15 November 2012
EMA/CHMP/755312/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zytiga (abiraterone)

Procedure no. EMEA/H/C/002321/II/0004/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Table of contents

List of abbreviations

ACTH	adrenocorticotrophic hormone
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AR	androgen receptor
BPI-SF	Brief Pain Inventory-Short Form
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CRPC	castration-resistant prostate cancer
CT	computed tomography
CYP17α	cytochrome P450 17α-hydroxylase/C17,20-lyase
DHEA	Dehydroepiandrosterone
ECOG	Eastern Cooperative Oncology Group
FACT-P	Functional Assessment of Cancer Therapy-Prostate
FWB	Functional well being
HR	hazard ratio
IARC	International Agency for Research on Cancer
IDMC	Independent Data Monitoring Committee
ITT	intent-to-treat
LDH	lactate dehydrogenase
LFT	liver function test
LHRH	luteinizing hormone releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
OS	overall survival
PCS	prostate cancer score
PCWG2	Prostate Cancer Working Group 2
PSA	prostate-specific antigen
PRO	patient-reported outcomes
PWB	Physical well being
P-Y	patient-years
RECIST	Response Evaluation Criteria In Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	system organ class

1. Background information on the procedure

1.1. Type II and group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N V submitted to the European Medicines Agency on 13 June 2012 an application for a group of variations including an extension of indication.

This application concerns the following medicinal product:

Medicinal product:	**International non-proprietary name:**	**Presentations:**
Zytiga	abiraterone	See Annex A

The following variations were requested in the group:

Variations requested		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

The MAH applied for an extension of the prostate cancer indication in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the Package Leaflet was proposed to be updated accordingly. In the second variation in the group, updates to sections 4.6 and 5.3 of the SmPC have been proposed based on the results of reproductive and developmental non-clinical studies. Minor modifications to the SmPC, Labelling and Package Leaflet have also been proposed.

The group of variations proposed amendments to the SmPC, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/63/2010 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

Additional market protection

The applicant requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication.

Scientific advice

The applicant received Scientific Advice from the CHMP on 20 November 2008. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Arantxa Sancho-Lopez Co-Rapporteur: Robert James Hemmings

Submission date:	13 June 2012
Start of procedure:	24 June 2012
Rapporteur's preliminary assessment report circulated on:	21 August 2012
CoRapporteur's preliminary assessment report circulated on:	17 August 2012
Joint Rapporteur's updated assessment report circulated on:	14 September 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	20 September 2012
MAH's responses submitted to the CHMP on:	12 October 2012
Joint Rapporteur/Co-Rapporteur assessment report on the MAH's responses circulated on:	29 October 2012
CHMP opinion:	15 November 2012

2. Scientific discussion

2.1. Introduction

Prostate cancer is the most common cancer and the second leading cause of cancer deaths among males in most Western countries. In 2008, 323,000 men were diagnosed with prostate cancer in the European Union and 71,000 patients died from the disease (GLOBOCAN 2008 (IARC)).

For men with disseminated disease, bone is the most common site of metastasis. Prostate cancer-related deaths occur as a result of complications of metastatic disease. The objective of therapy is control of disease while maintaining quality of life. The initial approach is generally androgen deprivation therapy (ADT). Despite hormonal therapy, most patients with disease recurrence will progress within 12 to 18 months.

Castrate-resistant prostate cancer (CRPC) is defined by disease progression despite androgen deprivation therapy (ADT) and may present as either a continuous rise in serum prostate-specific antigen (PSA) levels, the progression of preexisting disease, and/or the appearance of new metastases.

Based on the results of 2 randomised controlled trials, it is currently recommended that for men with clinical or biochemical evidence of progression and evidence of metastases, treatment with docetaxel 75 mg/m2 administered intravenously every 3 weeks with 5 mg oral prednisone twice daily should be offered to improve overall survival, disease control, symptom palliation and quality of life (Tannock et al, 2004; Petrylak et al, 2004).

Treatment options for symptomatic bone disease are radiation or radionuclide agents and bisphosphonates or the RANK ligand inhibitor, denosumab. However, the prognosis of mCRPC patients is still poor, with a median survival of approximately 1 to 2 years.

Abiraterone acetate is a prodrug of abiraterone, an orally active inhibitor of the enzyme, CYP17α (17α-hydroxylase/C17, 20-lyase). Abiraterone acts as an androgen biosynthesis inhibitor by blocking two important enzymatic activities in the synthesis of testosterone in the testes, adrenals, and within the prostate tumour.

Zytiga contains abiraterone and it was approved in the EU on 5 September 2011, in combination with prednisone or prednisolone, for the treatment of metastatic castration-resistant prostate cancer (mCRPC) in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. The recommended dose is 1000 mg (four 250 mg tablets) given once daily.

With this group of variation applications, the MAH proposed to extend the approved mCRPC indication to include the treatment of metastatic CRPC in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy. Consequently, the MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and the Package Leaflet was proposed to be updated accordingly. In the second variation in the group, updates to sections 4.6 and 5.3 of the SmPC have been proposed based on the results of reproductive and developmental non-clinical studies. Minor modifications the SmPC, Labelling and Package Leaflet have also been proposed.

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical information contained in this application summarised new data from additional primary pharmacology, pharmacokinetic and toxicology studies which included reproductive and developmental toxicity studies submitted as a second type II variation in the group of variation.

An environmental risk assessment (ERA) was submitted in support of the extension of indication application. In the course of the assessment, a further updated ERA was submitted in MAH's response to a CHMP recommendation at the time of the Marketing Authorisation. The assessment of this information was integrated into the assessment of environmental aspects of this application.

2.2.2. Pharmacology

Primary pharmacodynamic studies

The Applicant has provided an update of primary pharmacology data on abiraterone acetate available from recent literature reports (Mostaghel EA et al, 2011; Cai C et al, 2011; Soifer HS et al, 2012; Richards J et al, 2012). The pharmacology data obtained from these publications provided evidence that abiraterone reduces CRPC growth via suppression of CYP17-mediated intratumoural androgen biosynthesis and regulation of androgen receptor activity. By targeting CYP17, resistance to abiraterone may occur through upregulation of CYP17 and/or induction of androgen receptor and androgen receptor splice variants. These findings are in line with earlier data described in the marketing authorisation application for Zytiga.

Moreover, findings of abiraterone inhibition of direct androgen receptor activation by agonists in cell culture studies suggest an additional pharmacological activity that could contribute to the antitumour activity of abiraterone.

2.2.3. Pharmacokinetics

The pharmacokinetics of abiraterone acetate has been studied in additional pharmacokinetic and toxicokinetic studies. These included exposure evaluation of abiraterone and abiraterone acetate in vivo after single and repeated administration of abiraterone acetate to transgenic mice, pregnant rats and juvenile rats. For pharmacokinetic modelling purposes, pharmacokinetics and plasma levels of abiraterone acetate and of abiraterone were studied after i.v. administration to beagle dogs. In addition, pharmacokinetics and plasma levels of abiraterone were studied after i.v. dosing of abiraterone to beagle dogs. Presystemic elimination of abiraterone acetate and abiraterone was studied in portal-vein catheterised dogs after administration of abiraterone acetate (data not shown, see discussion on non-clinical aspects).

In two in vitro pharmacokinetic drug interactions studies, the potential of abiraterone acetate and abiraterone to inhibit CYP2C8, CYP2B6 and CYP2C19 was evaluated using pooled human liver microsomes. Both abiraterone acetate and abiraterone were strong inhibitors of CYP2C8 with 50% inhibitory concentration (IC50) values of 1.3 and 1.6 μM, respectively and both were weak inhibitors of CYP2B6 and CYP2C19 with IC50 $\geq$10 μM, the highest soluble concentration. Based on the extremely low human plasma concentrations of abiraterone acetate (<0.01 µM), no interaction of abiraterone acetate with CYP2C8 is expected. However, taking into account peak plasma concentrations of abiraterone up to 0.6 µM (clinical study COU-AA-006) and the in vitro IC50 of 1.6 µM, abiraterone has the potential to interact with CYP2C8.

2.2.4. Toxicology

A new repeat dose toxicity study, reproductive and developmental studies to assess the effects of abiraterone acetate and abiraterone on male and female fertility, embryo-foetal development and juvenile toxicity studies in rats, specific studies to evaluate the toxic potential of impurities and mechanistic studies to address effects of abiraterone acetate and abiraterone on different hormones have been submitted.

Repeat dose toxicity

The repeat-dose toxicity study submitted is summarised in the following Table 1.

Table 1: Additional repeat-dose toxicity study with abiraterone

Study N° / Type of Study	Species/ N° / Sex / Group or Test System	Dose (mg/kg/day) / Route	GLP Compliance
TOX9688 / 28 Days Repeat-Dose Toxicity	CByB6F1 Mice (Tg.rasH2 non-transgenic littermate) / 304 / M-F / 5	0, 125, 375, 750 and 1500 / Oral gavage	Yes
Noteworthy Findings: 1500: ↓ motor activity (2/10), ruffled fur (2/10) and a hunched appearance (6/10) during the first week of dosing only. At 125: ↓ red blood cell parameters (red blood cells, haemoglobin, hematocrit) and an ↑ in ALP in males; ↑ in liver weights of females; degeneration and ↑d number of interstitial cells in testes; staging, predominantly proestrus in vagina; centrilobular hypertrophy, periportal subacute inflammation and multifocal subcapsular necrosis of hepatocytes in liver of both sexes. At 375: similar effects to 125 mg/kg/day, except ↓ red blood cell that was not present; ↑ in liver weight in both genders with histopathological changes more pronounced; atrophy in uterus; extramedullary hematopoiesis in spleen of female. At 750: similar effects to 375 mg/kg/day, ↑ in body weights and weight gains; ↓ red blood cell in males; ↑ of ALP levels and ↓ K values in males; atrophy in testes leading to ↓ in testes weights; ↑ in spleen weights of both sexes as the result of extramedullary hematopoiesis; metestrus stage in vagina. At 1500 similar but more pronounced effects as seen at lower dose; ↑ in mean platelet volume in both sexes; in platelet counts of males; in reticulocytes of females, and in red cell distribution width (RDW) of males and females; ↓ mean corpuscular haemoglobin concentration (MCHC) in both sexes; ↑ in total proteins, albumin, albumin/globulin ratio and cholesterol, ↓ K; ↑ in total and indirect bilirubin of females and direct bilirubin in males; ↑ in ALT, AST, GLDH in females; small testes; thinning of the uterus; accumulation of cellular debris with oligospermia in the epididymides; estrus stage in vagina. **NOAEL:** Not established		

Reproduction toxicity

Reproductive and developmental studies to assess the effects of abiraterone acetate and abiraterone in male and female fertility, as well as embryo-foetal development, juvenile toxicity and hormone-profiling studies in rats are summarised in the following Table 2.

Table 2: Reproduction toxicity studies with abiraterone

Study N° / Type of Study	Species/ N° / Sex / Group or Test System	Dose (mg/kg/day) / Route	GLP Compliance
TOX10095 / Fertility Toxicity: Subset I = 4 weeks Subset II and III= 4 weeks pre-pairing and until completion of mating + 8 or 16 weeks recovery	Sprague Dawley rats / 108 / M / 3	0, 30 and 300 / Oral gavage	Yes
Noteworthy Findings: At 30: ↓ of BWG in the first week; ↑ in small coagulating gland, epididymides, prostate, seminal vesicles and testes, and ↑ of swollen livers; reduction in testis and epididymal weights; marginal ↑ in the number of abnormal sperm, predominantly decapitate sperm. In female, reduced numbers of corpora lutea, implantations and live embryos and an ↑ in the extent of pre-implantation loss as a result of the treatment-related effect in males. At 300: Similar but more pronounced observations than that at 30; ↓ food intake during the first week and ↓ BWG throughout treatment; pale swollen livers; ↓ absolute and weight-related sperm counts abnormal sperm, predominantly as decapitate sperm or with abnormal heads. After 8 weeks recovery, there was a slight ↓ in the percentage of motile and progressively motile sperm, and a marginal ↑ in decapitate sperm, and swollen livers (in 2 males) Changes resolved after 16 weeks recovery. **NOAEL: Males:** not established **Females:** not applicable		

TOX10096 / Fertility Toxicity: Subset I = 4 weeks Subset II and III= 2 weeks + 4 or 8 weeks recovery	Sprague Dawley rats / 144 / F/ 3	0, 30 and 300 / Oral gavage	Yes
Noteworthy Findings: At 30: ↓ BWG during the pregnancy dosing period; oestrous cycles disrupted without effects on the copulation or fertility indices or the pre-coital interval. At 300: ↑ BWG during the pre-pairing period (second week of dosing) and ↓ BWG during the pregnancy dosing period; oestrous cycles disrupted with females showing extended periods of oestrus and ↑d cycle length, without effects on copulation, fertility indices and the pre-coital interval; slight ↓ number of implantations with an ↑ in pre-implantation loss. All changes resolved by 4 weeks recovery. **NOAEL: Males:** not established **Females:** not applicable			
TOX10115 / Embryo-Foetal Development Toxicity: From GD 6 to GD 17	Sprague Dawley rats / 88 + 12 for TK / F / 4	0, 10, 30 and 100 / Oral gavage	Yes
Noteworthy Findings: At 10: ↓ BWG (start of treatment); ↑ late resorptions and post-implantation loss; ↓ ano-genital distance in male fetuses. At 30: ↓ BWG (post treatment) with ↓ food consumption; ↓ corrected mean maternal weight gain; ↑ number of late resorptions and post-implantation loss resulted in fewer live fetuses; red vaginal discharge, ↓ ano-genital distance in male fetuses. At 100: 3F died or sacrificed (GD 18-21): ↓ BWG (through the study); anemia (4F); ↓ corrected mean maternal weight gain; complete litter resorption (3/18 F); ↓ ano-genital distance in fetuses of both genders ; ↓ fetal weight; **NOAEL: F0 Females:** < 10 mg/kg/day F1 **Litters:** < 10 mg/kg/day.			
TOX10066 Non-Pivotal / Embryo-Foetal Development Toxicity: From GD 6 to GD 17	Sprague Dawley rats / 24 / F / 4	0, 30, 100 and 300 / Oral gavage	No
Noteworthy Findings: At 30: red vaginal discharge (1F); ↓ BWG (post treatment); ↑ postimplantation loss; ↑ number of late resorptions; ↓ live fetuses; ↓ ano-genital distance. At 100: red vaginal discharge (3F); ↓ BWG during treatment (peak between GD6 and GD9) and post-treatment; ↓ corrected mean maternal weight gain; ↑ post-implantation loss; ↑ number of late resorptions; ↓ live fetuses; ↓ ano-genital distance. At 300: 2 F died (GD20); red vaginal discharge (5F); ↓ BWG during treatment (peak between GD6 and GD13) and post-treatment; ↓ corrected mean maternal weight gain; ↑ post-implantation loss; ↑ number of late resorptions; ↓ live fetuses; ↓ fetal weight; marked ↓ incidence of apparently male fetuses; ↓ ano-genital distance **NOAEL:** not established			
TOX10036 / Preliminary Juvenile Toxicity: From Day Day 18 of age	Sprague Dawley rats / 80 + 126 for TK / M-F / 4	0, 30, 100 and 300 / Oral gavage	No
Noteworthy Findings: At 30: ↓ testis and epididymal weights. At 100: ↓ BWG (between day 18 and day 22 of age); ↓ testis and epididymal weights. At 300: similar effects but more pronounced than lower dosis **NOAEL:** not established			
TOX10194 / Mechanistic study: hormone profiling. 2 weeks	Sprague Dawley rats / 60 / M-F / 3	0, 50 and 400 / Oral gavage	No
Noteworthy Findings: At 50: ↓ BWG (M: x0.66); ↑ progesterone AUC_{0-24h} (M: x33); ↓ testosterone (M: x0.19); ↑ LH (M: x5.63). At 400: ↓ BW (M: x0.93); ↓ BWG (M: x0.42); ↓ FC (M: x0.89); ↑ progesterone AUC_{0-24h} (M: x43); ↓ testosterone (M: x0.10); ↑ LH (M: x6.90) **NOAEL:** not established			

Other toxicity studies

Additional studies on impurities, undertaken since the marketing authorisation, were submitted for completeness of information (data not shown).

2.2.5. Ecotoxicity / environmental risk assessment

In accordance with the Guideline on the Environmental Risk Assessment (ERA) of Medicinal Products for Human Use (CHMP/SWP/4447/00), the MAH has evaluated the environmental impact of abiraterone acetate for this new indication and submitted an updated ERA report. Moreover, during the procedure, the MAH submitted an extended partial life cycle study with fathead minnow (Pimephales promelas) aimed to assess the specific mode of action of abiraterone acetate according to the OECD recommendations for endocrine disrupting substances. This study had been recommended by the CHMP in conclusion to the assessment of the Marketing Authorisation application of Zytiga. The study was submitted with a further updated ERA report in which the toxicity NOEC was further refined to 0.013 µg/L based on the study above. In the same report, the PECsurfacewater was further refined to 0.005 µg/L, which is below the 0.01 µg/L threshold triggering a phase II assessment, but the phase II

assessment had already been conducted. Updated results of the main studies are summarised in the following Table 3.

Table 3: Summary of main study results

Substance (INN/Invented Name): To be assigned					
CAS-number (if available): 154229-19-3					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	5.12			Potential PBT YES
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	5.12			B
	BCF	625 (for low conc, 0.13 microg/L) 576 (for high conc, 1.3 microg/L			not B
Persistence	DT_{50} or ready biodegradability	$DT_{50,}$ freshwater= 2.3 days			not P
Toxicity	NOEC or CMR	NOEC (fathead minnow partial life cycle) = 0.013µg/L			T
PBT-statement :	The compound is considered as T				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.005	µg/L			> 0.01 threshold (N*)
Other concerns (e.g. chemical class)					N/A
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} > 22,387 Kg/L (log K_{oc} > 4.35)			List all values
Ready Biodegradability Test	OECD 301	12.56 %			Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = 2.3 days $DT_{50,\ sediment}$ = ND $DT_{50,\ whole\ system}$ = 4.9 and 3.3 days % shifting to sediment = sediment-bound residue 28.2% and 22.1%			Evidence of primary biodegradation was observed for [^{14}C] abiraterone acetate in the aerobic water/sediment test samples.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC	1000	µg/L	*Pseudokirchneriella subcapitata.* NOEC value is the same for both measures of growth (biomass and growth rate)
Daphnia sp. Reproduction Test	OECD 211	NOEC	0,47	µg/L	
Fish, Early Life Stage Toxicity Test/*Species*	Modified Partial Life-Cycle Exposure with Fathead Minnow (OECD 229)	NOEC	0.013	µg/L	*Pimephales promelas* (Fathead Minnow)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC	> 10^6	µg/L	NOEC = 1000 mg/L
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	625 (for low conc,	L/kg	%lipids: Percent lipids at steady

			0.13 µg/L) 576 (for high conc, 1.3 µg/L		state (wet weight tissue basis) low = 3.46% and high 3.76 % Percent lipids at steady state (dry weight tissue basis) low = 19.65 % and high 22.74 %
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	18 55.1 %	Days	See comments in conclusion section
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	250	mg/kg	The nitrate production was inhibited by 3,9% on day 28. The empirical EC_{10}, EC_{25} and EC_{50} values for nitrogen transformation were estimated to be > 250 mg/kg dry soil
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100 for all species	mg/kg	Bean (*Phaseolus vulgaris)* Oat *(Avena sativa)* Tomato *(Lycopersicon esculentum)*
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	63	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	1000 for mortality; 500 for re-production	mg/kg	
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius*

* The phase II assessment had been conducted at the time of the MAA, upon which time the $PEC_{surfacewater}$ had been calculated at 0.018 µg/L

2.2.6. Discussion on non-clinical aspects

The new pharmacokinetic studies showed that abiraterone acetate is rapidly converted to abiraterone in mice, rats and dogs. This is consistent with the findings described in the marketing authorisation application in humans and all animal species (mice, rats and monkeys).

In portal-vein-catheterised beagle dogs, abiraterone was the main dose-related entity found in the portal vein after abiraterone acetate administration, indicating that abiraterone acetate was extensively hydrolysed to abiraterone during absorption from the gastrointestinal tract.

Abiraterone acetate is expected to have no clinical drug-drug interaction (DDI) as the exposure to abiraterone acetate is extremely low. On the other hand and based on therapeutic plasma concentrations of abiraterone and in vitro IC50 values, abiraterone is expected to be a weak inhibitor of CYP2B6 and CYP2C19 and a potentially strong inhibitor of CYP2C8. In contrast with CYP1A2 and CYP2D6, for which abiraterone was also a potent in vitro inhibitor, no clinical DDI study has been submitted for CYP2C8.

The MAH submitted additional toxicology studies conducted in the course of development and which expand the toxicological information for Zytiga. These studies do not give rise to any concern. However, in study TOX10066, 2 females of the group treated with 300 mg/kg of abiraterone acetate were found dead on day 20 of pregnancy and in study TOX10115 3 females of the group treated with

100 mg/kg of abiraterone acetate were sacrificed or found dead on day 18-21 of pregnancy. Therefore, pregnant rats may be more sensitive to abiraterone acetate than non-pregnant rats. Moreover, developmental or reproductive toxicology studies are not required for the approved and the proposed indication for Zytiga. Fertility studies are not required for late stage or advanced cancer patients, as detailed in the ICH S9 guideline (EMEA/CHMP/ICH/646107/2008) and embryofoetal toxicity studies are not applicable for Zytiga as it is administered to adult men strictly.

No carcinogenicity studies were submitted. At the time of the marketing authorisation, the MAH committed to submit the data of a 2-year rat carcinogenicity study and a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse. These studies are included in the RMP as additional pharmacovigilance activities and the results are expected by 2Q 2013 and 3Q/4Q 2012, respectively. The MAH informed that the submission of the mouse study is imminent, in compliance with the due date in the RMP.

The information regarding environmental aspects is considered adequate. The ERA indicates that the proposed use of abiraterone acetate is unlikely to represent a risk to the environment.

2.2.7. Conclusion on the non-clinical aspects

The studies submitted added to the knowledge of non-clinical aspects for Zytiga. There are no remaining non-clinical issues. Considering the above data, abiraterone acetate is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

This variation application to extend the indication of Zytiga, in combination with prednisone or prednisolone, to the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy, is based on the results of pivotal study COU-AA-302. Phase 1 studies (COU-AA-015 and COU-AA-006) and phase 1/2 studies (COU-AA-001 (and EXT), COU-AA-002, COU-AA-003 (and EXT), COU-AA-BMA, COU-AA-BE) of abiraterone (acetate) in the new target population of chemotherapy naïve patients, supported the initial marketing authorisation application for Zytiga and were described therein.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

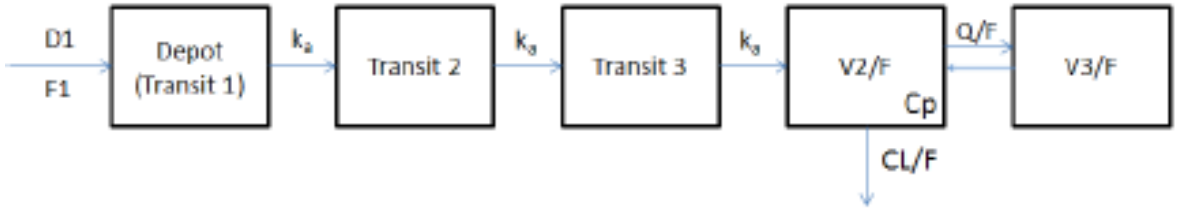
The PK of abiraterone after oral administration of abiraterone acetate was previously described in both healthy subjects and in subjects with mCRPC who had already received docetaxel-based chemotherapy using a NONMEM approach. A 2-compartment model with first order elimination was used to describe the disposition of the compound. A 3-compartment transit model was used to characterise the systemic absorption of the drug. The administration of abiraterone acetate with or without food affected the values of absorption-related parameters. In general, the administration of abiraterone acetate with a meal significantly increased the systemic exposure to abiraterone. In addition, subjects with mCRPC who had already received docetaxel-based chemotherapy had a CL/F mean value

approximately 33% lower than healthy subjects. None of the other demographic characteristics evaluated significantly influenced the PK of abiraterone.

Additional PK information from the pivotal study of this application, COU-AA-302, was used in updated analyses of PK data submitted. These updated analyses were focused on the evaluation of the PK of 1,000 mg abiraterone acetate administered orally once daily and specifically on the assessment of PK differences between patients with mCRPC who had previously received docetaxel with those who had not received prior cytotoxic chemotherapy.

The population pharmacokinetic model previously developed was used as the basis of the current analysis, which is a 2-compartment model with first order elimination. A 3-compartment transit model was used to characterise the systemic absorption of the drug (see Figure 1).

Figure 1: Schematic of the population pharmacokinetic model



CL/F = apparent oral drug clearance; Cp = plasma abiraterone concentration; D1 = duration of zero order input; F1 = relative bioavailability; ka = first-order absorption rate constant; Trans1-3 = Transit compartment 1, 2 and 3; V2/F = apparent central volume of distribution, V3/F = apparent peripheral volume of distribution, Q/F = apparent inter-compartmental flow.

The covariates identified in the previous population pharmacokinetic analysis were included in the current model: food-intake was considered consistent with the modified-fasting condition and all patients enrolled in Study COU-AA-302 were patients with mCRPC. In addition to the already known effect of these covariates, potential differences between the mCRPC patients who had (in Studies COU-AA-006 and COU-AA-301) or had not (in Study COU-AA-302) received prior chemotherapy were evaluated.

All parameters obtained were consistent with those obtained in the previous population PK analysis. Abiraterone PK was confirmed to be characterised by an extensive CL/F and large V2/F and V3/F. Absorption-related parameters were confirmed to be affected by the intake of a meal, and in particular by the fat content of the meal (data not shown).

2.3.3. Discussion on clinical pharmacology

The PK assessment of abiraterone acetate in chemotherapy-naïve patients with mCRPC who are asymptomatic or mildly symptomatic indicated no significant differences compared with patients with mCRPC who had received prior docetaxel-based chemotherapy. This conclusion is based on the following:

- The exploratory analysis, where the observations from subjects in Study COU-AA-302 were well described by the VPC based on the previously developed model using PK data collected from subjects with mCRPC who had received prior chemotherapy
- The external validation procedure based on the previously developed model, in which the calculated prediction errors were well within the predefined threshold levels;

- The model fit of all the available data (final model run), providing estimates of the PK parameters not showing large differences from those estimated based on the previous PK modeling exercise;
- The model fit including 2 distinct CL/F terms for the 2 subpopulations, which did not significantly improve the model compared with the one in which the 2 subject populations were considered homogeneous.

2.4. Clinical efficacy

This application in support of the approval of "abiraterone acetate in combination with prednisone (or prednisolone) for the treatment of chemotherapy-naïve patients with metastatic castration-resistant prostate cancer (mCRPC) who progress after androgen deprivation therapy (ADT) and who are asymptomatic or mild symptomatic" is mainly based on 3 studies: COU-AA-001/EXT, COU-AA-002 and COU-AA-302.

The pivotal study is COU-AA-302 a phase 3, multinational, randomised, double-blind, placebo controlled study conducted at 151 study sites in the US, Europe and Australia comparing the efficacy and safety of abiraterone acetate plus prednisone with placebo plus prednisone in medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who have not received cytotoxic chemotherapy. Planned enrolment was approximately 1,000 subjects. Subjects were stratified according to Eastern Cooperative Oncology Group (ECOG) performance status Grade (0 versus 1) and were then assigned randomly in a 1:1 ratio to receive abiraterone acetate plus prednisone or placebo plus prednisone.

Studies COU-AA-001/EXT, COU-AA-002 are phase 1/2, open label, single arm, dose-escalation studies investigating abiraterone acetate therapy in men with CRPC who had no previous chemotherapy for prostate cancer. They were also submitted and assessed during the MAA procedure.

Study COU-AA-301 conducted in patients with mCRPC previously treated with docetaxel is considered as supportive studies in the current proposed indication.

2.4.1. Dose response studies

No new studies have been carried out in the claimed population (see discussion on Clinical efficacy).

2.4.2. Main study

COU-AA-302

This was a phase III, multinational, randomised, double-blind, placebo controlled study conducted at 151 study sites in the US, Europe and Australia comparing the efficacy and safety of abiraterone acetate plus prednisone with placebo plus prednisone in medically or surgically castrated asymptomatic or mildly symptomatic men with mCRPC who had not received cytotoxic chemotherapy.

Methods

Study participants

Mean Inclusion Criteria

- Mean (≥ 18 year) able to provide written informed consent and authorisation of data protection.
- Histologically or cytologically confirmed adenocarcinoma of the prostate

- Metastatic disease documented by positive bone scan or metastatic lesions, other than liver or visceral metastasis, on computed tomography (CT) or magnetic resonance imaging (MRI). If lymph node metastasis was the only evidence of metastasis, it must have been ≥2 cm in diameter.
- Documented prostate cancer progression by prostate-specific antigen (PSA), according to adapted Prostate Cancer Clinical Trials Working Group-2 (PCWG2), or radiographic progression according to modified Response Evaluation in Solid Tumors (RECIST) criteria
- Asymptomatic or mildly symptomatic from prostate cancer, as defined by a score of 0 or 1 (asymptomatic) or 2-3 (mildly symptomatic) on the Brief Pain Inventory-Short Form (BPI-SF) Question No. 3
- Surgical or medical castration, as demonstrated by serum testosterone levels of <50 ng/dL (<2.0 nM). If the subject was treated with luteinizing hormone-releasing hormone (LHRH) agonists, the therapy must have been initiated at least 4 weeks prior to Cycle 1 Day 1 and must have continued throughout the study.
- Previous antiandrogen therapy followed by documented PSA progression after discontinuing the antiandrogen (≥4 weeks since last flutamide, ≥6 weeks since last bicalutamide or nilutamide) prior to enrollment
- ECOG performance status Grade 0 or 1
- Adequate haematological, renal and liver function.
- Ability to swallow the study medication whole as a tablet
- Life expectancy of at least 6 months
- Subjects who had partners of childbearing potential must have been willing to use a method of birth control with adequate barrier protection as determined to be acceptable by the principal investigator and sponsor during the study and for 13 weeks after the last study medication administration.

Exclusion Criteria

- Active infection or other medical condition that would have made prednisone/prednisolone (corticosteroid) use a contraindication
- Any chronic medical condition that required a higher dose of corticosteroid than 5 mg prednisone/prednisolone twice a day
- Pathological finding of small cell carcinoma of the prostate
- Known liver, brain, or visceral organ metastasis
- Use of opiate analgesics for cancer-related pain, including codeine and dextropropoxyphene, within 4 weeks of Cycle 1 Day 1
- Prior cytotoxic chemotherapy or biologic therapy for the treatment of CRPC
- Radiation therapy for treatment of the primary tumor within 6 weeks of Cycle 1 Day 1
- Radiation or radionuclide therapy for treatment of mCRPC
- Prior therapy with ketoconazole for prostate cancer lasting more than 7 days
- Prior systemic therapy with an azole drug (eg, fluconazole, itraconazole) within 4 weeks of Cycle 1 Day 1
- Prior flutamide treatment within 4 weeks of Cycle 1 Day 1 (subjects whose PSA did not decline for 3 or more months in response to antiandrogen given as a second-line or later intervention required only a 2-week washout prior to Cycle 1 Day 1).
- Prior bicalutamide or nilutamide within 6 weeks of Cycle 1 Day 1 (subjects whose PSA did not decline for 3 or more months in response to antiandrogen given as a second-line or later intervention required only a 2-week washout prior to Cycle 1 Day 1).

- Uncontrolled hypertension (systolic blood pressure [BP] ≥160 mmHg or diastolic BP ≥95 mmHg). Subjects with a history of hypertension were allowed, provided BP was controlled by antihypertensive therapy.
- Active or symptomatic viral hepatitis or chronic liver disease
- History of pituitary or adrenal dysfunction
- Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events in the 6 months prior to screening, severe or unstable angina, or New York Heart Association (NYHA) Class II through IV heart disease or cardiac ejection fraction measurement of <50% at baseline
- Atrial fibrillation, or other cardiac arrhythmia requiring medical therapy
- Other malignancy, except nonmelanoma skin cancer, with a ≥30% probability of recurrence within 24 months
- Current enrollment in an investigational drug or device study or participation in such a study within 30 days of Cycle 1 Day 1
- Condition or situation which, in the investigator's opinion, might have put the subject at significant risk, confounded the study results, or interfered significantly with subject's participation in the study

Treatments

Patients were randomised to receive abiraterone 1000 mg (4x 250 mg tablets) or 4x placebo tablets orally once daily and prednisone or prednisolone 5 mg orally twice daily. Prednisolone was used in Europe. Placebo was supplied by the sponsor as a tablet formulation matching abiraterone tablets in size, colour and shape. Treatment was to be initiated within 72 hours (3 calendar days) of randomisation. Treatment was administered on a continuous schedule and each cycle of treatment was considered to be 28 days. In line with the current recommendations in the SmPC, food was not to be consumed for at least 2 hours before and for at least 1 hour after the study drug.

Patients were to receive treatment until documented disease progression (radiographic or unequivocal clinical progression [need to discontinue due to cancer pain requiring immediate administration of chronic opiate analgesics, deterioration of ECOG PS to Grade 3 or higher or immediate need to initiate cytotoxic chemotherapy or have either radiation therapy or surgical intervention for complications due to tumour progression]), unacceptable toxicity or a decision by the subject to discontinue study treatment. Study medication was to continue in those subjects who had increasing PSA values in the absence of radiographic or unequivocal clinical progression. If a subject experienced radiographic progression in the absence of unequivocal clinical progression, the subject could continue on study medication at investigator discretion until signs of unequivocal clinical progression were evident. Cross-over at disease progression of patients in the placebo arm to the abiraterone arm of the study was not permitted.

Allowed and prohibited concomitant medications/therapies are summarised in the following Table 4.

Table 4: Permissible and prohibited concomitant medications, COU-AA-302

Permissible medications	Prohibited concomitant medications
LHRH agonists to maintain testosterone <50 ng/dL (<2.0 nM) (mandatory for subjects who did not undergo orchiectomy)	Any other investigational drug therapy (for any reason)
Conventional multivitamins, selenium and soy supplements	5 a-reductase inhibitor

Additional systemic glucocorticoid administration, such as a stress dose of glucocorticoid, was permitted if clinically indicated for a life threatening medical condition and was to be documented as a concomitant drug	Chemotherapy
	Immunotherapy
Bisphosphonate usage was allowed only if subjects were receiving the medication prior to study Day 1	Bicalutamide, nilutamide, flutamide
Transfusions and haematopoietic growth factors were permitted per institutional practice guidelines	Systematic ketoconazole (or other azole drugs such as fluconazole and itraconazole)
If the permissibility of a specific drug/treatment was in question, the sponsor was to be contacted	Diethylstilbestrol, PC-SPES, and other preparations such as saw palmetto thought to have endocrine effects on prostate cancer
	Radiopharmaceuticals such as strontium (89Sr) or samarium (153Sm)
	Aldactone or Spironol (spironolactone) Digoxin, digitoxin, and other digitalis drugs
	Cyproterone acetate
	Fludrocortisone acetate (Florinef)

Objectives

The primary objective of this study was to compare the clinical benefit of abiraterone acetate plus prednisone to placebo plus prednisone in men with asymptomatic or mildly symptomatic chemotherapy-naïve metastatic CRPC.

The secondary objectives of this study were:

- To establish additional clinically relevant improvements in prostate cancer subjects treated with abiraterone acetate in comparison with placebo
- To characterise the safety profile of abiraterone acetate in this subject population
- To characterise the pharmacokinetics of abiraterone acetate when administered concurrently with prednisone

Outcomes/endpoints

The study had two co-primary endpoints: radiographic progression-free survival (rPFS) and overall survival (OS).

rPFS was defined as the time from randomisation to the first occurrence of 1 of the following: disease progression by bone scan (according to modified PCWG2 criteria), progression by CT or MRI (according to modified RECIST) or death (independent radiographic review of sequential imaging assessments).

The determination of rPFS was adapted from defined criteria formulated by the PCWG2 to enhance the reliability and objectivity of the endpoint. These criteria required bone scans to be performed at an increased frequency (every 8 weeks) for the first 24 weeks (6 cycles) of the study and confirmatory bone scans of new lesions performed to minimise the false positive rate. Additionally, to avoid bias, the scans were reviewed by an independent assessor, blinded to the subject's treatment assignment, clinical information (signs and symptoms data as well as clinical laboratory data, including PSA concentrations) and progression status.

OS was defined as the time from randomisation to the date of death regardless of cause. Overall survival was determined by investigator observation during the treatment period and follow-up period.

Secondary endpoints included: time to initiation of cytotoxic chemotherapy, time to opiate use for cancer pain, time to ECOG PS deterioration by at least 1 grade, time to PSA progression, PSA response rate, objective response rate (by independent review), patient-reported outcome measures (PRO), biomarker data (selected sites only) and safety parameters.

Sample size

The overall level of significance for the study was 0.05, which was allocated between the co-primary endpoints (0.01 for rPFS and 0.04 for OS). The exact timing of the analysis was carried out according to the pre-specified number of events for each endpoint. The median rPFS was estimated at approximately 4 months, while the estimated median OS for this population has been reported to be in the range of 20 to 22 months. With a planned sample size of approximately 1,000 subjects, and an estimated enrollment rate of 50 subjects per month (20 months to complete enrollment), a study duration of approximately 64 months was planned for the study.

One analysis of rPFS was planned. Assuming that the hazards for the 2 treatment groups follow a proportional hazard model, it was estimated that 378 rPFS events would be required to provide 91% power in detecting a median rPFS of 4 months in the placebo group compared with 6 months for the abiraterone acetate group (HR=0.667) at a 2-tailed level of significance of 0.01.

Assuming that the hazards for the 2 treatment groups would follow a proportional hazards model for OS, the test to detect a difference between a median OS of 22 months in the placebo group and a median OS of 27.5 months in the abiraterone acetate group (HR=0.80) at a 2-tailed significance level of 0.04 with a power of 85%, would require 773 events.

Randomisation

Patients were assigned randomly in a 1:1 ratio to receive either abiraterone acetate plus prednisone or placebo plus prednisone.

Blinding (masking)

This was a double-blind study.

Statistical methods

The ITT population was used for all efficacy analyses, and all analyses of disposition, demographic, and baseline disease characteristics. The primary analysis of the primary and secondary efficacy endpoints was based on the stratified log rank test; sensitivity analyses using the non-stratified log rank test, and Cox proportional hazards model also were performed as supportive analyses. Distribution curve, median and 95% confidence interval for the co-primary endpoints were estimated using the Kaplan-Meier method.

Only 1 analysis was planned for the co-primary rPFS endpoint. The OS endpoint incorporated group sequential design by including 3 interim analyses and one final analysis using the O'Brien-Fleming boundaries as implemented by Lan-DeMets alpha spending method to ensure that the type I error rate was not inflated.

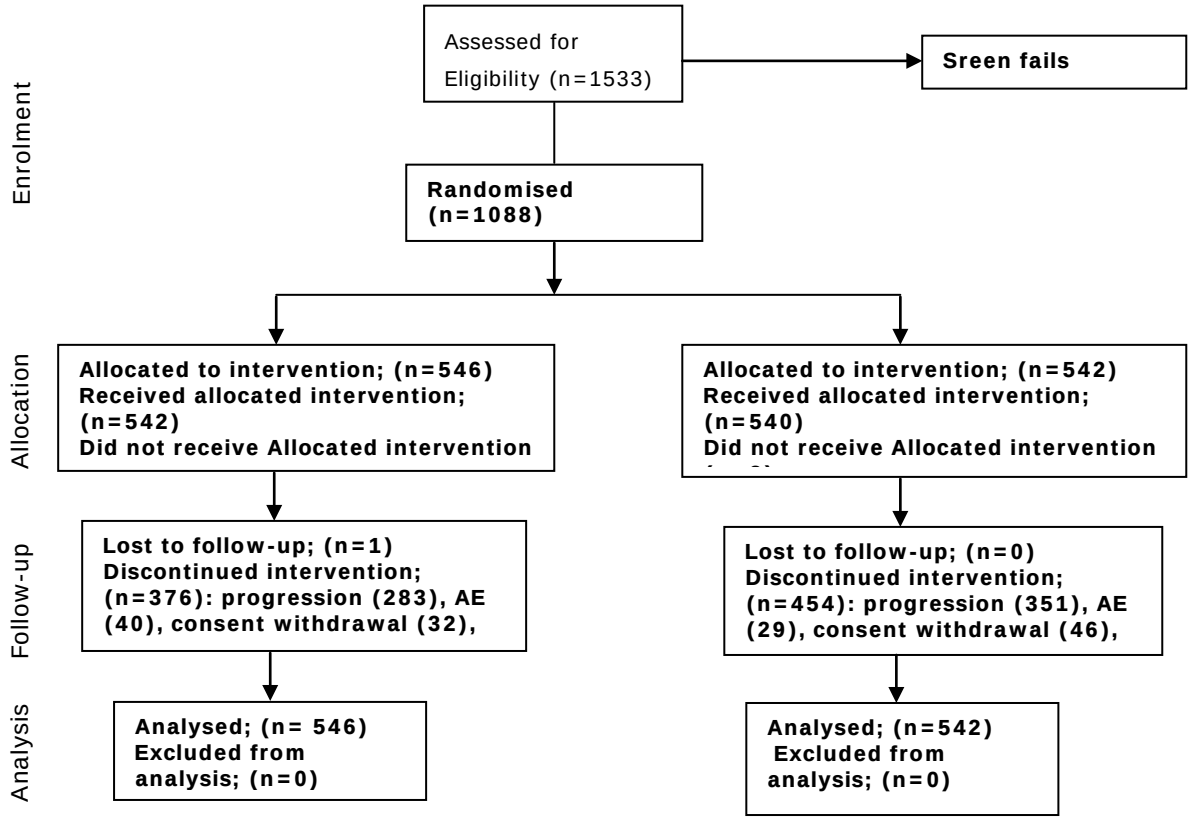
Table 5: Statistical Operating Characteristics for OS

Variable	Analyses			
	Interim 1* (~15% of Total Events)	Interim 2 (40% of Total Events)	Interim 3 (55% of Total Events)	Final
Projected Observed OS Events	116	311	425	773
Efficacy Boundary (HR)	0.336	0.672	0.751	0.861
Cumulative Stopping Probability Under (H_0)	<0.0001	0.0005	0.0034	0.0400
Clinical cutoff date	20 Dec 2010	20 Dec 2011	22 May 2012	Estimated 2014

HR=Hazard ratio; H_0 = 0% improvement; H_1 = 25% improvement; *At the time of the primary rPFS analysis

Results

Participant flow



Recruitment

The first patient was enrolled on 28 April 2009 and the last patient entered the study on 23 June 2010.

Conduct of the study

Protocol amendments were as follows:

Amendment 1: April 14, 2010 - 971 subjects randomised

- Expansion of genetic analyses

Amendment 2: June 7, 2011 - 1,088 subjects randomised

- Inclusion of an additional interim analysis of the OS co-primary endpoint and adjustment of the timing of the interim analyses for OS
- Addition of a strategy to adjust for a potential cross-over effect

Amendment 3: April 2, 2012 - 1,088 subjects randomised

- Updated eligibility criteria and modified schedule of events for subjects who will cross over from placebo to abiraterone after the study drug assignments were unblinded
- Provided information on the IDMC recommendation to unblind the treatment assignments.

Major protocol deviations are summarised in the following Table 6.

Table 6: Major protocol deviations, study COU-AA-302, ITT population

	AA (N=546)	Placebo (N=542)	Total (N=1088)
Total no. subjects with a deviation	67 (12.3%)	55 (10.1%)	122 (11.2%)
Eligibility criteria not met	30 (5.5%)	24 (4.4%)	54 (5.0%)
Prohibited concurrent medication	20 (3.7%)	13 (2.4%)	33 (3.0%)
Treatment discontinuation criteria not followed	5 (0.9%)	13 (2.4%)	18 (1.7%)
IP Dosing error	6 (1.1%)	3 (0.6%)	9 (0.8%)
Drug Dispensing error (e.g., incorrect kit number)	2 (0.4%)	4 (0.7%)	6 (0.6%)
Assessment/Visit/Phone Follow-Up Not Done	2 (0.4%)	2 (0.4%)	4 (0.4%)
Other Deviation	3 (0.5%)	1 (0.2%)	4 (0.4%)
Assessment not performed properly per protocol	0	1 (0.2%)	1 (0.1%)
Dose modification/toxicity management not followed	1 (0.2%)	0	1 (0.1%)
Note: Percentages calculated with the number of subjects in each group as denominator.			

Baseline data

Baseline demographic and disease characteristics are summarised in the following Table 7.

Table 7: Baseline demographic and disease characteristics, study COU-AA-302, ITT

	AA (N=546)	Placebo (N=542)	Total (N=1088)
Demographics Baseline			
Age (years)			
N	546	542	1088
< 65	135 (24.7%)	155 (28.6%)	290 (26.7%)
65-69	112 (20.5%)	103 (19.0%)	215 (19.8%)
70-74	114 (20.9%)	119 (22.0%)	233 (21.4%)
≥75	185 (33.9%)	165 (30.4%)	350 (32.2%)
Mean (SD)	70.5 (8.80)	70.1 (8.72)	70.3 (8.76)
Median	71.0	70.0	70.0
Range	(44, 95)	(44, 90)	(44, 95)
Ethnicity			
Hispanic or Latino	25 (4.6%)	24 (4.5%)	49 (4.5%)
Not Hispanic or Latino	520 (95.4%)	515 (95.5%)	1035 (95.5%)
Race			
White	520 (95.4%)	510 (94.4%)	1030 (94.9%)
Black	15 (2.8%)	13 (2.4%)	28 (2.6%)
Asian	4 (0.7%)	9 (1.7%)	13 (1.2%)
Other	6 (1.1%)	8 (1.5%)	14 (1.3%)

Baseline Disease Characteristics			
Time From Initial Diagnosis to First Dose (years)			
N	542	540	1082
Mean (SD)	6.7 (4.85)	6.5 (4.77)	6.6 (4.81)
Median	5.5	5.1	5.3
Range	(0, 28)	(0, 28)	(0, 28)
PSA at Initial Diagnosis (ng/mL)			
N	470	454	924
Mean (SD)	174.01 (540.433)	219.69 (888.783)	196.46 (732.545)
Median	22.30	21.00	22.00
Range	(0.4, 5036.0)	(0.3, 9726.3)	(0.3, 9726.3)
Tumour Stage at Diagnosis			
N	541	541	1082
T0	0	2 (0.4%)	2 (0.2%)
T1, T1a, T1b, T1c	65 (12.0%)	71 (13.1%)	136 (12.6%)
T2, T2a, T2b, T2c	151 (27.9%)	149 (27.5%)	300 (27.7%)
T3, T3a, T3b, T3c	173 (32.0%)	162 (29.9%)	335 (31.0%)
T4, T4a, T4b	31 (5.7%)	39 (7.2%)	70 (6.5%)
TX	42 (7.8%)	35 (6.5%)	77 (7.1%)
Unknown	77 (14.2%)	79 (14.6%)	156 (14.4%)
Not Applicable	2 (0.4%)	4 (0.7%)	6 (0.6%)
Lymph Node Stage at Diagnosis			
N	542	540	1082
N0	218 (40.2%)	220 (40.7%)	438 (40.5%)
N1	61 (11.3%)	58 (10.7%)	119 (11.0%)
N2	16 (3.0%)	10 (1.9%)	26 (2.4%)
N3	8 (1.5%)	8 (1.5%)	16 (1.5%)
NX	118 (21.8%)	114 (21.1%)	232 (21.4%)
Unknown	117 (21.6%)	121 (22.4%)	238 (22.0%)
Not Applicable	4 (0.7%)	9 (1.7%)	13 (1.2%)
Metastasis Stage at Diagnosis			
N	542	541	1083
M0	239 (44.1%)	230 (42.5%)	469 (43.3%)
M1, M1a, M1b, M1c	135 (24.9%)	142 (26.2%)	277 (25.6%)
MX	75 (13.8%)	88 (16.3%)	163 (15.1%)
Unknown	91 (16.8%)	75 (13.9%)	166 (15.3%)
Not Applicable	2 (0.4%)	6 (1.1%)	8 (0.7%)
Gleason Score at Initial Diagnosis			
N	488	508	996
<7	65 (13.3%)	64 (12.6%)	129 (13.0%)
7	160 (32.8%)	190 (37.4%)	350 (35.1%)
2+5	0	1 (0.2%)	1 (0.1%)
3+4	81 (16.6%)	90 (17.7%)	171 (17.2%)
4+3	78 (16.0%)	98 (19.3%)	176 (17.7%)
>7	263 (53.9%)	254 (50.0%)	517 (51.9%)
Extent of Disease at study entry			
N	544	542	1086
Bone	452 (83.1%)	432 (79.7%)	884 (81.4%)
Bone Only	274 (50.4%)	267 (49.3%)	541 (49.8%)
Soft Tissue or Node	267 (49.1%)	271 (50.0%)	538 (49.5%)
Bone, Soft Tissue, or Node	544 (100.0%)	542 (100.0%)	1086 (100.0%)
Other	4 (0.7%)	7 (1.3%)	11 (1.0%)

Numbers analysed

Efficacy analyses were performed using the ITT population, which included all randomised subjects (1,088 randomised subjects: 546 subjects in the abiraterone acetate group and 542 subjects in the

placebo group). The safety population included all subject in the randomised population who received any study medication.

Outcomes and estimation

Co-primary endpoints

Results for the co-primary endpoint of radiographic progression-free survival (rPFS) are summarised in the following Table 8 and Figure 2.

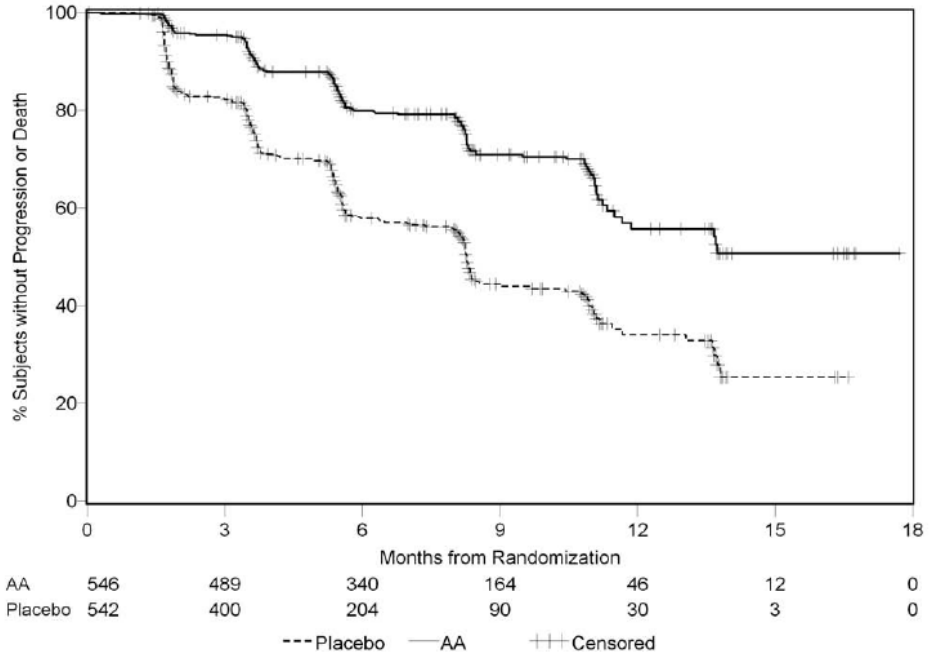
Table 8: rPFS primary analysis (independent review, cut-off date: 20 Dec 2010) and updated analysis (investigator review, cut-off date: 20 Dec 2011), stratified analysis, COU-AA-302

	Primary Analysis		Updated Analysis	
	Abiraterone (N=546)	Placebo (N=542)	Abiraterone (N=546)	Placebo (N=542)
Event	150 (27.5%)	251 (46.3%)	271 (49.6%)	336 (62.0%)
Censored	396 (72.5%)	291 (53.7%)	275 (50.4%)	206 (38.0%)
Time to event (months)				
25th percentile (95% CI)	8.28 (8.02, 9.49)	3.65 (3.52, 4.04)	8.15 (7.03, 8.28)	3.61 (3.48, 3.75)
Median (95% CI)	NE (11.66, NE)	8.28 (8.12, 8.54)	16.46 (13.80, 16.79)	8.25 (8.05, 9.43)
75th percentile (95% CI)	NE (NE, NE)	NE (13.63, NE)	NE (27.60, NE)	19.32 (16.39, 22.21)
Range	(0.0+, 17.7+)	(0.0+, 16.6+)	(0.0+, 27.9+)	0.0+, 27.7+)
6-mo event-free rate	0.799	0.579	0.794	0.564
12-mo event-free rate	0.557	0.340	0.583	0.371
18-mo event-free rate	0.507	0.254	0.444	0.262
24-mo event-free rate	-	-	0.377	0.181
30-mo event-free rate	-	-	0.289	0.155
p value[a]	< 0.0001		< 0.0001	
Hazard ratio (95% CI)[b]	0.425 (0.347, 0.522)		0.530 (0.451, 0.623)	

AA=abiraterone acetate; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; ITT=intent-to-treat; NE=not estimable; rPFS=radiographic progression-free survival. Note: + = censored observation. The radiographic progression and death are considered in defining the rPFS event.

[a] p value is from a log-rank test stratified by ECOG performance status (0 or 1). [b] Hazard ratio is from stratified proportional hazards model. Hazard ratio < 1 favours AA.

Figure 2: rPFS (independent review), cut-off date: 20 Dec 2010, COU-AA-302, ITT



At time of the first interim OS analysis (20 December 2010 - 209 events), the median OS was not reached in either arm of treatment. Results of the second interim analysis for Overall Survival (20 December 2011, 333 events) and the third interim analysis (22 May 2012, 434 events) are summarised in the following Table 9 and Figures 3 and 4.

Table 9: Overall survival, 2nd interim analysis (cut-off date: 20 Dec 2011) and 3rd interim analysis (cut-off date: 22 May 2012), stratified analysis, COU-AA-302, ITT

	2nd Interim Analysis		3rd Interim Analysis	
	AA (N=546)	Placebo (N=542)	AA (N=546)	Placebo (N=542)
Event	147 (26.9%)	186 (34.3%)	200 (36.6%)	234 (43.2%)
Censored	399 (73.1%)	356 (65.7%)	346 (63.4%)	308 (56.8%)
Overall survival (months)				
25th percentile (95% CI)	21.19 (19.15, 24.38)	18.76 (17.84, 20.47)	21.29 (19.15, 23.33)	18.86 (17.81, 20,60)
Median (95% CI)	NE (NE, NE)	27.24 (25.95, NE)	35.29 (31.24, 35.29)	30.13 (27.30, 34.10)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)	35.29 (NE, NE)	34.69 (34.10, NE)
Range	(0.0+, 30.0+)	(0.0+, 30.8+)	(0.0+, 35.3)	0.0+, 35.7+)
6-month event-free rate	0.980	0.972	0.980	0.972
12-month event-free rate	0.912	0.901	0.807	0.901
18-month event-free rate	0.807	0.778	0.694	0.778
24-month event-free rate	0.707	0.600	0.570	0.628
30-month event-free rate	0.616	0.458	0.570	0.521
36-month event-free rate	0.000	0.000	0.000	0.146
p value[a]	0.0097		0.0151	
Hazard ratio (95% CI)[b]	0.752 (0.606, 0.934)		0.792 (0.655, 0.956)	

AA=abiraterone acetate; CI=confidence interval; ITT=intent-to-treat; NE=not estimable
Note: + =censored observation.
[a] p value is from a log-rank test stratified by ECOG PS score (0 or 1).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours AA.

Figure 3: Overall Survival, COU-AA-302, ITT, 2nd interim analysis, cut-off date: 20 Dec 2011

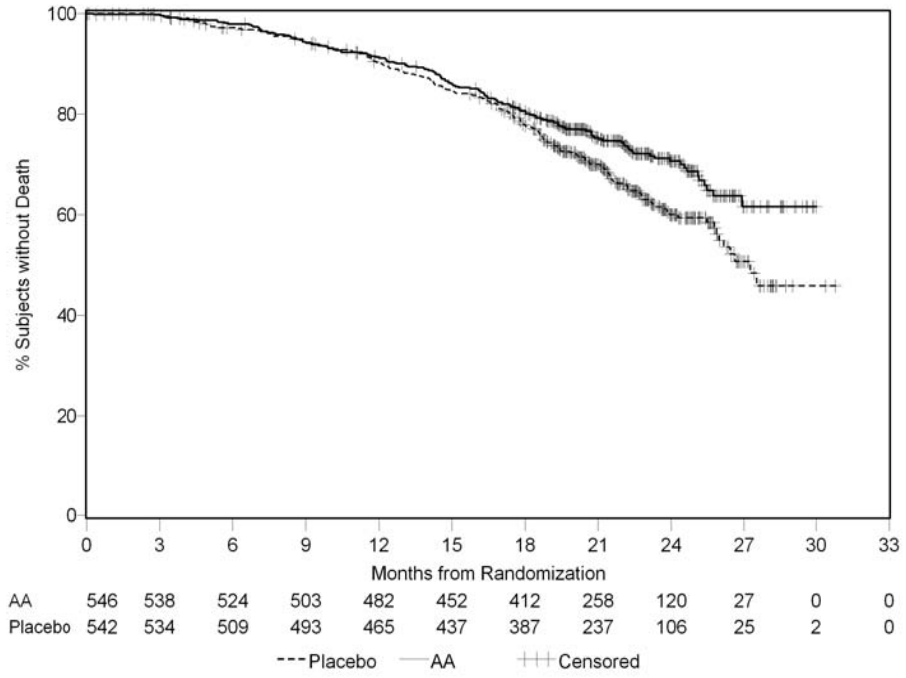
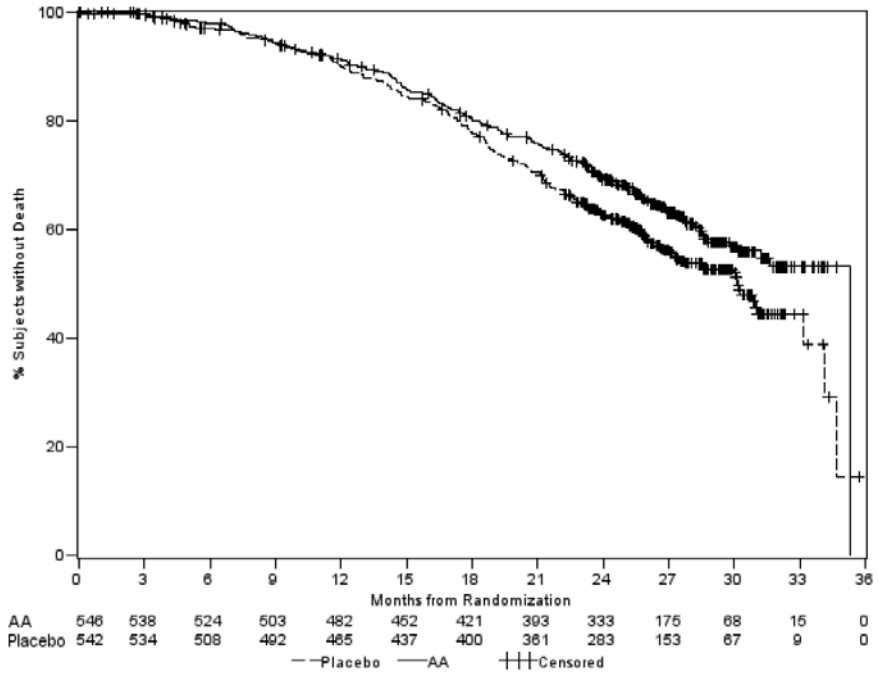


Figure 4: Overall Survival, COU-AA-302, ITT, 3rd interim analysis, cut-off date: 22 May 2012



Secondary endpoints

Results for the key secondary efficacy parameters are summarised in the following table and figures.

Figure 5: Time to a) opiate use for prostate cancer pain, b) initiation of cytotoxic chemotherapy, c) deterioration in ECOG performance status ≥1, d) PSA progression

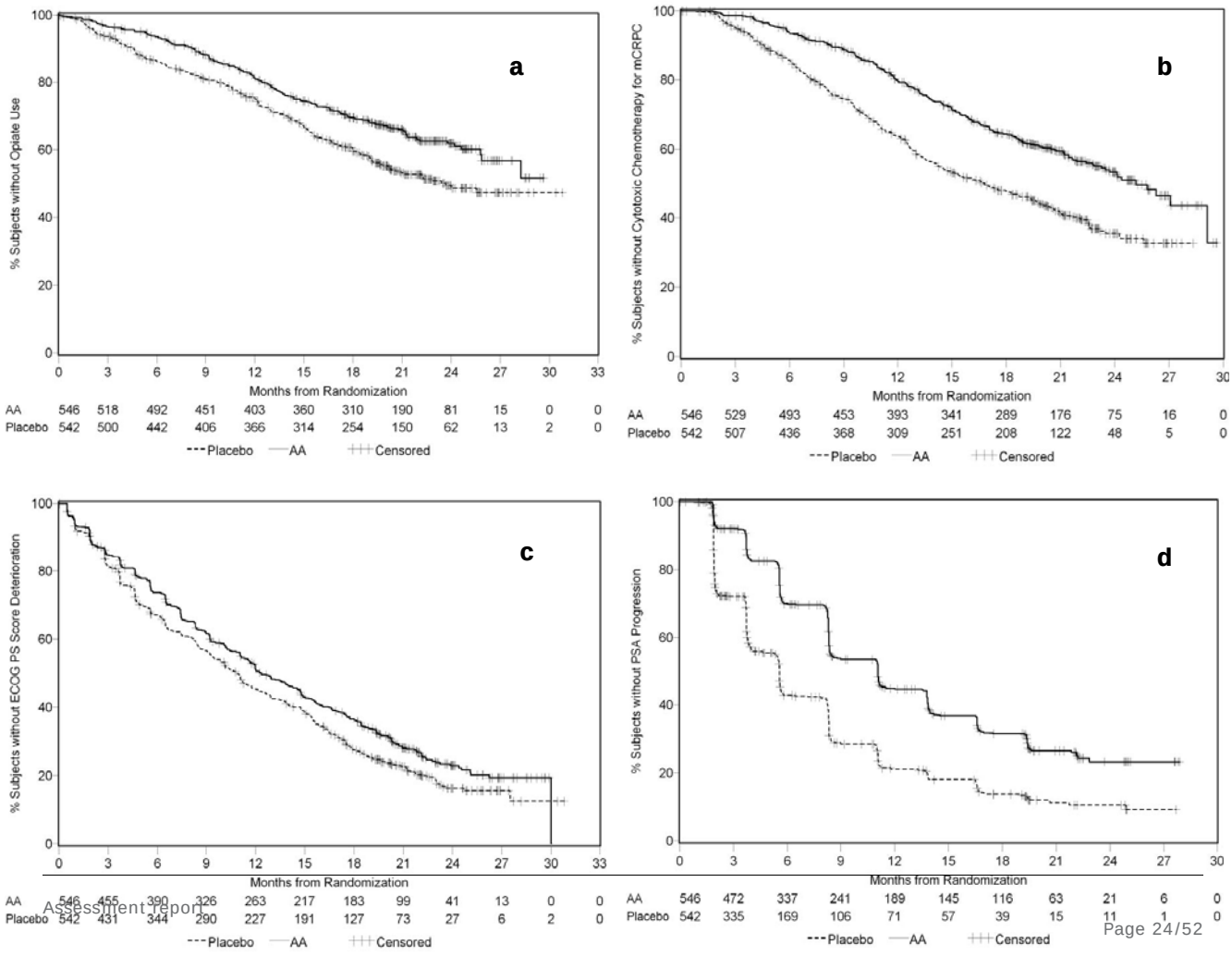


Table 10: Summary of Main Secondary Efficacy Analyses, COU-AA-302, ITT

	AA Number of events n (%)	AA Median months (95% CI)	Placebo Number of events n (%)	Placebo Median months (95% CI)	Hazard Ratio (95% CI)	P value
Time to Opiate Use for Cancer Pain						
Interim 2 (CCO 20 Dec 2011)	**183 (33.5)**	**NE (28.25, NE)**	**235 (43.4)**	**23.66 (20.24, NE)**	**0.686[a] (0.566, 0.833)**	**0.0001[b]**
Interim 1 (CCO 20 Dec 2010)	83 (15.2)	NE (NE, NE)	126 (23.2)	16.7 (16.6, NE)	0.595[a] (0.4505, 0.7861)	0.0002[b]
Time to Initiation of Chemotherapy						
Interim 2 (CCO 20 Dec 2011)	**220 (40.3)**	**25.17 (23.26, NE)**	**298 (55.0)**	**16.82 (14.55, 19.38)**	**0.580[a] (0.487, 0.691)**	**<0.0001[b]**
Interim 1 (CCO 20 Dec 2010)	100 (18.3)	17.3 (15.4, NE)	176 (32.5)	14.2 (13.0, NE)	0.473a (0.3691, 0.6051)	<0.0001[b]
Time to ECOG Performance Status Deterioration						
Interim 2 (CCO 20 Dec 2011)	**390 (71.4)**	**12.29 (11.33, 14.29)**	**411 (75.8)**	**10.87 (9.49, 11.76)**	**0.821[a] (0.714, 0.943)**	**0.0053[b]**
Interim 2 with Confirmation of Deterioration (CCO 20 Dec 2011)-post hoc[c]	268 (49.1)	19.58 (17.74, 23.85)	306 (56.5)	15.51 (13.83, 16.92)	0.754[a] (0.639, 0.888)	0.0007[b]
Interim 1 (CCO 20 Dec 2010)	244 (44.7)	12.0 (10.3, 14.3)	279 (51.5)	10.2 (9.1, 11.1)	0.782[a] (0.6582, 0.9300)	0.0054[b]
Time to PSA Progression						
Interim 2 (CCO 20 Dec 2011)	**339 (62.1)**	**11.07 (8.51, 11.24)**	**381 (70.3)**	**5.55 (5.39, 5.59)**	**0.488[a] (0.420, 0.568)**	**<0.0001[b]**
Interim 1 (CCO 20 Dec 2010)	191 (35.0)	13.8 (11.1, NE)	306 (56.5)	5.6 (5.3, 5.6)	0.398[a] (0.3303, 0.4790)	<0.0001[b]

CCO=clinical cutoff; CI=confidance interval, ITT=intent to treat; NE=not estimable.

[a] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA.

[b] p value is from a log-rank test stratified by ECOG PS Grade (0 or 1).

[c] A post hoc analysis was performed for the deterioration in ECOG performance status grade by ≥1 grade with confirmation of deterioration at the next visit. This analysis addresses potential transient fluctuations in performance status.

With regard to other secondary efficacy parameters:

- A confirmed PSA response was observed in 62% of subjects in the abiraterone group and 24% of subjects in the placebo group (p<0.0001).

- Objective response rate results by RECIST in patients with measurable disease at baseline and based on independent review were as follows:

Table 11: Objective response rate, COU-AA-302

	AA (N=546)	Placebo (N=542)
Subjects with measurable disease at baseline	220	218
Complete response	24 (11%)	8 (8%)
Partial response	54 (25%)	26 (12%)
Non-Responder	142 (64.5%)	184 (84.4%)
p value	< 0.0001	
Relative Risk (95% CI)	2.273 (1.591, 3.247)	

- Patient-reported outcomes were measured using the Brief Pain Inventory-Short Form (BPI-SF) and the Functional Assessment of Cancer Therapy Prostate (FACT-P) instrument.

For both treatment groups, the cumulative compliance rate for completion of the BPI-SF was 95% or greater for every assessment. Treatment with abiraterone significantly reduced the risk of average pain intensity progression by 18% compared with placebo (HR=0.817; 95% CI: 0.668, 0.999; p=0.0490). The median time to average pain intensity progression was 26.7 months in the abiraterone group and 18.4 months in the placebo group.

Treatment with abiraterone decreased the risk of FACT-P (Total Score) degradation by 22% compared with placebo (HR=0.778; 95% CI: 0.659, 0.918; p=0.0028). The median time to degradation was 12.7 months in the abiraterone group and 8.3 months in the placebo group.

Table 12: FACT-P scores, COU-AA-302

FACT-P Subscale	Median (95% CI) Time to Degradation (months)		Hazard ratio (95% CI)	p-value
	AA	Placebo		
FACT-P (Total Score)	12.65 (11.07, 14.00)	8.31 (7.39, 10.61)	0.778 (0.659, 0.918)	0.0028
TOI	13.86 (11.99, 16.49)	9.26 (8.31, 11.07)	0.745 (0.630, 0.882)	0.0006
PCS	11.10 (8.64, 13.80)	5.78 (5.49, 8.31)	0.703 (0.598, 0.827)	
FACT-G	16.56 (13.86, 19.35)	11.07 (8.51, 14.75)	0.758 (0.634, 0.906)	0.0023
PWB	14.78 (13.63, 16.82)	11.07 (9.10, 13.80)	0.759 (0.637, 0.904)	0.0020
SFWB	18.40 (13.83, NE)	16.59 (11.07, NE)	0.940 (0.775, 1.139)	0.5283
EWB	22.11 (17.35, NE	14.16 (13.34, 19.45)	0.714 (0.586, 0.869)	0.0008
FWB	13.34 (11.01, 15.74)	8.35 (7.39, 10.12)	0.760 (0.644, 0.898)	0.0012

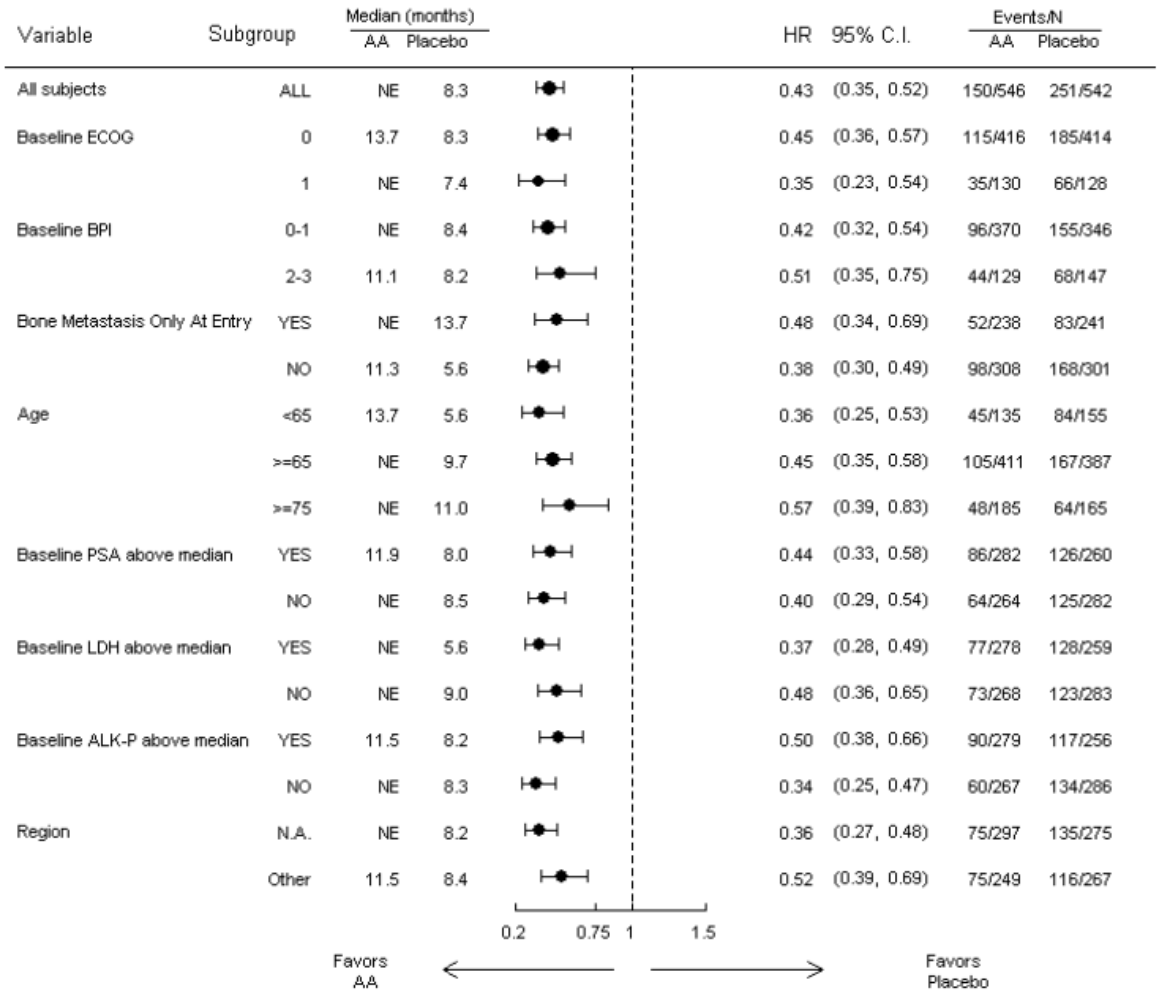
EWB=Emotional Well Being; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-P; Functional Assessment of Cancer Therapy-Prostate; FWB=Functional Well Being; PCS=Prostate Cancer Scale; PWB=Physical Well Being; SFWB=Social/Family Well Being; TOI=Total Outcome Index

A delay in median time to average pain intensity progression of >8 months and >4 month delay in the degradation in the FACT-P (Total Score) was observed, indicating that quality of life was generally preserved in those subjects treated with abiraterone.

Ancillary analyses

Subgroup analyses for the co-primary endpoint of rPFS are summarised in the following Figure 6.

Figure 6: Subgroup Analyses of Radiographic Progression-Free Survival



The HR within each subgroup was estimated using a nonstratified Cox proportional hazard model.

AA=abiraterone acetate; ALP=alkaline phosphatase; BPI=Brief Pain Inventory; C.I.=confidence interval; ECOG=Eastern Cooperative Oncology Group; HR=hazard ratio; LDH=lactic dehydrogenase; N.A.=North America; NE=not estimable; No.=number; PSA=prostate-specific antigen

Additional multivariate and subgroup analyses for the co-primary endpoint of OS, based on the second interim analysis (cut-off date: 20 Dec 2011) are summarised in the following Table 13 and Figure 7.

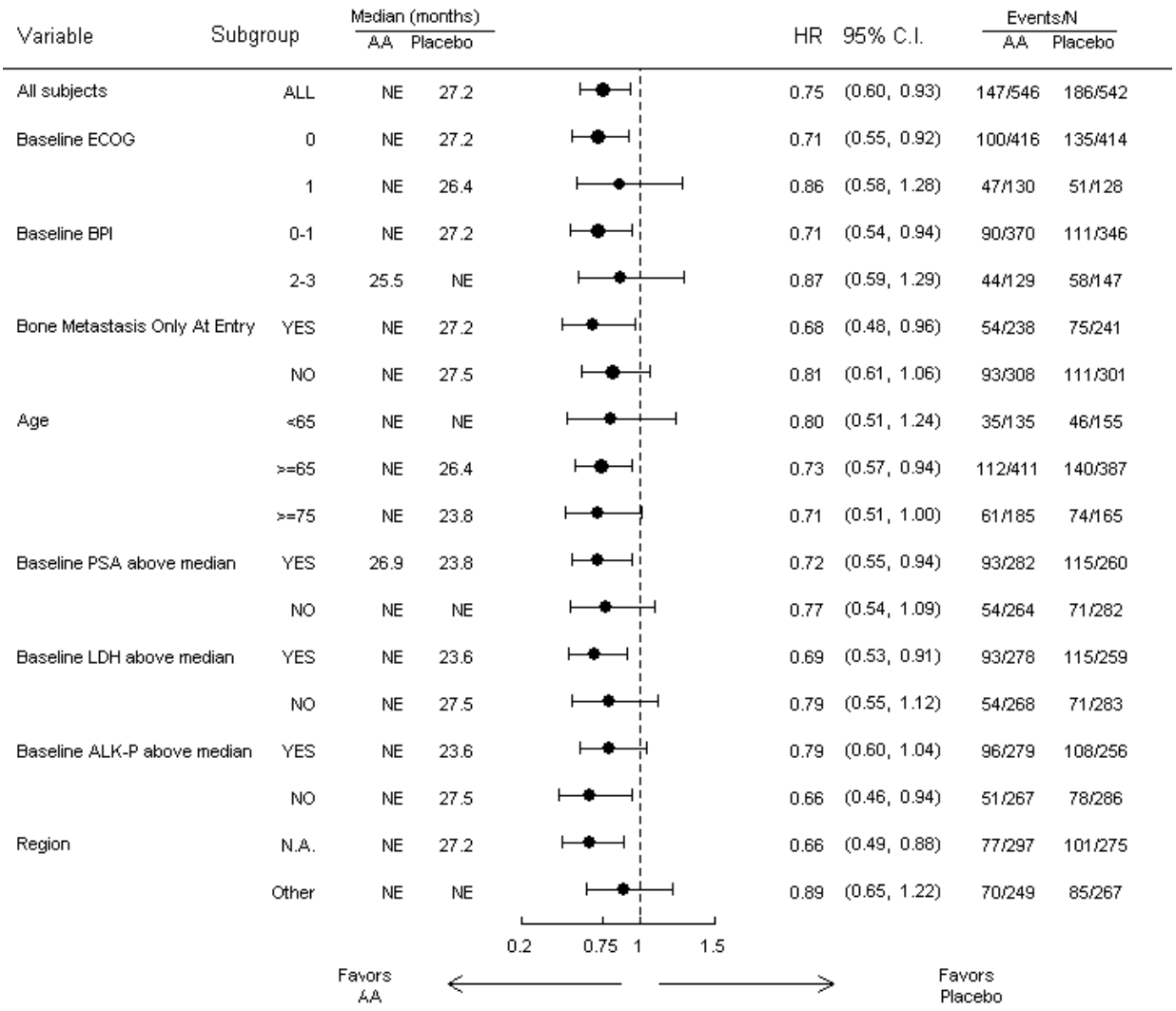
Table 13: Overall Survival - Nonstratified Proportional Hazards Model (Multivariate Analysis)

	Model Fit		Hazard Ratio	
Model Parameter	Coeff. (SE)	p-value	Estimate	95% C.I.
Treatment (AA vs. Placebo)	-0.39 (0.112)	0.0005	0.676	(0.543,0.842)
Treatment (AA vs. Placebo, 3rd interim analysis)	-0.31 (0.097)	0.0017	0.736	(0.609, 0.891)
ECOG score (1 vs. 0)	0.15 (0.125)	0.2444	1.157	(0.905, 1.477)
Log(Baseline Serum PSA (ng/mL))	0.17 (0.041)	< 0.0001	1.184	(1.093, 1.282)
Log(Baseline Lactate Dehydrogenase (IU/L))	1.15 (0.210)	< 0.0001	3.145	(2.085, 4.745)
Log(Baseline Alkaline Phosphatase (IU/L))	0.33 (0.089)	0.0002	1.393	(1.171, 1.657)
Baseline Haemoglobin (g/dL)	-0.10 (0.043)	0.0215	0.905	(0.832, 0.985)

Bone metastasis only at baseline (Yes vs. No)	-0.34 (0.115)	0.0032	0.712	(0.568, 0.892)
Age	0.02 (0.007)	0.0006	1.023	(1.010, 1.036)

ECOG= Eastern Cooperative Oncology Group; PSA= prostate-specific antigen. Model dependent variable is overall survival, expressed as days from date of randomisation to date of death from any cause. If the hazard ratio is < 1, then result favours the first level of the parameter (as listed above). 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.

Figure 7: Subgroup Analyses of Overall Survival



Finally, the MAH submitted numerous sensitivity analyses (data not shown).

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14: Summary of efficacy for trial COU-AA-302

Title: A Phase 3, Randomised, Double-blind, Placebo-Controlled Study of Abiraterone Acetate Plus Prednisone in Asymptomatic or Mildly Symptomatic Subjects With Metastatic Castration-Resistant Prostate Cancer			
Study identifier	COU-AA-302; NCT-00887198; 2008-008004-41		
Design	Multinational, multicenter, randomised, double-blind, placebo-controlled		
	Duration of main phase:		Until documented radiographic disease progression or unequivocal clinical progression.
Hypothesis	Superiority		
Treatments groups	Abiraterone acetate		1,000 mg (administered as 4 x 250 mg tablets) orally once daily at least 1 hour before or 2 hours after a meal + prednisone/prednisolone 5 mg orally twice daily. Each cycle of treatment was 28 days. (N=546)
	Placebo		4 matching placebo tablets orally once daily at least 1 hour before or 2 hours after a meal + prednisone/prednisolone 5 mg orally twice daily. Each cycle of treatment was 28 days. (N=542)
Endpoints and definitions	Co-Primary endpoint	Radiographic Progression-Free Survival (rPFS)	Time from randomisation to the occurrence of 1 of the following, whichever occurred first: 1. A subject was considered to have progressed by bone scan (PCWG2 criteria) 2. Progression of soft tissue lesions measured by CT or MRI as defined by modified RECIST 3. Death from any cause.
	Co-Primary endpoint	Overall Survival (OS)	Time from randomisation to death from any cause.
	Secondary endpoint	Time to opiate use for cancer pain	The time interval from the date of randomisation to the date of opiate use for cancer pain.
	Secondary endpoint	Time to initiation of cytotoxic chemotherapy	The time interval from the date of randomisation to the date of initiation of cytotoxic chemotherapy for prostate cancer.
	Secondary endpoint	Time to clinical deterioration in ECOG performance status by $\geq$ 1 grade	The time interval from the date of randomisation to the first date at which there was at least a 1 grade change (worsening) in the ECOG performance status grade.
	Secondary endpoint	Time to PSA progression	The time interval from the date of randomisation to the date of PSA progression as defined in the protocol-specific PCWG2 criteria.
Database lock	20 December 2011 (2nd Interim analysis)		
Results and Analysis			
Analysis description	**Primary rPFS Analysis, First Interim OS Analysis**		
Analysis population and time point description	Intent to treat 20/12/2010		
Descriptive statistics and estimate variability	Treatment group	Abiraterone acetate	Placebo
	Number of subject	546	542
	rPFS (median, months)	NE	8.28
	95% CI	(11.66, NE)	(8.12, 8.54)
Effect estimate per comparison	Co-Primary endpoint (rPFS)	Comparison groups	Abiraterone acetate vs placebo
		HR from stratified proportional hazards model	0.425
		95% CI	(0.347, 0.522)
		Stratified log-rank P-value	<0.0001
Notes	Stratification factors for the primary analysis (log rank): ECOG performance status score (0, 1); rPFS assessed by independent radiographic review; NE=not estimable		

Analysis description	**Second Interim OS analysis, Updated rPFS Analysis**		
Analysis population and time point description	Intent to treat 20/12/2011		
Descriptive statistics and estimate variability	Treatment group	Abiraterone acetate	Placebo
	Number of subject	546	542
	rPFS (median, months)	16.46	8.25
	95% CI	(13.80, 16.79)	(8.05, 9.43)
	OS (median; months)	NE	27.24
	95% CI	(NE, NE)	(25.95, NE)
	Time to Opiate Use (median; months)	NE	23.66
	95% CI	(28.25, NE)	(20.24, NE)
	Time to Initiation of Cytotoxic Chemotherapy (median; months)	25.17	16.82
	95% CI	(23.26, NE)	(14.55, 19.38)
	Time to ECOG Performance Score Increased >= 1 (median; months)	12.29	10.87
	95% CI	(11.33, 14.29)	(9.49, 11.76)
	Time to PSA Progression (median; months)	11.07	5.55
	95% CI	(8.51, 11.24)	(5.39, 5.59)
Effect estimate per comparison	Co-Primary endpoint (rPFS)	Comparison groups	Abiraterone acetate vs placebo
		HR from stratified proportional hazards model	0.530
		95% CI	(0.451, 0.623)
		Stratified log-rank P-value	<0.0001
	Co-Primary endpoint (OS)	Comparison groups	Abiraterone acetate vs placebo
		HR from stratified proportional hazards model	0.752
		95% CI	(0.606, 0.934)
		Stratified log-rank P-value	0.0097
	Secondary endpoint: (Time to Opiate Use)	Comparison groups	Abiraterone acetate vs placebo
		HR from stratified proportional hazards model	0.686
		95% CI	(0.566, 0.833)
		Stratified log-rank P-value	0.0001
	Secondary endpoint: (Time to Initiation of Cytotoxic Chemotherapy)	Comparison groups	Abiraterone acetate vs placebo
		HR from stratified proportional hazards model	0.580
		95% CI	(0.487, 0.691)
		Stratified log-rank P-value	<0.0001
	Secondary endpoint: (Time to ECOG Performance Score Increased >=1)	Comparison groups	Abiraterone acetate vs placebo
		HR from stratified proportional hazards model	0.821
		95% CI	(0.714, 0.943)
		Stratified log-rank P-value	0.0053
	Secondary endpoint:	Comparison groups	Abiraterone acetate vs placebo

	(Time to PSA Progression)	HR from stratified proportional hazards model	0.488
		95% CI	(0.420, 0.568)
		Stratified log-rank P-value	<0.0001
Notes	Stratification factors for the primary analysis (log rank): ECOG performance status score (0, 1); rPFS: assessed by the investigator review; NE=not estimable		

Analysis performed across trials (pooled analyses and meta-analysis)

Broad comparison of efficacy results across the Phase II and Phase III studies indicate consistent positive results for abiraterone in the treatment of patients with prostate cancer.

Table 15: Comparison of Efficacy Across Studies

	Studies in Chemotherapy Naïve Subjects				Studies in Subjects Previously Treated With Docetaxel	
	COU-AA-001/EXT	COU-AA-002	COU-AA-302		COU-AA-301	
	AA N=42	AA N=33	AA N=546	Placebo N=542	AA N=797	Placebo N=398
Median radiographic PFS (months)	NA	NA	Not Reached	8.3	5.6	3.6
Median Overall Survival (months)	NA	Not Reached	Not Reached	27.2	14.8 (CSR) 15.8 (Update)	10.9 (CSR) 11.2 (Update)
Estimated 2-year survival rate (% subjects)	NA	79%	71%	60%	36%b	24%b
Objective Response rate (CR + PR) (% subjects)	19%c	35%	36%	16%	14%	3%
PSA response rate (≥50% decline) (% subjects)	64%	79%	62%	24%	29%	6%
Median Time to PSA progression (months)	10.8	16.3	11.1	5.6	10.2	6.6

AA=abiraterone acetate; CR= complete response; EXT=extension; N=number of subjects; NA= Not assessed; PFS=progression-free survival; PR= partial response; PSA=prostate-specific antigen

[a]Overall survival data are presented from the Study COU-AA-301 updated data (September 2010 cutoff date).

[b]Study COU-AA-301 reported 18-month survival rates

[c]objective responses of population with measureable or non-measureable disease

2.4.3. Discussion on clinical efficacy

Earlier dose escalation studies of up to 2,000 mg per day presented in the initial dossier showed that the MTD for abiraterone acetate was not reached. Additionally, the 1,000 mg oral daily dose administered as four 250 mg tablets was chosen for study based upon pharmacokinetic, pharmacodynamic and efficacy data and was approved to treat men with mCRPC who had received

prior docetaxel-based chemotherapy. Ten (10) mg prednisone (or prednisolone) daily is administered concurrently to ameliorate mineralocorticoid-related toxicities that were observed in earlier studies of abiraterone acetate. This same dosing regimen was used for the studies that support this application which extends the observations of treatment benefits to chemotherapy naïve patients with mCRPC.

Studies COU-AA-001, COU-AA-001EXT and COU-AA-002 were conducted in men with CRPC who had no previous chemotherapy for prostate cancer. These studies were submitted to support the dosing in the initial dossier. Of note, the dose chosen has demonstrated to improve the life expectancy in those patients pre-treated with docetaxel.

Thus and taken together, the current authorised dosing is considered acceptable for this new indication: "1,000 mg administered orally once daily in combination with 5 mg prednisone or prednisolone twice daily. ZYTIGA must be taken without food and on an empty stomach as taking ZYTIGA with food increases systemic exposure. Therefore, no food should be consumed for at least 2 hours prior and 1 hour after the dose of ZYTIGA is taken".

Design and conduct of clinical studies

COU-AA-302 was a phase 3, multinational, randomised, double-blind, placebo controlled study in which most of the comments and discussion during the CHMP Scientific Advice were considered.

Eligible patients were asymptomatic or mildly symptomatic [0-1 or 2-3 BPI-SF] subjects with metastatic [bone (scan), soft tissue (CT, MRI) or Node ($\geq$ 2cm Ø)] castration [surgical or LHRH; serum testosterone < 50 ng/dL] – resistant [antiandrogens followed by PSA progression] prostate cancer, who had evidence of tumor progression [PSA (PCWG2) or radiographic (modified RECIST)]. Prior cytotoxic chemotherapy or biologic therapy was not allowed. ECOG Grade 0 or 1 was allowed.

These inclusion-exclusion criteria had the aim of recruiting asymptomatic or mildly symptomatic chemotherapy naïve mCRPC patients after failure of androgen deprivation therapy. Traditionally, patients with clear clinical and radiological progression are candidates to receive chemotherapy, usually docetaxel based therapy. However, patients with metastasis (no progression) but without clinical symptomatology are not treated with docetaxel and have limited alternative therapeutic options.

Several symptomatic patients (7.5% with >4 BPI-SF baseline) were included in the study. This number could be even higher since the use of opiate analgesics (not allowed for cancer related pain but allowed for non-cancer related pain) may have modified the pain perception from the patient who received opiate analgesic [28 patients (~3%)]. However, to obtain a representative patient population in this respect is practically difficult considering the real clinical practice. Importantly, the proportion of patients under the mentioned circumstances (7.5% >4 BPI-SF at baseline and ~3% who received opiate analgesic) was relative low. Therefore, this issue was considered resolved.

Regarding the comparator, prednisolone/prednisolone alone can be considered as an appropriate comparator, since there are few data on the safety of combinations of other secondary agents with prednisone and globally no consensus standard of care for best second line hormonal therapy. In addition, the use of corticoids in prostate cancer has been explored in several studies which have highlighted its antitumor effects and palliative activity.

The main endpoints of the pivotal study were radiologic progression free survival (rPFS) and overall survival (OS) as co-primary endpoints and three key secondary endpoints which capture the main clinical progressions: time to opiate use for cancer pain, time to initiation of cytotoxic chemotherapy and time to clinical deterioration in ECOG performance status by $\geq$ 1 grade. Other efficacy endpoints were also included. During the discussion meeting of CHMP Scientific Advice, it was discussed that a global endpoint capturing all events (global PFS) could be preferred to a free combination of endpoints,

one being primary the other ones being secondary. In the end, agreement was reached on the proposed primary endpoint and on the fact that at least two of the three secondary endpoints related to a clinical benefit should be positive in order to consider the whole study as an acceptable evidence for a clinical benefit.

Only 1 analysis was planned for the co-primary rPFS endpoint (378 events), while three interim analyses [15%, 40% and 55% of total death events (773)] were pre-planned for OS. The purpose of the planned interim analyses was to allow the early termination of the study if superiority was irrefutably demonstrated, while the collection of survival data was continued. Amendments to the protocol had to be implemented to modify the initial planned interim analyses for OS and to introduce additional analyses so as to assess the crossover effect after the authorisation of abiraterone acetate for the treatment of mCRPC after docetaxel. Finally, after the second interim analysis, the IDMC recommended unblinding the treatment and allowing cross-over of subjects. Eventually, the proposed trial design makes the collection of clear and unbiased data for OS difficult. However and overall, the study appears to have been well-conducted and well-documented. No critical GCP issues have been highlighted during the assessment review.

Efficacy data and additional analyses

The efficacy results showed that:

- Abiraterone acetate substantially decreased the risk of radiographic progression or death (rPFS), 58% compared with placebo (HR=0.425; 95% CI: 0.347, 0.522; p<0.0001). Although the median rPFs in the abiraterone acetate arm (8.2 months in placebo arm) was not reached as of cut-off (20 December 2010), the robustness of the rPFS result is supported by the consistency between the independent and investigator assessment and the several sensitivity and subgroup analyses. The reduction in risk of progression was broadly maintained after an additional year (20 December 2011, investigator review, HR=0.530; CI: 0.451, 0.623; <0.0001) and rPFS was 16.5 months in the abiraterone group and 8.3 months in the placebo group.

- Upon submission of this application and based on the second interim analysis, overall survival data (HR=0.752; 95% CI: 0.606, 0.934; p=0.0097) showed a trend in the same direction as rPFS, although data were too immature to be considered conclusive. The median OS was still not reached in the abiraterone acetate group and was 27.24 months in placebo arm. The analysis did not reach the pre-specified statistical significance. In the third interim analysis median OS was 35.3 months (95% CI: 31.24, 35.29) in the abiraterone group and 30.1 months (95% CI: 27.30, 34.10) in the placebo group, HR was 0.79 (95% CI: 0.655, 0.956; p=0.0151). A favourable trend in the treatment effect of abiraterone on OS continues to be observed at this analysis.

- Results from the secondary endpoints support the benefit observed for the co-primary endpoints. Opiate use was documented for fewer subjects in the abiraterone group (34% vs. 43%). The median time to initiation of cytotoxic chemotherapy was more than 8 months longer in the abiraterone group (25.2 months) compared with the placebo group (16.8 months). The prolongation in the time to initiation of cytotoxic chemotherapy is consistent with the delay of disease progression. The time to deterioration of ECOG PS was statistically significant but the difference between the medians was moderate (12.3 months vs. 10.9 months). The median time to PSA progression was significantly longer and a confirmed PSA response was observed in more subjects in the abiraterone group. Over twice as many abiraterone treated subjects with measurable disease at baseline had an objective response. For PRO data, a delay in median time to average pain intensity progression of >8 months and a >4 month delay in the degradation in the FACT-P (Total Score) was observed for the abiraterone treated group compared to placebo. Biomarker data have not been presented.

The results from the biomarker analysis will be submitted by the MAH in 2013. A report describing the analysis of the TMPRSS2-ERG biomarker with correlations to clinical endpoints will be submitted no later than 31 March 2013. The statistical analysis and correlation of these results with the clinical data are currently in progress. A separate report describing the analysis of microRNA and mRNA will be completed and submitted no later than 20 December 2013.

2.4.4. Conclusions on the clinical efficacy

The prognosis of mCRPC patients is still poor (median survival of approximately 1 to 2 year). After patients become castration resistant, different hormonal managements can be used. However, globally there is neither clear consensus nor clear proof of efficacy of available treatments. Abiraterone acetate represents an option for this patient population.

Results were consistently favourable through the different analysis of rPFS and secondary endpoints. OS data though immature, tend to show a positive trend. Of note, it is highly unlikely to obtain unbiased OS data from this study in the future, due to crossover of patients in the placebo arm to the abiraterone arm after IDMC recommendation for unblinding the study.

In summary, abiraterone has demonstrated to improve the rPFS and the quality of life of chemotherapy-naïve mCRPC patients. Unfortunately, OS data may be affected by cross-over and hence, unequivocal evidence of increasing the life expectancy of abiraterone treated patients cannot be provided at this time. Nevertheless, taking into account the strong trend in OS and the fact that abiraterone has already demonstrated to increase the survival in post-chemotherapy setting, it does not seem unrealistic to believe that this treatment could improve the survival of pre-chemotherapy patients.

The CHMP recommends the following measures to be undertaken:

- To conduct an analysis of the TMPRSS2-ERG biomarker with correlations to clinical endpoints

- To conduct an analysis of microRNA and mRNA:

2.5. Clinical safety

2.5.1. Introduction

Safety evaluation in the claimed indication is based on data from patients enrolled and treated in study COU-AA-302. The safety profile of abiraterone was examined using:

- Analyses of safety data from the integrated safety population (Study COU-AA-301 and Study COU-AA-302) - 2,267 subjects with mCRPC: 1,333 subjects treated with abiraterone (791 subjects from Study COU-AA-301 and 542 subjects from Study COU-AA-302) and 934 control subjects treated with placebo (394 subjects from Study COU-AA-301 and 540 subjects from Study COU-AA-302)
- ADR analysis in Study COU-AA-302
- Individual summaries for Study COU-AA-006 (modified QT/QTc study) and Study COU-AA-015 (drug-drug interaction) - extended dosing and safety data not available at the time of the MAA.

Patient exposure

The extent of exposure to abiraterone in the pivotal study is summarised in the following Table 16.

Table 16: Extent of Exposure, Cumulative Summary, COU-AA-302, Safety Population

	AA (N=542)	Placebo (N=540)		AA (N=542)	Placebo (N=540)
	Total treatment duration (months)			Total number of cycles started	
N	542	540	N	542	540
> 0 months	542 (100.0%)	540 (100.0%)	≥1 cycle	542 (100.0%)	540 (100.0%)
≥3 months	506 (93.4%)	452 (83.7%)	≥2 cycles	538 (99.3%)	526 (97.4%)
≥6 months	439 (81.0%)	322 (59.6%)	≥3 cycles	520 (95.9%)	488 (90.4%)
≥9 months	381 (70.3%)	250 (46.3%)	≥4 cycles	507 (93.5%)	454 (84.1%)
≥12 months	302 (55.7%)	184 (34.1%)	≥5 cycles	484 (89.3%)	404 (74.8%)
≥15 months	244 (45.0%)	144 (26.7%)	≥10 cycles	392 (72.3%)	258 (47.8%)
≥18 months	207 (38.2%)	117 (21.7%)	≥15 cycles	282 (52.0%)	176 (32.6%)
≥21 months	131 (24.2%)	72 (13.3%)	≥20 cycles	207 (38.2%)	118 (21.9%)
≥24 months	70 (12.9%)	29 (5.4%)	≥25 cycles	101 (18.6%)	55 (10.2%)
≥27 months	17 (3.1%)	5 (0.9%)	≥27 cycles	71 (13.1%)	30 (5.6%)
Mean (SD)	14.31 (7.665)	10.36 (7.541)	Mean (SD)	15.9 (8.41)	11.5 (8.29)
Median	13.80	8.28	Median	15.0	9.0
Range	(0.3, 29.9)	(0.1, 28.1)	Range	(1, 33)	(1, 31)

Dose modifications and interruptions are summarised in the following Table 17.

Table 17: Dose modifications of abiraterone acetate or placebo, integrated safety population

	COU-AA-301		COU-AA-302		Combined	
	AA (N=791)	Placebo (N=394)	AA (N=542)	Placebo (N=540)	AA (N=1333)	Placebo (N=934)
Number of Dose Reductions						
0	760 (96.1%)	389 (98.7%)	507 (93.5%)	530 (98.1%)	1267 (95.0%)	919 (98.4%)
1	25 (3.2%)	5 (1.3%)	25 (4.6%)	10 (1.9%)	50 (3.8%)	15 (1.6%)
2	6 (0.8%)	0	10 (1.8%)	0	16 (1.2%)	0
Reason for Dose Reduction[a]	31 (3.9%)	5 (1.3%)	35 (6.5%)	10 (1.9%)	66 (5.0%)	15 (1.6%)
Adverse Event or Toxicity	15 (1.9%)	1 (0.3%)	5 (0.9%)	1 (0.2%)	20 (1.5%)	2 (0.2%)
Serious Adverse Event or Hospitalization	3 (0.4%)	0	0	0	3 (0.2%)	0
Restart Dosing	13 (1.6%)	3 (0.8%)	29 (5.4%)	8 (1.5%)	42 (3.2%)	11 (1.2%)
Other	3 (0.4%)	1 (0.3%)	1 (0.2%)	1 (0.2%)	4 (0.3%)	2 (0.2%)
Number of Dose Interruptions						
0	630 (79.6%)	327 (83.0%)	439 (81.0%)	475 (88.0%)	1069 (80.2%)	802 (85.9%)
1	115 (14.5%)	55 (14.0%)	71 (13.1%)	50 (9.3%)	186 (14.0%)	105 (11.2%)
2	25 (3.2%)	8 (2.0%)	24 (4.4%)	12 (2.2%)	49 (3.7%)	20 (2.1%)
3	15 (1.9%)	4 (1.0%)	5 (0.9%)	2 (0.4%)	20 (1.5%)	6 (0.6%)
>3	6 (0.8%)	0	3 (0.6%)	1 (0.2%)	9 (0.7%)	1 (0.1%)
Reason for Dose Interruption[a]	161 (20.4%)	67 (17.0%)	103 (19.0%)	65 (12.0%)	264 (19.8%)	132 (14.1%)
Adverse Event or Toxicity	77 (9.7%)	33 (8.4%)	71 (13.1%)	35 (6.5%)	148 (11.1%)	68 (7.3%)
Serious Adverse Event or Hospitalization	73 (9.2%)	28 (7.1%)	34 (6.3%)	26 (4.8%)	107 (8.0%)	54 (5.8%)
Other	30 (3.8%)	13 (3.3%)	12 (2.2%)	12 (2.2%)	42 (3.2%)	25 (2.7%)

Adverse events

A summary of adverse events in the integrated safety population is provided in Table 18.

Table 18: Summary of adverse events, integrated safety population

	COU-AA-301		COU-AA-302		Combined	
	AA (N=791)	Placebo (N=394)	AA (N=542)	Placebo (N=540)	AA (N=1333)	Placebo (N=934)
Treatment-Emergent Adverse Events (TEAEs)	784 (99.1%)	390 (99.0%)	537 (99.1%)	524 (97.0%)	1321 (99.1%)	914 (97.9%)
Drug-related	610 (77.1%)	305 (77.4%)	424 (78.2%)	413 (76.5%)	1034 (77.6%)	718 (76.9%)
Grade 3-4 TEAEs	478 (60.4%)	240 (60.9%)	258 (47.6%)	225 (41.7%)	736 (55.2%)	465 (49.8%)
Drug-related	182 (23.0%)	76 (19.3%)	122 (22.5%)	91 (16.9%)	304 (22.8%)	167 (17.9%)
Serious TEAEs	335 (42.4%)	172 (43.7%)	178 (32.8%)	142 (26.3%)	513 (38.5%)	314 (33.6%)
Drug-related	88 (11.1%)	41 (10.4%)	59 (10.9%)	54 (10.0%)	147 (11.0%)	95 (10.2%)
Grade 3-4	288 (36.4%)	148 (37.6%)	150 (27.7%)	117 (21.7%)	438 (32.9%)	265 (28.4%)
Drug-related Grade 3-4	76 (9.6%)	33 (8.4%)	53 (9.8%)	39 (7.2%)	129 (9.7%)	72 (7.7%)
TEAEs Leading to Treatment Discontinuation	162 (20.5%)	93 (23.6%)	55 (10.1%)	49 (9.1%)	217 (16.3%)	142 (15.2%)
Drug-related	43 (5.4%)	27 (6.9%)	29 (5.4%)	23 (4.3%)	72 (5.4%)	50 (5.4%)
TEAEs Leading to Death	105 (13.3%)	61 (15.5%)	20 (3.7%)	12 (2.2%)	125 (9.4%)	73 (7.8%)
Drug-related	8 (1.0%)	11 (2.8%)	5 (0.9%)	4 (0.7%)	13 (1.0%)	15 (1.6%)
All deaths within 30d of last dose	97 (12.3%)	55 (14.0%)	18 (3.3%)	8 (1.5%)	115 (8.6%)	63 (6.7%)
Underlying Disease	64 (8.1%)	41 (10.4%)	7 (1.3%)	3 (0.6%)	71 (5.3%)	44 (4.7%)
Other	29 (3.7%)	14 (3.6%)	10 (1.8%)	4 (0.7%)	39 (2.9%)	18 (1.9%)
Unknown	4 (0.5%)	0	1 (0.2%)	1 (0.2%)	5 (0.4%)	1 (0.1%)

The most frequently reported AEs, reported in ≥20% of subjects in either the abiraterone or placebo group were:

- Infections and Infestations (54% versus 39%)
- Fatigue (39% versus 34%)
- Back pain (32% in each treatment group)
- Arthralgia (28% versus 24%)
- Peripheral oedema (25% versus 20%)
- Nausea (22% in each treatment group)
- Constipation (23% versus 19%)
- Hot flush (22% versus 18%)
- Diarrhoea (22% versus 18%)
- Bone pain (20% versus 19%)
- Hypertension (22% versus 13%)

Grade 3 or 4 AEs were reported for a lower proportion of AA-treated subjects versus placebo-treated subjects in Study COU-AA-301 (60% versus 61%), but a higher proportion of AA-treated subjects versus placebo-treated subjects in Study COU-AA-302 (48% versus 42%). The 5 most frequently reported AEs of Grade 3 or 4 for the combined treatment groups were fatigue, back pain, anemia, bone pain, and arthralgia. With the exception of pulmonary embolism, which was reported in 1.4% of subjects in the combined placebo group, no individual Grade 4 AE was reported in ≥1% of subjects in either combined treatment group.

In Study COU-AA-302, the most frequently reported Grade 3 or 4 AEs (reported in ≥3% of subjects in either the abiraterone acetate or placebo group) were hypertension (4% versus 3%), back pain (3% versus 4%), alanine aminotransferase increased (5.4% versus 0.7%), and aspartate aminotransferase increased (3.0% versus 0.9%). Of note, Grade 3 and 4 AEs classified in the SOC of Cardiac Disorders were reported in 4% of subjects in the abiraterone group and 2% of subjects in the placebo group. Adrenal insufficiency was reported in no subject in the abiraterone acetate group and 1 subject in the placebo group.

With regard to adverse drug reactions (ADRs) and in order to assess the effect of the longer duration of exposure in the abiraterone groups, an analysis standardising for the difference in treatment duration was performed and reported as number of events per 100 patient-years (P-Y) of exposure (time on treatment). Adverse events with a difference of ≥5 events per 100 P-Y (abiraterone - placebo) were considered ADRs, provided that the criteria for relatedness outlined by the CIOMS Working Groups III and V3 (Evidence from Clinical Trials/Studies) were met. More than 1 event per patient may be included in this rate.

Four new ADRs are proposed on the basis of Study COU-AA-302 data: dyspepsia, increased AST, rash and haematuria. The most common ADRs seen with abiraterone (based on all clinical studies combined) are peripheral oedema, hypokalaemia, hypertension, urinary tract infection, haematuria, AST increased, ALT increased, dyspepsia and fractures.

ADRs in the integrated safety population of studies COU-AA-301 and -302 are summarised in the following Table 19.

Table 19: ADRs due to abiraterone in ≥ 1% of patients, integrated safety population

Infections and infestations	very common: urinary tract infection
Endocrine disorders	uncommon: adrenal insufficiency
Metabolism and nutrition disorders	very common: hypokalaemia common: hypertriglyceridaemia
Cardiac disorders	common: cardiac failure*, angina pectoris, arrhythmia, atrial fibrillation, tachycardia
Vascular disorders	very common: hypertension
Gastrointestinal disorders	common: dyspepsia
Hepatobiliary disorders	common: alanine aminotransferase increased, aspartate aminotransferase increased
Skin and subcutaneous tissue disorders	common: rash
Renal and urinary disorders	common: haematuria
General disorders and administration site conditions	very common: oedema peripheral
Injury, poisoning and procedural complications	common: fractures**

* Cardiac failure also includes congestive heart failure, left ventricular dysfunction and ejection fraction decreased

** Fractures includes all fractures with the exception of pathological fracture

Adverse events of special interest with abiraterone treatment include the mineralocorticoid-associated events of fluid retention/oedema, hypokalaemia, hypertension, hepatotoxicity and cardiac disorders.

Adverse events of special interest were reported in 66% of subjects in the abiraterone group and 50% of subjects in the placebo group. In study COU-AA-301, such events were reported in 60% of subjects in the abiraterone group and 47% of subjects in the placebo group.

Fluid retention/oedema events were reported in 28% of subjects in the abiraterone group and 24% of subjects in the placebo group. Most oedema AEs were Grade 1 or 2. No Grade 4 or 5 oedema events were reported. Serious fluid retention/oedema AEs were reported in 0.7% of subjects in both the abiraterone and placebo groups.

Hypokalaemia was reported in 17% of subjects in the abiraterone group and 13% of subjects in the placebo group. Hypokalaemia events of Grade 3 or 4 were reported for 2% of subjects in both treatment groups. SAEs were reported in 0.4% of the abiraterone group and 0.2% of the placebo group. No AEs of hypokalaemia led to discontinuation of the study medication. After standardising for the difference in duration of treatment exposure, an excess of 2 hypokalaemia events/100 P-Y (for all grades) was observed in the abiraterone group (24 in the abiraterone group and 22 in the placebo group).

Hypertension events were reported in 22% of subjects in the abiraterone group and 13% of subjects in the placebo group. No Grade 4 or 5 hypertensive events were reported. Grade 3 hypertensive events were reported in 4% of the abiraterone group and 3% of the placebo group. SAEs were reported less frequently in the abiraterone group (0.2% versus 0.6%). Difference in standardised rates was more pronounced for study COU-AA-302 (24 for the abiraterone group versus 20 for the placebo group) as compared with study COU-AA-301 (19 vs. 18). After standardising for the difference in duration of treatment exposure, an excess of 4 hypertension events/100 P-Y (for all grades) was observed in the abiraterone group (24 in the abiraterone group and 20 in the placebo group).

Hepatotoxicity is a known risk of abiraterone treatment and increases in hepatic enzymes (ALT and AST) and bilirubin are observed. In study COU-AA-302, hepatotoxicity adverse events reported as LFT abnormalities were observed in 18% of subjects in the abiraterone group and 11% in the placebo group. The most frequently reported preferred terms were AST and ALT increases. ALT increases were 12% in the abiraterone group compared with 5% in the placebo group and for AST 11% versus 5%. Grade 3 or 4 events of hepatotoxicity were reported in 8% of the abiraterone group versus 3% in the placebo group. Adverse events of hepatotoxicity leading to treatment discontinuation were reported at in 2.2% of the abiraterone group compared with 0.2% in the placebo group. No Grade 5 events of hepatotoxicity were reported and no cases meeting Hy's law criteria were identified. Hepatotoxicity SAEs were reported in 1.1% of subjects in the abiraterone group and 0.6% of subjects in the placebo group.

In contrast to study COU-AA-301, COU-AA-302 excluded subjects with New York Heart Association (NYHA) Class II heart failure. Cardiac disorders events were reported in 19% of subjects in the abiraterone group and 16% of subjects in the placebo group. The incidences of cardiac disorder AEs by subcategory were:

- Arrhythmias (abiraterone 14% vs. placebo 12%)
- Ischaemic heart disease (abiraterone 4% vs. ischaemic 3%)
- Cardiac disorders for other causes (3% in each treatment group)
- Cardiac failure (abiraterone 2.0% vs. placebo 0.4%)

Exposure-standardised rates (events of cardiac disorder per 100 P-Y) were lower for the abiraterone group (27/100 P-Y) compared with the placebo group (29/100P-Y) in study COU-AA-302 (the rates were higher for abiraterone in study COU-AA-301). A subject-level review of the cardiac failure events in study COU-AA-302 showed that most of the events were coincident with other cardiac events

(ischaemic events, arrhythmia). Cardiac disorder events of Grade 3 or 4 were reported for 6% of subjects in the abiraterone group and 3% of subjects in the placebo group (Grade 5 events 0.6% vs. 0.4%). Serious cardiac disorder events were reported in 7% of subjects in the abiraterone group and 3% of subjects in the placebo group (arrhythmias 3% versus 2%, ischaemic heart disease 2.4% versus 0.9%, cardiac failure 0.7% versus 0, cardiac disorders for other causes 0.4% in each treatment group). Cardiac disorder events led to treatment discontinuation in 0.6% of subjects the abiraterone group and 0.4% of subjects in the placebo group.

ECGs were obtained pre-dose (at the screening visit) and at approximately 2 hours post-dose (at Cycles 1, 2, and 5). The proportion of subjects with QTc interval prolongation of either >30 ms or >60 ms based on either method of correction was higher in the abiraterone group. Based on the QTcF method:

- 16% of subjects in the abiraterone group had a QTc interval prolongation of >30 ms
- 10% of subjects in the placebo group had a QTc interval prolongation of >30 ms
- 6% of subjects in the abiraterone group had a QTc interval prolongation of >60 ms
- 4% of subjects in the placebo group had a QTc interval prolongation of >60 ms

Based on the QTcB method:

- 24% of subjects in the abiraterone group had a QTc interval prolongation of >30 ms
- 19% of subjects in the placebo group had a QTc interval prolongation of >30 ms
- 8% of subjects in the abiraterone group had a QTc interval prolongation of >60 ms
- 5% of subjects in the placebo group had a QTc interval prolongation of >60 ms

Post-baseline QTcF values of >450 ms were higher in the abiraterone group than in the placebo group (27% versus 20%).

7% of subjects in both treatment groups experienced an osteoporosis-related event.

For squamous cell carcinoma and malignant melanoma, the imbalances observed in Study COU-AA-301 were also observed in Study COU-AA-302. Overall, the numbers of events were low.

Events of renal toxicity were reported for higher proportions of abiraterone treated patients versus placebo treated patients.

Overall, the adverse events of special interest are generally in keeping with the known safety profile of abiraterone.

Serious adverse event / deaths / other significant events

Serious adverse events (SAEs) in the integrated safety population are summarised in the following Table 20.

Table 20: Serious Adverse Events Reported in at Least 1% of Subjects in Any Group (Integrated Safety Population)

	COU-AA-301		**COU-AA-302**		Combined	
MedDRA SOC Term MedDRA Preferred Term	AA (N=791)	Placebo (N=394)	**AA (N=542)**	**Placebo (N=540)**	AA (N=1333)	Placebo (N=934)
Total no. subjects with a treatment-emergent serious adverse event	335 (42.4%)	172 (43.7%)	**178 (32.8%)**	**142 (26.3%)**	513 (38.5%)	314 (33.6%)

Infections and infestations	73 (9.2%)	22 (5.6%)	**45 (8.3%)**	**31 (5.7%)**	118 (8.9%)	53 (5.7%)
Pneumonia	19 (2.4%)	4 (1.0%)	**7 (1.3%)**	**4 (0.7%)**	26 (2.0%)	8 (0.9%)
Urinary tract infection	16 (2.0%)	4 (1.0%)	**8 (1.5%)**	**3 (0.6%)**	24 (1.8%)	7 (0.7%)
Sepsis	12 (1.5%)	2 (0.5%)	**4 (0.7%)**	**2 (0.4%)**	16 (1.2%)	4 (0.4%)
Nervous system disorders	55 (7.0%)	34 (8.6%)	**30 (5.5%)**	**13 (2.4%)**	85 (6.4%)	47 (5.0%)
Spinal cord compression	22 (2.8%)	17 (4.3%)	**5 (0.9%)**	**4 (0.7%)**	27 (2.0%)	21 (2.2%)
Renal and urinary disorders	47 (5.9%)	26 (6.6%)	**27 (5.0%)**	**25 (4.6%)**	74 (5.6%)	51 (5.5%)
Haematuria	11 (1.4%)	11 (2.8%)	**10 (1.8%)**	**4 (0.7%)**	21 (1.6%)	15 (1.6%)
Hydronephrosis	12 (1.5%)	3 (0.8%)	**2 (0.4%)**	**4 (0.7%)**	14 (1.1%)	7 (0.7%)
Urinary retention	8 (1.0%)	5 (1.3%)	**4 (0.7%)**	**3 (0.6%)**	12 (0.9%)	8 (0.9%)
Renal failure acute	6 (0.8%)	5 (1.3%)	**1 (0.2%)**	**0**	7 (0.5%)	5 (0.5%)
Musculoskeletal and connective tissue disorders	53 (6.7%)	39 (9.9%)	**14 (2.6%)**	**18 (3.3%)**	67 (5.0%)	57 (6.1%)
Bone pain	16 (2.0%)	13 (3.3%)	**2 (0.4%)**	**4 (0.7%)**	18 (1.4%)	17 (1.8%)
Back pain	8 (1.0%)	11 (2.8%)	**3 (0.6%)**	**4 (0.7%)**	11 (0.8%)	15 (1.6%)
Pain in extremity	4 (0.5%)	7 (1.8%)	**1 (0.2%)**	**1 (0.2%)**	5 (0.4%)	8 (0.9%)
Arthralgia	2 (0.3%)	4 (1.0%)	**1 (0.2%)**	**4 (0.7%)**	3 (0.2%)	8 (0.9%)
Gastrointestinal disorders	49 (6.2%)	26 (6.6%)	**16 (3.0%)**	**13 (2.4%)**	65 (4.9%)	39 (4.2%)
Vomiting	16 (2.0%)	9 (2.3%)	**2 (0.4%)**	**0**	18 (1.4%)	9 (1.0%)
General disorders and administration site conditions	47 (5.9%)	30 (7.6%)	**13 (2.4%)**	**12 (2.2%)**	60 (4.5%)	42 (4.5%)
Disease progression	12 (1.5%)	2 (0.5%)	**2 (0.4%)**	**1 (0.2%)**	14 (1.1%)	3 (0.3%)
Fatigue	9 (1.1%)	6 (1.5%)	**0**	**0**	9 (0.7%)	6 (0.6%)
Pyrexia	5 (0.6%)	9 (2.3%)	**2 (0.4%)**	**3 (0.6%)**	7 (0.5%)	12 (1.3%)
Pain	1 (0.1%)	6 (1.5%)	**0**	**1 (0.2%)**	1 (0.1%)	7 (0.7%)
Cardiac disorders	26 (3.3%)	6 (1.5%)	**29 (5.4%)**	**14 (2.6%)**	55 (4.1%)	20 (2.1%)
Atrial fibrillation	5 (0.6%)	3 (0.8%)	**7 (1.3%)**	**8 (1.5%)**	12 (0.9%)	11 (1.2%)
Metabolism and nutrition disorders	32 (4.0%)	14 (3.6%)	**13 (2.4%)**	**6 (1.1%)**	45 (3.4%)	20 (2.1%)
Dehydration	12 (1.5%)	5 (1.3%)	**5 (0.9%)**	**1 (0.2%)**	17 (1.3%)	6 (0.6%)
Respiratory, thoracic and mediastinal disorders	26 (3.3%)	18 (4.6%)	**15 (2.8%)**	**21 (3.9%)**	41 (3.1%)	39 (4.2%)
Pulmonary embolism	6 (0.8%)	10 (2.5%)	**8 (1.5%)**	**11 (2.0%)**	14 (1.1%)	21 (2.2%)
Dyspnoea	9 (1.1%)	4 (1.0%)	**2 (0.4%)**	**5 (0.9%)**	11 (0.8%)	9 (1.0%)
Blood and lymphatic system disorders	31 (3.9%)	17 (4.3%)	**7 (1.3%)**	**7 (1.3%)**	38 (2.9%)	24 (2.6%)
Anaemia	24 (3.0%)	14 (3.6%)	**5 (0.9%)**	**5 (0.9%)**	29 (2.2%)	19 (2.0%)

A summary of deaths within 30 days of last dose of study medication in the integrated safety population is provided in the following Table 21.

Table 21: Deaths within 30 days of last dose, integrated safety population

	COU-AA-301		**COU-AA-302**		Combined	
	AA (N=791)	Placebo (N=394)	**AA (N=542)**	**Placebo (N=540)**	AA (N=1333)	Placebo (N=934)
All deaths within 30 days of last dose	97 (12.3%)	55 (14.0%)	**18 (3.3%)**	**8 (1.5%)**	115 (8.6%)	63 (6.7%)
Underlying Disease	64 (8.1%)	41 (10.4%)	**7 (1.3%)**	**3 (0.6%)**	71 (5.3%)	44 (4.7%)
Other	29 (3.7%)	14 (3.6%)	**10 (1.8%)**	**4 (0.7%)**	39 (2.9%)	18 (1.9%)
Unknown	4 (0.5%)	0	**1 (0.2%)**	**1 (0.2%)**	5 (0.4%)	1 (0.1%)

Laboratory findings

29% of subjects in the combined abiraterone group and 20% of subjects in the combined placebo group had Grade 3 or 4 serum chemistry laboratory abnormalities during treatment. Abnormalities in ALP were the most frequently reported Grade 3 or 4 serum chemistry laboratory abnormality. Grade 3 or 4 phosphorus abnormalities were observed in 5% of the abiraterone group and 2% of the placebo group.

29% of subjects in the combined abiraterone group and 17% of subjects in the combined placebo group had Grade 3 or 4 haematologic laboratory abnormalities during treatment. Lymphocyte abnormalities were the most frequently reported Grade 3 or 4 abnormality for the combined treatment groups.

Most initial events of liver enzyme increase occurred within the first 3 months of abiraterone treatment (see adverse events of special interest).

Generally, the findings are in keeping with previous observations. AST increased is included as a new ADR.

Safety in special populations

Intrinsic Factors

- Adverse Events by Age

Patient age is not considered to be a significant prognostic factor in prostate cancer. Rates of AEs were generally higher in the subgroups with more advanced age.

- Adverse Events by Race

The small proportions of non-white subjects enrolled preclude any meaningful comparisons of AE profiles analyzed by race.

- Adverse Events by Baseline ECOG Performance Status Grade

Rates of AEs were generally higher in the subgroups with higher baseline ECOG performance status grade.

- Adverse Events by Baseline Hemoglobin

Rates of AEs were generally higher in the subgroups with baseline hemoglobin concentration <12.5 g/dL.

- Adverse Events by Baseline LDH

Rates of AEs were generally higher in the subgroups with baseline LDH >1xULN.

Extrinsic Factors

- Adverse Events by Geographic Region

The overall safety profile analysed by geographic region (North America versus other [Europe/Australia]) has been provided. North American sites contributed 55% of subjects enrolled in Study COU-AA-301 and 52% of subjects enrolled in Study COU-AA-302. Within the Study COU-AA-301 abiraterone acetate and placebo groups, lower rates of Grade 3-4 AEs, SAEs, and AEs leading to treatment discontinuation were reported for the North America subgroup as compared with the Europe/Australia subgroup. No such pattern was seen for either treatment group in study COU-AA-302.

Safety related to drug-drug interactions and other interactions

An addendum of study COU-AA-015 was submitted within the current application. The effect of abiraterone acetate plus prednisone on a single dose of the CYP2D6 substrate dextromethorphan was investigated in this study. The systemic exposure (AUC) of dextromethorphan was increased approximately 2.9-fold. The AUC24 for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when abiraterone acetate is administered with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal products that have a narrow therapeutic index. Dose reduction of medicinal products with a narrow therapeutic index that are metabolised by CYP2D6 should be considered. Examples of medicinal products metabolised by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone, and tramadol (the final 3 products requiring CYP2D6 to form their active analgesic metabolites).

Administration with food significantly increases the absorption of abiraterone acetate. The efficacy and safety of abiraterone acetate given with food have not been established. Abiraterone acetate must not be taken with food.

Discontinuation due to adverse events

Reasons for treatment discontinuation in the integrated safety population are summarised in the following Table 22.

Table 22: Reasons for Treatment Discontinuation (Integrated Safety Population)

	COU-AA-301		COU-AA-302		Combined	
	AA (N=791)	Placebo (N=394)	AA (N=542)	Placebo (N=540)	AA (N=1333)	Placebo (N=934)
Subjects with treatment on-going	125 (15.8%)	18 (4.6%)	166 (30.6%)	86 (15.9%)	291 (21.8%)	104 (11.1%)
Subjects discontinued from treatment	666 (84.2%)	376 (95.4%)	376 (69.4%)	454 (84.1%)	1042 (78.2%)	830 (88.9%)
Disease progression	275 (34.8%)	125 (31.7%)	283 (52.2%)	351 (65.0%)	558 (41.9%)	476 (51.0%)
Adverse event	105 (13.3%)	71 (18.0%)	40 (7.4%)	29 (5.4%)	145 (10.9%)	100 (10.7%)
Initiation of new anticancer treatment	125 (15.8%)	72 (18.3%)	NA	NA	125 (9.4%)	72 (7.7%)
Withdrawal of consent to treatment	76 (9.6%)	46 (11.7%)	32 (5.9%)	46 (8.5%)	108 (8.1%)	92 (9.9%)
Investigator discretion	37 (4.7%)	27 (6.9%)	NA	NA	37 (2.8%)	27 (2.9%)
Other	8 (1.0%)	9 (2.3%)	20 (3.7%)	28 (5.2%)	28 (2.1%)	37 (4.0%)
Death	27 (3.4%)	10 (2.5%)	NA	NA	27 (2.0%)	10 (1.1%)
Subject choice	7 (0.9%)	4 (1.0%)	NA	NA	7 (0.5%)	4 (0.4%)
Administration of prohibited medication	3 (0.4%)	1 (0.3%)	NA	NA	3 (0.2%)	1 (0.1%)
Dosing noncompliance	3 (0.4%)	3 (0.8%)	NA	NA	3 (0.2%)	3 (0.3%)
Lost to Follow-up	NA	NA	1 (0.2%)	0	1 (0.1%)	0
Placebo unblinding	0	8 (2.0%)	NA	NA	0	8 (0.9%)

Post marketing experience

The first marketing approval for abiraterone acetate was on 28 April 2011 in the United States. The estimated postmarketing exposure worldwide for abiraterone acetate from launch to 31 January 2012 was 2,245,830 person-days. No new ADRs have been detected for abiraterone acetate from post-marketing data.

2.5.2. Discussion on clinical safety

Exposure to abiraterone in COU-AA-302 is considered sufficient for assessment of the safety profile for this application. The median treatment duration was longer in the abiraterone group compared to the placebo group and approximately twice as long as that in study COU-AA-301. The median treatment duration was 13.8 months in the abiraterone group and 8.3 months in the placebo group. Fewer subjects in the abiraterone group discontinued and the most common reason for treatment discontinuation was disease progression.

Overall the adverse event profile is generally consistent with previous observations from study COU AA-301. A review performed by the MAH to identify any clinically meaningful new imbalances between studies identified dyspepsia, increased AST, rash and haematuria as new ADRs.

In study 302, a higher rate of deaths within 30 days of last dose was observed in the abiraterone group and was considered of concern. Of them, death causes categorised as 'other' were higher in the abiraterone group [10 (1.8%) vs 4 (0.7%)]. Focusing on AEs leading to death, infections seem to be the most relevant AE; 5 patients in abiraterone arm (0.9%) vs none in the control. Although differences in the number of deaths between arms can hardly be considered simply due to chance, no clear pattern of causality can be observed, considering the underlying disease of the target population and co-morbidities of patients.

Adverse events of special interest were generally in keeping with the known safety profile of abiraterone. As expected, mineralocorticoid-related toxicities such as fluid retention/oedema, hypokalaemia and hypertension were observed more frequently for subjects treated with abiraterone. However, protocol defined management strategies for hypokalaemia have been included in the SmPC.

Although hepatotoxicity was associated with abiraterone treatment during the assessment of the marketing authorisation application, it appeared to be more notable in the population of study 302. Considering that TEAEs AST/ALT increases as well as Grade 3 and 4 AST/ALT increases were higher in study 302 and that liver metastasis was an exclusion criterion in study 302 (not in 301), differences were considered of importance. However, the higher hepatotoxicity could be related to the fact that patients were treated with abiraterone for a longer time in study 302. The actual mechanism of abiraterone hepatotoxicity is unknown and further information has been included in the SmPC to manage this risk.

A higher rate of cardiac disorder events was noted and a warning regarding use of abiraterone in patients with a history of cardiovascular disease is included in section 4.4 of the SmPC.

With regards to the ECG data, the MAH continues to conduct ECG monitoring as part of the ongoing clinical development programme. This includes the following clinical studies: JPN-201, JPN-202 (triplicate ECG), central reader], ABI-PRO-3002, and a study in breast cancer patients (BCA-2001). These studies include 700 to 800 additional subjects. The RMP has been updated to include these studies as additional pharmacovigilance activities for the identified risk of cardiac disorders.

2.5.3. Conclusions on clinical safety

Treatment with abiraterone was tolerable for the majority of subjects and the safety profile was consistent with previous experience (except for four new ADR identified - dyspepsia, AST increased, rash and haematuria). Adverse events were generally manageable and no major safety concerns have been raised by this application.

2.5.4. PSUR cycle

The PSUR cycle remains unchanged. The next data lock point will be 27 October 2012.

2.6. Risk management plan

The MAH submitted an updated Risk Management Plan within this variation procedure.

Table 23: Summary of the risk management plan (including the changes related to the application presented highlighted)

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important Identified Risks:		
1) Hypertension 2) Hypokalaemia 3) Fluid retention/oedema	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional None	Routine As noted in the SmPC (Sections 4.4, 4.8, and 5.1), these adverse reactions are anticipated from the pharmacodynamic consequence of increased mineralocorticoid levels resulting from CYP17 inhibition, and are reduced in incidence and severity by co-administration of low-dose prednisone or prednisolone (10 mg daily); co-administration of a corticosteroid suppresses ACTH drive. Guidance on management of Grade ≥ 3 toxicities is provided (SmPC Section 4.2). Additional guidance for the physician is also provided in Sections 4.2, 4.4, and 4.8 of the SmPC. Additional None
4) Hepatotoxicity	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional Targeted follow-up with reporter through a guided questionnaire to collect additional information related to this safety concern.	Routine The SmPC (Sections 4.2 and 4.4) has precautions for patients who develop hepatotoxicity during treatment, including guidance for, dose reduction, retreatment, and appropriate monitoring (measuring serum transaminase before and during treatment). In addition, patients who develop severe hepatotoxicity (ALT or AST 20 times the ULN) anytime while on therapy are should be discontinued and patients should not be retreated. SmPC Sections 4.2, 4.4, and 4.8 provide guidance for the physician. Additional None

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
5) Cardiac disorders	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional Trials COU-AA-006 (QTc), JPN-201, JPN-202, ABI-PRO-3002, and 212082BCA2001 Targeted follow-up with reporter through guided questionnaires for events of arrhythmia and cardiac failure to collect clinical information related to this safety concern.	Routine The SmPC (Section 4.4) has precautions for monitoring (before and during treatment), and treating patients at risk for cardiac issues. Section 4.8 has additional information for the physician on the cardiovascular effects. Additional None
6) Osteoporosis including osteoporosis-related fractures	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional Targeted follow-up with reporter through a guided questionnaire to collect additional information related to this ~~risk~~safety concern.	Routine The SmPC (Section 4.4) and Package Leaflet provide information to the prescriber and patient about the potential for decreased bone density ~~that may~~to occur in men with mCRPC and that the use of abiraterone acetate in combination with a glucocorticoid could increase this effect. Also, the SmPC (Section 4.8) and the Package Leaflet provide information to the prescriber and patient about fractures as an adverse drug reaction and side effect. Additional None
Important Potential Risks:		
~~1) Osteoporosis including osteoporosis-related fractures~~	~~Routine pharmacovigilance as outlined in Section 2.1~~ ~~All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial.~~ ~~Additional~~ ~~Targeted follow-up with reporter through a guided questionnaire to collect additional information related to this safety concern.~~	~~Routine~~ ~~The SmPC (Section 4.4) and Package Leaflet provide information to the prescriber and patient about the potential for decreased bone density to occur in men with mCRPC and that the use of abiraterone acetate in combination with a glucocorticoid could increase this effect. Also, the SmPC (Section 4.8) and the Package Leaflet provide information to the prescriber and patient about fractures as an adverse drug reaction and side effect.~~ ~~Additional~~ ~~None~~
1) Anaemia	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional None	Routine The SmPC (Section 4.4) and Package Leaflet provide information to the prescriber and patient about the potential for anaemia to occur in men with mCRPC, including those undergoing treatment with abiraterone acetate. Additional None

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
2) Sexual dysfunction, decreased libido, and impotence	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional None	Routine The SmPC (Section 4.4) and Package Leaflet provide information to the prescriber and patient about the potential for sexual dysfunction to occur in men with mCRPC, including those undergoing treatment with abiraterone acetate. Additional None
3) Cataract	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional The mechanism of cataract formation in the rat ~~will be~~is being further investigated in nonclinical studies.	Routine None Additional None
4) Drug-drug interaction (CYP2D6)	Routine pharmacovigilance as outlined in Section 2.1 ~~Relevant~~All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional None	Routine The SmPC (Section 4.5) provides recommendations about the use of abiraterone acetate with medicinal products activated by or metabolised by CYP2D6. Additional None
5) Increased exposure with food	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional Trial 212082PCR2008 (food interaction trial)	Routine The SmPC provide directions for taking abiraterone acetate with food (SmPC Sections 4.2, 4.5, and 5.2). Additional guidance for the patient is provided for in the Package Leaflet. The secondary packaging provides instructions for correct administration. Additional None
Important Missing Information:		
1) Use in patients with active or symptomatic viral hepatitis	Routine pharmacovigilance as outlined in Section 2.1 Additional None	Routine The SmPC states that in clinical trials, patients with active or symptomatic hepatitis were excluded (SmPC Section 4.4) and advises that there are no data to support use in this patient population. Additional None
2) Use in patients with moderate/severe hepatic impairment and chronic liver disease	Routine pharmacovigilance as outlined in Section 2.1 Additional Trial 212082PCR1004 (pharmacokinetic trial in patients with hepatic impairment)	Routine The SmPC advises that there are no data on the clinical safety of abiraterone acetate in patients with pre-existing moderate or severe hepatic impairment (Child-Pugh Class B or C) and that no dose adjustment can be predicted. Use of ~~A~~abiraterone acetate ~~should be avoided~~in patients with moderate hepatic impairment is described in the SmPC (SmPC Sections 4.2, 4.4, 5.2) and is contraindicated in patients with severe hepatic impairment (SmPC Sections 4.2, 4.3, 4.4, 5.2). Therefore, there are no data to support use in this patient population. Additional

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
		None
3) Use in patients with severe renal impairment	Routine pharmacovigilance as outlined in Section 2.1 Additional None	Routine The SmPC states that there is no clinical experience in patients with prostate cancer and severe renal impairment and that caution is advised in these patients (SmPC Section 4.2). Therefore, there are no data to support use in this patient population. Additional None
4) 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%	Routine pharmacovigilance as outlined in Section 2.1 Additional<br~~None~~ Targeted follow-up with reporter through guided questionnaires for events of arrhythmia and cardiac failure to collect clinical information related to this safety concern.	Routine The SmPC contains precautions for use in patients with a history of cardiovascular disease, as the safety ~~of abiraterone acetate~~in patients with ~~left ventricular ejection fraction~~LVEF < 50% or NYHA Class III or IV heart failure (Trial COU-AA-301) or NYHA Class II to IV heart failure (Trial COU-AA-302) has not been established. ~~Before~~The SmPC also has additional precautions for monitoring (before and during treatment), ~~hypertension must be controlled and hypokalaemia must be corrected~~and treating patients at risk for cardiac issues (SmPC Section 4.4). Additional None
5) Drug-drug interaction (CYP2C8)	Routine pharmacovigilance as outlined in Section 2.1 Additional<br~~None~~ A drug-drug interaction clinical trial using a CYP2C8 probe substrate (protocol in development)	Routine The SmPC describes that, based on in vitro data, abiraterone is an inhibitor of the hepatic drug-metabolising enzyme CYP2C8. There are no clinical data on the use of abiraterone acetate with drugs that are substrates of CYP2C8 (SmPC Section 4.5). Additional None
6) Use in non-white patients	Routine pharmacovigilance as outlined in Section 2.1 All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP trial. Additional Trials 212082PCR3001, 212082JPN102, 212082PCR2007, ABI-PRO-3001, and ABI-PRO-3002.	Routine The SmPC presents the baseline demographics of the COU-AA-301 and COU-AA-302 trial population (SmPC Section 5.1). Additional None

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activity in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns.

Description	Due date
Additional surveillance of ongoing clinical trials, including a QTc trial (COU-AA-006) and other clinical trials (JPN-201, JPN-202, ABI-PRO-3002, and 212082BCA2001) with ECG monitoring (12-lead ECG, and 12-lead ECG [triplicate] with central laboratory evaluation). Targeted follow-up with reporter through guided questionnaires for events of arrhythmia and cardiac failure to collect clinical information related to this safety concern	30/09/2013 (COU-AA-006) 30/11/2013 (ABI-PRO-3002) 28/02/2014 (212082BCA2001) 30/06/2015

Description	Due date
	(JPN-201, JPN-202)

This pharmacovigilance activity is in addition to those already requested.
No additional risk minimisation activities were required beyond those included in the product information.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated. The new indication was reflected in section 4.1 of the SmPC. Particularly, a new contraindication in patients with severe hepatic impairment has been added to section 4.3 of the SmPC. Posology recommendations and warnings related to heart failure, mineralocorticoid toxicities, hepatotoxicity and hepatic impairment have been updated in sections 4.2 and 4.4 of the SmPC, accordingly. A new posology recommendation related to concomitant LHRH administration in patients not surgically castrated and new warnings related to hyperglycaemia, use with chemotherapy and potential risks of anaemia and sexual dysfunction have been introduced in the same sections. The existing warning in patients with a history of cardiovascular disease in section 4.4 of the SmPC has been updated. The newly identified ADRs of dyspepsia, haematuria, increased aspartate aminotransferase and rash, as well as safety information from the pivotal COU-AA-302 study were included in section 4.8 of the SmPC. The pivotal efficacy information from the pivotal COU-AA-302 study was included in section 5.1 of the SmPC. Finally, in the description of pharmacokinetic information in patients with hepatic impairment in section 5.2 of the SmPC, cross reference to other SmPC sections has been updated (4.2) or included (4.3. and 4.4).

In the second type II variation in the group of variation submitted, recommendations were updated in section 4.6 of the SmPC and the results from reproductive and developmental toxicity studies were included in secion 5.3.

The Package Leaflet has been updated in accordance with the above changes to the SmPC. Finally, minor changes were made to the SmPC , Labelling and Package Leaflet.

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the existing Package Leaflet for Zytiga 250 mg tablets. The bridging report submitted by the applicant has been found acceptable for the following reasons: the differences found had little impact on readability.

In addition, the list of local representatives in the PL has been revised to amend contact details for he representative of Cyprus.

3. Benefit-Risk Balance

Benefits

Beneficial effects

A single pivotal study supported this application. COU-AA-302 was a well-conducted and well-documented study, no major GCP triggers have been revealed during the assessment of the dossier. The Applicant sought CHMP scientific advice regarding the overall design of the study and no major deviations from the scientific advice were noted.

Treatment with abiraterone decreased the risk of radiographic progression or death by 58% compared with placebo and the reduction in risk of progression was maintained after an additional year of

follow-up. The results were consistently favourable across analyses, demonstrating the robustness of the primary analysis. Treatment with abiraterone resulted in a 25% decrease in the risk of death, although the p-value did not reach the nominal significance level. A favourable overall survival trend in the treatment effect was observed across all subgroups examined.

The results from the secondary endpoints support the benefit observed for the co-primary endpoints of rPFS and OS. In particular, opiate use was documented for fewer subjects and the median time to initiation of cytotoxic chemotherapy was significantly longer. For patient related outcome data, a delay in median time to average pain intensity progression and a delay in the degradation in the total score FACT-P was observed, indicating that quality of life was generally preserved in those subjects treated with abiraterone.

Treatment with abiraterone was tolerable for the majority of subjects and the safety profile was generally consistent with previous experience, although exposure to the drug was significantly longer than in previous studies. Adverse events were manageable and no major safety concerns have been raised for this application and indication.

Uncertainty in the knowledge about the beneficial effects

A single pivotal trial supports this application. There is a general demand for replication of scientific results. However, COU-AA-302 is considered adequate to support authorisation, with statistically compelling and clinically relevant results.

Overall survival did not reach the prespecified statistical significance based on an O'Brien-Fleming efficacy boundary at the interim analysis. A favourable trend in the treatment effect of abiraterone on OS was observed at the third interim analysis of OS, though it is noted that a stable estimate of the median survival is not yet available because of the high percentage of censored events. Longer follow-up is required to obtain this estimate.

At this point, at minimum an increase in rPFS together with a preservation of patient quality of life has been demonstrated. The effect seen in these two parameters in considered of sufficient relevance so as to support an indication for abiraterone in this clinical setting.

It is recognised that disease progression endpoint has not been a reliable predictor of overall survival in patients with prostate cancer. Nevertheless, as abiraterone increased OS in the post-docetaxel stage of the disease, it is safe to expect that the same treatment could be capable of prolonging survival in the pre-chemotherapy setting, also considering the strong trend observed for an improvement of OS.

The time to deterioration of ECOG PS was statistically significant but the difference between the medians was at best moderate. However, this was only a secondary endpoint.

Risks

Unfavourable effects

Exposure to abiraterone in COU-AA-302 is considered sufficient for assessment of safety and the median treatment duration was approximately twice that seen in study COU-AA-301. Fewer subjects in the abiraterone group discontinued and the most common reason for treatment discontinuation was disease progression.

Treatment with abiraterone was tolerable for the majority of subjects and overall the adverse event profile was generally consistent with previous experience and manageable. As expected, mineralocorticoid related toxicities were observed more frequently in the abiraterone group. Clinically meaningful imbalances between studies identified dyspepsia, AST increased, rash and haematuria as

new ADR. There were no unexpected SAEs. No new ADRs have been identified from post marketing data.

Uncertainty in the knowledge about the unfavourable effects

Potential QT signals were identified in study COU-AA-302. The Applicant continues to conduct ECG monitoring as part of the ongoing clinical development programme and has updated the RMP to include these studies as additional pharmacovigilance activities. Safety in patients NYHA Class II to IV heart failure has not established. Adequate warnings are found in Section 4.4 of the SmPC. More abiraterone treated subjects died within 30 days of the last dose of study medication, although the deaths have not been attributed to abiraterone toxicity. Overall, the uncertainties regarding the unfavourable effects are not considered to have a major impact.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Abiraterone is a well-tolerated anti-cancer therapy. The data derived from study COU-AA-302 are considered to demonstrate a clinically relevant benefit to patients who require additional therapeutic options. The magnitude of the effect is significant, particularly in terms of the observed delay in progression, the delay in the median time to initiation of cytotoxic chemotherapy and the reduction in the requirement for opiate use. A favourable overall survival trend was observed.

Treatment with abiraterone was tolerable for the majority of subjects and overall the adverse event profile was consistent with previous experience.

Benefit-risk balance

The favourable effects are considered to more than exceed the unfavourable effects/uncertainties and overall the benefit risk profile is considered to be positive.

The most influential factors for a positive opinion are the magnitude in the delay of progression and the clinically relevant advantage of the delay in time to initiation of chemotherapy and reduced opiate use. Furthermore, quality of life was generally preserved in patients treated with abiraterone compared to those treated with placebo. In line with previous experience, treatment with abiraterone was generally tolerable.

Discussion on the Benefit-Risk Balance

The prognosis of mCRPC patients is still poor (median survival of approximately 1 to 2 year). After patients become castration resistant and provided that they remain asymptomatic or have mild symptoms, so that chemotherapy is not yet indicated, different hormonal managements can be used; however, globally there is neither clear consensus nor clear proof of efficacy in terms of survival of available treatments. Such patients who are not in immediate need of chemotherapy may still benefit from alternative therapies. The data derived from study COU-AA-302 are considered to demonstrate a clinically relevant and significant advantage to this group of patients.

In conclusion, the overall benefit-risk balance of Zytiga in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated, is positive.

4. Recommendations

Final Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II
C.I.4	Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

Extension of Indication to include new population for Zytiga in combination with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom chemotherapy is not yet clinically indicated.

As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated in order to: add a new contraindication in patients with severe hepatic impairment, a new posology recommendation on concomitant LHRH administration in patients not surgically castrated and new warnings related to hyperglycaemia, use with chemotherapy and potential risks of anaemia and sexual dysfunction; update posology recommendations and warnings related to heart failure, mineralocorticoid toxicities, hepatotoxicity and hepatic impairment; update the existing warning in patients with a history of cardiovascular disease, the table of adverse drug reactions and cross references from the pharmacokinetic information to the safety sections of the SmPC; include information from the pivotal study in the SmPC.

In the second variation, recommendations were updated in section 4.6 of the SmPC and the results from reproductive and developmental toxicity studies were included in section 5.3 of the SmPC.

The Package Leaflet is updated in accordance. Finally, minor changes were made to the SmPC, Labelling and Package Leaflet.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested group of variations proposed amendments to the SmPC, Labelling and Package Leaflet.

Additional market protection

Furthermore, the CHMP reviewed the data submitted by the MAH, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004 and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies.

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