression;
- CTC response rate;
- and functional status based on Functional Assessment of Cancer Therapy–Prostate (FACT-P).

No adjustments for multiple testing were used for these other efficacy endpoints and each comparison between treatment groups used an alpha of 0.05.

The other biomarkers explored by the applicant were luteinizing hormone (LH) and testosterone. Consistent with inhibition of CYP17, testosterone concentrations decreased and LH concentrations increased transiently after administration of single dose abiraterone acetate in healthy subjects (Studies COU-AA-008 and COU-AA-016). In subjects with mCRPC, two steroids (deoxycorticosterone and corticosterone), which are upstream of CYP17, and which can serve as biomarkers of the completeness of CYP17 inhibition, reached peak levels at a dose of

750 mg. Higher abiraterone acetate doses of 1000 mg and 2000 mg did not raise concentrations of these two upstream steroids further (Study COU-AA-001).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. All the submitted clinical pharmacology related studies analyzed samples for abiraterone acetate and its active metabolite abiraterone. In clinical studies, abiraterone acetate plasma concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples.

In the mass balance study (COU-AA-007), the mean plasma Cmax and AUC values were approximately 330- and 402-fold higher, respectively, for total radioactivity in plasma than for abiraterone. These results suggest that the majority of circulating total radioactivity after administration of ^{14}C-abiraterone acetate was associated with downstream metabolites of abiraterone (> 92%). A total of 15 metabolites were detected in human plasma with the main circulating metabolites, abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31), accounting for 43.3% and 43.4% of the radioactivity, respectively. These two metabolites are inactive and were not measured in other clinical studies. Exposures of M45 exceeded human exposure at 1000 mg daily in both rat (at 400 mg/kg/day) and monkey (at 1000 mg/kg/day) at the highest administered doses. The exposure of M31 approximated the human exposure at 1000 mg in monkey, although it is approximately 20% of the human exposure in the rat.

Exposure-response

The applicant conducted two types of exposure-response analysis for effectiveness:

- Association of abiraterone exposures to prostate specific antigen (PSA) and then associating PSA dynamics to OS.
- Direct relationship between exposures of abiraterone and OS.

Because of the ambiguity regarding the appropriateness of PSA as a biomarker in prostate cancer patients, only direct exposure-response analysis relating abiraterone exposures to OS was reviewed.

Exploratory exposure-safety analysis for adverse events of interest (hepatotoxicity, hypokalemia, fluid retention/edema, and hypertension) is presented in Section 2.2.5 below.

2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for efficacy?

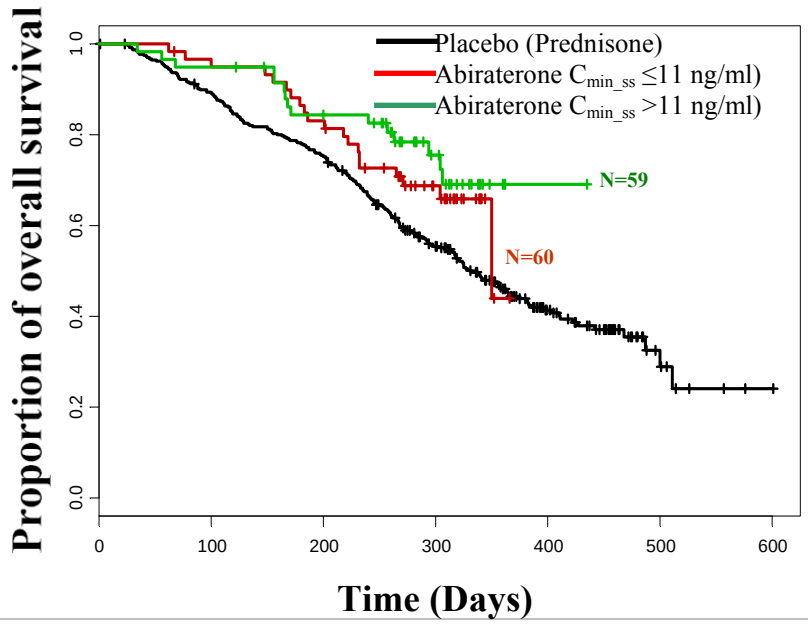
There were insufficient exposure data collected in the pivotal trial to support evidence of exposure-response for overall survival (OS).

An exploratory exposure-efficacy analysis for OS was conducted using data from the pivotal trial (COU-AA-301) following 1000 mg dose of abiraterone acetate (AA). The observed minimum concentration at steady-state (C_{min_ss}) available from 119 patients (15% of the total

enrolled in the AA arm) was used as the exposure variable. Due to the limited number of patients with observed C_{min_ss} levels, exposure data were divided by median into two groups: $C_{min\_ss} \leq 11.1$ ng/ml (N=60) and $C_{min\_ss} > 11.1$ ng/ml (N=59). Figure 3 shows no clear separation between the two exposure groups. However, there is a clear treatment effect as both the exposure groups in the treatment arm were well differentiated from the placebo arm. These results were consistent with the applicant's findings where a Kaplan Meier analysis was conducted using population predicted C_{min_ss} and area under the concentration curve at steady state (AUC_{ss}) values from 161 patients (Figure 4 of the Pharmacometrics review in appendix section 4.1).

Univariate and multivariate Cox proportional hazard analyses did not show C_{min_ss} as a predictor of survival while known risk factors like ECOG (Eastern Cooperative Oncology Group) status, baseline lactic acid dehydrogenase (LDH) and prior cytotoxic therapies were significant factors for survival (Table 3).

Figure 3: Kaplan-Meier Plot for OS (Jan 2010 Cutoff Date, Interim Analysis) Stratified by Exposure Group.



Small black, green and red vertical ticks on the plots are censored observations.

Table 3: Cox-Proportional Hazard Model for OS (Jan 2010 Cutoff Date, Interim Analysis)

Predictor		Slope estimate	SE on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
Univariate						
C_{min_ss} per 10 ng/ml		-0.03238	0.06398	0.61	0.97	0.85, 1.09
LDH per 100 IU/L		0.21577	0.0366	<0.0001	1.24	1.15, 1.33
ECOG	0 vs. 2	-1.60598	0.54367	0.003	0.20	0.07, 0.58
	1 vs. 2	-0.81436	0.41754	0.05	0.44	0.19, 1.00
Prior cytotoxic therapy (1 vs. 2)		-0.94248	0.34447	0.006	0.39	0.19, 0.77
Type of Progression (Radio=1 and PSA=0)		-0.27642	0.40287	0.49	0.75	0.34, 1.67
Multivariate						
C_{min_ss} per 10 ng/ml		-0.01655	0.05038	0.74	0.98	0.89, 1.10
LDH per 100 IU/L		0.24325	0.04127	<0.0001	1.28	1.18, 1.38
ECOG	0 vs. 2	-1.61903	0.55016	0.003	0.19	0.07, 0.58
	1 vs. 2	-1.16793	0.43824	0.007	0.31	0.13, 0.73
Prior cytotoxic therapy (1 vs. 2)		-1.10198	0.35752	0.002	0.33	0.16, 0.67

2.2.5 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety?

As described above, there were insufficient PK data collected in the pivotal trial COU-AA-301 to evaluate the exposure-response for the safety endpoints: hepatotoxicity, hypokalemia, fluid retention/edema and hypertension. Furthermore, there were no PK data collected in phase 2 studies COU-AA-003 and COU-AA-004. PK data collected in early phase 1/2 studies COU-AA-001 and COU-AA-002 could not be used to generate a pooled safety database because of problems with the bioanalytical assay. Specifically, abiraterone acetate had limited stability in blood and plasma in the absence of sodium fluoride and a metabolite with the same mass transition as abiraterone co-eluted with abiraterone.

For Study COU-AA-301, summary statistics of the proportion of patients having adverse events (AEs) by C_{min_ss} category are presented in Table 4.

Table 4: Summary of Adverse Events (AEs) by Exposure Group in COU-AA-301

Exposure Group	Mean C_{min_ss} (ng/ml)	Adverse Event	Proportion of patients with all grade AE's (%)
Lower (Below median C_{min_ss})	6.2	Elevated ALT	1/60 (1.7)
Higher (Above median C_{min_ss})	35.2		2/59 (3.4)
Lower (Below median C_{min_ss})	6.2	Hypokalemia	7/60 (12)
Higher (Above median C_{min_ss})	35.2		11/59 (18)
Lower(Below median C_{min_ss})	6.2	Peripheral edema	21/59 (36)
Higher (Above median C_{min_ss})	35.2		16/60 (27)
Lower (Below median C_{min_ss})	6.2	Hypertension	9/60 (15)
Higher (Above median C_{min_ss})	35.2		5/59 (8.5)

2.2.6 Does this drug prolong the QT or QTc interval?

In a multi-center, open-label, single-arm trial, 33 patients with mCRPC received abiraterone acetate 1000 mg once daily at least 1 hour before or 2 hours after a meal in combination with prednisone 5 mg orally twice daily (Study # COU-AA-006). Assessments up to Cycle 2 Day 2 showed no large changes in the QTc interval (i.e., >20 ms) from baseline.

Serial sets of three time-matched ECGs were obtained on Day -1 of Cycle 1 and Day 1 of Cycles 1 and 2. When data from Cycle 1 and Cycle 2 were combined, the upper bound of the two-side 90% CI for ΔQTcI from Cycle 1 Day -1 baseline was < 10 ms. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline was 4.2 ms, observed at 0.5 hours post-dose on Day 1 Cycle 1. In addition, no significant concentration-QT relationship was detected using the pooled data from multiple treatment cycles. No significant QTc prolongation was observed following daily dosing of abiraterone acetate. No major changes in HR, PR interval or QRS interval duration were noted.

The therapeutic dose of 1000 mg daily was not sufficient to address the high abiraterone exposure scenarios when patients take 1000 mg daily of abiraterone acetate with a high-fat meal (17- and 10-fold increase in Cmax and $AUC_{0-\infty}$, respectively) or when patients taking 1000 mg of abiraterone acetate daily have moderate hepatic impairment (2.7- and 3.6-fold increase in

Cmax and AUC $_{0-\infty}$, respectively). The QT-IRT review stated that the exposure-response relationship trends upward with increasing exposure; however, a 2.6-fold increase in abiraterone exposure has a model predicted ΔQTcI of 1.1 ms (upper 90% CI: 6.6 ms), which is < 10 ms for this exposure scenario. Exposures resulting from administration of abiraterone with a low- or high-fat meal were not explored by QT- IRT as the applicant recommends against administration of abiraterone concomitantly with food.

In the food effect trial (COU-AA-009), 8 out of 36 patients had increases from baseline in QTcB interval of > 30 msec: 6 subjects following a low-fat meal (> 31 - 39 msec) and 2 subjects following dosing with a high-fat meal (33 and 36 msec). There were no post-dose vital sign measurements or changes reported as AEs. The mean values in diastolic BP for the high-fat meal group within 0.5 to 12 hours post-dose were from 3 to 8 mmHg lower than corresponding pre-dose values.

2.2.7 Is the dose and dosing regimen selected by the applicant consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

The applicant states that a dose of 1000 mg dosed at least (b) hour before or (b) hours after food was selected because it offered the most consistent pharmacological and endocrinologic effect and the following were considered:

- A near maximal increase was observed in the mean deoxycorticosterone and corticosterone (steroids upstream of CYP17 that may serve as biomarkers of the completeness of CYP17 inhibition) levels at the 750 mg dose whereas higher doses of 1000 mg and 2000 mg did not further raise the levels. Testosterone and androstenedione concentrations were below the lower limit of detection at the three doses.
- No dose limiting toxicities were observed up to a dose of 2000 mg and a maximum tolerated dose was not determined in early studies.
- The safety profile was considered manageable at the 1000 mg dose level (Study COU-AA-301).
- A marked food effect was observed (Studies COU-AA-001 and COU-AA-BE).

Pharmacokinetic characteristics of the drug and its major metabolites

2.2.8 What are the single dose and multiple dose PK parameters?

Single Dose PK in Healthy Volunteers

Abiraterone acetate is hydrolyzed to abiraterone after oral administration. Abiraterone exhibits approximately linear pharmacokinetics over the dose range of 250 to 1000 mg. Based on the applicant's non compartmental PK analyses from the healthy volunteer studies (Table 5):

- The median abiraterone **Tmax** occurs around 2 hours post-dose.
- Abiraterone exhibits a bi-exponential PK profile with a mean terminal elimination **half-life** of 15.2 hours, with means across studies ranging from 12.7 to 19 hours.

- Abiraterone exposure after a 1000 mg dose of abiraterone acetate had an overall mean (across studies) Cmax of 93.5 ng/mL and AUC∞ of 503 ng*h/mL.
- High **variability** was observed with between-subject variability ranging from 32.7% to 119.8% for Cmax and from 40.5% to 140.6% for AUC∞.

Table 5: Pharmacokinetic Parameters for Abiraterone after Administration of 1000 mg Abiraterone Acetate under Fasting Conditions in Healthy Volunteers

Study		Cmax (ng/mL)	Tmax(h)	AUC_{∞} (ng*h/mL)	$T_{1/2}$ (h)
	N	Mean (SD)	Median (Range)	Mean (SD)	Mean (SD)
COU-AA-005	234	86.0 (47.5)	2 (1 - 8)	465 (212)	14.9 (4.1)
COU-AA-008	8	112 (36.7)	1.8 (1 - 3)	617 (249)	12.7 (1.9)
COU-AA-009	35	90.9 (65.3)	2 (1 - 4)	509 (338)	15.7 (3.7)
COU-AA-010	19	101 (119)	2 (1 - 4)	583 (819)	15.4 (3.0)
COU-AA-011	8	85.7 (46.6)	1.8 (1 - 3)	330 (166)	13.1 (4.2)
COU-AA-012	8	104 (124)	1.5 (1 - 4)	497 (523)	19.0 (4.1)
COU-AA-014	64	93.4 (41.6)	2 (1 - 6)	529 (250)	15.2 (3.2)
COU-AA-016	57	120 (67.5)	2(1 - 4)	610 (275)	16.2 (4.5)
POOLED	**433**	**93.5 (58.6)**	**2 (1 - 8)**	**503 (299)**	**15.2 (4.0)**

Only PK data of patients with no hepatic or renal impairment were used from Studies COU-AA-011 and COU-AA-012. Blood samples for PK analysis of abiraterone were collected at pre-dose (within 0.5 hour prior to dose) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours post-dose in all the studies.

PK in mCRPC Patients

In Study COU-AA-006, 1000 mg of abiraterone acetate was administered once daily along with 5 mg of prednisone twice daily. PK samples were collected in Cycle 1 (28 day treatment cycles) on Days 1 and 8 at pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose and on Days 6 and 7 at pre-dose. In Cycle 2 PK samples were only collected on Day 1 using the same schedule as on Cycle 1 Day 1.

Single Dose:

The Cycle 1 Day 1 mean Cmax and AUC_{∞} values were 1.95- and 1.58- fold higher, respectively, than those reported in healthy subject studies with comparable median Tmax values of approximately 2 hours (Table 6) . Inter-subject variability in subjects with mCRPC was approximately 140% for Cmax and 101% for AUC_{∞}.

Multiple Dose:

In Study COU-AA-006, steady state concentrations were achieved by Day 8 of daily dosing (intensive PK sampling was performed on Days 1 and 8 of Cycle 1). A mean abiraterone accumulation ratio of 2 was observed at steady state (Figure 4). Inter-subject variabilities were approximately 79% for Cmax and 64% for $AUC_{0\text{-}24h}$ after multiple day dosing which were lower than the variabilities seen after a single dose. The single and multiple dose PK parameters are summarized in Table 6 below.

Figure 4: Mean (±SD) Plasma Concentration-Time Profiles of Abiraterone after a Single Administration and After Once Daily Administration of 1000 mg Abiraterone Acetate to Male Patients with Metastatic CRPC in Study COU-AA-006.

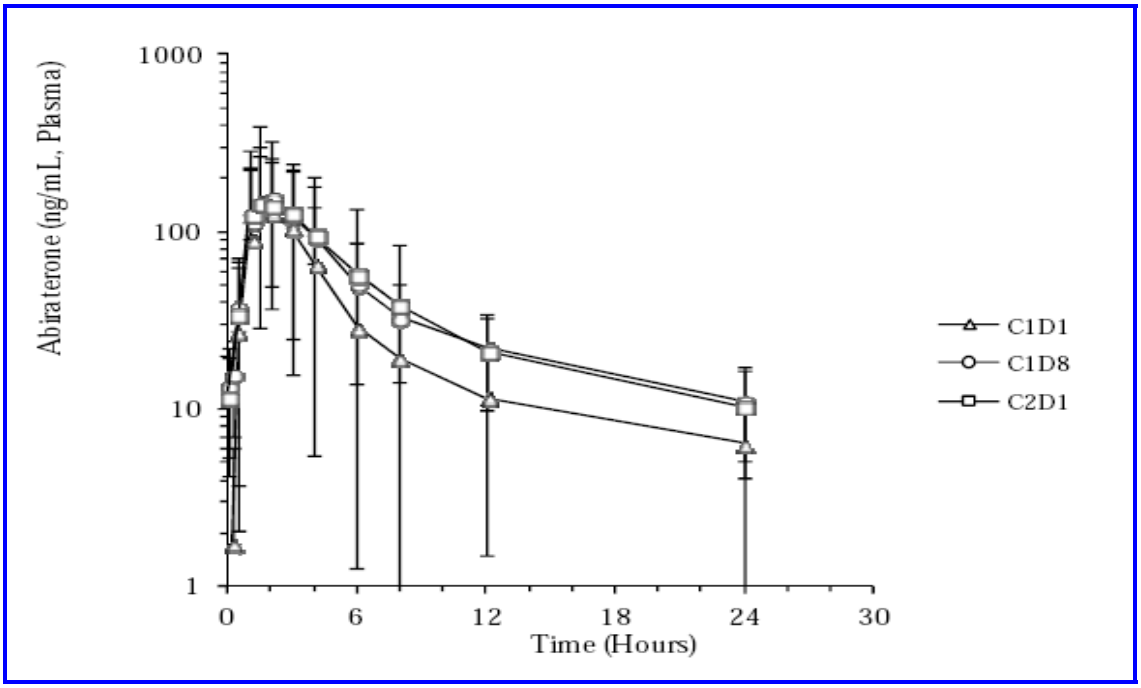


Table 6: Mean (±SD) Single Dose and Steady State Pharmacokinetic Parameters for Abiraterone after Administration of 1000 mg Abiraterone Acetate Daily in Patients with mCRPC in Study COU-AA-006

PK Parameter	C1D1 (N=33)	C1D8 (N=33)	C2D1 (N=33)
Cmax (ng/mL)	182 (254)	207 (142)	226 (178)
Tmax (hr)	2 (1 - 4)	2 (1 - 4)	2 (1-6)
AUC_{last} (hr*ng/mL)	675 (729)	976 (527)	1014 (649)
AUC_{∞} (hr*ng/mL)	798 (809)	1179 (582)	1173 (690)
$T_{1/2}$ (hr)	11.5 (4.1)	12.3 (4.1)	11.6 (5.4)
CL/F (L/hr)	2006 (1233)	1251 (1193)	1198 (782)
V/F (L)	34520 (24896)	23676 (26777)	19669 (13358)

Tmax is reported as median (range). Plasma samples were collected pre-dose and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post-dose.

2.2.9 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

In Study COU-AA-006, mean abiraterone Cmax and AUC_{∞} values after a single dose of abiraterone acetate were 1.95- and 1.58- fold higher, respectively, than those reported in healthy subject studies. The median Tmax values were approximately 2 hours in healthy volunteers and patients. High variability was observed in both the healthy volunteer studies and the studies with patients. Inter-subject variabilities in patients with mCRPC were approximately 140% for Cmax and 107% for $AUC_{0\text{-}24h}$ for the single dose PK. Inter-subject variabilities in healthy volunteer

studies ranged from 32.7% to 119.8% for Cmax and from 40.5% to 140.6% for AUC∞. Although the mean exposures appear higher in patients, the results are confounded by the use of fasting (over night fast and no food for 4 hours post dose) in healthy volunteer studies versus the use of modified fasting (no food for at least 2 hours before or 1 hour after dose) in the patient studies. The use of prednisone (weak CYP3A4 inducer) in the patient studies maybe a confounding factor, although CYP3A4 induction would have the opposite effect resulting in lower abiraterone exposures in patients when compared with healthy volunteers. However, the difference in exposures between patients and healthy volunteers is within the limits of inter-individual variability observed for abiraterone and is likely not clinically relevant.

2.2.10 What are the characteristics of drug absorption?

Abiraterone acetate is converted into the active metabolite abiraterone with a mean **T_{max}** for abiraterone of 2 hours. Based on *in vitro* studies using Caco-2 cell monolayers, both abiraterone and abiraterone acetate have a low apparent permeability and are not substrates of P-glycoprotein (P-gp). Based on the low solubility and permeability, the applicant classifies abiraterone acetate as a BCS Class IV compound. The absolute bioavailability has not been established.

In Study COU-AA-009, systemic exposure of abiraterone increased with the administration of food compared to the fasted state. Compared with the fasted state, the geometric mean for abiraterone Cmax and AUC $_{0-\infty}$ increased by approximately 7- and 5-fold, respectively, when administered with a low-fat meal and by approximately 17- and 10-fold, respectively, when administered with a high-fat meal. The median abiraterone Tmax and mean $T_{1/2}$ were not affected by administration of food (Table 21).

In Study COU-AA-010, systemic exposures of abiraterone were approximately 4.5-fold higher when abiraterone acetate was administered as an oral liquid olive oil formulation compared with oral tablets (Table 7). The Tmax and $T_{1/2}$ were comparable with both formulations. The results from these two studies indicate that fat increases the bioavailability of abiraterone following administration of abiraterone acetate tablets.

Table 7: Estimated Geometric Means and Ratios with Associated 90% CI between Pharmacokinetic Parameters of Abiraterone: Oral Liquid Olive Oil Formulation versus Oral Tablet Formulation in Study COU-AA-010.

Parameter	1000 mg Liquid Formulation (LS Mean) N=18	1000 mg (4 * 250mg) Tablets (LS Mean) N=18	Liquid/ Tablet (%)	90% CI (%)	Intra-subject CV (%)
Cmax (ng/mL)	347	76	456	(353.0, 589.8)	46.3
$AUC_{0-\infty}$ (hr*ng/mL)	1907	433	441	(367.9, 528.4)	31.9
AUC_{0-t} (hr*ng/mL)	1893	421	450	(373.9, 540.8)	32.5

Parameter data were natural log (ln) transformed and dose normalized prior to analysis.

2.2.11 What are the characteristics of drug distribution?

Plasma Protein Binding

Abiraterone is highly bound to human plasma proteins (98.8 to 99.9%). It is highly bound to both human serum albumin (HSA) ranging from 95.6 to 99.9% and human α_1-acid glycoprotein (AAG) ranging from 89.4 to 95.7%. Plasma protein binding of abiraterone acetate has not been investigated.

In (b) (4) Study # 8202266 ultrafiltration was used, *in vitro*, to determine the extent of binding of C-abiraterone (0.1, 0.5, 1, 5 and 10 µM) to plasma proteins in rat, monkey and human plasma and in solutions of isolated plasma proteins HSA and AAG. In human plasma, the plasma protein binding of ^{14}C –abiraterone was determined to be 98.8 to 99.1% and was found to be concentration independent in the range studied. A mean Cmax of approximately 0.64 nM is observed in clinical studies at a dose of 1000 mg which is included in the concentration range for this protein binding study. Abiraterone was highly bound to 45 mg/mL of HSA (95.6% to 97.6%) and 1 mg/mL of human AAG (94.3% to 95.7%).

In Study # FK7603 equilibrium dialysis was used, *in vitro*, to determine the extent of binding of ^{14}C-abiraterone to plasma proteins in mouse, rat, rabbit, monkey and human plasma (175, 350 and 1750 ng/mL about 0.5 – 5 µM) and in solutions of 43 mg/mL HSA and 0.7 – 2.0 mg/mL AAG (1750 ng/mL). The binding of ^{14}C-abiraterone was determined to be 99.9% to human plasma, 99.9% to HSA and 89.4 to 94.4% to human AAG.

Equilibrium *in vitro* analysis (Study # FK7448) was also used with plasma samples obtained from the hepatic impairment trial (COU-AA-011) that enrolled volunteers with mild and moderate hepatic impairment. The unbound fraction (fu) of abiraterone in the plasma of subjects with mild hepatic impairment, moderate hepatic impairment and normal hepatic function was 0.22 ± 0.12%, 0.19 ± 0.06 % and 0.19 ± 0.07% respectively (99.8% protein binding irrespective of hepatic function). Considering hepatic clearance may be affected by fu (CLh= Qh * (CLint * fu/ Qh + [CLint * fu]), this analysis was performed to ensure that the results observed in the hepatic impairment trial were not confounded by fu as protein binding may be affected in hepatically impaired individuals. The results of this analysis indicate that the conclusions were not confounded by protein binding and that protein binding did not change based on hepatic function.

Blood to Plasma Ratio

In the human mass balance study COU-AA-007, the mean whole blood to plasma $AUC_{0-\infty}$ ratio (AUC_R) was 0.523, indicating that the radioactivity was preferentially retained in the plasma component of blood**.**

Tissue Distribution

The apparent steady state volume of distribution (Vd) is 19 669 ± 13 358 L, which may suggest that abiraterone is extensively distributed to peripheral tissues. The Vd may be overestimated due to the likely low bioavailability of abiraterone acetate.

Transporter Proteins

Based on *in vitro* studies with Caco-2 cells, abiraterone and abiraterone acetate are not substrates for P-gp. Abiraterone has little inhibition effect on P-gp whereas abiraterone acetate inhibits P-gp significantly, with an IC_{50} of 10.8 μM *in vitro*. However, since abiraterone acetate was not detectable in the plasma of most human PK samples collected, the likelihood of an *in vivo* interaction is low.

No studies have been conducted with other transporter proteins.

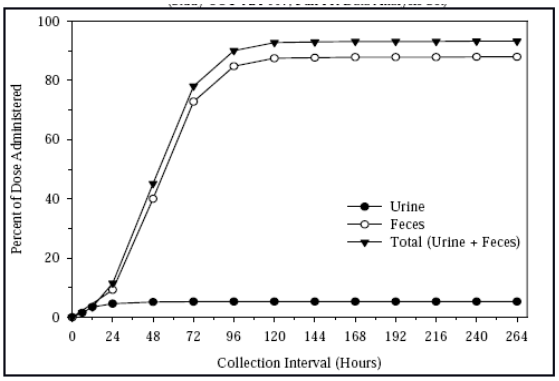
2.2.12 Does the mass balance study suggest renal or hepatic as the major route of elimination?

The phase 1, open-label, single dose, mass balance study of ^{14}C labeled abiraterone acetate in healthy male subjects suggests that renal is a minor route of elimination.

Eight healthy male volunteers received a single dose of 1000 mg (approximately 100 μCi) of ^{14}C-labeled abiraterone acetate (Figure 5).

- The mean total **recovery** of radioactivity in urine and feces combined was approximately 93% with approximately 5% recovered in **urine** and 88% recovered in **feces**.
- The main metabolite excreted in urine N-oxide-abiraterone sulfate (M31) was present at approximately 4% of the dose and neither abiraterone acetate nor abiraterone were detected in the urine.
- The major components in feces included unchanged abiraterone acetate and abiraterone at approximately 55% and 22% of the dose, respectively.
- The mean $\mathbf{CL_R}$ value of 1.44 L/hr was less than the typical glomerular filtration rate (GFR) in the kidney (approximately 7.5 L/hr).

Figure 5: Mean Cumulative Percent of Radioactive Dose Recovered in Urine and Feces at Specified Intervals after a Single 1000 mg (100 μci) Oral Dose of [^{14}C]-Abiraterone Acetate to Healthy Male Subjects in Study COU-AA-007.



The absolute bioavailability of abiraterone acetate is unknown. Compared to other studies, the systemic exposure (Cmax and AUC) values for abiraterone are significantly lower in this study (10 fold lower). The applicant states that this may be because the regular formulation is micronized and has excipients that were not used in this non-micronized radioactive drug

material. These two factors may confound the results of the mass balance study. However, since neither abiraterone acetate nor abiraterone are detected in urine it is likely that the renal route is not a significant route of elimination and abiraterone undergoes extensive metabolism. In addition, $\mathbf{CL_R}$ (amount of drug excreted in the urine/$AUC_{0-\infty}$) was far less than GFR (1.4 vs. 7.5 L/hr).

2.2.13 What are the characteristics of drug metabolism?

Abiraterone acetate is converted to abiraterone and the conversion is likely through esterase activity (the applicant has not identified esterases involved) and is not mediated by cytochrome P450 (CYP). The main circulating metabolites in human plasma are abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31), accounting for about 43% of exposure each (about 87% together). Based on *in vitro* studies, CYP3A4 is involved in the formation of the phase 1 metabolites, SULT2A1 is predominantly involved in the formation of abiraterone sulphate metabolites and UGT1A4 is predominantly involved in the formation of abiraterone glucuronide metabolites.

In vitro

Metabolic Profiling and Identification

^{14}C-Abiraterone acetate was stable in human plasma over a 120-second incubation period at 37ºC and the applicant states that this suggests that esterases in human plasma are not responsible for the conversion of ^{14}C –abiraterone acetate to ^{14}C –abiraterone. However, the esterases responsible for the conversion have not been identified.

Experiment # 8202268 was performed to determine the specific involvement of CYP450, UGT and SULT isoenzymes in the metabolism of ^{14}C-Abiraterone using human hepatic microsomes, cytosol and recombinant human isoenzymes.

- The conversion of ^{14}C –abiraterone acetate (5 μM) to ^{14}C-abiraterone (deacetylation) in human hepatic microsomes (0.5 mg/mL) was rapid, with conversion nearly complete after 0.33 minutes of incubation. This conversion did not require NADPH suggesting that it was not CYP mediated.
- Seven metabolites were identified for ^{14}C –abiraterone in pooled human hepatic microsomes and cytosol.
- **CYP3A4** was involved in the formation of the *in vitro* phase 1 metabolites designated as CYP M1, M2, M3 and M4.
- **SULT2A1** was predominantly involved in the formation of the abiraterone sulphate metabolite designated SULT M1.
- **UGT1A4** was predominantly involved in the formation of abiraterone glucuronide metabolites designated UGT M1 and M2 with a minor contribution of UGT1A3.

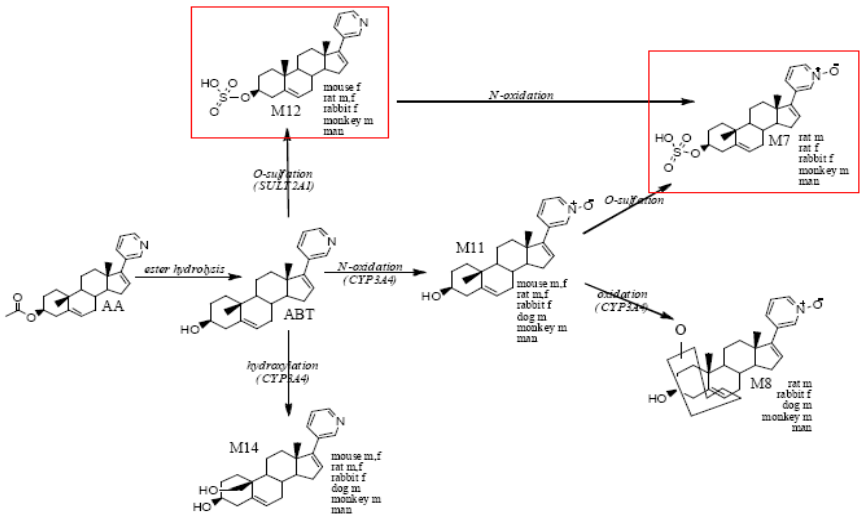
Experiment # 400380 was performed to profile and tentatively elucidate the structure of metabolites following abiraterone acetate incubation with human cryopreserved hepatocytes. The results indicated, that the major *in vitro* biotransformation pathway of abiraterone acetate in human was its deacetylation producing abiraterone (CB7598) followed by sulfate and glucuronic acid conjugation, alone or in combination with oxidation and mono and dioxidation of

abiraterone.

Experiment # FK7389 investigated the *in vitro* metabolism of abiraterone acetate in liver microsomes and hepatocytes of male and female mouse, male and female rat, male dog, female rabbit, male monkey and human.

- The metabolism of ^{14}C-abiraterone acetate with regard to the disappearance of the parent drug was extensive since within less than 5 minutes all abiraterone acetate was completely converted to abiraterone by ester hydrolysis in all animal and human microsomes and hepatocytes tested.
- In liver microsomes, 9 metabolites (coded M2, M3, M4, M5, M8, M11, M13, M14 and M15) were detected. Major human metabolites were M14, M8 and M11. M3 and M15 were minor human metabolites. M14 and M8 were also major metabolites in male rat and dog microsomes.
- In hepatocytes, 10 metabolites (coded M1, M2, M5, M6, M7, M8, M9, M10, M12 and M14) were detected. In most animal (except male mouse and dog) and human hepatocytes, M12 (abiraterone sulfate) was clearly the major metabolite. (The major metabolites also identified in the human mass balance study are shown in Figure 6 in red boxes)
- The major *in vitro* metabolic pathway of abiraterone acetate in man was ester hydrolysis producing abiraterone followed by O-sulfate conjugation (M12) or followed by mono- (M11 and M14) and di-oxidation (M8), which could include hydroxylation as well as N-oxidation.
- The *in vitro* metabolic profiles in human and monkey were qualitatively as well as quantitatively comparable.

Figure 6: The Proposed Major *In Vitro* Metabolic Pathways. The Major Metabolites Identified in the Human Mass Balance Study, Abiraterone Sulphate and N-oxide Abiraterone Sulphate are shown in red.



The purpose of Experiment # **8216184** was to determine the concentrations of radioactivity and the purpose of Experiment # **8216188** was to profile and identify the metabolites in blood, plasma, urine and fecal samples and the percent of dose in urine and fecal samples collected

from eight healthy male subjects in Study COU-AA-007. Plasma, urine and fecal samples were collected pre-dose and up to 96 hours post dose.

- In Study COU-AA-007, the mean plasma exposures were approximately 400 fold higher for total radioactivity in plasma than for abiraterone suggesting that the majority of circulating total radioactivity was associated with downstream metabolites of abiraterone (92.4%).
- A total of 15 metabolites were detected in human plasma using LC-MS/MS and/or radio-HPLC analysis with the main circulating metabolites, abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31), accounting for 43.3% and 43.4% of the radioactivity, respectively (Table 8).
- The other detectable metabolites each accounted for 0.3 to 1.7% of the total radioactivity AUC_{0-8}.
- The maximum mean concentrations of drug-derived radioactivity in blood and plasma were observed at 4 hours post-dose.
- The mean $T_{1/2}$ values of the major metabolites M31 and M45 were 21.6 hours and 2.47 hours, respectively. The applicant states that the half-life of M31 maybe overestimated due to limited sampling time with the AUC calculated up to 8 hours.

Table 8: Pharmacokinetic Parameters of Metabolites in Plasma after a Single 1000 mg (100 µci) Oral Dose of [^{14}C]-Abiraterone Acetate to Healthy Male Subjects in Study COU-AA-007.

	M23	M31	M38	M45 M74*	M61/M73	M62	M65	M68	M70	M72
AUC_{0-8h} (ng eq h/g)	139	**7980**	110	**8000**	92.1	94.8	153	305	103	59.8	NC
$AUC_{0-\infty}$ (ng eq h/g)	NC	NC	NC	9880	NC	NC	NC	NC	NC	NC	NC
AUC_{0-8h} metabolite/ AUC_{0-8h} total radioactivity (%)	0.76	**43.3**	0.6	**43.4**	0.50	0.51	0.83	1.66	0.56	0.32	NC
Cmax (ng.eq/g)	44.1	**1410**	32.7	**1620**	28.0	26.3	31.5	65.0	23.4	17.8	19.0
Tmax (hours)	3.0	4.0	3.0	4.0	8.0	4.0	3.0	6.0	8.0	3.0	3.0
$T_{½}$ (hours)	NC	21.6	2.58	2.47	NC	NC	NC	NC	NC	NC	NC

2.2.14 What are the characteristics of drug excretion?

Elimination

In Study COU-AA-007**,** a mean of 87.9% of the dose was recovered in feces and 5.3% was recovered in urine through the last collection interval. The mean total recovery of radioactivity in urine and feces combined was approximately 93%. Urine and fecal samples were collected at the intervals of -12 - 0 hours (pre-dose) and 0 - 6, 6 -12, 12 - 24, 24 - 48, 48 - 72, 72 – 96 hours post dose and at 24 hour intervals until clinic discharge criteria (2 samples below the limit of quantification or ≥ 90% of dose recovered) were met. In the absence of absolute bioavailability data, 88% of drug in feces may suggest limited systemic absorption of abiraterone acetate and not that the fecal/biliary route is the major route of excretion. However, since 4% of the dose was excreted in urine as the metabolite M31 with neither abiraterone acetate nor abiraterone

detected in the urine, it is likely that limited unchanged drug is eliminated renally and the drug undergoes extensive metabolism.

Clearance

The apparent steady-state CL of abiraterone in patients estimated using non compartmental PK analyses is 1198 ± 782 L/hr. The apparent steady-state Vd of abiraterone is estimated as 19 669 ± 13 358 L.

Half-life

Abiraterone exhibits a bi-exponential PK profile with a mean terminal elimination **half-life** of 12 hours in patients with mCRPC.

2.2.15 Based on PK parameters, what is the degree of linearity or non-linearity based in the dose-concentration relationship?

The doses of 250, 500, 750 and 1000 mg were evaluated in 2 studies (Studies COU-AA-008 and COU-AA-016). The PK of abiraterone appears to increase with an increase in dose with no major deviations from dose proportionality. Although the analysis of dose proportionality is confounded due to the presence of large inter-individual variability in exposure, there does not appear to be a major deviation from dose proportionality.

Study COU-AA-008 was a dose escalation study designed to evaluate PK and safety of single dose abiraterone acetate in healthy adult male subjects. Systemic exposure of abiraterone generally increased with an increase in abiraterone acetate dose up to 1000 mg, but no formal statistical assessment of dose-proportionality was done.

Study COU-AA-016 was a single-dose, randomized, open-label, 4-way crossover study to evaluate the effect of dose on the PK of abiraterone in healthy adult male subjects. Systemic exposure as measured by Cmax, AUC_{last} and $AUC\infty$ increased with increasing dose (Table 9).

Table 9: Mean (±SD) Plasma Pharmacokinetic Parameters for Abiraterone after Single Doses of Abiraterone Acetate Ranging from 250 – 1000 mg in Healthy Fasting Subjects in Study COU-AA-016.

PK Parameter	250 mg (N=27)	500 mg (N=29)	750 mg (N=28)	1000 mg (N=29)
Cmax (ng/mL)	39.9 (25.3)	67.0 (34.7)	87.0 (43.3)	125 (76.4)
Tmax (hr)	2 (1-6)	2 (1-4)	2 (1-4)	2 (1-4)
AUC_{last} (hr*ng/mL)	195 (109)	336 (156)	438 (189)	607 (298)
AUC_{∞} (hr*ng/mL)	210 (105)	345 (155)	449 (189)	621 (300)
$T_{1/2}$ (hr)	14.4 (4.5)	15.3 (4.1)	16.5 (4.5)	16.0 (4.6)

Tmax is reported as median (range)

Using a linear fixed effects model (Table 10), the test to reference ratio was within the 80 – 125% confidence interval limits for Cmax at 500, 750 and 1000 mg and for AUC at 500 mg. The 90% confidence intervals did not fall into the 80 – 125% range for the AUC at 750 and 1000 mg although some overlap could be seen. Inter-subject variability was relatively high, with CVs

ranging from 49.8 to 63.4% for Cmax and from 42.0 to 55.8% for the AUCs. Intra-subject variability for most subjects was approximately 31% for AUC∞ and 42% for Cmax.

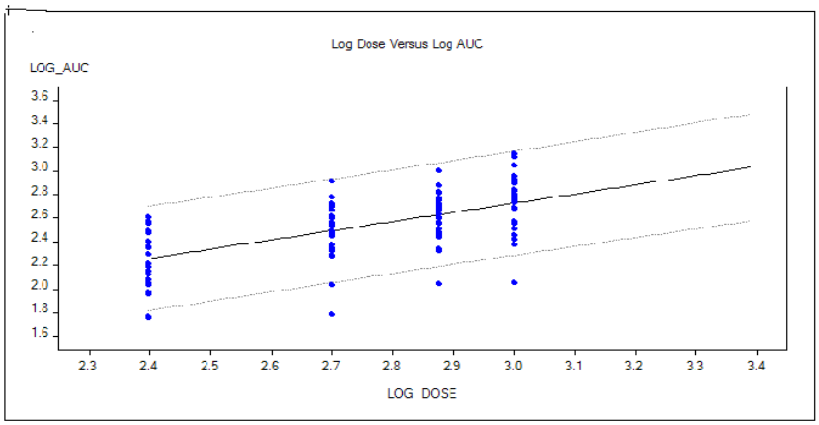
Table 10: Statistical Analysis of Dose-Normalized Pharmacokinetic Parameters Estimated After Single Doses of Abiraterone Acetate Ranging from 250 – 1000 mg in Healthy Fasting Subjects in Study COU-AA-016.

PK Parameter	Dose	LS Mean (normalized to 250 mg)	Test/Reference Ratio (%)	90% CI
Cmax (ng/mL)	250 (Reference)	31.33		
	500	29.83	95.23	(79.02, 114.77)
	750	26.12	83.39	(69.20, 100.49)
	1000	25.68	81.98	(68.02, 98.80)
AUC_{∞} (hr*ng/mL)	250	181.16		
	500	160.54	88.62	(77.00, 102.00)
	750	139.85	77.20	(67.09, 88.83)
	1000	140.36	77.48	(67.32, 89.17)

Parameter data were natural log (ln) transformed and dose normalized prior to analysis.

The Clinical Pharmacology Reviewer applied a power model to test dose proportionality. The results suggested that the slope for the power model on logarithmic scale for AUC is 0.80 with a 90% confidence interval of (0.69, 0.92), which is overlapped with the confidence interval of (0.8, 1.25). Although the analysis of dose proportionality is confounded due to the presence of large inter-individual variability in exposure, there does not appear to be a major deviation from dose proportionality.

Figure 7: Log AUC (ng*hr/mL) Plotted Against Log of Dose (mg) in the Dose Proportionality Study COU-AA-016 in the Dose Range of 250 to 1000 mg.



The dotted lines indicate the confidence interval around the estimates

2.2.16 How do the PK parameters change with time following chronic dosing?

A mean abiraterone accumulation ratio of 2 was observed at steady state with similar exposures on Day 1 of Cycle 2 (28 day treatment cycles) as compared to Day 8 of Cycle 1 after daily

dosing. In mCRPC patients, inter-subject variability was approximately 79% for Cmax and 64% for AUC_{24h} after multiple day dosing compared to 140% for Cmax and 107% for AUC_{24h} after a single dose in mCRPC patients.

2.2.17 What is the inter- and intra-subject variability of PK parameters in volunteers and patients, and what are the major causes of variability?

High variability was observed with between-subject variability ranging from 32.7% to 119.8% for Cmax and from 40.5% to 140.6% for AUC in healthy volunteers. Inter-subject variability was approximately 79% for Cmax and 64% for AUC_{24h} after multiple day dosing compared to 140% for Cmax and 107% for AUC_{24h} after a single dose in mCRPC patients.

The applicant describes the absorption of abiraterone acetate as complex and highly variable. The large variability seen is likely due to abiraterone acetate having low solubility and permeability (BCS Class IV). BCS Class IV drugs are generally considered to have poor and highly variable bioavailability.

In study COU-AA-009, the inter-subject variability (CV %) in the exposure parameters decreased with administration of food, specifically with increasing fat content. Inter-subject variabilities of 72, 55 and 37 % were observed for $AUC_{0-\infty}$ when abiraterone was taken under fasting conditions, with a low fat meal and with a high fat meal, respectively. However, since it is impractical to standardize meals in clinical practice a large variability in exposure may be seen if abiraterone acetate is dosed with a meal, because a high fat meal increases the AUC 10-fold and a low fat meal increases the AUC 4-fold when compared to fasting conditions (overnight fast and fast for 4 hours post-dose). The impact of modified fasting (fast atleast 2 hours before and 1 hour after dose) that was used in the studies in mCRPC patients and is proposed for use clinically is unclear based on the data submitted in the submission.

2.3 INTRINSIC FACTORS

2.3.1 What intrinsic factors (age, race, weight, height, genetic polymorphisms and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

No formal studies have been conducted to assess the effect of age, race, weight, height or genetic polymorphisms on exposure and response. The applicant's population pharmacokinetic (Pop PK) model did not identify weight or age as covariates on clearance. The effect of race was difficult to assess using a Pop PK approach as > 93% of the patients were Caucasian in the clinical trials.

Relationship between Race and Exposure

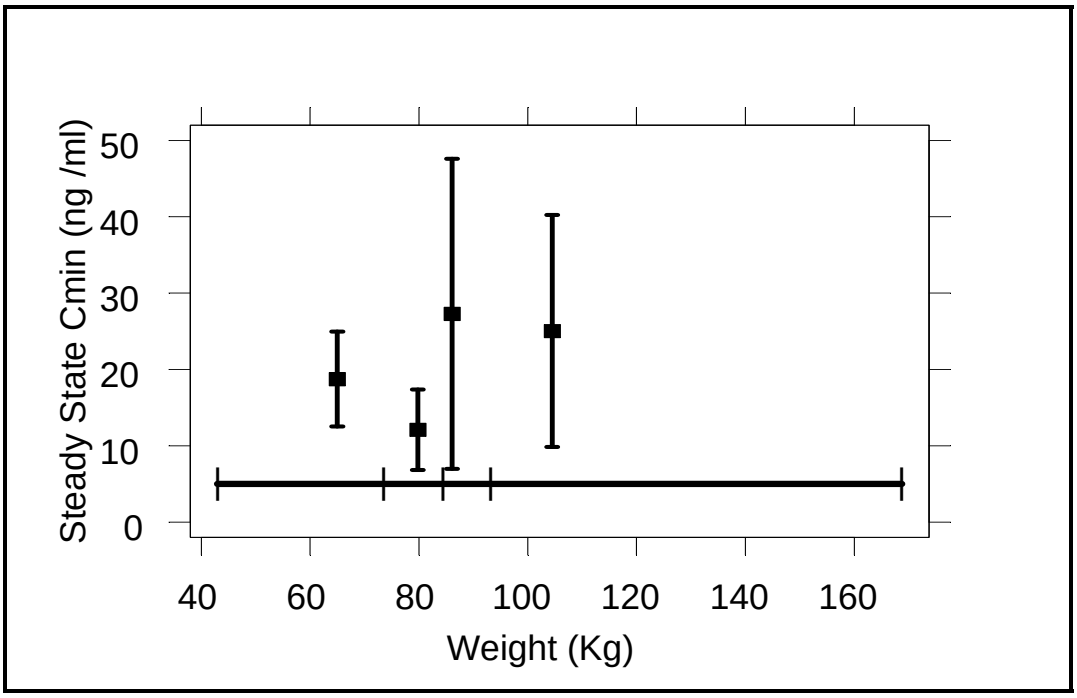
The potential effects of race/ethnicity on the pharmacokinetics of abiraterone were not formally investigated. The vast majority of subjects enrolled in the clinical studies were Caucasian males

(> 93 %). The reason for this is unclear. The incidence of prostate cancer is higher in Blacks/African Americans compared to other races (234.6 per 100000 men in Blacks compared to 150.4 per 100,000 men in Caucasians). In addition, abiraterone acetate is a SULT2A1 substrate. SULT2A1 polymorphisms associated with decreased activity and expression have been identified in African Americans (BA Thomae et al. Pharmacogenomics J. 2002; 2(1): 48-56 and Wilborn TW et al. J Steroid Biochem Mol Biol. 2006; 99(4-5):209-14). Considering, the number of African Americans in the clinical studies was very limited and no genotyping was performed in the clinical trials, the influence of the polymorphisms is difficult to determine.

Relationship between Weight and Exposure

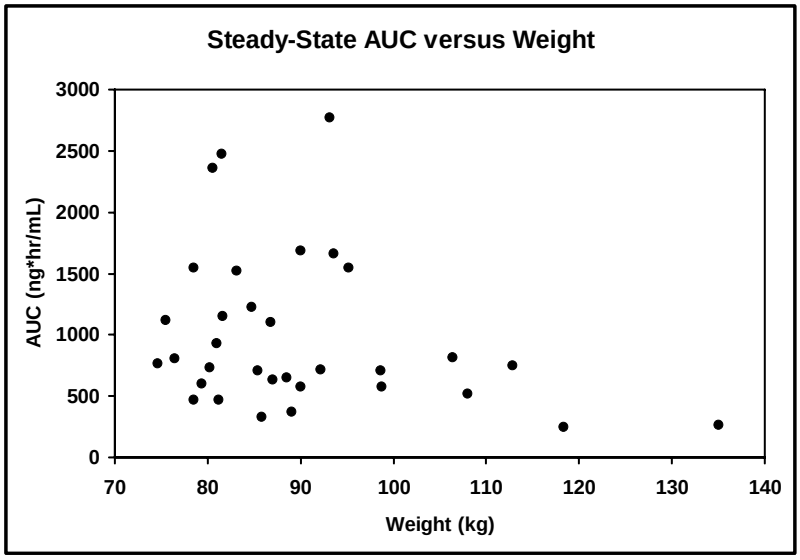
No significant differences were observed in the pharmacokinetics of abiraterone based on weight. Figure 8 shows the weight of 119 patients from Study COU-AA-301 divided into quartiles against observed steady-state Cmin values. Figure 9 shows 33 patients from Study COU-AA-006, with the steady-state AUC plotted against weight (75 - 135 kg).

Figure 8: Abiraterone Observed Steady-State Cmin (ng/mL) from 119 Patients from Study COU-AA-301 Following 1000 mg Daily Doses of Abiraterone Acetate Plotted Against Body Weights Divided Into Quartiles. The Plot Shows No Relationship Between Exposures and Weight.



The vertical black bars represent the mean with 95% confidence interval. The body weight range in each weight quartile is denoted by the horizontal black line. Exposures are demonstrated as black squares at the median body weight of each quartile.

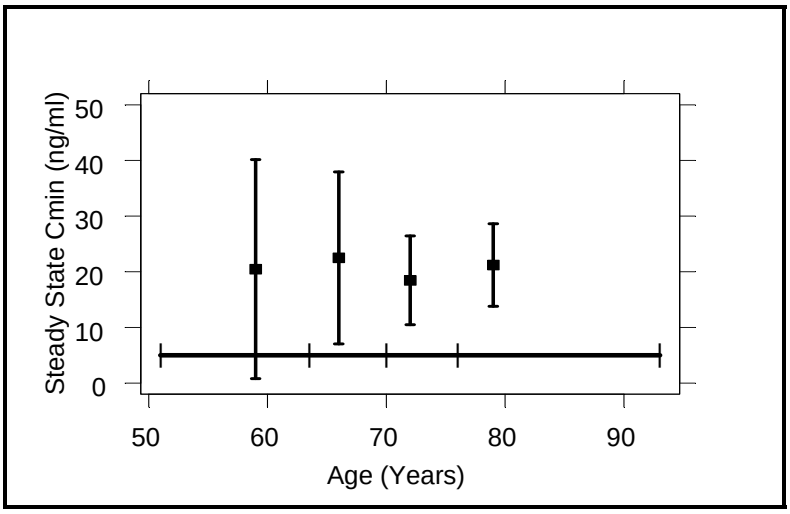
Figure 9: Abiraterone Steady-State AUC (ng*hr/mL) Plotted Against Weight (75 - 135 kg) in 33 Patients from Study COU-AA-006 Who Received Daily Doses of 1000 mg Abiraterone Acetate. The Plot Shows No Relationship Between Exposures and Weight.



Relationship between Age and Exposure

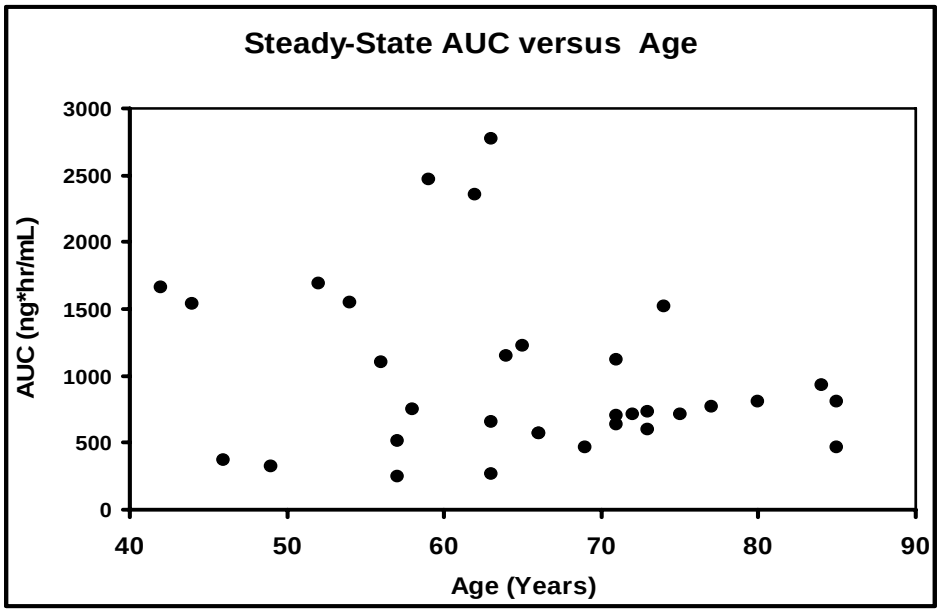
No significant differences were observed in the pharmacokinetics of abiraterone based on age. Figure 10 shows the age of 119 patients from study COU-AA-301 divided into quartiles versus the steady-state Cmin values. Figure 11 shows 33 patients from study COU-AA-006 with the steady-state AUC plotted against age (42 – 85 years).

Figure 10: Abiraterone Observed Steady-State Cmin (ng/mL) from 119 Patients from Study COU-AA-301 Following 1000 mg Daily Doses of Abiraterone Acetate Plotted Against Ages Divided Into Quartiles. The Plot Shows No Relationship between Exposures and Age.



The vertical black bars represent the mean with 95% confidence interval. The age range in each age quartile is denoted by the horizontal black line. Exposures are demonstrated as black squares at the median age of each quartile.

Figure 11: Abiraterone Steady-State AUC (ng*hr/mL) Plotted Against Age (42 -85) in 33 Patients from Study COU-AA-006 Who Received Daily Doses of 1000 mg Abiraterone Acetate. The Plot Shows No Relationship between Exposures and Age.



Relationship between Hepatic Impairment and Exposure:

In a dedicated hepatic impairment trial (COU-AA-011), systemic exposure of abiraterone for the mild hepatic impairment cohort (Child-Pugh Classification A) was comparable to that in the normal hepatic function cohort. The geometric mean Cmax was approximately 16% lower than that in the normal hepatic function cohort, while the geometric mean AUC was approximately 1.1 fold higher. Based on geometric mean estimates, the Cmax was 2.7 higher and AUC was 3.6 fold higher in the moderate hepatic impairment group (Child-Pugh Classification B) compared to the normal hepatic function group. The mean elimination $T_{1/2}$ was approximately 4.6 to 5.5 hours longer for the mild and moderate hepatic impairment cohorts compared to the normal hepatic function cohort (Table 11 and 12). Large inter-subject variability in Cmax, AUC_{last}, and $AUC\infty$ was seen in all cohorts (CV = 84% [52 – 115]).

Table 11: Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Abiraterone Comparing Healthy Volunteers with Mild or Moderate Hepatic Impairment to Volunteers without Hepatic Impairment in Study COU-AA-011

Parameter	Comparisons	LS Mean		T/R (%)	90% CI (%)	CV (%)
		Test	Ref			
Cmax (ng/mL)	Mild vs. Normal	62.7	74.5	84.2	(45.02 , 157.50)	83.6
	Moderate vs. Normal	204	74.5	274	(146.35 , 512.00)	83.6
$AUC_{0\text{-last}}$ (ng*hr/mL)	Mild vs. Normal	316	283	112	(59.56 , 209.51)	84
	Moderate vs. Normal	1025	283	362	(193.03 , 679.00)	84
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	Mild vs. Normal	326	293	111	(59.61 , 208.35)	83.5
	Moderate vs. Normal	1044	293	357	(190.98 , 667.46)	83.5

Plasma samples were collected up to 96 hours post-dose.

Table 12: Mean (±SD) Pharmacokinetic Parameters for Abiraterone after Administration of 1000 mg Abiraterone Acetate Daily in Healthy Volunteers with Mild or Moderate Hepatic Impairment and Volunteers without Hepatic Impairment in Study COU-AA-011

Parameters	Cohort 1 – Mild (N=8)	Cohort 2 – Moderate (N=8)	Cohort 3 – Normal (N=8)
Cmax (ng/mL)	71.9 ± 40.2	297 ± 258	85.7 ± 46.6
Tmax[a] (hr)	2.00 (0.500, 3.00)	1.50 (1.00, 2.00)	1.75 (1.00, 3.00)
$AUC_{0\text{-last}}$ (ng*hr/mL)	355 ± 191	1530 ± 1350	321 ± 166
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	365 ± 194	1562 ± 1389	330 ± 166
$T_{1/2}$ (hr)	17.7 ± 7.91	18.6 ± 5.04	13.1 ± 4.19
CL/F (L/hr)	3397 ± 1560	1466 ± 1330	3917 ± 2365
Vd/F (L)	76347 ± 36122	32510 ± 27078	66912 ± 34717

[a]Tmax is reported as median and range. Plasma samples were collected up to 96 hours post-dose.

The unbound fractions of abiraterone in plasma were similar among subjects with mild hepatic impairment, moderate hepatic impairment and normal hepatic function with values of 0.22 ± 0.12%, 0.19 ± 0.06 % and 0.19 ± 0.07% respectively (99.8% protein binding irrespective of hepatic function). Considering hepatic clearance may be affected by fu (CLh= Qh * (CLint * fu/ Qh + [CLint * fu]), the results of this protein binding study indicate that the conclusions from the hepatic study were not confounded by protein binding because protein binding did not change based on hepatic function.

Relationship between Renal Impairment and Exposure:

In a dedicated open-label reduced design study (COU-AA-012), the mean abiraterone PK parameters were comparable between volunteers with normal renal function (N=8) and those with end stage renal disease (ESRD) on hemodialysis (N=8). Table 14 shows the PK parameters following administration of abiraterone acetate to the volunteers without renal impairment (healthy volunteer cohort) or to the volunteers with ESRD. The data from one patient were removed from the normal renal function group because the patient had abiraterone exposures which were 5 to 6 fold higher than the mean exposure in the group. In this study a 1000 mg dose was given 1 hour after dialysis and samples were collected up to 96 hours post dose. Theoretically, this study design may not completely rule out the possibility that severe renal impairment or ESRD may have effects on the PK of abiraterone. Since the patients underwent dialysis shortly before abiraterone acetate administration, the dialysis may have acted to reduce the potential effect of ESRD on the PK of abiraterone.

Table 13: Mean (±SD) Pharmacokinetic Parameters for Abiraterone after Administration of 1000 mg Abiraterone Acetate Daily in Healthy Volunteers with ESRD and Healthy Volunteers without Renal Impairment in Study COU-AA-012

Parameters	ESRD (N = 8)	Normal Renal Function (N = 8)
Cmax (ng/mL)	50.2 ± 37.7	104 ± 124
Tmax[a] (hr)	3.00 (1.00, 6.00)	1.50 (1.00, 4.00)
$AUC_{0\text{-last}}$ (ng*hr/mL)	305 ± 267	485 ± 513
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	315 ± 265	497 ± 523
$T_{1/2}$ (hr)	16.0 ± 2.00	19.0 ± 4.08
CL/F (L/hr)	5060 ± 3034	3168 ± 1638
Vd/F (L)	118926 ± 74377	80346 ± 32619

Plasma samples were collected up to 96 hours post-dose.

Table 14: Mean (±SD) Pharmacokinetic Parameters for Abiraterone after Administration of 1000 mg Abiraterone Acetate Daily in Healthy Volunteers with ESRD and Healthy Volunteers without Renal Impairment in Study COU-AA-012 With One Patient's Data Removed From the Normal Renal Function Group Because the Patient Had Exposures 5 to 6 Fold Higher Than the Mean Exposure in the Group.

Parameters	ESRD (N = 8)	Normal Renal Function (N = 7)
Cmax (ng/mL)	50.2 ± 37.7	60.6 (23.5)
Tmax[a] (hr)	3.00 (1.00, 6.00)	1.50 (1.00, 4.00)
$AUC_{0\text{-last}}$ (ng*hr/mL)	305 ± 267	307 (108)
$AUC_{0\text{-}\infty}$ (ng*hr/mL)	315 ± 265	315 (108)
$T_{1/2}$ (hr)	16.0 ± 2.00	18.2 (3.67)
CL/F (L/hr)	5060 ± 3034	3539 (1357)
Vd/F (L)	118926 ± 74377	88952 (23453)

[a]Tmax is reported as median and range. Plasma samples were collected up to 96 hours post-dose.

2.3.2 Based upon what is known about exposure-response relationships and their variability and the groups studied, healthy volunteers vs. patients vs. specific populations, what dose adjustments, if any, are recommended for each of these groups? If dose adjustments are not based upon exposure-response relationships, describe the alternative basis for the recommendation.

Pediatric patients

Safety and effectiveness have not been established in pediatric patients.

Renal impairment

In a dedicated open label reduced design study (COU-AA-012), the mean abiraterone PK parameters were comparable between the patients with normal renal function and those with ESRD on hemodialysis. No dose adjustments are recommended for patients with renal impairment.

Hepatic impairment
In a dedicated hepatic study (COU-AA-011), the systemic exposure of abiraterone for the mild hepatic impairment cohort (Child-Pugh Classification A) was comparable to that for the normal hepatic function cohort. Based on geometric mean estimates, the Cmax was 2.7 fold higher and AUC was 3.6 fold higher in the moderate hepatic impairment group (Child-Pugh Classification B) compared to the normal hepatic function group. Large inter-subject variability in Cmax and AUC∞ was seen in all cohorts (CV = 84% [52 – 115]).

A dose adjustment is not necessary in patients with mild hepatic impairment as the systemic exposure of abiraterone was comparable to that in individuals with normal hepatic function. The applicant proposes that abiraterone acetate should not be used in patients with moderate and severe hepatic impairment. However, a dose adjustment recommendation is warranted in moderate hepatic impairment to provide patients with an appropriate dose that matches exposures seen in patients with normal hepatic function receiving 1000 mg of abiraterone acetate. The rate of all Grade 3/4 toxicities seen in Study COU-AA-301 was ≤ 1% for the abiraterone acetate group, including hepatotoxicity such as ALT increases.

Since frequent LFT monitoring is proposed in the label, the use of abiraterone acetate can be well managed in patients with moderate hepatic impairment. A dose reduction from 1000 mg to 280 mg is estimated to adjust for the change in exposure (3.6 fold change in AUC) in patients with moderate hepatic impairment. Since abiraterone acetate is available as a 250 mg tablet, a dose of 250 mg daily is recommended. Although the 250 mg recommended dose is 11% less than the estimated 280 mg dose, the exposure at the 250 mg dose should be in a similar range as a 280 mg dose as a result of the high inter subject variability in exposure of > 50%.

For patients with severe hepatic impairment, the Clinical Pharmacology reviewer recommends that the label state that abiraterone acetate has not been studied in patients with pre-existing severe hepatic impairment and should be avoided in these patients. A PMR will be requested for the applicant to conduct a study to evaluate the effect of severe hepatic impairment on the PK of abiraterone after an oral dose of abiraterone acetate. For this study, the applicant will need to consider development of a lower dosage form in order to allow for administration of a safe dose in patients with severe hepatic impairment.

A dose modification is recommended for any patient that develops hepatotoxicty while on the drug. Across all abiraterone acetate clinical studies, liver function test elevations (ALT or AST increases of > 5 X the upper limit of normal [ULN] or bilirubin increases > 1.5 X ULN) were reported in approximately 2% of patients who received abiraterone acetate, typically during the first 3 months after starting treatment. The applicant proposes the italicized labeling language below.

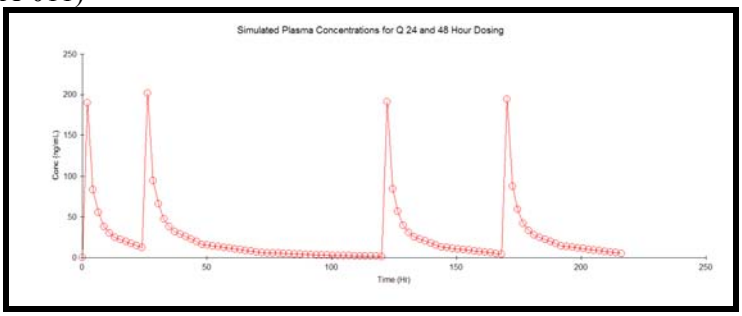
(b) (4)

(b) (4)

In the phase 3 pivotal trial the dose was reduced from 1 000 mg to 750 mg for ALT > 5X ULN and bilirubin > 3X ULN. It is not clear how a dose reduction to 500 mg will affect the efficacy as an exposure response relationship has not been established. In addition, in a biomarker study a near maximal increase was observed in mean deoxycorticosterone and corticosterone (steroids upstream of CYP17 that serve as biomarkers of the completeness of CYP17 inhibition) levels at the 750 mg dose, whereas higher doses of 1000 mg and 2000 mg did not raise the levels. Therefore, based on this patients may benefit from a step dose reduction from 1000 mg to 750 mg and then to 500 mg if not tolerated.

Furthermore, in patients that have hepatic impairment at baseline a 50% or 75% dose reduction may be limited by the lowest dosage form of 250 mg. The Clinical Pharmacology reviewer therefore assessed if alternate day dosing would be appropriate in patients with moderate hepatic impairment who require a dose reduction due to elevations in ALT > 5 X ULN and bilirubin > 3X ULN. Simulations were performed based on non-parametric superposition using WinNonLin 5.2.1. Figure 8 shows the simulated concentrations comparing a daily dose of 1000 mg to an every other day dose of 1000 mg. The simulation was based on mean plasma concentrations seen with a single dose of a 1000 mg dose in patients with moderate hepatic impairment. The simulation included a dose at 0 and 24 hours for the 1000 mg daily dosing which had a predicted AUC_{0-48} of 2210 ng/mL and a 1000 mg dose at 120 and 168 hours for alternate day dosing regimen. The $AUC_{120-168}$ was predicted as 1209 ng/mL which was approximately half of the exposure seen over 48 hours when two 1000 mg daily doses were used. The simulated Cmax values were similar with the two dosing regimens (162 ng/mL for 1000 mg daily dosing and 150 ng/mL for 1000 mg alternate day dosing). However, it was unclear how the change in dosing regimen would affect the efficacy as the PK/PD relationship of this enzyme inhibitor is unclear. The low concentrations on Day 2 of every other day dosing may not be sufficient for inhibition of the target enzyme (CYP17), and will therefore not be recommended.

Figure 12: Simulated Plasma PK Concentration Time Profiles for Daily Dosing and Alternate Day Dosing Predicted From Single Dose Plasma Concentrations In Moderate Hepatic Impairment (Study COU-AA-011)



Simulation doses included Time 0 and 24 for daily dosing and 120 and 168 for alternate day dosing.

2.3.3 What pregnancy and lactation use information is there in the application?

The safety and effectiveness of abiraterone acetate have not been established in pregnancy and in lactating women as this drug is for use in men with prostate cancer.

2.4 EXTRINSIC FACTORS

2.4.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

The effects of extrinsic factors such as herbal products, diet, smoking and alcohol use on the dose-exposure and/or dose-response for abiraterone acetate were not assessed in a formal study.

Drug-drug interactions

2.4.2 Is there an *in vitro* basis to suspect in vivo drug-drug interactions?

As a substrate

Abiraterone acetate was converted to abiraterone (deacetylation) in human hepatic microsomes and the conversion did not require NADPH suggesting it is not CYP mediated. Abiraterone is a substrate for CYP3A4, SULT2A1 and UGT1A4. **CYP3A4** is involved in the formation of phase 1 metabolites, **SULT2A1** is predominantly involved in the formation of the abiraterone sulphate metabolites and **UGT1A4** is predominantly involved in the formation of abiraterone glucuronide metabolites. The major metabolites in human plasma are abiraterone sulphate (SULT2A1) and N-oxide abiraterone sulphate (SULT2A1 and CYP3A4). The PK of abiraterone may be affected by strong CYP3A4 inhibitors and inducers, but this has not been evaluted *in vivo*.

As an inhibitor or inducer

In vitro studies on human hepatic microsomes showed that abiraterone is a strong inhibitor of **CYP1A2** and **CYP2D6** and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5 (Refer to Table 15). The inhibition of CYP2D6 and CYP1A2, with the largest I/Ki ratios, by abiraterone was further explored *in vivo*.

Based on the Ki values obtained from *in vitro* studies with human hepatic microsomes, abiraterone acetate is a strong inhibitor of CYP2D6, CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2E1, CYP2C9 and CYP3A4/5. However, since abiraterone acetate is below the LOQ of 0.2 ng/mL in human plasma, it is unlikely that the interactions with any of the CYPs studied will be clinically meaningful with the [I]/Ki ratio for the most potent CYP2C19 inhibition by abiraterone acetate determined to be < 0.004. Abiraterone acetate also slightly induced CYP1A2 expression and activity in a non-concentration dependent manner.

Study # 400378 was performed to determine the potential of abiraterone acetate (0.1 -10 μM) to induce or inhibit the activity of CYP1A2, CYP2C9 and CYP3A4 activities in primary cultures of

human hepatocytes. Any effects would unlikely be clinically relevant because abiraterone acetate is undetectable in human plasma.

- Abiraterone acetate was shown to be a slight inducer for CYP1A2 activity (1.3% of the induction level of the positive control) in a non concentration-dependent manner.
- Abiraterone acetate was shown to be a weak inhibitor of CYP3A4 activity (30% between 1 and 10 µM; Ki or IC50 not provided) in a non concentration-dependent manner.
- Abiraterone acetate had no effect on CYP2C9 activity with concentrations ranging from 0.1 to 10 µM.

Study # 400379 was performed to determine the potential for inhibition of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4/5 (*CYP2C8 was not assessed*) by abiraterone acetate (0.1 -10 µM) and abiraterone (0.1 -10 µM).

- Abiraterone (CB7598) was a not an inhibitor for human CYP2A6 and CYP2E1 while it was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5 and a potent inhibitor of CYP1A2 and CYP2D6 over the concentrations tested.
- Abiraterone acetate (CB7630) exhibited no inhibition towards CYP2A6, but showed a moderate inhibition towards CYP2E1, CYP2C9 and CYP3A4/5 and a potent inhibition towards CYP1A2 and CYP2C19 over the concentration range tested.

Table 15: CYP450 Inhibition Potential for Abiraterone Acetate and Abiraterone Using the Average Cmax at the Clinical Dose of 1000 mg to Calculate the [I]/Ki.

CYP450 Enzymes	Abiraterone Acetate	Abiraterone	
	Ki (µM)	Ki (µM)	[I]/Ki calculated from Cmax of clinical dose (0.68 µM)
CYP2A6	N/D	N/D	N/A
CYP2E1	31.8	N/D	N/A
CYP2C9	17.6	29.8	0.023
CYP2C19	0.12	46.3	0.015
CYP3A4/5	11.4	8.01	0.085
CYP1A2	0.32	0.44	1.55
CYP2D6	0.16	0.39	1.74

2.4.3 Is the drug a substrate of CYP enzymes?

Abiraterone is a CYP3A4 substrate, but it has not been evaluated *in vivo* with strong CYP3A4 inhibitors and inducers (See Section 2.4.2). Studies with strong CYP3A4 inhibitors and inducers will be required as a PMR.

2.4.4 Is the drug an inhibitor and/or an inducer of CYP enzymes?

In vitro studies on human hepatic microsomes suggested that abiraterone is a strong inhibitor of **CYP1A2** and **CYP2D6** and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. The inhibition of CYP1A2 and CYP2D6 by abiraterone was further explored, *in vivo*. Based on the Ki values obtained from *in vitro* studies in human hepatic microsomes, abiraterone acetate is a strong inhibitor of CYP2D6, CYP1A2 and CYP2C19 and a moderate inhibitor of CYP2E1, CYP2C9 and CYP3A4/5. However, since abiraterone acetate is below the LOQ of 0.2 ng/mL in

human plasma, it is unlikely that the interaction will be clinically meaningful with the [I]/Ki ratio for the most potent CYP2C19 inhibition by abiraterone acetate determined to be < 0.004. The inhibitions of CYP2D6 and CYP1A2 were further explored *in vivo*. Abiraterone acetate also slightly induced CYP1A2 expression and activity in a non-concentration dependent manner in primary cultures of human hepatocytes.

The interaction potentials between abiraterone acetate and a sensitive substrate of CYP2D6, or abiraterone acetate and a sensitive substrate of CYP1A2 were evaluated in a multi-center, open-label study in subjects with mCRPC (COU-AA-015). The effect of multiple doses of abiraterone acetate 1000 mg daily plus prednisone 5 mg twice daily on the CYP2D6 substrate dextromethorphan hydrobromide (HBr) (single dose of 30 mg) was evaluated in Group A. This group consisted of 18 patients who were CYP2D6 extensive metabolizers (ultra metabolizers and intermediate metabolizers were included in this group) at screening. The CYP2D6 status was determined using the xTAG^{TM} Mutation Detection system for P450-2D6 (Luminex Molecular Diagnostics). The effect of multiple doses of abiraterone acetate plus prednisone on CYP1A2 was assessed using theophylline (single dose of 100 mg) in Group B (n=16).

The systemic exposure of dextromethorphan was approximately 3 fold higher based on the ratios of the geometric means for the Test/Reference when dextromethorphan was co-administered with abiraterone acetate. The geometric mean dextrorphan Cmax values were similar in the presence and absence of abiraterone acetate, whereas geometric mean AUC values were approximately 33% higher (1.3 fold higher) when dextromethorphan was co-administered with abiraterone acetate.

Table 16: Mean (±SD) and Estimated Geometric Means and Ratios with Associated 90% CI of Pharmacokinetic Parameters for Dextromethorphan (Sensitive CYP2D6 Substrate) and Its Metabolite Dextrophan after Administration of a Single 30 mg Dose of Dextromethorphan Hydrobromide Alone (Day -8) and after Administration of a Single 30 mg Dose of Dextromethorphan Hydrobromide (Day 8) in Combination with Multiple Doses of Abiraterone Acetate 1000 mg daily (Dosed Day 1 to 8) in Healthy Volunteers Who Were Deemed CYP2D6 Extensive Metabolizers in Study COU-AA-015.

	Dextromethorphan (Parent)		**Dextrophan (Metabolite)**	
PK Parameters	**DextroAlone(N=18)**	**Dextro+AA (N=18)**	**DextroAlone (N=18)**	**Dextro+AA (N=18)**
Cmax (ng/mL)	3.49 (4.82)	7.12 (4.99)	373 (118)	401 (131)
Tmax (hr)	3.0 (1.6- 10.0)	3.0 (1.6-4.1)	2.0 (2.0-6.0)	3.0 (2.0-8.0)
AUC_{0-24} (ng*hr/mL)	35.5 (56.0)	70.0 (73.2)	2903 (1010)	3756 (1289)
AUC_{0-last} (ng*hr/mL)	44.4 (76.1)	90.7 (110)	3122 (1145)	4183 (1495)
$AUC_{0-\infty}$ (ng*hr/mL)	52.4 (88.7)	101 (132)	3168 (1149)	4291 (1503)
$T_{1/2}$ (hr)	10.6 (5.2)	10.8 (2.8)	7.8 (3.0)	9.3 (3.7)
Ratio of Geometric Means (Test/Reference)				
	Dextro. Alone/ Dextro + AA for Dextromethorphan % (90%CI) N=18		**Dextro. Alone/ Dextro + AA for Dextrorphan % (90%CI) N=18**	
Cmax (ng/mL)	275.36 (212.43 - 356.95)		108.12 (99.18 - 117.87)	
AUC_{0-24} (ng*hr/mL)	268.14 (216.71 - 331.77)		129.26 (123.28 -135.54)	
AUC_{0-last} (ng*hr/mL)	302.21 (239.26 - 381.72)		133.98 (127.93 - 140.32)	
$AUC_{0-\infty}$ (ng*hr/mL)	287.47 (230.21 - 358.98)		135.70 (129.29 - 142.42)	

The systemic exposure of theophylline was also comparable when it was co-administered with abiraterone acetate compared to when theophylline was administered alone. The ratios of the

geometric mean 90% CI of theophylline Cmax and AUC_{24h} values were within the 80% to 125% equivalence range.

Table 17: Mean (±SD) and Estimated Geometric Means and Ratio with Associated 90% CI of Pharmacokinetic Parameters for theophylline (Sensitive CYP1A2 Substrate) after Administration of a Single 100 mg Dose of theophylline Alone (Day -8) and after Administration of a Single 100 mg Dose of theophylline (Day 8) in Combination with Multiple Doses of Abiraterone Acetate 1000 mg daily (dosed Day 1 to 8) in Healthy Volunteers in Study COU-AA-015.

	Theophylline		Ratio of Geometric Means (Theo Alone/Theo+AA) % (90%CI) N=15
PK Parameters	**Theo Alone (N=16)**	**Theo+AA (N=15)**	
Cmax (ng/mL)	1928 (680)	2014 (645)	102.36 (88.84 -117.94)
Tmax (hr)	8.0 (3.0-48.0)	8.0 (1.5-32.0)	N/A
AUC_{0-24} (ng*hr/mL)	32525 (14263)	34837 (10986)	108.03 (97.91 -119.20)
AUC_{0-last} (ng*hr/mL)	49131 (24134)	52806 (19233)	109.36 (95.49 -125.24)
$AUC_{0-\infty}$ (ng*hr/mL)	58903 (36235)	57923 (22098)	112.85 (96.66 -131.75)
$T_{1/2}$ (hr)	13.0 (6.1)	12.7 (3.3)	N/A

2.4.5 Are other metabolic/transporter pathways important?

Based on *in vitro* Caco-2 cells, abiraterone and abiraterone acetate are not substrates for P-gp. Abiraterone has little inhibitory effect on P-gp whereas abiraterone acetate inhibits P-gp significantly, with an IC_{50} of 10.8 μM *in vitro*. However, since abiraterone acetate was not detectable in human plasma in most PK samples collected the likelihood of an *in vivo* interaction is low.

No studies have been conducted with other transporter proteins.

2.4.6 Does the label specify co-administration of another drug and, if so, has the interaction potential between these drugs been evaluated?

Abiraterone acetate 1000 mg is to be used with prednisone 5 mg twice daily. The studies in mCRPC were performed using abiraterone acetate 1000 mg in combination with prednisone 5 mg twice daily. The potential for a pharmacokinetic interaction is difficult to assess because all the studies with abiraterone acetate in combination with prednisone were performed in patients with mCRPC and no formal drug-drug interaction study has been performed. The healthy volunteer studies that used abiraterone acetate alone have lower mean exposures compared to those seen in mCRPC studies. The increase in exposure in mCRPC compared to healthy volunteers is unlikely due to co-administration of prednisone, as it is a weak to moderate inducer of CYP3A4. Rather, the difference in exposure between healthy volunteers and mCRPC patients is likely due to multiple other unknown factors which may include differences in dosing with regard to food. In particular, the healthy volunteer studies used overnight fasting before dosing with a 4 hour fast after dosing, while the patients were given the dose 2 hours after or 1 hour before food.

2.4.7 Are there any in vivo drug-drug interaction studies that indicate the exposure alone and/or exposure-response relationships are different when drugs are co-administered?

No *in vivo* drug-drug interaction studies were conducted with prednisone or any strong CYP inducers/inhibitors. *In vivo*, abiraterone acetate causes an increase in the exposure of CYP2D6 substrates (3 fold increase on the sensitive substrate dextromethorphan).

2.5 GENERAL BIOPHARMACEUTICS

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Abiraterone acetate (drug substance) can likely be classified as a BCS Class IV drug due to low solubility and low permeability characteristics reported by the applicant. It has not received official BCS classification/designation from the FDA. The solubility studies submitted were performed at 20°C and not 37°C but do suggest that abiraterone acetate (drug substance) has low solubility in aqueous media.

Solubility

Abiraterone acetate is practically insoluble in aqueous media over a wide range of pH values and slightly soluble in 0.1 N HCl solution. Table 18 includes the solubility results in aqueous media as a function of pH after equilibration for at least 24 hours at 20°C.

Table 18: Solubility of Abiraterone Acetate in Aqueous Media as a Function of pH at 20 °C for at least 24 Hours

Media	Solubility in g/100 mL Solution	pH of Solution	Solubility Description[a]
0.1 N HCl	0.011	1.0	Very slightly soluble
0.01 N HCl	0.002	2.0	Practically insoluble
Citrate-HCl buffer pH 2	0.002	2.0	Practically insoluble
Citrate–NaOH buffer pH 5	<0.001	5.0	Practically insoluble
Phosphate buffer pH 7	<0.001	7.0	Practically insoluble
Water	<0.001	8.8	Practically insoluble
Borate-KCl-NaOH buffer pH 9	<0.001	9.0	Practically insoluble
Phosphate-NaOH buffer pH 12	<0.001	11.7	Practically insoluble
0.1 N NaOH	<0.001	12.9	Practically insoluble

Although the solubility of abiraterone acetate is very limited in aqueous media, it is soluble in organic solvents. Table 19 includes the solubility results in various organic solvents after equilibration for at least 24 hours at 20°C.

Table 19: Solubility of Abiraterone Acetate in Organic Solvents after Equilibration for at least 24 hours at 20°C

Media	Solubility in g/100 mL Solution	Solubility Description[a]
1-Methoxy-2-Propanol	12	Freely soluble
1-Octanol	9.3	Soluble
2-Propanol	4.9	Soluble
N,N-Dimethylacetamide	11	Freely soluble
N,N-Dimethylformamide	7.8	Soluble
Acetone	6.4	Soluble
Acetonitrile	1.6	Sparingly soluble
Dichloromethane	>30[b]	Freely soluble
Diethyl Ether	5.7	Soluble
Dimethyl Sulfoxide	1.4	Sparingly soluble
Ethanol	5.2	Soluble
Ethyl Acetate	9.8	Soluble
Ethyl methyl Ketone	12	Freely soluble
Hexane	0.66	Slightly soluble
Isobutyl methyl Ketone	8.5	Soluble
Methanol	4.0	Soluble
Methylbenzene	33	Freely soluble
Polyethylene Glycol 400	1.5	Sparingly soluble
Propylene Glycol	1.1	Sparingly soluble
Tetrahydrofuran	>30[b]	Freely soluble

Permeability

Studies performed using Caco-2 cell monolayers indicated that abiraterone acetate and abiraterone have a low apparent permeability. The apparent permeability values of abiraterone acetate are < 3.69 $x10^{-6}$ cm/s in the A to B direction and < 1.58 $x10^{-6}$ cm/s in the B to A direction. The apparent permeability of abiraterone is < 3.46 $x10^{-6}$ cm/s in the A to B direction and < 4.60 $x10^{-6}$ cm/s in the B to A direction.

2.5.2 What is the composition of the to-be-marketed formulation?

The immediate release 250 mg tablets are formulated with microcrystalline cellulose, lactose monohydrate, croscarmellose sodium, povidone, sodium lauryl sulfate (SLS), colloidal silicon dioxide and magnesium stearate as excepients.

Table 20: Composition of Immediate Release Abiraterone Acetate 250 mg Tablets

Component	Reference to Quality Standard[a]	Function	mg/tablet
Abiraterone Acetate	Company Standard	Active	250.00
Lactose Monohydrate	NF/Ph. Eur.		(b) (4)
Microcrystalline Cellulose	NF/Ph. Eur.		
Croscarmellose Sodium	NF/Ph. Eur.		
Povidone (b) (4)	USP/Ph. Eur.		
Sodium Lauryl Sulfate	NF/Ph. Eur.		
Colloidal Silicon Dioxide	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)	USP/Ph. Eur.		
Total Tablet Weight:			715.0

2.5.3 What moieties should be assessed in bioequivalence studies?

The parent compound, abiraterone acetate, and its active metabolite, abiraterone were assessed in all the clinical studies. Since abiraterone acetate was not detectable in most studies and abiraterone is the active moiety, abiraterone will need to be assessed in any bioequivalence studies.

2.5.4 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Study COU-AA-009 was a phase 1, single dose, open-label, three-period, crossover study to determine the effect of food on the pharmacokinetics of abiraterone acetate in healthy male subjects. The three periods tested the effect of fasting (overnight fast and no food for 4 hours post dose), a low fat meal (298.7 total calories of calories with 7.3% from fat) or a high fat meal (total calories of 826.3 with 56.5% from fat) on the PK of abiraterone. PK samples were collected up to 96 hours post dose and a 7 day wash-out was used between treatments. At 1000 mg, systemic exposure of abiraterone, increased with the administration of food compared to the fasted state. The median abiraterone Tmax and mean $T_{1/2}$ were not affected by administration of food. Compared with the fasted state, the geometric mean for abiraterone Cmax and AUC $_{0-\infty}$ increased by approximately 7- and 5-fold, respectively, when administered with a low-fat meal and by approximately 17- and 10-fold, respectively, when administered with a high-fat meal (Table 21).

Table 21: Estimated Geometric Means and Ratios with Associated 90% CI for Pharmacokinetic Parameters of Abiraterone Comparing Administration of 1000 mg Abiraterone Acetate under Fasting Conditions Versus Administration with Standardized Low-fat or High-fat Meals in Study COU-AA-009.

Parameter[a] (Units)	Treatment (Test)	LS Mean[b] N[c]	1000 mg Fed (Test)	N[c]	1000 mg Fasted (Reference)	Test/ Reference (%)[d]	90% Confidence Interval (%)[e]	Intrasubject CV (%)[f]
C_{max} (ng/mL)	high-fat	35	1190	35	70.7	1683	(1353.36 , 2093.43)	59.0
	low-fat	35	513	35	70.7	726	(583.65 , 902.81)	59.0
$AUC_{0-\infty}$ (ng*hr/mL)	high-fat	35	4077	35	421	969	(815.55 , 1152.16)	45.4
	low-fat	35	1942	35	421	462	(388.48 , 548.82)	45.4
AUC_{0-t} (ng*hr/mL)	high-fat	35	4056	35	409	992	(831.11 , 1183.02)	46.5
	low-fat	35	1929	35	409	472	(395.35 , 562.75)	46.5

Reference: Table 10.2-3b.
[a] Parameter data were ln-transformed prior to analysis.
[b] For AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}, LS means from the ANOVA, transformed back to the linear scale (ie, geometric means); For t_{max}, medians were reported.
[c] N is the number of observations in each treatment used in the model.
[d] Ratio of parameter means (expressed as a percent), transformed back to the linear scale.
[e] 90% CI for ratio of parameter means (expressed as a percent), transformed back to the linear scale.
[f] Intra-subject CV% for ln-transformed parameter from the ANOVA.

Overall, 12 of the 36 (33.3%) subjects reported Grade 1 or 2 adverse events (AEs). No Grade 3 or 4 AEs or SAEs were reported and no subject was discontinued from the study due to an AE. Eight subjects had increases from baseline in the QTcB interval of > 30 msec: 6 subjects following a low-fat meal (> 31 - 39 msec) and 2 subjects following dosing with a high-fat meal (33 and 36 msec). There were no post-dose vital sign measurements or changes reported as AEs. The mean values in diastolic blood pressure for the high-fat meal group within 0.5 to 12 hours post-dose were from 3 to 8 mmHg lower than corresponding pre-dose values.

In all the single dose studies (healthy volunteer studies), abiraterone acetate was dosed following an overnight fast and no food was allowed for at least 4 hours post-dose. In the studies in patients with mCRPC, abiraterone acetate was taken at least 1 hour before or at least 2 hours after a meal. This latter dosing schedule is proposed by the applicant with 1000 mg of abiraterone acetate tablets taken at least (b) (4) hour before or at least (b) (4) hours after a meal.

2.5.5 Has the applicant developed an appropriate dissolution method and specification that will assure *in vivo* performance and quality of the product?

Yes.

2.6 ANALYTICAL SECTION

2.6.1 Were relevant metabolite concentrations measured in the clinical pharmacology and biopharmaceutics studies?

Yes. All the submitted clinical pharmacology related studies analyzed samples for abiraterone acetate and its active metabolite abiraterone. In clinical studies, abiraterone acetate concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples. The evolution of the LC-MS/MS bioanalytical methods for abiraterone and abiraterone acetate in human plasma initially started in 2005.

(b) (4)

In the mass balance study (COU-AA-007), a total of 15 metabolites were detected in human plasma with the main circulating metabolites, abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31), accounting for 43.3% and 43.4% of the radioactivity, respectively. Radioactivity in the samples was profiled by radio-HPLC and metabolites were identified using co-chromatography with known standards and by using LC-MS/MS methods. An LC-MS/MS research method was developed and used to measure the concentrations of the two main metabolites in human plasma samples (M45 and M31).

Abiraterone acetate and abiraterone have been analyzed in human urine and fecal samples from Study COU-AA-007 by radio-HPLC. Profiling and identification of metabolites were also performed in plasma, urine and fecal samples. Radioactivity in the samples was profiled by radio-HPLC and metabolites were identified using co-chromatography with known standards and by using LC-MS/MS methods.

Plasma samples from a drug-drug interaction study (Study COU-AA-015) were analyzed for dextromethorphan and dextrorphan using a LC-MS/MS method at (b) (4) (b) (4) ((b) (4) and for theophylline at (b) (4)

Table 22: Summary of Bioanalytical Methods Used in Clinical Studies for Pharmacokinetic Measurements of Abiraterone and Abiraterone Acetate

Study ID (Location)	Matrix	Analyte	Concentration range[a]	Method	Method Validation report (location)	Bioanalytical study number
COU-AA-001 (Mod5.3.3.2\COU-AA-001)	plasma	Abiraterone Abiraterone Acetate	5 – 500 nM (1.75 – 175 ng/ml) 5 – 500 nM (1.96 - 196 ng/ml)	LC-MS/MS	(b) (4)	Validation Report 5 Validation Report 5
COU-AA-002 (Mod5.3.3.2\COU-AA-002)	plasma	Abiraterone Abiraterone Acetate	5 – 500 nM (1.75 – 175 ng/ml) 5 – 500 nM (1.96 - 196 ng/ml)	LC-MS/MS		Validation Report 5 Validation Report 5
COU-AA-BE (Mod5.3.3.2\COU-AA-BE)	plasma	Abiraterone Abiraterone Acetate	5 – 500 nM (1.75 – 175 ng/ml) 5 – 500 nM (1.96 - 196 ng/ml)	LC-MS/MS		Validation Report 5 Validation Report 5
COU-AA-005 (Mod5.3.1.2\COU-AA-005)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1601 BA1601
COU-AA-006 (Mod5.3.5.2\COU-AA-006)	plasma	Abiraterone Abiraterone Acetate Abiraterone Sulphate Metabolite Abiraterone oxidated Sulphate Metabolite	0.200-200 ng/mL 0.200 – 50.0 ng/mL 100 – 20000 ng/mL 89.3 – 17860 ng/mL	LC-MS/MS		8212-170 8212-170 BA1732 (qualified) BA1732 (qualified)
COU-AA-007 (Mod5.3.3.1\COU-AA-007)	plasma	Abiraterone Abiraterone Acetate	0.200-200 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		8212-170 8212-170
COU-AA-008 (Mod5.3.3.1\COU-AA-008)	plasma	Abiraterone Abiraterone Acetate	0.200-200 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		8212-170 RPT-COU-2009-001
COU-AA-009 (Mod5.3.3.1\COU-AA-009)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1601 BA1601
COU-AA-010 (Mod5.3.1.1\COU-AA-010)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1656 BA1656
COU-AA-011 (Mod5.3.3.3\COU-AA-011)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1601 BA1601
COU-AA-012 (Mod5.3.3.3\COU-AA-012)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1601 BA1601
COU-AA-014 (Mod5.3.3.1\COU-AA-014)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS	(b) (4)	BA1601 BA1601
COU-AA-015 (Mod5.3.3.4\COU-AA-015)	plasma	Abiraterone Abiraterone Acetate Dextromethorphan Dextrorphan Theophylline	0.200-200 ng/mL 0.200 – 50.0 ng/mL 0.0500 – 50.0 ng/mL 0.800 – 800 ng/mL 5.00 – 2000 ng/mL	LC-MS/MS		8212-170 8212-170 P668-ACPB P668-ACPB 2100-555
COU-AA-016 (Mod5.3.3.1\COU-AA-016)	plasma	Abiraterone Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1656 BA1656
COU-AA-301 (Mod5.3.5.3\COU-AA-010)	plasma	Abiraterone Abiraterone Acetate Abiraterone Acetate	0.200-500 ng/mL 0.200 – 50.0 ng/mL 0.200 – 50.0 ng/mL	LC-MS/MS		BA1601 BA1601 RPT-COU-2009-001

Note: Studies in Modules 2.7.1 and 2.7.2 are included in this appendix.
[a] Lower limit of quantification (LLOQ) is the lower end of the concentration range

(b) (4)

2.6.2 Which metabolites have been selected for analysis and why?

All the submitted clinical pharmacology related studies analyzed samples for abiraterone acetate and its active metabolite abiraterone. In clinical studies, abiraterone acetate concentrations were below detectable levels (< 0.2 ng/mL) in > 99% of the analyzed samples. The main circulating metabolites, abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31) are considered inactive and were not measured in trials apart from the mass balance trial.

2.6.3 For all moieties measured, is free, bound, or total measured? What is the basis for that decision, if any, and is it appropriate?

Abiraterone is highly bound to human plasma proteins (98.8 – 99.9%). The total concentration of abiraterone in plasma was measured in the clinical trials. In Study # COU-AA-011, the values for the unbound fraction of abiraterone in plasma from subjects with mild hepatic impairment, moderate hepatic impairment and normal hepatic function were 0.22 ± 0.12%, 0.19 ± 0.06 % and 0.19 ± 0.07%, respectively (99.8% protein binding irrespective of hepatic function). Therefore, the measurement of total concentrations in all trials is likely appropriate.

2.6.4 What bioanalytical methods are used to assess concentrations? (Refer to the guidance for industry on Bioanalytical Method Validation, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf)

Plasma abiraterone acetate and its active metabolite abiraterone were analyzed using LC-MS/MS bioanalytical methods for plasma samples. Radioactivity in the urine and fecal samples was profiled by radio-HPLC and metabolites were identified using co-chromatography with known standards and by using LC-MS/MS methods.

The bioanalytical methods for abiraterone and abiraterone acetate from (b) (4) (b) (4) are summarized in Table 23 below.

Table 23: Method Validation Summaries for the Bioanalytical Methods for Abiraterone and Abiraterone Acetate developed by the (b) (4)

Method Name	Abiraterone (b) (4) Method Validation Report 5 (Mod5.3.1.4\Validation Report 5)
Matrix	(b) (4)
Validated concentration range	
Inter-run accuracy (%)	
Inter-run precision (%CV)	
Intra-run accuracy (%)	
Intra-run precision (%CV)	
Intra-run accuracy (20-fold dilution) (%)	
Intra-run precision (20-fold dilution) (%CV)	
Selectivity (interference <20% of LLOQ)	
Stability in sodium citrate blood	
Matrix effects	
Stability in sodium citrate plasma	
Processed sample stability	
Stability in stock solution DMSO	

Method Name	Abiraterone Acetate (b) (4) Method Validation Report 5 (Mod5.3.1.4\Validation Report 5)
Matrix	(b) (4)
Validated concentration range	
Inter-run accuracy (%)	
Inter-run precision (%CV)	
Intra-run accuracy (%)	
Intra-run precision (%CV)	
Intra-run accuracy (20-fold dilution) (%)	
Intra-run precision (20-fold dilution) (%CV)	
Selectivity (interference <20% of LLOQ)	
Stability in sodium citrate blood	
Matrix effects	
Stability in sodium citrate plasma	
Processed sample stability	
Stability in DMSO stock solution	

Method Name	(b) (4) Abiraterone high range method (Mod5.3.1.4\COU-2008-002 [amended] and Mod5.3.1.4\COU-2008-007)	(b) (4) Abiraterone low range method (Mod5.3.1.4\COU-2009-001 [amended + addendum] and Mod5.3.1.4\COU-2009-002)
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (dilution) (%)		
Intra-run precision (dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile:DMSO 1:1 solution		

Method Name	(b) (4) Abiraterone Acetate high range me... (Mod5.3.1.4\COU-2008-002 [amended] and Mod5.3.1.4\COU-2008-007)	(b) (4) Abiraterone Acetate low range me... (Mod5.3.1.4\COU-2009-001 [amended + addendum] and Mod5.3.1.4\COU-2009-002)
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (dilution) (%)		
Intra-run precision (dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile stock solution		

Method Name	Abiraterone (b) (4) high range method (Mod\5.3.1.4\8201-029)	Abiraterone (b) (4) low range method (Mod5.3.1.4\8212-170)
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (10-fold dilution) (%)		
Intra-run precision (10-fold dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile:DMSO 1:1 stock solution		
Stability in acetonitrile stock solution		

Method Name	Abiraterone Acetate (b) (4) high range method (Mod\5.3.1.4\8201-029)	Abiraterone Acetate (b) (4) low range method (Mod5.3.1.4\8212-170)
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (10-fold dilution) (%)		
Intra-run precision (10-fold dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile/DMSO 1/1 stock solution		
Stability in acetonitrile stock solution		

Method Name	Abiraterone Janssen R&D validation (Mod5.3.1.4\BA1601)	Abiraterone Janssen R&D partial validation of other injection volume (Mod5.3.1.4\BA1601)
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (5-fold dilution) (%)		
Intra-run precision (5-fold dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile:DMSO 1:1 stock solution		
Stability in acetonitrile stock solution		

Method Name	Abiraterone Janssen R&D validation (Mod5.3.1.4\BA1601)	Abiraterone Janssen R&D partial validation of other injection volume (Mod5.3.1.4\BA1601)
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (5-fold dilution) (%)		
Intra-run precision (5-fold dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile:DMSO 1:1 stock solution		
Stability in acetonitrile stock solution		

Method Name	(b) (4) Abiraterone full validation (Mod5.3.1.4\BA1656)	(b) (4) Abiraterone partial validation of other injection volume (Mod5.3.1.4\BA1656 [amendment])
Matrix		(b) (4)
Validated concentration range		
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (dilution) (%)		
Intra-run precision (dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile:DMSO 1:1 stock solution		
Stability in acetonitrile stock solution		

Method Name	(b) (4) Abiraterone full validation (Mod5.3.1.4\BA1656)	(b) (4) Abiraterone partial validation of other injection volume (Mod5.3.1.4\BA1656 [amendment])
Matrix	EDTA NaF plasma	EDTA NaF plasma
Validated concentration range		(b) (4)
Inter-run accuracy (%)		
Inter-run precision (%CV)		
Intra-run accuracy (%)		
Intra-run precision (%CV)		
Intra-run accuracy (dilution) (%)		
Intra-run precision (dilution) (%CV)		
Selectivity (interference <20% of LLOQ)		
Matrix effects		
Stability in EDTA NaF blood		
Stability in EDTA NaF plasma		
Processed sample stability		
Stability in acetonitrile/DMSO 1/1 stock solution		
Stability in acetonitrile stock solution		

2.6.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques are used?

The validated LC-MS/MS methods for plasma PK analyses by (b) (4) (**Study # 8212-170**) , Janssen R&D (**Study # BA1601**) and (b) (4) (**Study # BA1656**) were used in the Clinical Pharmacology studies submitted in this NDA. Plasma concentrations of abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31) plasma samples were analyzed using a method by Janssen R&D (**Study # BA1732**). A (b) (4) method (**Study # P668-ACPB**) was used for plasma dextromethorphan concentrations and a (b) (4) method (**Study # 2100-555**) was used for theophyline plasma PK samples.

The (b) (4) analytical methods consist of a low range method (0.2 – 200 ng/mL) and a high range method (2 – 2000 ng/mL) for abiraterone in undiluted samples. The Janssen R&D and (b) (4) analytical methods both consist of a low range method (0.2 – 50 ng/mL) and a high range method (2 – 500 ng/mL) for abiraterone in undiluted samples (Table 23). The mean steady state Cmax seen in patients with mCRPC receiving abiraterone acetate 1000 mg daily was 226 ± 178 ng/mL, so the range of concentrations in the clinical trials were in the range of the standard curves for all the analytical methods. In study COU-AA-009, the mean Cmax observed in the high fat meal group was 1270 ± 478 ng/mL. The Janssen R&D method was used to analyze samples in study COU-AA-009. The concentration range in the calibration curve for the Janssen R&D method using diluted samples is 1 – 2500 ng/mL and the concentrations in Study COU-AA-009 were in this range. The methods were appropriate for analyses of abiraterone concentrations in all the trials.

Results for abiraterone and abiraterone acetate were calculated using peak area ratios of analyte to internal standard and calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression. The methods had correlation coefficients of the curves ranging from 0.9993 to 0.9999.

Results for theophylline, dextromethorphan and dextrophan were calculated using peak area ratios of analyte to internal standard and calibration curves were generated using a weighted ($1/x^2$) linear least-squares regression. Correlation coefficients of the curves ranged from 0.9979 to 0.9989.

2.6.6 What is the QC sample plan?

Six replicates of QC samples were performed at each of the LLOQ, low QC, medium QC and high QC concentrations for abiraterone and abiraterone acetate. Intra- and inter-assay results demonstrated a RSD for QC samples to be ≤15.0% (≤20.0% at the LLOQ).

3 DETAILED LABELING RECOMMENDATIONS

Only relevant clinical pharmacology sections are included. The underlined words are the proposed changes added by the clinical pharmacology reviewer and the sponsors proposed language that has not been accepted has a strike-through line through it.

8 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4 APPENDICES

4.1 PHARMACOMETRICS REVIEW

OFFICE OF CLINICAL PHARMACOLOGY

PHARMACOMETRIC REVIEW

Application Number	202379
Submission Date	18 Dec, 2010
Compound (Dosing Regimen)	Abiraterone Acetate (AA) 1000 mg in combination with low dose oral prednisone (10 mg q.d.)
Clinical Division	DDOP
Primary PM Reviewer	Nitin Mehrotra, Ph.D.
PM Team Leader	Christine Garnett, Pharm.D.

Table of Contents

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The following key questions were addressed in this pharmacometric review.

1.1.1 Is there evidence of exposure-response relationship for efficacy?

There were insufficient exposure data collected in the pivotal trial to support evidence of exposure-response for overall survival (OS).

An exploratory exposure-efficacy analysis for OS was conducted using data from the pivotal trial (COU-AA-301) following a 1000 mg dose of AA. The observed C_{min_ss} available from 119 patients (15% of the total enrolled in the AA arm) was used as the exposure variable. Due to a limited number of patients with observed C_{min_ss} levels, exposure data were divided by median into two groups: $C_{min\_ss} \leq 11.1$ ng/ml (N=60) and $C_{min\_ss} > 11.1$ ng/ml (N=59). **Figure 1** shows no clear separation between the two exposure groups. However, there is a clear treatment effect as both the exposure groups in the treatment arm were well differentiated from the placebo arm. These results were consistent with the applicant's findings where a kaplan meier analysis was conducted using population predicted C_{min_ss} and AUC_{ss} values from 161 patients (**Figure 4**). A univariate and multivariate Cox proportional hazard analysis did not show C_{min_ss} as a predictor of survival, while known risk factors like ECOG (Eastern Cooperative Oncology Group) status, baseline lactic acid dehydrogenase (LDH), prior cytotoxic therapies were significant factors for survival (Table 1).

Figure 1: Kaplan-Meier Plot for OS (Jan 2010 cutoff date, interim analysis) stratified by Exposure Group. Small black, green and red vertical ticks on the plots are censored observations.

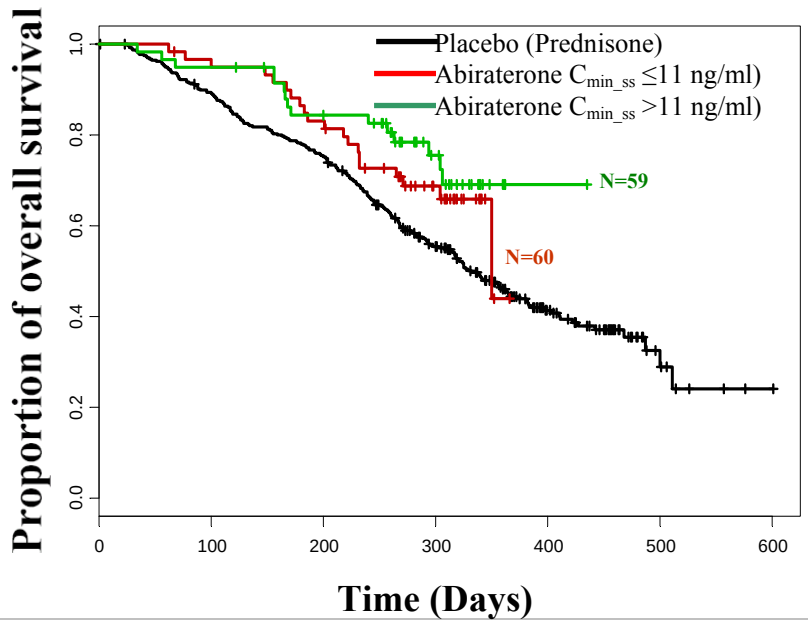


Table 1: Cox-proportional hazard model for OS (Jan 2010 cutoff date, interim analysis)

Predictor		Slope estimate	SE on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
Univariate						
C_{min_ss} per 10 ng/ml		-0.03238	0.06398	0.61	0.97	0.85, 1.09
LDH per 100 IU/L		0.21577	0.0366	<0.0001	1.24	1.15, 1.33
ECOG	0 vs. 2	-1.60598	0.54367	0.003	0.20	0.07, 0.58
	1 vs. 2	-0.81436	0.41754	0.05	0.44	0.19, 1.00
Prior cytotoxic therapy (1 vs. 2)		-0.94248	0.34447	0.006	0.39	0.19, 0.77
Type of Progression (Radio=1 and PSA=0)		-0.27642	0.40287	0.49	0.75	0.34, 1.67
Multivariate						
C_{min_ss} per 10 ng/ml		-0.01655	0.05038	0.74	0.98	0.89, 1.10
LDH per 100 IU/L		0.24325	0.04127	<0.0001	1.28	1.18, 1.38
ECOG	0 vs. 2	-1.61903	0.55016	0.003	0.19	0.07, 0.58
	1 vs. 2	-1.16793	0.43824	0.007	0.31	0.13, 0.73
Prior cytotoxic therapy (1 vs. 2)		-1.10198	0.35752	0.002	0.33	0.16, 0.67

1.1.2 Is there an evidence of exposure-response for safety?

As described above, there were insufficient PK data collected in the pivotal trial COU-AA-301 to evaluate the exposure-response for the safety endpoints hepatotoxicity, hypokalemia, fluid retention/edema, and hypertension. Furthermore, there were no PK data collected in phase 2 studies COU-AA-003 and COU-AA-004. PK data collected in early phase 1/2 studies COU-AA-001 and COU-AA-002 could not be used to generate a pooled safety database because of problems with the bioanalytical assay. Specifically, abiraterone acetate had limited stability in blood and plasma in the absence of sodium fluoride and a metabolite with the same mass transition as abiraterone co-eluted with abiraterone.

For Study COU-AA-301, summary statistics of the proportion of patients having adverse events (AEs) by C_{min_ss} category are presented in **Table 2**.

Table 2: Summary of AEs by Exposure Group in COU-AA-301

Exposure Group	Mean C_{min_ss} (ng/ml)	Adverse Event	Proportion of patients with all grade AE's (%)
Lower (Below median C_{min_ss})	6.2	Elevated ALT	1/60 (1.7)
Higher (Above median C_{min_ss})	35.2		2/59 (3.4)
Lower (Below median C_{min_ss})	6.2	Hypokalemia	7/60 (12)
Higher (Above median C_{min_ss})	35.2		11/59 (18)
Lower(Below median C_{min_ss})	6.2	Peripheral edema	21/59 (36)
Higher (Above median C_{min_ss})	35.2		16/60 (27)
Lower (Below median C_{min_ss})	6.2	Hypertension	9/60 (15)
Higher (Above median C_{min_ss})	35.2		5/59 (8.5)

1.1.3 Is the proposed (b) (4) dose reduction (b) (4) appropriate for management of hepatotoxicity?

No. The two-step dose reduction (1000 to 750 to 500 mg) which gives an option of treating a patient at 750 mg before further reducing the dose to 500 mg should be utilized to manage hepatotoxicity (defined as ALT or AST > 5 x ULN or Bilirubin > 3 x ULN).

- Efficacy at lower doses or exposures (500 mg dose) is unknown. Reducing the exposures by (b) (4) could result in loss of efficacy.

- Both 750 mg and 1000 mg doses had similar biomarker activity in study COU-AA-001 (phase 1/2 dose ranging study). A near maximal increase was observed in mean deoxycorticosterone and corticosterone (steroids upstream of CYP17 that serve as biomarkers of the completeness of CYP17 inhibition) levels at the 750 mg dose whereas higher doses of 1000 and 2000 mg did not raise the levels. At these doses, testosterone and androstenedione concentrations were below the lower limit of detection. Thus, having an option to be treated at 750 mg may reduce the likelihood of experiencing hepatotoxicity while maintaining efficacy.

- The two-step dose reduction was specified in the protocol for study COU-AA-301 to manage hepatotoxicity and other toxicities. The majority of the patients (21/27) followed the step dose reduction scheme in the pivotal trial. Approximately 60% (16/27) of the patients had their dose reduced to 750 mg and did not need further dose reduction. Five patients had step dose reductions from 1000 to 750 to 500 mg. (b) (4) Thus, having an option to be treated at the 750 mg dose may reduce the likelihood of experiencing hepatotoxicity while maintaining efficacy (**Table 3**).

Table 3. Dose reductions in pivotal trial COU-AA-301

	Abiraterone Acetate (N=791)	**Placebo (N= 394)**
Total Dose Reductions	27 (3.4%)	5 (1.3%)
Maximum AA dose reduction		
1000 to 750 mg	16	5†
(b) (4)	(b) (4)	(b)
1000 to 250 mg	0	-
1000 to 750 to 500 mg	5	-
Due to Elevated ALS/AST	3 (0.4%)	0

(b) (4)

† Since the actual amount of placebo dose was not reported, it was assumed that one dose reduction meant reduction from 1000-750 mg.

1.2 Recommendations

Division of Pharmacometrics finds the NDA acceptable from a clinical pharmacology perspective and has the following recommendations for the applicant.

- The applicant is encouraged to collect sparse pharmacokinetic data (at least for one cycle at steady state) from ALL subjects in their future trials. The purpose is to develop exposure response relationships for efficacy and safety endpoints to support proposed dosing recommendations.

- The applicant should update their safety database with additional data from the future trials to justify their dose modification strategies using exposure-safety analysis.

1.3 Label Statements

Please see section 3 of the clinical pharmacology review for detailed labeling recommendations.

2 Pertinent Regulatory Background

Abiraterone acetate and its active metabolite abiraterone are selective steroidal inhibitors of 17α hydroxylase/C17, 20-lyase (CYP17), an enzyme that is used in the production of androgens in the testes and adrenal glands. Abiraterone acetate is rapidly converted to abiraterone after oral administration. The indication sought in the current application is for abiraterone acetate in combination with prednisone in patients with metastatic castration resistant prostate cancer (CRPC) who have received prior chemotherapy containing a (b) (4)

Before 2010, the only approved treatment known to improve survival in patients with mCRPC was docetaxel, a cytotoxic agent administered in combination with prednisone. Recently, cabazitaxel in combination with prednisone was approved in the United States (U.S.) for hormone-refractory metastatic prostate cancer following a docetaxel-containing regimen. Cabazitaxel and prednisone improved survival by median 2.4 months compared with mitoxantrone and prednisone (hazard ratio [HR]=0.70; p<0.0001). However, patients treated with cabazitaxel experience a high incidence of Grade 3 or 4 neutropenia and febrile neutropenia. Thus, the applicant mentions that an unmet need exists for new therapies that prolong OS after chemotherapy without producing the side effects associated with cytotoxic agents and claims that the safety profile of abiraterone acetate across studies in mCRPC was distinct from the safety profile of cytotoxic therapies, which are associated with AEs such as myelosuppression (including febrile neutropenia) and stomatitis that can compromise quality of life during treatment of mCRPC.

The applicant in the current NDA submission conducted two phase 1 dose ranging studies to come up with 1000 mg daily dosing regimen of AA for the pivotal trial. The pivotal trial was a phase 3 multinational, randomized, multicenter, double-blind, placebo-controlled study of abiraterone acetate (1000 mg daily) and prednisone in patients with mCRPC whose disease had progressed on or after docetaxel-based chemotherapy. This study randomized 1195 patients 2:1 to receive 1000 mg of abiraterone acetate daily plus 5 mg of prednisone twice daily or placebo plus prednisone, respectively. In regions where prednisone was not available, prednisolone was provided. The primary efficacy endpoint was OS with a median OS of 14.8 months in the abiraterone acetate arm versus 10.9 months in the placebo arm (P < 0.0001) with a hazard ratio of 0.646. AEs of special interest included liver function abnormalities and mineralocorticoid-related toxicities such as hypertension, hypokalemia, and peripheral edema.

3 Results of Sponsor's Analysis

3.1 Exposure-Response Analysis for Effectiveness

The applicant conducted two types of exposure-response analysis for effectiveness:

- Association of abiraterone exposures to prostate specific antigen (PSA) and then associating PSA dynamics to OS.
- Direct relationship between exposures of abiraterone and OS.

Because of the ambiguity regarding the appropriateness of PSA as a biomarker in prostate cancer patients, only direct exposure-response analysis relating abiraterone exposures to OS was reviewed and will be discussed.

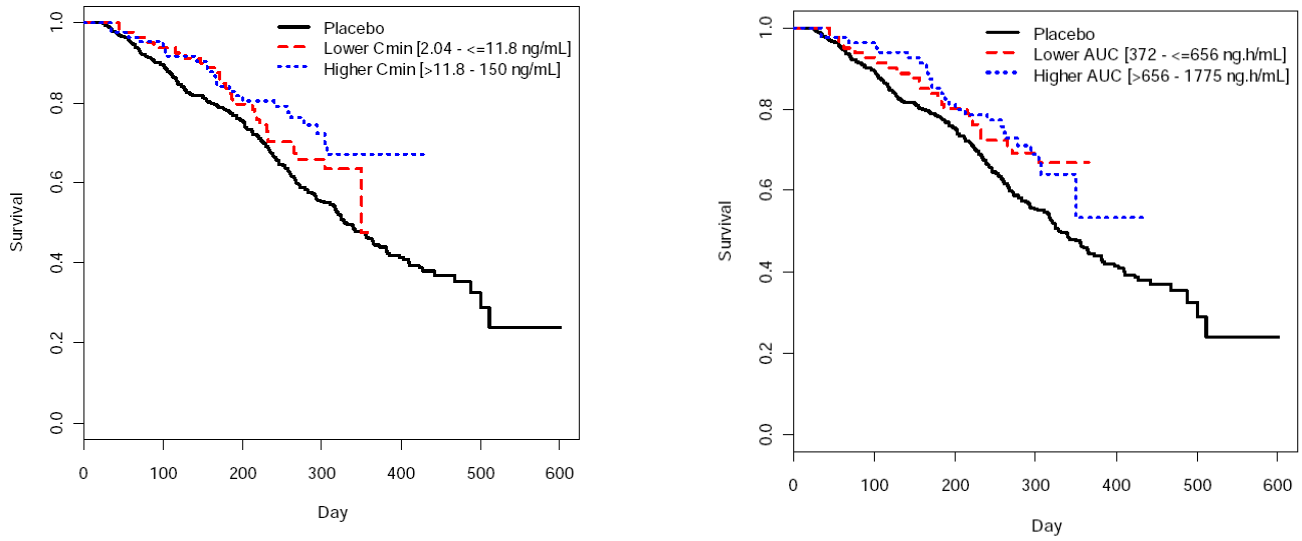
3.1.1 Methods

The patients with PK data were divided by median C_{min}. Lower C_{min} group included patients with $C_{min} \leq 11.8$ ng/mL (N=81), and higher C_{min} group included patients with $C_{min} > 11.8$ ng•hr/mL (N=80). A similar analysis was conducted using the population predicted steady state AUC. The patients with PK were divided by median AUC. The lower AUC group included patients with AUC ≤ 656 ng•hr/mL (N=81), and the higher AUC group included patients with AUC > 656 ng•hr/mL (N=80).

3.1.2 Conclusions

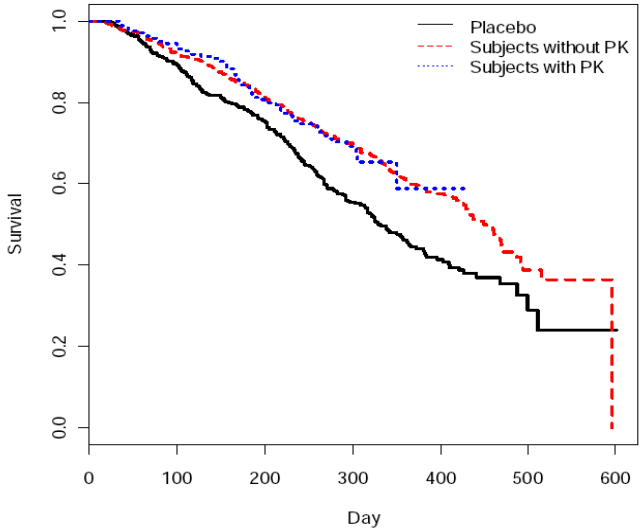
No separation between the survival curves of lower and higher exposure groups were observed (**Figure 2**). **Figure 3** shows that the survival curves of patients with and without PK overlapped indicating that patients with PK data are representation of the treatment group.

Figure 2: Exposure-response relationship of abiraterone for OS using steady state C_{min} (left panel) and steady state AUC (right panel). The black solid line is the survival curve for placebo group; the red dashed line is the survival curve for subjects with lower exposure and the blue dotted line is the survival curve for subjects with higher exposure.



Source: cou-aa-pop-pk, Figure 3.1 and 3.2, Page 133-134

Figure 3: Comparison of survival probability over time (kaplan-meier survival curve) in the PK subpopulation (n=161) to that in subjects without PK samples (n=636) in the COU-AA-301 trial. The black solid line is the survival curve for the placebo group; the red dashed line is the survival curve for subjects without PK samples; and the blue dotted line is the survival curve for subjects with PK samples.



Source: cou-aa-pop-pk, Figure 3.4.11,Page 146

Reviewer's Comments:

- *These were the main differences in the reviewer's exposure-response analysis for effectiveness.*
  - *The applicant used population predicted C_{min_ss} from 161 patients who had PK data while the reviewer utilized observed C_{min_ss} (N=119) to perform the analysis. Nevertheless, the conclusions were similar for both approaches.*
  - *The applicant submitted two sets of survival data in the NDA submission. The first survival dataset was based on the January 2010, the cutoff date of the pre-specified interim analysis. The second updated survival dataset was submitted after 97% of the planned number of events for the final analysis took place (September 2010 cutoff). The exposure-response analysis was conducted using both the survival datasets.*
  - *The reviewer performed both univariate and multivariate regression using Cox proportional hazard analysis to explore if C_{min_ss} was a predictor of OS.*

4 Reviewer's Analysis

4.1 Exposure-Response Analysis for Effectiveness

4.1.1 Objectives

To explore the exposure-response relationship using the primary end point (OS). The aim of the present analysis was to perform:

- exposure-response analysis using observed C_{min_ss} for both interim analysis dataset (January 2010 cutoff) and updated survival dataset (September 2010 cutoff).
- univariate and multivariate (adjusting for confounding risk factors) Cox-proportional hazard analysis to explore if C_{min_ss} was a predictor of OS.

4.1.2 Methods

The primary efficacy assessment was OS defined as the time interval from the date of randomization to the date of death due to any cause. Survival time of living subjects was to be censored at the last date a subject was known to be alive or lost to follow up.

Data from only pivotal trial (COU-AA-301) were used for this analysis to focus only on efficacy in patients (CRPC patients) for which the indication is proposed. Pharmacokinetic data were available for 161/798 (20%) of the subjects. However, observed steady state trough concentrations were available for 119 (15%) patients, which was utilized for the exploratory exposure-response analysis for OS. Thus, the exposure-response dataset only consisted of these 119 patients, which is a major limitation of the analysis. Since observed C_{min_ss} was available for only 119 patients, the data were divided into two groups by median C_{min_ss} (11.1 ng/ml): Lower exposure group ($C_{min\_ss} \leq 11.1$ ng/ml) and higher exposure group ($C_{min\_ss} > 11.1$ ng/ml).

4.1.3 Datasets

The datasets utilized for the analysis are summarized below**.**

Study Number	Name	Link to EDR
COU-AA-301	atrisk.xpt	\\cdsesub1\EVSPROD\NDA202379\\0000\m5\datasets\cou-aa-301-os\analysis\datasets\atrisk.xpt
	osupdate.xpt	\\cdsesub1\EVSPROD\NDA202379\\0000\m5\datasets\cou-aa-301\analysis\datasets\osupdate.xpt
	dosemod.xpt	\\cdsesub1\EVSPROD\NDA202379\\0000\m5\datasets\cou-aa-301-os\analysis\datasets\dosemod.xpt
Population PK/PD report	abi-004-v4-csv.xpt	\\cdsesub1\EVSPROD\NDA202379\\0000\m5\datasets\cou-aa-pop-pk\analysis\pk-datasets\abi-004-v4-csv.xpt

4.1.4 Software

SAS 9.2 and TIBCO Spotfire S-Plus 8.1were used for analyses.

4.1.5 Model

A Kaplan Meier analysis was performed for OS stratified by two exposure groups. Common risk factors (ECOG, baseline LDH, prior cytotoxic therapy (1 vs. 2), radio progression or PSA only progression) were compared between the two exposure groups. A cox-proportional hazard analysis was also conducted to test the significance of C_{min_ss} as an independent predictor for survival, and also after adjusting for other risk factors.

4.1.6 Results

The **Table 4** below shows the mean and 90% CI of exposures in the lower and higher exposure groups.

Table 4: C_{min_ss} in the lower and higher exposure groups.

Group	N	Mean C_{min_ss} (5^{th}, 95^{th} percentile)
Lower exposure ($C_{min\_ss} \leq 11.1$ ng/ml)	60	6.2 (1.3, 10.7)
Higher exposure ($C_{min\_ss} > 11.1$ ng /ml)	59	35.2 (12.5, 115.8)

The exposure-efficacy analysis for updated OS data showed that higher exposure group had numerically higher median survival (**Figure 4**). This analysis was however confounded by other risk factors which were not balanced within the two exposure groups (**Table 5).** The lower exposure group had a larger proportion of patients who had ECOG=2 and also a slightly higher proportion of patients with two prior cytotoxic therapies. The mean baseline LDH level was also higher in lower exposure group.

Figure 4: Kaplan-Meier Plot for OS (September 2010 cutoff date, updated analysis) stratified by Exposure Group. Small black, green and red vertical ticks on the plots are censored observations.

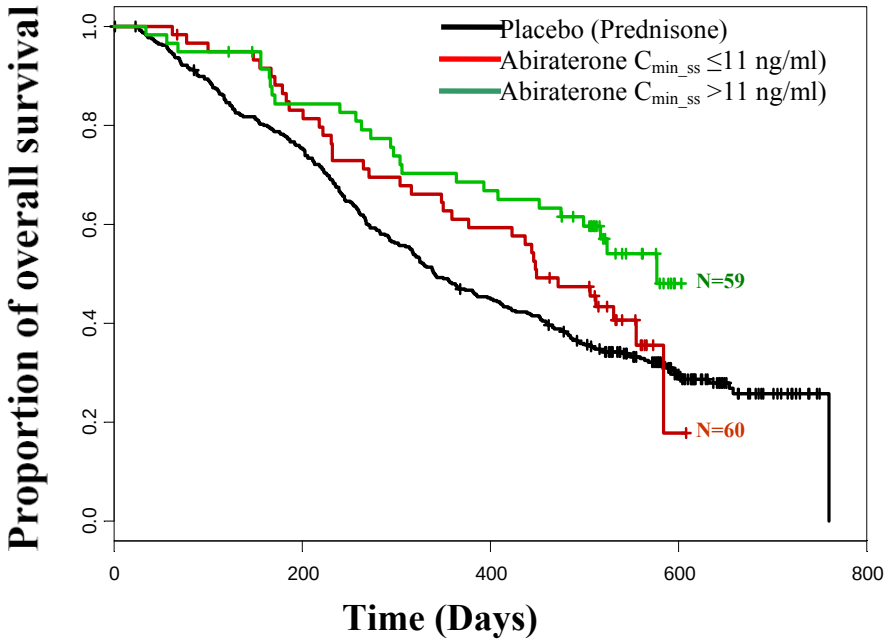


Table 5: Distribution of risk factors (Baseline LDH, ECOG status, prior cytotoxic therapies, type of progression) in lower and higher C_{min_ss} group.

Exposure Group	Mean LDH (IU/L)	Prior Cytotoxic therapies=2 (%)	Number of Patients with ECOG status = 2 (%)	Type of Progression=Radio progression (%)
Lower Exposure (N=60)	303	20 (33)	9 (15)	46 (77)
Higher Exposure (N=59)	267	15 (25)	5 (8)	40 (68)

Furthermore, the univariate or multivariate Cox-proportional hazard analysis did not demonstrate C_{min_ss} as a significant covariate for survival (**Table 6**).

Table 6: Cox-proportional hazard model for OS (September 2010 cutoff date, updated analysis)

Predictor		Slope estimate	SE on estimate	P-value	Hazard ratio (HR)	95% HR confidence limits
Univariate						
$C_{min\ ss}$ per 10 ng/ml		-0.03861	0.04996	0.44	0.96	0.87, 1.06
LDH per 100 IU/L		0.22799	0.03559	<0.0001	1.25	1.17, 1.35
ECOG	0 vs. 2	-1.23185	0.39068	0.001	0.29	0.14, 0.63
	1 vs. 2	-1.00846	0.35250	0.004	0.37	0.18, 0.73
Prior cytotoxic therapy (1 vs. 2)		-0.73643	0.26462	0.005	0.48	0.29, 0.80
Type of Progression (Radio=1 and PSA only=0)		-0.44849	0.31290	0.15	0.64	0.35, 1.18
Multivariate						
$C_{min\ ss}$ per 10 ng/ml		-0.02807	0.04021	0.49	0.97	0.89, 1.05
LDH per 100 IU/L		0.26131	0.03899	<0.0001	1.30	1.2, 1.4
ECOG	0 vs. 2	-1.22721	0.39513	0.002	0.29	0.14, 0.64
	1 vs. 2	-1.30984	0.36359	0.0003	0.27	0.13, 0.55
Prior cytotoxic therapy (1 vs. 2)		-0.90055	0.27539	0.0011	0.41	0.24, 0.70

In summary, the lack of exposure-response relationship for efficacy could be due to the low number of subjects who had PK data in the pivotal trial. Thus, nothing conclusive could be said about efficacy at the lower doses of 750 or 500 mg.

4.2 NDA Filing and Review Form

Office of Clinical Pharmacology

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA/BLA Number	**202-379**	**Brand Name**	**Zytiga®**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Abiraterone Acetate**
Medical Division	**Oncology**	**Drug Class**	**Androgen biosynthesis inhibitor**
OCP Reviewer	**Elimika Pfuma, Pharm.D. / Ph.D.**	**Indication(s)**	**Proposed:** The treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients who have received prior chemotherapy containing a (b) (4)
OCP Team Leader	**Jeanne Fourie Zirkelbach , Ph.D.**	**Dosage Form**	250 mg tablets
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**	**Dosing Regimen**	**Proposed:** 1 gram of oral abiraterone acetate administered once daily at least (b) hour before or (b) hours after a meal, with prednisone 10 mg daily
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**		
Date of Submission	**20-December-2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Cougar**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**20-June-2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study # COU-AA-007**
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**3**		**Ultra filtration and equilibrium dialysis methods both using isolated human plasma proteins and the third studyused equilibrium dialysis with blood samples from male volunteers with different levels of hepatic function. All determined the protein biding of abiraterone, but not abiraterone acetate.**

Pharmacokinetics -	**X**	**12**		**Single dose – 7 phase 1 studies in healthy volunteers and 2 organ impairment studies.** **Multiple dose - 2 Phase 1 studies and sparse PK in Phase 3 Study COU-AA-301 in patients with mCRPC**
HEALTHY VOLUNTEERS-				
single dose:	**X**	**9**		**7 phase 1 studies in healthy volunteers(COU-AA-005, COU-AA-007, COU-AA-008, COU-AA-009, COU-AA-010, COU-AA-014 and COU-AA-016) and 2 organ impairment studies (COU-AA-011 and COU-AA-012).**
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**3**		**Drug interaction Study # COU-AA-015, QT study # COU-AA-006 and the pivotal Phase 3 Study COU-AA-301 in patients with mCRPC**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		**Dose proportionality was assessed in Study# COU-AA-016**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**X**	**1**		**Study # COU-AA-015 studies the effect of abiraterone acetate on CYP2D6 and CYP1A1 substrates**
In-vitro:	**X**	**7**		**(b) (4) 8202265, (b) (4) 400378, (b) (4) 400379, (b) (4) 400380, (b) (4) 8216188, FK7389, (b) (4) 8202268**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		**Study COU-AA-012 in healthy volunteers with normal renal function or ESRD**
hepatic impairment:	**X**	**1**		**Study COU-AA-011 in healthy volunteers with normal or mild and moderate hepatic impairment**
PD - QT Study:	**X**	**1**		**QT study # COU-AA-006**
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**			
Population Analyses -				

Data rich:	**X**	**4**		**COU-AA-006, COU-AA-008, COU-AA-009, COU-AA-014**
Data sparse:	**X**	**1**		**COU-AA-301. Both rich and sparse PK were used in POPPK analysis**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**		**Study COU-AA-010 &COU-AA-014**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		**Study COU-AA-005**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		**Study COU-AA-009**
Bio-waiver request based on BCS				
BCS class	**X**	**1**		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**26**		

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/s/

ELIMIKA PFUMA
04/15/2011

NITIN MEHROTRA
04/16/2011

JEANNE FOURIE
04/18/2011
Concurrence with primary reviewer noted.

CHRISTINE E GARNETT
04/18/2011

NAM ATIQUR RAHMAN
04/20/2011

ADDENDUM to ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-379/N-000
Submission Dates:	03/31/11
Brand Name:	Zytiga
Generic Name:	Abiraterone Acetate
Formulation:	Immediate release (IR) tablet
Strength:	Only one strength, 250 mg
Sponsor:	Centocor Ortho Biotech
Type of submission:	An NDA amendment
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Original NDA 202-379 submitted under 505 (b)(1) on 12/20/10 for Zytiga (abiraterone acetate) was reviewed by the Biopharmaceutics team on 03/08/11. It was concluded that the proposed dissolution method as shown below was acceptable.

Apparatus: **USP 2 (Paddle) at 50 rpm**
Medium: **Phosphate buffer (pH 4.5) 900 mL containing 0.25% SLS, at 37ºC**

However, it was recommended that the dissolution specification be tightened as follows:

Change from: **Q=** (b) (4) **at 45 min**
to: **Q=** (b) (4) **at 30 min**

On 03/15/11, an Agency's letter was sent to the applicant requesting the above change. The applicant responded on 03/21/11 with additional stability-dissolution data and a new dissolution specification proposal of Q= (b) (4) at 30 min. On 03/29/11, a teleconference was held between the Agency and the applicant. After the T-con, the first Biopharmaceutics review addendum was completed on the same day and the Agency still recommended **Q=** (b) (4) **at 30 min**.

This second Biopharmaceutics addendum is to address the applicant's response submitted on 03/31/11 that the applicant agreed with the Agency's proposed dissolution specification and updated the specifications table (under section M32P51). Therefore, this NDA is acceptable from the Biopharmaceutics perspective. No further action is needed at this time.

_____ 04/06/11

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 04/06/11

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

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/s/

TIEN MIEN CHEN
04/06/2011

PATRICK J MARROUM
04/06/2011

ADDENDUM to ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-379/N-000
Submission Dates:	03/21/11 and 03/29/11
Brand Name:	Zytiga
Generic Name:	Abiraterone Acetate
Formulation:	Immediate release (IR) tablet
Strength:	Only one strength, 250 mg
Sponsor:	Centocor Ortho Biotech
Type of submission:	An NDA amendment and a teleconference
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Original NDA 202-379 submitted under 505 (b)(1) on 12/20/10 for Zytiga (abiraterone acetate) was reviewed by the Biopharmaceutics team on 03/08/11. It was concluded that the proposed dissolution method as shown below was acceptable.

Apparatus: **USP 2 (Paddle) at 50 rpm**
Medium: **Phosphate buffer (pH 4.5) 900 mL containing 0.25% SLS, at 37ºC**

However, it was recommended that the dissolution specification be tightened as follows:

Change from: **Q=** (b) (4) **at 45 min**
to: **Q=** (b) (4) **at 30 min**

On 03/15/11, an Agency's letter was sent to the applicant requesting the above change. The applicant responded on 03/21/11 with additional stability-dissolution data and a new dissolution specification proposal of Q= (b) (4) at 30 min.

On 03/29/11, a teleconference was held between the Agency and the applicant to discuss the setting of the dissolution specification for Zytiga 250 mg IR tablets. At the end of the teleconference the following conclusions were reached:

- The applicant wished to discuss further internally (with their firm) the setting of the dissolution specification to Q= (b) (4) at 30 min on an interim basis.
- If the applicant agrees with the above interim dissolution specification, an updated specifications table will be submitted by 03/31/11.
- The sponsor could provide additional dissolution data and discuss with the Agency later, e.g., one year, if a modification to the approved dissolution specification is indeed necessary.
- The applicant understood that if they do not agree with the Agency's recommended dissolution specification of Q= (b) (4) at 30 min, this may result in a deficiency issue to be included in the complete response action letter.

_____ _____03/29/11_____

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ _____03/29/11_____

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

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/s/

TIEN MIEN CHEN
03/30/2011

ANGELICA DORANTES
03/30/2011

ONDQA BIOPHARMACEUTICS REVIEW

NDA#:	202-379/N-000
Submission Date:	12/20/10, 01/27/11, and 03/07/11
Brand Name:	Zytiga
Generic Name:	Abiraterone Acetate
Formulation:	Immediate release (IR) tablet
Strength:	Only one strength, 250 mg
Sponsor:	Centocor Ortho Biotech
Type of submission:	Original
Reviewer:	Tien-Mien Chen, Ph.D.

SUMMARY

Abiraterone acetate is a pro-drug which is converted *in vivo* to abiraterone, a selective inhibitor of the enzyme 17a-hydroxylase/C17,20-lyase (CYP17). This enzyme is required for androgen biosynthesis and is expressed in testicular, adrenal and prostatic tumor tissues. CYP 17 catalyzes the conversion of pregnenolone and progesterone into the testosterone precursors, DHEA, and androstenedione, respectively.

On 12/20/10, the sponsor submitted NDA 202-379 under 505 (b)(1) for Zytiga (abiraterone acetate) seeking approval for the IR 250 mg tablets. Only one strength is proposed. Abiraterone acetate is a new molecular entity (NME) which was developed previously under IND 71,023. Abiraterone acetate is reported as a BCS Class 4 drug.

Zytiga (abiraterone acetate) is indicated for the use with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration-resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4) The recommended dose for the indication is 1 g (4 x 250 mg tablets) orally as a single daily dose that must not be taken with food.

The proposed commercial, to-be-marketed (TBM) formulation was used to manufacture the registration stability and Phase III clinical trial material. The TBM tablet is to be debossed, whereas the clinically tested tablet is non-debossed. Comparative dissolution testing was requested and the sponsor submitted the dissolution data to address the debossing issue. The dissolution development report, dissolution data, and the proposed dissolution method using surfactant SLS (sodium lauryl sulfate), and specifications were submitted. They are reviewed here. The proposed dissolution method and specification are summarized below.

Apparatus:	**USP 2 (Paddle) at 50 rpm**
Medium:	**Phosphate buffer (pH 4.5) 900 mL containing 0.25% SLS, at 37ºC**
Specifications:	**Q= (b) (4) at 45 min**

The above dissolution method was reviewed and found acceptable. The mean comparative dissolution profiles showed that the commercial (debossed) tablets and the clinically tested (non-debossed) tablets are similar or near super-imposable.

RECOMMENDATION
From the Biopharmaceutics perspective, this NDA is acceptable. However, the proposed dissolution specifications need to be revised. The following comment needs to be conveyed to the sponsor.

COMMENT: (Needs to be sent to the sponsor)
Your proposed dissolution method as shown below is acceptable.

Apparatus: **USP 2 (Paddle) at 50 rpm**
Medium: **Phosphate buffer (pH 4.5) 900 mL containing 0.25% SLS, at 37ºC**

However, a mean of (b) (4) of Zytiga IR tablet dissolved in 30 min, therefore, your proposed dissolution specifications need to be tightened as follows.

Change from: **Q=(b) (4) at 45 min**
to: **Q=(b) (4) at 30 min**

Before this NDA can be approved, you need to revise and implement the proposed dissolution specifications.

BACKGROUND
Abiraterone acetate was developed under IND 71,023. Abiraterone acetate is a pro-drug which is converted *in vivo* to abiraterone, a selective inhibitor of the enzyme 17a-hydroxylase/C17,20-lyase (CYP17). This enzyme is required for androgen biosynthesis and is expressed in testicular, adrenal and prostatic tumor tissues. CYP 17 catalyzes the conversion of pregnenolone and progesterone into the testosterone precursors, DHEA and androstenedione, respectively.

Testosterone stimulates the development and progression of prostate cancer. Androgen deprivation therapies (GnRH analogues or orchiectomy) block the testicular source of testosterone and reduce testosterone concentrations to castrate levels but do not have an effect on the adrenal or peripheral sources, which continue to supply androgens to prostate tumor cells and promote disease progression. The sponsor reported that further reduction of testosterone concentrations below the castrate level by inhibition of CYP17 following administration of abiraterone acetate slows the progression of prostate cancer.

CURRENT SUBMISSION
On 12/20/10, the sponsor submitted NDA 202-379 under 505 (b)(1) for Zytiga (abiraterone acetate) seeking approval for the IR 250 mg tablets. Abiraterone acetate is an NME. Only one strength is proposed. So, there is no biowaiver issue. Zytiga (abiraterone acetate) is indicated for the use with prednisone for the treatment of metastatic (b) (4) (b) (4) (b) (4) (castration-resistant prostate cancer) in patients who have received prior chemotherapy containing a (b) (4) The recommended dose for the indication is 1 g (four 250 mg tablets) orally as a single daily dose that must not be taken with food.

The proposed commercial TBM formulation was used to manufacture the registration stability and Phase III clinical trial material. The TBM formulation is to be debossed, however, the clinically tested formulation is non-debossed. The dissolution development report, dissolution data, and the proposed dissolution method and specifications were submitted. Additional information on the comparative dissolution was requested on 01/18/11 to address the difference in debossing issues and the sponsor responded on 01/27/11 and on 03/07/11. They are reviewed here.

FORMULATION COMPARISONS
Abiraterone acetate is reported as a BCS Class 4 drug. The TBM formulation (No. JNJ-212082-AAA-G-002) is shown below, which has been tested clinically.

Table 1. The Formulation/Composition of Zytiga (Abiraterone Acetate) IR 250 mg Tablet for Commercial Production

Component	Reference to Quality Standard[a]	Function	mg/tablet
Abiraterone Acetate	Company Standard	Active	250.00
Lactose Monohydrate	NF/Ph. Eur.	(b) (4)	
Microcrystalline Cellulose	NF/Ph. Eur.		
Croscarmellose Sodium	NF/Ph. Eur.		
Povidone (b) (4)	USP/Ph. Eur.		
Sodium Lauryl Sulfate	NF/Ph. Eur.		
Colloidal Silicon Dioxide	NF/Ph. Eur.		
Magnesium Stearate	NF/Ph. Eur.		
(b) (4)	USP/Ph. Eur.		
Total Tablet Weight:			715.0

[a] Where multiple compendia are listed, the compendium applied is specific to the applicable region of the submission.

(b) (4)

NA = Not applicable

DISSOLUTION METHODOLOGY AND SPECIFICATIONS

The dissolution development report was submitted. It explored 1). Water and various pH media, 0.01 N HCl, 0.1 N HCl, phosphate butter, 4.5 and 6.8, 2). Various surfactants, polysorbate and SLS, and 3) Paddle (USP Apparatus 2) at rotational speed of 50 and 75 rpm. The sponsor's proposed dissolution method and specification are summarized below.

Apparatus: **USP 2 (Paddle) at 50 rpm**
Medium: **Phosphate buffer (pH 4.5) 900 mL containing 0.25% SLS, at 37ºC**
Specifications: **Q=** (b) (4) **at 45 min**

The sponsor reported that the above dissolution method has also been used to test Phase I, II, and III tablet clinical trial material, as well as the registration stability batches. The mean dissolution profiles of 6 registration batches are shown below.

Figure 1. Mean Dissolution Profiles (n=6 tablets/batch) of Six Registration Batches at Initial Time (t=0)

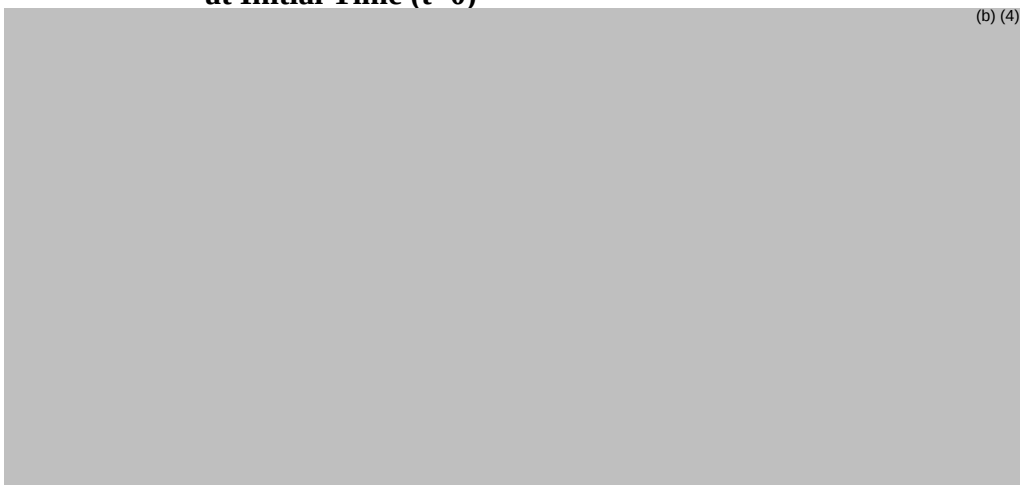

Table 2. Mean Dissolution Data (n=6 tablets/batch) of the Three Registration Batches

Batch No. /Time	15 Min	30 Min	45 Min	60 Min
R0304A001	(b) (4)			
R0314A001				
R0315A00156				

Batch Nos. R0304A001, and R0315A001 were also the biobatches used in the Phase 1 and pivotal clinical studies. The batch information is shown below.

Table 3. Registration Batch Information

Batch No.	Size	Site of Manufacture	Date of Manufacture
R0304A001[1]	(b) (4)	Patheon	May, 09
R0314A001		Patheon	May, 09
R03015A001[1,2]		Patheon	July, 09
HGX		Patheon	Dec., 09
TKN		Patheon	Feb., 10
WBB		Patheon	Mar., 09

[1] Biobatches.
[2] Full production batch.

The TBM tablet is to be debossed, however, the clinically tested formulation is non-debossed. Comparative dissolution data to address the debossing issue between the TBM and the clinically tested tablets was requested on 01/18/11 and submitted on 01/27/11 and further on 03/07/11 for review as shown below.

Figure 2. Mean Dissolution Profiles (n=12 tablets/batch) for Debossed Batch (No. CNTC) and Plain, Non-Debossed Batch (No. CXPG).

Table 4. Mean Dissolution Data of The Above Two Batches (n=12 tablets/batch)

Batch No. /Time	5 Min	10 Min	15 Min	20 Min	30 Min	45 Min	60 Min
CXPG(non-Debossed) RSD[1]	(b) (4)						
CNTC (Debossed) %RSD							

[1]. %RSD (% relative s

The information on the batch size and manufacturing of these two batches was not provided. It was requested on 03/01/11 and the sponsor submitted on 03/07/11 as shown below. Please see their individual dissolution data in Appendix 2 for details.

Table 5. Batch Information on Drug Product Batches CXPG and CNTC

DP Batch (Bulk Batch)	Manufacturing Date	Theoretical Batch Size	Site of Manufacture
CXPG (CXYK)	03 November 2010	(b) (4)	Patheon
CNTC (CNSH)	04 January 2011		Patheon

Reviewer's Comments:

1. The sponsor's proposed dissolution method was reviewed and found acceptable. However, since (b) (4) of drug dissolved in 30 min, the dissolution specifications need to be revised as followed.

   Change from: **Q= (b) (4) at 45 min**
   to: **Q= (b) (4) at 30 min**

2. The mean comparative dissolution profiles showed that the commercial (debossed) tablets and the clinically tested (non-debossed) tablets are similar or near super-imposable.

_____ 03/07/11

Tien-Mien Chen, Ph.D. Date
Reviewer
ONDQA Biopharmaceutics

_____ 03/07/11

Patrick Marroum, Ph.D. Date
ONDQA Biopharmaceutics

CC: NDA
Patrick Marroum, Angelica Dorantes, Tien-Mien Chen

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/s/

TIEN MIEN CHEN
03/08/2011

PATRICK J MARROUM
03/08/2011

CLINICAL PHARMACOLOGY
FILING FORM/CHECKLIST FOR NDA # 202-379

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**202-379**	**Brand Name**	**Zytiga®**
OCP Division (I, II, III, IV, V)	**V**	**Generic Name**	**Abiraterone Acetate**
Medical Division	**Oncology**	**Drug Class**	**Androgen biosynthesis inhibitor**
OCP Reviewer	**Elimika Pfuma, Pharm.D. / Ph.D.**	**Indication(s)**	**Proposed:** The treatment of metastatic castration-resistant prostate cancer (mCRPC) in patients who have received prior chemotherapy containing a (b) 8
OCP Team Leader	**Jeanne Fourie Zirkelbach , Ph.D.**	**Dosage Form**	250 mg tablets
Pharmacometrics Reviewer	**Nitin Mehrotra, Ph.D.**	**Dosing Regimen**	**Proposed:** 1 gram of oral abiraterone acetate administered once daily at least (b) hour before or (b) hours after a meal, with prednisone 10 mg daily
Pharmacometrics Team Leader	**Christine Garnett, Pharm.D.**		
Date of Submission	**20-December-2010**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**Cougar**
Medical Division Due Date		**Priority Classification**	
PDUFA Due Date	**20-June-2011**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**2**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		**Study # COU-AA-007**
Isozyme characterization:				
Blood/plasma ratio:	**X**	**1**		
Plasma protein binding:	**X**	**3**		**Ultra filtration and equilibrium dialysis methods both using isolated human plasma proteins and the third studyused equilibrium dialysis with blood samples from male volunteers with different levels of hepatic function. All determined the protein biding of abiraterone, but not abiraterone acetate.**

Pharmacokinetics -	**X**	**12**		**Single dose – 7 phase 1 studies in healthy volunteers and 2 organ impairment studies.** **Multiple dose - 2 Phase 1 studies and sparse PK in Phase 3 Study COU-AA-301 in patients with mCRPC**
Healthy Volunteers-				
single dose:	**X**	**9**		**7 phase 1 studies in healthy volunteers(COU-AA-005, COU-AA-007, COU-AA-008, COU-AA-009, COU-AA-010, COU-AA-014 and COU-AA-016) and 2 organ impairment studies (COU-AA-011 and COU-AA-012).**
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**3**		**Drug interaction Study # COU-AA-015, QT study # COU-AA-006 and the pivotal Phase 3 Study COU-AA-301 in patients with mCRPC**
Dose proportionality -				
fasting / non-fasting single dose:	**X**	**1**		**Dose proportionality was assessed in Study# COU-AA-016**
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:	**X**	**1**		**Study # COU-AA-015 studies the effect of abiraterone acetate on CYP2D6 and CYP1A1 substrates**
In-vitro:	**X**	**7**		**(b) (4) 8202265, (b) (4) 400378, (b) (4) 400379, (b) (4) 400380, (b) (4) 8216188, FK7389, (b) (4) 8202268**
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		**Study COU-AA-012 in healthy volunteers with normal renal function or ESRD**
hepatic impairment:	**X**	**1**		**Study COU-AA-011 in healthy volunteers with normal or mild and moderate hepatic impairment**
PD - QT Study:	**X**	**1**		**QT study # COU-AA-006**
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**			
Population Analyses -				

Data rich:	**X**	**4**		**COU-AA-006, COU-AA-008, COU-AA-009, COU-AA-014**
Data sparse:	**X**	**1**		**COU-AA-301. Both rich and sparse PK were used in POPPK analysis**
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**		**Study COU-AA-010 &COU-AA-014**
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**1**		**Study COU-AA-005**
replicate design; single / multi dose:				
Food-drug interaction studies	**X**	**1**		**Study COU-AA-009**
Bio-waiver request based on BCS				
BCS class	**X**	**1**		
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**26**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?	X			
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?		X		The sponsor did not submit absolute bioavailability data
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				

9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?		X		For the drug-drug interaction study, the sponsor used xTAG™ Mutation Detection system for P450-2D6 (Luminex Molecular Diagnostics) and summarizes details of this CYP2D6 test.
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			No exposure–response for safety analyses were submitted
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	Applicant is applying for waiver
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			No exposure–response information is in the proposed label
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? <u>Yes</u>

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None.

Elimika Pfuma, Pharm.D. / Ph.D.	14-January-11
Clinical Pharmacology Reviewer	Date
Jeanne Fourie Zirkelbach, Ph.D	14-January-11
Clinical Pharmacology Team Leader	Date
Nitin Mehrotra , Ph.D	14-January-11
Pharmacometrics Reviewer	Date
Christine Garnett, Pharm.D.	14-January-11
Pharmacometrics Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELIMIKA PFUMA
01/18/2011

JEANNE FOURIE
01/19/2011
Concurrence with primary reviewer noted.