



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for abiraterone acetate

Proprietary Product Name: Zytiga

Sponsor: Janssen-Cilag Pty Ltd

October 2012

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Copyright

© Commonwealth of Australia 2012

This work is copyright. You may reproduce the whole or part of this work in unaltered form for your own personal use or, if you are part of an organisation, for internal use within your organisation, but only if you or your organisation do not use the reproduction for any commercial purpose and retain this copyright notice and all disclaimer notices as part of that reproduction. Apart from rights to use as permitted by the *Copyright Act 1968* or allowed by this copyright notice, all other rights are reserved and you are not allowed to reproduce the whole or any part of this work in any way (electronic or otherwise) without first being given specific written permission from the Commonwealth to do so. Requests and inquiries concerning reproduction and rights are to be sent to the TGA Copyright Officer, Therapeutic Goods Administration, PO Box 100, Woden ACT 2606 or emailed to <tga.copyright@tga.gov.au>.

Contents

I. Introduction to product submission	4
Submission details	4
Product background	4
Regulatory status	5
Product Information	5
II. Quality findings	5
Drug substance (active ingredient)	5
Drug product	6
Biopharmaceutics	6
Advisory committee considerations	8
Quality summary and conclusions	8
III. Nonclinical findings	9
Pharmacodynamics	9
Pharmacokinetics	13
Toxicology	14
Nonclinical summary and conclusions	20
IV. Clinical findings	24
Pharmokinetics	25
Pharmacodynamics	48
Dosage selection for the pivotal studies	55
Efficacy	57
Safety	80
Preliminary benefit-risk assessment	99
List of questions	102
V. Pharmacovigilance findings	105
Risk management plan	105
Safety specification	105
VI. Overall conclusion and risk/benefit assessment	107
Quality	107
Nonclinical	108
Clinical	108
Risk management plan	110
Risk-benefit analysis	111
Outcome	112
Attachment 1. Product Information	112

I. Introduction to product submission

Submission details

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	27 February 2012
<i>Active ingredient(s):</i>	Abiraterone acetate
<i>Product Name(s):</i>	Zytiga
<i>Sponsor's Name and Address:</i>	Janssen-Cilag Pty Ltd 1-5 Khartoum Road Macquarie Park NSW 2113
<i>Dose form(s):</i>	Uncoated tablet
<i>Strength(s):</i>	250 mg
<i>Container(s):</i>	HDPE (high density polyethylene) bottle
<i>Pack size(s):</i>	120 tablets
<i>Approved Therapeutic use:</i>	Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostatic cancer [mCRPC]) in patients who have received prior chemotherapy containing a taxane.
<i>Route(s) of administration:</i>	Oral
<i>Dosage:</i>	1 g daily (4 tablets)
<i>ARTG Number (s)</i>	AUST R 180314

Product background

This AusPAR describes an application by the sponsor, Janssen-Cilag Pty Ltd, to register a new chemical entity, abiraterone acetate (Zytiga) 250 mg tablets for the treatment of metastatic castration resistant prostatic cancer (mCRPC) after failure of taxane chemotherapy.

Abiraterone acetate is a selective inhibitor of the enzyme cytochrome P450 17 α -hydroxylase/C17,20-lyase (CYP17), which is required for androgen biosynthesis in the testes and adrenal gland, and also in cancerous prostate tissue. There are currently no selective inhibitors of CYP17 on the Australian Register of Therapeutic Goods (ARTG); abiraterone acetate is the first agent in this class. Deprivation of androgen is an established method for treatment of mCRPC.

Current androgen deprivation treatments for prostate cancer include orchidectomy and gonadotrophin releasing hormone (GnRH) agonists and antagonists. These treatments interrupt androgen production from the testes only.

Docetaxel is currently approved for the treatment of patients with androgen independent (hormone refractory) prostate cancer; it was registered in 2005 by the Australian Drug Evaluation Committee (ADEC) for the first line treatment of hormone resistant prostate cancer. The submission which resulted in the approval of docetaxel for this indication could be considered to be a 'related submission' to the current submission to register abiraterone acetate. For the second line treatment of hormone refractory metastatic prostate cancer after failure of docetaxel, cabazitaxel (Jevtana) was approved in December 2011 following consideration by the Advisory Committee on Prescription Medicines (ACPM).

Regulatory status

The overseas regulatory status at the date of the application is summarised in Table 1.

Table 1: Summary of international regulatory status of Zytiga.

Country	Submission Date	Approval Date	Approved Indication
EU – Centralised Procedure*	17 December 2010	5 September 2011	ZYTIGA is indicated with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.
United States of America	17 December 2010	28 April 2011	ZYTIGA in combination with prednisone is indicated for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC) who have received prior chemotherapy containing docetaxel.
Canada	22 December 2010	27 July 2011	ZYTIGA is indicated with prednisone for the treatment of metastatic prostate cancer (castration-resistant prostate cancer) in patients who have received prior chemotherapy containing docetaxel.
Switzerland	17 January 2011	20 September 2011	For treatment in combination with LHRH agonists and prednisone or prednisolone in patients with advanced metastatic prostate cancer with progression following treatment with docetaxel.
Brazil	25 May 2011	7th November 2011	ZYTIGA TM is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing docetaxel.
New Zealand	Not submitted yet	N/A	N/A

*The rapporteur for the EU centralised procedure is Spain and the co-rapporteur is the United Kingdom.

Product Information

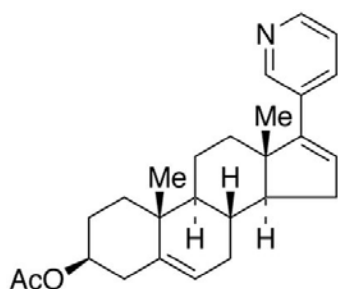
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality findings

Drug substance (active ingredient)

Abiraterone acetate is a semisynthetic steroid with multiple chiral centres (Figure 1), all of which are controlled so that abiraterone acetate is a single stereoisomer. It is basic (pKa 5.19), but aqueous solubility is very low (maximum solubility is in acid, for example, 0.01 g in 100 mL in 0.1 N HCl, so that 250 mg would dissolve in 2.3L acid; 1 g in 9L).

Figure 1: Chemical structure and molecular characteristics of abiraterone acetate (Zytiga).



Molecular Formula:

abiraterone acetate: $C_{26}H_{33}NO_2$

abiraterone: $C_{24}H_{31}NO$

Molecular Weight:

abiraterone acetate: 391.55 Daltons

abiraterone: 349.51 Daltons

The drug substance is crystalline; only one polymorphic form has been well characterised. The drug substance stability is acceptable.

Drug product

The uncoated Zytiga tablets are unscored and use common excipients. Tablet manufacture is conventional. Tablets are packed in HDPE bottles with a child resistant closure (120 tablets).

The recommended dose is 1 g (four 250 mg tablets) as a single daily dose 'that must not be taken with food'.

A satisfactory toxicological justification was submitted for the approved impurity limits.

Tablet dissolution limits were set to the satisfaction of the evaluator.

The shelf life is affected by increases in levels of two epoxides, formed by oxidative degradation. A shelf life of 24 months, store below 25°C is recommended.

Biopharmaceutics

Abiraterone acetate is converted *in vivo* to abiraterone ('M50') by esterases. Abiraterone was measured in bioavailability studies.

Absolute bioavailability

An absolute bioavailability study was not performed. The sponsor was unable to develop an acceptable intravenous (IV) formulation. The PSC (Pharmaceutical Subcommittee) considered the sponsor's justification for not providing an absolute bioavailability study acceptable. The size of the food effect (see below) means that the fasting absolute bioavailability must be very low (<10%).

Bioequivalence

A 250 mg capsule dosage form was used in early Phase I/II studies. A 250 mg tablet formulation was developed for later Phase I/II clinical trials. Tablets for Phase III trials used the same qualitative formulation. The Phase III formulation is identical to the proposed commercial tablets. It has been made at two manufacturing sites.

Dissolution comparison of the Phase I/II and Phase III tablet formulations "proved inconclusive". The bioequivalence of the tablets formulations was compared in studies:

Study COU-AA-014 was a single dose, open, four period crossover study comparing the bioavailability of abiraterone from the clinical trial tablet formulation with the commercial

tablet formulation manufactured at both an old and a new manufacturing site (one dose was repeated). The study used 18 subjects, with 4 x 250 mg tablet doses. The proposed (new) tablets were not bioequivalent to either of the comparison products, with the new site tablets giving higher bioavailability (Table 2).

Table 2: Study COU-AA-014 pharmacokinetic (PK) data analysis set.

	Ratio of Geometric Means (Test/Reference)		
	Treatment C/A	Treatment B/A	Treatment C/B
	% (90%CI) (N=14)	% (90%CI) (N=14)	% (90%CI) (N=14)
C _{max}	101 (85.11-119.14)	95.7 (80.98-113.16)	105 (88.72-124.72)
AUC _{48h}	113 (101.08-127.13)	99.6 (88.86-111.63)	114 (101.34-127.83)
AUC _{last}	115 (102.30-129.06)	99.6 (88.78-111.85)	115 (102.52-129.70)
AUC _∞	115 (102.63-129.19)	100 (89.16-112.09)	115 (102.52-129.42)

[A = Phase I/II Clinical Trial tablet; B = old site III tablet; C = new site commercial]

Bioequivalence studies are liable to be difficult with a drug showing very large food effects.

COU-AA-005 was a single dose, open, two way crossover bioequivalence study just comparing the proposed formulation made at the old site and at the new site. This study used a much larger number of subjects (n=120). The tablets were bioequivalent (with the new site tablets having somewhat lower bioavailability).

Food effects

Study COU-AA-009 was a single dose, open, three way crossover study of the effect of fasting versus low fat versus high fat meals on the bioavailability of abiraterone acetate in 36 healthy subjects. Food dramatically increases bioavailability (vastly outside standard bioequivalence ranges; CI [confidence intervals] not shown here) (Table 3).

Table 3: Mean (standard deviation) plasma PK parameters and statistical comparison of abiraterone (Study COU-AA-009).

PK Parameter	Unit	Treatment A High-Fat Meal 1000 mg N=35	Treatment B Low-Fat Meal 1000 mg N=36	Treatment C Fasted State 1000 mg N=35
C _{max}	ng/mL	1270 (487)	558 (307)	90.9 (65.3)
t _{max}	h	2.0 (1.5-4.0)	3.0 (1.0-6.0)	2.0 (1.0-4.0)
AUC _{last}	ng*h/mL	4347 (1607)	2079 (1000)	499 (336)
AUC _∞	ng*h/mL	4370 (1616)	2092 (1004)	509 (338)
t _{1/2}	h	17.9 (4.87)	17.6 (4.33)	15.7 (3.68)

If doses are taken with food, exposure is potentially 10 fold higher. It is likely that variable timing of food intake will affect bioavailability: effects of different pre dose fasting times have not been investigated. The PI warns that doses “must not be taken with food”.

The sponsor states that in the pivotal efficacy study (COU-AA-301), patients were instructed to take “4 tablets by mouth at least 1 hour before a meal or 2 hours after a meal any time up to 10 pm every day”. Dosing instructions were printed on the abiraterone acetate/placebo clinical trial bottle labels as “Take four [4] tablets once daily by mouth at least one [1] hour before a meal or two [2] hours after a meal” (or the equivalent in the multi language labels).

If there are safety concerns with higher doses or with very variable abiraterone exposures it might be appropriate to include a label direction on the carton. The PI could be more specific.

Advisory committee considerations

This application was considered by the PSC of the ACPM at its 140th meeting in August 2011.

The PSC supported the questions in relation to the limits for the particle size of the drug substance and the release specification for dissolution of the drug product.

The PSC considered that the sponsor should be asked to:

- Commit to conducting process validation on three consecutive commercial scale tablet batches. Drug substance manufactured at both sites should be used in formulating the validation batches.
- Provide batch analyses and stability data for tablet batches formulated with drug substance manufactured at both sites.

These issues have now been satisfactorily addressed.

The PSC noted the dramatic and significant effect of food, particularly the fat content of food, on the bioavailability of abiraterone. The PSC noted that there was no precise information on the effects of variation in the relative timing of food and dosing on bioavailability. The PSC considered that minimising variability of exposure in individual subjects due to variations in day to day dietary intake was prudent. The PSC therefore considered that if the proposed dosing in relation to food differs from that used in clinical trials, the Delegate should consider recommending similar protocol used in the clinical trial studies.

The food effects are addressed above.

Population pharmacokinetic analysis

The PSC:

- Considered that information on the proportion of patients who achieved a steady state C_{min} (minimum plasma drug concentration) greater than an EC80 (effective concentration of 80%) would have been very helpful as this would be a better indicator of overall survival (OS).
- Noted that the impact of combinations of common covariates on the dose required to achieve various percentages of patients above the EC50 (effective concentration of 50%) or EC80 was not explored with the chosen population PK model. The Committee agreed that information on this would provide an insight on the patients at the margins who would usually require special attention.
- The PSC agreed that the issues identified above could be examined from the models and would provide valuable insight into the proper use of abiraterone in these very ill patients (and subsets of patients) who would usually require special attention, and a more thorough justification of the dose selected. This could/should be explored in a formal review of a population analysis.
- Such aspects are outside the expertise of the Pharmaceutical Chemistry Section.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and biopharmaceutical aspects. Comments in relation to the effect of food on bioavailability and related labelling aspects are drawn to the committee's attention.

III. Nonclinical findings

The overall data for this application complied with the scope of nonclinical studies recommended in published guidelines.¹

The main toxicity studies were performed in cynomolgus monkeys and rats. Rodents are known to have some limitations for predicting potential human toxicities of agents affecting the hormonal milieu because of differences in physiology and responsiveness. However these species remain useful for investigations of non hormonal toxicities of agents. Both rodents and primates were adequate human models in terms of abiraterone acetate PK.

Primary pharmacology studies were adequate but not extensive, and there were no dedicated studies investigating potential for secondary pharmacology targets. However, the potential effects of abiraterone acetate on a range of CYP450 isozymes other than CYP17 were investigated in PK studies and repeat dose toxicity studies were adequate to reveal the range of activities expected with this drug.

Studies have not been performed to assess the reproductive toxicity or carcinogenic potential of abiraterone acetate. These are not required to support the proposed indication but such studies may be required to support any future applications, including those to amend and/or extend the indications for abiraterone acetate.

There were no nonclinical studies of abiraterone acetate in combination with prednisone or prednisolone or against a background of previous taxane use (as proposed for registration). Nonclinical studies of this type are not routinely warranted.¹ In the case of this application, there is substantial clinical experience with prednisone and prednisolone and (presumably) with docetaxel; and the nonclinical profile of abiraterone acetate has been characterised adequately in the context of the current application. Reassessment of the need for nonclinical studies of drug interactions with indicated concomitant medicines may be required for future applications regarding abiraterone acetate.

Pharmacodynamics

Testosterone stimulates the development and progression of prostate cancer, but eventually androgen deprivation therapies (GnRH analogues and orchiectomy) may become ineffective as testosterone continues to be supplied by and within sources including the adrenal gland and the tumour itself; and processes associated with androgen production or activity promotion become up regulated.²

The production of testosterone involves CYP17 mediated conversion of pregnenolone and progesterone into the testosterone precursors dehydroepiandrosterone and androstenedione. The development of CYP17 inhibitors for the treatment of mCRPC aims to reduce testosterone production beyond that afforded by existing androgen deprivation therapies. It is anticipated that this reduction will in turn slow the testosterone dependent progression of the prostate tumour.

Abiraterone (formulated as the acetate for practical purposes) apparently has emerged from a series of studies specifically designed to identify the necessary chemical structures

¹ European Medicines Agency, "ICH Topic S9 Nonclinical Evaluation for Anticancer Pharmaceuticals Step 3: Note for Guidance on Nonclinical Evaluation for Anticancer Pharmaceuticals", December 2008, Web, accessed 10 August 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002867.pdf>.

² Montgomery RB, et al. (2008) Maintenance of intratumoral androgens in metastatic prostate cancer: a mechanism for castration-resistant tumor growth. *Cancer Res.* 68: 4447-4454.

of agents that would effectively inhibit CYP17. The active, abiraterone, is cleaved from the acetate moiety by esterases.

Inhibition of CYP17 activity by abiraterone was demonstrated adequately in *in vitro* studies. There were no studies directly showing that abiraterone inhibits CYP17 activity in prostate tumour tissues; however, an *in vivo* study in a mouse model of prostate cancer (see below) showed a reduction in tumour tissue androgen levels following IP (intraperitoneal) administration of abiraterone acetate. Evidence for effective inhibition of testosterone production also comes from studies of intact rats or mice, where IP abiraterone acetate resulted in decreased systemic androgen levels and caused associated atrophy of testosterone sensitive tissues to a level similar to that produced by castration. Further, atrophy of hormone sensitive reproductive organs and decreased systemic androgen levels were consistently observed in the repeat dose toxicity studies of PO (oral) abiraterone acetate in rodents and monkeys. These findings support the rationale for using abiraterone acetate to reduce circulating levels of androgens.

Only one nonclinical study, in a mouse model of androgen independent CRPC, investigated if this activity translated into a potential effective treatment for the proposed indication. In this study, IP treatment of mice 5 days/week for 4 weeks was associated with increased survival time, and reductions in prostate tumour volume, serum PSA (prostate specific antigen) levels and prostate tumour androgen levels. Changes were also found in genetic transcripts that code for factors associated with the development of prostate cancer.

The single nonclinical efficacy study was provided as a published abstract of a study presented at the American Association Cancer Research Special Conference in 2009; it was therefore was not comprehensive in detail. However, it was notable that the beneficial effect of abiraterone acetate in this model rapidly reversed after treatment ceased, and progression of disease appeared to become more rapid than in the control rats. A rebound increase in serum testosterone levels once treatment ceased was also observed in some of the repeat dose toxicity studies of abiraterone acetate in rats.

Resistance to treatment with abiraterone acetate

An abstract presented to the 2011 Genitourinary Cancers Symposium and published after this application was submitted for evaluation reports on a study in mouse models of androgen independent CRPC that investigated resistance to abiraterone acetate treatment.³ The results of this study suggested that resistance to abiraterone acetate treatment may be due to upregulation of the abiraterone target CYP17 and/or induction of androgen receptors and splice variants that confer ligand independent receptor trans activation.

Resistance to abiraterone acetate treatment is apparently a known phenomenon, although the mechanisms are not fully understood. The nonclinical data submitted contained no mention of or studies investigating resistance to abiraterone acetate treatment. However, it is acknowledged that this phenomenon is currently under investigation in clinical trials, including in Australia (for example, at the Australian Prostate Cancer Research Centre in Queensland).⁴

³ Mostaghel E, et al. (2011) Tumor response and adaptation to CYP17 inhibition in prostate cancer: Induction of steroidogenesis and androgen receptor splice variants. *J. Clin. Oncol.* 29: supplement 7, abstract 18.

⁴ <http://www.australianprostatecentre.org/research/therapeutics/mechanisms-of-abiraterone-resistance-in-prostate-cancer>

Secondary effects associated with the primary pharmacology of abiraterone

The main secondary effects of abiraterone are expected to occur alongside its intended effects and result from the inhibition of CYP17 mediated conversion of pregnenolone and progesterone into cortisol. Reduced cortisol levels in humans cause an increase in ACTH (adrenocorticotrophic hormone) levels and, ultimately, an increase in the production of mineralocorticoids such as deoxycorticosterone, corticosterone and aldosterone. To reduce anticipated toxicities associated with mineralocorticoid excess (fluid retention/oedema, hypokalaemia and hypertension), the sponsor proposes that a corticosteroid (prednisone or prednisolone) be co administered with abiraterone acetate in patients.

Evidence of mineralocorticoid excess/toxicity was minimal in the animal repeat dose toxicity studies, and was manifested mainly by increased adrenal gland weight and hypertrophy or atrophy of adrenal gland zones. However, marked increases in the levels of ACTH and aldosterone (as well as in progesterone) and associated decreases in cortisol levels (as well as in dehydroepiandrosterone and testosterone levels) were observed in repeat dose toxicity studies in monkeys.

Hormonal perturbations due to the primary pharmacological effect of lowering testosterone levels might also be anticipated to result in unintended secondary effects; however, these would be similar to those caused by other anti androgen therapies, including castration, already being administered to the patient population.

Other secondary pharmacology activity

Abiraterone (formulated as the acetate for practical purposes) apparently has emerged from a series of studies specifically designed to identify the necessary chemical structures of agents that would effectively inhibit CYP17. Further, CYP17 is not known to be involved in processes other than the synthesis of corticosteroids and hormones. For these reasons, it would reasonably be expected that abiraterone has a relatively narrow activity profile with little potential for direct interaction with unrelated biochemical and physiological systems and processes. The lack of extensive investigations for secondary targets for activity, in the context of this application, is justifiable on this basis and on the basis that the major (but not all) toxicities associated with abiraterone acetate are related to inhibition of CYP17.

Potential for effects on other CYP450 isozymes

The possibility has been raised by published authors⁵ that abiraterone may affect the activity of other CYP isozymes by, for example, causing nonspecific 'heme iron complexation'. Using cell expressed human recombinant isozymes, these investigators found that abiraterone has some selectivity for CYP17 (IC_{50} = 72 nM) over CYP11B1 (involved in glucocorticoid metabolism; IC_{50} = 1608 nM), CYP11B2 (involved in mineralocorticoid metabolism; IC_{50} = 1751 nM), and CYP3A4 (IC_{50} = 2704 nM; compared with human abiraterone C_{max} [maximum plasma drug concentration] \geq 500 nM).

The potential effects of abiraterone on a range of CYP isozymes was also investigated in the nonclinical studies submitted. *In vitro* assays using human hepatocytes showed abiraterone was a competitive, potent inhibitor of CYP2D6 and CYP1A2 activity (K_i [inhibition constant] 0.39-0.44 μ M); and a competitive moderate inhibitor of CYP3A4/5 (K_i 8 μ M), CYP2C9 (K_i 29.8 μ M) and CYP2C19 (K_i 46.3 μ M).

⁵ Pinto-Bazurco Mendieta MA, et al. (2008) Synthesis, biological evaluation, and molecular modeling of abiraterone analogues: novel CYP17 inhibitors for the treatment of prostate cancer. *J. Med. Chem.* 51:5009-5018.

After PO treatment of rats with abiraterone acetate for one month, increases were found in the activity of CYP1A1/2 (males only), CYP4A1 (males and females); decreases were observed in the activity of CYP2E1 (males and females), CYP3A1/2 (males) and CYP2B (males); and increases (females) or decreases (males) were found in CYP3A1/2 activity. In this study, many of the effects were not large: the most marked and consistent effect was the increase (by 50-82%) in the activity of CYP4A1, which has a role in arachidonic acid and fatty acid metabolism.

The above investigations prompted clinical investigation of the potential for interactions between abiraterone and drugs metabolised by CYP2D6 and CYP1A2.

Docetaxel and prednisolone are metabolised mainly by CYP3A4, however, the effect of abiraterone on this isozyme is weak. There were no studies investigating if abiraterone affects the conversion of prednisone to prednisolone, which is mediated via 11 β -hydroxydehydrogenase (which is not part of the CYP system). There were also no studies investigating the effects of other drugs on the activity of abiraterone, particularly drugs effecting CYP3A4, which is involved in the metabolism of abiraterone (see below).

It is noted that the US FDA (Food and Drug Administration) has requested the sponsor conduct post market *in vitro* studies of the effects of abiraterone acetate on CYP2C8 (and subsequent clinical interaction studies if warranted by the *in vitro* findings). Presumably this is because CYP2C8 is involved in the metabolism of paclitaxel (as well as other drugs such as the antidiabetic agents repaglinide and rosiglitazone, amodiaquine, and torasemide; and is also involved in fatty acid metabolism).⁶

The FDA has also requested post market studies investigating whether the PK of abiraterone are affected by strong inhibitors or inducers of CYP3A4 (involved in producing one of the main abiraterone metabolites), as well as a study in patients with hepatic impairment.

Presumably, findings from these studies, and any actions arising, will be advised to the TGA when they become available.

Activity of metabolites

The major circulating metabolites of abiraterone in humans are abiraterone sulfate and the N-oxide of abiraterone sulfate, each accounting for 43% of the circulating drug related material after a 1000 mg dose in humans. Each of these metabolites occur at concentrations >100 times the respective concentration of abiraterone and they are less or as persistent as the parent ($t_{1/2}$ [half life] 24-28 h), with $t_{1/2}$ values of about 2.5 h for abiraterone sulfate (M45) and 21.6 h for the N-oxide of abiraterone sulfate (M31).

Both of these metabolites are active against CYP17, with the sulfate metabolite being approximately 7 times more potent than abiraterone against rat testicular microsomal CYP17. These metabolites have also been found to affect adrenal steroidogenesis, including inhibition of ACTH induced secretion of androstenedione and testosterone from a guinea pig adrenocortical tumour cell line, albeit less potently (>200 times) than the parent abiraterone.

Given the above, it is considered that the major metabolites of abiraterone will most likely contribute to the activity of abiraterone acetate.⁷

⁶ Konkel A, Schunck WH. (2011) Role of cytochrome P450 enzymes in the bioactivation of polyunsaturated fatty acids. *Biochim. Biophys. Acta*. 1814:210-222.

⁷ Sponsor comment: "We are not sure if this is a correct conclusion due to several reasons. First, in NCI-H295R human adrenal cortical tumour cells the metabolites (IC₅₀ in μ M range) were markedly less active than abiraterone (IC₅₀ 3.1 nM) activity, and markedly lower for the metabolites than for abiraterone in NCI-H295R human adrenal cortical cell lines. Secondly, in one system (rat testicular

Pharmacokinetics

The PK of abiraterone acetate were adequately characterised in species used for the main toxicity studies (rats and monkeys) and are considered sufficiently comparable to those in humans after repeated PO dosing of abiraterone acetate.

Circulating levels of the pro drug are negligible in all species investigated, due to rapid conversion of abiraterone acetate by esterases to the active, abiraterone. Levels of both the pro drug and abiraterone were determined in most of the nonclinical studies. *In vitro* studies with hepatocytes from a number of species (including humans) found that 100% of abiraterone acetate was converted to abiraterone within 5 minutes; however, esterases are also present in the blood and gut and therefore extra hepatic conversion *in vivo* is also possible. The metabolism of the active abiraterone also appears to be rapid and extensive, with oral bioavailability of 2% reported in monkeys and 37% in mice. Poor oral bioavailability of abiraterone is also likely in humans, since two major metabolites account for > 90% of circulating drug related material based on AUC (area under the plasma concentration-time curve).

As mentioned above, the absorption of abiraterone acetate is affected by food and vehicle, which accounts for the recommendation that it be administered without food in humans to reduce variation in absorption and to mimic conditions used in most of the clinical trials. In almost all nonclinical studies, the same vehicle was used to administer abiraterone acetate; however, individual variability in exposure was relatively high within and across studies. This is not a major issue because plasma drug levels were measured in most studies, reducing the need for extensive extrapolation across studies.

Sex differences in the PK of abiraterone were observed in rats (where exposure was substantially greater in males than in females) but they were less prominent in monkeys (where there were negligible differences except at the highest doses where exposure was higher in females than in males); however, this is not relevant to the current application.

Tissue distribution

Abiraterone shows an extensive but not exceptional tissue distribution pattern, except for the finding of high affinity for and prolonged retention in melanin containing tissues. This finding often prompts studies of potential phototoxicity, particularly for drugs that absorb light over 290-700 nm wavelengths and reach the skin or eyes.⁸ According to the nonclinical overview:

"No photosafety assessment was performed since the UV-Vis absorption spectra for abiraterone acetate and abiraterone showed that maximum absorption occurred at approximately 255 nm, with limited absorption between 290 and 700 nm."

The lack of photosafety studies for abiraterone is acceptable on this basis.

microsome) there was activity of the sulfate metabolite (not for the N-oxide abiraterone sulfate metabolite); however, in that study the IC₅₀ of abiraterone was markedly higher than in other studies (as well as the IC₅₀ for the positive control ketoconazole markedly higher than in other studies). And thirdly, the metabolites do have a much more hydrophilic character than abiraterone; the distribution of those metabolites is restricted, which results in high plasma concentrations, but (most probably) markedly lower concentrations at the tumour site."

⁸ European Medicines Agency, "Committee for Proprietary Medicinal Products (CPMP): Note for Guidance on Photosafety Testing", 27 June 2002, Web, accessed 13 August 2012
<http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50003353.pdf>.

Metabolism

The metabolism of abiraterone acetate was investigated adequately in species used for the main toxicology studies (rats and monkeys) as well as in humans.

The metabolic pathways appear to be similar in all species investigated, with minor quantitative differences in the extent of formation of individual metabolites between species and sexes not considered significant.

Ester hydrolysis of abiraterone acetate to abiraterone by esterases occurs rapidly in all species. Although up to about 40 metabolites of abiraterone have been identified, there are two main ones in all species investigated: abiraterone sulfate (produced by SULT [sulfotransferases]) and the N-oxide of abiraterone sulfate (produced by CYP3A4 mediated oxidation followed by SULT mediated sulfation). Together, these account for about 85% of the drug associated material in plasma following 1000 mg dose of abiraterone acetate in humans, and they are found at levels at least 100 times higher than abiraterone. Both metabolites are also found in the circulation of animals used for the main toxicity studies.

As mentioned above, the pharmacological activity profile of the main metabolites appears to be qualitatively similar to that of the parent, abiraterone, and these are likely to contribute to the efficacy as well as toxicity of abiraterone acetate.

Excretion

In rats and humans, abiraterone acetate was excreted mainly ($\geq 90\%$) via the faeces as metabolites, unchanged pro drug (probably unabsorbed) and abiraterone, with minor amounts of metabolites (mainly the N-oxide) excreted in urine. Evidence for substantial ($\sim 20\%$ of a dose) entero biliary circulation of abiraterone metabolites was found in rats.

Drug interaction studies

Specific interaction studies were not performed in whole animals; however, studies investigating the effects of abiraterone on CYP isoforms other than CYP17 indicate potential for these to occur (see above: 'Potential for effects on other CYP450 isozymes'). Potential for interactions with the P-glycoprotein (P-gp) transporter were not identified with abiraterone.

As noted above (see: 'Introduction' section of Nonclinical Findings), the need for nonclinical studies of drug interactions with indicated concomitant medicines may be required for future applications regarding abiraterone acetate.

Toxicology

The main toxicity studies were conducted in mice (2 week study only), rats and monkeys, with abiraterone acetate administered PO once daily as a suspension in 0.4% (w/v) aqueous methylcellulose. No studies were done with the proposed capsule formulation, but it contains common excipients and interactions between abiraterone acetate and these are not expected. Assays used to measure plasma concentrations of abiraterone in some of the toxicity studies were confounded by the presence of a co eluting peak, which resulted in the over estimation of abiraterone exposure by $\sim 20\%$. This issue did not affect exposure estimates in the 9 month monkey and 6 month rat study, and it is not considered to have substantially affected the validity and robustness of the studies.

The duration of studies in monkeys (1-9 months) and rats (1-6 months) was appropriate to support chronic use of medicines in humans, as recommended in relevant guidelines.⁹ Doses used were associated with exposure (AUC) to abiraterone similar to or lower than that expected in humans (Table 4). However, they were sufficient to cause pharmacological effects as well as dose limiting (or fatal) toxicity, and therefore the dose range used is considered adequate for assessing the potential toxicity profile of abiraterone acetate.

Exposure to the main abiraterone metabolites in humans (after 1000 mg/day abiraterone acetate) when compared with that in rats (doses up to 400 mg/kg/day) and monkeys (up to 1000 mg/kg/day) in the repeat dose toxicity studies was provided in the nonclinical overview. Based on AUC, exposure to abiraterone sulfate in both species and to the N-oxide abiraterone sulfate metabolite in monkeys was similar to or slightly (generally <5x) higher than expected human exposure; exposure to N-oxide abiraterone sulfate was only about 20% of human exposure in rats. Doses greater than those used in the above comparison (up to 750 mg/kg in rats, up to 2000 mg/kg/day in monkeys) were used for shorter treatment periods, but with at the higher doses, exposures to metabolites are likely to have been greater than that expected in humans.

Overall, the toxicology program with abiraterone acetate was adequate to reveal the toxicity profile of this drug in a rodent and a non human primate species.

⁹ European Medicines Agency, "ICH Topic S 4 Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing): Note for Guidance on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing (CPMP/ICH/300/95)", May 1999, Web, accessed 13 August 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002800.pdf>.

Table 4: Exposure ratios for abiraterone acetate.

Duration, route, sex (sample time) (Study No.)	Abiraterone acetate dose (mg/kg/day)	Abiraterone C _{max} (ng/mL) at respective doses; (¹ respective animal:human exposure ratio)	Abiraterone AUC _(0-∞ or 24 h) (ng.h/mL) at respective doses (¹ respective animal:human exposure ratio)
Mouse (male / female data)			
2 weeks PO, ♂ and ♀ (day 21) (TOX9586)	125 500 2000	973 / 1,109 (4.3 / 5) 1,187 / 1,737 (5 / 7.6) 3,672 / 2,627 (16 / 11.6)	1,839 / 1,307 (1.9 / 1.3) 5,139 / 5,414 (5 / 5.5) 32,242 / 13,015 (32 / 13)
Rat (male only or male / female data)			
1 month PO, ♂ only (day 28) (1632/1) ²	40 126 400	192-390 (0.8-1.7) 482-1,188 (2-5) 430-582 (2-2.6)	566-1,362 (0.6-1.4) 2,255-3,508 (2.3-3.5) 2,002-3,182 (2-3)
1 month PO, ♂ only (7565)	40 126 400	Most likely similar to data shown above or below at these dose levels	Most likely similar to data shown above or below at these dose levels
1 month PO, ♂ and ♀ (day 27) (TOX9587)	40 400	237 / 44.8 (1 / 0.2) 520 / 152 (2.3 / 0.7)	996 / 151 (1 / 0.2) 4,398 / 1,359 (4.4 / 1.4)
3 months or (HD only) 7 weeks, PO, ♂ and ♀ (day 28) (7777-100) ³	50 250 750	261 / 13.2 (1.2 / 0.06) 417 / 50.6 (1.8 / 0.2) 546 / 150 (2.4 / 0.7)	683 / 45.9 (0.7 / 0.05) 2,461 / 252 (2.5 / 0.3) 4,544 / 1,034 (4.5 / 1)
6 months PO, ♂ and ♀ (day 183) (7777-105)	50 150 400	138 / 132 (0.6 / 0.5) 251 / 276 (1.1 / 1.2) 494 / 291 (2 / 1.3)	1,132 / 710 (1.1 / 0.7) 2,220 / 1,734 (2.2 / 1.7) 5,586 / 3,106 (5.6 / 3.1)
Cynomolgus monkey (male / female data)			
1 month PO, ♂ and ♀ (week 4) (1818-001)	10 50 250 1000	4.7 / 6.1 (0.02 / 0.02) 15.3 / 14.7 (0.07 / 0.06) 37.5 / 37.5 (0.2 / 0.2) 38.5 / 157.1 (0.2 / 0.7)	ND / ND 111 / 144 (0.1 / 0.14) 219 / 288 (0.2 / 0.3) 317 / 885 (0.3 / 0.9)
3 month PO, ♂ and ♀ (day 91) (7777-101)	250 750 2000	146 / 103 (0.6 / 0.5) 61.6 / 99.8 (0.3 / 0.4) 115 / 243 (0.5 / 1)	1,252 / 947 (1.3 / 0.95) 774 / 999 (0.8 / 1.0) 1,604 / 2,961 (1.6 / 2.9)
9 months PO, ♂ and ♀ (day 273) (7777-103)	250 500 1000	139 / 87.5 (0.6 / 0.4) 183 / 466 (0.8 / 2.1) 270 / 185 (1.2 / 0.8)	610 / 489 (0.6 / 0.5) 1,139 / 4,154 (1.1 / 4) 2,095 / 1,223 (2.1 / 1.2)

¹ A comparison of exposure expected in humans with that in animals is based on human exposure data from clinical trial COU-AA-006, where C_{max} was 226 ng/mL and AUC_(0-24 h) was 993 ng.h/mL after 1000 mg/day abiraterone acetate.

² The min-max value from 3 individual males is shown;

³ Doses originally were 250, 750 and 2000 mg/kg/day but they were reduced to those shown in the table on day 9-10 because of severe, including fatal, toxicity at 2000 mg/kg/day.

ND – not determined because concentrations were mostly below the assay detection limit

Findings associated with the pharmacological activity

Histopathological changes expected to occur as a direct result of abiraterone mediated inhibition of androgen synthesis were observed in virtually all studies at all dose levels in male animals. These comprised testicular atrophy and degeneration, reduced spermatogenesis and Leydig cell hyperplasia; prostate gland atrophy and decreased secretions; and decreased secretions or hypospermia in seminal vesicles and epididymides. Associated changes comprised atrophy of the adrenal gland (zona reticularis), hyperplasia of the chromophobe cells in the *pars distalis* of the pituitary, and atrophy or hypertrophy of the mammary glands. In females, the pharmacological action of abiraterone was manifested as ovarian hypertrophy/hyperplasia, increased number of follicles/cysts in the ovaries, atrophy in the uterus and cervix, and adrenal cortex hypertrophy.

Decreases in testosterone and subsequent increases in LH (Luteinizing hormone) levels (due to lack of negative feedback from testosterone on pituitary) were demonstrated in rats; while monkeys were found to have decreased testosterone, cortisol and

dehydroepiandrosterone levels, and higher adrenocorticotrophic hormone, aldosterone, and progesterone levels.

The above changes were very slowly reversible after treatment ceased, and a rebound increase in testosterone levels after treatment ceased in rats was notable.

Adverse effects not associated with the pharmacology of abiraterone

Bile duct hyperplasia

Irreversible bile duct/oval cell hyperplasia, characterised by an increased number and prominence of small ductular structures/cells within portal areas (in some cases affecting up to 100% of portal tracts, but without evidence of apoptosis) was a major finding in most of the studies in rats and monkeys. According to the investigators, the finding was morphologically consistent with “ductular reaction”, a term used in human pathology to describe similar appearing ductular changes of uncertain pathophysiology. This finding was considered irreversible and adverse by at least one of the investigating pathologists.

Bile duct hyperplasia increased in severity with dose but was not dependent on abiraterone exposure because the latter often did not increase with dose. The severity also increased with duration of treatment, however, the onset of effect appeared to be rapid as the lesion was observed in one (of three) 1 month rat studies.

Increases in ALP (alkaline phosphatase) and bilirubin were consistently observed in the rat and monkey studies (increases in bile acids were also found in a 1 month rat study), although bile duct hyperplasia was also found in the absence of these biochemical changes.

It is not clear if bile duct hyperplasia observed in the repeat dose toxicity studies is due to a local cytotoxic effect of abiraterone and/or its metabolite/s, or to pharmacological effects of abiraterone on liver fatty and bile acid metabolism (which involve CYP isozymes). Regardless, the liver burden of abiraterone acetate and abiraterone in humans is at least as high as it is in rodents and monkeys, suggesting that the toxicities to this organ may be of potential clinical relevance.

It is acknowledged that the proposed PI includes information about the potential for hepatotoxicity in patients taking abiraterone acetate.

Bile duct hyperplasia is often associated with chemical toxins and carcinogens. Therefore, the development of this toxicity, and a reassessment of its potential risks, may need to be revisited for any future applications regarding abiraterone acetate.

Other effects on the liver

Other changes observed in the liver comprised centrilobular hypertrophy, vacuolation hepatic and hyperplasia and may be associated with hepatic enzyme induction, which was demonstrated in rat. Hepatocyte necrosis was observed at 500 and 2000 mg/kg/day in the 2 week study in mice, along with fatty vacuolation (fatty) mononuclear phagocytic aggregates and inflammation; and in rats dying intercurrently after 750 mg/kg/day PO abiraterone acetate for > 3 months. The significance of the latter toxicity to humans is questionable given the lack of similar findings in the monkey studies.

Cataracts

Cataracts and lens fibre swelling developed in rats given ≥ 50 mg/kg/day PO abiraterone acetate in the 6 month study, with a no effect dose not established for this effect. Exposure to abiraterone (AUC) at the lowest dose in this study was similar to that expected in humans.

The severity and incidence of cataracts were dependent on dose and treatment duration because similar changes were not apparent in shorter duration studies (1-3 months) using the same or higher dose levels.

The mechanism by which abiraterone acetate caused cataracts in rats was not investigated and remains unknown. The effect is probably not related to the retention of abiraterone in melanin containing tissues because albino rats were used in this study; and cataracts were not observed in any of the monkey studies. Changes in serum chemistry that might have been associated include decreases in cholesterol, although this effect was not observed at all cataractogenic doses, and, more markedly, decreases in triglycerides (by ~70% at all dose levels that caused cataracts). While a link between these changes is speculation, it is interesting to note that triglyceride levels were markedly increased in the 9 month study in monkeys, a species which did not develop cataracts.

The potential relevance of cataracts to the use of abiraterone acetate in humans is unclear but the risk to the intended patient population is not considered high given the lack of similar findings in monkeys treated for up to 9 months.

Pulmonary toxicity and local irritation

Inflammatory lesions consisting of alveolar macrophages, inflammatory cell infiltrates, haemorrhage, foreign body granuloma, foci of foamy and pigmented macrophages, and, in the extreme, pulmonary fibrosis, alveolar septal fibrosis, and pneumocyte hypertrophy, were observed in most of the repeat dose toxicity studies in rats and in the 2 week study in mice, but in none of the monkey studies. The incidence and severity appeared to be mainly dependent on duration of treatment, although changes were observed at the higher doses when given for shorter periods.

Specific investigations determined that the changes were due to a local effect of abiraterone acetate/abiraterone on the lungs following aspiration of the drug. Inflammatory changes in the turbinates of affected rats and needle like crystalloid clear spaces in the exudates (considered possible drug precipitate) were observed. There was no other evidence for pulmonary toxicity in any of the nonclinical studies, and given the lack of similar effects in monkeys, this seems a reasonable conclusion. However, the underlying mechanism and whether or not it is due to a direct cytotoxic effect of the drug on particular cell types was not investigated.

Gastrointestinal intolerance was not widely observed in the repeat dose toxicity studies: degeneration of the stomach was found in 3 monkeys given 1000 mg/kg/day PO abiraterone acetate in a 1 month study but not in other studies (including those of longer duration with higher doses), while erosions and/or distended stomach was observed only in rats dying intercurrently after treatment for more than 3 months.

These findings are reassuring of acceptable local tolerance; however, local tolerance issues may need to be revisited if there are relevant changes to the abiraterone acetate formulation and/or route of administration.

Cardiac toxicity

Subacute inflammation of the heart was found in male rats after 7 weeks of treatment with abiraterone acetate 750 mg/kg/day (reduced from 2000 mg/kg/day for the first 10 days). This was an isolated finding and occurred at doses which were fatal in some animals. There was no evidence for effects on the cardiovascular system in any of the other nonclinical studies (in rats or monkeys) or in standard safety pharmacology studies in monkeys *in vivo* (with abiraterone acetate doses (2000 mg/kg PO) sufficiently high to cause toxicity with repeated dosing) and in hERG (human Ether-à-go-go-Related Gene) potassium channels *in vitro*.

This finding is therefore not considered to provide evidence for a potential cardiotoxic effect of abiraterone acetate.

Other toxicities in moribund animals

Other notable treatment related effects of abiraterone acetate were observed in moribund animals; these comprised:

- degeneration/necrosis of skeletal muscle in almost all rats dying intercurrently after 750 or 2000 mg/kg/day; and
- acanthosis/hyperkeratosis/degeneration/necrosis of skin and muscle structures.

The investigators noted that these effects were most likely treatment related because skin and its adnexa contain androgen receptors and these effects do not typically occur as a nonspecific expression of moribundity.

Genotoxicity

A full and extensive range of standard genotoxicity assays was performed with abiraterone acetate or with abiraterone itself, all of which were negative. Exposure to phase I (oxidative) abiraterone metabolites was likely to be adequate in these assays; however exposure to the sulfate metabolites and glucuronide conjugates was probably negligible since SULT and UGT (UDP glucuronosyltransferase) enzymes are not substantially found in S9 microsomal fractions and relevant co substrates were not added. The genotoxic potential of the main human circulating metabolites, the sulfate and the N-oxide sulfate derivatives, in particular, would not have been assessed in these studies.

As mentioned elsewhere, the major metabolites retain pharmacological activity and in the case of the sulfate, this is more potent than abiraterone itself.¹⁰ Therefore, genotoxicity studies with these metabolites were probably warranted. Concern over the lack of these studies is mitigated by the fact that:

- they do not contain structural alerts for genotoxicity;
- the activity profile of these substances is likely to be similar to that observed with abiraterone (which is not genotoxic); and
- the likely benefits of abiraterone acetate for the proposed indication, which in any case involves prior use of a clastogen, is likely to outweigh the (untested) risk of genotoxicity due to the metabolites.

The adequacy of genotoxicity studies in terms of exposure to the main human metabolites of abiraterone may need to be reassessed for future applications.

Toxicity studies with impurities

Specifications for four individual impurities (R601249, R601252, R601251 and R601250) in the proposed formulation and in the drug substance exceed the limit acceptable without qualification or justification (0.2% for individual impurities in the finished product, for drug doses >100 mg-2 g/day).**Error! Bookmark not defined.** R601252 is the active metabolite, abiraterone, and therefore the proposed limit for this substance as an impurity (NMT [Not More Than] 0.4%) is acceptable.

All of the above impurities were assessed in a dedicated 1 month rat study (or the usual toxicity studies for R601250) and in genotoxicity assays in which they were present at levels adequate to qualify the proposed limits (NMT 0.5% for R601249, NMT 0.4% for R601251 and NMT 0.8% for R601250). None of these studies provide evidence for

¹⁰ Sponsor comment: "This was seen in one rat study, but may not be generalisable. The activity was markedly lower for the metabolites than for abiraterone in NCI-H295R human adrenal cortical cell lines."

concern due to the presence of these substances. These substances were also variably present in drug batches used for the routine toxicity studies. The proposed impurity specifications are considered qualified on this basis.

The sponsor has also conducted computer-assisted investigations to identify impurities with potential genotoxicity structural alerts. These investigations and subsequent mutagenicity assays in *S. typhimurium* identified two positive substance - abiraterone acetate mesylate and JNJ-47838843-AAA (R601254, not further defined). Limits for these have been reduced to < 1.5 ppm (< 1.5 µg/day), which is acceptable for genotoxic impurities in human medicines according to published guidelines.¹¹

The above named impurities are also above acceptable limits in the abiraterone acetate drug product, but at levels are lower than those proposed for the finished product. An additional two impurities, R601245 and R601246, are specified at NMT 0.2% each in the drug substance but not in the finished product. These two impurities were present in repeat dose toxicity studies and in genotoxicity assays at levels that were adequate to qualify the limits in the drug substance.

Carcinogenicity studies, reproductive toxicity studies & studies in juvenile animals

These were not submitted and are not required to support the registration of abiraterone acetate for the proposed indications; but such studies may be required for any future application to amend or extend these indications.

Risk management plan

No comments.

Nonclinical summary and conclusions

Summary

- The sponsor has applied to register the new chemical entity abiraterone acetate for the treatment of mCRPC in patients who have received prior chemotherapy containing a taxane. Abiraterone acetate 250 mg is to be supplied in tablet form (Zytiga) for oral administration of 1000 mg once daily, along with prednisone or prednisolone. A maximum treatment duration is not stated.
- Abiraterone acetate is a pro drug for the active ingredient, abiraterone which inhibits CYP17 mediated conversion of pregnenolone and progesterone into the testosterone precursors dehydroepiandrosterone and androstenedione. After PO administration, the acetate is rapidly converted to the free drug and systemic levels of the pro drug are negligible.
- Co administration of a corticosteroid (prednisone or prednisolone) is anticipated to reduce toxicities associated with mineralocorticoid excess (fluid retention/oedema, hypokalaemia and hypertension) expected to result from abiraterone inhibition of CYP17 mediated conversion of pregnenolone and progesterone into cortisol.
- Nonclinical data for this application complied with the scope of nonclinical studies recommended in published guidelines.¹ A full range of GLP (Good Laboratory Practice)

¹¹ European Medicines Agency, "Committee for Medicinal Products for Human Use (CHMP): Guideline on the Limits of Genotoxic Impurities (CPMP/ICH/300/95)", 28 June 2006, Web, accessed 13 August 2012 < http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002903.pdf>.

compliant, high quality, well documented PK, repeat dose toxicity and genotoxicity studies in an adequate range of species/*in vitro* models has been performed with abiraterone acetate administered by the intended clinical route (PO) for toxicity studies. Doses used were adequate in terms of eliciting expected primary pharmacological effects up to dose limiting toxicity.

- Studies have not been performed to address the following.
 - Genotoxicity of main human metabolites;
 - Carcinogenicity;
 - Reproductive toxicity;
 - Effects in juvenile animals.

The requirement for any or all of the above will need to be assessed for any future applications concerning abiraterone acetate, including applications to amend or extend the indications and to substantially change the formulation. There were also no nonclinical studies of abiraterone acetate in combination with prednisone or prednisolone or against a background of previous taxane use (as proposed for registration).

- Inhibition of CYP17 activity by abiraterone (shown to be irreversible in some assays) was demonstrated *in vitro* in human testicular microsomes, with IC₅₀ values ranging from 2.9-4 nM up to 73 nM depending on the assay conditions (compared with human abiraterone C_{max} > 500 nM). Inhibition of CYP17 by abiraterone was also demonstrated against human CYP450 expressed in *E. Coli* (IC₅₀ = 54 nM) and in rat testicular microsomes (IC₅₀ = 220 nM).
- The main human circulating metabolites of abiraterone, abiraterone sulfate and the N-oxide of abiraterone sulphate, also inhibit CYP17 and affect adrenal steroidogenesis. These metabolites occur in human circulation at levels substantially (> 100 times) greater than abiraterone and may be expected to contribute to the drug's activity.¹²
- Inhibition of testosterone production was demonstrated in intact rats or mice, where IP abiraterone acetate was associated with decreased systemic androgen levels and associated atrophy of testosterone sensitive tissues to a level similar to that produced by castration. Atrophy of hormone sensitive male reproductive organs and decreased systemic androgen levels were consistently observed in the repeat dose toxicity studies of PO abiraterone acetate in rodents and monkeys. These findings support the rationale for using abiraterone acetate to reduce circulating levels of androgens.
- In an *in vivo* study in a mouse model of castration resistant prostate cancer, IP abiraterone acetate treatment for 5 days/week for 4 weeks was associated with increased survival time, and reductions in prostate tumour volume, serum PSA levels and prostate tumour androgen levels. Changes were also found in genetic transcripts that code for factors associated with the development of prostate cancer.
- A rebound acceleration of tumour development occurred once treatment ceased. Rebound increases in serum testosterone levels once treatment ceased was also observed in some of the repeat dose toxicity studies of abiraterone acetate in rats.

¹² Sponsor comment: "Activity was markedly lower for the metabolites than for abiraterone in NCI-H295R human adrenal cortical cell lines. In one (rat testicular microsme) system, there was activity of the sulfate metabolite (not for the N-oxide abiraterone sulfate metabolite). However, in that study IC₅₀ of abiraterone was markedly higher than in other studies (as well as the IC₅₀ for the positive control ketoconazole markedly less than in other studies)."

- Recent published literature not submitted in the application indicates that resistance to abiraterone acetate treatment may develop in patients with mCRPC. There were no studies addressing this in nonclinical data submitted.
- Specific studies investigating potential secondary targets for abiraterone acetate or abiraterone were limited to those showing weak to negligible binding and/or activity at glucocorticoid, oestrogen, androgen and progesterone receptors. The same range of similar studies with the main circulating abiraterone metabolites in humans was also unremarkable.
- Studies addressing specificity for CYP17 showed abiraterone at clinically relevant concentrations is also a competitive, potent inhibitor of CYP2D6 and CYP1A2; and a competitive moderate inhibitor of CYP3A4/5, CYP2C9 and CYP2C19. An increase in the activity of CYP4A1, which has a role in arachidonic acid and fatty acid metabolism, was also found in an *in vivo* study in rats.
- A standard set of safety pharmacology studies showed no evidence for acute effects of abiraterone on the major physiological systems (the CVS [cardiovascular system], respiratory system, GIT [gastrointestinal tract] and CNS [central nervous system]).
- The PK of abiraterone acetate were adequately characterised in species used for the main toxicity studies (rats and monkeys) and are considered sufficiently comparable to those in humans after repeated PO dosing of abiraterone acetate.
- Oral absorption of abiraterone acetate is independent of the P-glycoprotein transporter; appears to be poor (probably < 10% of a dose); is enhanced by food and affected by the type of vehicle; and is most likely limited by dose. The oral bioavailability of abiraterone is also very low (2% reported in monkeys and 37% in mice). T_{max} after PO administration is rapid (within 2 h) in all species investigated but it becomes prolonged with increasing dose and/or duration of treatment.
- In animals, increases in exposure to abiraterone were generally less than dose proportional and were dose limited. Exposure at a given dose decreased with increasing duration of dosing, possibly due to induction of metabolism and/or changes in absorption. The elimination half life of abiraterone after short term PO dosing was relatively short (1.5-2 h) in mice and rats and slightly longer (2-4 h) in monkeys, but it was prolonged with increasing dose and duration of treatment (up to ~5 h in rats, 10 h in monkeys). Half life values at steady state in patients are reported as 24-28 h.
- Abiraterone is > 98% bound to plasma proteins (99.9% to human serum albumin and ≥ 90% to human α1-acid glycoproteins). Therefore, no adjustments for species differences in the extent of drug protein binding are required for abiraterone. The drug does not show any particular affinity for red blood cells.
- Abiraterone acetate related compounds were distributed to all tissues in rats, including the prostate gland and other reproductive organs, brain and spinal cord. Drug-associated material was cleared from all tissues by 8 h after a single PO dose, with the exception of the lymph nodes, excretory organs, pituitary gland and bone marrow where it persisted for up to 24 h. There was evidence for substantial drug retention in pigmented tissues. Whole body tissue distribution studies after repeated dosing were not done, and therefore it is not known if drug accumulates in particular tissues with repeated dosing.
- The metabolism of abiraterone acetate in all species investigated involves rapid ester hydrolysis of abiraterone acetate to abiraterone and extensive metabolism of abiraterone by several pathways involving sulfation, N-oxidation, hydroxylation, dehydration, and conjugation with sulfate and glucuronic acid.

- The major enzymes involved are CYP3A4 for phase I (oxidative) metabolites, the SULT isozyme SULT2A1 (with a minor contribution by SULT1E1) and the UGT UGT1A4 (with a minor contribution from UGT1A3). There were no studies investigating whether drugs that induce or inhibit these enzymes affect the metabolism of abiraterone.
- At least 40 metabolites of abiraterone have been identified but only the pharmacologically active metabolites abiraterone sulfate and the N-oxide of abiraterone sulfate are significant in humans (and in other species investigated).
- Abiraterone acetate was excreted mainly ($\geq 90\%$) via the faeces as metabolites, unchanged pro drug (probably unabsorbed) and abiraterone, with minor amounts of metabolites (mainly the N-oxide) excreted in urine. Evidence for substantial ($\sim 20\%$ of a dose) entero biliary circulation of abiraterone metabolites was found in rats.
- The main toxicity studies were performed in mice (2 week study only), rats and monkeys, with abiraterone acetate administered PO once daily as a suspension in 0.4% (w/v) aqueous methylcellulose. No studies were done with the proposed capsule formulation, but it contains common excipients and no interactions are expected with abiraterone acetate.
- The duration of studies in monkeys (1-9 months) and rats (1-6 months) was appropriate to support chronic use of medicines in humans, as recommended in relevant guidelines.⁹ The dose range was adequate to explore the toxicity profile up to dose limiting or fatal toxicity in animals: exposure (AUC) to abiraterone and to the main human metabolites in these studies was lower or $< 5x$ higher than that expected in humans.
- Findings associated with the expected pharmacological effect occurred at virtually all doses in all studies and consisted of decreased testosterone/other androgen levels, and (in monkeys) increases in the levels of ACTH, aldosterone and progesterone, and decreases in the levels of cortisol. Atrophic changes to male reproductive organs and (less marked) changes to adrenal gland and pituitary organ weights and/or histopathology were consistently observed. These changes were reversible 4 weeks after treatment ceased.
- Bile duct/oval cell hyperplasia was the most prominent toxicity not associated with the pharmacological effect of abiraterone. Bile duct hyperplasia developed in monkeys at all doses (≥ 250 mg/kg/day) in the 3 and 9 month studies, and in rats at doses ≥ 50 mg/kg/day for 3-6 months and at 400 mg/kg/day in a one month study. The effect increased in severity with dose and duration of treatment and occurred at abiraterone and main metabolite exposures (AUC) lower than those expected in humans. Increases in alkaline phosphatase and serum bilirubin were also observed in these studies; however, bile duct hyperplasia was sometimes observed in the absence of changes to these markers. The effect was generally not reversed within a 4 week recovery period after treatment ceased.
- The mechanism underlying the development of bile duct hyperplasia in animals was not explored. It is acknowledged that hepatic toxicity is observed with abiraterone acetate in patients and that the proposed PI contains information about this toxicity.
- Cataracts and lens fibre swelling developed in rats (at ≥ 50 mg/kg/day abiraterone acetate for 6 months), with a no effect dose not established. Exposure to abiraterone (AUC) at the lowest dose was similar to that expected in humans. Ocular toxicity was not observed in any of the monkey studies at exposure levels similar to those expected in humans. The potential clinical relevance of the finding in rats is not known but the risk for humans is not considered substantial in the context of this application, particularly given the absence of ocular toxicity in a primate species.

- A full range of genotoxicity studies with abiraterone acetate and abiraterone was unremarkable. However, exposure to the main human metabolites of abiraterone was probably negligible in these studies and therefore, the genotoxic potential of these substances has not been addressed.
- The proposed specifications for abiraterone acetate include higher than acceptable limits (according to relevant guidelines) for four impurities in the finished product and the drug substance, and for an additional two in the drug substance only. Adequate nonclinical studies were provided to qualify these.

Conclusions

There is adequate nonclinical evidence to support the use of abiraterone acetate to reduce circulating androgen levels. The main toxicities observed in rats and monkeys given abiraterone acetate PO for up to 6 and 9 months, respectively, were associated with the pharmacology of the drug.

Bile duct hyperplasia was also a major toxicity in most of the animal studies and this is unrelated to the pharmacology of abiraterone acetate. It is acknowledged that the proposed Product Information includes information about the potential for hepatotoxicity, and that the development of this toxicity can be monitored as part of a post-market monitoring program.

Overall, the nonclinical program adequately explored the pharmacology and toxicity of abiraterone acetate in the context of the current application. There were no findings that preclude approval of this application. The PI document should be amended as suggested.

The need for studies to investigate matters not addressed in this application, including potential for reproductive toxicity, carcinogenicity and use in juveniles, should be determined for any future application concerning abiraterone acetate.

IV. Clinical findings

The clinical dossier documented a full development program of clinical pharmacology, efficacy and safety studies. The clinical submission contained the following information:

- eleven clinical pharmacology studies, including ten providing PK data and one providing pharmacodynamic (PD) data;
- one population PK/PD analysis;
- one pivotal efficacy/safety study;
- two dose finding studies;
- two other efficacy/safety studies;
- one Integrated Summary of Safety (ISS);
- two Phase I/II studies not evaluated due to methodological issues; and
- literature references provided for background information.

The submitted studies were stated to have been conducted in compliance with Good Clinical Practice (GCP), including the archival of essential documents. All studies were conducted according to appropriate ethical standards.

Pharmokinetics

The submission included PK data from eleven Phase I studies including a total of 309 subjects, and 1 population PK (PopPK) study including pooled sampling data from a total of 256 subjects (4,200 samples) from three Phase I studies in healthy volunteers, one Phase Ib study in patients with mCRPC, and one Phase III study in patients with mCRPC. In addition to the eleven Phase I studies with evaluable PK data, the submission also included non evaluable PK data from three early studies in patients with mCRPC (Studies COU-AA-001, -002 and -BE). In these three studies, the bioanalytical assay for abiraterone plasma concentrations could not be validated.

All single dose abiraterone acetate PK studies were conducted in healthy males; this was because the sponsor considered that multiple dose studies in healthy subjects would be unacceptable due to prolonged ablation of androgen biosynthesis. Therefore, multiple dose abiraterone acetate PK studies were conducted in patients with mCRPC.

Single dose Studies COU-AA-005, -007, -008, -009, -010, -014, -016 were conducted in healthy adult males aged between 18 and 55 years (inclusive) with a BMI (Body Mass Index) of 18 kg/m² to 30 or 32 kg/m² (inclusive). Single dose Studies COU-AA-011 (hepatic impairment) and COU-AA-012 (renal impairment) were conducted in males aged between 40 and 80 years (inclusive) with a BMI of 18 kg/m² to 35/38 kg/m² (inclusive), with healthy subjects being matched to impaired subjects based on mean age (\pm 7 years) and mean BMI (\pm 15%). Multiple dose Studies COU-AA-006 (PK and PD [QT/QTc]) and COU-AA-015 (PK interaction) were conducted in male subjects \geq 18 years of age, in patients with mCRPC who had progressed on GnRH therapy, and had PSA levels \geq 2 ng/mL. In addition to the single and multiple dose studies, the submission also included a population PK, PD, PK/PD study in 256 subjects from three Phase I studies in healthy adult males (Study COU-AA-008, -009, -014), one Phase Ib study in patients with mCRPC (Study COU-AA-006), and one Phase III study in patients with mCRPC (Study COU-AA-301).

In all single dose studies (except mass balance Study COU-AA-007), abiraterone acetate tablets were administered orally in the morning with 240 mL of water following an overnight fast. No food was allowed to be ingested for at least 4 h following dose administration. Subjects were advised to remain seated, standing or ambulatory for at least 1 h following dose administration. Serial blood samples for PK analysis were collected pre dose and generally up to 96 h post dose. For multiple dose studies, subjects with mCRPC were instructed to take abiraterone acetate tablets at least 1 h before a meal or at least 2 h after a meal.

The standard range of plasma PK parameters were calculated based on actual PK blood sampling times, relative to dosing, using conventional non compartmental methods consistent with relevant TGA adopted guidelines. Subjects with sufficient data for PK parameter estimations were included in the analyses. The exception is the population analysis, which used a nonlinear mixed effects approach to estimate PK parameters based on sparse sampling data. All plasma, urine, and faecal analytes reported in the eleven evaluated studies were assayed by validated bioanalytical methods.

In addition to the *in vivo* PK studies, the submission also included a number of *in vitro* human biomaterial studies supporting the clinical pharmacology data. Interpretation of the human biomaterial data had regard to the mean peak and trough plasma concentrations of abiraterone achieved following multiple dosing with 1 g abiraterone acetate to subjects with mCRPC under modified fasting conditions observed in Study COU-AA-006. In this study, mean C_{\max} and C_{\min} values were 226 ng/mL (\sim 0.65 μ M) and 8.9 ng/mL (\sim 0.026 μ M), respectively, for total (bound plus unbound) abiraterone.

Pharmacokinetics in healthy subjects

Absorption

Sites and mechanisms of absorption

The PK studies indicate that abiraterone acetate is rapidly converted to abiraterone with little or no abiraterone acetate being detected in plasma following oral administration. Maximum plasma concentrations of abiraterone are observed at 2 h after dosing following single and repeat dose administration.

In vitro studies performed using Caco-2 cell monolayers found that abiraterone acetate and abiraterone had low apparent permeability and are not substrates for P-gp (Covance 8202265). In the presence of a P-gp inhibitor (cyclosporine A or verapamil), no notable changes were observed in the apparent permeability and efflux ratio of abiraterone confirming that abiraterone is not a substrate of P-gp. Abiraterone had little inhibitory effect on P-gp mediated transport of digoxin (a P-gP substrate), but abiraterone acetate inhibited P-gP significantly at high concentrations with an IC₅₀ of 10.8 µM.

Comment: The in vitro Caco-2 cell monolayer studies showed low apparent permeability of abiraterone and abiraterone acetate. These results are consistent with the BCS (Biopharmaceutics Classification System) Class IV categorisation of abiraterone acetate and the results from the Phase I clinical PK studies discussed below.

Bioavailability

Absolute bioavailability

There were no absolute bioavailability studies in humans in the submission.

Comment: This is a significant deficiency in the PK data. The lack of an absolute bioavailability study was discussed at the pre submission meeting between the TGA and the sponsor (TGA minutes). The sponsor was informed that the PSC of the ACPM requires absolute bioavailability studies to be conducted for all new chemical entities before approval is granted, and that the TGA has not approved some new chemical entities because such studies have not been conducted. However, the sponsor was also informed that for medicines for life threatening conditions with no available therapy the TGA did make an occasional exception to the requirement for an absolute bioavailability study before approval. The sponsor has provided a justification for not submitting an absolute bioavailability study. This justification indicates that the absolute bioavailability of abiraterone acetate was not investigated because an acceptable IV formulation for administration to humans could not be developed due to no solvents being available to provide sufficient solubility. The justification stated that, although 1 g of drug substance was soluble in pure ethanol or propylene glycol solutions, the volume of alcohol required for the solution exceeded the acceptable limits (60 mL) of the study centre for dosing healthy subjects. From a clinical perspective, the sponsor's justification is acceptable.

Bioavailability relative to an oral solution or micronised suspension

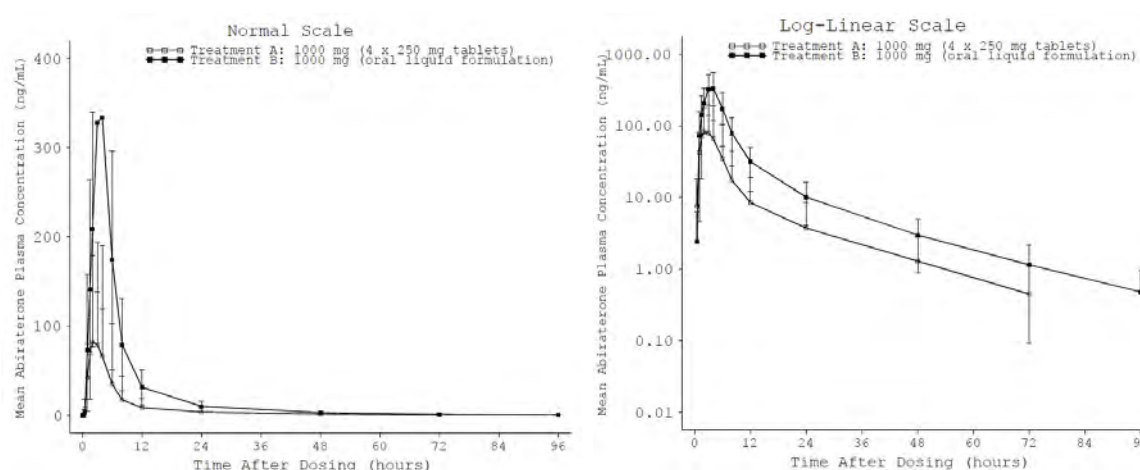
Study COU-AA-010

The submission included one study which investigated the oral bioavailability of abiraterone acetate tablets relative to a liquid olive oil formulation (Study COU-AA-010). In this single centre, open label, single dose, two period, crossover study, 22 healthy male subjects aged between 18 and 55 years were randomised to 1 of 2 treatment sequences (AB, BA). Treatment A (reference) was abiraterone acetate 1 g administered as 4 x 250 mg tablets with 240 mL of water, and Treatment B (test) was abiraterone acetate 1 g formulated in 30 mL olive oil prepared in unit dose containers. PK parameters of abiraterone are summarised below in Table 5.

Table 5: Abiraterone mean (SD) plasma PK parameters (Study COU-AA-010).

	Treat A: 1 mg (4 x 250 mg) [n=19]	Treat B: 1 mg (oral liquid) [n=19]
C _{max} (ng/mL)	101 (119)	396 (214)
t _{max} (hr) median (range)	2.00 (1.00, 4.00)	3.00 (2.00, 6.00)
AUC _{0-t} (ng*hr/mL)	572 (813)	2114 (1085)
AUC _{0-∞} (ng*hr/mL)	583 (819)	2131 (1098)
t _{1/2} (hr)	15.4 (2.97)	15.8 (4.04)

The abiraterone concentration-time profiles (linear-linear and log-linear) are summarised in Figure 2. For both treatments, mean plasma abiraterone concentrations increased rapidly following single oral dose abiraterone acetate, with the median t_{max} for the tablet formulation being 2 h and for the liquid formulation being 3 h.

Figure 2: Abiraterone concentration-time profiles; linear scale (Study COU-AA-010).

The relative bioavailability results for abiraterone comparing test Treatment B (1 g liquid olive oil) with reference Treatment A (1 g as 4 x 250 mg tablets) are summarised below in Table 6.

Table 6: Bioavailability abiraterone mean (standard deviation): liquid [T] versus tablet [R] (Study COU-AA-010).

Parameter	Liquid [T] ^a 1000 mg [n=18]	Tablet [R] ^a 4x250 mg [n=18]	[T]/[R] % Ratio ^b	90% CI ^c	Intrasubject CV% ^d
C _{max} (ng/mL)	347	76.0	456	[352.99 , 589.76]	46.3
AUC _{0-∞} (ng*hr/mL)	1907	433	441	[367.86 , 528.41]	31.9
AUC _{0-t} (ng*hr/mL)	1893	421	450	[373.94 , 540.75]	32.5

^a LSMs from ANOVA. Ln (natural log) parameter means calculated by transforming the Ln means back to the linear scale (that is, geometric means).

^b Ratio of parameter means for Ln transformed parameter (expressed as a percent). Ln transformed ratios transformed back to the linear scale.

^c 90% CI for ratio (%) of parameter means of Ln transformed parameter. Ln transformed CIs transformed back to the linear scale.

^d Intra subject coefficient of variation (expressed as a percent) for log transformed parameter from ANOVA.

Comment: COU-AA-010 was good quality relative bioavailability study. The liquid formulation was an olive oil solution rather than an aqueous solution, presumably due to the poor aqueous solubility of abiraterone acetate preventing formulation of an aqueous solution. Systemic exposure to abiraterone (C_{\max} , AUC) was approximately 4.5 fold greater following the liquid formulation relative to the tablet formulation. However, the median t_{\max} and mean $t_{1/2}$ values were similar for both oral formulations. The SD values for the abiraterone C_{\max} and AUC parameters were high relative to the corresponding mean values indicating that intersubject variability is high. Intersubject variability of the tablet formulation was greater than that of the liquid formulation. In addition, intrasubject variability of abiraterone was also high with the CV being >30% for the C_{\max} and AUC parameters. The study did not analyse the PKs of abiraterone acetate as the majority of plasma concentrations for this analyte were below the LOQ (limit of quantification). The tablet formulation used in this study was not the one proposed for Australian registration.

Bioequivalence of clinical trial and market formulations

The pivotal clinical efficacy and safety study (COU-AA-301) used three different abiraterone acetate tablet formulations: clinical trial and commercial formulations and a commercial formulation. The commercial formulation is stated by the sponsor to be identical to the formulation proposed for registration. The submission included one oral relative bioavailability study comparing the three formulations (clinical trial, commercial, and commercial) (Study COU-AA-014), and one pivotal oral relative bioavailability study comparing the (clinical trial) and (commercial) formulations (Study COU-AA-005). These two studies are reviewed below.

Study COU-AA-014

Study COU-AA-014 was conducted in healthy men to determine the relative bioavailability of abiraterone acetate tablets manufactured at using the clinical trial process and the commercial process, and tablets manufactured using the commercial process identical to the one proposed for registration. Single 1 g doses (4 x 250 mg tablets) of each product were given in an open label, randomised, crossover study to fasting healthy adult male subjects using a six sequence, three treatment crossover, four period (extra period) design. Three subjects were to be randomised to each of the six treatment sequences. There was a seven day washout between each dosing period. The design allowed for estimation of the relative bioavailabilities of the three tablet formulations. The design also allowed for the estimation of intra and inter subject coefficients of variation (CV%) for the relevant abiraterone PK parameters.

The inter subject variability (CV%) for all exposure parameters (C_{\max} , $AUC_{0-\text{last}}$, AUC_{0-48} , and $AUC_{0-\infty}$) ranged from 51.8% to 54.8% for Treatment A (clinical trial), from 41.1% to 45.1% for Treatment B (commercial), and from 37.0% to 41.0% for Treatment C (commercial).

The median t_{\max} for each of the three abiraterone treatments was 2 h, and the mean $t_{1/2}$ values were similar for each of the three treatments ranging from 14.5 to 15.8 h.

Estimates of intra subject CV% values for C_{\max} , $AUC_{0-\text{last}}$, AUC_{0-48} , and $AUC_{0-\infty}$ for the PK evaluable analysis population were 29.9%, 20.4%, 20.2%, and 20.2%, respectively.

Comment: COU-AA-014 was a good quality oral relative bioavailability study. The study showed that the (commercial) and (clinical trial) formulations were bioequivalent, with the 90% CI of the ratios for the C_{\max} and AUC values being completely enclosed within the standard bioequivalence interval of 80% to 125%. The 90% CI for the C_{\max} ratios for the comparison between (commercial) and both the formulations were within the 80% to

125% bioequivalence interval. However, the AUC values were approximately 15% higher for the (commercial) formulation relative to both the formulations, with the upper 90% CI interval for the relevant AUC ratios being marginally above the upper bound bioequivalence interval of 125%. Consequently, the (commercial) formulation can not be considered to be bioequivalent to the two formulations in the study. Intra subject variability in abiraterone C_{max} and AUC values was lower than inter subject variability. Detectable plasma concentrations in abiraterone acetate were not found in any subject (BQL). Consequently, no PK parameters were determined for abiraterone acetate.

Study COU-AA-005

Study COU-AA-005 was conducted in healthy men to determine the bioequivalence of abiraterone acetate tablets manufactured by the clinical trial process and the commercial process. The study was taken subsequent to COU-AA-014 in a substantially larger number of subjects. The sponsor states that the abiraterone acetate commercial formulation is identical to the formulation proposed for registration. There was a single 1 g dose (4 x 250 mg tablets) of each formulation given in an open label, randomised, two way crossover study; each dose was given to approximately 120 healthy fasting adult male subjects. There was a seven day washout period between each dosing period.

The median t_{max} was identical for both studies (2 h) and the mean $t_{1/2}$ was similar (~15 h).

Intra subject variability (CV%) for C_{max} , AUC_{last} , and AUC_{∞} was 31.9%, 25.0%, and 23.4%, respectively.

Comment: Study COU-AA-005 was a good quality bioequivalence study in a large number of healthy male subjects. It showed that the (clinical trial) and (commercial) tablet formulations were bioequivalent as regards the C_{max} and AUC values. The 90% CI for the ratios of all exposure parameters were within the 80% to 125% bioequivalence interval. Intra subject variability in C_{max} , AUC_{last} , and AUC_{∞} was moderate as assessed by the CV%. The study was conducted subsequent to the three-way, relative bioavailability Study COU-AA-014 which compared the tablets manufactured by (clinical trial and commercial) and (commercial). In Study COU-AA-014, the (clinical trial) and (commercial) tablets were bioequivalent as regards the C_{max} , but not as regards the AUC. The difference between the two studies is probably due to the substantially larger number of subjects in Study COU-AA-005 ($n = \sim 120$) compared with Study COU-AA-014 ($n=14$). The larger number of subjects would tend to mitigate the effects of the high inter subject and intra subject variability in abiraterone exposure parameters.

Bioequivalence of different dosage forms and strengths

Not applicable as only one dosage form (tablet) of one strength (250 mg) is being proposed for registration.

Bioequivalence to relevant registered products

Not applicable as there are no registered products.

Influence of food

Study COU-AA-009

The submission included one study investigating the effect of food on the bioavailability of abiraterone acetate administered to healthy men in the fed and fasting state. The study was Phase I, randomised, open label, single dose, six sequence, three period, and crossover in design in which a single 1 g dose of abiraterone acetate (4 x 250 mg tablets) was administered to approximately 36 normal healthy male subjects under fasted and fed conditions. The three treatments were:

1. Treatment A taken after an overnight fast approximately 30 minutes after a standardised high fat meal with no additional food being ingested for 4 h post dose;

2. Treatment B taken after an overnight fast approximately 30 minutes after a standardised low fat meal with no additional food being ingested for 4 h post dose; and
3. Treatment C taken after an overnight fast of at least 10 h with no food being ingested for 4 h post dose.

There was a seven day washout between dosing periods. The sponsor states that the abiraterone formulation used in this study is not identical to the one proposed for registration.

The mean (SD) PK parameters for abiraterone for each of the three treatments are summarised below in Table 7. The inter subject variability (CV%) in the exposure parameters decreased with food, specifically with increasing fat content. In the fasted state, 71.8% and 66.5% inter subject variability were observed for C_{max} and $AUC_{0-\infty}$, respectively. With a low fat meal, 55.0% and 48.0% inter subject variability were observed for C_{max} and $AUC_{0-\infty}$, respectively, and with a high fat meal, 38.4% and 37.0% inter subject variability were observed for C_{max} and $AUC_{0-\infty}$, respectively.

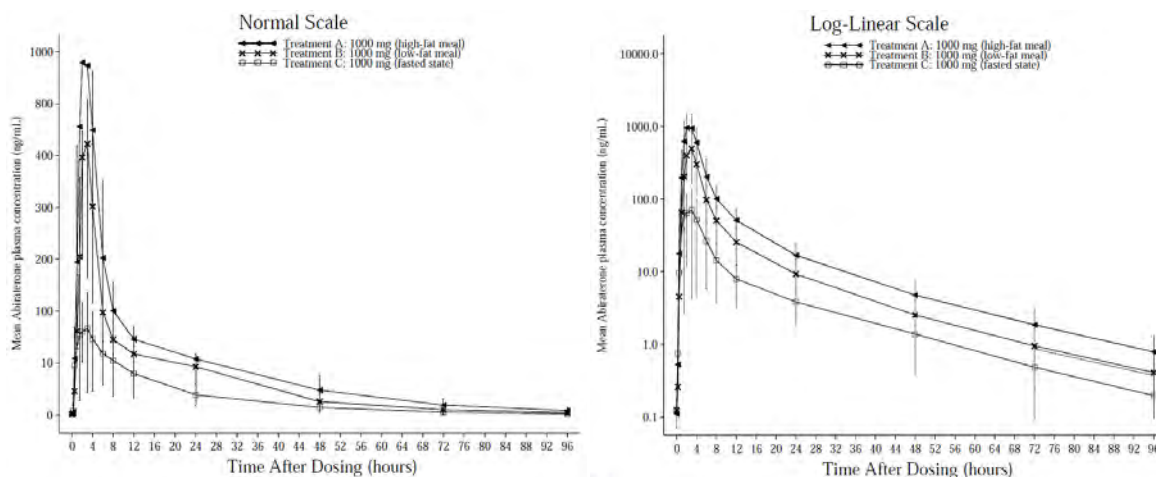
Table 7: Abiraterone mean (SD) PK parameters; full PK data analysis population (Study COU-AA-009).

PK Parameter	Units	Treatment A 1000 mg Abiraterone Acetate High-fat Meal N=35	Treatment B 1000 mg Abiraterone Acetate Low-fat Meal N=36	Treatment C 1000 mg Abiraterone Acetate Fasted State N=35
C_{max}	ng/mL	1270 (487)	558 (307)	90.9 (65.3)
t_{max}^a	hr	2.00 (1.50, 4.03)	3.00 (1.00, 6.00)	2.00 (1.00, 4.03)
AUC_{0-4}	ng*hr/mL	4347 (1607)	2079 (1000)	499 (336)
$AUC_{0-\infty}$	ng*hr/mL	4370 (1616)	2092 (1004)	509 (338)
$t_{1/2}$	hr	17.9 (4.87)	17.6 (4.33)	15.7 (3.68)

^a Median (min, max) shown for t_{max} .

The mean concentration-time profiles for abiraterone following the three treatments are summarised below in Figure 3. The median t_{max} for each of the three treatments was similar ranging from 2 to 3 h, and the mean $t_{1/2}$ values were also similar for each of the three treatments ranging from 15.7 h to 17.9 h.

Figure 3: Abiraterone concentration-time profiles; normal and log-linear scales (Study COU-AA-009).



The results for the comparisons for the C_{\max} , $AUC_{0-\infty}$ and AUC_{0-t} values for abiraterone under both fed treatments (high fat meal and low fat meal) (test) relative to the fasted treatment (reference) are summarised below in Table 8.

Table 8: PKs for treatment comparisons fed and fasted; PK evaluable data analysis set (Study COU-AA-009).

Parameter ^a (Units)	Treatment (Test)	LS Mean ^b				Test/ Reference (%) ^d	90% Confidence Interval (%) ^e	Intrasubject CV (%) ^f
		N ^c	1000 mg Fed (Test)	N ^c	1000 mg Fasted (Reference)			
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

^a Parameters were log-transformed before analysis.

^b For AUC_{0-t} , $AUC_{0-\infty}$, and C_{\max} , LS means from the ANOVA, transformed back to the linear scale (i.e. geometric means).

^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.

Comment: Study COU-AA-009 was a good quality food effect study. It showed that administration of abiraterone acetate in the fed state markedly increased exposure to abiraterone, relative to the fasted state. The geometric mean values for abiraterone C_{\max} and $AUC_{0-\infty}$ increased by approximately 7 and 5 fold, respectively, when administered with a low fat meal, and approximately 17 and 10 fold, respectively, when administered with a high fat meal. The 90% CI for abiraterone C_{\max} and both AUC ratios (high fat meal/fasted, low fat meal/fasted) were all outside the 80% to 125% standard bioequivalence range, indicating that food significantly increased the bioavailability of abiraterone. Inter subject variability in the exposure parameters of C_{\max} and AUC decreased with increasing fat content in the meal. However, both inter subject and intra subject variability in C_{\max} and both AUC parameters were high. Concentrations of abiraterone acetate in most subjects were BLQ (below the level of quantification), indicating that abiraterone acetate was almost completely converted to abiraterone.

Given the marked effect of high and low fat content meals on systemic exposure to abiraterone, and the high inter subject and intra subject variability in exposure parameters (C_{\max} and AUC), it can be predicted that the normal variation in the content and composition of meals has the potential to result in highly variable abiraterone exposures following administration of abiraterone acetate tablets. Information provided by the sponsor indicates that they considered recommending that abiraterone acetate be taken with a fixed diet. However, due to existence of anorexia, nausea, vomiting, and other gastrointestinal symptoms in patients with mCRPC, and dietary restrictions associated with comorbidities commonly seen in this patient population, prescribing a fixed diet was deemed to be impractical. Therefore, the sponsor proposes that abiraterone acetate must not be taken with food, and should be taken at least 2 h after eating and no food should be eaten for at least 1 h after taking the drug. There are no data on the bioavailability of abiraterone acetate administered with this regimen. In the fed food study, abiraterone acetate was administered at least 10 h after an overnight fast and no food was ingested for 4 h post dose. However, the proposed “modified fasting” regimen was used in the pivotal clinical efficacy and safety Study COU-AA-301.

Single dose pharmacokinetics

In the PK pooled dataset, after a single 1 g dose of abiraterone acetate tablets under fasting conditions, the median t_{\max} was 2 h (range: 1-8 hours), the mean $t_{1/2}$ was 15.2 h (CV 26.1%), the mean C_{\max} was 93.5 ng/mL (CV 62.6%), and the mean AUC_{∞} was estimated to be 503 ng•h/mL (CV 59.4%).

Dose proportionality

Exposure to abiraterone after administration of abiraterone acetate tablets at doses of 250, 500, 750, and 1000 mg (1 g) to fasting healthy male subjects was evaluated in two PK studies (Studies COU-AA-008 and COU-AA-016). Study COU-AA-008 was a sequential cohort, ascending dose (250, 500, 750, 1000 mg) study in 32 patients (8 in each cohort). Safety and tolerability were assessed for each lower dose before exposing the next cohort to the higher dose. The primary objective of the study was to determine the PK profile of abiraterone acetate after single oral dose administration. Definitive conclusions about dose proportionality were precluded since the study was not formally designed to assess dose proportionality. This study is considered to be an exploratory study.

Study COU-AA-016 was designed to formally evaluate dose proportionality and document the single dose PKs of abiraterone acetate in healthy subjects (n=32). The study was single centre (USA), open label, randomised, and crossover in design with the four abiraterone acetate doses being 250 mg (1 x 250 mg tablet), 500 mg (2 x 250 mg tablets), 750 mg (3 x 250 mg tablets), and 1000 mg (4 x 250 mg tablets). There was a minimum seven day washout period between treatments. The PK parameters are summarised below in Table 9. Inter subject variability was high with CVs% ranging from 49.8% to 63.4% for C_{\max} and from 42.0% to 55.8% for the AUCs. Intra subject variability was also high and ranged from 31.3% for AUC_{∞} to 42.8% for C_{\max} .

Table 9: Mean (SD) PK parameters after abiraterone acetate; full PK data analysis set (Study COU-AA-016).

Parameter	unit	Dose Cohort			
		250 mg (N=27)	500 mg (N=29)	750 mg (N=28)	1000 mg (N=29)
C_{\max}	ng/mL	39.9 (25.3)	67.0 (34.7)	87.0 (43.3)	125 (76.4)
t_{\max}	h	2 (1-6)	2 (1-4)	2 (1-4)	2 (1-4)
AUC_{last}	h.ng/mL	195 (109)	336 (156)	438 (189)	607 (298)
AUC_{∞}	h.ng/mL	210 (105) ^a	345 (155)	449 (189)	621 (300)
$t_{1/2}$	h	14.4 (4.5) ^a	15.3 (4.1)	16.5 (4.5)	16.0 (4.6)
C_{\max} Ratio		0.32	0.54	0.70	1
AUC_{last} Ratio		0.32	0.55	0.72	1
AUC_{∞} Ratio		0.34 ^a	0.55	0.72	1

^a n = 26 as lambda z could not be determined for Subject 001-013. Median (Min-Max) reported for t_{\max} .

The geometric mean ratios for C_{\max} , AUC_{last} and AUC_{∞} , and associated 90% CIs are summarised below in Table 10.

Table 10: Dose normalised PK parameters; full PK data analysis set (Study COU-AA-016).

	Treatment:			Ratio: Test /		
Parameter ^a	Test/ Reference	N	LS Mean ^b	Reference (%) ^c	90% Confidence Interval (%) ^d	Intra- Subject CV (%)
C_{\max} (ng/mL)	250 mg	27	117.9719	124.0651	102.9441 - 149.5193	42.8185
	500 mg	27	108.7663	114.3839	94.9602 - 137.7808	
	750 mg	27	98.0017	103.0634	85.5178 - 124.2087	
	1000 mg	27	95.0888			
AUC_{last} (ng*hr/mL)	250 mg	27	630.2862	120.5624	103.6323 - 140.2584	34.2106
	500 mg	27	586.5384	112.1943	96.4796 - 130.4685	
	750 mg	27	523.4354	100.1238	86.0638 - 116.4808	
	1000 mg	27	522.7882			
AUC_{∞} (ng*hr/mL)	250 mg	26	750.7903	128.6622	111.6198 - 148.3066	31.2650
	500 mg	26	663.4501	113.6948	98.7087 - 130.9560	
	750 mg	26	579.3291	99.2791	86.1287 - 114.4372	
	1000 mg	26	583.5361			

^a Parameter data were Ln transformed and dose normalised prior to analysis.

^b LS means based on dose normalised PK parameters from the mixed effects model, transformed back to the linear scale (that is, geometric means).

^c Ratio of parameter means (expressed as a percent), transformed back to the linear scale. Ratios are based on dose normalised PK parameters.

^d 90% CI for ratio means (expressed as a percent), transformed back to the linear scale. CIs are based on dose normalised PK parameters.

Comment: This was a good quality dose proportionality study. Statistical analysis of the dose normalised geometric mean C_{max} and AUC parameters showed that the decrease in abiraterone exposure from 1000 mg to 750 mg was dose proportional, while abiraterone exposure was not dose proportional when comparing the reference dose of 1000 mg with the 500 mg and 250 mg doses. Comparison of the dose normalised geometric means of C_{max} and AUC between abiraterone acetate 750 mg and 1000 mg showed a difference of 3% or less, the 90% CI for the ratio of the geometric means was within the 80% to 125% range. Comparison of exposures after 500 mg and 250 mg to the 1000 mg reference dose showed a greater than dose proportional decrease in abiraterone exposure. Dose normalised geometric means for C_{max} , AUC_{last} and AUC_{∞} differed by 14%, 12%, and 14%, respectively, when comparing the 500 mg to the 1000 mg dose. The 90% CIs of these parameters were outside the 80% to 125% bioequivalence range. When comparing the 250 mg dose to the 1000 mg dose, the difference was larger with values of 24%, 21%, and 29% for C_{max} , AUC_{last} and AUC_{∞} , respectively. The 90% CIs for these parameters were also outside the 80% to 125% range.

Bioavailability during multiple dosing

There were no multiple dosing studies in healthy volunteers due to concerns about potential prolonged inhibition of androgen biosynthesis. Therefore, multiple dosing PK data were derived from patients with mCRPC (Study COU-AA-006).

Effect of administration timing

The recommended dose of abiraterone is 1 g (4 x 250 mg tablets) once daily without reference to morning or evening administration. The relationship to meals has been discussed above.

Distribution

Volume of distribution

In the population PK study, the central and peripheral distribution volumes were estimated to be 5630 L and 17400 L, respectively, and the inter departmental clearance was estimated to be 1350 L/h. The large volumes of distribution suggest extensive tissue distribution.

Plasma protein binding

Three *in vitro* studies were conducted to assess plasma protein binding of abiraterone (Studies Covance 8202266, FK7448, and FK7603). In Covance 8202266, in humans the percentages of ^{14}C abiraterone bound to plasma proteins were independent of concentration between 0.1 and 10 μM , with mean percent bound values ranging from 98.8% to 99.1%. In solutions of isolated human serum albumin (HSA) and human α 1-acid glycoprotein (AAG), the percentages of ^{14}C abiraterone bound to plasma proteins were independent of concentration between 0.1 and 10 μM , with mean percent bound values ranging from 95.6% to 97.6% and 94.3% to 95.7%, respectively. These data indicate that binding of ^{14}C abiraterone in human plasma is primarily or exclusively due to binding to albumin and AAG. In this study, ^{14}C abiraterone acetate was stable in human plasma over a 120 second incubation period at 37°C. Due to the typically high activity of esterase enzymes, conversion of ^{14}C abiraterone acetate to ^{14}C abiraterone would have been evident within the 120 second incubation period. Consequently, it appears that there are no esterases in human plasma capable of converting abiraterone acetate to abiraterone.

In Study FK7448, protein binding of abiraterone in pre dosed plasma from male subjects with mild or moderate hepatic impairment from a single dose open label PK study of abiraterone acetate was compared with subjects with normal hepatic function (Study COU-AA-01). The *in vitro* data showed that the unbound fraction of abiraterone in plasma of subjects with mild hepatic impairment, moderate hepatic impairment and normal hepatic function was 0.22%, 0.19% and 0.19% respectively. In Study FK7603, plasma protein binding from human males was found to be 99.9% (that is, fraction unbound 0.1%), and remained constant over the concentration range from $\sim 0.5 \mu\text{M}$ to $\sim 5 \mu\text{M}$. Binding to HSA was 99.9% and to anti albumin autoantibodies (AAA) was 89.4% to 94.4%. The results from this study confirmed those from Study Covance 8202266.

Comment: The *in vitro* studies showed that plasma protein binding of abiraterone at therapeutic concentrations in humans is high (in the order of 98.8% to 99.9%), and that mild/moderate hepatic impairment has no significant effect on the unbound fraction. The high plasma protein binding is primarily or exclusively due to HSA and AAG binding.

Erythrocyte distribution

In the mass balance Study COU-AA-007, the mean C_{max} , AUC_{0-t} , and $\text{AUC}_{0-\infty}$ values for total radioactivity in plasma were higher than those observed for total radioactivity in whole blood. The mean whole blood to plasma $\text{AUC}_{0-\infty}$ ratio (AUC_R) was 0.523, indicating that the majority of the total radioactivity remains in the plasma rather than being distributed into the blood cells.

Tissue distribution

The volume of distribution data from the population PK study indicate that abiraterone is extensively distributed. However, there are no human data on the distribution of abiraterone to specific tissues (apart from whole blood). Tissue distribution data in rats indicated that the highest concentrations of abiraterone were found in liver, adrenal gland, kidney (cortex), and gastrointestinal tissues. Other tissues with high concentrations included fat, brain/spinal cord, pancreas, and large intestine.

Metabolism

Interconversion between enantiomers

Abiraterone acetate is a single enantiomer containing eight stereochemical elements: six chiral centres (3*S*, 8*R*, 9*S*, 10*R*, 13*S*, 14*S*) and two centres of geometrical isomerism (5*Z* and 16*E*). Due to the steroidal skeleton of the molecule, inter conversion is not expected.

Sites of metabolism and mechanisms/enzyme systems involved

Biotransformation of abiraterone acetate was studied *in vitro* in human liver microsomes and cryopreserved hepatocytes.

In Study CR 400378, abiraterone acetate was evaluated *in vitro* to assess induction/suppression of CYP1A2 (7-ethoxyresorufin *O*-deethylation), CYP2C9 (diclofenac 4-hydroxylation), and CYP3A4 (testosterone 6 β -hydroxylation) activities in primary cultures of human hepatocytes from one donor. Abiraterone induced CYP1A2 activity 1.1 to 1.6 fold compared with the vehicle control across the tested concentrations of abiraterone acetate (0.1, 1.0 and 10 μ M), indicating that the drug is a concentration independent "slight" inducer of CYP1A2 activity. The concentration independent induction of CYP1A2 activity was \sim 0.8% that of omeprazole (which was used in the study as prototype inducer of CYP1A2 activity). The low level of CYP1A2 induction observed with abiraterone was considered "not to be biologically significant". Abiraterone had no effect on CYP2C9 across the concentrations of abiraterone acetate tested (0.1, 1.0, and 10 μ M). Abiraterone inhibited CYP3A4 activity by 20% at a abiraterone acetate concentration of 0.1 μ M and 30% at both 1.0 and 10 μ M (that is, inhibitory effect is "slight" and concentration independent).

In Study CR 400379, the potential of abiraterone and abiraterone acetate to inhibit human CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1 and 3A4/5 activities was assessed using probe substrates. The apparent K_m (Michaelis constant) and K_i were determined for each CYP450 assay from Michaelis-Menten plots using nonlinear regression. The effects of the two compounds on CYP450 isoform inhibition were analysed using Michaelis-Menten or/and Lineweaver-Burk plots. Abiraterone in the tested conditions was not an inhibitor of human CYP2A6 and CYP2E1; was a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5; and was a potent inhibitor of CYP1A2 and CYP2D6 with an apparent K_i of 0.44 μ M and 0.39 μ M, respectively. Abiraterone acetate in the tested conditions exhibited no inhibition of CYP2A6; showed moderate inhibition of CYP2E1, CYP2C9 and CYP3A4/5; and was a potent inhibitor of CYP1A2 and CYP2C19 with an apparent K_i of 0.32 μ M and 0.16 μ M, respectively.

Comment: The first step in the biotransformation of abiraterone acetate is ester hydrolysis to abiraterone, followed by conjugation alone (primarily sulphate, glucuronic acid or both), or in combination with oxidation of abiraterone (mono, di, or tri oxidation). Biotransformation of abiraterone acetate to abiraterone appears to be one directional. The data from Study CR 400379 showed that both abiraterone and abiraterone acetate were potent inhibitors of CYP1A2 and CYP2D6 activity. The K_i for CYP1A2 and CYP2D6 inhibition due to abiraterone was 0.44 and 0.39, respectively. The mean peak plasma concentration of abiraterone following repeat dosing of 1 g abiraterone acetate to subjects with mCRPC under modified fasting conditions was 226 ng/mL (that is, 0.68 μ M) (Study COU-AA-006). Consequently, based on the K_i data, clinically significant interactions between abiraterone acetate and drugs which are substrates of CYP1A2 or CYP2D6 could not be excluded. This was further investigated in a clinical PK drug-drug interaction study between abiraterone acetate and dextromethorphan (Dex; a CYP2D6 substrate) and theophylline (a CYP1A2 substrate) (Study COU-AA-015). This study showed that systemic exposure to Dex increased by approximately 2 fold when co administered with abiraterone acetate, while there was no clinically significant increase in theophylline exposure when co administered with abiraterone acetate.

Metabolites identified in humans

In the mass balance Study COU-AA-007, eight healthy subjects received three capsules containing a single total fasting dose of 1 g 14 C labelled abiraterone acetate (\sim 100 μ Ci). Abiraterone acetate concentrations in plasma were below the LOQ in most of the samples assayed indicating that abiraterone acetate was rapidly converted to abiraterone. A total

of 15 metabolites were detected in human plasma. The percentage of total radioactivity in plasma (AUC_{8h}) represented by the metabolites was approximately 92.4%. The two main circulating metabolites identified in the plasma were M45 (proposed as abiraterone sulphate) and M31 (proposed as N-oxide abiraterone sulphate), and these two metabolites represented approximately 43.4% and 43.3% of the total radioactivity in plasma, respectively. SULT2A1 is involved in the formation of abiraterone sulphate. No drug interaction is expected involving the sulphation of abiraterone as SULT2A1 is expressed at very high levels in the liver. Phase I metabolites are formed by CYP3A enzymes; however, in the human mass balance study the contribution of all non conjugated Phase I metabolites to the total radioactivity was relatively minor (<5% total radioactivity). Consequently, clinically significant drug interactions with co administration of abiraterone acetate and CYP3A4 inhibitors are not expected to occur. Additionally, mainly UGT1A4 and to a lesser extent UGT1A3 are involved in the formation of Phase II glucuronidated metabolites, and the contribution of glucuronidated metabolites to the total radioactivity was also found to be relatively minor (<5% total radioactivity). The metabolites M31 and M45 exhibited weak pharmacological activity compared with abiraterone (nonclinical overview).¹³

Comment: The results from the mass balance study indicate that following oral administration abiraterone acetate is rapidly converted to abiraterone which then undergoes extensive metabolism.

Pharmacokinetics of metabolites

In the mass balance Study COU-AA-007, the value of AUC_{8h} represented by the metabolites was approximately 92.4%. The two main metabolites identified in the plasma were M45 (proposed as abiraterone sulphate) and M31 (proposed as N-oxide abiraterone sulphate), and these two metabolites represented approximately 43.4% and 43.3% of the total radioactivity in plasma, respectively. In the faeces, M45 was identified at 0.48% of the dose and M31 was not detected. In the urine, the main metabolite excreted was M31 and accounted for 4.22% of the dose and M45 was not detected. The PK parameters for the M31 and M45 metabolites are summarised below in Table 11.

Table 11: Mean PK parameters of the main metabolites in plasma (Study COU-AA-007).

PK Parameter (units)	Pooled Mean	
	M31	M45
C_{max} (ng·eq/g)	1410	1620
t_{max} (h)	4.0	4.0
AUC_{8h} (ng eq·h/g)	7980	8000
AUC_{∞} (ng eq·h/g)	NC	9880
AUC_{8h} metabolite/		
AUC_{8h} total radioactivity (%)	43.3	43.4
$t_{1/2}$ (h)	21.6 ^a	2.47 ^a

^a As the C_{max} was used to calculate the half lives, the values should be treated with caution.

Eq = Equivalents ¹⁴C Abiraterone

NC = Not calculated

The mean AUC_{8h} for total radioactivity in plasma was calculated to be 18426.02 ng eq·h/g.

¹³ Sponsor comment: "We agree with this statement but wonder how such a statement correlates with the statements made in the nonclinical evaluation section that implied the metabolites have stronger activity."

Comment: Systemic exposure to the two metabolites was similar as assessed by C_{\max} and AUC_{8h} , and the mean t_{\max} values were identical (4 h). Both metabolites contributed ~43% to the total plasma radioactivity. The half life values of the two metabolites markedly differed, but these values should be interpreted with caution as they were estimated following limited sampling over only 8 h. Furthermore, the C_{\max} and AUC results for abiraterone in the mass balance study following administration of ^{14}C abiraterone capsules were markedly lower than the corresponding results in the PK studies in which abiraterone acetate was administered in a tablet formulation.

Consequences of genetic polymorphism

No data on genetic polymorphisms.

Excretion

Routes and mechanisms of excretion

In the mass balance Study COU-AA-007, total recovery of radioactivity in urine and faeces combined was approximately 93.2% over the 264 h post dose, with the majority (~90%) of the radioactivity being recovered in the first 96 h post dose. Mean recovery of total administered radioactivity was 5.3% in the urine and 87.9% in the faeces. In the faeces, the major components were unchanged abiraterone acetate and unchanged abiraterone (M50) accounting for 55.3% and 22.5% of the dose, respectively; this suggested limited absorption of abiraterone acetate. Of the main circulating metabolites, abiraterone sulphate (M45) was observed at 0.48% of the dose while *N*-oxide abiraterone sulphate (M31) was not detected in faeces. Three additional metabolites were also detected and together they accounted for 3.56% of the dose. In the urine, the main metabolite excreted was M31 (proposed as *N*-oxide abiraterone sulphate) accounting for 4.22% of the dose. Nine additional metabolites were detected by radio-HPLC (high performance liquid chromatography), seven of which were characterised by LC-MS (liquid chromatography-mass spectrometry). Each of these additional metabolites represented <0.3% of the total radioactive dose recovered in urine. Abiraterone acetate, abiraterone, and M45 (abiraterone sulphate) were not detected in urine.

Half life and total clearance

The mean half life from the pooled PK data in healthy volunteers was 15.2 h with the range in individual studies being from 12.7 to 19.0 h. The Pop-PK study estimated that the typical oral apparent clearance (CL/F) following 1 g of abiraterone acetate was 2,240 L/h for a healthy subject. In patients with mCRPC, the Pop-PK study estimated that there was a 33% reduction in apparent clearance resulting in a typical apparent clearance of 1,505 L/h. It was postulated that the lower apparent clearance in mCRPC patients relative to healthy subjects could possibly be explained by an “interplay” among multiple factors in the patient population such as age, weight, serum albumin levels, or testosterone levels. However, this could not be formally tested by simultaneously including all potential predictors in the population PK model, since the large variability observed in the data resulted in model convergence problems. The effect of health status on clearance might also be confounded by differences in food intake, as well as differences in concomitant medication use as patients with mCRPC were exposed to a wide variety of co medications including prednisone or prednisolone. In the population PK study, inter individual variability in CL/F was estimated to be 30% (CV%).

Non renal clearance

In the mass balance Study COU-AA-007, fifteen metabolites were identified in the plasma and the percentage of total radioactivity in plasma (AUC_{8h}) represented by the metabolites was approximately 92.4%. Mean plasma C_{\max} , AUC_{last} , and AUC_{∞} values were approximately 330, 357 and 402 fold higher, respectively, for total radioactivity in plasma than for abiraterone, while abiraterone acetate concentrations in plasma were below the

LOQ in most of the samples assayed. The results suggest that abiraterone acetate is extensively converted into abiraterone, which is then cleared by hepatic metabolism.

Renal clearance

In the mass balance Study COU-AA-077, urinary excretion of radiolabelled material accounted for only 5.3% of a 1 g dose of ^{14}C abiraterone acetate, with the M31 metabolite (*N*-oxide of abiraterone sulphate) being 4.2% of the total dose. Neither unchanged abiraterone acetate nor abiraterone was observed in urine indicating that urinary elimination is not a significant clearance mechanism for abiraterone acetate or abiraterone.

Intra and inter individual variability of pharmacokinetics

Both inter individual and intra individual variability in abiraterone exposure parameters were high following oral administration of abiraterone acetate. In healthy subjects, inter subject variability (CV%) ranged from 32.7% to 119.8% for C_{\max} , and from 40.5% to 140.6% for AUC_{∞} . In Study COU-AA-005, in which 119 healthy male subjects received the commercial formulation proposed for registration, inter subject variability (CV%) in C_{\max} and AUC_{∞} was 58.4% and 48.7%, respectively, and intra subject variability (CV%) for the corresponding parameters was 31.9% and 23.4%, respectively. Based on simulations in patients with mCRPC in the Pop-PK study, inter individual variability (CV%) at steady state was high being 91% for the C_{\max} and 83% for the AUC despite various components built into the model to account for variability.

Pharmacokinetics in the target population

The submission included one multi dose PK and QT/QTc study in patients with mCRPC (Study COU-AA-006). The primary objective of this study was to evaluate the effects of abiraterone acetate plus prednisone on cardiac QT/QTc interval by using PKs and time matched ECGs (electrocardiograms) in subjects with mCRPC. The secondary objectives of this study included evaluation of the PKs of abiraterone acetate and abiraterone after multiple doses of abiraterone acetate. The study was multicentre (four sites), open label, and single arm in design. It was conducted in the USA (three sites) and Canada (one site) in approximately 34 subjects with mCRPC who had failed GnRH therapy and had a PSA ≥ 2 ng/mL, and had received no more than one course of chemotherapy. Subjects received abiraterone acetate 1 g once daily (4 \times 250 mg tablets) in combination with prednisone twice daily with each treatment cycle being 28 days (continuous), and underwent time matched 12 lead ECG and PK sample collection. On Cycle 1 Day -1, subjects underwent baseline ECG measurements over 24 h, and additional ECG measurements were undertaken over 24 h on Cycle 1 Day 1 and Cycle 2 Day 1, with time matched collections of PK samples on these days. PK samples were also collected on Cycle 1 Day 8 over 24 h, and a pre dose sample was collected on Cycle 1 Day 6 and Cycle 1 Day 7. Subjects were to receive study treatment until disease progression. The abiraterone acetate 25 mg tablets were the commercial formulation provided by the sponsor. The PK results (mean [SD]) for abiraterone are summarised below in Table 12.

Table 12: PK results mean (SD) for abiraterone in patients with mCRPC (Study COU-AA-006).

PK		C1D1	C1D8	C2D1
Parameter	Unit	(N=33)	(N=33)	(N=33)
C_{\max}	ng/mL	182 (254)	207 (142)	226 (178)
t_{\max}	h	2 (1-4)	2 (1-4)	2 (1-6)
AUC_{24h}	ng*h/mL	675 (725)	965 (520)	993 (639)
AR C_{\max}		----	1.8 (1.8)	2.0 (2.4)
AR AUC_{24h}		----	2.0 (1.5)	2.2 (2.3)

C1D1=Cycle 1 Day 1; C1D8=Cycle 1 Day 8; C2D1=Cycle 2 Day 1; Median (min-max) presented for t_{max} ; AR=C1D8/C1D1 and C2D1/C1D1; AR calculated as mean of the individual subject ARs.

The plasma-concentration time curves over 24 h for abiraterone on cycle 1 day 1 (C1D1), cycle 1 day 8 (C1D8), and cycle 2 day 1 (C2D1) showed that plasma abiraterone declined in a biphasic manner (the curves have been inspected but not included in this evaluation report).

Comment: This was a good quality study. It showed that exposure after multiple dosing on C1D8 and C2D2 increased about 2 fold relative to exposure after single dosing on C1D1. The accumulation ratios (ARs) for C_{max} and AUC_{24h} were similar on C1D8 and C2D1, suggesting that steady state concentrations had been reached at Day 8 of dosing or earlier. The estimated half life in healthy volunteers of 15.2 h suggests that steady state concentrations following once daily dosing will be reached in healthy subjects at about 76 h (that is, 5 half lives). Based on an AR of 2.0 to 2.2 in patients with mCRPC, it can be estimated that the effective half-life of abiraterone is 24 to 28 h. This suggests that clearance of abiraterone is lower in patients with mCRPC compared with healthy subjects. This was observed in the population PK study where apparent clearance of abiraterone in patients with mCRPC was about 33% lower compared with healthy subjects (1505 L/h versus 2240 L/h, respectively).

Pharmacokinetics in other special populations

Pharmacokinetics in subjects with impaired hepatic function

The PK of abiraterone following a single oral dose of abiraterone acetate 1 g were examined in subjects with pre-existing mild (n=8) or moderate (n=8) hepatic impairment and in matched controls (n=8) with normal hepatic function (Study COU-AA-011). Hepatic impairment was defined using Child-Pugh (CP) criteria, with mild impairment being defined as CP Class A (total score 5-6) and moderate impairment being defined as CP Class B (total score 7-9). The results are summarised below in Table 13. Inter subject CV% in the exposure parameters ranged from 86.9% (C_{max}) to 88.9% (AUC_{∞}) for subjects with moderate hepatic impairment, 53.3% (AUC_{∞}) to 56.0% (C_{max}) for subjects with mild hepatic impairment, and 50.4% (AUC_{∞}) to 54.4% (C_{max}) for subjects with normal hepatic function.

Table 13: PK parameters mean (SD) in hepatic impairment; full PK data analysis set (Study COU-AA-011).

PK Parameter	Cohort 1	Cohort 2	Cohort 3
	Mild Hepatic Impairment N=8	Moderate Hepatic Impairment N=8	Normal Hepatic Function N=8
C_{max} (ng/mL)	71.9 (40.2)	297 (258)	85.7 (46.6)
t_{max} ^a (hr)	2.00 (0.500, 3.00)	1.50 (1.00, 2.00)	1.75 (1.00, 3.00)
AUC_{0-last} (ng*hr/mL)	355 (191)	1530 (1350)	321 (166)
$AUC_{0-\infty}$ (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 Median (min, max) presented for t_{max} .

The comparative results for the PK parameters are summarised below in Table 14. The protocol specified that the no effect boundaries of the 90% CI of the ratio of the means for abiraterone for the C_{max} and AUC values was to be 0.80 to 1.25.

Table 14: PK parameters mean (SD) hepatic impairment; full PK data analysis set (Study COU-AA-011).

Parameter (units)	Comparison	LS Mean ^a				Test/Reference (%) ^b	90% Confidence Interval (%) ^c	Total CV (%) ^d
		N	Test	N	Reference			
C_{max} (ng/mL)	Mild vs Normal	8	62.7	8	74.5	84.2	(45.02 , 157.50)	83.6
	Moderate vs Normal	8	204	8	74.5	274	(146.35 , 512.00)	83.6
AUC_{0-last} (ng*hr/mL)	Mild vs Normal	8	316	8	283	112	(59.56 , 209.51)	84.0
	Moderate vs Normal	8	1025	8	283	362	(193.03 , 679.00)	84.0
$AUC_{0-\infty}$ (ng*hr/mL)	Mild vs Normal	8	326	8	293	111	(59.61 , 208.35)	83.5
	Moderate vs Normal	8	1044	8	293	357	(190.98 , 667.46)	83.5

^a Least squares means from ANOVA. For AUC_{0-last} , $AUC_{0-\infty}$, and C_{max} , means were calculated by transforming the natural log means back to the linear scale (that is, geometric means).

^b Ratio of parameter means for natural log transformed parameter (expressed as a percent). Natural log transformed ratios transformed back to the linear scale.

^c 90% CI for ratio of parameter means of natural log transformed parameter (expressed as a percent). Natural log transformed confidence limits transformed back to the linear scale.

^d Total coefficient of variation (expressed as a percent) for log transformed parameter from the model.

Comment: This was a good quality study. It showed that exposure to abiraterone was markedly increased in subjects with moderate hepatic impairment with the mean C_{max} and AUC_{∞} ratios (moderate/normal) being 274% and 357%, respectively. The corresponding figures in subjects with mild hepatic impairment were 84.2% and 111%, respectively. The 90% CI for all C_{max} and AUC ratios for the comparisons between subjects with impaired hepatic function relative to normal hepatic function were outside the 80% to 125% interval prespecified as the “no effect boundaries”. The PK results suggest that abiraterone acetate can be administered to patients with mild hepatic impairment as the C_{max} was about 16% lower and the AUC_{∞} was about 11% higher in subjects with mild hepatic impairment relative to subjects with normal hepatic function. The PK results suggest that abiraterone should not be administered to patients with moderate hepatic impairment due to the marked increased in exposure relative to subjects with normal hepatic function. There were no data in patients with severe hepatic impairment, but based on the PK results in patients with moderate hepatic impairment abiraterone acetate should not to be administered to patients with severe hepatic impairment.

Pharmacokinetics in subjects with impaired renal function

The submission included one study in patients with renal impairment (Study COU-AA-012). The study was an open label, single dose (1 g of abiraterone acetate administered as 4 x 250 mg tablets following a 6 h food fast), reduced/staged design study. Stage I compared the PKs of abiraterone acetate and abiraterone in male subjects aged between 40 and 80 years (inclusive) with end stage renal disease (ESRD) who were on a stable haemodialysis schedule with male subjects with normal renal function (CrCL [creatinine clearance] >80 mL/min) matched for mean age and mean BMI. Stage II provided for evaluation of cohorts with mild or moderate renal impairment based on the outcomes of Stage I relating to drug related toxicity and/or increased systemic exposure. Based on the results of Stage I, Stage II was not undertaken. The PK results for the 8 patients in the ESRD group and the 8 matched patients in the normal renal function group are summarised below in Table 15.

Table 15: PK parameters ESRD versus normal renal function; full PK analysis population (Study COU-AA-012).

PK Parameter	Units	ESRD (N=8)	Normal Renal Function (N=8)
C_{max}	ng/mL	50.2 (37.7)	104 (124)
t_{max}^a	hr	3.00 (1.00, 6.00)	1.50 (1.00, 4.00)
AUC_{0-last}	ng*hr/mL	305 (267)	485 (513)
$AUC_{0-\infty}$	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)

^a Median (min, max) presented for t_{max} .

The test [ESRD]/reference [normal] ratio for C_{max} was 53.1% [95%CI: 26.8, 105.2] for the LS means derived from ANOVA (analysis of variance). The corresponding value for the AUC_{0-last} was 62.8% [95%CI: 32.4, 121.7], and for the AUC_{∞} was 65.0% [95%CI: 34.2, 123.2]. Inter subject variability (CV%) was 91.0% for the C_{max} , 87.1% for the AUC_{0-last} , and 83.4% for the AUC_{∞} .

The observed values for the C_{max} and AUC were higher than those anticipated based on the mass balance study which found that neither unchanged abiraterone acetate nor abiraterone was excreted in the urine. Review of the data from individual subjects identified one subject in the normal renal function cohort with C_{max} and AUC values 5 to 6 fold higher than other subjects in the cohort. No protocol related deviations could be identified to account for these results. After excluding PK data from this subject from the analysis, mean abiraterone C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ values were similar for both the ESRD and normal renal function cohort (Table 16).

Table 16: PK parameters ESRD versus normal renal function; full PK analysis population (excluding one subject from the normal renal function cohort with high exposure parameters) (Study COU-AA-012).

PK Parameter	Units	ESRD N=8	Normal Renal Function N=7
C_{max}	ng/mL	50.2 (37.7)	60.6 (23.5)
t_{max}^a	hr	3.00 (1.00, 6.00)	1.50 (1.00, 4.00)
AUC_{0-last}	ng*hr/mL	305 (267)	307 (108)
$AUC_{0-\infty}$	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 Median (min, max) presented for t_{max} .

Note: The results exclude one subject from the normal renal function cohort with high exposure parameters.

Comment: This was a satisfactory study. The decision to reanalyse the PK data by excluding one patient in the normal renal function cohort with high exposure parameters is considered to be reasonable. The data suggest that in subjects with ESRD on haemodialysis, the C_{max} or AUC values did not notably differ from those in subjects with normal renal function. The data suggest that no abiraterone acetate dosage adjustments are required in mCRPC patients with ESRD being treated with the drug.

Pharmacokinetics according to age

There were no specific studies investigating the effects of age on the PKs of abiraterone acetate. Limited data from the Pop-PK study suggested that age did not affect the CL/F of abiraterone.

Pharmacokinetics related to genetic factors (sex, ethnicity, genetic polymorphism)

There were no specific studies investigating the effects of genetic factors on the PKs of abiraterone acetate. The drug is not indicated in female patients.

Pharmacokinetic interactions

Pharmacokinetic interactions demonstrated in human studies

In vitro data from studies in human liver microsomes showed abiraterone to have no inhibitory effect on CYP2A6 and CYP2E1, a moderate inhibitory effect on CYP2C9, CYP2C19, and CYP3A4/5, and a potent inhibitory effect on CYP1A2 and CYP2D6. In addition, abiraterone showed little inhibition on P-gp in studies performed using Caco-2 monolayers.

In order to further investigate the inhibitory effect abiraterone on CYP2D6 and CYP1A2, an *in vivo*, multicentre, open label, PK drug-drug interaction study in patients with mCRPC was undertaken to evaluate the effects of multiple dose abiraterone acetate plus prednisone on single dose Dex (CYP2D6 substrate) and single dose theophylline (CYP1A2 substrate) (Study COU-AA-015).

Dex was given alone on Cycle 1 Day -8 and in combination with abiraterone acetate on Cycle 1 Day 8. Abiraterone acetate (1 mg [4 x 250 mg]) plus prednisone were to be taken daily and continued until disease progression. Extensive CYP2D6 metabolisers were given a single Dex 30 mg dose on Cycle 1 Day -8 under fasting conditions and a second single dose of Dex 30 mg on Cycle 1 Day 8 under fasting conditions. The PK parameters for Dex are summarised below in Table 17.

Table 17: Mean (SD) PK parameters of Dex; PK data analysis set (Study COU-AA-015).

PK Parameters	Dextromethorphan	
	Dextro. Alone N=18 ^a	Dextro. + Abir. Acetate N =18
C _{max} (ng/mL)	3.49 (4.82)	7.12 (4.99)
t _{max} (h) ^b	2.98 (1.58-10.02)	3.00 (1.55-4.08)
AUC ₂₄ (h.ng/mL)	35.5 (56.0)	70.0 (73.2)
AUC _{last} (h.ng/mL)	44.4 (76.1)	90.7 (110)
AUC _∞ (h.ng/mL)	52.4 (88.7)	101 (132)
t _{1/2} (h)	10.6 (5.2)	10.8 (2.8)

^a For AUC_∞ and t_{1/2}, N = 17

^b Median (min, max) values reported for t_{max}

The 90% CIs for the ratio of geometric means of all Dex exposure parameters were outside the 80% to 125% bioequivalence range. The C_{max} ratio [Dex/AA] was 275% [95%CI: 212, 357], and the AUC_∞ ratio [Dex/AA] was 287% [95%CI: 230, 359]. Intra subject variability (CV%) for all Dex exposure parameters ranged from approximately 38% to 47%.

Theophylline was given alone as a single 100 mg dose on Cycle 1 Day -8 and in combination with abiraterone acetate on Cycle 1 Day 8. Abiraterone acetate (1 g [4 x 250 mg]) plus prednisone were to be taken daily and continued until disease progression. The PK parameters for theophylline are summarised below in Table 18.

Table 18: Mean (SD) PK parameters of theophylline; PK data analysis set (COU-AA-015).

PK Parameters	Theophylline	
	Theo. Alone N=16 ^a	Theo. + Abir. Acetate N=15 ^b
C _{max} (ng/mL)	1928 (680)	2014 (645)
t _{max} (h) ^c	8.03 (3.00-47.98)	8.00 (1.50-32.00)
AUC ₂₄ (h.ng/mL)	32525 (14263)	34837 (10986)
AUC _{last} (h.ng/mL)	49131 (24134)	52806 (19233)
AUC _∞ (h.ng/mL)	58903 (36235)	57923 (22098)
t _{1/2} (h)	13.0 (6.1)	12.7 (3.3)

^a For AUC_∞ and t_{1/2}, N = 15

^b For AUC_∞ and t_{1/2}, N = 12

^c Median (min, max) values reported for t_{max}.

The 90% CIs for the geometric means ratios of theophylline C_{max} and AUC₂₄ values were within the 80% to 125% bioequivalence range. However, the upper bound of 90% CI of geometric means ratios of theophylline AUC_{last} and AUC_∞ values were outside the 80% to 125% range. The C_{max} ratio [Theo/AA] was 102% [95%CI: 89, 118], and the AUC_∞ ratio [Theo/AA] was 113% [95%CI: 97, 132].

Comment: This was a good quality PK drug-drug interaction study. The study showed that exposure to Dex markedly increased when it was co administered with abiraterone, with the mean C_{max} and AUC_∞ ratios [Dex/AA] being 275% [95%CI: 212, 357], and 287% [95%CI: 230, 359], respectively. These results indicate that abiraterone acetate should be co administered with drugs known to be metabolised by CYP2D6 only if considered to be clinically necessary, and that dose reduction of the co administered drug should be considered. The study also showed that exposure to theophylline also increased when co administered with abiraterone acetate. However, the increases in theophylline C_{max} and AUC_∞ of 2% and 13%, respectively, are unlikely to be clinically significant. Consequently, no dose adjustments for CYP1A2 inhibitors are required when co administered with abiraterone acetate.

Clinical implications of in vitro findings

In vitro data from studies in human liver microsomes showed abiraterone to have no inhibitory effect on CYP2A6 and CYP2E1, a moderate inhibitory effect on CYP2C9, CYP2C19, and CYP3A4/5, and a potent inhibitory effect on CYP1A2 and CYP2D6. In addition, *in vitro* studies with Caco-2 monolayers showed that abiraterone acetate inhibited P-gp with an IC₅₀ of 10.8 µM (well above the estimated C_{max} in patients with mCRPC of ~ 0.65 µM [226 ng/mL]). The *in vivo* PK interaction data from Study COU-AA-015 showed that exposure to Dex (a CYP2D6 substrate) increased approximately 2.8 fold, indicating that abiraterone acetate should be co administered with drugs known to be metabolised by CYP2D6 only if considered to be clinically necessary, and that dose reduction of the co administered drug should be considered. The *in vivo* interaction study also showed that abiraterone acetate can be co administered with drugs metabolised by CYP1A2 (despite the *in vivo* data which showed it to be a potent CYP1A2 inhibitor).

The *in vitro* data showed that abiraterone had a moderate inhibitory effect on CYP2C9, CYP2C19, and CYP3A4/5. There are no *in vivo* PK studies exploring the potential clinical significance of these interactions. The *K_i* (µM) for abiraterone for CYP2C9, CYP2C19, and CYP3A4/5 was 29.8, 46.3, and 8.01, respectively. These concentrations are well above the steady state abiraterone C_{max} seen in patients with mCRPC of 226 ng/mL (that is, ~0.65 µM), which provides some reassurance relating to co administration. Nevertheless, based on the *in vitro* data co administration of abiraterone with drugs metabolised by these enzymes should be undertaken cautiously. The *in vitro* data also showed that abiraterone had no inhibitory effects on CYP2A6 and CYP2E1, which provides reassurance that

abiraterone acetate is unlikely to significantly effect the PKs of drugs metabolised by these enzymes if co administered.

CYP3A4 is involved in the metabolism of abiraterone, but there are no *in vivo* drug-drug interaction studies exploring the effect of CYP3A4 inhibitors or inducers on the PKs of abiraterone acetate. However, the sponsor speculated that as abiraterone is also metabolised through a SULT2A1 mediated pathway any inhibition of CYP3A4 metabolism could result in a shift to the *O*-sulphate conjugation pathway. SULT2A1 is expressed in high concentrations in the liver and may be less susceptible to saturation or inhibition by other drugs. Alternatively, CYP3A4 inducers could potentially reduce the systemic exposure of abiraterone by increasing metabolism. The absence of *in vivo* studies evaluating the inhibition and induction of CYP3A4 on abiraterone metabolism is considered to be a deficiency in the data. UGT1A4 and UGT1A3 are also involved in the formation of Phase II glucuronidated metabolites. However, these pathways are considered to be minor so the impact of significant clinical drug interactions appears to be limited.

Evaluator's overall conclusions on pharmacokinetics

- Orally administered abiraterone acetate was rapidly and extensively converted to abiraterone. Consequently, the majority of abiraterone acetate plasma concentrations were below the lower limit of quantification (that is, 0.200 ng/mL) of the HPLC/MS/MS assay, and no PK analyses were performed for abiraterone acetate. Therefore, all PK analyses involved plasma concentrations of abiraterone.
- Abiraterone acetate is classified as a BCS Class IV compound (low solubility and low permeability). The sponsor was unable to prepare a suitable IV abiraterone acetate formulation for human administration. Consequently, no absolute bioavailability study was submitted. In the absence of an absolute bioavailability study, the submission included an oral relative bioavailability study comparing abiraterone acetate (1 g) administered as tablet (4 x 250 mg) and liquid olive oil (30 mL) formulations (Study COU-AA-010). This study showed that systemic exposure to abiraterone was approximately 4.5 fold higher following administration of the liquid relative to the tablet, while the median t_{\max} and mean $t_{1/2}$ values were similar for the two formulations. The oral relative bioavailability study suggests that abiraterone acetate tablets are incompletely absorbed when administered fasting.
- In a food-effect Study COU-AA-009, administration of a single 1 g (4 x 250 mg tablets) dose of abiraterone acetate with food markedly increased exposure to abiraterone compared with fasting administration. Mean abiraterone C_{\max} and AUC_{∞} values increased by approximately 7 and 5 fold, respectively, when administered 30 minutes after a low fat meal, and by approximately 17 and 10 fold, respectively, when administered 30 minutes after a high fat meal. The sponsor proposes that abiraterone acetate should be administered at least 2 h after eating and that no food should be eaten for at least 1 h after taking the drug (that is, modified fasting regimen). However, this modified fasting regimen differs from that in the fed-fasting study in which subjects fasted overnight for at least 10 h prior to scheduled administration of abiraterone acetate and no food was eaten for 4 h post dose. There are no bioavailability data relating to abiraterone acetate when administered using the proposed modified fasting regimen. This is a deficiency in submitted data.
- The pivotal clinical efficacy and safety Study COU-AA-301 included tablets manufactured by (commercial) and (clinical trial and commercial). Study COU-AA-014 investigated the relative bioavailability of the three tablet formulations and showed that while the (clinical trial) and (commercial) formulations were bioequivalent, the (commercial) formulation was not bioequivalent to the two formulations. However, a

subsequent pivotal Study COU-AA-005 in a large number of subjects showed that the (commercial) and (clinical trial) formulations were bioequivalent. Consequently, based on the results from Study COU-AA-005 it can be reasonably concluded that the abiraterone acetate tablet formulations used in the pivotal efficacy and safety study are bioequivalent.

- In the pooled data in healthy male subjects, after a single fasting dose of abiraterone acetate 1 g, the mean C_{\max} of abiraterone was 93.5 mg/mL (CV 62.6%), the mean AUC_{∞} was 503 ng•h/mL (CV 59.4%), the median t_{\max} was 2 h (range: 1, 8 h) and the mean $t_{1/2}$ was 15.2 h [range: 12.7, 19.0]. In the dose proportionality Study COU-AA-016, exposure to abiraterone increased following single dose abiraterone acetate over the range 250 mg to 1 g. However, statistical analysis of dose normalised mean C_{\max} and AUC parameters showed that while the 750 mg was proportional to the reference dose of 1 g (1000 mg), exposure to both the 250 mg and 500 mg doses were more than proportional to the reference dose of 1 g. The dose being proposed for all patients is 1 g once daily administered as a single dose. However, the sponsor proposes lower doses based on toxicity (that is, 500 mg once daily). This should not create a significant clinical problem although the 500 mg dose is more than dose proportional relative to the 1 g dose (that is, exposure ~ 12% to 14% greater than predicted).
- In the multiple dose Study COU-AA-006, in patients with mCRPC the mean C_{\max} and AUC_{24h} of abiraterone after a single fasting dose of abiraterone acetate 1 g were 182 ng/mL (CV 139.6%) and 675 ng•h/mL (CV 107.4%) respectively. After 28 days of continuous daily dosing, steady state mean C_{\max} and AUC_{24h} increased ~2.0 fold and ~2.2 fold to 226 ng/mL (CV 78.8%) and 993 ng•h/mL (CV 64.4%), respectively. The estimated accumulation ratios for C_{\max} and AUC_{24h} of 2.0 and 2.2, respectively, are compatible with an effective half life after multiple dosing of 24 to 28 h. The longer half life in subjects with mCRPC compared with healthy subjects suggests that the abiraterone clearance is reduced. In the Pop-PK study, apparent clearance was 33% lower in subjects with mCRPC compared with healthy controls.
- The inter and intra subject variability in systemic exposure to abiraterone is high. Inter subject variability in healthy subjects ranged from 32.7% to 119.8% for C_{\max} and from 40.5% to 140.6% for AUC_{∞} . The estimated inter subject variability in patients with mCRPC, based on simulated data, was 91% for $C_{\max,ss}$ and 83% for AUC_{ss} (Pop-PK study). In Study COU-AA-005, the commercial formulation proposed for registration was administered as a single 1 g dose (4 x 250 mg tablets) to healthy males. In this study, inter subject variability (CV%) in the C_{\max} and the AUC_{∞} was 58.4% and 48.7%, respectively, and intra subject variability (CV%) for the corresponding parameters was 31.9% and 23.4%, respectively.
- The *in vitro* Caco-2 monolayer study showed that abiraterone acetate and abiraterone had low apparent permeability and were not substrates for P-gP (Study Covance 8202265). Following oral administration, abiraterone acetate is rapidly converted into abiraterone by non identified esterases. In the protein binding Study Covance 820226, abiraterone acetate did not undergo conversion to abiraterone when incubated in human plasma. This suggests that there are no esterases in human plasma capable of converting abiraterone acetate into abiraterone. Consequently, conversion of abiraterone acetate to abiraterone might be due to esterases located in the liver and/or in gastro intestinal tissues rather than the plasma.
- Abiraterone binding to plasma proteins is high and ranged from 98.8% to 99.1% (Study Covance 82206). Binding was independent of abiraterone concentration at concentrations of 0.1 μ M and 10 μ M (that is, ~34.9 ng/mL to 34,900 ng/mL). Similar abiraterone binding was demonstrated for HSA (95.6% to 97.6%) and AAG (94.3% to 97.5%) (Study Covance 82206). The plasma protein binding data indicates that abiraterone binding should remain constant over the plasma concentration range

expected in patients with mCRPC (8.9 ng/mL to 226 ng/mL). *In vitro* data showed that the unbound fraction of abiraterone in plasma of subjects with mild hepatic impairment, moderate hepatic impairment and normal hepatic function was 0.22%, 0.19% and 0.19% respectively (Study FK7448).

- In the POP-PK study, the central and peripheral volumes of distribution were estimated to be 5,630 L and 17,400 L, respectively, indicating extensive tissue distribution. In the mass balance Study COU-AA-007, following a single dose of radioactive abiraterone acetate under fasting conditions, the mean C_{max} and AUC values for total radioactivity in plasma were approximately 2 fold higher than those in whole blood, indicating very limited distribution of drug related material into blood cells. The mean whole blood to plasma $AUC_{0-\infty}$ ratio (AUC_R) was 0.523.
- In the mass balance Study COU-AA-007, following a fasting single 1 g oral dose of ^{14}C abiraterone acetate administered in hand packed capsules, the mean plasma C_{max} , AUC_{last} , and AUC_{∞} values for total radioactivity in plasma were approximately 330, 357 and 402 fold higher, respectively, than for abiraterone. These data indicate that abiraterone undergoes extensive metabolism following its conversion from abiraterone acetate. There were a total of 15 metabolites of abiraterone detected in human plasma. The two main metabolites identified in the plasma were M45 (proposed as abiraterone sulphate), and M31 (proposed as N-oxide abiraterone sulphate), and these two metabolites represented approximately 43.4% and 43.3% of the total radioactivity in plasma, respectively. The primary metabolic pathways for abiraterone include sulfation and N-oxidation, as well as hydroxylation, dehydration, and glucuronidation. SULT2A1 is involved in the formation of abiraterone sulphate. Phase I metabolites are formed by CYP3A enzymes, however in the human mass balance study the contribution of all non conjugated Phase I metabolites to the total radioactivity was relatively minor (< 5% total radioactivity). Additionally, Phase II glucuronidated metabolites (< 5% total) are formed mainly by UGT1A4 and to a lesser extent UGT1A3.
- In the mass balance Study COU-AA-007, total recovery of radioactivity in urine and faeces combined was approximately 93.2% over 264 h post dose, with approximately 90% of the total radioactivity being recovered in the first 96 h post dose. Mean recovery of total administered radioactivity was 5.3% in the urine and 87.9% in the faeces. In the faeces, the major components were unchanged abiraterone acetate and abiraterone accounting for 55.3% and 22.5% of the dose, respectively, suggesting limited absorption of abiraterone acetate. Of the main circulating metabolites, abiraterone sulphate (M45) was observed at 0.48% of the dose while N-oxide abiraterone sulphate (M31) was not detected in faeces. Three additional metabolites were also detected and together they accounted for 3.56% of the dose. In the urine, the main metabolite was M31 and accounted for 4.22% of the dose. Nine additional metabolites were detected by radio-HPLC, seven of which were characterised by LC-MS. Each of these additional metabolites represented less than 0.3% of the radioactive dose recovered in urine. Abiraterone acetate, abiraterone, and M45 (proposed to be abiraterone sulphate) were not detected in urine. The results from the mass balance study suggest that abiraterone is primarily cleared by hepatic metabolism with negligible renal clearance of unchanged abiraterone.
- The mean $t_{1/2}$ from the pooled PK data in healthy volunteers was 15.2 h with the range in individual studies being from 12.7 to 19.0 h. In the Pop-PK study, typical oral apparent clearance following an oral 1 g dose of abiraterone acetate was estimated to be 2240 L/h for healthy subjects and 1505 L/h for patients with mCRPC (that is, 33% reduction relative to healthy subjects). It was postulated that the lower clearance in mCRPC patients relative to healthy subjects could possibly be explained by an "interplay" among multiple factors in the patient population, such as age, weight,

serum albumin levels, or testosterone levels. However, this could not be formally tested by including all parameters at once in the Pop-PK model, since the large variability observed in the data resulted in model convergence problems. In addition, the effect of health status on clearance might be confounded by differences in food intake, as well as differences in concomitant medication use as patients with mCRPC were exposed to a wide variety of co medications.

- In subjects with moderate hepatic impairment (CP Class B), exposure to abiraterone was markedly increased following a single oral dose of abiraterone 1 g relative to subjects with normal hepatic function, with the mean C_{max} and AUC_{∞} ratios [moderate/normal] being 274% [90%CI: 146, 412] and 357% [90%CI: 191, 667], respectively (Study COU-AA-011). In subjects with mild hepatic impairment (CP Class A), the mean C_{max} was about 16% lower relative to subjects with normal hepatic function (C_{max} ratio 84.2% [90%CI: 45, 147]), and the mean AUC_{∞} was about 11% higher (AUC_{∞} ratio 111% [90%CI: 60, 208]). These results suggest that abiraterone acetate should not be administered to patients with moderate (or severe) hepatic impairment, but can be administered to patients with mild hepatic impairment with no dosage adjustment.
- In subjects with ESRD on haemodialysis, there were no marked changes in systemic exposure to abiraterone relative to subjects with normal renal function following a single oral abiraterone 1 g dose. This suggests that abiraterone can be administered to patients with all levels of renal impairment without dose adjustment.
- *In vitro* data from studies in human liver microsomes showed abiraterone to have no inhibitory effect on CYP2A6 and CYP2E1, a moderate inhibitory effect on CYP2C9, CYP2C19, and CYP3A4/5, and a potent inhibitory effect on CYP1A2 and CYP2D6. In addition, *in vitro* studies with Caco-2 monolayers showed that abiraterone acetate inhibited P-gp with an IC_{50} of 10.8 μM (well above the estimated C_{max} in patients with mCRPC of $\sim 0.65 \mu M$ [226 ng/mL]). The *in vivo* PK interaction Study COU-AA-015 showed that co administration of abiraterone acetate and Dex markedly increased exposure to Dex, with the C_{max} and AUC_{∞} ratios [Dex/AA] being 275% [95%CI: 212, 357], and 287% [95%CI: 230, 359], respectively. These data indicate that abiraterone acetate should be co administered with drugs known to be metabolised by CYP2D6 only if considered to be clinically necessary, and that dose reduction of the co administered drug should be considered. However, the PK data from Study COU-AA-015 relating to the effect of abiraterone acetate on the C_{max} and AUC parameters of theophylline (a CYP1A2 substrate) suggests that abiraterone can be co administered with drugs known to be metabolised by CYP1A2, despite the *in vitro* data indicating that abiraterone is a potent inhibitor of CYP1A2.
- The *in vitro* data showed that abiraterone had a moderate inhibitory effect on CYP2C9, CYP2C19, and CYP3A4/5. There are no *in vivo* PK studies exploring the potential clinical significance of these interactions. The K_i (μM) for abiraterone for the CYP2C9, CYP2C19, and CYP3A4/5 was 29.8, 46.3, and 8.01. These concentrations are well above the steady state abiraterone C_{max} seen in patients with mCRPC of 226 ng/mL (that is, $\sim 0.65 \mu M$), which provides reassurance. Nevertheless, co administration of abiraterone with drugs metabolised by these enzymes should be undertaken cautiously. The *in vitro* data showed that abiraterone had no inhibitory effects on CYP2A6 and CYP2E1, which provides reassurance that abiraterone acetate is unlikely to significantly affect the PKs of drugs metabolised by these enzymes if co administered.
- CYP3A4 is involved in the metabolism of abiraterone, but there are no *in vivo* drug-drug interaction studies exploring the effects of CYP3A4 inhibitors or inducers on the PKs of abiraterone acetate. The absence of *in vivo* studies evaluating the inhibition and induction of CYP3A4 on abiraterone metabolism is considered to be a deficiency in the

submission. However, the sponsor speculates that as abiraterone is also metabolised through a SULT2A1 mediated pathway any inhibition of CYP3A4 metabolism could result in a shift to the *O*-sulphate conjugation pathway. SULT2A1 is expressed in high concentrations in the liver and may be less susceptible to saturation or inhibition by other drugs. Alternatively, CYP3A4 inducers could potentially reduce the systemic exposure of abiraterone by increasing metabolism. UGT1A4 and UGT1A3 are also involved in the formation of Phase II glucuronidated metabolites. However, these pathways are considered to be minor so the impact of significant clinical drug interactions appears to be limited.

- There are no PK data investigating co administration of abiraterone acetate and prednisone or prednisolone. However, the sponsor speculates that co administration of prednisone or prednisolone in patients is not expected to result in changes in abiraterone exposure as the drugs are considered weak inducers and not inhibitors of CYP3A4, the CYP isoenzyme most relevant to the metabolism of abiraterone.
- No specific clinical PK studies have been done to investigate the potential effects of age, race, ethnicity, and genetic factors on the disposition and PD of abiraterone acetate or abiraterone. Abiraterone acetate is not indicated for use in women. Limited data from the Pop-PK analysis suggest that age did not significantly affect the apparent clearance of abiraterone.

Pharmacodynamics

Studies providing pharmacodynamic data

Study COU-AA-006

The primary objective of this study was to evaluate the effects of abiraterone acetate plus prednisone on the cardiac QT/QTc interval by using PK and time matched ECGs in subjects with mCRPC. One of the secondary objectives of the study was to evaluate the PKs of abiraterone acetate and abiraterone after multiple doses of abiraterone acetate. The subject population consisted of 33 males with mCRPC aged from 42 to 85 years. The study reviewed a total of 3,068 evaluable ECGs out of 3,168 expected ECG extractions. Serial sets of three time matched ECGs were obtained according to the following schedule:

- **Cycle 1 Day -1:** pre dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post dose ECG using Central Laboratory 12-Lead Holter machine on C1D-1 were time matched on the clock (within 30 minutes) to the time the ECGs were obtained on C1D1.
- **Cycle 1 Day 1 and Cycle 2 Day 1:** pre dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 h post dose ECGs using Central Laboratory 12-Lead Holter machine.
- **Cycle 4 Day 1:** pre dose ECGs using Central Laboratory standard 12-Lead ECG machine.
- **Every 3 cycles on Day 1 after Cycle 4 until Cycle 10 Day 1:** pre dose ECGs were to be obtained using Central Laboratory standard 12-Lead ECG machine.
- **End of study visit:** ECGs were to be obtained using local site ECG machine.

QTcF: central tendency

The *primary endpoint* was the change from baseline of the rate corrected QT interval (Fridericia's corrected QT interval [QTcF]). At both Cycle 1 Day 1 and Cycle 2 Day 1, mean QTcF changes remained stable after initial dosing and after multiple dosing of abiraterone acetate. The mean QTcF change range was from -6.0 to 2.3 msec on Cycle 1 Day 1 and from -11.9 to -1.7 msec on Cycle 2 Day 1. The upper limit of the 90% CI of the mean baseline corrected QTcF change at each post dose time point was below 10 msec for both

Cycle 1 Day 1 (maximum of upper limits = 5.4 msec) and Cycle 2 Day 1 (maximum of upper limits = 2.4 msec).

QTcF: categorical analysis

There were 33 subjects evaluable for ECG analysis on C1D-1 (Cycle 1 Day -1) and C2D1. The number of subjects with at least one QTcF value > 450 msec to ≤ 480 msec on C1D-1, C1 D1, and C2D1 was 11 (33.3%), 9 (28.1%), and 7 (21.2%), respectively. There were no subjects with QTcF values > 480 msec. The number of subjects experiencing a change from baseline in the QTcF meeting specified criteria are summarised below in Table 19. No subjects experienced an increase in QTcF from baseline of ≥ 60 msec.

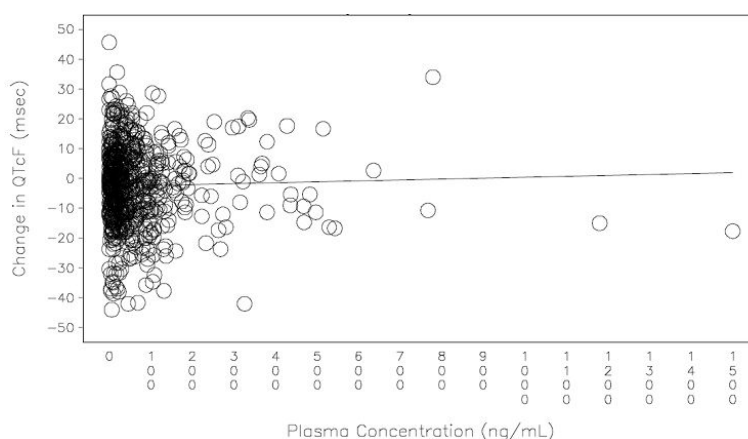
Table 19: Subjects experiencing a change in QTcF categories from baseline.

CATEGORY	GROUP					
	C1D1PRE		C1D1POS		C2D1	
	N	(%)	N	(%)	N	(%)
< 0 msec	17	54.8	1	3.1	4	12.1
≥ 0 TO < 30 msec	12	38.7	31	96.9	27	81.8
≥ 30 TO < 60 msec	2	6.5	0	0.0	2	6.1
≥ 60 msec	0	0.0	0	0.0	0	0.0

PK/PD relationship

Most abiraterone acetate concentrations in plasma were below the LOQ and were not included in the analyses. Consequently, only abiraterone concentrations were included in the PK/PD analysis. To evaluate the PK/PD relationship, an ANCOVA (analysis of covariance) model with effect for subject and plasma concentration as a covariate for the change in QTc was fitted to the data. In addition, the change in QTcF was plotted against the corresponding abiraterone plasma concentration. To further examine the relationship between QTc and C_{\max} , a linear regression model was fitted to the data with QTc as the dependent variable and the corresponding C_{\max} as the independent variable. Individual change from baseline in the QTcF interval and corresponding abiraterone plasma concentrations showed no apparent relationship (see Figure 4, below). The results were similar for the scatter plot of abiraterone C_{\max} versus the change from baseline in QTcF, Day 1 of Cycles 1 and 2 (reference line on a linear mixed effects model with intercept = -2.7289 [p=0.2642] and Slope=0.0036 [p=0.6149]).

Figure 4: Scatter plot of plasma concentration of abiraterone versus change from baseline in QTcF, Day 1 of Cycles 1 and 2 (Study COU-AA-006).



The reference line was based on a linear mixed effects model with intercept = -2.7015 (p=0.0214) and Slope = 0.0031 (p=0.4737).

A linear mixed effects model was fitted to the data with change from baseline in QTcF as dependent variable and abiraterone concentration as a predictor and subject as a random effect. The statistical analysis (Cycle 1 Day 1 and Cycle 2 Day 2) showed no significant correlation between the change in QTcF from baseline and plasma abiraterone

concentration (estimated slope = 0.0031 [SE 0.0043] with associated 90% CI [-0.0040, 0.0102]). Similarly, there was no statistically significant correlation between individual peak abiraterone plasma concentrations (C_{\max}) and the corresponding change from baseline in QTcF at individual T_{\max} (estimated slope = 0.0036 [SE 0.0071] with associated 90% CI [-0.0084, 0.0156]).

Comment: The PD and PK/PD data relating to changes in the QTcF interval do not give rise to concern. The QTcF results for both the central tendency and categorical analyses are consistent. Neither the absolute values nor changes from baseline in QTcF duration are considered to give rise to clinically significant signals (that is, QTcF duration > 500 msec or QTcF increase from baseline \geq 60 msec). The maximum absolute increase in the QTcF from baseline did not exceed 5 msec, and the upper bound of the two sided 90% CI for the baseline adjusted QTcF duration across all post dose time points were below 10 msec on C1D1 and C2D1. The number and percentage of patients with QTcF > 450 msec was lower at steady state (C2D1) than following initial dosing (C1D1). Two subjects on C2D1 had an increase from baseline in QTcF of greater than 30 msec, but less than 60 seconds post dose (C2D1). The increases in QTcF in these two subjects were 35.7 msec and 34.0 msec. No subjects experienced an absolute increase in QTcF of > 480 msec or an increase in QTcF from baseline of \geq 60 msec. No relationship between change in QTcF and abiraterone plasma concentration was observed.

The QT study did not follow the design features of a “Thorough QT/QTc study” outlined in the relevant TGA adopted guidelines.¹⁴ The following reasons were provided by the sponsor for not complying with the guideline: (1) a suprathreshold dose of abiraterone acetate could not be administered to patients because the safety and tolerability of doses exceeding 1 g once daily had not been established; (2) a placebo arm was not possible due to ethical issues associated with prolonged dosing of this mCRPC population with a placebo; and (3) having a positive control arm was not appropriate due to the patients' compromised health state. For these reasons, the sponsor adopted an “Intensive QT design”, as an alternative to a “Thorough QT/QTc study” design. The features of this “Intensive QT design” were: standardised digital 12-Lead Holter recorders were provided to the investigational site; multiple ECG timepoints, with ECGs extracted in triplicate to reduce variability, were included in the study design; a full day of time matched baseline ECGs were collected to reduce the variability of the ECG intervals, including training of the site and having the subject rest before the ECG collection time to reduce both high frequency artefact and HR noise; the overreading cardiologist was blinded to time and date of the recording; and use of the Fridericia's rate correction for the QT interval. Overall, it is considered that in this study the “Intensive QT design” is an acceptable alternative to the “Thorough QT/QTc study” design.

Population PKs and PDs of abiraterone

In addition to the population PK data discussed previously, the study included an exposure-response analysis to:

1. investigate the relationship between abiraterone exposure and PDs of PSA through modelling longitudinal profiles of PSA;
2. identify potential baseline covariates that may influence the the PDs of PSA;

¹⁴ European Medicines Agency, “ICH Topic E 14 The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs: Note for Guidance on the Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Nonarrhythmic Drugs (CHMP/ICH/2/04)”, November 2005, Web, accessed 14 August 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC50002879.pdf>.

3. to identify appropriate PSA dynamic endpoints for modelling OS in patients with CRPC following administration of abiraterone acetate;
4. investigate the relationship between the selected PSA dynamic endpoint and the relative risk of death; and
5. identify other potential prognostic factors associated with OS in patients with CRPC following treatment with abiraterone acetate.

The exposure-response models were developed using only the data from the pivotal Phase III Study COU-AA-301. Analyses were based on subjects who received at least one dose of abiraterone acetate or placebo, with a minimum of one PSA measurement per subject; a total of 1195 subjects were randomised to either abiraterone acetate (n=797) or placebo (n=398). The PSA concentrations from both treatment and placebo arms were used for model development, with a total of 4056 PSA measurements (98.3%) from 1184 subjects (99.1%) being used to develop the base PSA PD model.

A tumor growth inhibition (TGI) model best described the longitudinal PD response of PSA following treatment. Exposure to abiraterone was found to significantly affect the PSA reduction rate (k_{red} , $p < 0.0001$). While both steady state C_{min} and AUC showed an E_{max} type relationship with PSA reduction rate, steady state C_{min} provided a significantly better model fit than AUC and was chosen to be the PK parameter of choice to link to PSA PDs. Further analysis of baseline covariates demonstrated that there was a clear rising trend between k_{red} and baseline testosterone, while a decreasing trend between k_{red} and baseline lactate dehydrogenase (LDH) was observed. The equation below describes the relationship between the PSA reduction rate in the i th subject and their respective covariate values where, k_{red}^0 is the typical PSA reduction rate when exposure to abiraterone is zero and η_i is the difference between the individual and population mean PSA reduction rates on a log scale that is assumed to follow a normal distribution with a mean of zero and variance of ω^2 .

$$k_{red,i} = k_{red}^0 \left(1 + \frac{1.72 C_{min,i}}{4.75 + C_{min,i}} \right) \left(\frac{Testosterone_i}{4.99} \right)^{0.213} \left(\frac{LDH_i}{227} \right)^{-0.669} e^{\eta_i}$$

The parameter estimates of the final model are listed below in Table 20. After adjusting for other covariates (testosterone and LDH), the maximum drug effect on k_{red} was 2.72 times that of the placebo effect, and the EC_{50} was estimated to be approximately 4.75 ng/mL.

Table 20: Parameter estimates of final PK and PD models for PSA.

Parameter	Population Mean (%SE)	Interindividual Variability, %CV (%SE)
PSA Progression Rate		
k_{prog} (day ⁻¹)	0.00815 (1.54)	63.6 (6.48)
PSA Reduction Rate		
k_{red} (day ⁻¹)	0.00687 (2.35)	116 (6.85)
Cancer Resistance		
λ_i (day ⁻¹)	0.00609 (4.25)	78.2 (2.69)
Baseline		
B (ng/mL)	124 (7.03)	166 (16.8)
Drug Effect on k_{red}		
E_{max}	1.72 (24.9)	
EC_{50} (ng/mL)	4.75 (17.8)	
Covariates on k_{red}		
Lactate Dehydrogenase (power)	-0.669 (6.52)	
Testosterone (power)	0.213 (10.84)	
Additive Error	0.084 (6.99)	

CV = coefficient of variation

SE = relative standard error

PSA = prostate specific antigen

E_{\max} = maximum effect

EC_{50} = concentration for 50% of the maximum effect

Semi parametric Cox PH models were used to describe the survival data. The final model included six prognostic factors and the HR (Hazard Ratio), associated 90% CI and associated partially explained variability are summarised below in Table 21. Model predicted post treatment PSA doubling time was strongly associated with survival as it could explain ~13% of the variability in the survival time after adjusting for other baseline covariates in the final model. The concordance index of the final multivariate model was 0.81, indicating a high level of predictive discrimination.

Table 21: Final multivariate Cox PH model estimated for OS in patients with mCRPC.

Prognostic Factor	HR (95% CI)	P-value	EV(%)
Predicted post-treatment PSA doubling time from baseline (month)	0.88 (0.862-0.898)	<0.0001	12.83
Body weight (kg)	0.988 (0.982-0.993)	<0.0001	1.48
Baseline ECOG (2 vs. 0 and 1)	2.007 (1.582-2.546)	<0.0001	1.26
Baseline albumin (g/dL)	0.359 (0.282-0.458)	<0.0001	2.71
Log baseline lactate dehydrogenase (IU/L)	2.748 (2.361-3.199)	<0.0001	5.35
Time since prior chemotherapy (month)	0.993 (0.987-0.999)	0.033	0.18

EV(%) = Partially explained variability in survival time for corresponding variables (calculated as relative gain in prediction accuracy after including the respective variable in the multivariate Cox proportional hazards model)

HR = hazard ratio

CI = confidence Interval

ECOG = Eastern Cooperative Oncology Group

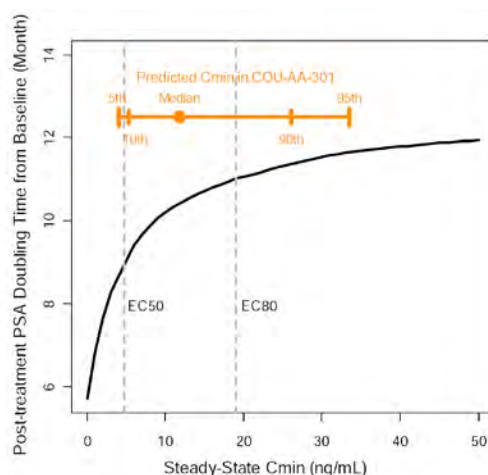
PSA = prostate specific antigen

Note: Prediction error (PE) for null model was 0.352; PE for the final covariate mode: 0.23; the overall relative gain in prediction accuracy (EV%) was 34.5%; The concordance index (C-index) of the final model was 0.81.

Further analysis showed that baseline dehydroepiandrosterone (DHEA) was also a marginally statistically significant factor for patient survival, after adjusting for other covariates in the final survival model (HR=0.996; 95% CI: 0.993, 0.999; p=0.04), although little improvement of the overall model prediction was gained after including the baseline DHEA into the survival model.

The simulated relationship between steady state C_{\min} and model based post treatment PSA doubling time (PSADT) is shown below in Figure 5. Approximately 90% of subjects in the PK subpopulation had a steady state C_{\min} greater than the model estimated EC_{50} value (4.75 ng/mL), which the sponsor states “supports the adequacy of the choice of 1 g dose used in the Phase III Study COU-AA-301”.

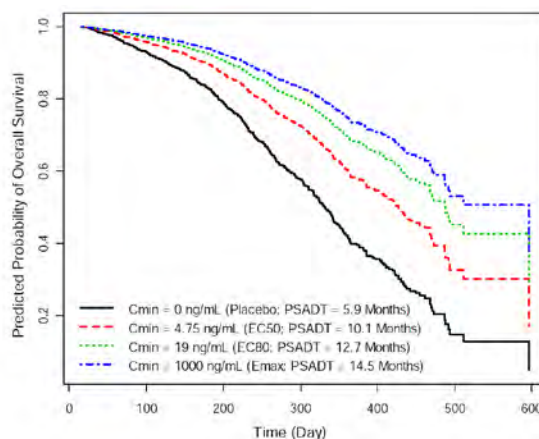
Figure 5: Simulated post treatment PSA doubling time from baseline versus steady state C_{min} .



Note: The simulation was performed for 1000 virtual subjects with baseline testosterone and lactate dehydrogenase values randomly sampled from the Study COU-AA-301 patient population. The black solid curve represents the median prediction of the 1000 simulated subjects.

The predicted probability of OS for a typical subject at different C_{min} concentrations is summarised below in Figure 6.

Figure 6: Predicted probability of OS for a typical subject at different exposure (C_{min}) levels and corresponding post treatment PSA doubling times based on the TGI model.



Note: The typical subject was defined as baseline ECOG = 0 or 1; baseline body weight = 82.6 kg; baseline albumin = 4.1 g/dL; baseline LDH = 227 IU/L; and time since prior chemotherapy = 14 months. All the covariate values are the median of the study population used in the analysis.

Comment: The population PK/PD study was good quality. A TGI model best described the longitudinal PD response of PSA following treatment with abiraterone acetate. Increased exposure to abiraterone significantly increased the rate of PSA reduction, and the exposure-response in PSA dynamics was best described by an E_{max} function of steady state C_{min} with an EC_{50} of 4.75 ng/mL and a maximum effect of 2.72 times that of placebo after adjusting for baseline lactate dehydrogenase and testosterone levels. The model demonstrated that PSA dynamics was an intermediate biomarker of OS in the study population. Compared with other predicted PSA dynamic endpoints, the model predicted post treatment PSA doubling time carried the most prognostic information. Post treatment PSA doubling time could explain ~20% variability in survival time alone in a univariate analysis and ~13% survival variability after adjusting for other baseline covariates. In addition to model predicted post treatment PSA doubling time, low baseline body weight, high baseline ECOG (Eastern Cooperative Oncology Group) score, low baseline albumin

concentrations, high baseline lactate dehydrogenase, short time since prior chemotherapy, and low baseline DHEA levels were also identified as statistically significant prognostic factors as regards OS. Approximately 90% of subjects in the PK subpopulation had a steady state C_{min} greater than the model estimated EC_{50} value of 4.75 ng/mL, following an abiraterone dose of 1 g per day in the pivotal clinical efficacy and safety Study COU-AA-301.

Summary of pharmacodynamics

The information in the following summary is derived from conventional PD studies in humans unless otherwise stated.

Primary pharmacodynamic effects

The pivotal clinical efficacy and safety Study COU-AA-301 included assessment of testosterone, DHEA-S, and androstenedione in a subset of abiraterone acetate and placebo treated subjects with mCRPC using ultrasensitive LC/LC-MS/MS assays. It was found that a commercial testosterone assay had inadequate sensitivity to distinguish the abiraterone acetate group from the placebo group. The ultrasensitive assay found that androgen concentrations were lower after treatment in the abiraterone acetate group compared with the placebo group. These results confirmed the mechanism of action of abiraterone acetate and the drug's ability to reduce androgen concentrations to lower levels than those achieved with medical or surgical castration.

Secondary pharmacodynamic effects

Human data relating to secondary PD effects (ECG changes) were derived from Study COU-AA-006 in patients with mCRPC. The study showed that abiraterone acetate administered as repeat daily dose of 1 g in combination with prednisone 5 mg twice daily had no significant effects on the QTcF interval as assessed by both central tendency and categorical analysis using time matched ECGs and abiraterone plasma concentrations.

Time course of pharmacodynamic effects

The PK/PD study in patients with mCRPC from the pivotal efficacy and safety Study COU-AA-301 showed that a TGI model best described the longitudinal PD response of PSA following treatment with abiraterone acetate. Model predicted post treatment PSA doubling time carried the most prognostic information relating to OS. PSA dynamics was an intermediate biomarker of OS in the study population. Post treatment PSA doubling time could explain ~13% of the survival variability after adjusting for other baseline covariates. In addition to model predicted post treatment PSA doubling time, low baseline body weight, high baseline ECOG score, low baseline albumin, high baseline LDH, short time since prior chemotherapy, and low baseline DHEA levels were also identified as statistically significant prognostic factors relating to OS. Simulated post treatment PSA doubling time increased with increasing steady state abiraterone C_{min} exposure.

Relationship between drug concentration and pharmacodynamic effects

The PK/PD study in patients with mCRPC from the pivotal efficacy and safety Study COU-AA-301 showed that exposure to abiraterone acetate significantly increased the rate of PSA reduction. The study showed that exposure-response in PSA dynamics was best described by an E_{max} function of steady state C_{min} with an EC_{50} of 4.75 ng/mL and a maximum effect of 2.72 times that of the placebo effect, after adjusting for baseline LDH and testosterone levels. Approximately 90% of subjects in the PK subpopulation had a steady state C_{min} greater than the model estimated EC_{50} value, suggesting that 1 g of abiraterone daily is an adequate dose.

Genetic, gender and age related differences in pharmacodynamic response

No data.

Pharmacodynamic interactions

No data.

Evaluator's overall conclusions on pharmacodynamics

The data relating to DHEA, testosterone, and androstenedione concentrations in subjects with mCRPC confirmed the mechanism of action of abiraterone acetate. The PD modelling data showed that simulated post treatment PSA doubling time increased with increasing steady state abiraterone C_{min} exposure. The PD model showed that post treatment PSA doubling time carried the most prognostic information relating to OS. Overall, the PD model identified post treatment PSA doubling time, low baseline body weight, high baseline ECOG score, low baseline albumin serum concentrations, high baseline LDH, short time since prior chemotherapy, and low baseline DHEA levels as statistically significant prognostic factors relating to OS. Abiraterone acetate administered as repeat daily dose of 1 g in combination with prednisone 5 mg twice daily had no significant effects on the QTcF interval in patients with mCRPC as assessed by both central tendency and categorical analysis using time matched ECG analysis and abiraterone plasma concentrations.

Dosage selection for the pivotal studies

The abiraterone acetate dose selected for the pivotal Study COU-AA-301 was 1 g (4 x 250 mg tablets) administered once daily at least 1 h before a meal or 2 h after a meal at any time up to 10.00 pm. The submitted data indicate that this dose is based on findings from two Phase I dose escalating Studies COU-AA-001 and COU-AA-002.

The first Phase I dose escalating Study COU-AA-001, was an open label, single arm, single centre study designed to assess the efficacy, safety, tolerability and PKs of abiraterone acetate in combination with GnRH agonists in chemotherapy naïve patients who had failed hormone therapy. In the dose escalation phase, abiraterone acetate was provided in a capsule formulation and tested at doses of 250 mg (n=3), 500 mg (n=3), 750 mg (n=3), 1 g (n=3) and 2 g (n=3) in order to determine the mean tolerated dose (MTD) based on dose limiting toxicity (DLT). One patient discontinued in each of the 250 mg, 500 mg and 2 g cohorts, and four patients discontinued in the 1 g cohort. There were no DLTs any dose levels. The AEs (adverse events) reported at all dose levels were predominantly toxicity Grades 1 or 2.

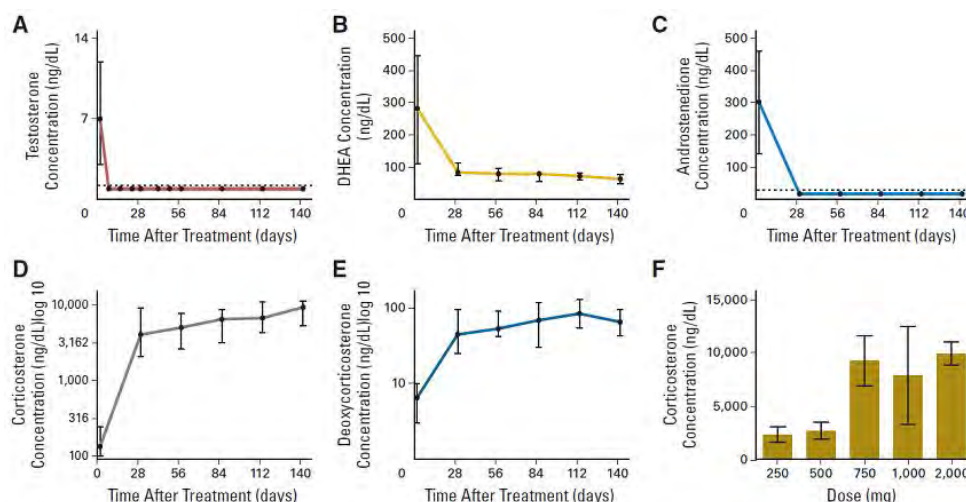
The second Phase I dose escalating study COU-AA-002 was an open label, single arm, study designed to determine MTD, PKs, and food effects in chemotherapy naïve subjects with CRPC who were permitted to have had previous treatment with ketoconazole for treatment of prostate cancer. In the dose escalation phase it was planned to examine abiraterone doses of 250 mg, 500 mg, 750 mg, 1 g and 2 g. However, following a protocol amendment the maximum dose was changed from 2 g to 1 g based on the results from Study COU-AA-001. The Clinical Safety Report stated that this was justified since in Study COU-AA-001 “no DLTs were observed at any dose level up to 2 g/day and the MTD was not reached”, and “a plateau of biological effects” occurred at the 1 g dose level. In Study COU-AA-002, no DLTs were observed at 250 mg, 500 mg, 750 mg or 1 g.

The submission included a publication reporting the Phase I results from Study COU-AA-002.¹⁵ The first author of this study was also the Principal Investigator of Study COU-AA-002. The authors noted that dose escalation was not discontinued as a result of the presence of DLTs, and that abiraterone acetate was well tolerated through to the highest dose level evaluated (1 g/d) with no MTD observed and no apparent toxicity differences among patients who had or had not received prior ketoconazole for the treatment of prostate cancer. On the basis of the safety results, endocrinological results, PKs, and PDs (PSA levels) an abiraterone acetate dose of 1 g was recommended for further study.

The results (“biological effects”) in Study COU-AA-001 stated to support the decision to lower the maximum dose from 2 g to 1 g in the dose escalating phase of Study COU-AA-002. However, relevant pituitary/adrenal/gonadal endocrine levels from the dose escalating stage of Study COU-AA-001 could be identified in a publication describing the Phase I results from this study.¹⁶ This publication was submitted by the sponsor as a reference. The first author of the paper (Dr Gerhardt Attard) was listed in the Study COU-AA-001 protocol as a co investigator, and the Principal Investigator (Dr JS de Bono) was listed as a co author of the published paper.

In Attard et al., abiraterone acetate at all doses increased mean corticosterone concentration, but a plateau effect was observed at Day 28 for 750 mg to 2 g doses (Figure 7). Treatment with abiraterone acetate results in significant suppression of testosterone, DHEA, and androstenedione. Abiraterone was found to crossreact with the DHEA assay used, which may explain the detectable levels of DHEA in abiraterone acetate treated subjects. At every time point on treatment, levels of testosterone and androstenedione in all patients were less than the lower limit of sensitivity of the assay used. The study stated that it was not designed to compare antitumour activity at difference dose levels. The authors recommended a Phase II dose of 1 g daily on the basis of a plateau in the increase of upstream steroids at doses greater than 750 mg daily and “clinical responses observed at all dose levels and of the absence of DLTs”.

Figure 7: Pharmacodynamic effects of abiraterone (from Attard et al.).



Note: Median levels (error bars represent interquartile ranges) for serum levels testosterone (A), DHEA (B) and androstenedione (C). Median levels (log10 values on y-axis; error bars represent interquartile ranges) for serum levels

¹⁵ Ryan CJ, et al. (2010) Phase I clinical trial of the CYP17 inhibitor abiraterone acetate demonstrating clinical activity in patients with castration-resistant prostate cancer who received prior ketoconazole therapy. *J. Clin. Oncol.* 28:1481-1488.

¹⁶ Attard G, et al. (2008) Phase I clinical trial of a selective inhibitor of CYP17, aldosterone acetate, confirms that castration-resistant prostate cancer commonly remains hormone driven. *J. Clin. Oncol.* 26:4653-4571.

of corticosterone (D) and deoxycorticosterone (E). Mean values (error bars represent 1SD) of corticosterone (F) at Day 28 for every dose level (250 mg (n=3); 500 mg (n=2); 750 mg (n=3); 1000 mg (n=6); and 2000 mg (n=3)).

Comment: There are no formal dose ranging studies exploring the efficacy of abiraterone acetate in combination with prednisone/prednisolone for the proposed indication. No MTD was identified in the dose escalating phase of either Study COU-AA-001 or COU-AA-002.

Efficacy

Pivotal efficacy study: Study COU-AA-301

Study Design, objectives, locations, and dates

The *primary objective* was to demonstrate that treatment with abiraterone acetate improves survival among men with mCRPC whose disease had progressed on, or after, one or two chemotherapy regimens, at least one of which contained docetaxel.

The *secondary objectives* were: to further evaluate the safety profile of abiraterone acetate and prednisone; to further characterise the PKs of abiraterone acetate when administered concurrently with prednisone; to further explore the potential utility of circulating tumour cells (CTCs) as a surrogate for clinical benefit; and to evaluate the impact of abiraterone acetate and prednisone on functional status and symptom measures.

The *study design* was a Phase III, multinational, multicentre, randomised, double blind, placebo controlled clinical trial conducted at 147 sites in the USA, Europe, Australia, and Canada. The study included 1195 randomised patients of whom 797 were randomised to abiraterone acetate combined with prednisone/prednisone and 398 to placebo combined with prednisone/placebo. In this Clinical Evaluation Report (CER), reference to the abiraterone acetate group means the abiraterone acetate combined with prednisone/prednisolone group, and reference to the placebo group means the placebo combined with prednisone/prednisolone group.

The protocol specified that one *interim analysis* was to be conducted after approximately 534 deaths had been observed (67% of 797 total planned events), and that one *final analysis* was to be conducted after 797 deaths had been observed. The interim analysis was reviewed by an Independent Data Monitoring Committee (IDMC). The primary purpose of the interim analysis was to ensure the safety of the subjects in the study. However, the IDMC also reviewed the efficacy data at the time of the interim analysis.

The study consisted of a screening period within 14 days prior to Cycle 1 Day 1, a treatment period lasting until documented disease progression or unacceptable toxicity occurred, and a follow up period for survival every three months up to 60 months. While treatment was administered on a continuous schedule, each treatment cycle was 28 days in duration. Safety and dosing compliance were evaluated during Cycle 1 at Day 15, on Day 1 of each subsequent cycle, at treatment discontinuation if applicable, and at the end of study visit.

The study was sponsored by Cougar Biotechnology Inc., which was acquired by, and became a wholly owned subsidiary of Johnson & Johnson Inc. in July 2009. The coordinating investigators were located at the Institute of Cancer Research/Royal Marsden Hospital, Sutton, Surrey UK, and the Memorial Sloan-Kettering Cancer Center, New York, NY, USA. The study was initiated on 8 May 2008 (first subject enrolled) and the date of last subject was enrollment was 28 July 2008. The date of data cutoff was 22 January 2010 for the Clinical Safety Report dated 2 December 2010. The data at this cutoff date was used for the interim analysis, which was also the primary analysis for this study. The submission included an update on OS based on the clinical cut off date of 20 September 2010 in a report issued on 6 December 2010.

The study protocol and amendments were reviewed by an IEC (Independent Ethics Committee) or an IRB (Independent Review Board). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and undertaken in compliance with GCP and applicable regulatory requirements. Subjects or their legally acceptable representatives provided written consent to participate in the study

Comment: Docetaxel combined with prednisone or prednisolone (5 mg twice daily) is the current standard of care in Australia for the treatment of androgen independent (hormone refractory) prostate cancer [Cancer Council Australia/Australian Cancer Network 2010]. There are no approved treatments in Australia for patients with mCRPC who fail to respond to docetaxel. Consequently, treatments which demonstrate a meaningful clinical benefit for these patients would be a significant clinical advance.

The clinical cutoff for the protocol specified interim analysis was reached on 22 January 2010, at which time 552 deaths had been observed (that is, 69% of the 797 planned total events). The database was locked on 11 August 2010 for the IDMC review of efficacy and safety which took place on 20 August 2010. On review of the efficacy data, the IDMC concluded that the prespecified efficacy boundary had been crossed; this was based on 552 deaths observed at the time of analysis (nominal alpha level, 0.0141) and that there was a significant OS benefit for subjects in the abiraterone acetate group compared with the placebo group. Based on these results, the IDMC recommended that patients being treated with placebo be crossed over to abiraterone acetate. The IDMC also noted that at the time of the interim analysis that there were no additional safety signals that would warrant a change in study management. Pursuant to the IDMC recommendations, the study was unblinded and the protocol amended to allow all patients in the placebo group who were either still participating in the treatment phase or who were in the long term survival follow up phase to crossover to abiraterone acetate, provided that they met the criteria specified in the amended protocol. The data were based on the interim analysis. The interim analysis, based on the 522 deaths reached on 22 January 2010, constitutes the primary analysis as a consequence of the study being unblinded with cross-over of subjects from placebo to abiraterone acetate being allowed. The planned final analysis is to occur after 797 total deaths and this analysis has not yet been submitted.

Inclusion and exclusion criteria

Medically or surgically castrated male subjects of at least 18 years of age with mCRPC whose disease had progressed on or after docetaxel based chemotherapy were eligible for the study. Subjects who had been treated with more than two different previous cytotoxic chemotherapy regimens for mCRPC were excluded from the study. The inclusion criteria included: histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology; at least one but not more than two cytotoxic chemotherapy regimens for mCRPC (at least one regimen must have contained docetaxel), and if docetaxel containing chemotherapy was used more than once this was to be considered as one regimen; documented prostate cancer progression as assessed by the investigator with at least one of the following, PSA progression according to the Prostate Specific Antigen Working Group (PSAWG) criteria or radiographic progression in soft tissue or bone with or without PSA progression; ongoing androgen deprivation with serum testosterone < 50 ng/dL (< 2.0 nM); ECOG performance status score of 2 or less; and specified haematology and serum biochemistry parameters.

The exclusion criteria included: serious or uncontrolled coexistent nonmalignant disease, including active and uncontrolled infection; abnormal serum bilirubin levels (that is, serum bilirubin $\geq 1.5 \times$ ULN (Upper Limit of Normal; except for subjects with documented Gilbert's disease), abnormal liver transaminase levels (that is, AST [aspartate aminotransferase] or ALT [alanine aminotransferase] $\geq 2.5 \times$ ULN, or $\geq 5 \times$ ULN with known liver metastases); active or symptomatic viral hepatitis or chronic liver disease; history of pituitary or adrenal dysfunction; clinically significant heart disease defined by

specified criteria; prior therapy with abiraterone acetate or other CYP17 inhibitor(s), or investigational agent(s) targeting the androgen receptor; prior therapy with ketoconazole for prostate cancer; or medical conditions or comorbidities that could have interfered with a subject's participation in the study.

In addition to specified inclusion and exclusion criteria the study also included criteria for treatment discontinuation. These included: disease progression characterised by PSA progression, radiographic progression, and symptomatic or clinical progression; initiation of new anticancer treatment; sustained AEs; dosing noncompliance; subject choice (withdrew consent); or administration of prohibited medications. Subjects who withdrew from the study were not replaced.

Study treatments

Abiraterone acetate was supplied as 250 mg tablets. In order to maintain the study blind, placebo was supplied by the sponsor as a tablet matching abiraterone acetate tablets in size, colour, and shape. Open label prednisone 5 mg tablets were provided by the sponsor or prescribed. In regions where prednisone was not marketed, prednisolone was substituted.

All subjects were required to commence treatment within 72 h of randomisation. All subjects were instructed to take 4 tablets (abiraterone acetate or placebo) at least 1 h before a meal or 2 h after a meal any time up to 10.00 pm each day. If abiraterone acetate dose or placebo was missed, subjects were instructed to omit the dose. Subjects were also instructed to take 5 mg prednisone/prednisolone twice daily. Prednisone/prednisolone did not need to be taken at the same time as abiraterone acetate or placebo. If a dose of prednisone/prednisolone was missed subjects were instructed to omit the dose. Treatment was administered continuously with each treatment cycle being 28 days.

Subjects were to receive treatment until documented disease progression defined as having: (1) radiographic progression; (2) PSA progression, and (3) symptomatic or clinical progression. Study treatment could be discontinued in the event of unacceptable toxicity or for initiation of new antitumor therapy at the discretion of the investigator, for dosing noncompliance, subject choice, or for administration of prohibited medications.

If a dose reduction of study medication was indicated, then subjects were instructed to take 3 tablets daily (that is, 750 mg of abiraterone acetate). If a further dose reduction was indicated, then subjects were instructed to take 2 tablets daily (that is, 500 mg of abiraterone acetate). Up to 2 dose reductions were allowed, but recurring toxicities at the 500 mg daily dose resulted in the subject being removed from the study. Re-initiation of study medication after resolution of AEs was to be discussed with and approved by the sponsor's medical monitor.

The study included protocols for amending study medication in cases of hypokalaemia, hypertension, oedema, hepatotoxicity, and non mineralocorticoid related toxicities.

Prior and concomitant therapy

Investigators were informed that abiraterone acetate may *possibly interact* with concomitant medications, particularly those that are metabolised or activated by CYP 2C19, 2D6, and 1A2. The use of any concurrent medication (prescription or over the counter) from screening through the study treatment phase was to be recorded on the relevant CRF along with the reason for treatment. Concurrent enrollment in another clinical investigational drug or device study was prohibited.

Permissible medications included: Luteinizing hormone releasing hormone (LHRH) agonists to maintain testosterone <50 ng/dL (mandatory for subjects who did not undergo orchiectomy); conventional multivitamins, selenium, and soy supplements; additional systemic glucocorticoid administration such as "stress dose" glucocorticoid if clinically indicated for a life threatening medical condition; bisphosphonates were allowed only if

subjects were receiving the medications prior to Study Day 1; and transfusions and haematopoietic growth factors were permitted per institutional practice guidelines. If the permissibility of a specific drug/treatment was in question, the sponsor was to be contacted.

Permissible interventions including:

- palliative radiation: course of involved field radiation (single or multi fraction) to a single site; radiation to more than one site of disease was not permitted;
- bisphosphonates: addition of a bisphosphonate or change to the type of bisphosphonate was only allowed if a new skeletal related event or bone progression was documented; and
- glucocorticoids: an increase in the dose of prednisone/prednisolone or addition of a more potent glucocorticoid to treat prostate cancer related signs and symptoms, such as fatigue and pain, was to be considered a disease progression event

Prohibited medications included: 5 α -reductase inhibitors; chemotherapy; immunotherapy; ketoconazole; diethylstilbestrol; PC-SPES (herbal product)¹⁷; other preparations such as saw palmetto (berry extract) thought to have endocrine effects on prostate cancer; radiopharmaceuticals such as strontium (⁸⁹Sr) or samarium (¹⁵³Sm); and spironolactone.

Comment: Abiraterone acetate was administered at least 1 h before or 2 h after a meal. As discussed previously in the PK section of this CER, this particular modified fasting regimen has not been investigated in a fed fasting PK study. The pivotal fed fasting PK study showed that abiraterone acetate administered with food increased exposure (AUC levels) to abiraterone 5 to 10 fold (depending on the fat content of the meal) relative to fasting administration (that is, following a minimum of 10 h overnight fast with no food for 4 h after administration).

The control treatment included prednisone/prednisolone combined with placebo rather than placebo alone. This is considered to be acceptable as the addition of prednisone/prednisolone reduces the risk of mineralocorticoid related toxicities resulting from the pharmacological effects of abiraterone acetate.

The prespecified criteria for modifying treatment of the study drug in cases of hypokalaemia, hypertension, oedema, hepatotoxicity or non mineralocorticoid related toxicities were acceptable. The criteria specified that study treatment was to be discontinued immediately, and not re-started, if Grade 4 AST, ALT, or bilirubin abnormalities occurred (that is, increase in AST or ALT to >20 x ULN; increase in total bilirubin to >10 x ULN). In addition, if hypokalaemia, hypertension, and non mineralocorticoid related toxicities recurred despite optimal management and two dose level reductions the study medication was to be discontinued. The dose modifying criteria for the toxicities did not allow for dose reductions of the study drug below 500 mg once daily, with the first dose reduction being to 750 mg and the second to 500 mg once daily.

Criteria for discontinuing due to disease progression

To discontinue study treatment, all three of the following criteria were required:

1. *PSA progression* as defined by PSAWG eligibility criteria (25% increase over baseline) with minimum PSA increase of 5 ng/mL.
2. *Radiographic progression* defined by at least one of the following:

¹⁷ DiPaola RS, et al. (1998) Clinical and biological activity of an estrogenic herbal combination (PC-SPES) in prostate cancer *N. Engl. J. Med.* 339: 785-791.

- a. Progression on bone scans with ≥ 2 new lesions not consistent with tumour flare, confirmed on a second bone scan ≥ 6 weeks later that shows ≥ 1 additional new lesion.
 - b. Soft tissue disease progression by modified RECIST (Response Evaluation Criteria In Solid Tumours) criteria (baseline LN [lymph node] size must be ≥ 2.0 cm to be considered target or evaluable lesion).
3. *Symptomatic or clinical progression* defined by one of the following:
- a. Pain progression: Worsening of pain due to metastatic bone disease defined as an increase of $\geq 30\%$ in the worst pain over the past 24 h on the BPI-SF (Brief Pain Inventory Short Form) numeric rating scale observed at two consecutive evaluations 4 weeks apart without decrease in analgesic usage score, or an increase in analgesic usage score $\geq 30\%$ observed at two consecutive evaluations 4 weeks apart; to qualify as progression, the patient must have a BPI-SF score ≥ 4 .
 - b. Development of a SRE (skeletal related event) defined as pathologic fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.
 - c. Any increase in prednisone or prednisolone dose or a change to a more potent glucocorticoid such as dexamethasone, to treat prostate cancer related signs and symptoms, such as fatigue and pain is considered a disease progression event.
 - d. Treating physician decides to initiate new systemic anti cancer therapy.

Comment: The sponsor postulated that, consistent with the rationale for continuation of LHRH analogues after the development of mCRPC, prostate cancer cells that are growth arrested following treatment with abiraterone acetate are likely to resume proliferating when the drug is discontinued and that continued abiraterone acetate therapy may potentially slow down the progression of disease in a subpopulation of tumour cells that retain sensitivity to androgen deprivation. Based on this consideration, study treatment was continued until both radiographic and PSA progression had occurred, accompanied by signs of clinical progression such as pain progression or skeletal related events or if the treating physician decides to initiate new systemic anti cancer therapy. These criteria were intended to maintain study treatment with asymptomatic radiographic or PSA progression, given the absence of approved agents or alternative treatment options available for protocol participants who have failed both castration and chemotherapy.

Efficacy variables and outcomes

The *primary efficacy endpoint* was *OS*, measured from the date of randomisation to the date of 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. Survival status was assessed at 3 month intervals up to 60 months, and could be collected by telephone interviews or chart review.

The *secondary efficacy endpoints* were time to *PSA progression*, *radiographic progression free survival (PFS)*, and *PSA response rate*.

- *Serum PSA measurements* were undertaken at a central laboratory and were assessed at screening; Cycle 1 Day 1; on Day 1 of Cycles 4, 7, and 10; every third cycle thereafter; at treatment discontinuation; and at the end of study visit. PSA measurements were analysed by the PSAWG criteria.
- *Tumour measurements* (CT [computed tomography] scan, MRI [magnetic resonance imaging], bone scans, other imaging procedures) and response evaluation were assessed at screening; on Day 1 of Cycles 4, 7, and 10; and at treatment discontinuation, if applicable. Tumor response was assessed utilising imaging measurements as defined by modified RECIST criteria.

- *Radiologic assessment* of SREs (pathological fracture, spinal cord compression) was undertaken as needed.

There were a number of prespecified *subgroup analyses* planned for the primary efficacy endpoint.

Comment: The primary and secondary endpoints are satisfactory. These endpoints are considered to be reliable measures of clinical benefit in patients with mCRPC. In addition, the OS and PFS efficacy endpoints meet the relevant TGA adopted guideline relating to the clinical assessment of anticancer medicines.¹⁸ This guideline states that “acceptable endpoints (for Phase III confirmatory studies) include OS and PFS/DFS (progression free survival/disease free survival). If PFS/DFS is the selected primary endpoint, OS should be reported as a secondary and vice versa”. The other efficacy endpoints and the subgroup analyses of the primary efficacy endpoint (OS) are considered to be exploratory. The assessment of the PSA using PSAWG criteria is an acceptable and standard method, and the use of a central laboratory to measure PSA reduces the potential for measurement bias. The imaging methods used to measure tumour size are considered to be acceptable, as is the assessment of tumour response defined by modified RECIST criteria.

Sample size

The study stated that patients with mCRPC after disease progression on or after docetaxel based chemotherapy are expected to have an estimated median OS of 12 months. The planned sample size of approximately 1158 subjects (772 [abiraterone acetate group]; 386 [placebo group]) provided 85% power to detect a 20% decrease in the risk of death for the abiraterone acetate treated group (HR = 0.80). The sample size was calculated by assuming: a median survival of 15 months for the abiraterone acetate group and a median survival of 12 months for the placebo group; a two tailed significance level of 0.05; an enrollment period of approximately 13 months; and a study duration of ~30 months to observe the required 797 total events.

Comment: The assumptions on which the calculation of sample size is based are acceptable. The specified additional median survival time of three months for subjects in the abiraterone plus prednisone group is small but is considered to be clinically meaningful in patients with mCRPC who have received prior chemotherapy containing a taxane.

Randomisation and blinding methods

Subjects were stratified according to baseline ECOG performance status score (0-1 versus 2); worst pain over the past 24 h on the BPI-SF (0-3 [absent] versus 4-10 [present]); one versus two prior chemotherapy regimens; and type of disease progression (PSA progression only versus radiographic progression with or without PSA progression).

The randomisation schedule was generated by an independent statistician. The InForm system generated a subject specific code that was entered into a centralised Interactive Web Response System (IWRS). The IWRS assigned unique subject identification numbers and following stratification subjects were randomly assigned to abiraterone acetate or placebo in a 2:1 ratio. All subjects, family members, study personnel (at the study site, the sponsor, or participating CRO [Contract Research Organisation]), and members of the IDMC were to remain blinded to treatment assignment until completion of the study with the following exceptions: independent biostatistician and statistical programmer; the

¹⁸ European Medicines Agency, “Committee for Medicinal Products for Human Use (CHMP): Guideline on the Evaluation of Anticancer Medicinal Products in Man (CPMP/EWP/205/95/Rev.3/Corr.2)”, 14 December 2005, Web, accessed 14 August 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/12/WC500017748.pdf>.

IDMC only if unblinding became necessary; laboratory personnel performing blood serum concentration assays for PK analysis and other laboratory tests, such as testosterone and dihydroepiandrosterone sulphate (DHEA-S), in order to avoid futile PK analysis of placebo specimens that did not contain abiraterone.

Comment: Randomisation and blinding were satisfactory. The 2:1 randomisation ratio resulted in twice as many patients being assigned to treatment with abiraterone acetate than with placebo. The stratification factors were satisfactory and mitigated the chance of bias between the two treatment groups resulting from imbalances in patients with different prognostic factors.

Statistical methods

Interim analysis

The protocol specified that an interim analysis of the primary efficacy endpoint (OS) using the intention to treat (ITT) population was to be conducted after approximately 534 deaths had been observed (that is, 67% of 797 planned total events). The stopping boundaries controlled the overall two sided level of significance at an alpha of 0.05, and provide 85% power to detect a HR (abiraterone acetate:placebo) of 0.80. Under the assumption of exponentially distributed survival times, a HR of 0.80 equates to a 25% improvement in median OS for the abiraterone acetate group compared with the placebo group. The O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending function was used for the efficacy boundary. The cumulative alpha spent was 0.0124 and 0.0500 for the interim and final analysis, respectively. Operating characteristics for the stopping boundaries are summarised below in Table 22.

Table 22: Stopping boundaries for the interim and final analyses (Study COU-AA-301).

Variable	Analyses	
	Interim	Final
Observed OS events	534	797
Anticipated time to analysis (months)	19	30
Anticipated enrollment (n)	1,158	1,158
Efficacy boundary (HR)	0.7975	0.8628
Cumulative stopping probability under H_0	0.0124	0.0500
Cumulative stopping probability under H_A	0.4864	0.8500

HR=Hazard ratio; H_0 = 0% improvement; H_A = 25% improvement.

Comment: The methodology adopted for the planned interim analysis is considered to be acceptable. The key features of the analysis were: prespecified in the protocol; based on a group sequential design; planned to be undertaken after approximately 67% of the total deaths had occurred; stopping boundaries satisfactorily controlled overall statistical significance and power; method adopted to define the efficacy boundaries is well known and commonly used; and a IDMC was used to evaluate the results. Following review of the interim analysis the study was unblinded and patients in the placebo group allowed to crossover to placebo as the IDMC considered that there was a significant OS benefit for subjects in the abiraterone acetate group compared with the placebo group.

General statistical analysis

The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics. The ITT population included all subjects randomised according to assigned treatment group, regardless of the actual treatment received. The safety population included all subjects in the randomised population who received any study medication.

OS was the primary efficacy endpoint, and the distribution of OS and median OS were estimated for each treatment group using the Kaplan-Meier method. Statistical inference was evaluated according to the group sequential testing design using a stratified log-rank test. The Cox proportional hazards model with prespecified covariates was performed as a

supportive multivariate analysis. For the secondary efficacy endpoints, comparisons between treatment groups were conducted according to Hochberg's test procedure to adjust for multiple testing. For other efficacy endpoints, no adjustments for multiple testing were planned, and each comparison between treatment groups was carried out at a nominal alpha of 0.05.

Planned sensitivity analyses of the primary (OS), secondary and other efficacy endpoints (pain palliation rate and time to pain progression) were undertaken to assess the robustness and consistency of the endpoints. The sensitivity analyses were based on nonstratified analysis of the primary endpoint OS, analysis of the pain palliation rate (percent of pain reduction in increments of 10%), and analysis of time to pain progression. The results from these analyses were not adjusted for multiple testing, and each analysis was compared at a nominal significance level of 0.05.

For the subgroup analyses, the HR within each subgroup was estimated using a Cox proportional hazards non stratified model. Results from these analyses were considered to be consistent with the primary analysis if the 95% CI for the HR within a subgroup included the point estimate for the primary analysis.

Comment: The statistical methods are considered to be satisfactory. The methods are conventional and appropriate. Hochberg's method used to adjust for multiplicity of testing of the secondary efficacy endpoints is a standard and acceptable method. The analyses of the other (that is, non primary/non secondary) efficacy endpoints were not adjusted for multiplicity, with the nominal significance level for each comparison being 0.05. In addition to the specified sensitivity analyses, the submission also included a sensitivity analysis excluding subjects with major protocol deviations. This analysis appears to have been required by the FDA.

Participant flow

The study included 1195 subjects and these subjects comprised the ITT population. Of the 1195 subjects, 10 did not receive study treatment, resulting in a safety population of 1185 treated subjects. The specific reason for not having received study treatment was documented for four of the ten subjects: one had a cardiac event during the screening phase; two did not meet study eligibility criteria; and one was confirmed to have brain metastases during the screening phase. The distribution of randomised subjects by the IWRS stratification factors is summarised below in Table 23, and the reasons for treatment discontinuation (per sponsor review) are summarised below in Table 24.

Table 23: Subject disposition by stratification factors; ITT population (Study COU-AA-301).

Stratification Factor	AA (N=797)	Placebo (N=398)	Total (N=1195)
ECOG performance status			
0 or 1	712 (89.3%)	354 (88.9%)	1066 (89.2%)
2	85 (10.7%)	44 (11.1%)	129 (10.8%)
Pain			
Present	353 (44.3%)	175 (44.0%)	528 (44.2%)
Absent	444 (55.7%)	223 (56.0%)	667 (55.8%)
Number of prior cytotoxic chemotherapy regimens			
1	572 (71.8%)	285 (71.6%)	857 (71.7%)
2	225 (28.2%)	113 (28.4%)	338 (28.3%)
Evidence of disease progression			
PSA only	261 (32.7%)	134 (33.7%)	395 (33.1%)
Radiographic progression with or without PSA progression	536 (67.3%)	264 (66.3%)	800 (66.9%)

Table 24: Treatment discontinuations, per sponsor review; safety population (Study COU-AA-301).

	AA (N=791)	Placebo (N=394)
Subjects treated	791 (100.0%)	394 (100.0%)
Treatment discontinued	569 (71.9%)	340 (86.3%)
Treatment ongoing	222 (28.1%)	54 (13.7%)
Reasons for discontinuation		
Disease progression	219 (27.7%)	112 (28.4%)
Initiation of new anticancer treatment	107 (13.5%)	64 (16.2%)
Adverse event	98 (12.4%)	70 (17.8%)
Withdrawal of consent to treatment	70 (8.8%)	40 (10.2%)
Investigator discretion	36 (4.6%)	27 (6.9%)
Death	21 (2.7%)	9 (2.3%)
Other	7 (0.9%)	10 (2.5%)
Subject choice	5 (0.6%)	4 (1.0%)
Administration of prohibited medication	3 (0.4%)	1 (0.3%)
Dosing noncompliance	3 (0.4%)	3 (0.8%)

Protocol deviations

The sponsor's medical monitor assessed all protocol deviations prior to treatment unblinding in order to identify those with the potential to affect the evaluation of efficacy or safety. Major protocol deviations were reported in a 15.2% (n=182) of all subjects: 15.3% (n=122) and 15.1% (n=60) of subjects in the abiraterone acetate and placebo groups, respectively (Table 25). Enrollment and entry criteria deviations were the most common, accounting for 8.2% of subjects in the abiraterone acetate group and 8.5% of subjects in the placebo group. The most frequent criterion violated was the use of prior ketoconazole (1.5% of subjects in both groups). Other criteria were violated in ≤ 1% of subjects. The use of prior chemotherapy containing docetaxel was not documented for 1 subject who was randomly assigned to the placebo group, but never received study medication.

Table 25: Summary of major protocol deviations; ITT population (Study COU-AA-301).

	AA (N=797)	Placebo (N=398)	Total (N=1195)
Total no. subjects with a deviation	122 (15.3%)	60 (15.1%)	182 (15.2%)
Enrollment and entry criteria	65 (8.2%)	34 (8.5%)	99 (8.3%)
Prohibited concurrent medication(s)	41 (5.1%)	16 (4.0%)	57 (4.8%)
Investigational product ^a	11 (1.4%)	4 (1.0%)	15 (1.3%)
Tests/assessments/exams/procedures	8 (1.0%)	5 (1.3%)	13 (1.1%)
Treatment discontinuation not followed per protocol sect. 6.8	1 (0.1%)	6 (1.5%)	7 (0.6%)

AA=abiraterone acetate; ITT=intent-to-treat; sect.=section

^a This category is comprised of the following deviations: subject missed >14 days per 28-day cycle of study medication in the absence of toxicity, dosing error during treatment, and drug dispensing error.

Note: Percentages calculated with the number of subjects in each group as denominator. Only sponsor-derived major deviations are tabulated.

Treatment compliance

Drug logs of investigational tablets dispensed and returned were maintained throughout the study period. Compliance with study medication administration was assessed on Day 1 of every treatment cycle. In both treatment groups, > 90% of subjects had 90% or higher treatment compliance for abiraterone acetate or placebo. In both treatment groups, > 95% of subjects had 90% or higher treatment compliance for prednisone/prednisolone. Treatment discontinuation because of dosing noncompliance was infrequent, occurring in 0.4% of subjects in the abiraterone acetate group and 0.8% of subjects in the placebo group.

Dose modification of study medication (reductions and interruptions)

The proportion of subjects requiring one or two *dose reductions* in the abiraterone acetate group was 2.9% (n=23) and 0.6% (n=5), respectively, and in the placebo group the

corresponding proportions were 1.3% (n=5) and 0%, respectively. The reasons for dose reductions (abiraterone acetate versus placebo) were: AE or toxicity (1.6% versus 0.3%); SAE (serious adverse event) or hospitalisation (0.3% versus 0%); restart dosing (1.6% versus 0.8%); and other (0.4% versus 0.3%)

The proportion of subjects requiring *dose interruptions* was 17.2% (n=137) and 16.5% (n=65) in the abiraterone acetate and placebo groups, respectively. The majority of subjects requiring dose interruptions had only one dose interruption. The main reasons for dose interruptions (abiraterone acetate versus placebo) were: AE or toxicity (8.8% versus 8.4%); SAE or hospitalisation (7.7% vs 6.9%); and other 2.9% versus 3.0%.

Comment: The stratification factors in the ITT population were well balanced between the two groups. However, the CSR (Clinical Safety Report) indicates that differences were noted for some subjects relating to the category of the ITT stratification factor as recorded in the IWRS randomisation system compared with the final data entered in the eCRF (electronic Case Report Form), and that after randomisation these differences were corrected by the investigators. Overall, there were 203 (17.0%) subjects for whom there were differences in the ITT stratification factors as recorded in the IWRS randomisation system compared with the final data entered in the eCRF: 18.2% (145/797) in the abiraterone acetate group and 14.6% (58/398) in the placebo group. These differences (abiraterone acetate group versus placebo group) related to the number of prior cytotoxic chemotherapy regimens (6.8% versus 6.0%), evidence of disease progression (6.1% versus 5.3%), pain (5.9% versus 4.5%), and ECOG performance status (1.5% versus 0.3%). In view of the recording differences, sensitivity analysis of the primary efficacy endpoint (OS) was conducted using stratification factors based on eCRF data and the results of these analyses were similar to those based on the IWRS data.

Treatment discontinuations (per sponsor review) occurred more commonly in the placebo group (86.3%) than in the abiraterone acetate group (71.9%). The most common reason for treatment discontinuation in both treatment groups was disease progression, which occurred with a similar frequency in both the abiraterone acetate group (27.7%) and the placebo group (28.4%). The most notable difference between the two groups was in discontinuations due to AEs which occurred more frequently in the placebo group (17.8%) than in the abiraterone acetate group (12.4%). The sponsor found that the reasons for discontinuation of study treatment were not recorded consistently across study centre, particularly with respect to disease progression. Therefore, to improve consistency and provide a more accurate representation of study data, the sponsor medically reviewed the blinded data for each subject and recategorised the reasons for discontinuation accordingly. The major difference between the two reviews was the greater incidence of AEs resulting in treatment discontinuation for both treatments in the non sponsor review (18.1% and 21.6% in the abiraterone acetate and placebo groups, respectively).

Baseline data

The baseline demographic characteristics of the treatment groups were well balanced, as were baseline disease characteristics, baseline laboratory values (PSA, Hb [haemoglobin], LDH, ALP), baseline BPI-SF pain scores, and baseline analgesic usage scores.

In both groups, the median age was 69 years, 28% were ≥ 75 years, and ~93% were White. In both groups, the mean (SD) weight was 84.3 (16.3) kg, the mean (SD) height was 175 (7) cm, and the mean (SD) BSA was 2.02 (0.22) m². The median time since initial diagnosis to first dose was longer in the abiraterone acetate group (2303 days) than in the placebo group (1982 days).

Most subjects (abiraterone acetate versus placebo) had a baseline ECOG performance status score of 0 or 1 (89.7% versus 88.7%), radiographic progression with or without PSA progression (70.1% versus 68.6%), bone metastases (89.2% versus 90.4%), and Gleason score ≥ 8 at initial diagnosis (51.1% versus 54.0%). In both groups, 45% of

subjects had pain present at baseline. Liver metastases were reported more commonly in the abiraterone acetate group (11.3%) than in the placebo group (7.6%), as were lung metastases (13.0% and 11.4%, respectively). Erectile dysfunction at baseline was reported in 6.0% of subjects in the abiraterone acetate group and 7.3% of subjects in the placebo group.

Baseline median PSA concentrations were high in both groups (129 and 138 ng/mL in the abiraterone acetate and placebo groups, respectively [normal range: 0 to 4 ng/mL]). Median Hb concentrations were indicative of mild anaemia in both groups (11.8 g/dL in both groups [normal range: 12.5 to 17 g/dL]). Baseline median LDH and ALP concentrations were elevated in both groups (LDH: 223 and 238 IU/L in the abiraterone acetate and placebo groups, respectively [normal range: 100 to 250 IU/L]), while the median ALP in both groups was within the normal range (134 IU/L [normal range: 25 to 160 IU/L]). Mean baseline BPI-SF pain and analgesic usage scores of the 2 groups were similar.

Concomitant and subsequent therapies

Prior prostate cancer therapies

The use of prior therapies was well balanced between the two treatment groups. All patients in both treatment groups had received one or two prior cytotoxic chemotherapy regimens; one prior regimen had been used in 70.0% of subjects in the abiraterone acetate group and 69.1% in the placebo group with the corresponding figures for two regimens being 30% and 30.9%. The inclusion criteria specified that subjects were to have received at least one regimen that contained docetaxel, and if docetaxel containing chemotherapy was used more than once, this was considered as one regimen and was only counted once. Prior use of docetaxel was reported in all subjects in both treatment groups. The next most frequently used chemotherapeutic agent in both treatment groups was mitoxantrone (13.3% [105/791] and 14.5% [57/398] in the abiraterone acetate and placebo groups, respectively).

Prior use of GnRH analogues was reported in 94.7% (782/791) of subjects in the abiraterone acetate group and 94.9% (374/394) of subjects in the placebo group. Prior use of anti androgens was reported in 81.5% (645/791) subjects in the abiraterone acetate group and 82.0% (323/394) of subjects in the placebo group, with the most commonly used agent in both groups being bicalutamide. There were three subjects who did not receive prior hormonal therapy (all three were randomised but did not receive treatment and were determined to be screen failures, and were only included in the ITT population).

Prior use of other medications

The most frequently used non prostate cancer medications were analgesics (68.0% [538/791] and 67.5% [266/394] of subjects in the abiraterone acetate and placebo groups, respectively). The next most commonly used medications were “drugs for treatment of bone diseases”, with these being almost exclusively bisphosphonates (bisphosphonates: 41.2% [326/394] and 44.2% [174/791] of subjects in the abiraterone acetate and placebo groups, respectively). Other medications used in ~30% of subjects in both treatment groups were protein pump inhibitors, anti thrombotic agents, oral glucocorticoids, lipid modifying agents (predominantly HMG CoA reductase inhibitors), mineral supplements, vitamins, anti inflammatory and anti rheumatic agents, and agents acting on the rennin angiotensin system. Drugs used for the treatment of erectile dysfunction had been used by 1.1% subjects in the abiraterone acetate group and 2.0% of subjects in the placebo group.

Concomitant therapies used during the study

Concomitant medications during the study were taken by all subjects in both treatment groups. GnRH analogues were taken by 92.3% (737/791) of subjects in the abiraterone acetate group and 93.4% (368/394) of subjects in the placebo group. Except for those subjects who had a history of orchiectomy, subjects were to continue to receive GnRH analogues during the study. All but three subjects were medically or surgically castrate. The most common class of concomitant non endocrine medication taken by subjects in both groups was natural opium alkaloids (62.1% [491/791] and 67.3% [265/394] of subjects in the abiraterone acetate and placebo groups, respectively). Overall, the general pattern of concomitant medication use during the study was similar to the prior use of medication.

Subsequent cancer therapy

In the abiraterone acetate group, 25.8% (206/797) of subjects received subsequent anti cancer therapy compared with 35.7% (142/398) of subjects in the placebo group. Of these, 18.9% (151/797) of subjects in the abiraterone acetate group and 22.4% (89/142) of subjects in the placebo group received subsequent chemotherapy, with the most commonly used agent being docetaxel (8.3% and 9.3%, respectively). Radiation therapy was received by 7.0% (56/797) of subjects in the abiraterone acetate group and 9.8% (39/398) of subjects in the placebo group. The percentage of subjects in the abiraterone acetate and placebo groups, respectively, receiving other anti cancer treatments were: 5.3% (42/797) and 9.5% (39/398) for second line hormone treatment (primarily ketoconazole); 2.8% (22/797) and 5.0% (20/398) for investigational agent; 0.9% (7/797) and 2.3% (9/398) for biologic therapy; and 0.1% (1/797) and 0.3% (1/398) received an immunomodulatory agent (revlimid or thalidomide).

Results for the primary efficacy outcome

At the time of the clinical data cutoff for the interim analysis (22 January 2010), 552 deaths had been observed: 333 (41.8%) in the abiraterone acetate group and 219 (55.0%) in the placebo group. At the time of the interim analysis, the median follow up time for all subjects was 12.8 months. The interim analysis is the primary analysis due to the study being unblinded after this analysis and patients in the placebo group being offered the opportunity to cross-over to abiraterone acetate. The stratified analysis for OS (the primary efficacy endpoint) in the ITT population are summarised in Table 26, and the Kaplan-Meier survival curves are provided below in Figure 8.

Table 26: Overall survival, stratified analysis; ITT population (Study COU-AA-301).

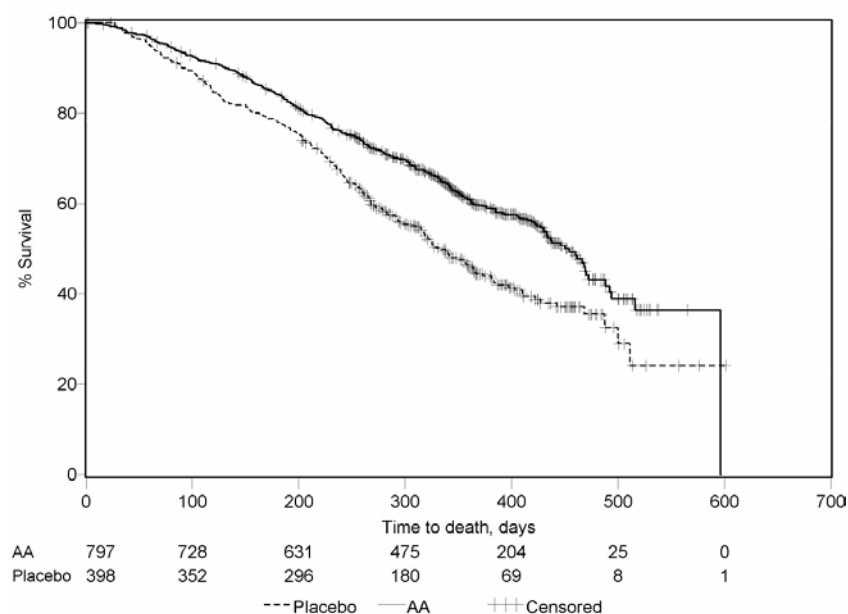
	AA (N=797)	Placebo (N=398)
Subjects randomized	797	398
Death	333 (41.8%)	219 (55.0%)
Censored	464 (58.2%)	179 (45.0%)
Overall survival (days) ^a		
25th percentile (95% CI)	252.0 (226.0, 275.0)	202.0 (169.0, 224.0)
Median (95% CI)	450.0 (430.0, 470.0)	332.0 (310.0, 366.0)
75th percentile (95% CI)	596.0 (NE, NE)	511.0 (487.0, NE)
Range	(1+, 596)	(1+, 601+)
6-month survival rate (95% CI)	0.840 (0.813, 0.864)	0.777 (0.733, 0.815)
12-month survival rate (95% CI)	0.597 (0.559, 0.632)	0.448 (0.394, 0.500)
18-month survival rate (95% CI)	0.364 (0.284, 0.445)	0.241 (0.134, 0.365)
p value ^b	< 0.0001	
Hazard ratio (95% CI) ^c	0.646 (0.543, 0.768)	

^a Survival time is calculated as days from date of randomization to date of death from any cause. Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.

^b p value is from a log-rank test stratified by ECOG performance status score (0-1, 2), pain score (absent, present), number of prior chemotherapy regimens (1, 2), and type of progression (PSA only, radiographic).

^c Hazard Ratio is from a stratified proportional hazards model. Hazard ratio <1 favours AA.

Figure 8: Overall survival, ITT population (Study COU-AA-301).



The results of the sensitivity analysis of OS using stratification factors based on eCRF data were: HR = 0.653 (95%CI: 0.549, 0.776); $p < 0.001$. These results are similar to those for the OS analysis using stratification factors based on IWRS data (that is, the primary analysis [Table 26]).

The results for the sensitivity analysis of OS using non stratified data were: HR = 0.664 (95% CI: 0.560, 0.788); $p < 0.0001$. These results were similar to those for the stratified analysis (that is, primary analysis [Table 26]).

The results for the sensitivity analysis of OS excluding 182 patients who had a major protocol deviation at the clinical cutoff data of 22 January 2010, showed that the HR was 0.636 (95%CI: 0.527, 0.769); $p < 0.0001$. In this sensitivity analysis, there had been 463 deaths (58% of the planned number for the final analysis) in 1013 patients without a major protocol violation: 41.0% (277/675) and 55.0% (186/338) in the abiraterone acetate and placebo groups, respectively. The median survival improved by 38% (450 days [14.8 months] in the abiraterone acetate group and 327 days [10.7 months] in the placebo group).

In the updated survival analysis at the clinical cutoff data of 20 September 2010, there had been a total of 775 deaths (97% of planned number for the final analysis), with 501 (62.9%) in the abiraterone acetate group and 274 (68.8%) in the placebo group with a median follow up of 20.2 months. The HR was 0.740 (95%CI: 0.638, 0.859); $p < 0.0001$. The median survival improved by 41% in the abiraterone group compared with the placebo group (482 days [15.8 months] and 341 days [11.2 months], respectively).

In the multivariate analysis, the treatment effect (abiraterone acetate versus placebo) on OS was statistically significant after adjustment for the stratification factors (see Table 27). The analysis also showed that each of the four stratification factors were statistically significant predictors of OS.

Table 27: Overall survival, non-stratified proportional hazards model (multivariate analysis) (Study COU-AA-301).

Model Parameter	Model Fit		Hazard Ratio	
	Coeff. (SE)	p value	Estimate	95% C.I.
Treatment (AA vs. placebo)	-0.4 (0.09)	< 0.0001	0.657	(0.554, 0.780)
ECOG score (0-1 vs. 2)	-0.9 (0.12)	< 0.0001	0.399	(0.317, 0.502)
Pain (absent vs. present)	-0.4 (0.09)	< 0.0001	0.667	(0.561, 0.793)
Prior chemotherapy regimens (1 vs. 2)	-0.2 (0.09)	0.0065	0.782	(0.655, 0.934)
Progression category (PSA only vs. radiographic)	-0.3 (0.10)	0.0106	0.779	(0.643, 0.943)

AA=abiraterone acetate; C.I.=confidence interval; Coeff.=coefficient; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; PSA=prostate-specific antigen; SE=standard error; vs.=versus

Note: Model dependent variable is overall survival, expressed as days from date of randomization to date of death from any cause. If the hazard ratio is <1, then result favors the first level of the parameter (as listed above).

Subjects who are not deceased at the time of analysis are censored on the last date the subject was known to be alive or lost to follow-up.

Comment: The study met its primary endpoint at the prespecified significance level ($p=0.0141$) required to cross the efficacy boundary for the interim analysis based on the 552 deaths. Treatment with abiraterone acetate decreased the risk of death by 35% compared with placebo (HR=0.646 [95% CI: 0.543, 0.768]; $p<0.0001$). Median survival improved by 36% in the abiraterone acetate group relative to the placebo group (450.0 days [14.8 months] and 332.0 days [10.9 months], respectively). A higher proportion of subjects in the abiraterone acetate group was alive than in the placebo group at all timepoints beyond the initial few months of dosing. There was a 33% improvement in the twelve month survival rate in the abiraterone group relative to the placebo group (~ 60% and ~ 45%, respectively). The various sensitivity analyses of OS supported the primary analysis. In an updated OS analysis of data at the clinical cutoff date of 20 September 2010, the HR statistically significantly favoured abiraterone acetate relative to placebo. The subgroup analysis (non stratified) showed that the OS hazard ratios favoured abiraterone relative to placebo for almost all of the tested subgroups.

Results for other efficacy outcomes

Results for the secondary efficacy outcomes

- **PSA progression** was documented in 31.9% ($n=254$) and 30.2% ($n=120$) of subjects in the abiraterone acetate and placebo groups, respectively, resulting in the censoring of data for a high proportion of subjects in both groups (68.1% [$n=543$] and 69.8% [$n=278$], respectively). Treatment with abiraterone acetate decreased the risk of PSA progression by 42% compared with placebo: HR=0.580; [95% CI: 0.462, 0.728]; $p<0.0001$. The median time to PSA progression was 309.0 days (10.2 months) in the abiraterone acetate group and 200.0 days (6.6 months) in the placebo group.
- **Radiographic disease progression or death** was documented in 72.4% ($n=577$) and 82.2% ($n=327$) of subjects in the abiraterone acetate and placebo groups, respectively. Treatment with abiraterone acetate decreased the risk of radiographically documented disease progression or death by 33% compared with placebo: HR=0.673 [95% CI: 0.585, 0.776]; $p<0.0001$. The median time to radiographic disease progression or death was 171.0 days (5.6 months) in the abiraterone acetate group and 110.0 days (3.6 months) in the placebo group.
- **PSA response** was documented as confirmed in 29.1% ($n=232$) and 5.5% ($n=22$) of subjects in the abiraterone acetate and placebo groups respectively. A PSA response was defined as a $\geq 50\%$ decline from baseline. For a PSA response to be confirmed, an additional central laboratory measurement obtained 4 or more weeks later had to also show at least a 50% decline from baseline. The likelihood of experiencing a confirmed PSA response was about 5 fold greater in the abiraterone acetate group than in the placebo group: RR = 5.266 [95%CI: 3.459, 8.018]; $p < 0.0001$.

Comment: Each of the three secondary endpoints favoured abiraterone acetate over placebo. These results were statistically significant after adjusting for multiple testing. The secondary efficacy endpoint analyses support the primary efficacy analysis. However, the absolute difference in the proportion of subjects with PSA progression was small and the median time difference to PSA progression was 3.6 months. The median time to radiographic disease progression or death was only two months longer in the abiraterone acetate group than in the placebo group.

Results for other efficacy endpoints

Other secondary endpoint analyses (non stratified) in the ITT populations which statistically significantly favoured abiraterone acetate compared with placebo were:

- objective response rate (14.0% versus 2.8%; RR=5.079 [95%CI: 2.068, 12.472]; $p<0.0001$);
- pain palliation rate (44.4% versus 27.0%; RR=1.645 [95%CI: 1.245, 2.173]; $p=0.002$);
- time to pain progression (HR=0.690 [95%CI: 0.532, 0.896]; $p=0.0051$);
- time to first skeletal related event (HR=0.637 [95%CI: 0.491, 0.825]; $p=0.0006$);
- modified progression free survival (HR=0.630 [95%CI: 0.551, 0.720]; $p<0.0001$);
- CTC response (51.6% versus 21.9%, RR=2.355 [95%CI: 1.600, 3.468]; $p<0.0001$).

There was no statistical adjustment for the multiplicity of pairwise comparisons. The results should be considered to be exploratory.

Functional status and symptom measure

There were a number of assessments of functional status and symptom measures. For the FACT-P (Functional Assessment of Cancer Therapy – Prostate) total score, mean (SD) change from baseline to treatment end was statistically significantly smaller in subjects in the abiraterone acetate group compared with subjects in the placebo group (-8 [19.7] versus -17 [22.9]; $p=0.0062$); smaller reductions from baseline indicate more favourable outcomes. For the Functional Assessment of Cancer Therapy – General total score, mean (SD) change from baseline to treatment end was non statistically significantly smaller in subjects in the abiraterone acetate group compared with subjects in the placebo group (-7 [14.6] versus -12 [15.6]; $p=0.0541$). Descriptive statistics only were provided for the BFI and the BPI-SF. The functional status and symptom measure assessments should be considered to be exploratory.

Other efficacy studies

Study COU-AA-004

Study COU-AA-004 was a Phase II, multicentre, open label, single arm study investigating the safety and efficacy of abiraterone acetate in castrated subjects with advanced prostate cancer who had failed androgen deprivation and docetaxel based chemotherapy. Subjects who had been treated with more than two previous chemotherapy regimens were excluded. The study was conducted at eight sites in the USA and the UK between 6 June 2007 and 14 August 2008, and the data cutoff was 22 January 2010. It was conducted in accordance with the Declaration of Helsinki and ICH GCP standards, and all patients gave written informed consent. The study was sponsored by Cougar Biotechnology Inc. and has been published.¹⁹

¹⁹ Morris DM, et al. (2010) Phase II multicenter study of abiraterone acetate plus prednisone therapy in patients with docetaxel-treated castration-resistant prostate cancer. *J. Clin. Oncol.* 28:1496-1501.

Inclusion criteria included: histologically or cytologically confirmed adenocarcinoma of the prostate, but not with neuroendocrine differentiation or of small cell histology; documented PSA progression according to PSAWG eligibility with a PSA > 5 ng/mL, or objective progression by RECIST for subjects with measurable disease; ongoing androgen deprivation with serum testosterone level of <50 ng/dL (<2.0 nM/L); and ECOG Performance Status of ≤ 2 (Karnofsky Performance Status²⁰ ≥ 50%). The inclusion and exclusion criteria have been summarized and are considered acceptable.

Treatment consisted of abiraterone acetate 1 g (4 x 250 mg tablets) once daily after an overnight fast, and prednisone (or prednisolone) 5 mg twice daily. Each treatment cycle was 28 days ± 2 days. Safety and dosing compliance were evaluated during Cycle 1 Day 8 ± 2 days visit. Treatment was to continue through 12 cycles, or until documented disease progression or unacceptable toxicity. If subjects had not progressed and were benefiting from the study treatment, they were allowed to continue beyond Cycle 12. Survival follow up was to continue for up to five years after study entry.

The primary efficacy endpoint was PSA response rate according to PSAWG criteria. A two sided 95% CI was calculated. A PSA response was defined as the first occurrence of ≥ 50% decrease from baseline during the study, which could be confirmed by a subsequent measurement that was at least four or more weeks after initial documentation.

The statistical analysis plan (SAP) stated that a total of 50 eligible subjects were to be treated with abiraterone acetate. If 12 or more out of the 50 evaluable subjects showed at least a 50% decline in PSA (PSAWG criteria), then the null hypothesis of lack of treatment effect (that is, response rate ≤ 15%) was rejected in favour of the alternative hypothesis that the response rate is ≥ 30% with 86% power and a significance level (alpha) of 6%. Based on the available data at the time of the study, the response rate was expected to be in the 25% to 35% range, with the width of the 95% CI being < 30% (±15%). No statistical interim analysis was planned. No formal statistical tests were planned. Standard descriptive statistical methods were used to summarize the results.

The study enrolled 58 subjects with advanced CRPC. Subjects were enrolled at eight sites in two countries (USA and UK), and enrollment was predominantly from the USA (54 [93%] subjects). Of the 58 subjects who received treatment with abiraterone acetate, two (3%) subjects completed the study by completing 12 cycles of study treatment and two (3%) subjects continued to receive study treatment past 12 cycles at the time of data cutoff (22 January 2010). The remainder of the subjects (54 [93%]) had discontinued

²⁰ The Karnofsky score runs from 100 to 0, where 100 is "perfect" health and 0 is death:

- 100% – normal, no complaints, no signs of disease
- 90% – capable of normal activity, few symptoms or signs of disease
- 80% – normal activity with some difficulty, some symptoms or signs
- 70% – caring for self, not capable of normal activity or work
- 60% – requiring some help, can take care of most personal requirements
- 50% – requires help often, requires frequent medical care
- 40% – disabled, requires special care and help
- 30% – severely disabled, hospital admission indicated but no risk of death
- 20% – very ill, urgently requiring admission, requires supportive measures or treatment
- 10% – moribund, rapidly progressive fatal disease processes
- 0% – death.

treatment, with disease progression (44 [76%]) as the most common reason for discontinuation. Only five (9%) subjects discontinued treatment due to adverse events.

The demographic and baseline disease characteristics of the enrolled subjects were generally consistent with those of the planned population described in the protocol. The mean (SD) age of the 58 subjects was 68.6 (9.8) years, 39 (67.2%) subjects were aged ≥ 65 years, and the majority of subjects were White (n=54 [93.1%]). The mean (SD) time from initial diagnosis to first dose of study treatment was 8.2 (4.8) years, the majority of subjects had baseline ECOG scores of 0 or 1 (96.5%) and the mean (SD) PSA was 482 (857) ng/mL.

Prior treatment for prostate cancer had been received by all patients, with 77.6% having been treated with radiotherapy, 55.2% with surgery, 5.2% with orchiectomy, and 100% with hormonal, immunological, and/or biological therapy. All subjects (100%) in this study had undergone prior androgen deprivation with medical or surgical castration as mandated by the protocol, including 57 (98.3%) subjects who received prior LHRH analogues, and three (5.2%) subjects who had undergone prior orchiectomy. All 58 (100%) subjects had received at least one prior course of docetaxel chemotherapy for prostate cancer as mandated by the protocol. The median number of prior chemotherapy regimens (any) received was 1 (range: 1-3), with 44 subjects (75.9%) receiving 1 prior line of chemotherapy and 13 subjects (22.4%) receiving 2 prior lines. There was one (0.5%) subject who had received 3 lines of prior chemotherapy, in violation of the protocol.

The primary efficacy endpoint was PSA response defined as the first occurrence of $\geq 50\%$ decrease from baseline during the study, which could be confirmed by a subsequent measurement that was at least 4 or more weeks after initial documentation. A confirmed PSA response of $\geq 50\%$ was reported in 22 of the 58 subjects (that is, 38% [95%CI: 26%, 52%]). The median number of cycles received by the 58 subjects was 3.0 (range: 1, 30), and the total median duration of treatment was 12.5 weeks (range: 2, 121).

The results for the secondary efficacy endpoints included: median time to PSA progression was 5.6 months (169 days [95% CI: 99, 225]), and the median PSA-PFS was 4.6 months (141 days [95%CI: 110, 200]); partial radiographic responses achieved by 3 (6%) subjects, median time to radiographic progression was 2.9 months (88 days [95% CI: 82, 333]), median time to radiographic PFS was 4.1 months (126 days [95% CI: 82, 333]); stable disease (RECIST) lasting for ≥ 6 months was reported for 21% of subjects; improvement in ECOG performance status by at least 1 unit at some point during the study was documented for 28% of subjects; and median OS was 16.2 months (492 days [95% CI: 373, 647]), with an estimated one year survival rate of 63.2% (95% CI [49.4, 74.3]).

Comment: The data from this Phase II, open label, single arm study provide limited support for the efficacy of abiraterone acetate in combination with prednisone/prednisolone for the treatment of mCRPC. However, in the absence of a control group no meaningful conclusions can be made about OS or DFS. The PSA response data were encouraging with 38% (95% CI: 26%, 52%) of subjects (22/58) achieving a confirmed $\geq 50\%$ reduction in PSA concentration from baseline. In a subgroup analysis, subjects with prior exposure to ketoconazole appeared to have a lower PSA response rate compared with subjects who had no prior ketoconazole exposure (26% versus 48%). In addition, a further subgroup analysis among responders showed that more subjects with prior ketoconazole exposure had PSA progression compared with subjects who were ketoconazole naïve (57% versus 27%, respectively). These findings were incorporated in the design of the pivotal Phase III Study COU-AA-301 where prior treatment with ketoconazole for prostate cancer was an exclusion criteria.

Studies COU-AA-003 and COU-AA-003EXT

Study COU-AA-003 was a Phase II, multicentre, open label, single arm study with a two stage design that evaluated anti tumour effects of abiraterone acetate in subjects with metastatic advanced prostate cancer who had failed prior taxane containing chemotherapy. The target enrollment was approximately 33 subjects enrolled from the USA and UK. Study COU-AA-003EXT was an open label extension study with the primary objective to provide additional treatment of abiraterone acetate to subjects who had completed 12 treatment cycles and continued to receive clinical benefit from treatment. Study COU-AA-003 was initiated on 20 November 2006 and the last subject was enrolled on 3 August 2007, and the corresponding dates for Study COU-AA-003EXT were 18 December 2008 and 7 January 2009. The studies were conducted in accordance with the Declaration of Helsinki and ICH GCP standards, and all patients gave written informed consent. The studies were sponsored by Cougar Biotechnology Inc.

Treatment consisted of abiraterone acetate 1 g (4 x 250 mg tablets) once daily after an overnight fast, and all ongoing subjects also received low dose glucocorticoid such as prednisolone/prednisone (5 mg twice daily) or dexamethasone (0.5 mg once daily). Each treatment cycle was 28 ± 2 days. Safety and treatment compliance were evaluated at the Cycle 1, Day 8 visit. Treatment was to continue through 12 cycles, or until documented disease progression, lack of disease response after six evaluable cycles of treatment, or unacceptable toxicity. Extension Study COU-AA-003EXT allowed responding subjects in the UK to continue receiving abiraterone acetate after 12 treatment cycles. Subjects continued treatment with the same dose and regimen of abiraterone acetate combined with low dose glucocorticoid administered during Study COU-AA-003. Treatment was to continue until death, loss to follow up, withdrawal of informed consent, sustained toxicity, disease progression, or the sponsor's decision to terminate development of abiraterone acetate. Survival follow up was to be performed every 12 weeks for up to three years after the subject's entry into the study.

The primary efficacy endpoint was the evaluation of PSA response rate according to PSAWG criteria. For Study COU-AA-003, the first 20 subjects who had three evaluable cycles (12 weeks) of study treatment were summarised and analysed as a binary endpoint for the Stage 1 assessment of PSA declined by $\geq 50\%$ according to the PSAWG criteria. The Week 12 PSA response rate for all subjects was also summarised.

The aim of the two stage design was to allow for the possibility of stopping subject accrual after the first stage. To test a null hypothesis that the PSA response rate is $\leq 10\%$ versus the alternative that it is $\geq 30\%$, an interim analysis occurred after the first 20 subjects (Stage 1) received three cycles of abiraterone acetate. The study was to be stopped if fewer than 3 PSA responders were observed after the first stage, otherwise 13 additional subjects were to be enrolled to proceed to the second stage. The null hypothesis of the PSA response rate of less $\leq 10\%$ was to be rejected with a power of 91% and an alpha of 4% if there were more than 7 responders out of 33 subjects at the end of the second stage. To account for subject withdrawals, more than 33 subjects were enrolled to achieve the required sample size. There was no adjustment for multiplicity and no inferential statistics for the hypothesis testing for the two stage design.

There were 47 subjects enrolled and included in the ITT population: 34 (72%) in the UK and 13 (28%) in the US. As of the data cutoff date of 22 January 2010, 6 (13%) subjects in the UK had completed Study COU-AA-003, and 6 (13%) were still receiving treatment (5 in the UK and 1 in the US). Study discontinuation had occurred in 41 (87%) subjects. The most common reason for discontinuation was disease progression (23 subjects; 49%), followed by AEs (11 subjects; 23%). As of the data cutoff, during the follow up phase 36 (76.7%) subjects died and 2 (4%) subjects were alive during follow up .

All 47 subjects were castrated males and 46 (98%) were White. The median age of all subjects was 67 years (range: 48 to 87 years), with 19 (40.4%) being < 65 years and the age groups 65 to 69 years, 70 to 74 years, and ≥75 years each comprising ~ 20% of subjects. The median baseline PSA was 403.0 ng/mL [range: 9.9 to 10325.0 ng/mL]; Gleason score²¹ was > 7 for 18 (38.3%) subjects, 7 for 15 (31.9%) subjects, and < 7 for 9 (19.1%) subjects (score missing for 5 subjects); the majority of subjects (57.4%) had an ECOG performance score of 1; and 33 (70.2%) subjects had bone and soft tissue as sites of metastatic disease, followed by viscera in 9 subjects (19%).

All 47 subjects had received prior hormonal, immunological, and/or biological therapy. Most subjects (33, 70.2%) had received radiotherapy, and 11 (23%) subjects had been treated with surgery (10 prostatectomy and 1 cryosurgery), but no subjects reported orchiectomy. All subjects (100%) had received prior docetaxel, and 8 (17%) had received prior mitoxantrone. All subjects (100%) had received 2 to 4 types of prior hormonal therapies, with the most commonly reported being LHRH (100%), anti androgens (46 subjects, 98%), and glucocorticoids (30 subjects, 63.8%). Prior treatment with ketoconazole for prostate cancer had been received by 9 (19.1%) subjects.

The PSA response (primary efficacy endpoint) results were: in Stage 1, 6/20 (30% [95% CI: 11.9, 54.3]) had a confirmed PSA decrease from baseline of at least 50% allowing the study to proceed to Stage 2; at the end of Stage 2, 17/47 (36% [95% CI: 22.7, 51.5]) subjects had a confirmed PSA decrease from baseline of at least 50%.

The results for the secondary efficacy endpoints were: confirmed PSA response of at least a 50% decrease in PSA from baseline to week 12 for the overall population achieved by 21/47 subjects (45% [95%CI: 30, 60]), and the corresponding figures for responses of at least 30% and 90% were 29/47 (62% [95%CI: 46, 76]) and 7/47 (15% [95%CI: 6, 28]); confirmed objective response rate (complete or partial) according to RECIST criteria achieved by 6 (26% [95%CI: 10, 48]) of 23 subjects with evaluable baseline data, and for the 40 subjects who were considered evaluable for response, 7 (18%) were assessed as having a partial response (6 confirmed) with no subjects having a complete response; median time to PSA progression was 5.6 months (169 days [95% CI: 113, 281]), and for the 21 subjects who were considered responders the median duration of PSA response was 5.6 months (169 days [95%CI: 141, 262]); the median OS was 12.5 months (380 days [95% CI: 311, 457]), and the median PFS was 15.0 months (457 days [95% CI: 163, 712]); the ECOG performance status score changed negligibly with abiraterone acetate therapy.

²¹ The Gleason Grading system is used to help evaluate the prognosis of men with prostate cancer. The Gleason score and the Gleason sum are one and the same; however, the Gleason grade and the Gleason score or sum are different. The biopsy Gleason score is a sum of the primary grade (representing the majority of tumour) and a secondary grade (assigned to the minority of the tumour), and is a number ranging from 2 to 10. The higher the Gleason score, the more aggressive the tumour is likely to act and the worse the patient's prognosis. Scores are associated with the following features:

Pattern 1: The cancerous prostate closely resembles normal prostate tissue. The glands are small, well formed, and closely packed.

Pattern 2: The tissue still has well formed glands, but they are larger and have more tissue between them.

Pattern 3: The tissue still has recognisable glands, but the cells are darker. At high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue.

Pattern 4: The tissue has few recognisable glands. Many cells are invading the surrounding tissue.

Pattern 5: The tissue does not have recognisable glands. There are often just sheets of cells throughout the surrounding tissue.

Comment: The data from this Phase II, open label, single arm study provide limited support for the efficacy of abiraterone acetate in combination with low dose glucocorticoids (following a protocol amendment) for the treatment of mCRPC. However, in the absence of a control group no meaningful conclusions can be made about OS or disease free progression. The PSA response data were encouraging with 6/20 subjects (30% [95% CI: 11.9, 54.3]) having a confirmed PSA decrease from baseline to week 12 of at least 50% (that is, null hypothesis at the 1st stage rejected). At the end of Stage 2, 17/47 subjects (36% [95% CI: 22.7, 51.5]) subjects had a confirmed PSA decrease from baseline to week 12 of at least 50% (that is, null hypothesis at the 2nd stage rejected). The PSA response data also showed that for the overall population, 21/47 subjects (45% [95%CI: 30, 60]) had a confirmed decrease of $\geq 50\%$ from baseline to Week 12. The median duration of treatment for the 47 patients in the study was 22.6 weeks [range: 1.7 to 147.9 weeks], and 12 (26%) subjects received at least 48 weeks of treatment

Studies COU-AA-001 and COU-AA-001EXT

Study COU-AA-001 was a Phase I/II, open label, one arm, single centre clinical trial evaluating the safety and efficacy of abiraterone acetate administered in capsule form daily to subjects with chemotherapy naïve castration refractory prostate cancer (CRPC) with a rising PSA despite hormonal therapy. The study was conducted at one centre in the UK in accordance with the Declaration of Helsinki, the guidelines of GCP, and applicable regulatory requirements. All subjects gave written informed consent. The study was originally sponsored by Cougar Biotechnology Inc. Study COU-AA-001 was initiated on 23 November 2005 (first subject enrolled) and the last subject completed on 20 November 2008, and Study COU-AA-001EXT was initiated on 20 July 2007 (first subject enrolled) and was still ongoing at the time of the report. The dose escalating data from this study has been discussed previously in this CER.

In the dose escalation stage (Phase I), if no CTCAE (Common Terminology Criteria for Adverse Events) grade 3 toxicity was documented in the first 28 days of continuous daily dosing in the starting cohort of 250 mg /day (n=3), the dose was escalated to 500 mg (n=3), 750 (n=3), 1 g (n=6) and finally to 2 g (n=3) mg/day. In the efficacy (activity) evaluation stage (Phase II), 36 subjects were treated with abiraterone acetate 1000 mg/day and 34 of these subjects completed the study. The primary efficacy end point was confirmed objective PSA response which was evaluated according to the PSAWG guidelines. All patients achieving a fall in PSA of $\geq 50\%$ from baseline (confirmed with a second value at least four weeks later) fulfilled the criteria for PSA response.

The Study COU-AA-001 protocol was amended on 24 April 2008 with patients not already receiving glucocorticoids being instructed to immediately begin a glucocorticoid regimen. The amendment justified the addition on the grounds that inhibition of 17α -hydroxylase and C17,20-lyase is anticipated to result in both impaired androgen and cortisol generation. The positive feedback of increased ACTH secretion may result not only in glucocorticoid rescue through the generation of the weaker glucocorticoid corticosterone, but also secondary hyperaldosteronism, which may lead to fluid retention and hypertension. The use of glucocorticoids, such as prednisolone 5 mg bd (twice daily) or dexamethasone 0.5 mg qd, administered together with abiraterone acetate was expected to reduce these side effects.

All subjects without disease progression after completion of 12 cycles of therapy (the maximum treatment period in Study COU-AA-001), were offered the opportunity to participate in a protocol extension (Study COU-AA-001 EXT), which permitted continuation of the study medications abiraterone acetate with dexamethasone or prednisolone until disease progression. Of the 34 subjects who completed Study COU-AA-001, 30 subjects (9 from Phase I and 21 from Phase II) entered the extension study.

The primary activity end point of confirmed PSA response (decline of $\geq 50\%$ from baseline) following three cycles of treatment was analysed in the 1 g abiraterone acetate therapy cohort (that is, with or without low dose glucocorticoids) consisting of 42 subjects from Stages 1 and 2 combined. Of the 42 subjects in this cohort, 25 (59.5% [95%CI: 43.3, 74.4]) had reductions of at least 50% in the PSA at Week 12. In the abiraterone 1 g therapy cohort (that is, without low dose glucocorticoids), 27 of the 42 subjects had a maximal confirmed reduction during the study of at least 50% (64.3% [95%CI: 48.0, 78.4]). In the abiraterone 1000 mg monotherapy cohort (that is, without low dose glucocorticoids), 24 of the 42 subjects had a maximal confirmed reduction during the study of at least 50% (57.1% [95%CI: 41.0, 72.3]). The median time to PSA progression was 330 days [95% CI: 197, 530]. The median time to PSA response duration was 141 days [95% CI: 85, 235].

Comment: The open label efficacy data from Study COU-AA-001 are considered not to be directly relevant to the application for the proposed extension of indication. The study was in subjects with chemotherapy naïve CRPC, and low dose glucocorticoids were added to abiraterone acetate only after a protocol amendment initiated more than two years after the first subject was enrolled. The study was single arm and included no comparison between abiraterone acetate and control on OS or PFS.

Study COU-AA-002

Study COU-AA-002 was a Phase I/II, multicentre, open label, dose escalation study initially investigating single agent therapy with abiraterone acetate in chemotherapy naïve subjects with CRPC who had ongoing gonadal androgen deprivation therapy or orchiectomy. The study was the first to use the tablet formulation. It was conducted in accordance with the Declaration of Helsinki, the guidelines of GCP, and applicable regulatory requirements. All subjects gave written informed consent. The study was sponsored by Cougar Biotechnology Inc. The study was conducted in the USA at five sites. It was initiated on 10 July 2006 and the database freeze was on 22 January 2010. The study has been published.¹⁵

Phase II of the study was an open label, multicentre, single arm study of abiraterone acetate 1 g once daily in chemotherapy naïve subjects with CRPC with no prior exposure to ketoconazole. The primary objective was to assess the proportion of subjects with a $\geq 50\%$ PSA decline during therapy. Following a protocol amendment all subjects were required to receive low dose glucocorticoids co administered once daily with abiraterone acetate. Subjects received up to 12 treatment cycles, until disease progression, or unacceptable toxicity was observed. Subjects reaching the end of 12 cycles without progressive disease or unacceptable toxicity could continue treatment. Survival data was to be collected for up to 60 months.

The primary efficacy endpoint was the proportion of subjects achieving a $\geq 50\%$ PSA decline by 12 weeks of therapy (that is, three cycles) according to PSAWG criteria. A sample size of 32 subjects was required to detect a PSA response rate of at least 50%, against a null hypothesis of 28%. This sample size calculation assumed a level of significance of 0.04 and power of 0.81. A total of 33 subjects were enrolled, and all subjects were included in the ITT and safety population, with 18 discontinuing and 15 ongoing. There were a number of secondary efficacy endpoints and these were consistent with Studies COU-AA-003 and COU-AA-004.

The confirmed PSA response rate of $\geq 50\%$ decline at Week 12 according to PSAWG criteria was observed in 22/33 subjects (67% [95%CI: 48.2%, 82.0%]), and the corresponding total results (confirmed plus not confirmed) were 24/33 (72.7% [95%CI: 54.5, 86.7]). The median PSA based PFS was 15.5 months (473 days [95% CI: 281, upper limit not estimable]).

Comment: The open label efficacy data from Study COU-AA-002 are considered not to be directly relevant to the application for the proposed extension of indication. The study was

in subjects with chemotherapy naïve CRPC, and low dose glucocorticoids were added to abiraterone acetate only after a protocol amendment more than two years after the first subject was enrolled. The study was single arm and included no comparison between abiraterone acetate and control on OS or PFS.

Analyses performed across trials

No efficacy analyses have been performed across trials

Evaluator's conclusions on clinical efficacy

- It is considered that the submitted data have satisfactorily established the efficacy of abiraterone acetate in combination with prednisone/prednisolone for the proposed indication
- The submission included one pivotal, Phase III, efficacy and safety Study COU-AA-301. The primary (interim) analysis showed that OS (the primary efficacy outcome) was statistically significantly increased in the abiraterone acetate group compared with the placebo group. A total of 552 deaths had been reported at the time of the clinical data cutoff of 22 January 2010 for the primary (interim) analysis: 333 (41.8%) deaths in the 797 subjects in the abiraterone acetate group and 219 (55.0%) deaths in the 398 subjects in the placebo group. At the time of the primary (interim) analysis, the median follow up for all subjects was 12.8 months.
- Treatment with abiraterone acetate decreased the risk of death by 35% compared with placebo (HR=0.646 [95% CI: 0.543, 0.768]; $p<0.0001$). Median survival improved by 36% in the abiraterone acetate group relative to the placebo group (450.0 days [14.8 months] and 332.0 days [10.9 months], respectively). The absolute difference in median survival time between the two treatment groups was 3.9 months. This difference is considered to be clinically meaningful in patients with mCRPC whose disease had progressed despite prior treatment with two chemotherapy regimens, one of which contained docetaxel. At all timepoints beyond the initial few months of dosing, a higher proportion of subjects in the abiraterone acetate group was alive than in the placebo group. There was a 33% improvement in the twelve month survival rate in the abiraterone acetate group relative to the placebo group (~ 60% versus ~ 45%, respectively).
- In a multivariate analysis, abiraterone acetate reduced the risk of death by 34% relative to placebo after adjustment for stratification factors: HR = 0.657 [95%CI: 0.554, 0.780]; $p<0.0001$. The analysis also showed that each of the four stratification factors was a statistically significant predictor of OS (that is, baseline ECOG status; pain; number of prior cytotoxic regimens; and evidence of disease progression).
- In the updated survival analysis at the clinical cutoff data of 20 September 2010 there had been a total of 775 deaths (97% of planned number for the final analysis), with 501 (62.9%) in the abiraterone acetate group and 274 (68.8%) in the placebo group, with a median follow up of 20.2 months. The HR was 0.740 [95%CI: 0.638, 0.859]; $p<0.0001$. The median survival improved by 41% in the abiraterone acetate group relative to the placebo group (482 days [15.8 months] and 341 days [11.2 months], respectively).
- Subgroup analyses of the primary efficacy endpoint (OS) supported the primary efficacy analysis, with the hazard ratios of all subgroups (apart from subjects with baseline ECOG status of 2) statistically significantly favouring the abiraterone acetate relative to placebo. The various sensitivity analyses of the primary efficacy endpoint (OS) supported the primary efficacy analysis.

- Analyses of the secondary efficacy endpoints in Study COU-AA-301 all statistically significantly favoured the abiraterone acetate group compared with the placebo group (that is, PSA progression, PSA response, and radiographic disease progression or death). In addition, analyses of all prespecified “other” efficacy endpoints also supported statistically significantly greater efficacy of abiraterone acetate compared with placebo. Exploratory analyses of endpoints relating to functional improvement also suggested greater improvement in the abiraterone group compared with the placebo group.
- The submission included no supportive randomised, double blind, placebo controlled studies. However, it did include two Phase II, open label, single arm studies in patients with CRPC whose disease had progressed on or after taxane regimens (Studies COU-AA-003 and COU-AA-004). These studies showed a confirmed PSA decline of $\geq 50\%$ from baseline in about 38% to 45% of subjects. These are encouraging results and provide limited support for the pivotal study. However, there were no supportive data examining OS and PFS benefit in patients treated with abiraterone acetate compared with a control group. The submission also included two open label, single arm Phase I/II studies in patients with chemotherapy naïve subjects with CRCP who had been treated initially with abiraterone acetate monotherapy (that is, not combined with prednisone/prednisolone). These two studies showed a confirmed PSA decline of $\geq 50\%$ from baseline in about 64% to 67% of chemotherapy naïve subjects. These results are encouraging, but the data from these two studies are considered to be not relevant to the current application.
- Overall, it is considered that the efficacy of abiraterone acetate combined with prednisone/prednisolone for the proposed extension of indication is supported by only one confirmatory pivotal study. There are no other confirmatory studies in the submission providing comparative OS and PFS data for abiraterone acetate and control. There is a TGA adopted “Points to Consider” guideline which discusses applications which include only one pivotal study.²² This guideline discusses the “general demand for replication of scientific results”, but notes that “clinical drug development differs from the situation with strictly experimental studies”. The guideline states that where confirmatory evidence is provided by only one pivotal study “this study will have to be exceptionally compelling”, but goes on to state “there is no formal requirement to include two or more studies in the Phase III program”.
- The “Points to Discuss” document lists factors which should be considered when determining whether the confirmatory evidence from one pivotal study is “exceptionally compelling”. It is considered that applying these factors to Study COU-AA-301 leads to the following conclusions: the study is internally valid and no significant sources of potential bias can be identified; the study is externally valid as the results from the study population can be extrapolated to the general population of patients with mCRPC whose disease has progressed despite previous chemotherapy with docetaxel (the standard of care); the absolute increase in median survival time of 3.9 months in the abiraterone acetate group compared with the placebo group is considered to be clinically meaningful; the statistical significance of the difference in OS survival (primary efficacy endpoint) between the abiraterone acetate group and the placebo group is “strong”, and is supported by the results of the statistical analysis of each of the three key secondary efficacy endpoints (that is, PSA progression, PSA response, and radiographic disease progression or death); the quality of the data was

²² European Medicines Agency, “Committee for Proprietary Medicinal Products (CPMP): Points to Consider on Application With 1. Meta-Analyses; 2. One Pivotal Study”, 31 May 2001, Web, accessed 15 August 2012 <http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf>.

good and quality assurance audits had been completed at 26 study sites; the study was internally consistent with all prespecified subgroup analyses of OS (apart from one) statistically significantly favouring abiraterone acetate over placebo, and supporting the primary efficacy analysis; no data on centre effects could be identified in the CSR; the tested hypothesis that abiraterone acetate will inhibit testosterone synthesis resulting in improved outcomes in patients with mCRPC is medically plausible.

Safety

Studies providing evaluable safety data

The submission included a comprehensive Summary of Clinical Safety (SCS) that assessed the safety of abiraterone acetate in 1873 subjects from 20 clinical studies. The SCS included data from 1464 subjects with CRPC included in an integrated safety population, data from 100 subjects with CRPC not included in the integrated safety population, and data from 399 non cancer subjects from PK studies. There were no studies which investigated only safety as a primary outcome. The sponsor based conclusions relating to the safety of abiraterone acetate combined with prednisone for the treatment of mCRPC primarily on the 1464 subjects in the integrated safety population. In this CER, the primary focus on safety is on the data from the pivotal efficacy and safety Study COU-AA-301.

The integrated safety population included a total of 1464 subjects, consisting of 1070 subjects with CRPC treated with abiraterone acetate 1 g daily with or without prednisone and 394 subjects treated with placebo, who received at least part of a 1 g dose of abiraterone acetate or placebo. The major contribution to the integrated safety population came from the pivotal Phase III efficacy and safety study in subjects treated with mCRPC (Study COU-AA-301). This study included 1185 subjects consisting of 791 treated with abiraterone acetate 1 g once daily combined with prednisone 5 mg twice daily, and 394 treated with placebo once daily combined with prednisone 5 mg twice daily. The 279 remaining subjects in the integrated safety population were pooled subjects treated with abiraterone acetate 100 mg once daily (without or without prednisone 5 mg twice daily) from Studies COU-AA-004, COU-AA-003, COU-AA-003EXT, COU-AA-BMA, COU-AA-001, COU-AA-001EXT, COU-AA-002 and COU-AA-BE. The clinical cutoff date for the integrated safety population included in the SCS was 22 January 2010.

In the SCS, data from 100 subjects with CRPC were presented separately from the data from the integrated safety population as extended dosing and safety data were not available by the clinical cutoff date. Of these 100 subjects, 12 in Study COU-AA-001 and 21 in Study COU-AA-002 were treated with abiraterone acetate doses other than 1 g, 33 were treated in Phase 1 PK study COU-AA-006, and 34 were treated in Phase 1 PK study COU-AA-015.

Data from 309 non cancer subjects who were treated in nine Phase I PK studies were also presented separately in the SCS from the integrated safety population data.

Patient exposure

The exposure data for the integrated safety population are summarised below in Table 28. In Study COU-AA-301, the median total treatment duration in the abiraterone acetate group was approximately twice as long as that in the placebo group: 32.1 weeks (range: 1, 81) versus 15.5 weeks (range: 1, 82), respectively. In the abiraterone acetate group in Study COU-AA-301, 479 (60.6%) subjects were treated for > 24 weeks and 210 (26.5%) were treated for > 48 weeks, and the corresponding figures for the total number of

subjects treated with abiraterone acetate in the integrated safety population were 642 (60.0%) and 297 (27.8%).

Table 28: Extent of exposure, integrated safety population.

	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Total treatment duration				
n	394	791	279	1070
0 < 12 Weeks	123 (31.2%)	143 (18.1%)	57 (20.4%)	200 (18.7%)
12 < 24 Weeks	121 (30.7%)	169 (21.4%)	59 (21.1%)	228 (21.3%)
24 < 36 Weeks	59 (15.0%)	116 (14.7%)	43 (15.4%)	159 (14.9%)
36 < 48 Weeks	37 (9.4%)	153 (19.3%)	33 (11.8%)	186 (17.4%)
48 < 60 Weeks	35 (8.9%)	120 (15.2%)	29 (10.4%)	149 (13.9%)
60 < 72 Weeks	16 (4.1%)	74 (9.4%)	14 (5.0%)	88 (8.2%)
≥72 Weeks	3 (0.8%)	16 (2.0%)	44 (15.8%)	60 (5.6%)
Mean (SD)	23.1 (17.65)	32.5 (19.99)	38.2 (31.51)	34.0 (23.66)
Median	15.5	32.1	28.3	31.9
Range	(1, 82)	(1, 81)	(0, 148)	(0, 148)

In Study COU-AA-301, a median of 8 cycles (range: 1-21) of treatment was initiated in the abiraterone acid group, compared with a median of 4 cycles (range: 1, 21) in the placebo group. In the total integrated safety population, the median treatment duration in abiraterone acetate treated subjects was identical to the abiraterone acetate group in Study COU-AA-301.

Adverse events

Overall profile

AEs were assessed by subject reports, physical examinations, and laboratory evaluations. Treatment emergent adverse events (TEAEs) were defined as those occurring or worsening in toxicity on or after the first dose and within 30 days after the last dose of study agent. In this CER, all adverse events not matter how categorised are TEAE unless otherwise stated. The severity of AEs was graded according to the National Cancer Institute's Common Toxicity Criteria (NCI CTCAE toxicity grade) Version 3.0. AEs were classified using Medical Dictionary for Regulatory Activities (MedDRA) Version 11.0.

The overall safety profile for the integrated safety population is summarised below in Table 29. In Study COU-AA-301, the proportion of subjects with AEs was similar in the two treatment groups, while the abiraterone acetate group had lower incidences of Grade 3 or 4 AEs, SAEs, AEs leading to treatment discontinuation, and AEs leading to death. There were no marked differences in the AE profile between the abiraterone acetate group in Study COU-AA-301, and the total abiraterone acetate group in the integrated safety population. However, the incidence of Grade 3 or 4 AEs (55% versus 46%), AEs leading to discontinuation (19% versus 15%), and AEs with an outcome of death (12% versus 5%) was higher in the abiraterone acetate group in Study COU-AA-301 compared with the abiraterone acetate group in the pooled Phase I/II studies.

Table 29: Overall safety profile; integrated safety population.

	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Treatment-Emergent Adverse Events (TEAEs) ^a	390 (99.0%)	782 (98.9%)	277 (99.3%)	1059 (99.0%)
Drug-related ^b	303 (76.9%)	604 (76.4%)	250 (89.6%)	854 (79.8%)
Grade 3-4 TEAEs	230 (58.4%)	431 (54.5%)	128 (45.9%)	559 (52.2%)
Drug-related ^b	74 (18.8%)	161 (20.4%)	54 (19.4%)	215 (20.1%)
Serious TEAEs ^a	163 (41.4%)	297 (37.5%)	100 (35.8%)	397 (37.1%)
Drug-related ^b	39 (9.9%)	70 (8.8%)	45 (16.1%)	115 (10.7%)
Grade 3-4	139 (35.3%)	254 (32.1%)	79 (28.3%)	333 (31.1%)
Drug-related Grade 3-4 ^b	31 (7.9%)	60 (7.6%)	28 (10.0%)	88 (8.2%)
TEAEs Leading to Abiraterone Acetate/Placebo Discontinuation	88 (22.3%)	148 (18.7%)	41 (14.7%)	189 (17.7%)
Drug-related ^b	23 (5.8%)	38 (4.8%)	18 (6.5%)	56 (5.2%)
TEAEs Leading to Death	58 (14.7%)	92 (11.6%)	14 (5.0%)	106 (9.9%)
Drug-related ^b	10 (2.5%)	4 (0.5%)	4 (1.4%)	8 (0.7%)

^a Does not include Grade 5 events.

^b Adverse events reported to be either related to abiraterone acetate/placebo or prednisone are classified as drug-related.

All adverse events (irrespective of relationship to study treatment)

Commonly occurring adverse events – all grades

In Study COU-AA-301, the most frequently reported AEs in the abiraterone acetate group (versus placebo group) were: fatigue (43.7% versus 42.9%); back pain (29.5% versus 32.7%), nausea (29.5% versus 31.5%), and constipation (26.0% versus 30.5%). AEs reported in at least 5% of subjects in either group in Study COU-AA-301 and $\geq 2\%$ more frequently in the abiraterone acetate group than in the placebo group were: arthralgia (27.2% versus 22.6%); oedema peripheral (24.9% versus 17.3%); hot flush (19.0% versus 16.8%); diarrhoea (17.6% versus 13.5%); hypokalaemia (17.1% versus 8.4%); urinary tract infection (11.5% versus 7.1%); cough (10.6% versus 7.6%); pollakiuria (7.2% versus 5.1%); dyspepsia (6.1% versus 3.3%); and upper respiratory tract infection (5.4% versus 2.5%).

In Study COU-AA-301, the median duration of treatment in the abiraterone acetate group was twice that in the placebo group. Therefore, to assess if the longer duration of exposure in the abiraterone acetate group resulted in a higher rate of events in that group, the sponsor provided standardised AE rates per 100 patient years (PY) of exposure (that is, events per 100 PY).

In Study COU-AA-301, the total standardised AE rate per 100 PY was 2070.7 in the abiraterone acetate group and 2626.2 in the placebo group. The most frequently reported AEs (that is, ≥ 30 events per 100 PY) in the abiraterone acetate group (versus placebo) were: fatigue (107.8 versus 141.4); anaemia (70.7 versus 103.7); arthralgia (68.0 versus 71.1); back pain (66.4 versus 103.1); nausea (66.4 versus 97.4); bone pain (62.9 versus 94.0); oedema peripheral (53.8 versus 44.1); vomiting (52.6 versus 78.5); constipation (52.2 versus 81.9); hypokalaemia (46.5 versus 28.7); pain in extremity (40.0 versus 60.2); diarrhoea (38.4 versus 41.3); hot flush (36.3 versus 41.8); anorexia (35.1 versus 51.0); asthenia (31.7 versus 37.2); and musculoskeletal pain (31.3 versus 41.3). The following AEs (events per 100 PY) occurred more frequently in the abiraterone group versus the placebo group with a difference of 5 or more events: peripheral oedema (53.8 versus 44.1); hypokalaemia (46.5 versus 28.7); and urinary tract infection (24.0 versus 18.3).

In Study COU-AA-301, the incidence of AEs in the System Organ Class (SOC) of Infections and Infestations was higher in the abiraterone acetate group compared with the placebo group (41.6% versus 34.0%, respectively), but not when standardised (114.3 versus 122.6 events/100 PY, respectively). Both the overall incidence and the standardized rate of urinary tract infection were higher in the abiraterone acetate group than in the placebo group (11.5% versus 7.1%, and 24.0 versus 18.3 events/100 PY, respectively). The overall incidence of pneumonia AEs was 3.2% in the abiraterone acetate group compared with 2.3% in the placebo group, but the standardised rates were similar in both groups (5.9 versus 5.7 events/100 PY, respectively).

In Study COU-AA-301, the incidence of AEs of Injury, Poisoning, and Procedural Complications SOC disorders was higher in the abiraterone acetate group compared with the placebo group (22.0% versus 14.2%), but the standardised rates were similar in both groups (50.6 versus 51.0 events/100 PY, respectively).

Erectile dysfunction was reported in one subject (0.1%) in the abiraterone acetate group and 1 subject (0.3%) in the placebo group.

Adverse events with toxicity of grade 3 or 4

In Study COU-AA-301, 54.5% of subjects in the abiraterone acetate group and 58.4% in the placebo group had Grade 3 or 4 AEs. The most frequently reported ($\geq 5\%$) Grade 3 or 4 AEs in the abiraterone acetate group (versus placebo group) were: fatigue (8.3% versus 9.9%); anaemia (7.5% versus 7.4%); back pain (5.9% versus 9.6%); and bone pain (5.6% versus 7.4%). No individual Grade 4 AEs occurred in $> 2\%$ of subjects in either group.

In Study COU-AA-301, the AE rate (events per 100 PY) for Grade 3 and Grade 4 AEs in the abiraterone acetate group versus placebo group were 231.7 versus 322.6, and 22.1 versus 37.2, respectively. The most commonly reported Grade 3 AE rates (≥ 5 events per 100 PY) in the abiraterone acetate (versus placebo group) were: fatigue (15.4 versus 22.9); anaemia (14.4 versus 15.5); bone pain (11.6 versus 17.2); back pain (9.3 versus 24.1); arthralgia (7.9 versus 10.3); and hypokalaemia (7.5 versus 2.3).

Adverse drug reactions (ADRs)

To determine which events were ADRs, the sponsor reviewed all AEs from subjects treated with 1 g of abiraterone acetate in Studies COU-AA-301, COU-AA-004, COU-AA-003, COU-AA-003EXT, COU-AA-BMA, COU-AA-001, COU-AA-001EXT, COU-AA-002 and COU-AA-BE. AEs were identified for additional review as ADRs if the event occurred in $\geq 1\%$ of subjects in the abiraterone acetate group, if the event also occurred at a higher incidence in the abiraterone acetate group compared with the placebo group, and if the absolute difference in the incidence between the two groups was $\geq 1\%$. The sponsor applied ADR assessment criteria based on the Council for International Organisations of Medical Sciences (CIOMS) Working Groups III and V (1999), and medical judgment to determine which terms were ADRs.

In Study COU-AA-301, ADRs all grades observed at a frequency of $\geq 1\%$ in the abiraterone acetate group and with a frequency of $\geq 1\%$ of that in the placebo group were: oedema peripheral (24.9% versus 17.3%); hypokalaemia (17.1% versus 8.4%); urinary tract infection (11.5% versus 0.5%); hypertension (8.5% versus 6.9%); ALT increased (2.7% versus 1.3%); tachycardia (2.7% versus 1.5%); cardiac failure 2.0% versus 1.0%; atrial fibrillation (2.1% versus 1.3%); angina pectoris (1.3% versus 0.5%); hypertriglyceridaemia (1.3% versus 0%); and arrhythmia (1.0% versus 0%).

Deaths and other serious adverse events

Deaths

Deaths occurring from the start of treatment to 30 days after the last dose of study medication were tabulated by cause of death. All deaths reported in the integrated safety population are summarised below in Table 30.

Table 30: All deaths; integrated safety summary.

Cause of Death	Placebo COU-AA- 301 (N=394)	AA COU-AA- 301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Total no subjects who died during treatment or within 30 days of last dose	52 (13.2%)	84 (10.6%)	11 (3.9%)	95 (8.9%)
Progressive disease	39 (9.9%)	60 (7.6%)	3 (1.1%)	63 (5.9%)
Other ^a	13 (3.3%)	23 (2.9%)	5 (1.8%)	28 (2.6%)
Unknown	0	1 (0.1%)	3 (1.1%)	4 (0.4%)

Note: Study COU-AA-301 data presented in this table were derived from the follow-up page of the CRF.

^a Subjects who died of "other" causes in Study COU-AA-301, within 30 days of last dose most frequently had unwitnessed events that were generically described as "cardiopulmonary arrest". Additional causes of death within 30 days were myocardial infarction, pulmonary embolism, and infection.

The AEs with an outcome of death occurring at any time during the study or during survival follow up, through to the clinical cutoff date of 22 January 2010. In Study COU-AA-301, in the abiraterone acetate group, 11.6% of subjects had an AE with an outcome of death compared with 14.7% in the placebo group. The most common AE with an outcome of death in both the abiraterone acetate and placebo groups was disease progression (8.3% versus 9.6%, respectively). All other AEs with an outcome of death were reported in ≤ 1.0% of subjects in both treatment groups. In none of the SOC's was death reported more frequently in the abiraterone acetate group than in the placebo group.

In the overall abiraterone acetate group (integrated safety population), 9.9% of subjects had an AE with an outcome of death (11.6% in Study COU-AA-301 and 5.0% in the pooled Phase I/II studies). In Study COU-AA-301, investigators were specifically instructed to record disease progression as an AE on the CRF. However, this was not done in the pooled Phase I/II studies. As a result, 6% of subjects in the overall abiraterone acetate group, and only 1% of subjects in the pooled Phase I/II studies group had disease progression AEs with an outcome of death. As of the data cutoff of 22 January 2010, no deaths had been reported in the 100 subjects in the supportive data (non integrated safety population), or in the 309 subjects in the non cancer Phase I PK studies.

Other serious AEs

In Study COU-AA-301, SAEs were reported in 37.5% of subjects in the abiraterone acetate group compared with 41.4% of subjects in the placebo group. The most common SAEs occurring with an incidence of ≥ 1% in either treatment group (abiraterone acetate vs placebo) were: anaemia (2.8% versus 3.3%); spinal cord compression (2.5% versus 4.3%); pneumonia (1.9% versus 1.0%); bone pain (1.8% versus 3.3%); urinary tract infection (1.8% versus 0.8%); vomiting (1.5% versus 2.3%); dehydration (1.5% versus 1.3%); disease progression (1.4% versus 0.5%); hydronephrosis (1.4% versus 0.8%); sepsis (1.1% versus 0.5%); haematuria (1.1% versus 2.8%); fatigue (0.9% versus 1.5%); urinary retention (0.9% versus 1.3%); dyspnoea (1.0% versus 0.9%); back pain (0.8% versus 3.3%); renal failure acute (0.8% versus 1.0%); pyrexia (0.6% versus 2.3%); pain in extremity (0.4% versus 1.8%); pulmonary embolism (0.4% versus 2.3%); arthralgia (0.3% versus 1.0%); and pain (0.1% versus 1.3%)

In Study COU-AA-301, Grade 3 or 4 SAEs were reported in 32.1% (23.9% [G3] and 8.2% [G4]) of subjects in the abiraterone acetate group compared with 35.3% (26.9% [G3] and 8.4% [G4]) of subjects in the placebo group. The most common Grade 3 or 4 SAEs occurring with an incidence of $\geq 1\%$ in either treatment group (abiraterone acetate versus placebo) were: spinal cord compression (2.3% versus 4.3%); anaemia (2.3% versus 1.8%); bone pain (1.6% versus 3.0%); pneumonia (1.3% versus 0.8%); dehydration (1.3% versus 1.3%); vomiting (1.3% versus 0.8%); disease progression (1.1% versus 0.3%); hydronephrosis (1.1% versus 0.5%); urinary tract infection (1.1% versus 0.5%); urinary retention (0.9% versus 1.3%); renal failure acute (0.8% versus 1.0%); pain in extremity (0.4% versus 1.5%); pulmonary embolism (0.4% versus 2.3%); pain (0.1% versus 1.3%); and arthralgia (0% versus 1.0%).

In Study COU-AA-301, AEs leading to hospitalisation were reported in 37.4% of subjects in the abiraterone acetate group and 41.4% of subjects in the placebo group. The most common AEs leading to hospitalisation and occurring with an incidence of $\geq 1\%$ in either treatment group (abiraterone acetate versus placebo) were: disease progression (4.2% versus 3.3%); anaemia (2.7% versus 3.3%); spinal cord compression (2.4% versus 4.3%); pneumonia (1.9% versus 1.3%); urinary tract infection (1.8% versus 0.8%); bone pain (1.8% versus 3.3%); dehydration (1.4% versus 1.3%); vomiting (1.5% versus 2.3%); sepsis (1.3% versus 0.5%); hydronephrosis (1.3% versus 0.8%); haematuria (1.1% versus 2.8%); renal failure acute (0.9% versus 1.3%); dyspnoea (0.9% versus 1.5%); urinary retention (0.9% versus 1.3%); pulmonary embolism (0.8% versus 1.8%); fatigue (0.8% versus 1.3%); back pain (0.6% versus 2.8%); pain in extremity (0.4% versus 1.8%); and arthralgia (0.3% versus 1.0%).

In the abiraterone acetate group (integrated safety population), SAEs occurred in 37.1% of subjects (37.5% in Study COU-AA-301 and 35.8% in the Phase I/II studies). In the supportive data (non integrated safety population), SAEs were reported in 5 of the 12 subjects who were treated at doses other than 1 g abiraterone acetate in Study COU-AA-001. SAEs were reported in 3 of the 21 subjects who were treated at doses other than 1 g abiraterone acetate in Study COU-AA-002. No SAEs were reported in Studies COU-AA-006 and COU-AA-015. Across all Phase I PK (non cancer) studies, one SAE was reported in Study COU-AA-014 (one subject experienced an SAE of abdominal pain, which led to study discontinuation).

Discontinuations due to AEs

Overall discontinuations and reasons

During study COU-AA-301, the sponsor found that the reasons for discontinuation of study medication were not recorded consistently across study centres, particularly with respect to disease progression. To improve consistency and provide a more accurate representation of discontinuations in Study COU-AA-301 the sponsor medically reviewed the blinded data for each subject and recategorised the reasons for discontinuation. All reasons leading to treatment discontinuation in the integrated safety population are summarised below in Table 31, with discontinuation reasons for Study COU-AA-301 being based on the sponsor's review.

Table 31: Reasons for treatment discontinuation; integrated safety population

	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Subjects treated	394 (100.0%)	791 (100.0%)	279 (100.0%)	1070 (100.0%)
Subjects with treatment on-going	54 (13.7%)	222 (28.1%)	58 (20.8%)	280 (26.2%)
Subjects discontinued from treatment ^a	340 (86.3%)	569 (71.9%)	221 (79.2%)	790 (73.8%)
Disease progression	112 (28.4%)	219 (27.7%)	164 (58.8%)	383 (35.8%)
Adverse event	70 (17.8%)	98 (12.4%)	29 (10.4%)	127 (11.9%)
Initiation of new anti-cancer treatment	64 (16.2%)	107 (13.5%)	2 (0.7%)	109 (10.2%)
Withdrew consent ^c	44 (11.2%)	75 (9.5%)	4 (1.4%)	79 (7.4%)
Investigator discretion ^b	27 (6.9%)	36 (4.6%)	0 (0.0%)	36 (3.4%)
Death	9 (2.3%)	21 (2.7%)	3 (1.1%)	24 (2.2%)
Other	10 (2.5%)	7 (0.9%)	4 (1.4%)	11 (1.0%)
Dosing non-compliance	3 (0.8%)	3 (0.4%)	3 (1.1%)	6 (0.6%)
Administration of prohibited medication ^b	1 (0.3%)	3 (0.4%)	0 (0.0%)	3 (0.3%)
Symptomatic deterioration	0 (0.0%)	0 (0.0%)	2 (0.7%)	2 (0.2%)
Completed treatment (12 cycles) ^d	0 (0.0%)	0 (0.0%)	10 (3.6%)	10 (0.9%)

^a Discontinuation reason for Study COU-AA-301 is based on sponsor review.

^b Discontinuation reason category was not collected for Phase I/II studies.

^c Withdrew consent includes Withdrawal of Consent to Treatment and Subject Choice (Study COU-AA-301).

^d Refers to subjects who completed 12 cycles of treatment, discontinued, and did not enter any study.

In Study COU-AA-301, treatment discontinuations were high in both groups, and were reported notably more commonly in the placebo group than in the abiraterone acetate group (86.3% versus 71.9%). The main reason for discontinuation in both groups was disease progression, and this occurred in a similar proportion of subjects in both the abiraterone acetate and placebo groups (27.7% and 28.4%, respectively). The major difference between the two groups was the higher proportion of patients discontinuing due to AEs in the placebo group compared with the abiraterone acetate group (17.8% versus 12.4%).

The proportion of subjects in the abiraterone acetate group (integrated safety population) who discontinued treatment was 73.8%, with 35.8% discontinuing due to disease progression and 11.9% discontinuing due to AEs. A higher proportion of abiraterone treated subjects in the Phase I/II studies discontinued due to disease progression (58.8%), compared with abiraterone treated subjects in Study COU-AA-301 (27.7%). The higher proportion in the Phase I/II studies is likely to be attributable to more rigorously defined criteria for disease progression in Study COU-AA-301, which mandated that subjects were to have had PSA progression, radiographic progression, and symptomatic or clinical progression in order to have discontinued due to disease progression.

Treatment discontinuations specifically due to AEs

In Study COU-AA-301, discontinuations due to AEs occurred in 18.7% of subjects in the abiraterone acetate group and 22.3% of patients in the placebo group. AEs leading to discontinuation and occurring in $\geq 1\%$ of subjects in either of the two groups (abiraterone acetate vs placebo) were: disease progression (6.1% versus 5.3%); spinal cord compression (0.9% versus 2.0%); and fatigue (0.6% versus 1.0%). SOC disorders leading to more frequent discontinuations in the abiraterone acetate group than in the placebo group were: general disorders and administration site conditions (7.8% versus 7.6%); cardiac disorders (1.8% versus 1.5%); gastrointestinal disorders (1.6% versus 1.0%); investigations (0.8% versus 0.5%), predominantly related to differences in increased AST

and ALT levels; renal and urinary disorders (0.8% versus 0.5%); injury poisoning and procedural complications (0.6% versus 0.3%); and neoplasms benign, malignant and unspecified, including cysts and polyps (0.6% versus 0.3%).

AEs leading to treatment discontinuation were reported in 17.7% of subjects in the abiraterone acetate group (integrated safety population), with the most frequently reported being disease progression (4.6% of subjects). In the pooled data (non integrated safety population), one subject in Study COU-AA-002 treated with 250 mg of abiraterone acetate discontinued due to an AE (Grade 3 syncope). In Study COU-AA-001, no subjects treated with doses other than 1 g of abiraterone acetate had AEs resulting in treatment discontinuation. In Studies COU-AA-006 and COU-AA-015, no subjects had AEs resulting in treatment discontinuation. Discontinuations due to AEs were reported in three subjects who were treated in the Phase I PK (non cancer) studies. In Study COU-AA-006, two subjects (2%) discontinued due to AEs: one with Grade 1 increases in AST and ALT; and one with Grade 2 vomiting. In Study COU-AA-014, one subject (6%) experienced an SAE resulting in discontinuation (abdominal pain).

AEs leading to dose modification/reduction/interruption

In Study COU-AA-301, 13.8% of subjects in the abiraterone acetate group had a dose modification/reduction/interruption of the study drug due to an AE compared with 12.2% of subjects in the placebo group. AEs leading to modification/reduction/interruption and occurring in $\geq 1\%$ of subjects in either of the two groups (abiraterone acetate vs placebo) were: vomiting (1.3% versus 2.0%); fatigue (1.0% versus 0.8%); hypokalaemia (1.0% versus 0.5%); asthenia (1.0% versus 0%); anaemia (0.9% versus 1.0%); and nausea (0.8% versus 1.8%).

In Study COU-AA-301, 9.9% of subjects in the abiraterone acetate group had a dose modification/reduction/interruption of prednisone/prednisolone compared with 7.4% of subjects in the placebo group. The only individual AE resulting in a dose modification/reduction/interruption in prednisone/prednisolone in $\geq 1\%$ of subjects in either group was vomiting (1.3% and 0.5%, placebo and abiraterone acetate groups, respectively).

Laboratory tests

Overview

The focus in this section is on the results from Study COU-AA-301. Laboratory assessments up to 30 days after the last treatment dose were included in the integrated analysis.

Liver function

LFT (liver function test) AEs are discussed later in this CER.

Kidney function

In Study COU-AA-301, the majority of subjects in both the abiraterone acetate and placebo groups were reported as having serum creatinine Grade 0 toxicity during treatment (87.9% and 90.4%, respectively). The proportion of subjects in the abiraterone acetate and placebo groups with worst on treatment Grade 1 or 2 serum creatinine was 11.7% in the abiraterone acetate group and 9.3% in the placebo group, while the proportion of subjects with worst on treatment Grade 3 or 4 serum creatinine was similar in both treatment groups (0.4% and 0.3%, respectively). The serum creatinine shift tables showed no significant differences between the two treatment groups. Inspection of the graphical representation of the mean serum creatinine concentration over the duration of the study showed that concentrations remained stable in both treatment groups and did not notably differ between the two groups.

Other biochemistry

In Study COU-AA-301, 91.9% and 89.3% of subjects in the abiraterone acetate and placebo groups, respectively, had baseline serum chemistry concentrations of Grade 0, 1, or 2. During the study, most subjects in both groups had serum chemistry abnormalities but most remained at Grade 2 or lower. Grade 3 or 4 serum chemistry abnormalities during treatment were reported in 32.6% of subjects in the abiraterone acetate group and 24.6% of subjects in the placebo group. The most frequently reported Grade 3 or 4 serum chemistry abnormality in each group was ALP occurring in 17.7% of subjects in the abiraterone acetate group and 13.4% of subjects in the placebo group. Elevations in ALP were attributed to progressive disease in the bone. No other Grade 3 or 4 serum chemistry abnormality (including low potassium) occurred in greater than 7% of subjects in the abiraterone acetate group or greater than 6% of subjects in the placebo group.

Haematology

In Study COU-AA-301, 92.9% and 93.3% of subjects in the abiraterone acetate and placebo groups, respectively, entered the study with Grade 0, 1, or 2 haematology concentrations. During the study, most subjects in both groups had haematologic abnormalities but most remained at Grade 2 or lower. The proportion of subjects with Grade 3 or 4 haematology worst grade abnormalities during treatment was 26.0% and 25.8% in the abiraterone acetate and placebo groups, respectively. The most common Grade 3 or 4 haematologic abnormality during treatment in both groups was lymphocyte abnormalities, occurring in 20.8% of subjects in the abiraterone acetate group and 22.9% of subjects in the placebo group. No other haematologic Grade 2, 3 or 4 abnormality (i.e. neutrophils, platelets, WBC) during treatment occurred in greater than 5% of subjects in the abiraterone acetate group or in greater than 3% of subjects in the placebo group. The proportion of subjects with Grade 3 or 4 haemoglobin abnormalities was 4.7% in the abiraterone acetate group and 3.2% in the placebo group. Inspection of the graphical representations of the mean values for haemoglobin (mean concentration), platelet count, WBC, and neutrophil count over the duration of the study showed that levels remained relatively stable in both treatment groups and did not notably differ between the two groups.

Urinalysis

In Study COU-AA-301, there were no data on changes in routine urinalysis parameters over the duration of the study as only baseline testing was undertaken.

Vital signs

In Study COU-AA-301, overall there were no significant differences in blood pressure, heart rate, respiration, or temperature between the abiraterone acetate and placebo groups over the course of the study. However, in the abiraterone acetate group four subjects had vital sign SAEs and one of these subjects discontinued study medication because of this event.

Electrocardiograms/MUGA/ECHO Scan

a. ECG

In Study AA-COU-301, a standard 12 lead ECG was performed at the screening visit, on Day 1 of Cycles 4, 7, and 10, at treatment discontinuation if applicable, and at the end of study visit. The sponsor considered the following to be limitations of the ECG data in the pivotal study: the study was not intended as a controlled QTc study; QTc values were calculated based on database entries of ventricular rate and QT from a local machine, and formal ECG interpretation was not always obtained and was not required per the protocol; and a single ECG was recorded per visit and ECG methodology was not standardised across study sites.

In Study COU-AA-301, QTcF (ms) change from baseline > 30 ms was reported in 15.9% (104/654) and 10.1% (31/306) of subjects in the abiraterone acetate and placebo groups respectively, and the corresponding proportions of subjects with changes > 60 ms were 5.2% (34/654) and 2.3% (7/306). The proportion of subjects (abiraterone acetate versus placebo) with post dose QTcF > 450 ms was 20.9% (141/675) versus 15.4% (48/311), QTcF > 480 ms 5.5% (38/675) versus 3.9% (12/311), and QTcF > 500 ms 2.2% (15/675) versus 1.9% (6/311). The mean (SD) maximum post baseline increase in QTcF was 25 (28) ms in the abiraterone group (n=394) and 21 (26) msec in the placebo group. Overall, the results showed that subjects in the abiraterone acetate group experienced greater increases in the QTcF interval compared with subjects in the placebo group. However, these results are difficult to interpret given the design deficiencies mentioned above.

The pivotal QTc study is COU-AA-006, which has been discussed in the Pharmacodynamic section of this report. This study showed that there was no significant difference between abiraterone acetate and placebo as regards the QTcF using PKs and time matched ECGs in subjects with mCRPC.

b. Multiple Gated Acquisition (MUGA)/Echocardiogram (ECHO) Scan

In Study COU-AA-301, MUGA (Multi Gated Acquisition) or ECHO (echocardiogram) scans performed at baseline and at one or more post baseline visits were reported in 27% (n=217) of subjects in the abiraterone acetate group and 29% (n=115) of subjects in the placebo group. The following were considered by the sponsor to be limitations of the MUGA and ECHO data: both intersubject and intrasubject variability in the MUGA or ECHO; MUGA or ECHO scans were performed at baseline and at the end of the study for subjects without prior mitoxantrone therapy; and MUGA or ECHO scans were performed every 3 cycles for subjects with prior mitoxantrone therapy.

Based on MUGA or ECHO scan results, the percentage of subjects who had a decrease in LVEF from baseline of at least 15% at any time during the study was similar in the abiraterone acetate and placebo groups (6.0% [13/217] and 5.2% [6/115], respectively).

Mitoxantrone has been associated with functional cardiac changes including congestive cardiac failure and decreased LVEF (left ventricular ejection fraction). In Study COU-AA-301, there were 162 (14%) subjects with a history of prior mitoxantrone administration enrolled in the MUGA/ECHO substudy (105 [13%] in the abiraterone acetate group and 57 [14%] in placebo group). Of these 162 subjects, 8 (5%) had a post baseline LVEF < 50% during the study and all 8 subjects had a baseline LVEF ≥ 50%. The change from baseline in LVEF ranged from 4% to 22% and was ≥10% in 7 of the 8 subjects. Of the 8 subjects, 5 had received abiraterone acetate and 3 had received placebo. Of the 8 subjects, 7 had pre existing cardiac risk factors in addition to prior mitoxantrone treatment, and the remaining subject had no additional reported cardiac risk factors.

AEs of special Interest

Overview

AEs of special interest were selected by the sponsor based on data obtained throughout the abiraterone acetate development program. The search criteria for the AEs of special interest were based on the AE term (Standardized MedDRA Query [SMQ]) and the laboratory assessment, as applicable. If a SMQ did not exist, a compilation of terms that reflected the event was used for extraction and analysis of the data. The SMQ AEs of special interest were fluid retention/oedema, hypokalaemia, hepatotoxicity (LFT abnormalities), hypertension, and cardiac disorders.

In Study COU-AA-301, SMQ AEs (all Grades) of special interest occurred in 55.2% and 43.9% of subjects in the abiraterone acetate and placebo groups, respectively, and Grade 3, 4, or 5 SMQ AEs of special interest occurred in 14.4% and 8.1%, of subjects in the two

groups, respectively. The AEs of special interest event rate per 100 PY of exposure were 202.6 in the abiraterone acetate group and 184.5 in the placebo group.

Fluid retention/oedema

All results in this section refer to Study COU-AA-301 unless stated otherwise. SMQ special events of interest categorised as fluid retention/oedema were reported in 30.5% of subjects in the abiraterone acetate group and 22.1% of subjects in the placebo group. Peripheral oedema accounted for most of these events (24.9% in the abiraterone acetate group and 17.3% in the placebo group).

Fluid retention/oedema events per 100 PY were 71.1 in the abiraterone acetate group and 65.3 in the placebo group (difference of ~6 events per 100 PY), with the corresponding rates for peripheral oedema being 53.8 and 44.1 (difference of ~10 events per 100 PY).

Grade 3 or 4 peripheral oedema was reported in 1.5% of subjects in the abiraterone acetate group and 0.8% of subjects in the placebo group, with no Grade 5 events being reported in either group. For the preferred term, oedema peripheral, SAEs were reported in 0.4% of subjects in the abiraterone acetate group and no subjects in the placebo group. No subjects in either group discontinued study medication or had oedema peripheral events with an outcome of death.

In the Phase I/II studies group, SMQ events categorized as fluid retention/oedema were reported in 35% of subjects. The preferred term, oedema peripheral, was reported in 28% of subjects and accounted for most of these events. Grade 3 oedema peripheral was reported in 0.4% of subjects; no Grade 4 or 5 events were reported. For the preferred term, oedema peripheral, SAEs and discontinuations were each reported in 0.7% of subjects. No peripheral oedema AEs with an outcome of death were reported.

Hypokalaemia

All results in this section refer to Study COU-AA-301 unless stated otherwise. SMQ special events categorised as hypokalaemia were reported in 17.1% of subjects in the abiraterone acetate group and 8.4% of subjects in the placebo group. Hypokalaemic events per 100 PY were 46.5 in the abiraterone group and 28.7 in the placebo group (difference of ~ 18 events per 100 PY).

Grade 3 or 4 hypokalaemia was reported in 3.8% of subjects in the abiraterone acetate group and 0.8% of subjects in the placebo group, with no Grade 5 events being reported in either group. For the preferred term, hypokalaemia, SAEs were reported in 0.8% of subjects in the abiraterone acetate group and no subjects in the placebo group. No subject in either group discontinued study medication due to hypokalaemia, and no hypokalaemia AEs with an outcome of death were reported.

In the Phase I/II studies, SMQ hypokalaemia was reported in 35% of subjects and Grade 3 or 4 hypokalaemia in 3% of subjects. For the preferred term, hypokalaemia, SAEs were reported in 3% of subjects and AEs leading to discontinuation were reported in 0.4% of subjects. One subject in Study COU-AA-BE died due to hypokalaemia.

Hypertension

All results in this section refer to Study COU-AA-301 unless otherwise stated. SMQ special events categorised as hypertension were reported in 9.7% of subjects in the abiraterone acetate group and 7.9% of subjects in the placebo group. Hypertension SMQ events per 100 PY were 19.1 in the abiraterone group and 20.1 in the placebo group (difference of 1 event per 100 PY).

Grade 3 hypertension was reported in 1.3% of subjects in the abiraterone acetate group and 0.3% of subjects in the placebo group, and no Grade 4 or 5 hypertension events were reported in either group. For the preferred term, hypertension, SAEs were reported in 0.4% of subjects in the abiraterone acetate group and no subjects in the placebo group. No

subject in either group discontinued study medication due to hypertension AEs, and no hypertension AEs with an outcome of death were reported.

In the Phase I/II studies group, SMQ special events categorised as hypertension were reported in 23% of subjects. Most events were individual AEs of the preferred term, hypertension, occurring in 22% of subjects. Grade 3 hypertension was reported in 1% of subjects, and no Grade 4 or 5 events were reported. For the preferred term, hypertension, SAEs were reported in 0.7% of subjects. No subject discontinued study medication for hypertension AEs, and no hypertension AEs with an outcome of death were reported.

Cardiac disorders

All results in this section refer to Study COU-AA-301 unless otherwise stated. SMQ special events categorised as cardiac disorders were reported in 13.4% and 10.7% of subjects in the abiraterone acetate and placebo groups, respectively. Cardiac disorder SMQ events per 100 PY were 32.9 in the abiraterone group and 28.1 in the placebo group (difference of ~5 events per 100 PY).

The most frequently reported cardiac disorder events were the preferred terms of tachycardia (2.7% and 1.5% of subjects in the abiraterone acetate and placebo groups, respectively), and atrial fibrillation (2.1% and 1.3%, respectively). Myocardial infarction was reported in 0.8% of subjects in each group. "Cardiac failure", which includes the preferred terms of cardiac failure, cardiac failure congestive, ejection fraction decreased, and left ventricular dysfunction, was reported in 2% of subjects in the abiraterone acetate group and 1% of subjects in the placebo group. There was a difference of ~2 events per 100 PY for atrial fibrillation between the two groups (4.7 events and 2.9 events in the abiraterone and placebo groups, respectively), and a difference between the two groups of ~ 1.5 events per 100 PY for tachycardia was also observed (4.7 and 3.4 events in the abiraterone and placebo groups, respectively).

No Grade 3, 4, or 5 tachycardia events were reported in either group. Grade 3 atrial fibrillation events were reported in 0.6% and 0.5% of subjects in the abiraterone acetate and placebo groups, respectively, with no subject in either group having a Grade 4 or 5 event. SAEs classified in the Cardiac Disorders SOC were reported in 2.9% of subjects in the abiraterone acetate group and 1.3% of subjects in the placebo group. The most frequently reported preferred terms under the Cardiac Disorders SOC were myocardial infarction (0.6% and 0.3% of subjects in the abiraterone acetate and placebo groups, respectively), and atrial fibrillation (0.5% of subjects in each group). No SAEs due to the preferred term tachycardia were reported in either group. AEs (all grades) classified in the Cardiac Disorders SOC leading to treatment discontinuation occurred in 1.8% and 1.5% of subjects in the abiraterone acetate and placebo groups, respectively. The most commonly reported preferred terms under the Cardiac Disorders SOC leading to treatment discontinuation were myocardial infarction (0.4% and 0.5% of subjects in the abiraterone acetate and placebo groups, respectively), and cardio respiratory arrest (0.5% and 0% subjects, respectively). The rate of cardiac events with an outcome of death was similar in the abiraterone acetate and placebo groups (1.1% and 1.3% of subjects, respectively).

In the Phase I/II studies, events categorised in the cardiac disorders SMQ were reported in 10.0% of subjects. The most frequently reported cardiac disorder events were the preferred terms, atrial fibrillation and syncope (1.8% each). "Cardiac failure" was reported in 0.4% of subjects. No Grade 3, 4, or 5 atrial fibrillation or tachycardia events were reported. Grade 3 syncope was reported in 2% of subjects, and no Grade 4 or 5 events were reported. SAEs in the Cardiac Disorders SOC were reported in 3% of subjects. The most frequently reported preferred SAE term under the Cardiac Disorders SOC was atrial fibrillation (1%). No SAEs due to the preferred term, tachycardia, were reported. AEs (all grades) in the Cardiac Disorders SOC led to treatment discontinuation in 2% of subjects. The most commonly reported preferred term under the Cardiac Disorders SOC leading to

treatment discontinuation was myocardial infarction (0.7%). AEs in the Cardiac Disorders SOC with an outcome of death were reported in 1.1% of subjects, with myocardial infarction being the most frequently reported event (0.7%).

Hepatic safety

a. Overview

The CSS (Cross Sectional Study) included an assessment of hepatic safety based on SMQ criteria for hepatic AEs ("hepatotoxicity [LFT abnormalities]"), hepatotoxicity laboratory abnormalities, and Hy's Law/eDish criteria for drug induced liver injury. As the assessments used the same clinical databases there was overlapping of results across the assessments which complicated the overall interpretation of the data. Furthermore, post database lock results were provided for some assessments but not for others resulting in minor numerical differences among the assessments.

In Study COU-AA-301, ~8 months after the first subject was enrolled the frequency of LFTs was increased to every 2 weeks for the first 3 months of treatment. The NCI-CTCA v3.0 criteria for LFT toxicities are summarised below in Table 32.

Table 32: Laboratory LFT toxicities (NCI-CTCAE v3.0).

LFT	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
ALT	> ULN -2.5 x ULN	> ULN -5 x ULN	> 5 - 20 x ULN	> 20 x ULN	-
AST	> ULN -2.5 x ULN	> ULN -5 x ULN	> 5 - 20 x ULN	> 20 x ULN	-
ALP	> ULN -2.5 x ULN	> ULN -5 x ULN	> 5 - 20 x ULN	> 20 x ULN	-
Bilirubin	> ULN - 1.5 x ULN	> 1.5 - 3 x ULN	> 3 - 10 x ULN	> 10 x ULN	-

SMQ search ("hepatotoxicity [LFT abnormalities]") - AEs of special interest

In Study COU-AA-301, hepatic SMQ AEs were reported in 10.4% (n=82) of subjects in the abiraterone acetate group and 8.1% (n=32) of subjects in the placebo group. However, when standardised for duration of exposure there were approximately 9 fewer events per 100 PY in the abiraterone group than in the placebo group (33.1 versus 42.4 per 100 PY, respectively). There was one case of hepatic encephalopathy reported in the placebo group and no cases in the abiraterone acetate group. The most frequently reported individual hepatic SMQ AEs (abiraterone acetate versus placebo) were the preferred terms of ALP increase (4.2% and 4.1%), AST increase (3.9% and 3.8%), ALT increase (2.7% versus 1.3%), and hyperbilirubinaemia (1.3% versus 1.8%). The event rates per 100 PY (abiraterone acetate versus placebo) for ALP increases were 9.1 versus 13.2, for AST increases were 10.4 and 10.9, for ALT increases were 5.3 and 4.0, and for hyperbilirubinaemia were 3.5 and 4.6.

In Study COU-AA-301, the incidence of Grade 3 and 4 ALP occurred in 1.3% (n=10) and 0.1% (n=1) of subjects in the abiraterone acetate group, respectively, and 1.3% (n=5) and 0.3% (n=1) of subjects, respectively, in the placebo group. Grade 3 and 4 AST increase occurred in 0.9% (n=7) and 0.1% (n=1) of subjects in the abiraterone acetate group, respectively, and the corresponding figures in the placebo group were 0.8% (n=3) and 0.3% (n=1). Grade 3 and 4 ALT increase occurred in 0.9% (n=7) and 0% (n=0) of subjects in the abiraterone acetate group, respectively, and the corresponding figures in the placebo group were 0.3% (n=1) and 0.3% (n=1). Grade 3 and 4 hyperbilirubinaemia occurred in 0.4% (n=3) and 0% (n=0) of subjects in the abiraterone acetate group, and the corresponding figures in the placebo group were 0.5% (n=2) and 0.3% (n=1). No Grade 5 ALP, AST or ALT increases, or hyperbilirubinaemia, were reported in either group.

In Study COU-AA-301, SAEs for the preferred terms ALP increased, AST increased, ALT increased, or hyperbilirubinaemia, were reported in 0.1%, 0.1%, 0.3%, and 0.1% of subjects in the abiraterone acetate group, respectively, and 0%, 0.3%, 0.3%, and 0.3% of subjects in the placebo group, respectively. Treatment discontinuations due to ALP increase, AST increase, ALT increase, or hyperbilirubinaemia were reported in 0.1%, 0.5%, 0.4%, and 0.1% of subjects in the abiraterone acetate group, respectively, and 0%, 0.3%, 0%, and 0% subjects in the placebo group, respectively. No AEs with an outcome of death were reported for any of these events in either group.

In the Phase I/II studies, hepatic SMQ AEs were reported in 27% of subjects. The most frequently reported individual AEs were the preferred terms AST increased (14%), ALP increased (9%), ALT increased (8%), and hypoalbuminaemia (7%). Grade 3 or 4 ALP increased were reported in 5.0% of subjects, Grade 3 ALT increased was reported in 1.1% of subjects, and Grade 3 AST increased was reported in 0.7% of subjects. No Grade 4 ALT increase or AST increase were reported, and no Grade 3 or 4 hyperbilirubinaemia was reported. No Grade 5 ALP increase, ALT increase, AST increase, or hyperbilirubinaemia were reported. SAEs of the preferred term AST increased and ALT increased were each reported in 1% of subjects. No SAEs of ALP increase or hyperbilirubinaemia were reported. No subjects discontinued treatment, and no AEs with an outcome of death were reported for any of these events.

b. Hepatotoxicity laboratory abnormalities

In Study COU-AA-301, Grade 3 ALT, AST, and total bilirubin laboratory abnormalities were observed in 1.2% (n=9), 1.4% (n=11), and 0.1% (n=0) of subjects, respectively, in the abiraterone acetate group and in 0.3% (n=1), 0.5% (n=2), and 0 subjects, respectively, in the placebo group. Grade 4 ALT, AST, and total bilirubin laboratory abnormalities were observed in 0%, 0.1% (n=1), and 0% subjects, respectively, in the abiraterone acetate group and in no subjects for any of these three parameters in the placebo group. Grade 3 ALT increases or AST increases and Grade 2 bilirubin increases typically occurred during the first three months of treatment in the abiraterone acetate group in Study COU-AA-301.

In Study COU-AA-301, many subjects in both treatment groups had baseline elevations in ALP, which is commonly observed in subjects with metastatic bone disease. Baseline Grade 1, 2, 3, or 4 ALP elevations occurred in 28%, 11%, 5% and 0.3% of subjects in the placebo group, and the corresponding values for subjects in the abiraterone acetate group were 26%, 12%, 4% and 0.3%. Post baseline elevations in ALP were frequent and were attributed to progressive disease in the bone. Grade 3 ALP laboratory abnormalities occurred in 17.1% and 12.9% of subjects in the abiraterone acetate and placebo groups, respectively, and Grade 4 ALP was observed in 0.6% and 0.5% of subjects, respectively.

In the Phase I/II studies, Grade 3 ALT, AST, and total bilirubin laboratory abnormalities were observed in 1.5%, 1.4%, and 0 subjects, respectively. Grade 4 ALT, AST, and total bilirubin laboratory abnormalities were observed in 0.4% subjects for all three parameters. In the overall abiraterone acetate group (integrated safety population), Grade 3 ALT or AST increases and Grade 2 bilirubin increases were reported in 1.2%, 1.4%, and 1.7% of subjects, respectively. In the Phase I/II studies, baseline Grade 3 ALP laboratory abnormalities occurred in 7% of subjects and baseline Grade 4 ALP was reported in no subjects. During the study, Grade 3 and 4 ALP laboratory abnormalities occurred in 20% and 0.7% of subjects, respectively.

c. Hy's Law and eDISH assessment

The sponsor applied Hy's Law criteria across all studies in the integrated safety population to assess the incidence of severe hepatotoxicity. Subjects were considered to be a Hy's Law case if they met the following criteria: peak ALT >3x ULN or AST >3x ULN and total bilirubin \geq 2x ULN at any time post baseline, with ALP \leq 2x ULN, and lacked an underlying clinical condition.

Due to the high prevalence of elevated ALP in the integrated safety population, the sponsor also assessed subjects using the electronic tool for drug induced serious hepatotoxicity (eDISH) methodology. The sponsor states that this method uses the same criteria as those of Hy's Law, except that ALP concentrations are excluded. The eDISH methodology was developed by the FDA, and the FDA websites indicates that the method uses ALT and total bilirubin levels.

The sponsor also undertook an additional search of the clinical database using both SMQ criteria for subjects who had Grade 3 or higher AEs of hepatotoxicity, or Grade 3 or higher liver function test abnormalities (ALT, AST, or total bilirubin). In Study COU-AA-301, both central and local laboratory values were considered for these assessments.

Hy's Law criteria potential cases – drug induced hepatic injury

The sponsor identified two subjects who potentially met Hy's Law criteria: one subject from Study COU-AA-301 and one subject from Study COU-AA-003. However, further review of these cases led the sponsor to conclude that neither subject could be considered to have met all Hy's law criteria. The subject in Study COU-AA-301 had metastatic liver disease at baseline, and the subject in Study COU-AA-003 had an elevated ALP level. Subsequent to the report of hepatotoxicity in the subject in Study COU-AA-301, the study protocol was amended to increase the frequency of monitoring for liver function test abnormalities and to provide specific guidance on the management of hepatotoxicity.

Although the sponsor considered the two cases mentioned above did not meet all Hy's Law criteria, it nevertheless considered them to be examples of drug induced liver injury. Examination of the narratives of these two cases confirms that both cases are consistent with abiraterone acetate induced liver injury. However, while the subject in Study COU-AA-301 had underlying metastatic liver disease at enrollment it appears that this was not contributing to significant functional impairment as baseline ALT, AST, and total bilirubin levels were within normal limits. In addition, although the subject had metastatic bone disease at baseline his baseline ALP was $\leq 2x$ ULN. The subject had a Grade 4 SAE of the preferred term, hepatotoxicity, on Study Day 32, with the ALT being $\sim 40x$ ULN, the AST being $\sim 35x$ ULN, and both the ALP and total bilirubin being $\sim 6x$ ULN. Viral hepatitis serology, including Epstein-Barr virus and cytomegalovirus, were negative. Treatment was permanently discontinued. Transaminase and a total bilirubin had returned to normal levels by Day 62, but ALP remained elevated at $2.7x$ ULN.

In Study COU-AA-003, the subject had an SAE of Grade 4 increased transaminases (AST: 832 IU/L, ALT 822 IU/L, ALP 304 IU/L) and an AE of Grade 2 increased bilirubin (2.28 mg/dL) on study Day 309. He was hospitalised for the elevated transaminase values, which lessened in severity to Grade 3 on Study Day 310, and then to Grade 1 on Study Day 315. Per the CIOMS, the Study Day 323 bilirubin value was 20 (units not specified). The event resolved within 8 days. The subject was rechallenged with abiraterone acetate and completed 12 cycles of treatment without recurrence.

eDISH criteria for hepatotoxicity

The sponsor identified eight subjects who met eDISH criteria for hepatotoxicity, including the two discussed above who were identified as meeting Hy's Law criteria. There were seven subjects from Study COU-AA-301 who met the eDISH criteria (four in the abiraterone acetate group [that is, 0.5%] and three [that is, 0.8%] in the placebo group), and one subject from Study COU-AA-003. The overall incidence in the integrated safety population of abiraterone acetate treated patients was 5/1070 (0.5%). Some, but not all of the relevant data for the eight subjects meeting eDISH criteria could be identified in the submission. Consequently, the sponsor is requested to provide relevant information relating to these patients in a tabulated summary.

SMQ criteria – Grade 3 or higher of hepatotoxicity (all hepatic AEs)

A total of 57 subjects were identified in the search of the clinical database using SMQ criteria for subjects who had Grade 3 or higher AEs of hepatotoxicity during treatment. Of these 57 subjects, 39 were from Study COU-AA-301 (27 [3.4%] in the abiraterone group and 12 [3.0%] in the placebo group) and 18 (6.5%) were abiraterone treated subjects from the Phase I/II studies. When limiting the Grade 3 or 4 AEs to the preferred terms ALT increased, AST increased, hyperbilirubinaemia, or transaminases increased, a total of 25 subjects were identified. Of these 25 subjects, 21 were from Study COU-AA-001 (16 [2.0%] in the abiraterone acetate group and 5 [1.3%] in the placebo group), and 4 were from the abiraterone acetate treated subjects from the Phase I/II studies.

SMQ criteria - Grade 3 or higher LFT abnormalities (ALT, AST, and total bilirubin)

A total of 38 subjects were identified in the search of the clinical database for subjects with Grade 3 or higher ALT, AST, or total bilirubin liver function test abnormalities. Of these 38 subjects, 30 were from Study COU-AA-301 (23 [2.9%] in the abiraterone group and 7 [1.8%] in the placebo group), and 8 [2.9%] were abiraterone acetate treated subjects from the Phase I/II studies. An additional subject from Study COU-AA-004 was identified as having Grade 3 ALT, AST, or total bilirubin liver function test abnormalities. However, laboratory data documenting ALT, AST, or total bilirubin concentration abnormalities from this subject were not present in the CRF at the time of the database lock and, therefore, this subjects was not included in the 38 identified subjects.

Other safety issues***Safety in special populations******Age***

In Study COU-AA-301, the frequency of drug related AEs (excluding Grade 5 events) increased with age across the three age cohorts treated with abiraterone acetate (<65 years, 65-64 years, >75 years), as did drug related Grade 3 or 4 SAEs, drug related AEs leading to discontinuation, and AEs leading to death. A similar pattern was observed in the three age cohorts treated with placebo. The integrated safety set included an examination of safety by age group.

Race

In Study COU-AA-301, White subjects accounted for 93% of the safety population and the imbalance between White and Non-White subjects prevented meaningful comparisons being made between the groups.

Baseline ECOG

In Study COU-AA-301, baseline ECOG scores of 1 were reported for 56% of subjects in the abiraterone acetate group and 55% of subjects in the placebo group. Baseline ECOG scores of 0 were reported for 34% of subjects in each group. In the abiraterone acetate and placebo groups, 10% and 11% of subjects, respectively, had baseline ECOG scores of 2. Formal comparative analyses across the ECOG groups were not done due to the relatively smaller proportion of subjects in the ECOG 2 subgroup in both treatment groups compared with the ECOG 0 and 1 subgroups. However, a higher incidence of Grade 3 or 4 AEs, SAEs, AEs leading to discontinuation, and AEs with an outcome of death were reported among subjects in the abiraterone acetate and placebo groups who had a baseline ECOG score of 1 or 2, compared with those who had a baseline ECOG score of 0. AEs leading to death were about 2 fold higher among subjects with an ECOG score of 0 who were treated with abiraterone acetate compared with placebo. In the ECOG 0 and 1 subgroups, the incidence of Grade 3 or 4 AEs, SAEs, AEs leading to discontinuation were lower in the abiraterone acetate group than in the placebo group.

Baseline liver metastases

In Study COU-AA-301, 11% of subjects in the abiraterone acetate group and 7% of subjects in the placebo group had liver metastases at baseline. There was a higher incidence of Grade 3 or 4 AEs, SAEs, AEs leading to discontinuation, and AEs with an outcome of death in subjects who had baseline liver metastases in both treatment groups, with a lower incidence of these AEs reported among subjects in the abiraterone acetate group compared with the placebo group.

Baseline haemoglobin

In Study COU-AA-301, in both the abiraterone acetate and placebo groups there was an inverse relationship between baseline haemoglobin level and the incidence of Grade 3 or 4 AEs, SAEs, AEs leading to discontinuation, and AEs with an outcome of death (that is, the lower the baseline haemoglobin the higher the incidence of these events). In both treatment groups, subjects with baseline haemoglobin levels < 10 g/dL had the highest incidence of events. Marked increases in the incidence of Grade 3 or 4 AEs were noted among subjects with decreased haemoglobin (69% for haemoglobin Grade >1, 60% for haemoglobin Grade = 1, and 41% for haemoglobin Grade = 0 in the abiraterone acetate group), and SAEs (55% for haemoglobin Grade >1, 40% for haemoglobin Grade = 1, and 28% for haemoglobin Grade = 0) in the abiraterone acetate group. Similar findings were observed in the placebo group.

Prior chemotherapy

In Study COU-AA-301, 30% of subjects in the abiraterone acetate group and 31% of subjects in the placebo group had two prior chemotherapies. Grade 3 or 4 AEs and SAEs were more common in subjects who had two prior chemotherapies than in those with one prior chemotherapy. In the abiraterone acetate group, Grade 3 or 4 AEs were reported in 62% of subjects with two prior chemotherapies and 51% of subjects with one prior chemotherapy, and SAEs were reported in 46% and 34% of subjects, respectively.

Safety related to drug-drug interactions

CYP3A4 is involved in the metabolism of abiraterone. However, increased AEs associated with increased exposure to abiraterone acetate if co administered with CYP3A4 inhibitors are unlikely because of an alternative SULT2A1 mediated metabolic pathway capable of metabolising increased concentrations of abiraterone. However, both *in vivo* and *in vitro* data show that abiraterone is an inhibitor of CYP2D6. Consequently, there is the potential for increased AEs associated with co administered drugs metabolised by CYP2D6 due to increased systemic exposure to these drugs.

Post marketing experience

There is no post marketing experience for abiraterone acetate as the drug is currently not approved for marketing in any country.²³

Evaluator's overall conclusions on clinical safety

- The major safety concern relates to the causal association between abiraterone acetate and drug induced liver injury. The sponsor identified two subjects in the integrated safety population who were considered to have developed abiraterone acetate induced liver injury. Both subjects appeared to meet Hy's Law criteria relating to AST, ALT, and bilirubin levels, but ALP levels were elevated in both subjects and one subject

²³ Sponsor comment: "This was true at submission but was not true at TGA approval as the product had been approved in the US, EU and Canada and launched by TGA approval."

had underlying metastatic liver disease. In both subjects, hepatotoxicity appeared to resolve following cessation of abiraterone acetate, and in one subject abiraterone acetate was apparently reintroduced without recurrence of hepatotoxicity. In the integrated safety population, there were 1070 patients treated with abiraterone acetate. Therefore, based on the two acknowledged cases of hepatotoxicity it can be estimated that the incidence of drug induced liver injury for abiraterone acetate is approximately 1/500 (0.2%) exposed subjects.

- It is possible that the incidence of drug induced hepatotoxicity could be higher than 1/500 (0.2%) exposed subjects. The analysis of the integrated safety population identified 8 subjects who met eDISH criteria. These eight subjects included seven subjects from Study COU-AA-301 (four in the abiraterone acetate group [that is, 0.5%] and three [that is, 0.8%] in the placebo group), and one from Study COU-AA-003. The overall incidence in the integrated safety population of abiraterone acetate treated patients was 5/1070 (0.5%). However, interpretation of the drug induced liver injury data is complicated by the occurrence of placebo (prednisone/prednisolone) treated subjects meeting eDISH criteria.
- More than three decades ago, Zimmerman estimated that the mortality rate from acute liver failure from drug induced hepatocellular injury (that is, transaminase elevations) accompanied by jaundice had a poor prognosis with a 10% to 50% mortality rate (that is, before availability of liver transplantation).²⁴ It can be reasonably assumed that it would be unlikely that patients with mCRPC which has progressed despite docetaxel treatment would be offered liver transplantation in the case of drug induced hepatic injury. Therefore, it can be inferred that drug related hepatic injury due to abiraterone acetate (which was characterised by elevated transaminases and bilirubin) is potentially associated with a mortality rate of 10% to 50% from acute liver failure. Based on an incidence rate of 1/500 for drug induced hepatic injury, and mortality rates of 10% to 50% from acute liver failure following drug induced liver impairment, it can be estimated that the potential risk of mortality from acute liver failure associated with abiraterone acetate is 1/1000 to 1/5000. The “rule of threes” suggests that 3000 to 15000 patients would have needed to have been exposed to abiraterone acetate in the clinical trial program for there to have been a 95% chance of observing one death from acute liver failure caused by the drug at respective rates of 1/1000 and 1/5000. Consequently, the number of patients exposed to the drug in the integrated safety population (n=1070) was too low to expect to have observed a fatality from acute liver failure causally associated with the drug.
- At the time of data cutoff (22 January 2010) in Study COU-AA-301, the median duration of treatment was twice as long in the abiraterone acetate group than in the placebo group (median of 8 cycles [32 weeks] initiated versus 4 cycles [16 weeks] initiated). This resulted in the sponsor expressing adverse event rates per 100 PY for many of the most commonly occurring events.
- In Study COU-AA-301, hepatic SMQ AEs at the database lock were reported in 10.4% (n=82) of subjects in the abiraterone acetate group and 8.1% (n=32) of subjects in the placebo group. However, when standardised for duration of exposure there were approximately 9 fewer events per 100 PY in the abiraterone group than in the placebo group (33.1 versus 42.4 per 100 PY, respectively). The main difference in hepatic SMQ AEs between the two treatment groups was a higher rate of ALT increased events in the abiraterone acetate group compared with the placebo group (2.7% versus 1.3%

²⁴ US Food and Drug Administration, Guidance for Industry: drug-induced liver injury: pre-marketing clinical evaluation, July 2009, Drug Safety. Watkins PB, et al. (2008) Using controlled clinical trials to learn more about acute drug-induced liver injury. *Hepatology* 48:1680-1689.

[absolute]; 5.3 versus 4.0 events per 100 PY [standardised]). Grade 3 and 4 ALT increases were reported in 0.9% and 0% of subjects in the abiraterone acetate group, while in the placebo group Grade 3 and Grade 4 ALT increases each occurred in 0.3% subjects. Treatment discontinuations due to increased ALT levels occurred in 0.4% of subjects in the abiraterone acetate group and no subjects in the placebo group. No subject in either group had AEs of ALP increase, AST increase, ALT increase, or hyperbilirubinaemia with an outcome of death.

- In Study COU-AA-301, Grade 3 ALT, AST, or total bilirubin AE laboratory abnormalities were observed in 1.2% (n=9), 1.4% (n=11), and 0.1% (n=0) of subjects, respectively, in the abiraterone acetate group and 0.3% (n=1), 0.5% (n=2), and 0% subjects, respectively, in the placebo group. Grade 4 ALT, AST, and total bilirubin AE laboratory abnormalities were observed in 0%, 0.1% (n=1), and 0% subjects, respectively, in the abiraterone acetate group and in no subjects for any of these three parameters in the placebo group. Grade 3 ALT/AST increases and Grade 2 bilirubin increases typically occurred during the first three months of treatment in the abiraterone acetate group in Study COU-AA-301.
- In Study COU-AA-301, treatment with abiraterone acetate compared with placebo did not increase the overall incidence of AEs, Grade 3 or 4 AEs, SAEs, AEs leading to treatment discontinuation, or AEs with an outcome of death. The overall incidence of AEs was similar in the abiraterone acetate and placebo groups, while Grade 3-4 AEs, SAEs (total), Grade 3-4 SAEs, AEs leading to treatment discontinuation, and AEs leading to death were all reported more frequently in the placebo group than in the abiraterone acetate group. Mineralocorticoid related toxicities related to the pharmacological action of abiraterone, were reported more frequently in the abiraterone acetate group than in the placebo group (that is, preferred terms of oedema peripheral [25% versus 17%], hypokalaemia [17% versus 8%], and hypertension [9% versus 7%]).
- In Study COU-AA-301, fluid retention/oedema SMQ occurred in 30.5% of subjects in the abiraterone acetate group and 22.1% of subjects in the placebo group. Fluid retention/oedema SMQ events per 100 PY were 71.1 in the abiraterone acetate group and 65.3 in the placebo group (difference of ~6 events per 100 PY), with the corresponding rates for peripheral oedema being 53.8 and 44.1 (difference of ~10 events per 100 PY). Peripheral oedema accounted for most of these events (24.9% in the abiraterone acetate group and 17.3% in the placebo group). Grade 3 or 4 peripheral oedema was reported in 1.5% of subjects in the abiraterone acetate group and 0.8% of subjects in the placebo group, with no Grade 5 events being reported in either group. Generalised oedema was reported in 0.6% of abiraterone treated patients and no placebo treated patients. For the preferred term, oedema peripheral, SAEs were reported in 0.4% of subjects in the abiraterone acetate group and no subjects in the placebo group. No subjects in either group discontinued study medication or had oedema peripheral events with an outcome of death.
- In Study COU-AA-301, hypokalaemia SMQ events were reported in 17.1% of subjects in the abiraterone acetate group and 8.4% of subjects in the placebo group (46.5 and 28.7 events per 100 PY, respectively). For the preferred term, hypokalaemia, SAEs were reported in 0.8% of subjects in the abiraterone acetate group and no subjects in the placebo group. No subject in either group discontinued study medication due to hypokalaemia, and no hypokalaemia AEs with an outcome of death were reported. However, in the pooled safety set there was one reported death due to hypokalaemia.
- In Study COU-AA-301, hypertension SMQ events were reported in 9.7% of subjects in the abiraterone acetate group and 7.9% of subjects in the placebo group (19.1 and 20.1 events per 100 PY). Grade 3 hypertension was reported in 1.3% of subjects in the abiraterone acetate group and 0.3% of subjects in the placebo group, and no Grade 4

or 5 hypertension events were reported in either group. For the preferred term, hypertension, SAEs were reported in 0.4% of subjects in the abiraterone acetate group and no subjects in the placebo group. No subject in either group discontinued study medication due to hypertension AEs, and no hypertension AEs with an outcome of death were reported.

- In Study COU-AA-301, cardiac disorders SMQ were reported in 13.4% and 10.7% of subjects in the abiraterone acetate and placebo groups, respectively (32.9 and 28.1 event per 100 PY). The most frequently reported cardiac disorders were the preferred terms of tachycardia (2.7% and 1.5% of subjects in the abiraterone acetate and placebo groups, respectively), and atrial fibrillation (2.1% and 1.3%, respectively). Myocardial infarction was reported in 0.8% of subjects in each group. The rate of cardiac events with an outcome of death was similar in the abiraterone acetate and placebo groups (1.1% and 1.3% of subjects, respectively).

Preliminary benefit-risk assessment

Preliminary assessment of benefits

- The pivotal study showed that treatment with abiraterone acetate decreased the risk of death by 35% relative to placebo: HR=0.646 [95% CI: 0.543, 0.768]; $p<0.0001$. At the cutoff date of 22 January 2010, there had been 333 (41.8%) deaths in the 797 subjects in the abiraterone acetate group and 219 (55.0%) deaths in the 398 subjects in the placebo group. Median follow up for all subjects was 12.8 months.
- Median survival improved by 36% in the abiraterone acetate group relative to the placebo group (450.0 days [14.8 months] and 332.0 days [10.9 months], respectively). The increased survival time in the abiraterone acetate group of 3.9 months is considered to be clinically meaningful in the population studied. At all time points beyond the initial few months of dosing, a higher proportion of subjects in the abiraterone acetate group was alive compared with subjects in the placebo group. There was a 33% improvement in the 12-month survival rate in subjects in the abiraterone acetate group relative to the placebo group (~ 60% versus ~45%, respectively).
- In a multivariate analysis, OS was statistically significantly increased in the abiraterone acetate group compared with the placebo group after adjustment for four prognostic baseline factors (that is, ECOG status; pain; number of prior cytotoxic regimens; and evidence of disease progression): HR = 0.657 (95%CI: 0.554, 0.780); $p<0.0001$.
- Analyses of the secondary efficacy endpoints in the pivotal study all statistically significantly favoured the abiraterone acetate group compared with the placebo group (that is, PSA progression, PSA response, and radiographic disease progression or death). In addition, exploratory analyses of other efficacy endpoints showed that outcomes were better in the abiraterone acetate group than in the placebo group (that is, objective response according to RECIST criteria, pain palliation rate, time to pain progression, time to first skeletal related event, modified progression free survival, CTC response rate). Exploratory analyses of endpoints relating to functional improvement also suggested greater improvement in the abiraterone acetate group compared with the placebo group.
- In an updated survival analysis at the later clinical cutoff data of 20 September 2010, there had been a total of 775 deaths (97% of planned number for the final analysis), with 501 (62.9%) in the abiraterone acetate group and 274 (68.8%) in the placebo group, with a median follow up of 20.2 months. The HR was 0.740 [95%CI: 0.638,

0.859]; $p < 0.0001$. The median survival improved by 41% in the abiraterone acetate group relative to the placebo group (482 days [15.8 months] and 341 days [11.2 months], respectively). This analysis should be considered supportive as study treatment was unblinded following the interim (that is, primary analysis) and subjects in the placebo group were given the opportunity to crossover to the abiraterone acetate group.

Preliminary assessment of risks

- It is considered that the most significant risk associated with abiraterone acetate treatment for the proposed indication relates to the causal association between the drug and hepatotoxicity. It is estimated that the risk of hepatotoxicity with abiraterone acetate is at least 1/500. From these results it can be estimated that there is a potential risk of death due to liver failure from drug induced hepatotoxicity of 1/1000 to 1/5000. There are also increased risks of mineralocorticoid toxicities associated with abiraterone treatment (that is, hypokalaemia, fluid retention/oedema).
- In an attempt to mitigate the risk of drug induced hepatotoxicity the sponsor recommends that serum transaminase and bilirubin levels should be measured prior to starting treatment with abiraterone acetate, every two weeks for the first three months of treatment, and monthly thereafter. The sponsor recommends that if clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum ALT, should be measured immediately. If at any time the ALT rises above 5x ULN or the bilirubin rises above 3x ULN, treatment with abiraterone should be interrupted immediately and liver function closely monitored. Retreatment with abiraterone acetate at a reduced dose may take place only after the LFTs have returned to baseline levels. The sponsor also recommends that if patients develop severe hepatotoxicity (ALT 20x ULN) at anytime while on therapy, abiraterone acetate should be discontinued and patients should not be retreated with the drug. There are no data on whether the proposed liver function monitoring regimen will mitigate the risk of abiraterone acetate induced hepatotoxicity.
- In the pivotal study, hepatic SMQ AEs at the database lock were reported in 10.4% (n=82) of subjects in the abiraterone acetate group and 8.1% (n=32) of subjects in the placebo group. However, when standardised for duration of exposure there were approximately 9 fewer events per 100 PY in the abiraterone acetate group than in the placebo group (33.1 versus 42.4 per 100 PY, respectively). The main difference in hepatic SMQ AEs between the two treatment groups was a higher rate of ALT increased events in the abiraterone acetate group than in the placebo group (2.7% versus 1.3% [absolute]; 5.3 vs 4.0 events per 100 PY [standardised]). Grade 3 and 4 ALT increases were reported in 0.9% and 0% of subjects, respectively, in the abiraterone acetate group, while in the placebo group Grade 3 and Grade 4 ALT increases each occurred in 0.3% subjects. Treatment discontinuations due to increased ALT levels occurred in 0.4% of subjects in abiraterone acetate group and no subjects in the placebo group. No subject in either group had AEs of ALP increase, AST increase, ALT increase, or hyperbilirubinaemia with an outcome of death. However, the number of patients exposed to abiraterone acetate in the pivotal study was too low to expect to observe mortality due from drug induced liver failure at the rates estimated for the drug.
- In Study COU-AA-301, Grade 3 ALT, AST, and total bilirubin AE laboratory abnormalities were observed in 1.2% (n=9), 1.4% (n=11), and 0.1% (n=0) of subjects, respectively, in the abiraterone acetate group and 0.3% (n=1), 0.5% (n=2), and 0 subjects, respectively, in the placebo group. Grade 4 ALT, AST, and total bilirubin AE laboratory abnormalities were observed in 0%, 0.1% (n=1), and 0% subjects, respectively, in the abiraterone acetate group and no subjects in the placebo group.

Grade 3 ALT/AST increases and Grade 2 bilirubin increases typically occurred during the first three months of treatment in the abiraterone acetate group in Study COU-AA-301.

- In the pivotal study, mineralocorticoid toxicities of fluid retention/oedema and hypokalaemia occurred more frequently in the abiraterone acetate group than in the placebo group: that is, fluid retention/oedema SMQ events 30.5% (71.1 per 100 PY) versus 22.1% (65.3 per 100 PY); and hypokalaemia SMQ events 17.1% (46.5 per 100 PY) versus 8.4% (28.7 per 100 PY). Hypertension SMQ events were reported in 9.7% of subjects in the abiraterone acetate group and 7.9% of subjects in the placebo group, but the respective rates per 100 PY were similar at 19.1 and 20.1 events, respectively. In the pivotal study, Grade 3 and 4 events and SAEs occurred uncommonly in both treatment groups for mineralocorticoid toxicities, no subjects discontinued study medication or had events with an outcome of death. Mineralocorticoid toxicities can be managed by dose reductions or interruptions and/or specific therapies.
- In the pivotal study, cardiac disorders SMQ were reported in 13.4% and 10.7% of subjects in the abiraterone acetate and the placebo groups, respectively (32.9 and 28.1 event per 100 PY). The most frequently reported cardiac disorders were the preferred terms of tachycardia (2.7% and 1.5% of subjects in the abiraterone acetate and placebo groups, respectively), and atrial fibrillation (2.1% and 1.3%, respectively). Myocardial infarction was reported in 0.8% of subjects in each group. The rate of cardiac events with an outcome of death was similar in the abiraterone acetate and placebo groups (1.1% and 1.3% of subjects, respectively).
- In the pivotal study, treatment with abiraterone acetate compared with placebo did not increase the overall incidence of AEs, Grade 3 or 4 AEs, SAEs, AEs leading to treatment discontinuation, or AEs with an outcome of death. The overall incidence of AEs was similar in the two treatment group, while Grade 3-4 AEs, total SAEs, Grade 3-4 SAEs, AEs leading to treatment discontinuation, and AEs leading to death were all reported more frequently in the placebo group than in the abiraterone acetate group.
- There are no safety data on patients with clinically significant heart disease. The pivotal study excluded subjects with clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past six months, severe or unstable angina, or NYHA (New York Heart Association) Class III or IV heart disease or cardiac ejection fraction of < 50% at baseline. Consequently, the use of abiraterone acetate in patients with these conditions should be undertaken with care, if at all.
- There are no safety data on patients with active or symptomatic viral hepatitis or chronic liver disease. However, given the potential of abiraterone acetate to cause hepatotoxicity it is recommended that treatment with this drug should be contraindicated in patients with active or symptomatic viral hepatitis. In addition, the drug should only be used in patients with mild chronic liver disease and should not be used in patients who meet the pivotal study exclusion criteria relating to bilirubin and transaminase levels (that is, serum bilirubin $\geq 1.5 \times \text{ULN}$ [except for subjects with documented Gilbert's disease] or ALT or AST $\geq 2.5 \times \text{ULN}$ [for subjects with known liver metastasis, AST or ALT $\leq 5 \times \text{ULN}$ allowed]).

Preliminary assessment of benefit-risk balance

- The benefit-risk balance of abiraterone acetate, given the proposed usage, is favourable. There are no treatments approved in Australia for patients with mCRPC who have failed to respond to docetaxel (that is, the standard of care).
- It is considered that abiraterone acetate provides a clinically meaningful benefit of increased median OS of 3.9 months compared with placebo. Median OS in the

abiraterone acetate group was 14.8 months compared with 10.9 months in the placebo group. Balanced against this clinical benefit is the risk of hepatotoxicity (1/500), the risk of mineralocorticoid toxicities of fluid retention/oedema (~6 additional events per 100 PY vs placebo) and hypokalaemia (~18 additional events per 100 PY versus placebo), and the risk of cardiac disorders (~5 additional events per 100 PY versus placebo), predominantly tachycardia and atrial fibrillation.

- In an attempt to mitigate the risk of drug induced hepatotoxicity the sponsor has recommended a liver function monitoring regimen, and has provided recommendations on dosage reduction and cessation of treatment in the event of ALT levels rising above prespecified values. However, there are no data on whether the proposed liver function monitoring regimen will mitigate the risk of abiraterone acetate induced hepatotoxicity, and clinical experience suggests that idiosyncratic drug induced hepatotoxicity still occurs despite regular liver function monitoring. In addition to regular monitoring, all patients should have pre treatment ALT/AST and total bilirubin levels assessed and should be excluded from treatment if levels are above those specified in the exclusion criteria of the pivotal clinical study (that is, serum bilirubin $\geq 1.5 \times \text{ULN}$ [except for subjects with documented Gilbert's disease] or ALT or AST $\geq 2.5 \times \text{ULN}$ [for subjects with known liver metastasis, AST or ALT $\leq 5 \times \text{ULN}$ allowed]).
- Reassurance regarding the overall safety of abiraterone acetate comes from the pivotal study which showed that compared with placebo treatment did not increase the incidence of total AEs, Grade 3 or 4 AEs, SAEs, AEs leading to treatment discontinuation, or AEs with an outcome of death. However, the mineralocorticoid related toxicities of peripheral oedema and hypokalaemia were reported more frequently in the abiraterone acetate group compared with the placebo, as were cardiac disorders.

Preliminary comments on clinical aspects of the safety specification in the draft risk management plan

The submission included a Risk Management Plan (RMP) that appears to have been specifically prepared for the EU (European Union) rather than Australia. The clinical aspects of the RMP are satisfactory and include the important identified risks of hypertension, hypokalaemia, fluid retention/oedema, and hepatotoxicity, and the important potential risks of cardiac disorders. It also identifies missing safety information in patients with active viral hepatitis and in patients with clinically significant heart disease.

Preliminary recommendation regarding authorisation

It is recommended that abiraterone acetate in combination with prednisone be approved for the treatment of metastatic advanced prostate cancer (castration resistance prostate cancer) in patients who have received prior chemotherapy containing a taxane.

List of questions

Clinical questions

Efficacy

1. In Study COU-AA-301, how many subjects switched from placebo to abiraterone acetate following unblinding? If switching is taken into account, how does this affect the analysis of OS subsequent to switching?

Sponsor's response:

Following unblinding, 66 subjects switched from placebo to abiraterone acetate. This crossover has no impact on the analysis of OS presented in the dossier, as the updated overall survival analysis for pivotal Study COU-AA-301 was based on a data cutoff of 20 September 2010 before the first patient cross over occurred in October 2010. Therefore, all survival results presented in the marketing application are free from the influence of placebo crossover to active abiraterone acetate.

Clinical comment on response:

The sponsor's response is satisfactory.

Safety

2. Please provide a tabulated summary of relevant data for the eight subjects meeting eDISH criteria. The table should include: study, subject ID, age, treatment, ALT maximum level as a function of ULN, AST maximum level as a function of ULN, ALP maximum level as a function of ULN, total bilirubin maximum level as a function of ULN, time from onset of treatment to maximum levels, concomitant liver disease (yes or no), concomitant bone metastases (yes or no), hospitalisation due to LFT abnormalities (yes or no), resolution of abnormal LFTs (yes or no), and rechallenge (yes or no).

Sponsor's response:

The sponsor provided tables summarising the relevant data from the eight subjects meeting eDISH criteria and the relevant medical history of these eight subjects.

Clinical comment on response:

The sponsor provided the requested information. The eDISH criteria are peak ALT or AST levels $> 3 \times$ ULN and total bilirubin level (TBL) $> 2 \times$ ULN with no other reason found to explain the findings. These criteria are similar to the components of Hy's Law, apart from the component relating to elevated ALP levels $> 2 \times$ ULN without initial findings of cholestasis. The eDISH criteria excluded patients with elevated ALP levels $> 2 \times$ ULN on the basis that such a finding would not be uncommon in patients with metastatic bone and/or liver disease.

3. Of the eight subjects meeting eDISH criteria, the sponsor acknowledged that two were considered to have experienced drug induced liver injury (DILI) due to abiraterone acetate. Please comment on why these two subjects meeting eDISH criteria were considered to have DILI, and why the remaining 6 subjects meeting eDISH criteria were considered not to have experienced DILI.

Sponsor's response:

The sponsor provided explanations for abiraterone treated patients not meeting eDISH criteria, new or updated narratives for abiraterone treated patients, and a list of AST, ALT and TBLs for the eight subjects meeting eDISH criteria for these parameters. The sponsor did not comment on the three patients treated with placebo who met the AST/ALT and TBL eDISH criteria.

Clinical comment on response:

The sponsor's response is satisfactory. Of the eight subjects meeting eDISH laboratory criteria for ALT/AST and TBLs, five had been treated with abiraterone acetate and three with placebo.

A review of the tabulated medical history of the two abiraterone acetate treated subjects who were considered by the sponsor to be DILI examples suggests that reasons other than DILI could account for the abnormal liver function findings: that is, liver metastases, and a

history of transaminitis and gall bladder stones. In addition, one subject appears to have been rechallenged and completed 12 cycles of treatment. It is not clear why these two subjects are considered by the sponsor to be examples of DILI given that both had liver disease that could have accounted for the observed serious hepatotoxicity.

For the remaining three abiraterone acetate treated subjects, the sponsor considers that the liver toxicities were most likely due to extensive hepatic metastatic disease, concomitant medication (paracetamol), blood product transfusions, or underlying infection. Review of the additional narratives provided with the sponsor's response shows that: (1) one subject had bone and liver metastases at enrollment and liver function tests were elevated at screening and throughout the study and, at the time of death, cholestasis was still present; and (2) another subject had metastatic bone and liver disease at enrollment although liver function was normal at screening and remained so throughout the first two months of treatment, but the size of the liver metastases increased while on treatment apparently associated with deteriorating liver function. Review of the available data from the sponsor's response and the original CSR shows that this subject had other possible reasons for abnormal liver function, apart from drug induced toxicity, including excessive paracetamol use, transfusion of blood products, and *Clostridium difficile* colitis.

Overall comment to sponsor's responses:

The sponsor's responses to the List of Clinical Questions are considered satisfactory. There are no further clinical questions relating to this submission.

Final benefit-risk assessment and recommendations

Final assessment of benefits

The clinical information submitted in the sponsor's response does not change the assessment of benefits in the original CER.

Final assessment of risks

The clinical information submitted in the sponsor's response does not change the assessment of risks in the original CER.

Final assessment of benefit-risk balance

The benefit-risk balance for abiraterone acetate, given the proposed usage, is favourable. The clinical information submitted in the sponsor's response does not change the favourable assessment of the benefit-risk balance provided in the original CER.

Final comments on clinical aspects of the safety specification in the draft risk management plan

The clinical information submitted in the sponsor's response does not change the comments on the clinical aspects of the safety specification in the draft risk management plan provided in the original CER.

Final recommendation regarding authorisation

It is recommended that the submission be approved. The clinical information submitted in the sponsor's response does not change the recommendation that the submission be approved provided in the original CER.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan that was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 33.

Table 33: Ongoing safety concerns for abiraterone acetate.

Important identified risks	<ul style="list-style-type: none"> • Hypertension • Hypokalaemia • Fluid retention/oedema • Hepatotoxicity
Important potential risks	<ul style="list-style-type: none"> • Cardiac disorders
Important missing information	<ul style="list-style-type: none"> • Use in patients with active viral hepatitis • Use in patients with heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class III or IV heart disease or cardiac ejection fraction measurement of < 50%

OPR reviewer comment:

It is recommended that the above summary of the Ongoing Safety Concerns is considered acceptable. In the updated RMP Version 2.0, dated 26 July 2011, the sponsor has added the below risks to the summary of safety concerns, which are also considered acceptable (Table 34).

Table 34: Ongoing safety concerns for abiraterone acetate in updated RMP Version 2.0.

Important identified risks:	Cardiac disorders
Important potential risks:	Osteoporosis
	Cataract
	Drug-drug interaction (CYP2D6)
	Increased exposure with food
Important missing information:	Use in patients with moderate/severe hepatic impairments and chronic liver disease
	Use in patients with severe renal impairment
	Use in non-white patients

Pharmacovigilance plan

Routine and additional pharmacovigilance (ongoing and planned clinical trials), is proposed by the sponsor to monitor ongoing safety concerns associated with abiraterone acetate (Table 35).

Table 35: Additional pharmacovigilance; Clinical trials.

Post authorisation study	Assigned safety concerns		
	Identified	Potential	Missing information
Non-clinical studies		Cataract	
Study 212082PCR2008		Increased exposure with food	
Study 212082PCR1004			Use in patients with moderate/severe hepatic impairment and chronic liver disease

Nonclinical studies

Cataracts will be assessed in ongoing nonclinical studies to further inform the mechanism of cataract formation.

Study 212082PCR2008

This is a multicentre, open label study to assess the short term safety of oral abiraterone acetate and oral prednisone administered after meals of various fat contents to subjects with mCRPC. The primary objective of this study is to establish the safety profile of oral abiraterone acetate and oral prednisone following short term administration after standardized low fat or high fat meals to subjects with mCRPC. Outcome measurements will include PK/PD evaluations and safety evaluations (medical history, vital sign measurements, physical examinations, body weight, concomitant therapy, AE reporting, and laboratory tests including blood chemistry, hematology, serum lipids, and urinalysis. Electrocardiograms and measurement of cardiac ejection fraction will also be evaluated for safety. Twenty four subjects will be enrolled in this study. Abiraterone acetate 1 g (four 250 mg tablets) will be taken orally once daily and prednisone 5 mg taken orally twice a day in cycles of 28 ± 2 days.

Study 212082PCR1004

Planned single dose, PK trial in subjects with severe hepatic impairment (protocol is being planned and will be available by end 2011).

OPR reviewer comment:

Targeted follow up through a guided questionnaire will be used to collect clinical information related to the ongoing safety concern hepatotoxicity. However, this questionnaire was not provided with the RMP. Nevertheless, this questionnaire was provided with the request for information response, and it considered acceptable to collect clinical information on hepatotoxicity AEs.

If this submission is approved, the sponsor should provide to the OPR the protocol for the planned single dose, PK trial in subjects with severe hepatic impairment (Study 212082PCR1004). In addition to the protocol, a summary should be provided on how this study is designed to further elucidate and monitor 'Use in patients with moderate/severe hepatic impairment and chronic liver disease'. Please consider factors such as study design, follow up duration and outcome measurements. A date or milestone that these documents will be provided should be submitted.

The milestones for reporting results of the ongoing clinical trials are acceptable.

Risk minimisation activities***Sponsor's conclusion in regard to the need for risk minimisation activities***

In the RMP, it is stated:

No specific risk minimisation activities are planned for abiraterone other than routine.

OPR reviewer comment:

In regard to the proposed routine risk minimisation activities, the draft product information and consumer medicine documents are considered satisfactory.

Potential for medication errors

In the RMP, it is stated:

As with any tablet that is self administered, there is the potential for patients to miss a dose or to take more than the prescribed dose. In the event of a missed dose of abiraterone acetate or the prednisone/prednisolone, treatment should resume the next day with the usual daily dose. There is also the potential that patients will forget to fast and take abiraterone acetate with food. Taking abiraterone acetate with food can result in increased exposure.

Abiraterone acetate should be prescribed by an experienced physician. Should medication errors occur, symptomatic treatment should be provided.

OPR reviewer comment:

This is considered sufficient. 'Increased exposure with food' is listed as a potential safety concern and has adequate routine risk minimisation activities in place (Australian PI).

Summary of recommendations

The OPR provides these recommendations in the context that the submitted RMP is supportive to the application;

It is recommended to the Delegate that the sponsor:

- Implement RMP Version 2.0, dated 26 July 2011, including the sponsor's response to the request for information/documents and any future updates be imposed as a condition of registration.
- If this submission is approved, the sponsor should provide to the OPR the protocol for the planned single dose, PK trial in subjects with severe hepatic impairment (Study 212082PCR1004). In addition to the protocol, a summary should be provided on how this study is designed to further elucidate and monitor 'Use in patients with moderate/severe hepatic impairment and chronic liver disease'. Please consider factors such as study design, follow-up duration and outcome measurements. A date or milestone that these documents will be provided should be submitted.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There are no objections to registration on chemistry, manufacturing or quality control grounds. As regards the bioavailability studies, the dramatic effect of food on bioavailability was raised as a possible area of concern. This is discussed further below.

The application was considered by the PSC at its August 2011 meeting. No objections to registration were raised.

Nonclinical

There are no preclinical objections to registration.

Toxicity was studied in rats and monkeys. Observed toxicities were generally consistent with the mechanism of action of the drug with decreased androgen levels, atrophy of male reproductive organs, and changes to adrenal glands and pituitary. Bile duct hyperplasia and other effects on the liver were also observed. Liver toxicity was also observed in clinical studies (see below).

Clinical

The clinical evaluator has recommended approval of the application.

Pharmacokinetics

Abiraterone acetate is rapidly converted to abiraterone by esterases, with plasma levels of abiraterone acetate generally being undetectable. The absolute bioavailability of abiraterone following oral administration has not been determined. A relative bioavailability study comparing the tablet with a liquid formulation of the drug demonstrated that bioavailability was 4.5 fold greater with the liquid formulation. T_{max} occurs at 2 h. Administration with food results in a marked increase in bioavailability (up to 17 fold increases in AUC). AUC and C_{max} are dose proportional over the range of 750 mg to 1 g, but are slightly greater than dose proportional at lower doses. In patients with mCRPC, systemic exposure increased 2 fold with multiple dosing over 7 days.

In the absence of a study using IV administration, the volume of distribution of the drug has not been determined. Apparent volume of distribution (V_d/F) was very high (5630 L for the central compartment and 17400 L for the peripheral compartment, based on a population PK analysis), suggesting extensive tissue distribution and/or low bioavailability. Protein binding was also high (~99%).

Following oral administration of a radiolabelled dose, only 5% of radioactivity is excreted in the urine, with none as unchanged abiraterone, indicating that the drug is metabolically cleared. Of the total radioactivity in plasma, 92% is in the form of metabolites. A total of 15 metabolites were identified. Two of these – abiraterone sulphate (M45) and N-oxide abiraterone sulphate (M31) – together contributed 87% of the total radioactivity in plasma. Preclinical data indicated that both of these metabolites are active (nonclinical evaluation) and therefore contribute to the overall activity of the drug. The purported main route of metabolism is via sulfation. A proportion of metabolism is also through the CYP450 enzyme system (CYP3A4). No studies have been conducted examining the effects of CYP3A4 inhibitors or inducers on the PK of abiraterone. Apparent clearance (CL/F) was high (2240 L/h) in healthy volunteers but estimated to be reduced by approximately 33% (to 1505 L/h) in mCRPC patients (p32). Half life was approximately 15 h in healthy volunteers and estimated to be 24-28 h in mCRPC patients.

Following oral administration of a radiolabelled dose, the majority of the dose (88%) is recovered in faeces. A large proportion is in the form of unchanged abiraterone acetate (55.3% of the dose) or unchanged abiraterone (22.5% of the dose), suggesting limited absorption.

Compared to subjects with normal hepatic function, systemic exposure was increased 3.6 fold in patients with moderate hepatic impairment. Exposure was not increased in

patients with mild hepatic impairment. The sponsor is proposing to include a statement in the PI advising that the drug should not be used in subjects with pre-existing moderate or severe hepatic impairment. Systemic exposure was not increased in subjects with end-stage renal impairment.

In clinical interaction studies abiraterone was found to be an inhibitor of CYP2D6 (2 fold increase in AUC of dextromethorphan) but not to have any effect on CYP1A2 (no clinically significant change in AUC of theophylline). Preclinical data suggested that abiraterone is unlikely to inhibit or induce other CYP450 enzymes.

Pharmacodynamics (PD)

In the pivotal placebo controlled efficacy study (see below), the effects of abiraterone treatment on androgen production were studied in a subgroup of patients. Abiraterone treatment was associated with reductions in testosterone, DHEA and androstenedione, consistent with the proposed mechanism of action for the drug.

A PK/PD analysis of the pivotal study demonstrated that increased exposure to abiraterone (as measured by C_{min}) was associated with an increased rate of reduction of PSA, and an increased post treatment PSA doubling time.

A separate study demonstrated that abiraterone does not have a clinically significant effect on QT interval.

Efficacy

The dose chosen for study in the pivotal efficacy study was 1 g per day. This choice was based upon the findings that: (a) dose limiting toxicity was not observed at doses up to 2 g per day, and (b) a plateau in the increase in upstream hormones (for example, corticosterone) was observed at a dose of 750 mg per day (Study COU-AA-001).

The main evidence for efficacy comes from a single randomised (2:1), double blind, placebo controlled, parallel groups (x2) design, phase III trial (Study COU-AA-301). The study has been published²⁵ and a copy of the publication is included in the agenda papers.

The trial enrolled subjects with metastatic, castration resistant prostate cancer who had received one or two prior cytotoxic chemotherapy regimens. One of these regimens must have included docetaxel.

Subjects were randomised to receive either:

- Prednisone (or prednisolone) 5 mg twice daily and abiraterone 1 g once daily; or
- Prednisone (or prednisolone) 5 mg twice daily and placebo.

Treatment was continued until disease progression. Subjects were required to have ongoing androgen deprivation (testosterone < 50 ng/dL) through prior orchidectomy or the use of a GnRH agonist.

The primary endpoint was overall survival. Results are summarised in the Table 36.

²⁵ de Bono JS, et al. (2011) Abiraterone and increased survival in metastatic prostate cancer. *N. Engl. J. Med.* 364:1995-2005.

Table 36: Additional pharmacovigilance; Clinical trials.

	Abiraterone	Placebo
First analysis (cut-off 22 January 2010)		
Median survival (months)	14.8	10.9
Hazard ratio (95% CI) p value	0.65 (0.54 – 0.77) < 0.0001	
Updated analysis (cut-off 20 September 2010)		
Median survival (months)	15.8	11.2
Hazard ratio (95% CI) p value	0.74 (0.64 – 0.86) < 0.0001	

A number of secondary endpoints were also examined. Treatment with abiraterone was associated with:

- A significant delay in time to PSA progression;
- A significant delay in time to radiographic progression;
- A significant increase in the rate of PSA response.

The results of a number of other exploratory endpoints also favoured the abiraterone arm. Quality of life measurements also suggested a beneficial effect for the abiraterone arm.

There were two supportive single arm phase II Studies COU-AA-004 and COU-AA-003 that used response rates as a measure of efficacy. The response rates observed (38% and 36% respectively) were consistent with that obtained in the pivotal study (29%).

Safety

In the submitted studies, a total of 1873 subjects were exposed to abiraterone including 1464 subjects with metastatic prostate cancer. A total of 642 subjects received treatment for periods greater than 6 months, and 297 subjects for periods greater than 12 months.

Compared to placebo, abiraterone was not associated with an increase in overall adverse events (AEs), grade 3-4 AEs, serious AEs, discontinuations due to AEs or fatal AEs.

In terms of individual AEs, abiraterone treatment was associated with increased incidences of the following compared to placebo:

- Hypokalaemia 17.1 % versus 8.4 %
- Peripheral oedema 24.9 % versus 17.3 %
- Hypertension 8.5 % versus 6.9 %

Such events are consistent with mineralocorticoid excess, which would be expected given the mechanism of action of the drug.

Abiraterone was associated with hepatotoxicity, with a small increase in the incidence of LFT abnormalities. There were two possible cases of severe DILI. The proposed PI recommends regular monitoring of LFTs.

The drug also appeared to be associated with a small increase in the incidence of cardiac disorders (13.4% versus 10.7%).

Risk management plan

The RMP proposed by the sponsor has been found to be acceptable by the TGA's OPR.

Risk-benefit analysis

Delegate considerations

Overall balance of benefits and risks

The pivotal study has demonstrated a clinically meaningful increase in survival, with prolongation of median survival by approximately 4.0-4.5 months compared to placebo. The overall toxicity of the drug appears modest. It is therefore considered that the benefits of the drug outweigh its risks. Approval of the application is thereby proposed.

Effect of food

Co administration with food results in a marked increase in bioavailability of the drug, with the potential for increased toxicity. In the draft PI and CMI (consumer medicine information), patients are instructed to take the drug at least 1 h before a meal or 2 h after a meal. Although the effects of food taken at these time points on the PK of abiraterone have not been studied, the instructions are the same as those given to participants in the pivotal study and are therefore considered acceptable.

Response from sponsor

The sponsor agrees with the Delegate's recommendation to approve abiraterone for the following proposed indication:

"Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane."

Janssen concurs with the Delegate, that our proposed product information text in relation to avoiding co administering abiraterone with food is acceptable. Our proposed text: "Zytiga should be taken at least two hours after eating and no food should be eaten for at least one hour after taking Zytiga" is consistent with the instructions given to patients in the pivotal clinical trials. In fact, the proposed product information wording is stronger in its warning to avoid food when taking abiraterone than the instructions given to patients in the clinical trials.

The sponsor also agrees with the Delegate, that our proposed product information wording regarding LFT monitoring is sufficient. Following the protocol modifications in the pivotal trial regarding LFT monitoring there were no further grade 3 or 4 LFT elevations. Given the proposed product information text for monitoring LFTs completely mirrors the protocol modifications, it is the sponsor's position that the text is appropriate.

Janssen has also incorporated the changes to the product information requested by the Delegate, the nonclinical evaluator and clinical evaluator.

Additionally, Janssen has included fractures as a new adverse reaction in the product information. This follows the incorporation of fractures into the latest version of the Company Core Data Sheet (CCDS) dated October 2011.

Furthermore, the sponsor has also initiated some minor editorial changes. These changes to the product information ensure consistency with the revised Australian Regulatory Guidelines for Prescription Medicines Appendix 8 dated May 2011.

Abiraterone has demonstrated a clinically meaningful increase in overall survival in its pivotal trial, coupled with a modest toxicity. Given the favourable benefit/risk profile, Janssen agrees with the Delegate's recommendation to approve Zytiga in line with the proposed indication.

Advisory committee considerations

The ACPM, taking into account the submitted evidence of pharmaceutical efficacy, safety and quality, agreed with the Delegate and considered this product to have a positive benefit-risk profile for the indication:

Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostatic cancer (mCRPC)) in patients who have received prior chemotherapy containing a taxane.

The ACPM supported the amendments proposed by the Delegate and evaluators to the PI and CMI and others that should be considered include:

a statement in the 'Precautions' section explaining that 17 α hydroxylase inhibition decreases glucocorticoid production.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided, would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Zytiga tablet containing 250 mg abiraterone acetate (oral administration). The approved indication reads as follows:

Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostatic cancer [mCRPC]) in patients who have received prior chemotherapy containing a taxane.

Specific conditions of registration applying to these therapeutic goods:

1. It is a condition of registration that the sponsor implements in Australia the abiraterone acetate RMP dated 26 July 2011 included with this submission, and any subsequent revisions, as agreed with the TGA and its OPR.
2. The protocol for the planned single dose, PK trial in subjects with severe hepatic impairment (Study 212082PCR1004) should be provided to the OPR. In addition to the protocol, a summary should be provided on how this study is designed to further elucidate and monitor "Use in patients with moderate/severe hepatic impairment and chronic liver disease". Factors such as study design, follow up duration, and outcome measurements should be considered. A date or milestone that these documents will be provided should also be provided.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia

Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605

www.tga.gov.au

Reference/Publication #

ZYTIGA®

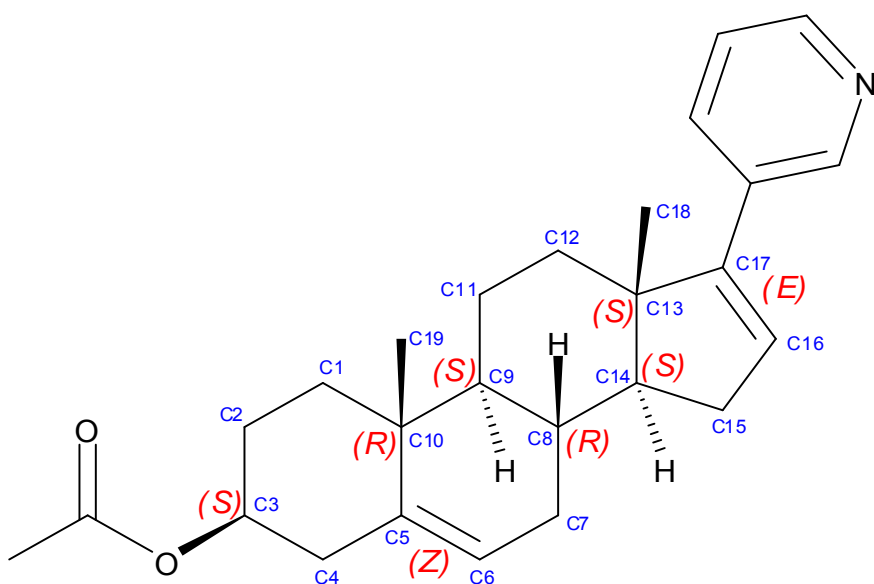
abiraterone acetate

PRODUCT INFORMATION

NAME OF THE MEDICINE

The chemical name of abiraterone acetate is 3 β -Acetoxy-17-(3-pyridyl)-androsta-5,16-diene.

Abiraterone acetate has the following chemical structure:



Molecular formula: C₂₆H₃₃NO₂
CAS Registry Number: 154229-18-2

Molecular weight: 391.55

DESCRIPTION

ZYTIGA tablets contain 250 mg of the active ingredient abiraterone acetate. The tablets also contain the inactive ingredients: lactose monohydrate; microcrystalline cellulose; croscarmellose sodium; povidone; sodium lauryl sulfate; magnesium stearate and colloidal silicon dioxide.

PHARMACOLOGY

Pharmacodynamics

Mechanism of action

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically abiraterone selectively inhibits the enzyme 17 α -hydroxylase/C17,20-lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular,

adrenal and in prostatic tumour tissues. It catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17 α hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals (see PRECAUTIONS).

Androgen-sensitive prostatic carcinoma responds to treatment that decreases androgen levels. Androgen deprivation therapies, such as treatment with luteinizing hormone-releasing hormone (LHRH) agonists or orchiectomy, decrease androgen production in the testes but do not affect androgen production by the adrenals or in the tumour. Treatment with abiraterone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH agonists (or orchiectomy).

Pharmacodynamic effects

Abiraterone decreases serum testosterone and other androgens to levels lower than those achieved by the use of LHRH agonists alone or by orchiectomy. Prostate specific antigen (PSA) serves as a biomarker in patients with prostate cancer. In a phase 3 clinical study of patients who failed prior chemotherapy with taxanes, 29% of patients treated with abiraterone, versus 6% of patients treated with placebo, had at least a 50% decline from baseline in PSA levels.

Effects on the QT interval

In a cardiovascular safety study in patients with metastatic advanced prostate cancer there were no significant effects of abiraterone acetate on the cardiac QT/QTc interval.

Pharmacokinetics

Following administration of abiraterone acetate, the pharmacokinetics of abiraterone and abiraterone acetate have been studied in healthy subjects, patients with metastatic advanced prostate cancer and subjects without cancer with hepatic or renal impairment. Abiraterone acetate is rapidly converted *in vivo* to abiraterone (see Pharmacodynamics).

Absorption

Following oral administration of abiraterone acetate in the fasting state, the median time to reach maximum plasma abiraterone concentration is approximately 2 hours.

Effect of food on absorption

Administration of ZYTIGA with food, compared with administration in a fasted state, results in up to a 17-fold increase in mean systemic exposure of abiraterone depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in highly variable exposures. Therefore, **ZYTIGA must not be taken with food**. ZYTIGA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water (see DOSAGE AND ADMINISTRATION).

Distribution

The plasma protein binding of ¹⁴C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5630 L, suggesting that abiraterone extensively distributes to peripheral tissues.

Metabolism

Following oral administration of ^{14}C -abiraterone acetate as capsules, abiraterone acetate is hydrolyzed to abiraterone, which then undergoes metabolism including sulphation, hydroxylation and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found in the form of metabolites of abiraterone. Of 15 detectable metabolites, 2 main metabolites, abiraterone sulphate and N-oxide abiraterone sulphate, each represent approximately 43% of total radioactivity.

The major enzymes involved in the metabolism of abiraterone are CYP3A4 for phase I (oxidative) metabolites, the sulfotransferase (SULT) isozyme SULT2A1, and UDP-glucuronosyl transferase (UGT) UGT1A4. No studies have been conducted to determine if drugs that induce or inhibit these enzymes affect the metabolism of abiraterone.

Elimination

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C -abiraterone acetate, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22 % of the administered dose, respectively).

Additional information on special populations

Hepatic impairment

The pharmacokinetics of abiraterone was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1 g dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairment. No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment. Abiraterone should not be used in patients with pre-existing moderate or severe hepatic impairment.

For patients who develop hepatotoxicity during treatment with abiraterone suspension of treatment and dosage adjustment may be required (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal impairment

The pharmacokinetics of abiraterone was compared in patients with end-stage renal disease on a stable hemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1 g dose did not increase in patients with end-stage renal disease on dialysis.

Administration of abiraterone in patients with renal impairment including severe renal impairment does not require dose reduction (see DOSAGE AND ADMINISTRATION).

CLINICAL TRIALS

The efficacy of abiraterone was established in a randomized placebo controlled multicenter phase 3 clinical study of patients with metastatic advanced prostate cancer (castration resistant prostate cancer) who had received prior chemotherapy containing a taxane. Patients were using a LHRH agonist or were previously treated with orchiectomy (n=1195). In the active treatment arm, abiraterone was administered at a dose of 1 g daily in combination with low dose

prednisone or prednisolone 5 mg twice daily (n=797). Control patients received placebo and low dose prednisone or prednisolone 5 mg twice daily (n=398).

Changes in either radiographic findings or PSA serum concentration independently do not always predict clinical benefit. Therefore, in this study it was recommended that patients be maintained on their study drugs until there was PSA progression (confirmed 25% increase over the patient's baseline/nadir) together with protocol-defined radiographic progression and symptomatic or clinical progression. The primary efficacy endpoint was overall survival.

Eleven percent of patients enrolled had an ECOG performance score of 2; 70% had radiographic evidence of disease progression with or without PSA progression; 70% had received one prior cytotoxic chemotherapy and 30% received two. Liver metastasis was present in 11% of patients treated with abiraterone.

In a planned analysis conducted after 552 deaths were observed, 42% (333 of 797) of patients treated with abiraterone compared with 55% (219 of 398) of patients treated with placebo had died. A statistically significant improvement in median overall survival was seen in patients treated with abiraterone (see Table 1).

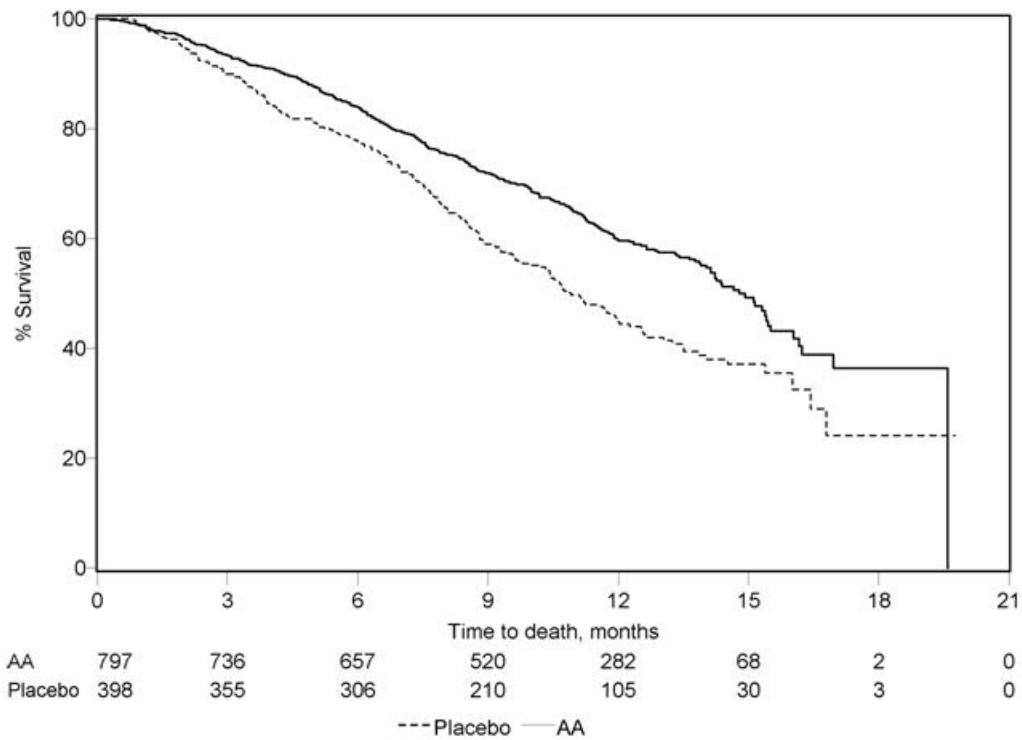
Table 1: Overall Survival of patients treated with either ZYTIGA or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy

	ABIRATERONE (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)	

*Hazard ratio <1 favours abiraterone

At all evaluation time points after the initial few months of treatment, a higher proportion of patients treated with abiraterone remained alive compared with the proportion of patients treated with placebo (see Figure 1).

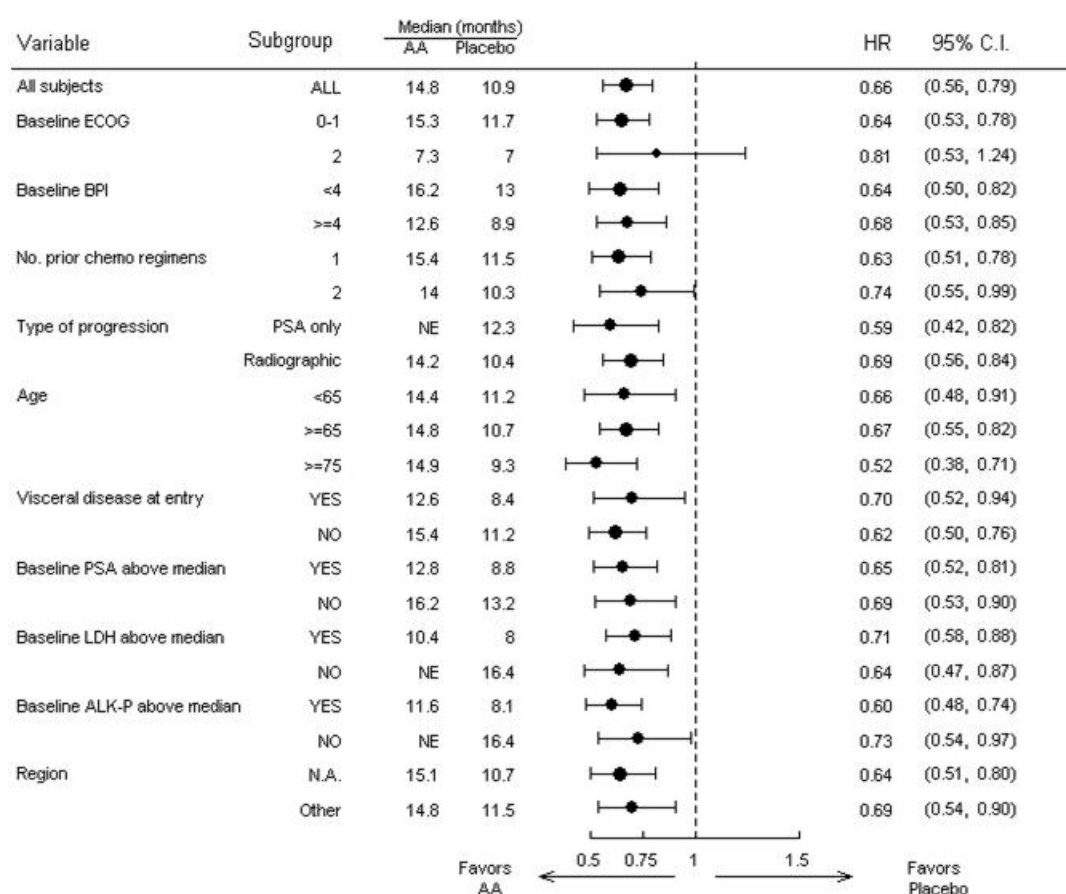
Figure 1: Kaplan Meier survival curves of patients treated with either abiraterone or placebo in combination with prednisone or prednisolone plus LHRH agonists or prior orchiectomy



AA = abiraterone acetate

Subgroup survival analyses showed a consistent survival benefit for treatment with abiraterone (see Figure 2).

Figure 2: Overall Survival by Subgroup: Hazard Ratio and 95% Confidence Interval



AA=abiraterone acetate; ALK-P=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group performance score; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not evaluable; No.=number

In addition to the observed improvement in overall survival, all secondary study endpoints favored abiraterone and were statistically significant after adjusting for multiple testing as follows.

Patients receiving abiraterone demonstrated a significantly higher total PSA response rate (defined as a $\geq 50\%$ reduction from baseline), compared with patients receiving placebo: 29% versus 6%, $p < 0.0001$.

The median time to PSA progression was 10.2 months for patients treated with abiraterone and 6.6 months for patients treated with placebo (HR= 0.580; 95% CI: [0.462, 0.728], $p < 0.0001$).

The median radiographic progression free survival was 5.6 months for patients treated with abiraterone and 3.6 months for patients who received placebo (HR= 0.673; 95% CI: [0.585, 0.776], $p < 0.0001$).

Pain

The proportion of patients with pain palliation was statistically significantly higher in the abiraterone group than in the placebo group (44% versus 27%, $p = 0.0002$).

A lower proportion of patients treated with abiraterone had pain progression compared to patients taking placebo at 6 (22% vs. 28%), 12 (30% vs. 38%) and 18 months (35% vs. 46%).

The time to pain progression at the 25th percentile was 7.4 months in the abiraterone group, versus 4.7 months in the placebo group.

Skeletal-Related Events

A lower proportion of patients in the abiraterone group had skeletal-related events compared with the placebo group at 6 months (18% vs. 28%), 12 months (30% vs 40%), and 18 months (35% vs. 40%). The time to first skeletal-related event at the 25th percentile in the abiraterone group was twice that of the control group at 9.9 months vs 4.9 months.

INDICATIONS

ZYTIGA is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in patients who have received prior chemotherapy containing a taxane.

CONTRAINDICATIONS

ZYTIGA is contraindicated in women who are or may potentially be pregnant.

PRECAUTIONS

Hypertension, hypokalemia and fluid retention due to mineralocorticoid excess

Abiraterone should be used with caution in patients with a history of cardiovascular disease. The safety of abiraterone in patients with left ventricular ejection fraction < 50% or NYHA Class III or IV heart failure has not been established. Before treatment with abiraterone, hypertension must be controlled and hypokalemia must be corrected.

Abiraterone may cause hypertension, hypokalemia and fluid retention (see ADVERSE EFFECTS) as a consequence of increased mineralocorticoid levels resulting from CYP17 inhibition (see Pharmacodynamics). Co-administration of a corticosteroid suppresses adrenocorticotrophic hormone (ACTH) drive, resulting in a reduction in the incidence and severity of these adverse reactions. Caution is required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalemia or fluid retention, e.g., those with heart failure, recent myocardial infarction or ventricular arrhythmia.

Blood pressure, serum potassium and fluid retention should be monitored at least monthly.

Hepatotoxicity

Marked increases in liver enzymes leading to drug discontinuation or dosage modification occurred in controlled clinical studies (see ADVERSE EFFECTS). Serum transaminase and bilirubin levels should be measured prior to starting treatment with abiraterone, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum ALT, should be measured immediately. If at any time the ALT rises above 5 times the upper limit of normal or the bilirubin rises above 3 times the upper limit of normal, treatment with abiraterone should be interrupted immediately and liver function closely monitored.

Re-treatment with ZYTIGA only may take place after the return of liver function tests to the patient's baseline and at a reduced dose level (see DOSAGE AND ADMINISTRATION).

If patients develop severe hepatotoxicity (ALT 20 times the upper limit of normal) anytime while on therapy, abiraterone should be discontinued and patients should not be re-treated with abiraterone.

Corticosteroid withdrawal and coverage of stress situations

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients need to be withdrawn from prednisone or prednisolone. If abiraterone is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess.

In patients on prednisone or prednisolone who are subjected to unusual stress, increased dosage of a corticosteroid may be indicated before, during and after the stressful situation. 17 α hydroxylase inhibition by abiraterone decreases glucocorticoid production.

Effects on fertility

Developmental or reproductive toxicology studies were not conducted with abiraterone acetate. In studies in rats (13-and 26-weeks) and monkeys (up to 39-weeks), decreases in testosterone levels, atrophy, aspermia/hypospermia, and hyperplasia in the reproductive system were observed at ≥ 50 mg/kg/day in rats and ≥ 250 mg/kg/day in monkeys and were consistent with the antiandrogenic pharmacological activity of abiraterone. These effects were observed at exposure levels similar to or lower than the human clinical exposure, based on abiraterone AUC. ZYTIGA is contraindicated in pregnancy (see CONTRAINDICATIONS and Use in Pregnancy).

Use in Pregnancy Category D

ZYTIGA is contraindicated in women who are or may potentially be pregnant (see CONTRAINDICATIONS).

There are no human or animal data on the use of abiraterone in pregnancy and abiraterone is not for use in women of child-bearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the foetus.

It is not known if abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of child-bearing potential, a condom is required along with another effective contraceptive method.

To avoid inadvertent exposure, women who are pregnant or women who may be pregnant should not handle ZYTIGA without protection, e.g., gloves.

Use in Lactation

ZYTIGA is not for use in women.

It is not known if either abiraterone acetate or its metabolites are excreted in human breast milk.

Carcinogenicity

Carcinogenicity studies were not conducted with abiraterone acetate.

Genotoxicity

Abiraterone acetate and abiraterone were devoid of genotoxic potential in the standard panel of genotoxicity tests including, an *in vitro* bacterial reverse mutation assay (the Ames test), an *in*

vitro mammalian chromosome aberration test (using human lymphocytes) and an *in vivo* rat micronucleus assay. Genotoxicity studies have not been conducted with the main human metabolites of abiraterone.

INTERACTIONS WITH OTHER MEDICINES

In vitro studies with human hepatic microsomes showed that abiraterone is a strong inhibitor of CYP1A2 and CYP2D6 and a moderate inhibitor of CYP2C9, CYP2C19 and CYP3A4/5. In a clinical study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP1A2 substrate theophylline, no increase in systemic exposure of theophylline was observed.

In the same study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 200%. The AUC₂₄ for dextromethorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when abiraterone is administered with drugs activated by or metabolized by CYP2D6, particularly with drugs that have a narrow therapeutic index. Dose reduction of narrow therapeutic index drugs metabolized by CYP2D6 should be considered.

Abiraterone is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors or inducers on the pharmacokinetics of abiraterone have not been investigated. Strong inhibitors and inducers of CYP3A4 should be avoided or used with caution.

Effect on ability to drive or operate machinery

No studies on the effects of abiraterone on the ability to drive or use machines have been performed. It is not anticipated that abiraterone will affect the ability to drive and use machines.

ADVERSE EFFECTS

Adverse drug reactions from clinical trials

The most common adverse reactions seen with abiraterone are peripheral edema, hypokalemia, urinary tract infection and hypertension.

Abiraterone may cause hypertension, hypokalemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In a phase 3 study anticipated mineralocorticoid effects were seen more commonly in patients treated with abiraterone versus patients treated with placebo; hypokalemia 17% versus 8%, hypertension 9% versus 7% and fluid retention (peripheral edema) 25% versus 17%, respectively. In patients treated with abiraterone, grades 3 and 4 hypokalemia and grades 3 and 4 hypertension were observed in 4% and 1% of patients, respectively. Mineralocorticoid effects generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse drug reactions (see PRECAUTIONS).

In studies of patients with metastatic advanced prostate cancer who were using a LHRH agonist, or were previously treated with orchiectomy, abiraterone was administered at a dose of 1 g daily in combination with low dose prednisone or prednisolone (10 mg daily). Patients were intolerant to or had failed up to two prior chemotherapy regimens, one of which contained a taxane.

Adverse drug reactions due to abiraterone in the phase 3 study that occurred at a rate of ≥1% (all grades) are shown in Table 2.

Table 2: Adverse drug reactions due to abiraterone in ≥1% of patients in a phase three study^a						
	Abiraterone 1g daily with prednisone or prednisolone n=791^b			Placebo with prednisone or prednisolone n=394^b		
System Organ Class Adverse Drug Reaction	All grades %	Grade 3 %	Grade 4 %	All grades %	Grade 3 %	Grade 4 %
General Disorders and Administration Site Conditions						
Edema peripheral	25	1	<1	17	1	0
Metabolism and Nutrition Disorders						
Hypokalemia	17	3	<1	8	1	0
Hypertriglyceridemia	1	<1	0	0	0	0
Infections and Infestations						
Urinary tract infection	12	2	0	7	1	0
Hepatobiliary Disorders						
Alanine aminotransferase increased	3	1	0	1	<1	<1
Vascular Disorders						
Hypertension	9	1	0	7	<1	0
Injury, poisoning and procedural complications						
Fractures	6	1	<1	2	0	0
Cardiac Disorders						
Cardiac failure ^c	2	2	<1	1	0	<1
Angina pectoris	1	<1	0	1	0	0
Arrhythmia	1	0	0	0	0	0
Atrial fibrillation	2	1	0	1	1	0
Tachycardia	3	0	0	2	0	0
a All patients were receiving an LHRH agonist or had undergone orchiectomy. b n = patients assessed for safety c Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased						

The adverse drug reaction, adrenal insufficiency, occurred uncommonly in the phase 3 clinical study.

Cardiovascular effects

The phase 3 study excluded patients with uncontrolled hypertension, clinically significant heart disease as evidenced by myocardial infarction, arterial thrombotic events in the past 6 months, severe or unstable angina, or New York Heart Association Class III or IV heart disease or cardiac ejection fraction measurement of <50%. All patients enrolled (both active and placebo-treated patients) were concomitantly treated with androgen deprivation therapy, predominately with the use of LHRH agonists, which has been associated with diabetes, myocardial infarction, cerebrovascular accident and sudden cardiac death. The incidence of cardiovascular adverse reactions in the phase 3 study was low in patients who received abiraterone and was similar to to the incidence in patients who received placebo (see Table 2).

Hepatotoxicity

Drug-associated hepatotoxicity with elevated ALT, aspartate transaminase (AST) and total bilirubin has been reported in patients treated with abiraterone. Across all clinical studies, liver function test elevations (ALT or AST increases of $> 5X$ ULN or bilirubin increases $> 1.5 X$ ULN) were reported in approximately 2% of patients who received abiraterone, typically during the first 3 months after starting treatment. In the phase 3 clinical study, patients whose baseline ALT or AST were elevated were more likely to experience liver function test elevations than those beginning with normal values. When elevations of either ALT or AST $> 5X$ ULN, or elevations in bilirubin $> 3X$ ULN were observed, abiraterone was withheld or discontinued. Hepatic metastases and baseline elevations in alkaline phosphatase associated with prostate cancer were present in a few of these patients. In two instances marked increases in liver function tests occurred (see section PRECAUTIONS). These two patients with normal baseline hepatic function, experienced ALT or AST elevations 15 to 40 X ULN and bilirubin elevations 2 to 6 X ULN. Upon discontinuation of abiraterone, both patients had normalization of their liver function tests and one patient was re-treated with abiraterone without recurrence of the elevations.

In clinical trials, the risk for hepatotoxicity was mitigated by exclusion of patients with active hepatitis or baseline ALT and AST $\geq 2.5X$ ULN in the absence of liver metastases and $> 5X$ ULN if liver metastases were present. Abnormal liver function tests developing in patients participating in clinical trials were vigorously managed by requiring treatment interruption and permitting re-treatment only after return of liver function tests to the patient's baseline (see DOSAGE and ADMINISTRATION). Patients with elevations of ALT or AST $> 20X$ ULN were not re-treated. The safety of re-treatment in such patients is unknown. The mechanism for hepatotoxicity associated with abiraterone is not understood.

DOSAGE AND ADMINISTRATION

The recommended dosage of ZYTIGA is 1 g (four 250 mg tablets) as a single daily dose that **must not be taken with food**. ZYTIGA should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water (see Pharmacokinetics – Absorption).

ZYTIGA is used with low-dose prednisone or prednisolone. The recommended dosage of prednisone or prednisolone is 10 mg daily.

Serum transaminases and bilirubin should be measured prior to starting treatment with ZYTIGA, every two weeks for the first three months of treatment and monthly thereafter. Blood pressure, serum potassium and fluid retention should be monitored monthly (see PRECAUTIONS).

Patients started on ZYTIGA who were receiving a LHRH agonist should continue to receive a LHRH agonist.

Hepatic impairment

No dosage adjustment is necessary for patients with pre-existing mild hepatic impairment. ZYTIGA should not be used in patients with pre-existing moderate or severe hepatic impairment.

For patients who develop hepatotoxicity during treatment with ZYTIGA (alanine aminotransferase (ALT) increases above 5 times the upper limit of normal or bilirubin increases above 3 times the upper limit of normal) treatment should be withheld immediately until liver function tests normalize (see PRECAUTIONS). Re-treatment following return of liver function tests to the patient's baseline may be given at a reduced dose of 500 mg (two tablets) once daily. For patients being re-treated, serum transaminases and bilirubin should be monitored at

a minimum of every two weeks for three months and monthly thereafter. If hepatotoxicity recurs at the reduced dose of 500 mg daily, discontinue treatment with ZYTIGA. Reduced doses should not be taken with food.

If patients develop severe hepatotoxicity (ALT 20 times the upper limit of normal) anytime while on therapy, ZYTIGA should be discontinued and patients should not be re-treated with ZYTIGA.

Renal impairment

No dosage adjustment is necessary for patients with renal impairment.

OVERDOSAGE

There have been no reports of overdose of ZYTIGA during clinical studies.

There is no specific antidote. In the event of an overdose, administration of ZYTIGA should be stopped and general supportive measures undertaken, including monitoring for arrhythmias. Liver function also should be assessed.

PRESENTATION AND STORAGE CONDITIONS

ZYTIGA tablets are white to off-white, oval tablets, debossed with "AA250" on one side.

ZYTIGA tablets are provided in high density polyethylene round white bottles fitted with a polypropylene cap. A bottle contains 120 tablets. Store below 25°C.

NAME AND ADDRESS OF SPONSOR

JANSSEN-CILAG Pty Ltd
1-5 Khartoum Rd Macquarie Park NSW 2113 Australia
NZ Office: Auckland New Zealand

POISON SCHEDULE OF THE DRUG

Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

1 March 2012

® ZYTIGA is a registered trademark of JANSSEN-CILAG