EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/CHMP/542871/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report
For
Zytiga
(abiraterone)

Procedure No.: EMEA/H/C/002321

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

AA	abiraterone acetate
AAS	atomic absorption spectroscopy
ACTH	adrenocorticotrophic hormone
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AIPC	androgen-independent prostate cancer
ALP	alkaline phosphatase
ALT	alanine aminotransferase
API	active pharmaceutical ingredient
AR	androgen receptor
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
BCF	Bio-Concentration Factor
BCS	Biopharmaceutics Classification System
BPI-SF	brief pain inventory-short form
BSE	bovine spongiform encephalopathy
CAS	Chemical Abstracts Service
CI	confidence interval
C_{max}	maximum plasma concentration
C_{min}	minimum plasma concentration
CMR	carcinogenic, mutagenic or toxic to reproduction
CRF	case report form
CRPC	castration-resistant prostate cancer
CSR	clinical study report
CT	computer-assisted tomography
CTC	circulating tumour cell
CYP17	cytochrome P450 17α-hydroxylase/C17,20-lyase
CYP	cytochrome P450
DDI	drug-drug interaction
DHEA	dehydroepiandrosterone
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
DT_{50}	Degradation Time for 50% of substance to be degraded under laboratory conditions
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EC_{50}	median (50%) effective concentration
E_{max}	maximum effect
ERA	Environmental Risk Assessment
ESRD	end-stage renal disease
EXT	extension
GC	gas chromatography
GCP	Good Clinical Practice
GGT	gamma-glutamyl-transferase
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practice
GnRH	gonadotropin-releasing hormone
HDPE	high density polyethylene
hERG	human Ether-à-go-go Related Gene
HPLC	high-performance liquid chromatography
HR	hazard ratio
HRPC	hormone-refractory prostate cancer
IC_{50}	median (50%) inhibitory concentration
ICH	International Conference for Harmonisation
IDMC	Independent Data Monitoring Committee
INN	International Non-proprietary Name
IR	infrared
ISO	International Organisation for Standardization
ITT	intent-to-treat

Ki	inhibition constant
K_{oc}	absorption coefficient
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LDH	lactic acid dehydrogenase
LFT	liver function test
LH	luteinizing hormone
LHRH	luteinizing hormone-releasing hormone
LLOQ	lower limit of quantitation
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Mass Spectrometry
Msec	millisecond
MTD	maximum tolerated dose
MUGA	multiple gated acquisition
NADPH	reduced (hydrogenated) form of Nicotinamide Adenine Dinucleotide Phosphate
ND	not determined
NE	non-estimable
NMR	Nuclear Magnetic Resonance
NOAEL	No Observable Adverse Event Level
NOEC	No Observed Effect Concentration
NOEL	No Observable Effect Level
NPC	numerical predictive check
NYHA	New York Heart Association
OECD	Organisation for Economic Co-operation and Development
OS	overall survival
PBT	Persistence, Bioaccumulation potential and Toxicity
PD	pharmacodynamic(s)
PEC	Predicted Environmental Concentration
$PEC_{surfacewater}$	local surface water concentration
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PPK	population pharmacokinetic(s)
PRA	Pharmaceutical Research Associates
PSA	prostate-specific antigen
PSADT	PSA doubling time
PSAWG	Prostate-Specific Antigen (PSA) Working Group
P-Y	patient-years
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria In Solid Tumours
RH	relative humidity
rPFS	radiographic progression-free survival
RR	response rate
UGT	UDP-glucuronosyl transferase
U.S.	United States
SAE	serious adverse event
SD	stable disease
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Queries
SOC	system organ class
SULT	sulfotransferase
t1/2	half-life
TEAE	treatment-emergent adverse event
TGI	tumour growth inhibition
t_{max}	time to reach the maximum observed plasma concentration
TNM	tumour-lymph nodes-metastasis classification system
TSE	transmissible spongiform encephalopathy
UV	ultraviolet
VPC	visual predictive check
XRD	x-ray diffraction
XRPD	x-ray power diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 17 December 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Zytiga, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 27 April 2010.

The applicant applied for the following indication: Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients who have received prior chemotherapy containing a taxane.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 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

Not applicable.

Market Exclusivity

Not applicable.

New active Substance status

The applicant requested the active substance abiraterone acetate contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 13 December 2007. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Zytiga has been given a Marketing Authorisation in the USA on 28 April 2011.

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**

- The application was received by the EMA on 17 December 2010.
- Accelerated Assessment procedure was agreed-upon by CHMP on 16 December 2010.
- The procedure started on 19 January 2011.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 April 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 April 2011.
- During the meeting on 19 May 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 20 May 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 17 June 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 July 2011.
- The Rapporteurs circulated an updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 16 July 2011.
- During the meeting on July 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Zytiga on 21 July 2011.

2. Scientific discussion

2.1. Introduction

Problem statement

Prostate cancer is the second most frequent cause of death from cancer in Western societies and affects one in six men. The median age at diagnosis is 72 years, so that many patients—especially those with localised tumours—may die of other illnesses without ever having suffered significant disability from the cancer. Prostate cancer may be cured when localised and it frequently responds to treatment when widespread. The rate of tumour growth varies from very slow to moderately rapid and some patients may have prolonged survival even after the cancer has metastasised to distant sites such as bone. The approach to treatment is influenced by age and coexisting medical problems. Side effects of various forms of treatment should be considered in selecting appropriate management. Different approaches exist with regard to the value of screening, the most appropriate staging evaluation, and the optimal treatment of each stage of the disease.

Survival of the patient with prostatic carcinoma is related to the extent of the tumour. When the cancer is confined to the prostate gland, median survival in excess of 5 years can be anticipated. Locally advanced cancer is usually not curable and a substantial fraction of patients will eventually die of the disease, though median survival may be as long as 5 years. Metastatic prostate cancer cannot be cured by current therapy. Median survival is usually 1 to 3 years and most such patients will die of prostate cancer. However, even in this group of patients, indolent clinical courses lasting for many years may be observed.

The 2010 TNM system specifies that the Gleason score be used to assess tumour grade. In addition, the 2010 TNM system has incorporated the pre-treatment serum Prostate Specific Antigen (PSA) level along with the Gleason score into anatomic stage/prognostic groups.

In brief, these TNM groups include:

- Group I-Low risk, localised tumours: anatomically T1 or T2a AND a serum PSA <10 ng/mL AND Gleason score ≤6
- Group IIA-Localised tumours with at least one feature associated with an intermediate level of risk: anatomically T2b OR serum PSA ≥10 and <20 ng/mL OR Gleason score of 7
- Group IIB-Localised tumours with at least one feature associated with a high risk for recurrence: anatomically T2c OR serum PSA ≥20 ng/mL OR Gleason score ≥8
- Group III-Locally advanced tumours, with extracapsular extension (T3 disease), regardless of the serum PSA or Gleason score
- Group IV-Any cancer with T4 spread OR positive lymph nodes (N1) OR distant metastases (M1)

For men with disseminated disease, bone is the most common site of metastasis. The objective of therapy is control of disease while maintaining quality of life. The initial approach is generally androgen deprivation therapy (ADT).

Androgen deprivation therapy has been the mainstay of prostate cancer management. It is documented that the proliferation of prostate cancer cells is regulated by androgens at the level of the androgen receptor (AR). In humans, approximately 90 % to 95 % of circulating testosterone is produced by the testes, and approximately 5 % to 10 % is produced by the adrenal glands. According to current practice guidelines, the initial treatment for advanced prostate cancer is androgen deprivation with medical or surgical castration. However, because these therapies only reduce androgen production by the testes and do not interfere with androgen production by the adrenals, approximately 5 % to 10% of baseline circulating testosterone remains.

Recent studies indicate that when prostate cancer progresses after hormone deprivation, the cancer cells continue to demonstrate AR mediated signalling. Furthermore, in metastatic CRPC (mCRPC), extratesticular (i.e., adrenal and intratumoral) testosterone represents an important source of androgen. At castrate concentrations of testosterone, the tissue (e.g., intra-tumour) levels of dehydroepiandrosterone (DHEA), dihydrotestosterone (DHT), and androstenedione all remain sufficient to activate the AR signalling pathways and promote prostate tumour growth.

Patients who progress on ADT in the face of castrate levels of testosterone are considered to have 'castration-resistant' prostate cancer. These patients have also been referred to as having hormone-refractory prostate cancer (HRPC) or androgen-independent prostate cancer (AIPC).

Nearly all men with metastatic prostate cancer eventually develop progressive disease after treatment with ADT. These men may still have clinically important responses to other hormonal interventions. Patients who have progressed on ADT and are not responsive to secondary hormonal therapies may benefit from chemotherapy.

The activity of docetaxel in men with castration-resistant prostate cancer was initially suggested by multiple phase II studies, in which docetaxel, with or without prednisone, was given on either a weekly or every three week schedule. These trials led to the evaluation of docetaxel in a number of combinations, including a direct comparison with mitoxantrone, which has established the combination of docetaxel plus prednisone as the standard of care for men with castration-resistant

prostate cancer. Docetaxel-based chemotherapy is the only treatment that has demonstrated an overall survival benefit in men with HRPC.

Recently, cabazitaxel was granted a marketing authorisation for the treatment of patients with hormone refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen, as its combination with prednisone improved median OS compared to mitoxantrone.

About the product

Abiraterone acetate is 3β-acetoxy-17-(3-pyridyl)-androsta-5,16-diene that is administered orally and it is available as an immediate release 250 mg tablet. It is rapidly converted in vivo to abiraterone, a selective, irreversible inhibitor of cytochrome P450 17α (17α-hydroxylase/C_{17-20} lyase; CYP17), an enzyme that is key in the production of androgens in all sites, including the testes and adrenal glands. This enzyme catalyzes two reactions: 17α hydroxylation of C_{21} steroids and cleavage of the $C_{17, 20}$ bond of C_{21} steroids. The 17α hydroxylation activity is a required step in cortisol biosynthesis, whereas the $C_{17, 20}$ bond side chain cleavage is essential for subsequent biosynthesis of androgens. This enzyme is expressed in testicular and adrenal tissues and catalyzes the conversion of pregnenolone or progesterone into dehydroepiandrosterone (DHEA) or androstenedione, respectively, two precursors of testosterone. Abiraterone causes reductions in testosterone levels by specifically inhibiting CYP17. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals.

The Applicant applied for the indication: *Abiraterone is indicated with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients who have received prior chemotherapy containing a taxane.* The finally approved indication was: *Zytiga is indicated with prednisone or prednisolone for the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen.* The recommended dose is 1000 mg (four 250 mg tablets) given once daily.

Type of Application and aspects on development

The Applicant requested accelerated assessment of their application which was granted.

With regard to paediatric studies, no paediatric investigation plan has been agreed. The incidence of prostate carcinoma increases with age and the disease is rarely diagnosed before the age of 50 years. The incidence in children was less than 25 cases between 1997 and 2001. Abiraterone is covered by a class waiver for prostate carcinoma which excludes rhabdomyosarcoma, which is a paediatric malignancy that may occur in the prostate, but it is not a carcinoma.

The Applicant received Scientific Advice from the CHMP on non-clinical development, paediatric requirements as well as on clinical efficacy and safety related to the pivotal study COU-AA-301.

2.2. Quality aspects

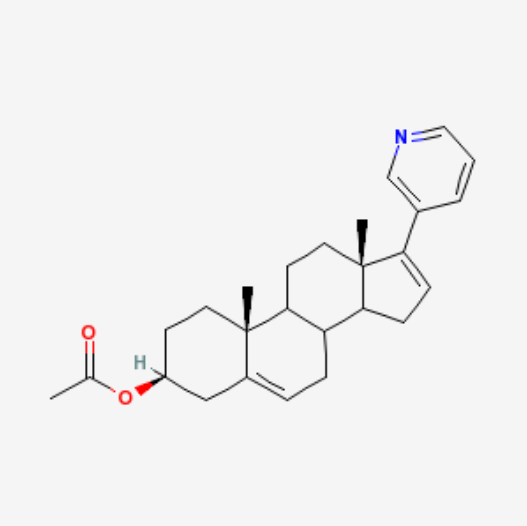
2.2.1. Introduction

Zytiga is presented as 250 mg immediate release tablets containing abiraterone acetate as active substance. The excipients used in the formulation of Zytiga are lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, povidone, sodium lauryl sulfate, magnesium stearate and colloidal silicon dioxide. There are no novel excipients used in this formulation.

Zytiga is administered via oral route and is packed in high density polyethylene (HDPE) bottles of 120 tablets with polypropylene child resistant closure and foil induction seal.

2.2.2. Active Substance

Abiraterone acetate is designated chemically as (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate and its structure is as follows:



Abiraterone acetate is a white to off-white powder practically insoluble in aqueous media (pH range 2.0 to 12.9), very slightly soluble in 0.1N HCl solution and soluble to freely soluble in organic solvents. Abiraterone acetate is classified as Class IV compound (low solubility low permeability) according to the biopharmaceutical classification system (BCS).

Abiraterone acetate is a single enantiomer containing 8 stereochemical elements: 6 chiral centers and 2 centers of geometrical isomerism. Abiraterone acetate is produced as a single enantiomer with its stereochemical elements introduced via the synthesis starting material prasterone acetate which is an enantiomerically pure material. The diastereomeric purity does not alter during the chemical synthesis process and this is confirmed by specific optical rotation results.

The synthetic process exclusively produces one physical form (polymorphic Form A). Characterization data obtained was consistent with crystalline unsolvated material. Distinct XRPD patterns, derived from solvents/conditions not used in the commercial synthesis process, lead to Unknown B, Unknown C, and Unknown D forms. Further characterization data for Unknown B and Unknown C suggested that they are unsolvated materials and metastable forms or thermodynamically less stable than Form A. This has been confirmed by X-ray powder diffraction (XRPD) studies comparing XRD patterns of multiple abiraterone acetate batches which did not show any unknown diffraction peaks.

Manufacture

Abiraterone acetate is manufactured by two manufacturers using very similar processes, and it is synthesized in 4 steps from one starting material. The critical steps and controls in the drug substance manufacture have been identified taking into account critical quality attributes of the active substance and a pre-determined set of principles. Process steps 1 to 3 were identified as being critical in terms of the impact on the impurity profile. The fate of the impurities has been

extensively investigated using spiking studies and was supported with data from a large number of batches. Critical process parameters are adequately defined and justified.

The structural elucidation has been satisfactorily demonstrated by means of IR, NMR, UV, MS, elemental analysis and optical rotation. All measurements were performed on the Reference Standard of the active substance. The analytical techniques were adequately described and validated.

Validation of the synthesis process has been performed on 3 consecutive full-scale batches.

Specification

The specifications of the active substance include visual inspection of the appearance, identity (IR and HPLC), assay (HPLC), residual solvents (GC Headspace), particle size (Laser Diffraction), water content (Ph.Eur.), heavy metals (Ph.Eur.), residue on ignition (Ph.Eur.), Palladium (atomic absorption spectroscopy (AAS) or inductively coupled plasma spectroscopy), and impurities (HPLC).

Stereo-isomeric control as well as polymorphic control of the active substance was found not to be necessary.

The control of the drug substance is considered to be appropriate and generally well justified.

The analytical methods described above have been adequately validated in accordance with available guidelines.

Stability

Stability studies were performed on abiraterone acetate stored in the proposed packaging, under ICH recommended storage conditions. Stability data on three batches stored at 25oC/60% RH for 12 months (long term conditions) and four batches stored at 40oC/75%RH for 6 months (accelerated conditions) was provided. Additionally, photostability was presented for one batch of active substance manufactured at full scale. No significant changes were observed on storage.

Batch data support the retest period as proposed by the Applicant. The active substance does not require any special storage conditions.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Abiraterone acetate tablets represent an immediate-release formulation for oral use packaged in high density polyethylene (HDPE) bottles of 120 tablets with polypropylene child resistant closure and foil induction seal.

Abiraterone acetate is practically insoluble in aqueous media over a wide range of pH and sparingly soluble to freely soluble in organic solvents. It is classified as BCS class IV. It is manufactured exclusively as a single form, Form A and it has been confirmed by XRPD that the drug product manufacturing process does not affect polymorphism. It has also been confirmed by XRPD that there is no change in physical form during the manufacturing process of the drug product.

The excipients used in the formulation of Zytiga are common ingredients for a solid oral dosage form. The excipients have been chosen based on preliminary formulation development experience and excipient compatibility studies. They are the same excipients and quantities used for the manufacture of Phase III clinical and registration stability batches. Lactose monohydrate and

microcrystalline cellulose are used as diluents, croscarmellose sodium as disintegrant, povidone as binder, magnesium stearate as lubricant and colloidal silicon dioxide as glidant. Sodium lauryl sulfate improves wetting of the active substance and therefore facilitates the granulation process.

The dissolution method has been adequately developed and its discriminating capability demonstrated. The results of the investigation of solubility and dissolution of the drug product were adequately summarised. The use of surfactant and the dissolution medium was justified. Sink conditions were confirmed. Discriminatory power of the method is evident for the specified single pull point at 45 minutes as proposed. The effect on particle size on manufacturability and tablet hardness has been evaluated. The comparative dissolution of tablets manufactured with varying API particle sizes demonstrate that tablet hardness was found to decrease with increasing drug substance particle size and for API D50 controlled between 3-10 µm little effect on dissolution performance could be observed. This is within the range of D50 observed for batches of API manufactured to date.

The formulation development from Phase I to Phase III clinical trials has been adequately described. The Phase I/II formulation is qualitatively the same as the Phase III formulation the only difference being the increase in magnesium stearate from 1.25% to 1.5% (with corresponding reduction in microcrystalline cellulose content) in the Phase III tablet. Bioequivalence studies were performed to demonstrate that the process changes from Phase II to Phase III did not impact on the *in vivo* performance of the product. It was concluded that tablets manufactured before and after the manufacturing process changes (clinical to commercial scale) and site transfer are bioequivalent. The dissolution profiles obtained by the proposed dissolution method between the batches used in the studies are comparable.

Adventitious agents

Lactose monohydrate is compliant with applicable BSE/TSE guidelines, as shown in the statement provided. Magnesium stearate is vegetable-sourced. All excipients are of Ph. Eur. quality.

Manufacture of the product

The manufacture of the finished product involves conventional processes including (1) mixing, (2) granulation, (3) Wet milling (4) drying, (5) Dry milling, (6) Blending, (7) Lubrication (8) tablet compression and (9) packaging. Critical steps identified and evaluated in manufacturing process development were wet granulation, drying and compression. The critical process parameters and the critical process controls.

Product specification

The specification for abiraterone acetate tablets include tests for appearance (visual examination), identification of abiraterone acetate (IR), assay (HPLC), impurities (HPLC), uniformity of dosage unit (Ph.Eur.) and dissolution (HPLC).

All methods have been satisfactorily validated. The HPLC method was validated for specificity, linearity, accuracy, range, repeatability, intermediate precision and robustness. The IR method for identification of abiraterone acetate was validated for specificity and repeatability. Uniformity of dosage unit method is described in the PhEur and therefore validation was deemed to be unnecessary.

Batch data was provided on nine batches manufactured at full scale. The results demonstrated that the process was consistent and reproducible at a relevant scale. Satisfactory reports on microbial contamination and water content have also been provided.

Stability of the product

The results of long term (up to 12 months at 25° C/60%RH), intermediate (up to 12 months at 30° C /75%RH) and accelerated stability studies (6 months at 40° C/75%RH) have been presented for nine batches stored in the proposed packaging. There were no significant changes in any parameter.

Three batches were tested under ICH light conditions. There were no notable changes to parameters during this study.

The proposed shelf life and storage conditions as stated in the SmPC were found to be acceptable. Based on the established stability data in-use stability testing of the drug product was not considered to be necessary.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical practice.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical studies were conducted in mice, rats and cynomolgus monkeys. In accordance with International Conference on Harmonization (ICH) S7A, safety pharmacology studies evaluating the potential effects of oral administration of abiraterone acetate on the central nervous, cardiovascular, respiratory and gastrointestinal systems were conducted in accordance with Good Laboratory Practice (GLP) regulations. The pivotal toxicology studies supporting the safety of abiraterone acetate were also conducted in compliance with GLP regulations and ICH guidelines, with some exceptions. The exceptions were generally in the single and repeat-dose toxicity studies in mice and an *in vitro* genotoxicity study in human lymphocytes. Also, *in vitro* pharmacology studies and some pharmacokinetics both *in vitro* and *in vivo*, do not comply with GLP. Any portions of the toxicology studies that were not fully GLP compliant were conducted in accordance with accepted scientific practice.

The Applicant received Scientific Advice from the CHMP pertaining to non-clinical aspects of the dossier and more specifically on the adequacy of the non-clinical data package to support the Marketing Authorisation Application.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Potter *et al.* (1995) reported the synthesis and initial activity of abiraterone and abiraterone acetate. Abiraterone was reported to have an IC_{50} of 2.9 nM and 4 nM for inhibition of $C_{17,20}$-lyase and 17α-hydroxylase respectively in human testicular microsomes. Abiraterone did not inhibit aromatase or 5α-reductase at high micromolar concentrations. Abiraterone acetate was slightly less potent with IC_{50}'s of 17 nM and 18 nM for inhibition of $C_{17,20}$-lyase and 17α-hydroxylase respectively.

Jarman *et al.* (1998) studied the *in vitro* inhibitory effect of abiraterone and some abiraterone analogues on human cytochrome CYP17. The study was designed to determine the contribution of the 16,17-double bond in the molecular structure of abiraterone to the irreversible nature of of CYP17 inhibition. By using human testicular microsomes, it was demonstrated that abiraterone inhibits CYP17 with an IC_{50} of 4 nM. After a dialysis of 24 hours, no recovery of the enzyme activity was observed, indicating irreversible inhibition of the enzyme by abiraterone. Additional experiments using abiraterone analogues showed that the 16,17-double bond was necessary for irreversible binding of abiraterone to CYP17.

Haidar *et al.* (2001, 2003) examined the effect of several compounds (including abiraterone and abiraterone acetate) on androgen biosynthesis *in vitro*. Microsomal fractions containing human or rat CYP17 were prepared from human or rat testes. In addition, E. coli coexpressing human CYP17 and NADPH-P450-reductase assay were also used to test the inhibitory effect of abiraterone and abiraterone acetate on these enzymes. The inhibitory potency of these compounds on these fractions was evaluated: IC_{50} values for human CYP17 of 73nM and 110nM were found for abiraterone and abiraterone acetate, respectively; 220nM and 1600nM were the abiraterone and abiraterone acetate IC_{50} values for the rat enzyme; and finally IC_{50}s of 54 and >2500nM were reported for the two compounds for the E.coli-expressed recombinant human CYP17.

These data indicate that abiraterone is more effective than the prodrug abiraterone acetate in inhibiting CYP17. In addition, reversibility of the inhibitory effect was evaluated. After a preincubation of abiraterone with the enzyme, the unbound inhibitor was removed with charcoal, and enzyme activity was determined after various time intervals (up to 320 minutes). It was demonstrated that there was no recovery of the enzyme activity indicating irreversible inhibition of the enzyme by abiraterone.

Duc *et al.* (2003) examined the effects of abiraterone and other compounds on $C_{17,20}$-lyase activity *in vitro* and *in vivo*. Abiraterone was tested in rat testis microsomes, wherein an IC_{50} of 5.8 nM was observed. Abiraterone acetate was also tested in rat testis microsomes, wherein an IC_{50} of 8.2 nM was observed.

Abiraterone, abiraterone sulphate and the *N*-oxide abiraterone sulphate were initially screened for receptor binding to human nuclear receptors at a single concentration of 1.0 µM. Ligand displacement assays were performed. All of the compounds were inactive when tested for glucocorticoid receptor binding, estrogen receptor-α binding, estrogen receptor-ß binding and androgen receptor binding. Abiraterone and abiraterone sulphate produced a weak inhibition, respectively, of the binding of [^{3}H]-progesterone to the human progesterone receptor. *N*-oxide abiraterone sulphate was essentially inactive.

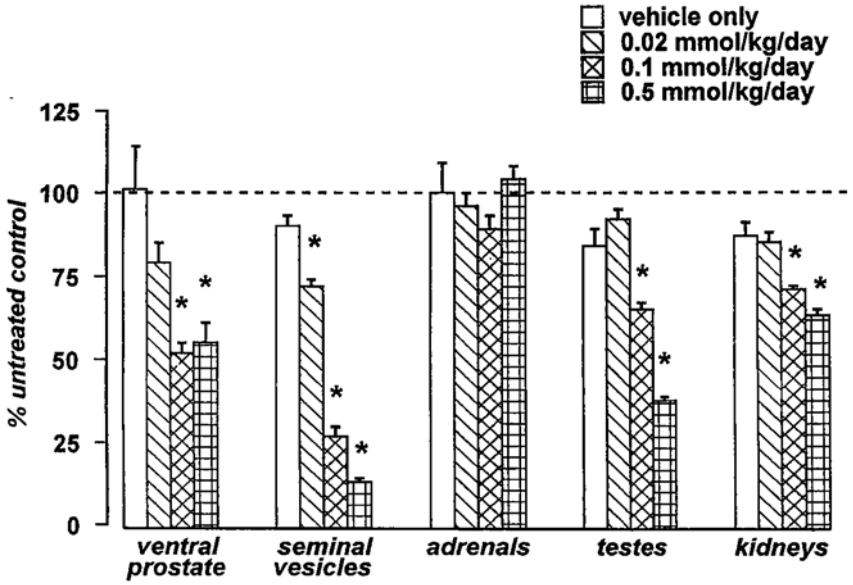
Abiraterone, abiraterone sulphate and the *N*-oxide abiraterone sulphate were tested for inhibition of steroidogenesis in the NCI-H295R human adrenal cortical tumour cells. Abiraterone showed maximal inhibition of androstenedione and testosterone production at the lowest tested concentration of 3.1

nM, which did not allow for calculation of an IC_{50}. Cortisol synthesis was also potently inhibited with an IC_{50} of 3.0 nM. Aldosterone was elevated by low concentrations (3.1 to 10 nM) of abiraterone, probably reflecting the shunting of the accumulated pregnenolone and progesterone substrates into the mineralocorticoid pathway due to inhibition of CYP17. All of these effects were consistent with a potent inhibition of the CYP17 pathway. At higher concentrations (0.312 to 10 µM), abiraterone suppressed aldosterone synthesis producing an IC_{50} of 2.7 µM. Abiraterone sulphate inhibited the synthesis of androstenedione, testosterone and cortisol with IC_{50}'s of 0.85, 0.73 and 2.8, µM respectively. *N*-oxide abiraterone sulphate inhibited the synthesis of androstenedione, testosterone and cortisol with IC_{50}'s of 1.3, 1.9 and 6.2 µM, respectively. At concentrations ranging from 1 to 10 µM, aldosterone synthesis was elevated above control values by both metabolites.

The *in vivo* effects of abiraterone acetate on circulating hormone levels and organ weights were investigated in mice and were compared with the effects after surgical castration.

Abiraterone acetate was given daily by intraperitoneal injection to adult male mice for 14 consecutive days at different concentrations. On Day 15, animals were anesthetized and blood was collected for testosterone and LH measurements. Other groups of mice were castrated and sacrificed at 1, 2, or 4 weeks after initiation of treatment, and selected organs were weighed. As expected, castration markedly decreased the weight of ventral prostate, seminal vesicles, and kidneys 2 weeks after surgery (data not shown). Treatment with abiraterone acetate also caused a marked weight reduction of several androgen-sensitive organs in a dose-dependent manner, as shown in the following figure 1. As observed in castrated animals, reduction of seminal vesicle weights by treatment with abiraterone acetate was more marked than that of the ventral prostate weights. No mortality or apparent signs of toxicity were observed in any animals.

Figure 1: Dose-related effects of 14 days treatment with abiraterone acetate on the organ weights of mice



Results are expressed as percent of untreated controls (n = 20 per group). *p<0.01 from vehicle controls. (adapted from Barrie *et al.*, 1994).

Plasma testosterone levels were markedly decreased in a dose-dependent manner by abiraterone acetate treatment and the testosterone reductions were maintained despite the compensatory increases in LH levels.

Table 1: Levels of plasma testosterone and LH after abiraterone acetate treatment

Treatment	Testosterone (nM)	LH (ng/ml)
Untreated	9.8 ± 5.6	0.63 ± 0.16
Vehicle	2.5 ± 1.2	0.8 ± 0.09
7.8 mg/kg/day	2.7 ± 0.5	3.4 ± 0.5
39.2 mg/kg/day	0.2 ± 0.1*	2.55 ± 0.45*
196 mg/kg/dday	0.1 ± 0.0*	2.55 ± 0.67*

LH = luteinizing hormone, * $p < 0.05$ vs. the vehicle group (extracted from Barrie *et al*., 1994)

Other studies have shown similar effects on organ weights and circulating hormone levels in rats. Duc *et al.* (2003) reported a reduction of ventral prostate weights and seminal vesicle weights (but no effect on testes weights) and decreased testosterone levels when abiraterone acetate was administered orally at 50 mg/kg/d (300 mg/m^2/d) for 3 consecutive days. In another study (Haidar *et al*., 2003), markedly decreased ventral prostate, complete prostate, seminal vesicles, and testes weights have been observed after a 14-day treatment period at 39.2 mg/kg/d (0.1 mmol/kg/day). In the same study, abiraterone acetate decreased testosterone levels from approximately 2.2 ng/ml (control) to 0.1 ng/ml.

Castration resistant prostate cancer (CRPC) may synthesize androgens *de novo* from cholesterol or metabolize adrenal androgens to maintain tissue androgen levels and support growth despite anorchid serum testosterone. It has previously been shown that the CRPC xenograft LuCaP 35V maintains tumoral androgen levels in castrate mice. Montgomery *et al*. (2009) further investigated the effects of abiraterone acetate on the growth of human CRPC xenograft LuCaP 35V in castrated male mice. These mice lack measurable serum adrenal androgens and are an excellent model for autonomous androgen production by tumor xenograft tissue. Treatment of mice bearing the LuCaP 35V xenograft with abiraterone acetate at a dose of 196 mg/kg (0.5 mmol/kg) intraperitoneally for 5 days every week for 21 days reduced androgen production in the tumor xenografts and significantly slowed tumor growth compared to control animals, as shown in the following figures 2 and 3.

Figure 2: Abiraterone acetate suppresses LuCaP35V xenograft tissue levels of androgens in the absence of circulating androgens or DHEA

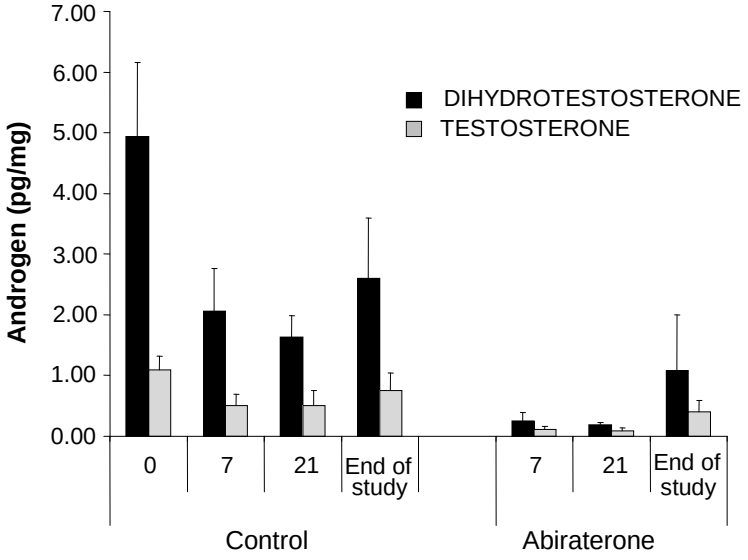
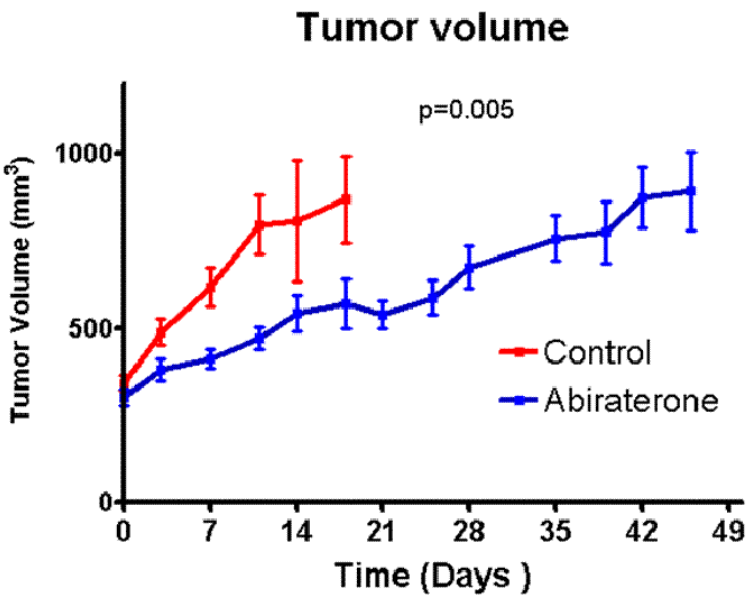


Figure 3: Abiraterone acetate treatment suppresses LuCaP35V growth



Median survival of abiraterone treated animals was 44 days compared to 21 days for controls (p = 0.0001). Prostate Specific Antigen (PSA) doubling times were also significantly better in the abiraterone acetate treated animals compared to controls (24.2 ± 2.2 days vs. 11.9 ± 1.8 days, p = 0.0005). Both PSA doubling time and tumor growth became more rapid at discontinuation of abiraterone. From this it can be concluded that the effect of the CYP17 inhibitor abiraterone in this model of human CRPC is independent of adrenal androgens and likely related to suppression of tissue androgen synthesis.

Secondary pharmacodynamic studies

No studies were submitted (see discussion on non-clinical aspects).

Safety pharmacology programme

The possible effects of abiraterone acetate on behaviour and neurologic and autonomic function was evaluated in a repeated dose oral toxicity study wherein abiraterone acetate was administered orally via gavage to male rats at a single dose of 40 or 400 mg/kg with a vehicle group. No test article-related mortality was noted throughout the study period. Behavioural assessment revealed a slight decrease in alertness and a decreased pinna reflex at 40 and 400 mg/kg. Peak observations were observed at 3 hours post-dosing on Day 0 and absent at the 24-h post-dosing observation. Also a slight increase in incidence for reacting to touch escape was noticed at 400 mg/kg at 24 hours post-dosing in 3 animals. There were no neurologic or autonomic abnormalities and no signs of general toxicity at any dose tested.

The cardiovascular safety profile was evaluated in two studies, one *in vitro* and one *in vivo*.

Abiraterone and abiraterone acetate, in the presence of 1% bovine serum albumin, were tested for their *in vitro* effects on the membrane currents in a HEK293 cell line expressing the hERG channel. The data are expressed as mean values (n = 3 or 4). Abiraterone inhibited the hERG potassium current at 10 and 27 µM by 2% and 6%, respectively. Due to this modest level of inhibition at the

highest concentration, which was close to the limits of solubility for the compound, the IC_{50} for abiraterone could not be determined. Abiraterone acetate inhibited the hERG potassium current at 1.3, 3, 10 and 27 µM by 2, 10, 38 and 84%, respectively. The IC_{50} for the inhibitory effect of abiraterone acetate on hERG potassium current was 12.2 µM. The inhibition observed with the vehicle alone was 0.3%, while the inhibition found with cisapride (90 nM), the positive control, was 92%..

The pharmacological effects of orally administered abiraterone acetate on the haemodynamic and electrocardiographic parameters were evaluated in male telemetered cynomolgus monkeys. There were no deaths noted in this study. The clinical signs observed were noted in one out of four animals administered 250 and 750 mg/kg and consisted of pale faeces the day following the treatment. One animal dosed with 2000 mg/kg presented soft and pale white faeces and liquid, the morning following treatment and two days following the dose administration, respectively. The administration of abiraterone acetate at dose levels up to 2,000 mg/kg had no effect on the hemodynamic and the electrocardiographic intervals (RR, PR, QRS, QT and QTc) in male cynomolgus monkeys following a 24-hour monitoring period. In addition, no overt arrhythmias/abnormalities were found on inspection of the ECG tracings over the 24-hour recording period.

The effect of orally administered abiraterone acetate on respiratory function was evaluated in rats. No test article-related clinical signs or mortality were observed in animals given any dose of abiraterone acetate. The tidal volume for animals given 750 mg/kg was significantly lower (-16%) than that of animals given vehicle control article. Changes in tidal volume did not occur in a dose-dependent manner. No other significant changes in respiration rate and minute volume were observed.

In a GLP gastric irritation toxicity study, male mice (10/group) were administered with single oral (gavage) dose of abiraterone acetate at 0 and 800 mg/kg, with a control group. At scheduled necropsy, no effects due to treatment with the control or abiraterone acetate were observed in the gastrointestinal tract and no abnormalities of the internal viscera or general condition of the mice were recorded.

Pharmacodynamic drug interactions

No relevant studies were submitted (see discussion on non-clinical aspects).

2.3.3. Pharmacokinetics

The nonclinical pharmacokinetics of abiraterone acetate and abiraterone was characterised in both *in vitro* and *in vivo* test systems. Almost all *in vivo* studies were part of the nonclinical toxicology studies in Albino Swiss mice, Sprague-Dawley (S-D) rats and cynomolgus monkeys in which abiraterone acetate was orally administered. Abiraterone acetate was dosed intravenously only once in cynomolgus monkeys and in male WHT mice due to its low solubility and no intravenous or oral dosing was performed with abiraterone.

Plasma levels of abiraterone acetate were generally below or scarcely above the limit of quantification after oral administration of abiraterone acetate and peak plasma concentrations of abiraterone were rapidly reached, in most cases within 1 to 2 h after dosing, in all species evaluated. The C_{max} in the different species was between 4.7 ng/ml in monkeys to 9,797 ng/ml in mice after oral administration and 19,783 ng/ml in monkeys after intravenous administration. Abiraterone acetate and abiraterone plasma concentrations were markedly higher after intravenous dosing than after oral dosing. The half-life was 2 h in mice, 1.29 to 3.82 h in rats and 2.6 to 11.8 h in monkeys.

No gender differences in mice and monkeys were reported, whereas in rats exposure to abiraterone in males was markedly higher than in females.

Plasma levels of abiraterone increased with increasing dose levels of abiraterone acetate but less than dose proportionally, both in single and repeat-dose studies.

^{14}C-abiraterone was detected in the tissues at 0.5 h after dosing in S-D rats and maximum concentrations were observed at 4 h post-dose. The highest ^{14}C-abiraterone concentrations were found in the liver at approximately 48 times the corresponding blood AUC. In adrenal gland, kidney (cortex) and gastrointestinal tract, the ^{14}C-abiraterone concentrations were 15-35 times the corresponding blood concentration, while in fat, brain, large intestine tissue, spinal cord and pancreas, the concentrations were 5 to 9 times the concentration in blood. Concentrations in prostate gland, lung, skin, myocardium, thyroid, pituitary gland and spleen were 2-5 times and in bone marrow, lymph nodes, seminal vesicles and uveal tract 2 times the corresponding blood concentration. In muscle, testis and eye, concentrations were lower than those in blood. Also, there were high concentrations of ^{14}C-abiraterone in bile.

Abiraterone was able to cross the blood brain barrier since ^{14}C-abiraterone had been measured in the cerebellum, cerebrum, medulla and spinal cord. ^{14}C-abiraterone was not retained in red blood cells because the blood/plasma concentration was 0.7.

At 24 h after dosing, ^{14}C-abiraterone was only detectable in a few tissues, i.e. adrenal gland (3.6% of radioactivity) and stomach (15.7% of radioactivity). In kidney, liver and preputial gland, ^{14}C-abiraterone concentrations were still measurable in at least one out of the three animals, but just above the limit of quantitation. These data indicated that upon repeated daily dosing only limited accumulation could be expected. The longest retention of ^{14}C-abiraterone was observed in the stomach.

^{14}C-abiraterone was selectively associated with melanin-containing tissues, in particular the uveal tract in which ^{14}C-abiraterone was detectable at 168 h after dosing, but it was not irreversibly bound to melanin, as has been reported in the pigmented LE rats.

In vitro, in Caco-2 cell monolayers, abiraterone and abiraterone acetate had a low apparent permeability and were not substrates of P-glycoprotein (P-gp). Abiraterone showed little inhibition of P-gp mediated transport of digoxin whereas abiraterone acetate inhibited P-gp significantly at high concentrations with a 50 % inhibitory concentration (IC_{50}) of 10.8 µM. So, although abiraterone acetate might increase the exposure of co-administered drugs which are substrates for P-gp, as abiraterone acetate is rapidly converted to abiraterone, no systemic inhibition of P-gp is expected.

Abiraterone was highly bound to plasma proteins (97.4% to 99.1% in rat, monkey and human) irrespective of the concentration of abiraterone tested. Indeed, in human plasma, abiraterone is primarily bound to serum albumin (95.6% to 97.6%) and human alpha-acid glycoprotein (94.3% to 95.7%). Other results from in vitro studies indicate that binding of ^{14}C-abiraterone to plasma proteins ranged from 99.81% to 99.92% in mouse, rat, rabbit, and in man. Binding was mainly to albumin (99.88 %) and to alpha-acid glycoprotein (89.4-94.4 %). Also in plasma from male patients with mild or moderate hepatic impairment the protein binding of abiraterone was 99.8 %.

No placental transfer studies were submitted (see discussion on non-clinical aspects).

Abiraterone acetate is rapidly hydrolyzed to abiraterone, followed by sulphate or glucuronic acid conjugation or both, alone or in combination with oxidation, or followed by mono-, di- and tri-oxidation of abiraterone, as reported in *in vitro* (in liver microsomes and cryopreserved hepatocytes from rat, monkey and man) and *in vivo* (in rats and monkeys) studies. The steroid and pyridine

moieties were both likely targets for enzymatic oxidative reactions as well as Phase II conjugation reactions.

The major *in vitro* metabolic pathway of abiraterone acetate in man was ester hydrolysis producing abiraterone followed by O-sulphate or O-glucuronic acid conjugation or followed by mono- and di-oxidation which could include hydroxylation as well as N-oxidation. From the in-vitro data it could further be concluded that the metabolism of abiraterone acetate in rat, monkey and man was qualitatively and quantitatively similar, with the exception of N-glucuronidated abiraterone sulphate, one minor human metabolite, which was not observed in the rat but it was found in monkey plasma.

In vivo, the metabolism of abiraterone acetate was initiated with hydrolysis of the acetate ester to abiraterone, followed by multiple hydroxylations and direct sulphation of the free hydroxyl group of abiraterone. Also combinations of hydrogenations, hydroxylation, and Phase II conjugation (sulphation and glucuronidation) have been observed.

The main circulating metabolite in rat is abiraterone sulphate. Other notable metabolites for both genders were several mono-oxy-abiraterone sulphate isomers and abiraterone. Notable metabolites for the male rats also included the hydrogenated-mono-oxy-abiraterone and mono-oxy-abiraterone sulphate. In plasma of females a mono-oxy-abiraterone sulphate isomer was noted. All other identified metabolites appeared to be very minor.

Abiraterone acetate was rapidly and mainly (89.9 to 93.4% of the administered dose) excreted in the faeces. The excretion of the product in urine was limited, accounting for less than 2 % of the administered dose. There were no differences in routes and rates of excretion between male and female rats.

No studies have been performed to evaluate the excretion of abiraterone acetate into milk (see discussion on non-clinical aspects).

In the *ex vivo* studies, abiraterone acetate and abiraterone did not inhibit CYP2A6, while CYP2C9 and CYP3A4/5 were moderately inhibited. Abiraterone acetate had a moderate inhibitory effect on CYP2E1 and a strong inhibitory effect on CYP2C19. On other hand, abiraterone did not inhibit CYP2E1 but moderately inhibited CYP2C19. Both had a strong inhibitory effect on CYP1A2 and CYP2D6, with K_i 0.32 and 0.16 µM, respectively, for abiraterone acetate and K_i 0.44 and 0.39 µM, respectively, for abiraterone.

After the administration of 40 and 400 mg/kg/day of abiraterone acetate to male and female rats, the microsomal protein content in liver was the same, while cytochrome p450 content increased in males. In females, abiraterone acetate had no effect on CYP1A1,2 and CYP2B enzymatic activities, while in males these activities were significantly increased and decreased, respectively. In both genders, at 400 mg/kg/day, there was significant increase in relative liver weight and induction of CYP4A1 activity. UGT, on other hand, was increased at both doses in females but only at 400 mg/kg/day in males. The activity of CYP2E1 decreased in both genders while CYP3A1,2 decreased in males and increased in females at 400 mg/kg/day. Also in male rats, DHEA sulphotransferase activity (SULT2A1) and in SULT2A1 activity towards abiraterone oxide (leading to formation of N-oxide abiraterone sulphate) increased significantly 40 and 400 mg/kg/day. In female rats, there was a statistically significant decrease in SULT2A1 activity towards DHEA at the highest dose and a dose-dependent decrease in SULT2A1 activity towards oxidized abiraterone (resulting in N-oxide abiraterone sulphate).

2.3.4. Toxicology

Single dose toxicity

The single-dose toxicity of abiraterone acetate was examined following oral administration in mice and rats.

In a non-GLP single dose toxicity study, male and female mice (5/sex/group) were administered a single oral (gavage) dose of abiraterone acetate at levels of 0, 125, 500 and 2,000 mg/kg. Additional mice were added for toxicokinetic evaluation (9/sex/group). There were no test article-related findings.

In a GLP single dose toxicity study, male rats (10/group) were administered a single oral (gavage) dose of abiraterone acetate at levels of 0 and 400 mg/kg. No deaths or treatment-related adverse effects were seen during the 14-day observation period. Body weight was not affected. Some changes in hematology and clinical chemistry were observed particularly a decrease in serum urea (90% of control). No gross findings were noted at necropsy.

Repeat dose toxicity

The toxicity of abiraterone acetate after repeated p.o. administration was studied in pivotal toxicity studies in rats (over 28 days, 13 and 26 weeks) and cynomolgus monkeys (over 28 days, 13 and 39 weeks) followed by a 4-week recovery period. A non-pivotal 15-day repeated dose study was performed in mice in support of a future carcinogenicity program for other clinical indications. Results of repeat-dose toxicity studies are summarised in the following table.

Table 2: Repeat-dose toxicity studies performed with abiraterone acetate

Study ID	**Species/Sex/ Number/Group**	**Dose/Route**	**Duration, (recovery)**	**NOEL/ NOAEL (mg/kg/day)**
TOX 9586	Albino Swiss (CD1) mice/ Both/ 40/ 4	0, 125, 500 and 2,000 mg/kg/day/ Oral	15 days	125/ND
	Major Findings: Deaths: 2 female died after 5 and 13 doses, respectively, at 2,000 mg/kg/day, Female genital tract: atrophy of uterus in 2/5 females at 2,000 mg/kg/day, Liver: hypertrophy of a very slight to moderate degree at 500 and 2,000 mg/kg/day, Male genital tract: atrophy of testes, epididymides, prostate, seminal vesicles and coagulating glands, in 3/5 males at 500 and 2,000 mg/kg/day. Minimal atrophy in one male at 125mg/kg/day, Spleen: slight to moderate of extramedullary haematopoiesis at 2,000 mg/kg/day, and increased reticulocyte count., Lung: aggregates of intra-alveolar macrophages in 1 male and 3 females at 2,000 mg/kg/day, Eyes:			
BIBRA 1632-1	Wistar rats / Male/ 80/ 4	0, 40, 126 and 400 mg/kg/day/ Oral	28 days, (28 days)	ND
	Major Findings: One rat from each of the 40 and 126 mg/kg treatment groups taken for unscheduled necropsy, Liver: panlobular hypertrophy and periportal vacuolation in 9/10 rats at 400 mg/kg/day, Male genital tract: dark testes, interstitial cell hyperplasia and reduction in spermatogenesis, atrophy of seminal vesicles and prostate at 400 mg/kg/day, Spleen: reduced lymphocytes in mantle zone, a slight in crease in compact cells in reticularis zona of adrenal cortex at 400 mg/kg/day, Lung: small red foci in7/10, inflammatory cell infiltrates, haemorrhage, foamy and pigmented macrophages male at 400 mg/kg/day			
ITR	S-D rats/ Male/ 80 / 4	0, 40, 126 and 400 mg/kg/day/ Oral	28 days, (28 days)	ND

7565	**Major Findings:** Male genital tract: small, soft and dark testes, small prostate and epididymides at 40, 126 and 400 mg/kg/day. Minimal to moderate Leyding cell hyperplasia at all dose groups. Focal tubular atrophy with hypospermia/ aspermia of the testes at the end of testing. Mononuclear cell infiltrate in the interstitium of the prostate in 2/10, 3/10 and 3/10 rats at 40, 126 and 400 mg/kg/day, respectively at the end of recovery., focal tubular atrophy, hypospermia/aspermia of the epididymides with degenerative germ cells and decreased secretion of the prostate with glandular atrophy in 1/10 and 1/10 rats at 40 and 400 mg/kg/day, respectively, at the end of recovery, Mammary glands: atrophy in 1/9 rats at 40 mg/kg/day and in 6/9 rats at 400 mg/kg/day during recovery, Pituitary: minimal to moderate hyperplasia of chromophobe cells in *pars distalis* at all dose groups			
7777-100	Crl:CD (S-D) rats/ Both/ 160/ 4	0, 250/50, 750/250 and 2000/750 mg/kg/day/ Oral	13 weeks, (4 weeks)	Can not be established
	Major Findings: From day 9 to 12 onwards, due to toxicity dose levels were reduced from 2000, 750, 250, mg/kg to 750, 250 and 50 mg/kg, respectively Deaths: 2 males and 4 females in 2000/750 mg/kg/day group sacrificed in a moribund condition and considered test-related, Female genital tract: atrophy of uterus and cervix at all doses and at 2000/750 mg/kg/day after recovery, Liver: increased weight in 750/250 mg/kg/day in both sexes at the end of dosing and high weight in males of all dose groups and females at 750/250 mg/kg/day after recovery. Bile hyperplasia adverse and not reversible in 2 males and 2 females at 750/250 mg/kg/day and in the most animals at 2000/750 mg/kg/day, Male genital tract: low weight of testes, epididymides, prostate and seminal vesicles in all doses groups. Discoloured or soft testes in males at all doses during dosing period and at 750/250 mg/kg/day after recovery. Atrophy of seminal vesicle, prostate and epididymis and/or hypospermia at all dose groups, Mammary glands: atrophy at all dose groups, Pituitary: hyperplasia/hypertrophy at all dose groups, Lung: alveolar macrophages at all dose groups, Heart: subacute inflammation in males given 2000/750 mg/kg/day			
777-105	Crl:CD (S-D) rats/ Both/ 240/ 4	0, 50, 150 and 400 mg/kg/day/ Oral	26 weeks, (4 weeks)	NOAEL <50 (m) NOAEL=50 (fem)
	Major Findings: Deaths: 1 male and 3 females were found dead on Days 56, 131, 145 and 98, respectively, and 7 males and 4 females were sacrificed in moribund conditions, all animals in 400 mg/kg/day group. Additionally, 1 male was found dead and 1 male and 4females were sacrificed at 400 mg/kg/day in TK group, Male genital tract: discoloured or soft testes, and small epididymis in all doses groups. Seminiferous tubule degeneration in all animals at the end of dosing and in 4/10 , 6/10, 10/10 animals at 50, 150 and 400 mg/kg/day at the end of recovery, respectively. Decreases in mean organ weight parameters for testis, prostate, epididymis, and seminal vesicle at all dose levels at the end of dosing as well as the end of recovery, except for for prostate only at at 150 and 400 mg/kg/day, Pituitary: increased weight at all dose levels, Female genital tract: increased weight of ovary at all dose levels (end of dosing) and at 150 and 400 mg/kg/day (end of recovery), correlated with hypertrophy/hyperplasia of ovarian interstitial cells, Lung: minimal inflammation, Liver: minimal to marked bile duct/oval cell hyperplasia in 5/12 male and 5/13 female rats at the end of dosing at 400 mg/kg/day, minimal to moderate bile duct/oval cell hyperplasia in 6/9 male and 5/10 female at 400 mg/kg/day (end of recovery). Minimal or slight capsular fibrosis in 2/9 males and 1/10 female at 400 mg/kg/day, Eyes: Discoloration. Cataracts in males at all doses and in females at 150 and 400 mg/kg/day			
1818-	Cynomolgus monkeys/ Both/ 60/ 6	0, 2, 10, 50, 250 and 1,000 mg/kg/day/ Oral	28 days, (4 weeks)	NOEL <2 NOAEL =1000

001	**Major Findings:** Mammary glands: oedema with fibrosis and epithelial hyperplasia of the male mammary ducts, Female genital tract: cystic follicles in the ovaries of all animals from 50 mg/kg/day onwards at the end of dosing and of 1 female at 50 mg/kg/day and 1 female at 250 mg/kg/day, at the end of recovery Epithelial plaque, decidual reaction and endometrial hyperplasia were still present in uterus in single animals of various dose groups.			
7777-101	Cynomolgus monkeys/ Both/ 44/ 4	0, 250, 750 and 2,000 mg/kg/day/ Oral	13 weeks (4 weeks)	NOEL =ND NOAEL <250
	Major Findings: Clinical chemistry and hormone levels: increased triglycerides and total bilirubin, decreased cortisol, dehydroepiandrosterone and high aldosterone and progesterone levels. ACTH levels increased in all groups at end of dosing and were slightly higher in animals at 2,000 mg/kg/day at the end of recovery, Liver: increased weight and slight bile duct hyperplasia in male and female at 250, 750 and 2,000 mg/kg/day at the end of dosing and at 2,000 mg/kg/day at the end of recovery., Mammary gland: minimal to slight hyperplasia in all dose groups at the end of dosing and minimal hyperplasia in 1 control male and 1 male at 2000 mg/kg/day at end of recovery.			
7777-103	Cynomolgus monkeys/ Both/ 44/ 4	0, 250, 500 and 1,000 mg/kg/day/ Oral	39 weeks (4 weeks)	NOAEL =ND
	Major Findings: Male genital tract: Moderate unilateral seminiferous tubule degeneration in 1 male at 1000 mg/kg/day at end of recovery. Slight atrophy of prostate, moderate increased of mineralization of seminal vesicle, atrophy/hyperplasia of testes at all doses at end of dosing, Female genital tract: Moderate to marked pseudodecidual changes in females at all doses at the end of dosing and minimal uterine pseudodecidual changes in 2 females after recovery, Liver: Increased weight. Minimal bile duct/oval cell hyperplasia in all male groups and 500 and 1000 mg/kg.day groups at the end of dosing and in 1 female previously at 1000 mg/kg/day, Adrenal cortex: Increased weight. Minimal to slight hypertrophy at all dose groups.			

Genotoxicity

Abiraterone acetate and abiraterone were investigated for their potential to induce point and/or gene mutations and chromosome aberrations in several *in vitro* and *in vivo* test systems, including the Ames reverse mutation assay, the *in vitro* chromosome aberration test, and the *in vivo* rat micronucleus test. In all studies, abiraterone acetate and abiraterone were not mutagenic in either *in vitro* or *in vivo* test systems (data not shown).

Carcinogenicity

No studies were submitted (see discussion on non-clinical aspects).

Reproduction Toxicity

No relevant studies were submitted (see discussion on non clinical aspects). The general toxicology studies provide relevant information to assess the effect on reproductive organs. In these studies, circulating testosterone levels were reduced significantly. As such, reproductive organ changes were observed, including reduction in organ weight, morphological and/or histopathological changes. All changes showed complete or partial reversibility. The reproductive organ changes are consistent with the pharmacology of abiraterone acetate/ abiraterone.

Toxicokinetic data

The toxicokinetics of abiraterone acetate were evaluated in the single and repeated-dose studies in mice, rats and monkeys. A comparison of interspecies toxicokinetic parameters is shown in the following table.

Table 3: Abiraterone exposure in male animals relative to man

Species	Dose (mg/kg)	AUC (ng.h/ml)	Exposure ratio
Rat (26-week)	50 150 400	1.132 2.220 5.586	1.14 2.24 5.63
Rat-MTD (13-week)	250	1.770	1.78
Monkeys (39-week)	250 500 1000	610 1.139 2.095	0.61 1.15 2.11
Monkeys[a]	2000	1.604	1.62
Man[b]	1 g	993	

[a] Data at highest dose in 13-week toxicity study in the male monkey. MTD in monkey exceeded 2,000 mg/kg/day
[b] Exposure ratio calculated based on total drug AUC values and a human $AUC_{0\text{-}24h}$ of 993 ng.h/ml (Day 1 of Cycle 2) at an abiraterone acetate dose of 1 g/day plus prednisone at 5 mg twice daily (N=33, Study COU-AA-006).

Local Tolerance

The oral route is the intended route of abiraterone acetate administration in patients with advanced metastatic prostate cancer. A gastric irritation study was performed in the mouse after a single oral dose (see safety pharmacology). No other local tolerance studies were submitted. All toxicology studies with abiraterone acetate were performed via oral (gavage) administration and no toxicity in the gastrointestinal tract was observed.

Other toxicity studies

Several impurities were present at low concentrations in one or more of the drug substance batches tested in the single- and repeat-dose toxicity studies and in genotoxicity studies. Specific studies were submitted which aimed to evaluate the potential toxicity of abiraterone acetate when spiked with these impurities, i.e. a 28-day repeated dose oral toxicity study in the rat, an *in vitro* bacterial reverse mutation (Ames) test and an *in vitro* chromosome aberration test. In addition, an Ames test was conducted with (pure) impurities having a structural alert. The repeat-dose toxicity showed similar findings as seen at the same dose without impurities. Genotoxicity assays were negative with the exception of one. The relevant impurity is monitored throughout the synthesis process and specified below the threshold of toxicological concern (data not shown).

2.3.5. Ecotoxicity/environmental risk assessment

Results of submitted studies to evaluate the environmental risk from abiraterone acetate are summarised in the following table.

Table 4: 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 or …	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 = 0,47 microg/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)	0,018	µg/L			> 0.01 threshold (Y)
Other concerns (e.g. chemical class)					(Y/N)
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*	OECD 210	NOEC	1.1	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, 0,13 microg/L) 576 (for high conc, 1,3 microg/L	L/kg	%lipids: Percent lipids at steady 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	OECD 216	%effect	250	mg/kg	The nitrate

Transformation Test					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	See comments in conclusion section
Collembola, Reproduction Test	ISO 11267	NOEC	1000 for mortality; 500 for reproduction	mg/kg	
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius*

In the context of the obligation of the MAH to take due account of technical and scientific progress, the CHMP recommends the following points for further investigation:

The Applicant should submit the results of the proposed extended partial life cycle study with fathead minnow (Pimephales promelas) to assess the specific mode of action of abiraterone acetate according to the OECD recommendations for endocrine disrupting substances as soon as available.

2.3.6. Discussion and conclusion on the non-clinical aspects

In vitro data demonstrate that abiraterone selectively and irreversibly inhibits CYP17, a key enzyme in androgen biosynthesis. At doses of 39.2-196 mg/kg/day that are well tolerated in rodents, abiraterone acetate was shown to suppress circulating androgen levels, decrease the growth of androgen dependent organs and inhibit the growth of human mCRPC xenograft tumors in castrated mice. Abiraterone sulphate and *N*-oxide abiraterone sulphate exhibited weak pharmacological activity (CYP17 inhibition) in human adrenocortical carcinoma cell lines, but the relevance of this finding *in vivo* is uncertain as sulphates are generally excluded by cell membranes.

No studies were performed to investigate the secondary pharmacodynamics of abiraterone acetate as, due to the selectivity and mechanism of action of abiraterone acetate in inhibiting CYP17, no off-target effects were observed in nonclinical studies. Most effects observed for abiraterone acetate appear to be related to androgen deprivation. These effects are well characterized by extensive literature on androgen physiology in nonclinical studies. Pharmacodynamic drug-drug interaction (DDI) studies have not been submitted. However, human DDI (PK) studies were part of the clinical development plan.

In *in vitro* and *in vivo* safety pharmacology studies, abiraterone acetate and abiraterone (*in vitro* hERG) had no relevant effects on CNS and cardiovascular systems and produced no gastric irritation at exposures exceeding the therapeutic exposure. Regarding the respiratory system, only non-specific changes in tidal volume were observed which did not occur in a dose-dependent manner.

Regarding pharmacokinetics, after oral dosing abiraterone acetate was rapidly converted to abiraterone in all species studied. Peak plasma concentrations of abiraterone were rapidly reached in all species after single and repeated dosing and plasma concentrations of abiraterone increased with

increasing dose levels of abiraterone acetate, but less than dose-proportional. Abiraterone acetate related RA was rapidly and widely distributed to almost all investigated tissues. Abiraterone sulphate exceeded human exposure in both rat and dog and *N*-oxide abiraterone sulphate approximated human exposure in the (male) monkey and was about 20% of the human exposure in rats. Abiraterone (acetate) strongly inhibited CYP1A2 and CYP2D6 *in vitro*.

One target organ of toxicity after repeated treatment with abiraterone acetate was the liver, as evidenced by increased liver weight, hepatocellular hypertrophy, bile duct/oval cell hyperplasia and associated increases in ALP, total bilirubin and to a lesser extent GGT (rat only). Biliary changes were not consistently observed in all studies and changes were partially to fully reversible. The mechanism underlying the hepatic changes reported in the rat and monkey repeated dose studies is currently being investigated in a 2-year rat carcinogenicity study, initiated in July 2010, and will be investigated in a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse both of which are being/will be conducted as an additional Pharmacovigilance activity (see Table 27).

In rats, cataracts were seen ophthalmologically in a dose-dependent manner at the end of the 26-week treatment period without evidence of reversibility. The mechanism was unclear, although a species-specific effect cannot be excluded since cataract was not observed in monkeys. The issue of cataract formation in the rat will also be followed up in the 2-year rat and the 6-month carcinogenicity studies mentioned above.

Carcinogenicity, developmental or reproductive toxicology studies were not conducted with abiraterone acetate in line with available guidance [ICH S9 (EMEA/CHMP/ICH/646107/2008)] stipulating that such studies are generally not required, with the exception of embryofoetal toxicity studies which are specifically not required for substances belonging to a class that has been well characterized as causing developmental toxicity which is the case for abiraterone. Thus, in all animal toxicity studies, circulating testosterone levels were significantly reduced. As a result, reduction in organ weights and morphological and/or histopathological changes in the reproductive organs, and the adrenal, pituitary and mammary glands were observed. All changes showed complete or partial reversibility. The changes in the reproductive organs and androgen-sensitive organs are consistent with the pharmacology of abiraterone. All treatment-related hormonal changes reversed or were shown to be resolving after a 4-week recovery period. Abiraterone is contraindicated in pregnancy.

Aside from reproductive organ changes seen in all animal toxicology studies, non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity. Carcinogenicity studies were not conducted.

The Environmental Risk of Abiraterone acetate has been assessed and it is concluded that abiraterone acetate is not a PB substance but it is T substance.

The CHMP considers the following measures necessary to address the non clinical issues:

The Applicant should submit the results of the ongoing 2-year rat carcinogenicity study and of a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse, accompanied by an expert report if any evidence of hepatic neoplasia and/or eye toxicity is reported (see Pharmacovigilance section).

The Applicant should submit the results of the proposed extended partial life cycle study with fathead minnow (Pimephales promelas) to assess the specific mode of action of abiraterone acetate according to the OECD recommendations for endocrine disrupting substances as soon as available.

2.4. Clinical aspects

2.4.1. Introduction

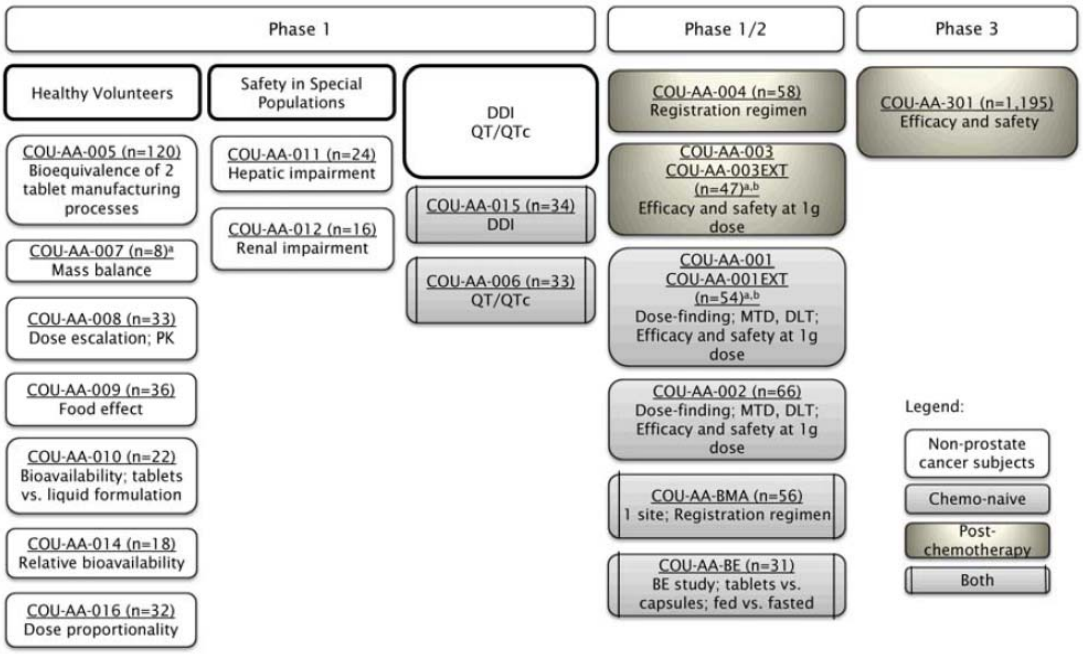
The application underwent accelerated assessment as it was considered of major interest from the point of view of public health and in particular from the view point of therapeutic innovation. The CHMP accepted the Applicant's request for accelerated assessment on the grounds of the poor prognosis of the target population and the high unmet medical need, the novel mechanism of action of the medicinal product which has the potential to offer an alternative therapeutic option and, finally, the adequacy/ completeness of the proposed data package which could allow the application to be assessed under an accelerated timetable.

The population included in the pivotal trial COU-AA-301 comprised metastatic prostate cancer patients resistant to castration therapy whose disease had progressed on or after docetaxel-based chemotherapy. As a result, although the Applicant sought an indication in relevant patients having received chemotherapy containing a(ny) taxane, claiming that docetaxel is the standard of care and that abiraterone is expected to provide analogous clinical benefit irrespective of the type of prior taxane-based chemotherapy, the finally approved indication reflected the patient population of the pivotal trial and it was restricted to men whose disease had progressed on or after docetaxel-based chemotherapy.

In a Scientific Advice procedure pertaining to clinical efficacy and safety related to study COU-AA-301, the CHMP concurred that the primary and secondary endpoints were appropriate and in accordance with available guidance, that the proposed statistical analysis plan, target population and choice of comparator were acceptable and that the safety database would be adequate to support a Marketing Authorisation Application but safety follow-up might be requested.

- Tabular overview of clinical studies

Figure 4: Clinical studies supporting the Zytiga MAA



[a]Capsules were used
[b]Patients enrolled in studies COU-AA-001 and COU-AA-003 had the opportunity to enrol in extension studies

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. Moreover, 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.

Certain sites of the pivotal trial have undergone inspections by EU regulatory authorities prior to the start of the assessment of the Marketing Authorisation Application for Zytiga. There were no critical findings. No non-compliance issues or specific GCP triggers have been raised during the assessment of the submitted dossier and further GCP inspections were not considered necessary for this Application.

2.4.2. Pharmacokinetics

The pharmacokinetics of abiraterone was evaluated in 9 Phase I studies in healthy male subjects (COU-AA-010; COU-AA-005; COU-AA-008; COU-AA-016; COU-AA-009; COU-AA-007; COU-AA-014; COU-AA-011; COU-AA-012); 2 Phase I studies in patients with mCRPC (COU-AA-015; COU-AA-006), and in 1 phase III study (COU- AA-001) in patients with mCRPC. Moreover, a population PK model was developed based on data from 256 patients from 3 Phase I studies (Studies COU-AA-008, COU-AA-009, and COU-AA-014), 1 Phase IB study (Study COU-AA-006) and 1 Phase III study (Study COU-AA-301).

Plasma pharmacokinetic parameters were calculated based on actual pharmacokinetic blood sampling times, relative to dosing, using log-transformed data and conventional non-compartmental methods. Subjects that had sufficient data for pharmacokinetic parameter estimations were included in the pharmacokinetic analysis. The exception is the population analysis which used a nonlinear mixed-effects approach to estimate the pharmacokinetic parameters based on sparse sampling data.

Bioanalytical methods used for clinical studies with pharmacokinetic measurements included different liquid chromatography-tandem mass spectrometry (LC-MS/MS) methods intended to measure abiraterone and its pro-drug, abiraterone acetate, in plasma. Non-chiral bioanalytical methods were developed as inter-conversion is not expected. Abiraterone acetate was detected in only a fraction of the total number of collected samples. Therefore all PK analysis has been carried out on abiraterone.

Absorption

Abiraterone is rapidly absorbed. The absolutely bioavailability is not known, although the bioavailability from the commercial tablet in the fasted state is unlikely to be higher than 10%, as the bioavailability can be increased by 10-fold in the fed state. Bioequivalence has been demonstrated between the formulation used in the clinical studies and the commercial formulation. Abiraterone acetate tablets intended for commercial process were shown to be bioequivalent to abiraterone acetate tablets used in clinical trials.

Across all studies, the mean C_{max}, AUC, and t1/2 after a single 1 g dose of abiraterone acetate under fasting conditions in healthy male subjects were approximately 93.5 ng/ml, 503 ng*h/ml, and 15 hours, respectively. The peak concentration of abiraterone was generally reached at 2 hours after dosing. Systemic exposure to abiraterone generally increased linearly with dose following single-dose administration of abiraterone acetate tablets at 250 mg, 500 mg, 750 mg, and 1 g doses under fasting conditions to healthy male subjects. The pharmacokinetics of abiraterone was dose-proportional for the 750 mg and 1 g dose levels.

In patients with mCRPC, the mean C_{max} and AUC of abiraterone after a single dose of 1 g abiraterone acetate under fasting conditions was approximately 182 ng/ml and 675 ng*h/ml, respectively. In these patients, after 28 days of continuous daily dosing, mean C_{max} and AUC were increased approximately 2.0- and 2.2-fold to 226 ng/ml and 993 ng*h/ml, respectively.

The estimated accumulation ratio (2.0 for C_{max}, 2.2 for AUC) is compatible with an effective half-life in a multiple-dose setting of 24 to 28 hours, higher than that estimated from single-dose studies under fasting conditions in healthy subjects. Overall, the exposure to abiraterone in patients with mCRPC was higher than in healthy male subjects.

A standardized high fat meal increased abiraterone systemic exposure by approximately 17- and 10-fold for C_{max} and $AUC_{0-\infty}$, while a low-fat meal increased abiraterone systemic exposure by approximately 7- and 5-fold for $AUC_{0-\infty}$ and C_{max} when compared to fasting subjects.

Distribution

The plasma protein binding of abiraterone at therapeutic concentrations was high and in the order of 98.8% to 99.9%. The apparent central volume of distribution was approximately 5630 L. The mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ values for total radioactivity in plasma were higher than those observed for total radioactivity in whole blood. The mean whole blood to plasma $AUC_{0-\infty}$ ratio was 0.523. This value indicates that the radioactivity associated with abiraterone and its metabolites is preferentially retained in the plasma component of blood.

Metabolism

Hydrolysis of abiraterone acetate to abiraterone is mediated by non-identified esterases, is not CYP-mediated, and is thought to occur mainly in the liver. Cleavage of the ester within gastrointestinal tissue during the absorption process cannot be excluded.

Abiraterone, the active metabolite responsible for the primary pharmacodynamic effect, is subsequently extensively metabolized. The primary metabolic pathways for abiraterone include sulfation and N-oxidation, as well as hydroxylation, dehydration, and glucuronidation pathways.

Direct sulfation of abiraterone and the formation of an N-oxide sulphate are the most prominent pathways of metabolism. The systemic exposure to metabolites is far greater than that to abiraterone. Following a single dose of radioactive abiraterone acetate under fasting conditions, the plasma AUC_{inf} of total radioactivity was approximately 400-fold higher than that of abiraterone. The 2 predominant metabolites in plasma, abiraterone sulphate and N-oxide of abiraterone sulphate, were both present at exposure concentrations at least 100 times higher than abiraterone based on a comparison of AUC_{0-8h} of the metabolites to AUC_{last} of abiraterone. The systemic exposure to 9 other quantified metabolites was similar or up to 4-fold higher than that of abiraterone.

Metabolism via SULT2A1 is the major pathway in vitro. However, based on excretion data, it cannot be concluded that the SULT2A pathway is the major pathway in vivo. In vivo abiraterone is a substrate of CYP3A4 and CYP3A4 is inhibited in vitro by abiraterone with moderate potency. It is unclear whether the observed metabolites are formed via CYP3A4. Additionally, Phase II glucuronidated metabolites are formed mainly by UDP-glucuronosyl transferase (UGT) 1A4 and to a lesser extent by UGT1A3.

In vitro, abiraterone was shown to inhibit the hepatic drug-metabolizing enzymes CYP1A2 and CYP2D6. From *in vitro* studies, clinically relevant effects on compounds transported by P-gp are not expected. The effects of abiraterone acetate on a single dose of the CYP1A2 substrate theophylline

showed no increase in systemic exposure of theophylline. The effect of abiraterone acetate on a single dose of the CYP2D6 substrate dextromethorphan showed that the systemic exposure of dextromethorphan increased.

Elimination

Following oral administration of ^{14}C-abiraterone acetate, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively). After oral administration of abiraterone acetate, with or without food, systemic concentrations of abiraterone acetate were very low, generally below 0.2 ng/mL.

Dose proportionality and time dependencies

Systemic exposure to abiraterone generally increased with increase in doses of abiraterone acetate from 250 mg to 1,000 mg. Abiraterone mean t1/2 and median t_{max} values appeared to be independent of dose.

The results of the PPK analysis indicated that the abiraterone PK parameters were time invariant over the period for which the PK data were available. No trend in the population or individual weighted residuals versus time (up to 3000 h) was seen in the structural model.

Although the mean pharmacokinetic parameters were fairly consistent across studies, the inter-individual variability in disposition of abiraterone was high. In healthy subjects, between-subject variability ranged from 32.7% to 119.8% for Cmax and from 40.5% to 140.6% for $AUC_{0-\infty}$.

Special populations

Systemic exposure to abiraterone after a single oral 1 g dose did not increase in 8 non-cancer patients with end-stage renal disease on dialysis. In these patients, clearance was comparable to the clearance in 8 normal renal function healthy subjects. Based on the results from the end-stage renal disease cohort, patients with mild or moderate renal were not studied.

In subjects without cancer and with mild hepatic impairment (Child-Pugh A) no relevant change in systemic exposure to abiraterone was observed compared to healthy matched control subjects (11% of AUC increase in mild pre-existing hepatic impairment). The systemic exposure (AUC) to abiraterone following a single 1 g dose of abiraterone acetate in the fasting state increased by approximately 260% in subjects without cancer and with pre-existing moderate hepatic impairment (Child-Pugh B). The mean half-life of abiraterone was prolonged to approximately 17.7 h in subjects with mild hepatic impairment and to approximately 18.6 h in subjects with moderate hepatic impairment.

All clinical study information thus far is derived from male subjects. The subjects in the index dataset of the PPK analysis had a median age of 42 years, with a range of 19 to 85 years. No formal clinical studies have evaluated the effect of age on the pharmacokinetics of abiraterone acetate. Abiraterone acetate has not been tested in paediatric subjects.

The potential effects of race/ethnicity on the pharmacokinetics of abiraterone were not formally investigated. The vast majority of subjects enrolled in the clinical studies were white males (>75%).

The subjects in the index dataset of the PPK analysis had a median weight of 81 kg, and ranged from 56 to 135 kg. Weight was not a significant covariate in the PPK analysis and thus, it does not justify a dose adjustment.

Pharmacokinetic interaction studies

The Applicant submitted the results of an *in vivo* drug-drug interaction study of abiraterone acetate plus prednisone with dextromethorphan (substrate of CYP2D6 metabolism) and theophylline (substrate of CYP1A2 metabolism). This was based on the results of the *in vitro* studies which could not preclude interaction based on the potent inhibitory effect of abiraterone on the two CYP isoforms.

Mean systemic exposure to dextromethorphan was approximately double when dextromethorphan was co-administered with abiraterone acetate compared to when dextromethorphan was administered alone. Mean systemic exposure to theophylline was comparable when theophylline was co-administered with abiraterone acetate compared to when theophylline was given alone (data not shown).

Pharmacokinetics using human biomaterials

The major findings of *in vitro* interaction studies using human biomaterials have been described in the non-clinical section together with results of similar studies using biomaterials of animal origin.

2.4.3. Pharmacodynamics

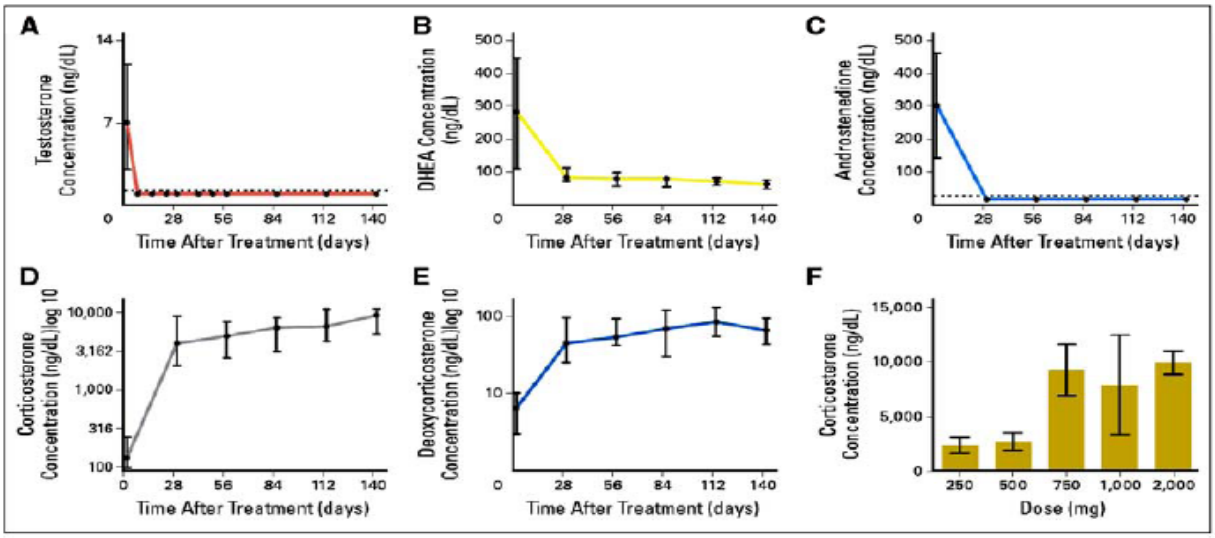
Mechanism of action

The inhibitory effect of abiraterone on human CYP17 activity has been demonstrated by several investigators. Using human testicular microsomes, Jarman *et al.* (1998) demonstrated that the concentration of abiraterone needed to irreversibly inhibit 50% of CYP17 activity (IC_{50}) was 4 nM. This observation was confirmed by other investigators who determined an approximate IC_{50} of 73 nM in human testicular microsomes (Haidar *et al.*, 2001, 2003). They also demonstrated that the prodrug, abiraterone acetate, can inhibit human CYP17 but was less potent than abiraterone producing an IC_{50} of 110 nM.

Primary and Secondary pharmacology

In terms of biomarkers for pharmacodynamic activity, the use of Prostate Specific Antigen (PSA) as a biomarker in determining activity of anti-cancer agents in prostate cancer patients is well recognised. Total testosterone and other androgens were also assessed as indirect pharmacodynamic markers and were regularly monitored as part of clinical laboratory assessments in healthy subject studies. In addition, 2 steroids upstream of CYP17 (deoxycorticosterone and corticosterone) increased following administration of abiraterone. Treatment with abiraterone acetate resulted in significant suppression of testosterone, DHEA, and androstenedione. At every time point on treatment and at every dose of abiraterone acetate, concentrations of testosterone and androstenedione in all subjects were less than the LLOQ of the assay used (androstenedione: 2 ng/dl, testosterone: 1 ng/dl).

Figure 5: Suppression of androgens and increase in mineralocorticoids by abiraterone



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With regard to PK/PD relationship, a sequential joint PK-PSA-survival modeling approach was used to describe the relationship between drug exposure and survival following intake of the study drug with PSA pharmacodynamics as an intermediate marker. This joint exposure-PSA-outcome model was factored as 2 sequential models:

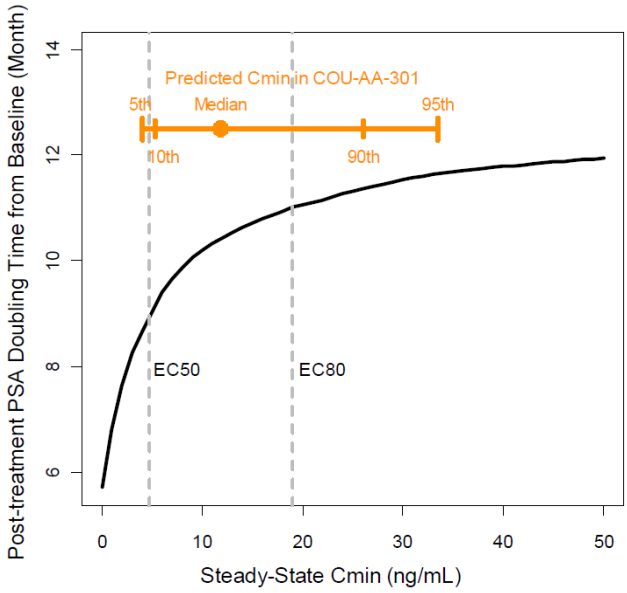
(1) an exposure-PSA model was used to describe the relationship between abiraterone exposure and PSA levels;

(2) a second model was used to describe the association between PSA dynamics and clinical outcome, overall survival.

The models were developed using the data from the Phase 3 Study COU-AA-301 only. Analyses were based on patients who received at least 1 dose of abiraterone acetate or placebo, and a minimum of 1 PSA measurement per patient was available (N=1,184). The primary efficacy variable in the study, overall survival, namely time to death and longitudinal profiles of PSA in COU-AA-301, were modeled.

Exposure to abiraterone significantly increased the rate of PSA reduction, and the exposure-response in PSA dynamics was best described by an E_{max} function of steady-state C_{min} with an EC_{50} of 4.75 ng/mL and a maximum effect of 2.72 times that of placebo effect after adjusting for baseline LDH and testosterone levels. The individual parameters from this model were used for the subsequent PSA-Survival modeling.

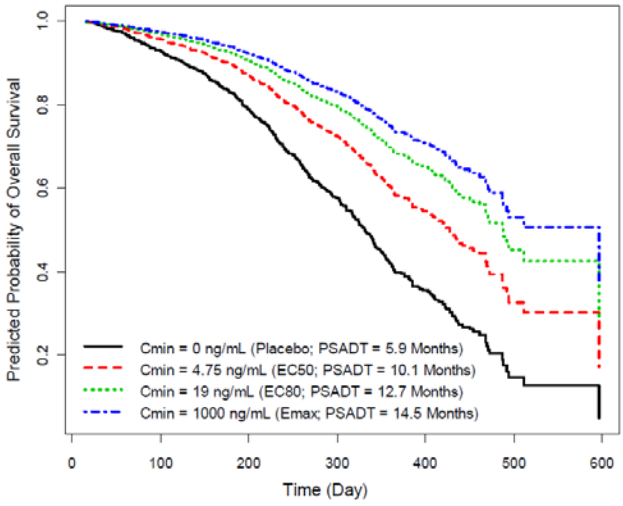
Figure 6: Simulated Post-treatment PSA Doubling Time (PSADT) from Baseline at Different Steady-state C_{min} Concentrations



The main objective of the PSA-Survival modeling was to explore the relationship between PSA dynamics and overall survival (relative risk of death), and to link overall survival to drug exposure through PSA dynamics following treatment.

The survival model demonstrated that PSA dynamics was an intermediate biomarker of overall survival in the study population. The predicted post-treatment PSADT could explain 20% variability in survival time alone in a univariate analysis and 13% survival variability after adjusting for other baseline covariates in the final multivariate model.

Figure 7: Predicted Probability of Overall Survival at Different Exposure (C_{min}) Levels and Corresponding Post-treatment PSA Doubling Times Based on the TGI Model



In addition to model-predicted post-treatment PSADT, low baseline body weight, high baseline ECOG score, low baseline albumin, high baseline lactate dehydrogenase, short time since prior chemotherapy, and low baseline DHEA levels were also identified as statistically significant prognostic factors.

A conventional sequential PK/PD approach was used to build the PPK/PD model (post-hoc PK data from the PPK + longitudinal PSA dynamics model + PSA survival model). The first two models were

developed in NONMEM VI. The last one is a statistical model based on Cox PH models. A tumour growth inhibition model (TGI) was used to link the drug exposure to tumor inhibition, in this case PSA reduction. No biases on the execution of the development of the PPK/PD study were detected. Inspection of the ranges and correlations between covariates showed the suitability of these data to be evaluated in the study.

Later on, the final PPK/PD model was validated (internal validation: visual predictive check (VPC) and numerical predictive check (NPC)) to confirm the internal robustness of the model. Finally, Monte Carlo simulations were performed to validate the sequential exposure-PSA-survival model. However, an external validation with new individuals was not performed.

Finally, in terms of secondary pharmacology, a QT/QTc study was submitted which employed an intensive QT design in patients, as opposed to a through design in healthy volunteers. Patients received 1000 mg abiraterone acetate and underwent time-matched 12-lead ECG and pharmacokinetic sample collection. The primary endpoint was the mean maximal change in QTc from baseline. ECG parameters were evaluated in conjunction with the Pharmacokinetic-Pharmacodynamic findings. Linear mixed models were applied to explore the relationship between plasma concentrations and change in QTcF. The average values from the 3 readings were used in the analysis.

Thirty three evaluable patients were enrolled, treated and analyzed for QTc, safety, and pharmacokinetics. Heart rate did not show evidence of any clinically significant change post abiraterone acetate administration. The mean QTcF change ranged from -3.4 to 2.3 msecs on Cycle 1 Day 1 to -10.1 to -1.7 msecs on Cycle 2 Day 1. The upper limit of the 90% CI of the mean baseline corrected QTcF change at each post-dose time point was below 10 msecs for both Cycle 1 Day 1 (maximum of upper limits = 5.4 msecs) and Cycle 2 Day 1 (maximum of upper limits = 2.4 msecs). The number and percentage of patients with at least 1 QTcF value > 450 msecs were 9 (28.2%) and 7 (21.2%) on Cycle 1 Day 1 and Cycle 2 Day 1 respectively compared to 11 (33.3%) on baseline. 2 patients experienced one instance each of a QTcF increase of >30 msecs but <60 msecs post-dose (35.7 msecs & 34.0 msecs). None of the patients experienced an increase in QTcF of >60 msecs. No patient had any instances of a QTcF of >480 msecs or 500msecs.

2.4.4. Discussion and conclusions on clinical pharmacology

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

Following oral administration of abiraterone acetate in the fasting state, the time to reach maximum plasma abiraterone concentration is approximately 2 hours.Administration of abiraterone acetate with food, compared with administration in a fasted state, results in up to a 10-fold (AUC) and up to a 17-fold (C_{max}**)** increase in mean systemic exposure of abiraterone, depending on the fat content of the meal. Given the normal variation in the content and composition of meals, taking ZYTIGA with meals has the potential to result in highly variable exposures. Therefore, ZYTIGA must not be taken with food. It should be taken at least two hours after eating and no food should be eaten for at least one hour after taking ZYTIGA. The tablets should be swallowed whole with water.

The plasma protein binding of ^{14}C-abiraterone in human plasma is 99.8%. The apparent volume of distribution is approximately 5,630 L, suggesting that abiraterone extensively distributes to peripheral tissues. Surprisingly for a drug with such a high plasma protein binding, values of apparent volume of distribution were extremely large. The low bioavailability and high variability

might partially explain this finding. Moreover, drug binding at the tissue level may play a role in this finding as well.

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

The mean half-life of abiraterone in plasma is approximately 15 hours based on data from healthy subjects. Following oral administration of ^{14}C-abiraterone acetate 1000 mg, approximately 88% of the radioactive dose is recovered in faeces and approximately 5% in urine. The major compounds present in faeces are unchanged abiraterone acetate and abiraterone (approximately 55% and 22% of the administered dose, respectively).

The pharmacokinetics of abiraterone acetate was examined in subjects with pre-existing mild or moderate hepatic impairment (Child-Pugh class A and B, respectively) and in healthy control subjects. Systemic exposure to abiraterone after a single oral 1000 mg dose increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively. The mean half-life of abiraterone is prolonged to approximately 18 hours in subjects with mild hepatic impairment and to approximately 19 hours in subjects with moderate hepatic impairmentThe pharmacokinetics of abiraterone acetate was compared in patients with end-stage renal disease on a stable haemodialysis schedule versus matched control subjects with normal renal function. Systemic exposure to abiraterone after a single oral 1000 mg dose did not increase in subjects with end-stage renal disease on dialysis.

In a study to determine the effects of abiraterone acetate (plus prednisone) on a single dose of the CYP2D6 substrate dextromethorphan, the systemic exposure (AUC) of dextromethorphan was increased approximately 2.9 fold. The AUC_{24} for dextrorphan, the active metabolite of dextromethorphan, increased approximately 33%.

Caution is advised when Zytiga is administered with medicinal products activated by or metabolised by CYP2D6, particularly with medicinal productss 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, flecanide, codeine, oxycodone and tramadol (the latter three products requiring CYP2D6 to form their active analgesic metabolites).

Based on *in vitro* data, Zytiga is a substrate of CYP3A4. The effects of strong CYP3A4 inhibitors (e.g., ketoconazole, itraconazole, clarithromycin, atazanavir, nefazodone, saquinavir, telithromycin, ritonavir, indinavir, nelfinavir, voriconazole) or inducers (e.g., phenytoin, carbamazepine, rifampin, rifabutin, rifapentine, phenobarbital) on the pharmacokinetics of abiraterone have not been evaluated, *in vivo*. Avoid, or use with caution, strong inhibitors and inducers of CYP3A4 during treatment. Moreover, an interaction study aimed to assess the effect of potent inducers and inhibitors of CYP3A4 on abiraterone pharmacokinetics is underway.

As no Dose Limiting Toxicities (DLTs) were observed in early dose-finding studies even at the 2000 mg/day dose (see Dose-response studies below), the choice of the 1000 mg/day dose that was taken forward in clinical development was questioned. However, in the early clinical development phase, no significant difference in concentrations of corticosterone and deoxycorticosterone were observed at doses higher than 750 mg (e.g. see panel F, Figure 5), suggesting a maximum inhibition

of CYP17 enzyme activity at this dose. PK/PD modelling demonstrates that 90% of patients in the Phase 3 study would have achieved steady-state C_{min} greater than the estimated EC_{50} value (see Figure 6). Therefore, the selection of the 1000 mg dose was endorsed.

Finally, the lack of an external validation set for the population PK/PD model was considered to limit the validity of the model which should only be considered for descriptive purposes. The implications of the model for the interpretation of the results into clinically relevant information are limited.

2.5. Clinical efficacy

Three studies were submitted in support of the use of abiraterone acetate in the claimed indication, i.e. in men with metastatic advanced castration-resistant prostate cancer (mCRPC) whose disease has progressed on or after docetaxel-based chemotherapy:

- Pivotal Study COU-AA-301: Phase 3 double-blind randomised trial (2:1) of abiraterone acetate (tablets) plus low-dose prednisone or prednisolone versus placebo plus low-dose glucocorticoids in patients with mCRPC whose disease had progressed on or after docetaxel-based chemotherapy (ITT population=1,195 patients); primary endpoint : overall survival;
- Study COU-AA-003 and COU-AA-003EXT: Phase 2 studies of abiraterone acetate (capsules) in patients with mCRPC whose disease had progressed on or after taxane-based chemotherapy (n=47 and 6 patients, respectively); primary endpoint: antitumour effect as measured by PSA response according to PSA WG criteria;
- Study COU-AA-004: Phase 2 study of abiraterone acetate (tablets) plus low-dose glucocorticoids in patients with mCRPC whose disease had progressed on or after taxane-based chemotherapy (n=58 patients); primary endpoint: antitumour effect (not otherwise specified in study design) and safety;

Further evidence of the efficacy of abiraterone acetate in mCRPC is derived from four additional Phase 1/2 studies testing abiraterone acetate in chemotherapy-naïve patients (Studies COU-AA-001, COU-AA-001EXT, and COU-AA-002) or evaluating the effect of food on abiraterone (tablets and capsules) pharmacokinetics in patients with or without prior chemotherapy (COU-AA-BE).

2.5.1. Dose response studies

Two Phase I dose-finding studies (COU-AA-001/EXT and COU-AA-002), both conducted in chemotherapy naïve mCRPC patients, investigated the pharmacokinetics, safety and tolerability of abiraterone acetate.

COU-AA-001/EXT

Study COU-AA-001 was an open label single arm Phase I/II study designed to evaluate the safety and efficacy of abiraterone acetate in chemotherapy-naïve hormone refractory prostate cancer patients who had failed LHRH analogue and/or antiandrogen therapy. The primary objectives of the study were to evaluate the safety, tolerability and recommended dose of abiraterone acetate and to evaluate the activity of abiraterone acetate at the recommended dose.

The starting dose for the dose escalation phase was 250 mg. The doses tested were 250, 500, 750, 1000 and 2000 mg/day. If <33% of patients (e.g. 0 of 3) experienced a Dose Limiting Toxicity (DLT), then the dose was defined as tolerable and dose escalation continued. If a DLT was observed in 33%-50% (e.g. 1 of 3) of patients in the first cycle, then the cohort was expanded to include at least 3 more patients (6 patients in total). If a DLT was observed in >50% (e.g. 2 of 3) of patients in the first cycle, this dose was considered above the MTD and dose escalation was stopped.

In the Phase II, the primary efficacy endpoint was confirmed objective PSA response, evaluated according to the PSAWG guidelines. Secondary endpoints were objective response (RECIST), duration of response for PSA and RECIST responses and time to disease progression.

18 patients were enrolled in Phase I and 36 patients were enrolled in Phase II. No DLTs were observed in patients in any of the dose cohorts in Phase I. In terms of efficacy, 60% of the patients had confirmed response (decline of ≥50% from baseline) with a median 330 days (95% CI: 197, 530) to PSA progression. 8 (19.0%) patients showed partial tumour response, 28 (66.7%) patients had stable disease and 2 (4.8%) patients had progressive disease.

COU-AA-002

Study COU-AA-002 was a Phase I/II, multicentre, open-label study investigating abiraterone acetate treatment in patients with CRPC who had had no previous chemotherapy for prostate cancer. The primary objectives were to determine the maximum tolerated dose (MTD) of abiraterone acetate and to assess the proportion of patients achieving a ≥50% prostate specific antigen (PSA) decline during therapy.

In the Phase I, dose escalation aimed to determine the maximum tolerated dose (MTD) and to determine the need for supplementation with corticosteroids. Planned doses were 250 mg, 500 mg, 750 mg, 1 g and 2000 mg/day. The Phase II evaluated the antitumour activity. Patients were to receive 1000 mg abiraterone acetate daily for up to 12 cycles, until disease progression or unacceptable toxicity was observed.

The planned dose for Phase II was the MTD from Phase I. However, the dose was determined to be 1000 mg/day as per Amendment 5.

Following Protocol Amendment 7 (6 October 2008), all patients were required to receive low-dose glucocorticoids such as prednisone (5 mg twice daily) or dexamethasone (0.5 mg once daily), in an effort to ameliorate mineralocorticoid side effects.

33 patients were enrolled in Phase I (dose escalation stage and pharmacokinetics) and 33 patients were enrolled in Phase II. No DLTs observed in patients in all dose cohorts in Phase I. No patients were treated at the 2000 mg/day dose level. In terms of efficacy, 58% of patients showed a confirmed PSA decline of ≥50% in the Phase I and in the Phase II 57.6% of patients achieved a confirmed maximal PSA decline of ≥50%. The median time to PSA progression was 15.9 months (477 days). In terms of tumour response, 9 (35%) patients achieved a partial response. Stable disease was seen in 12 patients (46%).

2.5.2. Main study

COU-AA-301

This was a phase 3, randomised, double-blind, placebo-controlled study of abiraterone acetate (CB7630) plus prednisone in patients with metastatic castration-resistant prostate cancer who had failed docetaxel-based chemotherapy. The study was conducted at 147 sites in the United States (U.S.), Europe, Australia, and Canada.

Methods

Study Participants

Main inclusion criteria:

- Men of at least 18 years of age
- Histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology and medically or surgically castrated
- 1 but not more than 2 different cytotoxic chemotherapy regimens for mCRPC (one of which must have contained docetaxel)
- Investigator documented prostate cancer progression (PSA progression according to PSAWG criteria or radiographic progression in soft tissue or bone with or without PSA progression)
- Ongoing androgen deprivation with serum testosterone <50 ng/dl (<2.0 nM)
- ECOG performance status score of 2 or less

Main exclusion criteria

- Serious or uncontrolled coexistent non-malignant disease, including active and uncontrolled infection
- Abnormal liver transaminase test concentrations
- Uncontrolled hypertension, viral hepatitis or chronic liver disease, history of pituitary or adrenal dysfunction, clinically significant heart disease, other malignancy, known brain metastasis
- Prior therapy with abiraterone, other CYP17 inhibitors, or investigational agents targeting the AR for metastatic prostate cancer or prior therapy with ketoconazole

Treatments

Eligible patients received either abiraterone acetate 1000 mg (administered as 4 x 250 mg tablets) once daily continuously or 4 placebo tablets orally once daily. Patients were dosed at least 1 hour before or 2 hours after a meal, any time up to 10 pm each day continuously. 5 mg of either prednisone or prednisolone was administered orally twice daily. Luteinizing hormone-releasing hormone (LHRH) agonists were mandatory for patients who did not undergo orchiectomy. Bisphosphonate usage was allowed if patients were receiving them prior to Day 1. Concurrent administration of other anticancer therapy, including cytotoxic, hormonal (except LHRH agonists) or immunotherapy was prohibited during the study treatment phase. Palliative radiation (1 course of involved field radiation (single or multi-fraction) to a single site was permitted.

Treatment was to be continued until disease progression, unacceptable toxicity or patient´s non-compliance or withdrawal. After discontinuation of treatment, patients were followed for disease progression and survival for up to 5 years.

Objectives

The primary objective was to demonstrate that treatment with abiraterone acetate and prednisone improves survival in patients with mCRPC whose disease had progressed on or after 1 or 2 chemotherapy regimens (including docetaxel).

Secondary objectives included evaluation of safety, functional status and symptomatology, further characterisation of the pharmacokinetics and assessment of the potential utility of circulating tumour cells (CTCs) as a surrogate for clinical benefit.

Outcomes/endpoints

The primary endpoint was Overall Survival (OS) defined as the interval from the date of randomization to the date of death from any cause. Survival follow up was to continue every 3 months for up to 60 months (5 years) after the patient's entry into the study.

The key secondary endpoints were the following:

- Time to PSA progression: The time interval from the date of randomization to the date of PSA progression as defined in the PSAWG criteria.

- Radiographic PFS: Progression-free survival based on imaging studies, i.e. the time interval from the date of randomisation to the date of the event as assessed by the investigator (radiographic disease progression or death). Radiographic progression was defined as soft tissue disease progression by modified RECIST (baseline lymph node size must be ≥2.0 cm to be considered a target lesion), or progression on bone scans with ≥2 new lesions not consistent with tumour flare, confirmed on a second scan ≥6 weeks later that shows ≥1 additional new lesion.

Non-target abnormality was to be recorded as present at baseline followed-by present/absent or increased/decreased. If no event existed, then PFS was to be censored at the last disease assessment on study. Progression-free survival of living patients with no assessment on-study and PFS of patients with no baseline assessment was to be censored at randomisation.

CT/MRI/other imaging procedures and bone scan were scheduled during screening and day 1, cycle 4, 7, 10 day 1.

- PSA Response Rate: Proportion of patients achieving a PSA decline of at least 50% according to PSAWG Criteria. PSA measurements were scheduled during screening, cycle 1 day 1, cycle 4, 7, 10 day 1, every 3 cycles beyond cycle 10 & end of study.

Other secondary endpoints included: objective response rate, pain palliation rate, time to pain progression, time to first skeletal related event, modified PFS, circulating tumour cell (CTC) response rate and functional status.

Sample size

The planned sample size of approximately 1,158 patients (772 patients: abiraterone acetate, 386 patients: placebo) provided 85% power to detect a 20% decrease in the risk of death for the abiraterone acetate-treated group (hazard ratio [HR]=0.80). This sample size was calculated by assuming the following: a median survival of 15 months for the abiraterone acetate group and a median survival of 12 months for the placebo group; a 2-tailed significance level of 0.05; an enrollment period of approximately 13 months; and a study duration of approximately 30 months to observe the required 797 total events.

One interim analysis and 1 final analysis were to be conducted after approximately 67% and 100% of the total 797 OS events had occurred, respectively. The purpose of the interim analysis was to terminate the study early if superiority was demonstrated for the abiraterone acetate group for the primary efficacy endpoint, OS.

Randomisation

The patients were randomly assigned to receive abiraterone acetate and prednisone/prednisolone or placebo and prednisone/prednisolone in a 2:1 ratio. They were stratified by the following baseline factors: Eastern Cooperative Oncology Group (ECOG) performance status score (0-1 versus 2), worst

pain over the past 24 hours on the Brief Pain Inventory - Short Form (BPI-SF) (0-3 [absent] versus 4-10 [present]), prior chemotherapy regimens (1 versus 2), and type of progression prior to study entry (PSA progression only versus radiographic progression with or without PSA progression).

Blinding (masking)

This was a double-blind study and in order to maintain the study blind, placebo was supplied as a tablet formulation matching abiraterone acetate tablets in size, color, and shape. All patients, family members, study personnel (at the study site, the Sponsor, or participating Clinical Research Organization), and members of the Independent Data Monitoring Committee (IDMC) were to remain blinded to treatment assignment until completion of the study, with certain well-justified exceptions.

Statistical methods

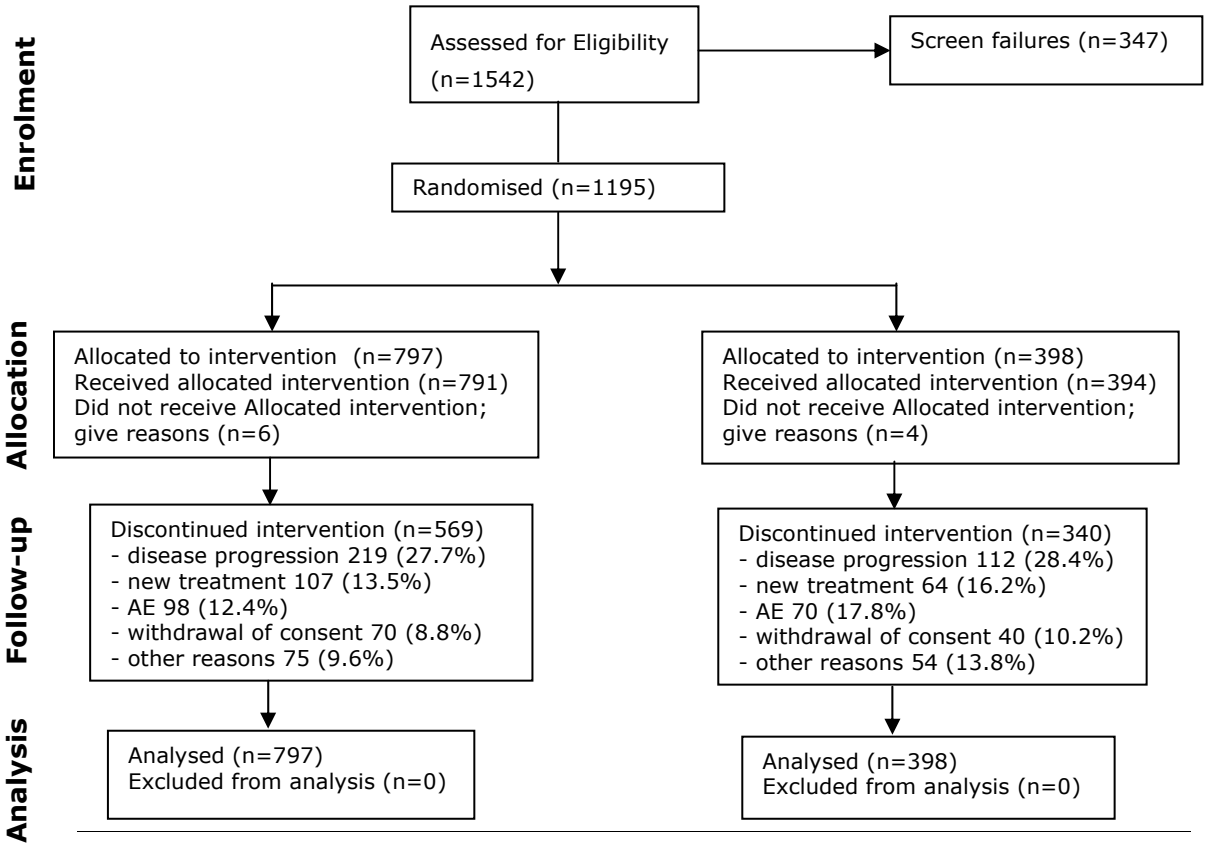
The primary endpoint (and all other time-to-event data) were analysed using the stratified log-rank test, stratified for the randomisation factors.

For the measurement of the primary endpoint, survival time of living patients was to be censored at the last date a patient was known to be alive or lost to follow up.

One interim analysis was to be conducted using group sequential design with the O'Brien-Fleming boundary after approximately 534 death events had been observed (67% of 797 total events) and the planned final analysis was to occur after 797 total deaths

Results

Participant flow



Recruitment

The first patient was enrolled on 8 May 2008 and the last one was enrolled on 28 July 2009. At the time of clinical cut-off (22 January 2010), blinded treatment was ongoing for 276 patients (222 patients (28%) in the abiraterone group and 54 (13,7%) in the placebo group).

Conduct of the study

There were three major protocol amendments after study initiation:

- Amendment 1 - text removed regarding congenital CYP17 deficiency, clarification of safety reporting, clarification of dose related event management and clarification of bone scan collection/ additional time points collection for prothrombin/thromoboplastin.
- Amendment 2 - text for guidance on dose reduction and patient management for drug related events, liver function tests (LFT), non-mineralocorticoid side effects, add section on routine monitoring of LFTs and imaging procedure revision for consistency
- Amendment 3 - recommendations made by the IDMC and provision of information to investigators allowing patients in the placebo group to receive abiraterone acetate

Protocol deviations were captured on tracking forms separate from the Clinical Report Forms (CRFs) and they were reviewed by the medical monitor.

- 15% of patients in both groups were identified as having major protocol deviations during the study
- The most common major protocol deviation was enrolment and entry criteria deviations (meeting eligibility criteria, prior use of ketoconazole), 8% of patients in the abiraterone acetate group and 9% of patients in the placebo group
- The second most common major protocol deviation was use of prohibited concurrent medications, 5% patients in the abiraterone acetate group and 4% of patients in the placebo group
- 1 patient in the abiraterone acetate group received a mixture of both abiraterone acetate and placebo during the study due to pharmacy error (assigned to abiraterone arm)

During the study, the Applicant found that the reasons for discontinuation of study treatment were not recorded consistently across study centres, particularly with respect to disease progression. To improve consistency and provide a more accurate representation of the study data, blinded data for each patient were medically reviewed and re-categorized the reasons for discontinuation accordingly.

Baseline data

Baseline demographics, baseline disease characteristics and prior therapy information are summarised in the following tables.

Table 5: Baseline demographics

	AA (N=797)	Placebo (N=398)	Total (N=1195)
Age (years)			
n	797	397	1194
< 65	232 (29.1%)	119 (30.0%)	351 (29.4%)
65-69	173 (21.7%)	87 (21.9%)	260 (21.8%)
70-74	172 (21.6%)	80 (20.2%)	252 (21.1%)
≥ 75	220 (27.6%)	111 (28.0%)	331 (27.7%)
Mean (SD)	69.1 (8.40)	68.9 (8.61)	69.0 (8.46)
Median	69.0	69.0	69.0
Range	(42, 95)	(39, 90)	(39, 95)
Sex			
n	797	398	1195
Male	797 (100.0%)	398 (100.0%)	1195 (100.0%)
Ethnicity			
n	796	397	1193
Hispanic or Latino	39 (4.9%)	7 (1.8%)	46 (3.9%)
Not Hispanic or Latino	757 (95.1%)	390 (98.2%)	1147 (96.1%)
Race			
n	796	397	1193
White	743 (93.3%)	368 (92.7%)	1111 (93.1%)
Black	28 (3.5%)	15 (3.8%)	43 (3.6%)
Asian	11 (1.4%)	9 (2.3%)	20 (1.7%)

Table 6: Baseline disease characteristics and prior therapy

	AA (N=797)	Placebo (N=398)	Total (N=1195)
Time since initial diagnosis to first dose (days)			
n	791	394	1185
Mean (SD)	2610.9 (1630.21)	2510.1 (1712.36)	2577.4 (1657.93)
Median	2303.0	1928.0	2198.0
Range	(175, 9129)	(61, 8996)	(61, 9129)
PSA at initial diagnosis (ng/mL)			
n	619	311	930
Mean (SD)	207.60 (835.658)	255.72 (855.441)	223.69 (842.171)
Median	27.00	35.50	28.90
Range	(0.1, 16065.9)	(1.1, 7378.0)	(0.1, 16065.9)
TNM stage at initial diagnosis			
n	797	398	1195
Stage I	0	0	0
Stage II	103 (12.9%)	52 (13.1%)	155 (13.0%)
Stage III	112 (14.1%)	49 (12.3%)	161 (13.5%)
Stage IV	297 (37.3%)	160 (40.2%)	457 (38.2%)
Incomplete reporting	285 (35.8%)	137 (34.4%)	422 (35.3%)

Gleason score at initial diagnosis			
n	697	350	1047
<7	104 (14.9%)	37 (10.6%)	141 (13.5%)
3+4=7	140 (20.1%)	61 (17.4%)	201 (19.2%)
4+3=7	97 (13.9%)	63 (18.0%)	160 (15.3%)
≥8	356 (51.1%)	189 (54.0%)	545 (52.1%)
Evidence of disease progression			
n	797	398	1195
PSA only	238 (29.9%)	125 (31.4%)	363 (30.4%)
Radiographic progression with or without PSA progression	559 (70.1%)	273 (68.6%)	832 (69.6%)
Extent of disease			
Bone	709 (89.2%)	357 (90.4%)	1066 (89.6%)
Soft tissue, not otherwise specified	0	0	0
Node	361 (45.4%)	164 (41.5%)	525 (44.1%)
Viscera, not otherwise specified	1 (0.1%)	0 (0.0%)	1 (0.1%)
Liver	90 (11.3%)	30 (7.6%)	120 (10.1%)
Lungs	103 (13.0%)	45 (11.4%)	148 (12.4%)
Prostate mass	60 (7.5%)	23 (5.8%)	83 (7.0%)
Other viscera	46 (5.8%)	21 (5.3%)	67 (5.6%)
Other tissue	40 (5.0%)	20 (5.1%)	60 (5.0%)
ECOG performance status			
n	797	398	1195
0 or 1	715 (89.7%)	353 (88.7%)	1068 (89.4%)
2	82 (10.3%)	45 (11.3%)	127 (10.6%)
Pain			
n	797	398	1195
Present	357 (44.8%)	179 (45.0%)	536 (44.9%)
Absent	440 (55.2%)	219 (55.0%)	659 (55.1%)
Baseline BPI-SF pain score (worst pain over last 24 hours)			
n	792	394	1186
Mean (SD)	3.4 (2.80)	3.4 (2.81)	3.4 (2.80)
Median	3.0	3.0	3.0
Range	(0, 10)	(0, 10)	(0, 10)
Baseline analgesic usage score			
n	790	395	1185
Mean (SD)	1.2 (1.08)	1.3 (1.06)	1.2 (1.07)
Median	1.0	1.0	1.0
Range	(0, 3)	(0, 3)	(0, 3)
Previous cancer therapy			
n	797	398	1195
Surgery	429 (53.8%)	193 (48.5%)	622 (52.1%)
Radiotherapy	570 (71.5%)	285 (71.6%)	855 (71.5%)
Hormonal	796 (99.9%)	396 (99.5%)	1192 (99.7%)
Other[a]	797 (100.0%)	398 (100.0%)	1195 (100.0%)
Number of prior cytotoxic chemotherapy regimens			
n	797	398	1195
1	558 (70.0%)	275 (69.1%)	833 (69.7%)
2	239 (30.0%)	123 (30.9%)	362 (30.3%)

Numbers analysed

Efficacy analyses were performed using the ITT population, which included all randomized patients (797 patients in the abiraterone acetate group and 398 patients in the placebo group). Ten patients did not receive study treatment (6 from the AA arm; 4 from the Placebo arm); they were however included in the allocated treatment arm for efficacy analyses although excluded from the safety population analyses.

Outcomes and estimation

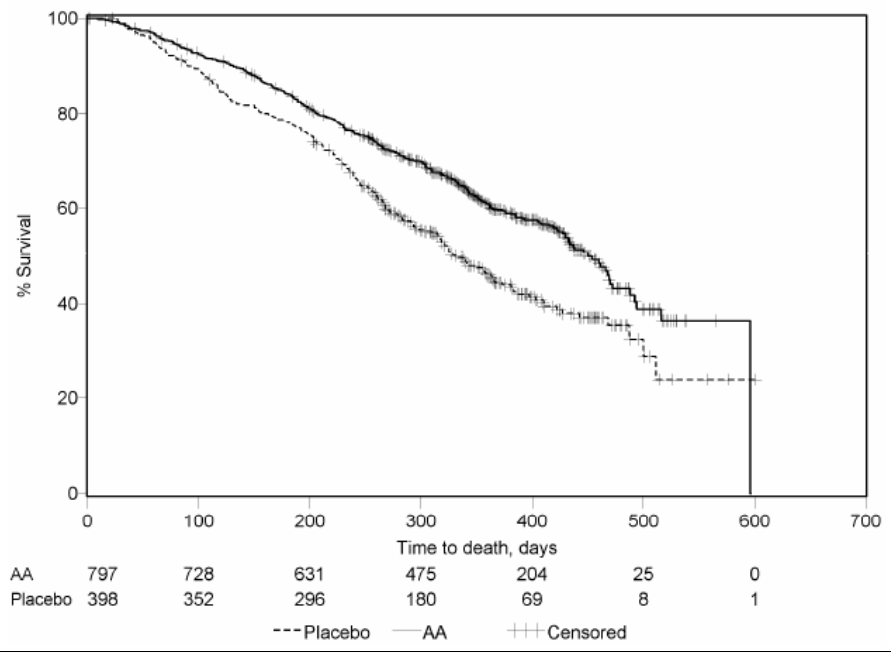
Primary endpoint

The efficacy results in terms of the primary endpoint of Overall Survival and for the primary analysis of 22 January 2010 are summarised in the following table and figure.

Table 7: Overall Survival - Stratified Analysis, study COU-AA-301, ITT Population, cut-off 22 Jan 2010

	Abiraterone	Placebo
Patients randomised	797	398
Death	333 (41.8%)	219 (55.0%)
Censored	464 (58.2%)	179 (45.0%)
Overall Survival (days)		
Median (95% CI)	450 (430, 470)	332 (310, 366)
Log-rank p-value (stratified)	< 0.0001	
Hazard ratio (95% CI)	0.646 (0.543, 0.768)	

Figure 8: Overall Survival, study COU-AA-301, ITT population, cut-off 22 Jan 2010

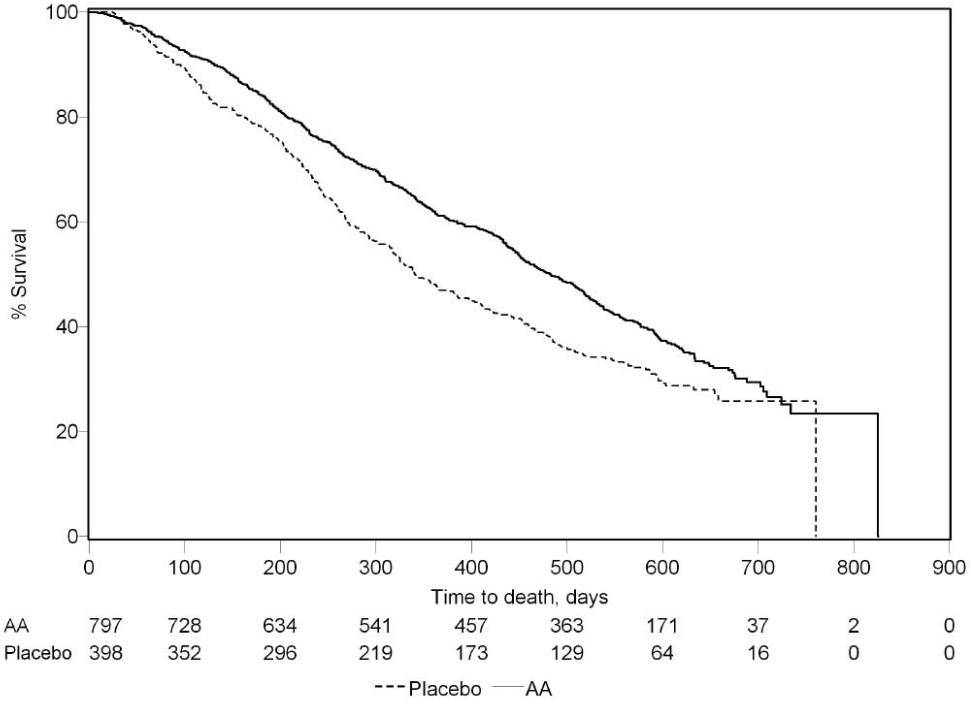


The Applicant also submitted the results of an updated OS analysis with a cut-off date of 20 September 2010, which are summarised in the following table and figure.

Table 8: Overall Survival, study COU-AA-301, ITT Population, cut-off 20 Sept 2010

	Abiraterone	**Placebo**
Patients randomised	797	398
Death	501 (62.9%)	274 (68.8%)
Censored	296 (37.1%)	124 (31.2%)
Overall Survival (days)		
Median (95% CI)	482.0 (451.0, 518.0)	341.0 (317.0, 400.0)
Log-rank p-value (stratified)	< 0.0001	
Hazard ratio (95% CI)	0.740 (0.638, 0.859)	

Figure 9: Overall Survival, study COU-AA-301, ITT population, cut-off 20 Sept 2010



Key secondary endpoints

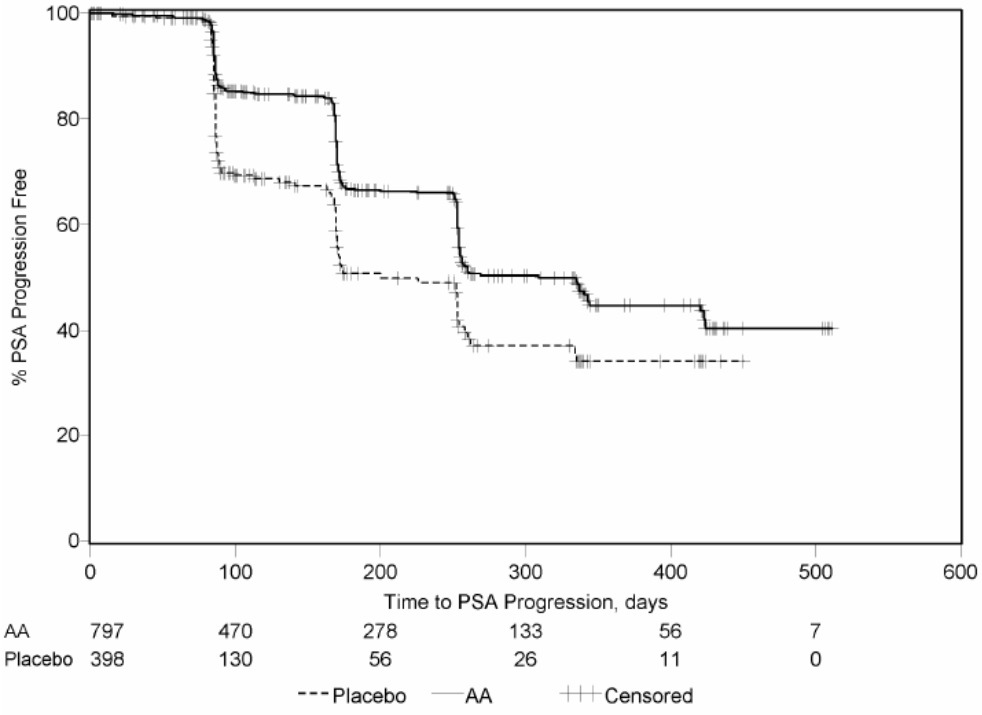
Results in terms of the key secondary endpoints of time to PSA progression, radiographic Progression Free Survival (rPFS) and PSA response rate are summarised in the following tables and figures.

Table 9: Time to PSA progression, study COU-AA-301, ITT population

	Abiraterone	Placebo
PSA progressed	254 (31.9%)	120 (30.2%)
Censored	543 (68.1%)	278 (69.8%)
Time to PSA progression (days)		
Median (95% CI)	309.0 (255.0, 421.0)	200.0 (170.0, 254.0)
log-rank p-value (stratified)	< 0.0001	
Hazard Ratio (95% CI)	0.580 (0.462, 0.728)	

NE=Not Estimable

Figure 10: Time to PSA progression, study COU-AA-301, ITT population



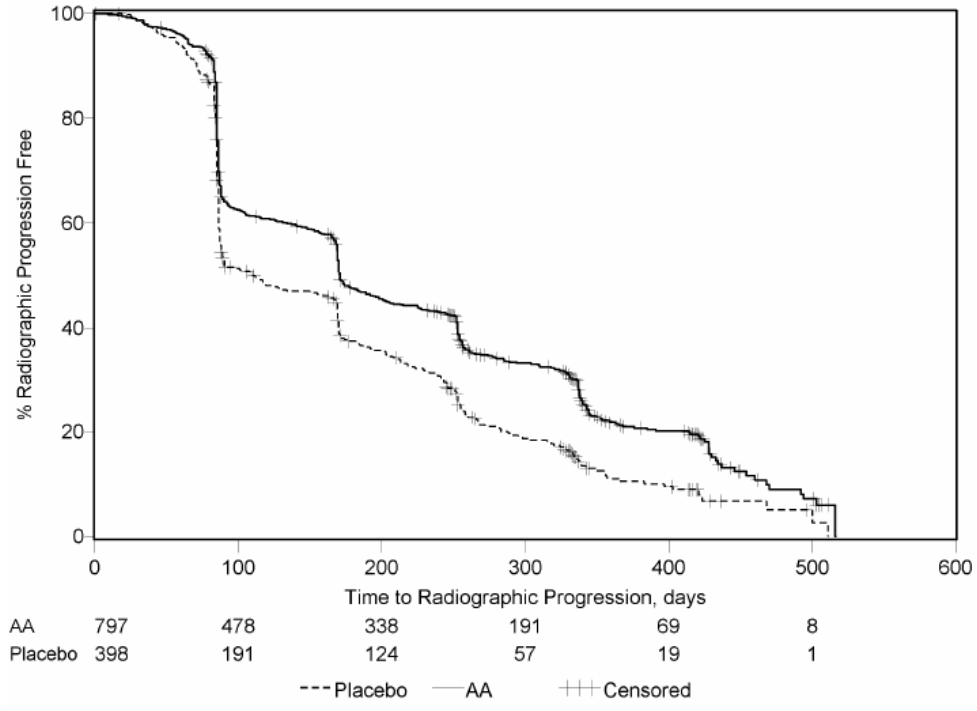
AA=abiraterone acetate; ITT=intent-to-treat; PSA=prostate-specific antigen

Table 10: Radiographic PFS – Stratified analysis, study COU-AA-301, ITT population

	Abiraterone	Placebo
Progressive disease or died	577 (72.4%)	327 (82.2%)
Censored	220 (27.6%)	71 (17.8%)
Radiographic progression-free survival (days)		
Median (95% CI)	171.0 (169.0, 192.0)	110.0 (88.0, 168.0)
log-rank p-value (stratified)	< 0.0001	
Hazard ratio (95% CI)	0.673 (0.585, 0.776)	

NE=Not Estimable

Figure 11: Radiographic Progression, Study COU-AA-301, ITT population



AA=abiraterone acetate; ITT=intent-to-treat

Table 11: PSA response rate – Nonstratified analysis, study COU-AA-301, ITT population

	Abiraterone	Placebo
Patients with PSA response	303 (38.0%)	40 (10.1%)
Confirmed	232 (29.1%)	22 (5.5%)
Unconfirmed	71 (8.9%)	18 (4.5%)
Relative risk (95% CI)	5.266 (3.459, 8.018)	
p value (p value is from a Chi-squared test)	< 0.0001	

Other secondary endpoints

The proportion of patients with pain palliation was statistically significantly higher in the abiraterone acetate group than in the placebo group (44% versus 27%, p=0.0002). A responder for pain palliation was defined as a patient who experienced at least a 30% reduction from baseline in the BPI-SF worst pain intensity score over the last 24 hours without any increase in analgesic usage score observed at two consecutive evaluations four weeks apart. Only patients with a baseline pain score of ≥ 4 and at least one post-baseline pain score were analysed (N=512) for pain palliation.

A lower proportion of patients treated with abiraterone acetate had pain progression compared to patients taking placebo at 6 (22% versus 28%), 12 (30% versus 38%) and 18 months (35% versus 46%). Pain progression was defined as an increase from baseline of ≥ 30% in the BPI-SF worst pain intensity score over the previous 24 hours without a decrease in analgesic usage score observed at two consecutive visits, or an increase of ≥ 30% in analgesic usage score observed at two

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

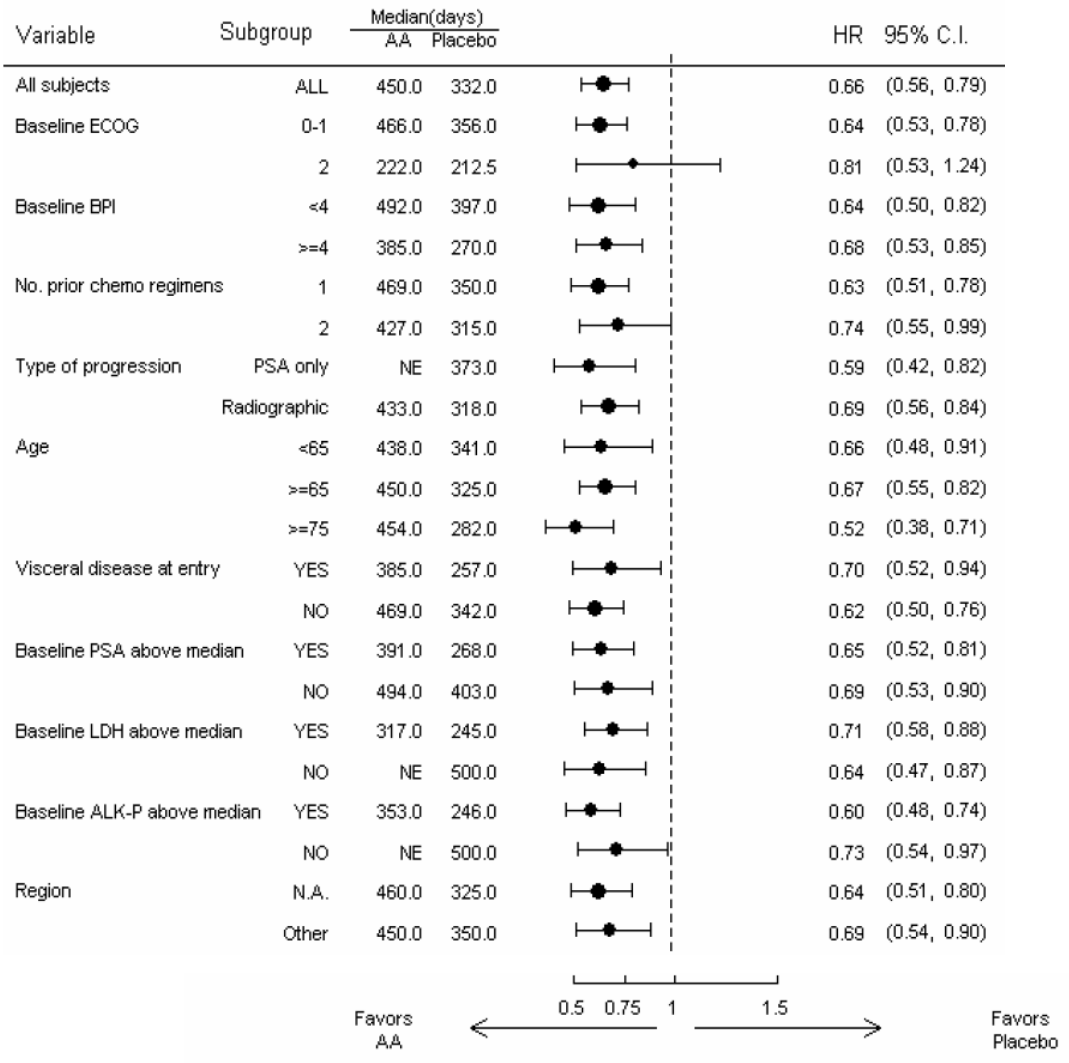
A lower proportion of patients in the abiraterone acetate group had skeletal-related events compared with the placebo group at 6 months (18% versus 28%), 12 months (30% versus 40%), and 18 months (35% versus 40%). The time to first skeletal-related event at the 25th percentile in the active treatment group was twice that of the control group at 9.9 months versus 4.9 months. A skeletal-related event was defined as a pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone.

Finally, results in terms of modified PFS and CTCs also showed differences in favour of abiraterone acetate and measures of functional status generally showed improvement in the abiraterone group compared to the placebo group (data not shown).

Ancillary analyses

Subgroup analyses for OS are shown in the following figure.

Figure 12: OS by subgroup -Nonstratified analysis, study COU-AA-301, ITT population



The treatment effect on OS was similar after adjustment for stratification factors in a multivariate analysis (HR=0.657; 95% CI: 0.554, 0.780; p<0.0001).

Summary of main study

The following tables summarise the efficacy results from the main study supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12: Summary of Efficacy for trial COU-AA-301

Title: A Phase 3, Randomised, Double-Blind, Placebo-Controlled Study of Abiraterone Acetate (CB7630) Plus Prednisone in Patients with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Docetaxel-Based Chemotherapy			
Study identifier	COU-AA-301, NCT-00638690, 2007-005837-13		
Design	multinational, multicentre, randomised, double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Until disease progression or unacceptable toxicity not applicable not applicable
Hypothesis	Superiority		
Treatments groups	Abiraterone acetate		1 g (administered as 4 x 250-mg tablets) orally once daily continuously at least 1 hour before or 2 hours after a meal + prednisone/ prednisolone 5 mg orally twice daily (N=797)
	Placebo		4 matching placebo tablets orally once daily continuously at least 1 hour before or 2 hours after a meal + prednisone/ prednisolone 5 mg orally twice daily (N=398)
Endpoints and definitions	Primary endpoint	Overall survival (OS)	Time from randomisation to death from any cause
	Secondary endpoint	Time to prostate-specific antigen (PSA) progression	Time from randomisation to the date of PSA progression as defined in the PSAWG criteria
	Secondary endpoint	Radiographic progression-free survival (PFS)	Time from randomisation to radiographic progression (modified RECIST criteria, see details in the text) as assessed by the investigator or death
	Secondary endpoint	PSA response rate (RR)	Proportion of patients achieving a PSA decline of at least 50% according to PSAWG criteria
Database lock	22/01/2010		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat, 22/01/2010 (534 events of death observed)		
Descriptive statistics and estimate variability	Treatment group	Abiraterone acetate	Placebo
	Number of patient treated	791	394
	OS (median, in days)	450 (14.8 months)	332 (10.9 months)
	95% CI	(430, 470)	(310, 366)
	Time to PSA progression (median, in days)	309 (10.2 months)	200 (6.6 months)
	95% CI	(255, 421)	(170, 254)

	Radiographic PFS (median, in days)	171 (5.6 months)	110 (3.6 months)
	95% CI	(169, 192)	(88, 168)
	PSA RR [Number of patients (%)]	303 (38.0%)	40 (10.1%)
	95% CI	(34.6%, 41.5%)	(7.3%, 13.4%)
	Confirmed PSA RR [Number of patients (%)]	232 (29.1%)	22 (5.5%)
	95% CI	(26.0%, 32.4%)	(3.5%, 8.2%)
Effect estimate per comparison	Primary endpoint (OS)	Comparison groups	Abiraterone acetate *vs* placebo
		HR from stratified proportional hazards model	0.646
		95% CI	(0.543, 0.768)
		Stratified log-rank p-value	<0.0001
	Secondary endpoint (time to PSA progression)	Comparison groups	Abiraterone acetate *vs* placebo
		HR from stratified proportional hazards model	0.580
		95% CI	(0.462, 0.728)
		Stratified log-rank p-value	<0.0001
	Secondary endpoint (radiographic PFS)	Comparison groups	Abiraterone acetate *vs* placebo
		HR from stratified proportional hazards model	0.673
		95% CI	(0.585, 0.776)
		Stratified log-rank p-value	<0.0001
	Secondary endpoint (confirmed PSA RR)	Comparison groups	Abiraterone acetate *vs* placebo
		Relative risk	5.266
		95% CI	(3.459, 8.018)
		Chi-squared p-value	<0.0001
Notes	Stratification factors for the primary analysis (logrank): ECOG performance status score (0-1, 2), pain score (absent, present), number of prior chemotherapy regimens (1, 2), and type of progression (PSA only, radiographic		
Analysis description	**Updated OS Analysis**		
Analysis population and time point description	Intent to treat, 20/09/2010 (775 events of death observed)		
Descriptive statistics and estimate variability	Treatment group	Abiraterone acetate	Placebo
	Number of patient	797	398
	OS (median, in days)	482	341
	95% CI	(451, 518)	(317, 400)
Effect estimate per comparison	Primary endpoint (OS)	Comparison groups	Abiraterone acetate *vs* placebo
		HR from stratified proportional hazards model	0.740
		95% CI	(0.638, 0.859)
		Log-rank p-value	<0.0001

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

A comparison of main efficacy results between the studies supporting the efficacy of abiraterone acetate is shown in the following table.

Table 13: Comparison of eficacy results across studies in patients with previous taxane-based chemotherapy for prostate cancer

Study Number Treatment Number of Patients (Analysis Population)	Median Overall Survival (Months)	Median Time to PSA Progression (Months)	Median Radiographic PFS (Months)	% of Patients with Confirmed PSA Response
COU-AA-301				
Abiraterone Acetate N=797 (ITT)	14.8	10.2	5.6	29
Placebo N=398 (ITT)	10.9	6.6	3.6	6
COU-AA-004				
Abiraterone Acetate N=58 (All Treated)	16.2	5.6	4.1	38
COU-AA-003/EXT				
Abiraterone Acetate N=47 (ITT)	12.5	5.6	15.0	Week 12: 36 Maximal: 45

Clinical studies in special populations

Pharmacokinetic studies in non-cancer adult patients with renal and liver dysfunction have been submitted. These are described under the clinical pharmacology and clinical safety sections.

Supportive studies

Two supportive phase II Studies (COU-AA-004 and COU-AA-003/EXT) were submitted.

Study COU-AA-004

Study COU-AA-004 was a phase II, multicentre, open-label, single-arm study that evaluated the safety and efficacy of abiraterone acetate in patients with CRPC whose disease had progressed on or after docetaxel-based chemotherapy. The study was carried out between the 06/06/07 and 22/01/10 in the USA. Patients received combination abiraterone acetate and prednisone from the beginning of the study in order to lower the incidence and severity of mineralocorticoid-related adverse events that are attributed to the pharmacologic mechanism of CYP17 inhibition. The Applicant claimed that the study was conducted in compliance with GCP.

Eligible patients received abiraterone acetate 1000 mg (administered as 4 x 250 mg tablets) orally once daily after an overnight fast, and prednisone 5 mg orally twice daily. Abiraterone acetate was administered on a continuous schedule, but each cycle of treatment was defined as 28 ± 2 days. Treatment was to continue through 12 cycles or until documented disease progression or unacceptable toxicity. Survival data was to be collected for up to 5 years after study entry.

Results

Fifty eight patients were enrolled and treated in the study. All patients received prior docetaxel chemotherapy and had undergone androgen deprivation with medical/surgical castration. Seventy six percent of patients had 1 line of prior chemotherapy and 24% had ≥2 lines. Ninety eight percent of patients received prior GnRH analogues and 5% of patients had undergone prior orchiectomy (3% had both).

The median age at baseline was 70 years and 26% of patients were 75 years of age or older. 93% of patients were white. ECOG performance status score was 0 for 42% of patients, 1 for 54% of patients and 2 for 4% of patients. The median baseline PSA concentration was 189.6 ng/ml.

At the time of data cut-off (22 January 2010), most patients (93%) had discontinued treatment; disease progression was the most common reason for discontinuation and was seen in 76% of the study population. The median duration of treatment was 12 weeks (range: 2 to 121 weeks). Two patients required dose reductions of abiraterone acetate due to adverse events.

Table 14: Key efficacy endpoints and results, study COU-AA-004

Endpoint	**Outcome**
PSA response rate (PSA response was defined as a decline in PSA concentration of >50% from baseline per PSAWG criteria)	38%
Duration of PSA response	At the time of clinical cut-off - median duration of PSA response was not reached
Time to PSA progression	Median time to PSA progression was 169 days (5.6 months; 95% CI: 99, 225 days)
Objective radiographic response rate	6% of patients achieved a Partial Response (PR) 46% of patients achieved Stable Disease (SD)
Time to radiographic progression	Median time to radiographic progression was 88 days (2.9 months; 95% CI: 82, 333 days)
rPFS	Median rPFS was 126 days (4.1 months; 95% CI: 82, 333 days)
OS	Median OS was 492 days (16.2 months; 95% CI: 373, 647 days), estimated 1-year survival rate of 63% (95% CI: 49, 74)
Clinical benefit response rate (defined as at least 1 of the following: PSA response by PSAWG criteria, radiographic response by modified RECIST criteria, stable disease by RECIST criteria lasting 6 months, or improvement by at least 1 unit in ECOG performance status score)	Clinical benefit response rate was 60%

Study COU-AA-003/EXT

Study COU-AA-003 was a Phase II, multicentre, open-label, single-arm study that evaluated the antitumour effects of abiraterone acetate in patients with CRPC whose disease had progressed on or after taxane-based chemotherapy, including docetaxel or paclitaxel. The study was carried out

between the 20/11/06 - 22/01/10 in the USA and the UK. Eligible patients received abiraterone acetate 1000 mg (administered as 4 x 250 mg capsules) orally once daily after an overnight fast. As of Amendment 2 of the study protocol (24 April 2008), all ongoing patients also received a low-dose corticosteroid, such as prednisone (5 mg twice daily) or dexamethasone (0.5 mg once daily). Abiraterone acetate was administered on a continuous schedule, but each cycle of treatment was defined as 28 ± 2 days. Treatment was to continue through to 12 cycles or until documented disease progression, lack of disease response after 6 evaluable cycles of treatment, or unacceptable toxicity. The Applicant claimed that the study was conducted in compliance with GCP.

Study COU-AA-003 EXT was an extension of Study COU-AA-003 that allowed responding patients to continue receiving abiraterone acetate after 12 cycles. Patients received the same dose and regimen of abiraterone acetate administered during Study COU-AA-003 along with a concurrent corticosteroid. Treatment was to continue until death, loss to follow-up, withdrawal of informed consent, sustained toxicity, disease progression or the Sponsor's decision to terminate the study.

Results

Forty seven patients were enrolled and treated in the study. All patients received prior taxane-based chemotherapy as mandated by the protocol and all patients had undergone androgen deprivation with medical or surgical castration. Moreover, 100% of patients received prior GnRH analogues.

The median age at baseline was 67 years and 19% of patients were 75 years of age or older. The majority of patients 98% were white. At baseline, the ECOG performance status score was 0 for 34% of patients, 1 for 57% of patients, and 2 for 9% of patients. The median baseline PSA concentration was 403.0 ng/ml.

At the time of data cut-off (22 January 2010), 41 (87%) patients had discontinued from the study and 6 (13%) patients were still receiving treatment. The most common reason for discontinuation was disease progression (49%) followed by adverse event (23%). The median duration of treatment was 23 weeks (range: 2 to 148 weeks). Two patients had their doses of abiraterone acetate reduced due to adverse events; neither of these patients was discontinued from the study due to toxicity.

Table 15: Key efficacy endpoints and results, study COU-AA-003/EXT

Endpoint	**Outcome**
Week 12 PSA response rates (PSA response defined as a decline in PSA concentration of >50% from baseline per PSAWG criteria)	PSA response rate at Week 12 was 36%
Maximal PSA response rates (based on all PSA assessments throughout the entire study)	The maximal confirmed PSA response rate was 45%
Duration of PSA response	Median duration of PSA response of 169 days (5.6 months; 95% CI: 141,,262 days)
Time to PSA progression	Median time to PSA progression was 169 days (5.6 months; 95% CI: 113, 281 days)
Objective response rate by RECIST criteria	Objective response rate (CR or PR) was achieved by 6 (26%) patients (95% CI: 10, 48) (n = 23, measureable disease at baseline)
OS	Median OS was 380 days (12.5 months; 95% CI: 311, 457 days)

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In the pivotal study COU-AA-301, patients having received prior ketoconazole therapy were excluded from the study. This is a relevant issue as ketoconazole, an antifungal drug not approved for this indication, is however widely used in mCRPC patients in many countries prior to initiation of any kind of chemotherapy. Lower response rates were observed in earlier studies of abiraterone acetate in mCRPC patients that had been previously treated with ketoconazole, although some activity was still observed in this setting (e.g. in study COU-AA-004, a PSA response rate of 26% was observed in patients having received prior ketoconazole treatment and 48% in those with no prior ketoconazole therapy). Therefore, although some activity following ketoconazole treatment may exist, it is expected to be lower and this has not been properly assessed in a controlled clinical trial. This information has been adequately addressed in sections 4.4 and 5.1 of the SmPC).

Demographics and baseline disease characteristics were well balanced between the 2 groups. Overall, characteristics of the study population properly reflect those of the target population for the intended indication with two possible exceptions: ECOG performance status score and race. As in many clinical trials, ECOG performance status score is on average far better than that encountered in the target population. Although it is true that poor PS patients are generally not suitable candidates for chemotherapy and often managed with best supportive care only, this would not be so much the case in the context of an oral drug with a favourable safety profile such as abiraterone. However, more of an issue is the fact that the black race was certainly underrepresented in this trial (<4%). The patient population of the pivotal trial is reflected in section 5.1 of the SmPC and use in non-white patients is reflected as important missing information in the Risk Management Plan.

Efficacy data and additional analyses

Results from the study revealed a median overall survival of 14.8 months for the abiraterone group and 10.9 months for the placebo group. The benefit in survival was confirmed in an updated analysis (cut-off of 20 September 2010), showing a median survival of 15.8 months for the abiraterone group versus 11.2 months for the placebo group. Treatment effect on OS was robust after adjustment for stratification factors in multivariate analysis and was consistently favourable across all subgroups (ECOG, pain score, prior lines of chemotherapy, type of progression, age, visceral disease, baseline PSA, LDH or alkaline phosphatase, and geographical region).

Secondary efficacy endpoints also consistently showed antitumoral activity of clinical relevance of this drug in this patient population. Finally, symptom-related endpoints, such as pain palliation, time to pain progression, skeletal-related events, and quality of life scores also tended to favour abiraterone-treated patients over placebo-control ones.

2.5.4. Conclusions on the clinical efficacy

In conclusion, the overall efficacy results of the study are considered mature enough and clearly positive. The primary endpoint, overall survival, is very relevant to the patient with advanced mCRPC with docetaxel-refractory disease and the magnitude of the observed effect (HR=0.646 interim analysis; HR=0.740 updated analysis) is considered clinically significant. In addition, all the other efficacy endpoints show very consistent results in favour of abiraterone acetate. Although the application relies on a single pivotal trial, the number of patients included, the design of the study (placebo-controlled trial with stratification for the most relevant prognostic factors, the robustness of

the primary endpoint, the relevance of the secondary endpoints for this clinical setting) and the outstanding results are considered compelling enough to support an overall favourable conclusion.

2.6. Clinical safety

The safety of abiraterone acetate administered as monotherapy with or without prednisone/ prednisolone has been evaluated in 1,873 patients included in 20 clinical studies (Figure 4). Eleven of them (n=1,564 patients) were performed in patients with advanced or metastatic castration-resistant prostate cancer (mCRPC) as follows:

- Phase 3 Study: COU-AA-301
- Phase 2 Studies: COU-AA-004, COU-AA-003/EXT, COU-AA-BMA
- Phase 1/2 Studies: COU-AA-001/EXT, COU-AA-002
- Phase 1 Studies: COU-AA-BE, COU-AA-006 (modified QT/QTc study [not a thorough QT design]), COU-AA-015 (drug-drug interaction [DDI] study)

In addition, 9 phase 1 pharmacokinetic studies with abiraterone acetate have been completed in non-cancer subjects (7 in adult healthy male volunteers and 2 in special populations with hepatic and renal impairment).

The integrated safety population consisted of 1,070 patients with CRPC who were treated with abiraterone acetate 1 g administered as a continuous daily dose with or without prednisone 5 mg twice daily and 394 patients treated with placebo and prednisone, totalling 1,464 patients in the following studies: COU-AA-301, COU-AA-004, COU-AA-003/EXT, COU-AA-BMA, COU-AA-001/EXT, COU-AA-002, and COU-AA-BE. Abiraterone acetate was administered orally as an immediate release 250 mg tablet, an immediate release 250 mg capsule, or a liquid. More than 90% of study patients received tablets.

Data from 100 patients with CRPC were provided separately from the integrated safety population data. This number included 12 patients in Study COU-AA-001 and 21 patients in Study COU-AA-002 who were treated with doses other than 1 g abiraterone acetate as well as 33 patients in the phase 1 pharmacokinetic Study COU-AA-006, and 34 patients in the phase 1 pharmacokinetic Study COU-AA-015 for whom extended dosing and safety data were not available by the clinical cut-off date (22 January 2010). Data from 309 non-cancer subjects who were treated in 9 Phase 1 pharmacokinetic studies were also provided separately from the integrated safety population data.

The integrated safety population data were presented in 4-column tables as follows:

- Study COU-AA-301 placebo group (n=394)
- Study COU-AA-301 abiraterone acetate group (n=791)
- Pooled data from Phase 1/2 studies (Studies COU-AA-004, COU-AA-003/EXT, COU-AA-BMA, COU-AA-001/EXT, COU-AA-002 and COU-AA-BE) in patients treated with 1 g abiraterone acetate continuous daily dose (n=279)
- Overall abiraterone acetate group (1 g continuous daily dose) (n=1,070)

Patient exposure

Information regarding extent of exposure, baseline demographic and disease characteristics as well as prior therapies is summarised in the following tables.

Table 16: Extent of exposure, Integrated Safety population

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

Table 17: Baseline demographics, Integrated Safety population

	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Age (yrs)				
n	394	791	279	1070
<65	119 (30.2%)	229 (29.0%)	79 (28.3%)	308 (28.8%)
65-69	87 (22.1%)	172 (21.7%)	58 (20.8%)	230 (21.5%)
70-74	79 (20.1%)	172 (21.7%)	65 (23.3%)	237 (22.1%)
≥75	109 (27.7%)	218 (27.6%)	77 (27.6%)	295 (27.6%)
Mean (SD)	68.9 (8.61)	69.1 (8.39)	69.2 (8.80)	69.1 (8.49)
Median	69.0	69.0	70.0	69.0
Range	(39, 90)	(42, 95)	(44, 91)	(42, 95)
Race				
n	394	790	279	1069
American Indian or Alaska Native	0 (0.0%)	3 (0.4%)	0 (0.0%)	3 (0.3%)
Asian	9 (2.3%)	11 (1.4%)	2 (0.7%)	13 (1.2%)
Black	15 (3.8%)	28 (3.5%)	8 (2.9%)	36 (3.4%)
Hispanic	2 (0.5%)	3 (0.4%)	3 (1.1%)	6 (0.6%)
White	365 (92.6%)	737 (93.3%)	261 (93.5%)	998 (93.4%)
Other	3 (0.8%)	8 (1.0%)	5 (1.8%)	13 (1.2%)

Table 18: Baseline disease characteristics, Integrated Safety population

Cancer Diagnosis	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Years since initial diagnosis to 1st dose				
n	394	791	277	1068
Mean (SD)	6.87 (4.688)	7.15 (4.463)	7.52 (4.667)	7.25 (4.518)
Median	5.28	6.31	7.05	6.45
Range	(0.2, 24.6)	(0.5, 25.0)	(0.6, 26.2)	(0.5, 26.2)
Stage at initial diagnosis				
n	394	791	279	1070
Stage I	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Stage II	52 (13.2%)	102 (12.9%)	23 (8.2%)	125 (11.7%)
Stage III	49 (12.4%)	111 (14.0%)	41 (14.7%)	152 (14.2%)
Stage IV	159 (40.4%)	294 (37.2%)	73 (26.2%)	367 (34.3%)
Incomplete reporting	134 (34.0%)	284 (35.9%)	142 (50.9%)	426 (39.8%)
Gleason score at initial diagnosis				
n	347	693	252	945
<7	37 (10.7%)	103 (14.9%)	45 (17.9%)	148 (15.7%)
3+4=7	61 (17.6%)	139 (20.1%)	58 (23.0%)	197 (20.8%)
4+3=7	62 (17.9%)	95 (13.7%)	13 (5.2%)	108 (11.4%)
≥8	187 (53.9%)	356 (51.4%)	136 (54.0%)	492 (52.1%)
Baseline Extent of Disease				
n	392	789	274	1063
Visceral (with or without bone or soft tissue)[a]	83 (21.2%)	211 (26.7%)	35 (12.8%)	246 (23.1%)
Bone only	169 (43.1%)	294 (37.3%)	69 (25.2%)	363 (34.1%)
Soft tissue only[b]	30 (7.7%)	60 (7.6%)	33 (12.0%)	93 (8.7%)
Bone and soft tissue only	110 (28.1%)	224 (28.4%)	137 (50.0%)	361 (34.0%)
Baseline Liver Metastasis				
n	394	791	248	1039
Yes	29 (7.4%)	89 (11.3%)	19 (7.7%)	108 (10.4%)
No	365 (92.6%)	702 (88.7%)	229 (92.3%)	931 (89.6%)
Baseline ECOG Performance Status				
n	394	791	275	1066
0	134 (34.0%)	271 (34.3%)	126 (45.8%)	397 (37.2%)
1	217 (55.1%)	439 (55.5%)	130 (47.3%)	569 (53.4%)
2	43 (10.9%)	81 (10.2%)	19 (6.9%)	100 (9.4%)
Baseline PSA (ng/mL)				
n	393	788	277	1065
Mean (SD)	400.58 (810.549)	439.18 (888.476)	520.40 (1331.318)	460.30 (1022.209)
Median	137.70	128.80	111.00	125.20
Range	(0.6, 10114.0)	(0.4, 9253.0)	(1.3, 10325.0)	(0.4, 10325.0)
Baseline Hemoglobin level				
n	389	779	276	1055
≥12.5 g/dL	129 (33.2%)	261 (33.5%)	109 (39.5%)	370 (35.1%)
10 g/dL to <12.5 g/dL	210 (54.0%)	411 (52.8%)	136 (49.3%)	547 (51.8%)
<10 g/dL	50 (12.9%)	107 (13.7%)	31 (11.2%)	138 (13.1%)

Table 19: Prior therapies, Integrated Safety population

Types of Therapy	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Radiotherapy	283 (71.8%)	565 (71.4%)	183 (65.6%)	748 (69.9%)
Surgery	191 (48.5%)	425 (53.7%)	115 (41.2%)	540 (50.5%)
Chemotherapy[a]	394 (100.0%)	791 (100.0%)	172 (61.6%)	963 (90.0%)
Lines of prior Chemotherapy[b]				
n	394	791	58	849
1	272 (69.0%)	553 (69.9%)	44 (75.9%)	597 (70.3%)
2	122 (31.0%)	238 (30.1%)	13 (22.4%)	251 (29.6%)
>2	0	0	1 (1.7%)	1 (0.1%)
Mitoxantrone	57 (14.5%)	105 (13.3%)	27 (9.7%)	132 (12.3%)
Hormonal/Immuno/Biological Therapy[c]	390 (99.0%)	785 (99.2%)	279 (100.0%)	1064 (99.4%)

Adverse events

An overview of adverse events (AEs) is shown in the following table.

Table 20: Overall safety profile

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

a Does not include Grade 5 events. b Adverse events reported to be either related to abiraterone acetate/placebo or prednisone are classified as drug-related. TEAEs= Treatment-emergent AEs are those occurring or worsening in toxicity on or after the first dose and within 30 days after the last dose of study agent. Treatment-emergent AEs are included regardless of toxicity grade or relationship to study medication

The most frequently reported AEs in the pivotal trial COU-AA-301 were fatigue (44% and 43% in the abiraterone and placebo arms, respectively), back pain (30% and 33%, respectively), nausea (30% and 32%, respectively), and constipation (26% and 31%, respectively), consistent with the natural history of advanced mCRPC. Most events were Grade 1 or 2. In the overall abiraterone acetate group, the most frequently reported AEs were fatigue (44%), nausea (28%), back pain (27%), and arthralgia and edema peripheral (26%). Grade 3 and 4 AEs are summarised in the following table.

Table 21: Grade 3 and 4 TEAEs reported in at least 1% of patients in any group

	Placebo COU-AA-301 (N=394)		AA COU-AA-301 (N=791)		AA Pooled Phase 1/2 (N=279)		Overall AA (N=1070)	
MedDRA SOC Term MedDRA Preferred Term	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Total no. subjects with a grade 3 or 4 treatment-emergent adverse event	186 (47.2%)	44 (11.2%)	347 (43.9%)	84 (10.6%)	114 (40.9%)	14 (5.0%)	461 (43.1%)	98 (9.2%)
Musculoskeletal and connective tissue disorders	90 (22.8%)	7 (1.8%)	148 (18.7%)	7 (0.9%)	31 (11.1%)	0	179 (16.7%)	7 (0.7%)
Back pain	37 (9.4%)	1 (0.3%)	44 (5.6%)	3 (0.4%)	10 (3.6%)	0	54 (5.0%)	3 (0.3%)
Bone pain	25 (6.3%)	4 (1.0%)	42 (5.3%)	2 (0.3%)	2 (0.7%)	0	44 (4.1%)	2 (0.2%)
Arthralgia	16 (4.1%)	0	33 (4.2%)	0	10 (3.6%)	0	43 (4.0%)	0
Musculoskeletal pain	8 (2.0%)	0	20 (2.5%)	1 (0.1%)	5 (1.8%)	0	25 (2.3%)	1 (0.1%)
Pain in extremity	20 (5.1%)	0	18 (2.3%)	1 (0.1%)	4 (1.4%)	0	22 (2.1%)	1 (0.1%)
Muscular weakness	5 (1.3%)	1 (0.3%)	17 (2.1%)	1 (0.1%)	1 (0.4%)	0	18 (1.7%)	1 (0.1%)
Groin pain	3 (0.8%)	0	7 (0.9%)	0	4 (1.4%)	0	11 (1.0%)	0
General disorders and administration site conditions	58 (14.7%)	5 (1.3%)	111 (14.0%)	6 (0.8%)	17 (6.1%)	0	128 (12.0%)	6 (0.6%)
Fatigue	36 (9.1%)	3 (0.8%)	64 (8.1%)	2 (0.3%)	12 (4.3%)	0	76 (7.1%)	2 (0.2%)
Asthenia	7 (1.8%)	1 (0.3%)	18 (2.3%)	0	2 (0.7%)	0	20 (1.9%)	0
Disease progression	2 (0.5%)	0	11 (1.4%)	2 (0.3%)	0	0	11 (1.0%)	2 (0.2%)
Oedema peripheral	3 (0.8%)	0	11 (1.4%)	1 (0.1%)	1 (0.4%)	0	12 (1.1%)	1 (0.1%)
General physical health deterioration	2 (0.5%)	0	8 (1.0%)	0	0	0	8 (0.7%)	0
Pain	6 (1.5%)	1 (0.3%)	5 (0.6%)	0	1 (0.4%)	0	6 (0.6%)	0
Pyrexia	5 (1.3%)	0	3 (0.4%)	0	1 (0.4%)	0	4 (0.4%)	0
Metabolism and nutrition disorders	41 (10.4%)	1 (0.3%)	87 (11.0%)	7 (0.9%)	20 (7.2%)	1 (0.4%)	107 (10.0%)	8 (0.7%)
Hypokalaemia	3 (0.8%)	0	27 (3.4%)	3 (0.4%)	6 (2.2%)	1 (0.4%)	33 (3.1%)	4 (0.4%)
Dehydration	7 (1.8%)	0	19 (2.4%)	0	3 (1.1%)	0	22 (2.1%)	0
Hyperglycaemia	6 (1.5%)	0	13 (1.6%)	0	4 (1.4%)	0	17 (1.6%)	0
Anorexia	12 (3.0%)	0	12 (1.5%)	0	3 (1.1%)	0	15 (1.4%)	0
Hyponatraemia	3 (0.8%)	0	10 (1.3%)	1 (0.1%)	3 (1.1%)	0	13 (1.2%)	1 (0.1%)
Hypophosphataemia	2 (0.5%)	1 (0.3%)	10 (1.3%)	1 (0.1%)	1 (0.4%)	0	11 (1.0%)	1 (0.1%)
Hypoglycaemia	4 (1.0%)	0	2 (0.3%)	0	0	0	2 (0.2%)	0
Hypocalcaemia	4 (1.0%)	0	1 (0.1%)	0	0	0	1 (0.1%)	0
Infections and infestations	17 (4.3%)	4 (1.0%)	56 (7.1%)	7 (0.9%)	24 (8.6%)	3 (1.1%)	80 (7.5%)	10 (0.9%)
Urinary tract infection	2 (0.5%)	0	17 (2.1%)	0	7 (2.5%)	1 (0.4%)	24 (2.2%)	1 (0.1%)
Pneumonia	4 (1.0%)	0	11 (1.4%)	3 (0.4%)	6 (2.2%)	1 (0.4%)	17 (1.6%)	4 (0.4%)
Sepsis	0	2 (0.5%)	4 (0.5%)	2 (0.3%)	3 (1.1%)	1 (0.4%)	7 (0.7%)	3 (0.3%)
Urosepsis	1 (0.3%)	0	3 (0.4%)	0	2 (0.7%)	1 (0.4%)	5 (0.5%)	1 (0.1%)
Blood and lymphatic system disorders	27 (6.9%)	7 (1.8%)	57 (7.2%)	14 (1.8%)	16 (5.7%)	2 (0.7%)	73 (6.8%)	16 (1.5%)
Anaemia	23 (5.8%)	6 (1.5%)	51 (6.4%)	8 (1.0%)	8 (2.9%)	2 (0.7%)	59 (5.5%)	10 (0.9%)
Thrombocytopenia	1 (0.3%)	1 (0.3%)	8 (1.0%)	3 (0.4%)	3 (1.1%)	0	11 (1.0%)	3 (0.3%)
Lymphopenia	2 (0.5%)	0	3 (0.4%)	0	7 (2.5%)	0	10 (0.9%)	0
Nervous system disorders	42 (10.7%)	9 (2.3%)	51 (6.4%)	16 (2.0%)	15 (5.4%)	3 (1.1%)	66 (6.2%)	19 (1.8%)
Spinal cord compression	13 (3.3%)	7 (1.8%)	11 (1.4%)	11 (1.4%)	5 (1.8%)	2 (0.7%)	16 (1.5%)	13 (1.2%)
Syncope	3 (0.8%)	0	5 (0.6%)	0	5 (1.8%)	0	10 (0.9%)	0
Headache	3 (0.8%)	0	8 (1.0%)	0	1 (0.4%)	0	9 (0.8%)	0
Neuropathy peripheral	2 (0.5%)	0	1 (0.1%)	0	3 (1.1%)	0	4 (0.4%)	0
Gastrointestinal disorders	30 (7.6%)	2 (0.5%)	59 (7.5%)	5 (0.6%)	14 (5.0%)	0	73 (6.8%)	5 (0.5%)
Abdominal pain	6 (1.5%)	0	16 (2.0%)	0	3 (1.1%)	0	19 (1.8%)	0
Vomiting	11 (2.8%)	0	13 (1.6%)	1 (0.1%)	4 (1.4%)	0	17 (1.6%)	1 (0.1%)
Nausea	10 (2.5%)	0	12 (1.5%)	1 (0.1%)	4 (1.4%)	0	16 (1.5%)	1 (0.1%)
Constipation	4 (1.0%)	0	8 (1.0%)	0	1 (0.4%)	0	9 (0.8%)	0
Gastrointestinal haemorrhage	0	0	4 (0.5%)	1 (0.1%)	4 (1.4%)	0	8 (0.7%)	1 (0.1%)
Diarrhoea	5 (1.3%)	0	5 (0.6%)	0	1 (0.4%)	0	6 (0.6%)	0

Investigations	12 (3.0%)	4 (1.0%)	45 (5.7%)	2 (0.3%)	23 (8.2%)	2 (0.7%)	68 (6.4%)	4 (0.4%)
Blood alkaline phosphatase increased	5 (1.3%)	1 (0.3%)	10 (1.3%)	1 (0.1%)	13 (4.7%)	1 (0.4%)	23 (2.1%)	2 (0.2%)
Alanine aminotransferase increased	1 (0.3%)	1 (0.3%)	7 (0.9%)	0	3 (1.1%)	0	10 (0.9%)	0
Aspartate aminotransferase increased	3 (0.8%)	1 (0.3%)	7 (0.9%)	1 (0.1%)	2 (0.7%)	0	9 (0.8%)	1 (0.1%)
International normalised ratio increased	1 (0.3%)	0	3 (0.4%)	0	3 (1.1%)	0	6 (0.6%)	0
Platelet count decreased	3 (0.8%)	2 (0.5%)	2 (0.3%)	0	1 (0.4%)	0	3 (0.3%)	0
Renal and urinary disorders	23 (5.8%)	1 (0.3%)	44 (5.6%)	8 (1.0%)	11 (3.9%)	0	55 (5.1%)	8 (0.7%)
Haematuria	9 (2.3%)	0	11 (1.4%)	0	3 (1.1%)	0	14 (1.3%)	0
Hydronephrosis	2 (0.5%)	0	12 (1.5%)	1 (0.1%)	0	0	12 (1.1%)	1 (0.1%)
Renal failure	2 (0.5%)	1 (0.3%)	3 (0.4%)	2 (0.3%)	5 (1.8%)	0	8 (0.7%)	2 (0.2%)
Urinary retention	6 (1.5%)	0	8 (1.0%)	0	0	0	8 (0.7%)	0
Renal failure acute	4 (1.0%)	0	4 (0.5%)	3 (0.4%)	0	0	4 (0.4%)	3 (0.3%)
Respiratory, thoracic and mediastinal disorders	11 (2.8%)	10 (2.5%)	18 (2.3%)	7 (0.9%)	11 (3.9%)	1 (0.4%)	29 (2.7%)	8 (0.7%)
Dyspnoea	7 (1.8%)	2 (0.5%)	8 (1.0%)	2 (0.3%)	7 (2.5%)	0	15 (1.4%)	2 (0.2%)
Pulmonary embolism	3 (0.8%)	6 (1.5%)	1 (0.1%)	2 (0.3%)	1 (0.4%)	0	2 (0.2%)	2 (0.2%)
Injury, poisoning and procedu complications	2 (0.5%)	2 (0.5%)	23 (2.9%)	3 (0.4%)	7 (2.5%)	1 (0.4%)	30 (2.8%)	4 (0.4%)
Femur fracture	0	0	1 (0.1%)	0	4 (1.4%)	0	5 (0.5%)	0
Vascular disorders	4 (1.0%)	1 (0.3%)	27 (3.4%)	2 (0.3%)	5 (1.8%)	0	32 (3.0%)	2 (0.2%)
Hypertension	1 (0.3%)	0	10 (1.3%)	0	4 (1.4%)	0	14 (1.3%)	0
Hypotension	1 (0.3%)	1 (0.3%)	6 (0.8%)	2 (0.3%)	0	0	6 (0.6%)	2 (0.2%)
Psychiatric disorders	7 (1.8%)	0	17 (2.1%)	1 (0.1%)	1 (0.4%)	0	18 (1.7%)	1 (0.1%)
Confusional state	4 (1.0%)	0	4 (0.5%)	0	1 (0.4%)	0	5 (0.5%)	0
Reproductive system and brea disorders	10 (2.5%)	0	7 (0.9%)	0	0	1 (0.4%)	7 (0.7%)	1 (0.1%)
Pelvic pain	10 (2.5%)	0	3 (0.4%)	0	0	0	3 (0.3%)	0

Adverse drug reactions (ADRs) in the integrated safety population are summarised in the following table. The most common ADRs observed with abiraterone acetate were oedema peripheral, hypokalemia, urinary tract infection, and hypertension. The ADR, adrenal insufficiency, occurred in at a rate <1%. The most common ADRs that resulted in drug discontinuation in Study COU-AA-301 were alanine aminotransferase increased and cardiac failure (each in <1% of patients).

Table 22: Adverse drug reactions observed in abiraterone acetate treated patients

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
Hepatobiliary disorders	common: alanine aminotransferase increased
General disorders and administration site conditions	very common: oedema peripheral

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

Adverse events of special interest in the pivotal study COU-AA-301, which include events related to mineralocorticoid excess (hypertension, hypokalemia, and fluid retention/edema), cardiac disorders, hepatotoxicity and urinary tract infections, are described in some detail below. In terms of incidence and in order to account for the longer duration of exposure in the abiraterone acetate group compared to the placebo group of the study (8 cycles versus 4 cycles, respectively) an analysis standardising for the difference in treatment duration was performed based on the event rate per 100 patient-years (P-Y) of exposure (time on treatment). The event rate was the total frequency for the reported AE standardised to 100 P-Y of exposure.

Fluid Retention/Oedema

Fluid retention/oedema was reported in 31% of patients in the abiraterone group and 22% of patients in the placebo group. The incidence of Grade 3 or 4 peripheral oedema was reported in 1.5% of patients in the abiraterone acetate group and 0.8% of patients in the placebo group. No Grade 5 events were reported; no patient discontinued study medication or had oedema peripheral events with an outcome of death. After standardising for the difference in duration of treatment exposure, a difference of 6 fluid retention/oedema events/100 P-Y was observed between the groups (71 events in the abiraterone acetate group and 65 events in the placebo group).

Hypokalaemia

Hypokalaemia was reported in 17% of patients in the abiraterone acetate group and 8% of patients in the placebo group. The incidence of Grade 3 or 4 hypokalaemia was reported in 3.8% of patients in the abiraterone acetate group and 0.8% of patients in the placebo group. There were no Grade 5 events and no hypokalaemia AEs with an outcome of death were reported. After standardising for the difference in duration of treatment exposure, a difference of 18 hypokalaemia events/100 P-Y was observed between the 2 groups (47 events in the abiraterone acetate group and 29 events in the placebo group).

Hypertension

Hypertension was reported in 10% of patients in the abiraterone acetate group and 8% of patients in the placebo group. The incidence of Grade 3 hypertension was reported in 1.3% of patients in the abiraterone acetate group and 0.3% of patients in the placebo group. There were no Grade 4 or 5 events and no patient discontinued study medication. No hypertension AEs with an outcome of death was recorded. After standardising for the difference in duration of treatment exposure, a difference of 1 hypertension SMQ event/100 P-Y was observed between the 2 groups (19 events in the abiraterone acetate group and 20 events in the placebo group).

Cardiac Disorders

Cardiac disorders were reported in 13% of patients in the abiraterone acetate group and 11% of patients in the placebo group. The most frequently reported cardiac events were tachycardia (3% in the abiraterone acetate and 2% in the placebo groups) and atrial fibrillation (2% in the abiraterone acetate and 1% in the placebo groups). Cardiac failure was reported in 2% of patients in the abiraterone acetate group versus 1% of patients in the placebo group. Myocardial infarction was reported in 0.8% of patients in each group. No Grade 3, 4, or 5 tachycardia events were reported in either group. Grade 3 atrial fibrillation events were reported in 0.6% of patients in the abiraterone acetate and in 0.5% patients in the placebo group. No patient had a Grade 4 or 5 event. After standardising for the difference in duration of treatment exposure, a difference of 5 cardiac disorders events/100 P-Y was observed between the 2 groups (33 events in the abiraterone acetate group and 28 events in the placebo group). A difference of 2 events/100 P-Y for atrial fibrillation and tachycardia were observed between the 2 groups (5 events in the abiraterone acetate group and 3

events in the placebo group) for each event. Based on a limited number of MUGA scan or echocardiogram results, the percentage of patients who had a decrease in left ventricular ejection fraction from baseline of at ≥15% at any time during the study was 6% in the abiraterone acetate group and 5% the placebo group. There were no pre-clinical safety signals identified to indicate that treatment with abiraterone acetate prolongs QT/QTc interval. However, the proportion of patients with QTc interval prolongation of either >30 ms or >60 ms was higher in the abiraterone acetate group when compared to the placebo group. The potential cardiotoxic effects of abiraterone acetate on the QT/QTc interval duration were assessed in patients with mCRPC using time-matched ECGs and pharmacokinetic analyses (COU-AA-006). In this study, the upper limit of the 90% CI of the mean baseline corrected QTcF change at each post-dose time point was <10 msecs and no significant increase or decrease in mean QTc values was observed at any of the measured time points. Overall, there was no relationship between change in QTcF and abiraterone concentrations.

Hepatotoxicity

Hepatotoxicity adverse events were observed in 10% of patients in the abiraterone acetate group and 8% of patients in the placebo group and increases in ALT were observed in 3% of abiraterone patients and 1% of placebo patients. The incidence of Grade 3 or 4 ALP increase was reported in 1% of patients in the abiraterone acetate group and 2% of patients in the placebo group. Grade 3 or 4 AST increase occurred in 1% of patients in each group. No Grade 5 ALP increase, AST increase, ALT increase, or hyperbilirubinaemia was reported in either group. There were a small number of treatment discontinuations due to ALP increase, AST increase, ALT increase, or hyperbilirubinaemia in the abiraterone acetate group. No AEs with an outcome of death were reported for any of these events. After standardising for the difference in duration of treatment exposure, a difference of 9 hepatotoxicity events/100 P-Y was observed between the 2 groups (33 events in the abiraterone acetate group and 42 events in the placebo group). A difference of 1 ALT event/100 P-Y was observed between the 2 groups (5 events in the abiraterone acetate group and 4 events in the placebo group). Hy's Law criteria were applied across all studies in patients with mCRPC to assess the incidence of severe hepatotoxicity and 2 patients (1 patient in the pivotal Study COU-AA-301 and 1 patient in Phase 2 Study COU-AA-003) were identified as potentially having met Hy’s Law criteria.

Urinary tract infections

The preferred term, urinary tract infection, was reported in 12% of patients in the Study COU-AA-301 abiraterone acetate group compared with 7% of patients in the placebo group; these were primarily Grade 1 or 2 events. After the standardisation the following results were found for the incidence of unrinary tract infections: 24 events/100 P-Y and 18 events/100 P-Y in the abiraterone and placebo arms, respectively.

Serious adverse event/deaths/other significant events

Deaths

As of the clinical cutoff date (22 January 2010), 11% of patients in the Study COU-AA-301 abiraterone acetate group and 13% of patients in the placebo group died during treatment or within 30 days of the last dose of study medication (abiraterone acetate or placebo), primarily due to progression of prostate cancer (8% and 10% of patients, respectively). In the overall abiraterone acetate group, 9% of patients died during treatment or within 30 days of the last dose. In the pooled Phase 1/2 studies group , 4% of patients died during treatment or within 30 days of the last dose.

Table 23: All deaths, Integrated Safety population

Cause of Death	Abiraterone COU-AA-301 (N=791)	Placebo COU-AA-301 (N=394)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Total number of patients who died on treatment or within 30 days of last dose	84 (10.6%)	52 (13.2%)	11 (3.9%0	95 (8.9%0
Progressive disease	60 (7.6%)	39 (9.9%)	3 (1.1%)	63 (5.9%)
Other	23 (2.9%)	13 (3.3%)	5 (1.8%)	28 (2.6%)
Unknown	1 (0.1%)	0	3 (1.1%)	4 (0.4%)

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

The incidence of AEs with an outcome of death that occurred at any time during the study or during survival followup, through the clinical cutoff date, is summarised in the following table.

Table 24: Causes of deaths and Treatment-Emergent Adverse Events leading to death

	Abiraterone COU-AA-301 (N=791)	Placebo COU-AA-301 (N=394)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Number of patients with a TEAE leading to death	92 (11.6%)	58 (14.7%)	14 (5.0%)	106 (9.9%)
General disorders and administration site conditions	73 (9.2%)	40 (10.2%)	4 (1.4%)	77 (7.2%)
Cardiac disorders	9 (1.1%)	5 (1.3%)	3 (1.1%)	12 (1.1%)
Infections and infestations	4 (0.5%)	3 (0.8%)	2 (0.7%)	6 (0.6%)
Respiratory, thoracic and mediastinal disorders	4 (0.5%)	4 (1.0%)	1 (0.4%)	5 (0.5%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1%)	2 (0.5%)	2 (0.7%)	3 (0.3%)
Renal and urinary disorders	2 (0.3%)	2 (0.5%)	1 (0.4%)	3 (0.3%)
Gastrointestinal disorders	1 (0.1%)	1 (0.3%)	1 (0.4%)	2 (0.2%)
Metabolism and nutrition disorders	0	0	2 (0.7%)	2 (0.2%)
Vascular disorders	0	0	2 (0.7%)	2 (0.2%)
Musculoskeletal and connective tissue disorders	0	0	1 (0.4%)	1 (0.1%)
Nervous system disorders	1 (0.1%)	1 (0.3%)	0	1 (0.1%)
Injury, poisoning and procedural complications	0	2 (0.5%)	0	0

Serious adverse events

The incidence of SAEs reported in at least 1% of patients in any group of the integrated safety population is summarised in the following table.

Table 25: Serious TEAEs reported in at least 1% of patients, Integrated Safety population

MedDRA SOC Term MedDRA Preferred Term	Placebo COU-AA-301 (N=394)	AA COU-AA-301 (N=791)	AA Pooled Phase 1/2 (N=279)	Overall AA (N=1070)
Total no. subjects with a treatment-emergent serious adverse event	163 (41.4%)	297 (37.5%)	100 (35.8%)	397 (37.1%)
Infections and infestations	20 (5.1%)	61 (7.7%)	28 (10.0%)	89 (8.3%)
Pneumonia	4 (1.0%)	15 (1.9%)	7 (2.5%)	22 (2.1%)
Urinary tract infection	3 (0.8%)	14 (1.8%)	8 (2.9%)	22 (2.1%)
Sepsis	2 (0.5%)	9 (1.1%)	5 (1.8%)	14 (1.3%)
Urosepsis	1 (0.3%)	3 (0.4%)	3 (1.1%)	6 (0.6%)
Nervous system disorders	34 (8.6%)	48 (6.1%)	22 (7.9%)	70 (6.5%)
Spinal cord compression	17 (4.3%)	20 (2.5%)	6 (2.2%)	26 (2.4%)
Dizziness	1 (0.3%)	3 (0.4%)	4 (1.4%)	7 (0.7%)
Syncope	2 (0.5%)	2 (0.3%)	4 (1.4%)	6 (0.6%)
Musculoskeletal and connective tissue disorders	39 (9.9%)	46 (5.8%)	20 (7.2%)	66 (6.2%)
Back pain	11 (2.8%)	6 (0.8%)	9 (3.2%)	15 (1.4%)
Bone pain	13 (3.3%)	14 (1.8%)	1 (0.4%)	15 (1.4%)
Arthralgia	4 (1.0%)	2 (0.3%)	5 (1.8%)	7 (0.7%)
Muscular weakness	1 (0.3%)	4 (0.5%)	3 (1.1%)	7 (0.7%)
Musculoskeletal pain	1 (0.3%)	3 (0.4%)	3 (1.1%)	6 (0.6%)
Pain in extremity	7 (1.8%)	3 (0.4%)	2 (0.7%)	5 (0.5%)
Gastrointestinal disorders	23 (5.8%)	41 (5.2%)	19 (6.8%)	60 (5.6%)
Vomiting	9 (2.3%)	12 (1.5%)	6 (2.2%)	18 (1.7%)
Nausea	3 (0.8%)	5 (0.6%)	7 (2.5%)	12 (1.1%)
Abdominal pain	2 (0.5%)	5 (0.6%)	5 (1.8%)	10 (0.9%)
Constipation	3 (0.8%)	5 (0.6%)	3 (1.1%)	8 (0.7%)
Diarrhoea	2 (0.5%)	3 (0.4%)	3 (1.1%)	6 (0.6%)
General disorders and administration site conditions	28 (7.1%)	40 (5.1%)	15 (5.4%)	55 (5.1%)
Fatigue	6 (1.5%)	7 (0.9%)	5 (1.8%)	12 (1.1%)
Disease progression	2 (0.5%)	11 (1.4%)	0	11 (1.0%)
Pyrexia	9 (2.3%)	5 (0.6%)	5 (1.8%)	10 (0.9%)
Pain	5 (1.3%)	1 (0.1%)	0	1 (0.1%)
Renal and urinary disorders	25 (6.3%)	43 (5.4%)	11 (3.9%)	54 (5.0%)
Haematuria	11 (2.8%)	9 (1.1%)	4 (1.4%)	13 (1.2%)
Hydronephrosis	3 (0.8%)	11 (1.4%)	0	11 (1.0%)
Renal failure	2 (0.5%)	3 (0.4%)	5 (1.8%)	8 (0.7%)
Urinary retention	5 (1.3%)	7 (0.9%)	0	7 (0.7%)
Renal failure acute	4 (1.0%)	6 (0.8%)	0	6 (0.6%)
Metabolism and nutrition disorders	14 (3.6%)	28 (3.5%)	19 (6.8%)	47 (4.4%)
Dehydration	5 (1.3%)	12 (1.5%)	5 (1.8%)	17 (1.6%)
Hypokalaemia	0	6 (0.8%)	7 (2.5%)	13 (1.2%)
Anorexia	2 (0.5%)	3 (0.4%)	6 (2.2%)	9 (0.8%)

Blood and lymphatic system disorders	16 (4.1%)	29 (3.7%)	14 (5.0%)	43 (4.0%)
Anaemia	13 (3.3%)	22 (2.8%)	12 (4.3%)	34 (3.2%)
Thrombocytopenia	1 (0.3%)	6 (0.8%)	3 (1.1%)	9 (0.8%)
Injury, poisoning and procedural complications	6 (1.5%)	23 (2.9%)	10 (3.6%)	33 (3.1%)
Femur fracture	0	1 (0.1%)	5 (1.8%)	6 (0.6%)
Cardiac disorders	5 (1.3%)	23 (2.9%)	8 (2.9%)	31 (2.9%)
Atrial fibrillation	2 (0.5%)	4 (0.5%)	3 (1.1%)	7 (0.7%)
Respiratory, thoracic and mediastinal disorders	16 (4.1%)	18 (2.3%)	12 (4.3%)	30 (2.8%)
Dyspnoea	4 (1.0%)	7 (0.9%)	8 (2.9%)	15 (1.4%)
Pulmonary embolism	9 (2.3%)	3 (0.4%)	1 (0.4%)	4 (0.4%)
Investigations	5 (1.3%)	10 (1.3%)	12 (4.3%)	22 (2.1%)
Alanine aminotransferase increased	1 (0.3%)	2 (0.3%)	3 (1.1%)	5 (0.5%)
Aspartate aminotransferase increased	1 (0.3%)	1 (0.1%)	4 (1.4%)	5 (0.5%)
Vascular disorders	2 (0.5%)	13 (1.6%)	8 (2.9%)	21 (2.0%)
Hypotension	1 (0.3%)	3 (0.4%)	4 (1.4%)	7 (0.7%)

Laboratory findings

The proportion of patients who had Grade 3 or 4 hematologic abnormalities during treatment was identical (26%) in each group of study COU-AA-301. Lymphocytes abnormalities were the most common Grade 3 or 4 hematologic abnormality in each group, occurring in 21% of patients in the abiraterone acetate group and 23% of patients in the placebo group. No other hematologic abnormality occurred in greater than 5% of patients in the abiraterone acetate group or greater than 3% of patients in the placebo group. In the overall abiraterone acetate group, 22% of patients had Grade 3 or 4 hematologic abnormalities during treatment. Lymphocytes abnormalities were the most frequently occurring Grade 3 or 4 haematologic abnormality and they were reported in 18% of patients.

In study COU-AA-301, shifts from Grade 0 or 1 to Grade 3 or 4 for lymphocytes abnormalities were reported in 12% of patients in the abiraterone acetate group and 10% of patients in the placebo group; shifts in hemoglobin were reported in 4% and 2% of patients, respectively. In the overall abiraterone acetate group, shifts from Grade 0 or 1 to Grade 3 or 4 for lymphocytes abnormalities were reported in 10% of patients, and for hemoglobin were reported in 3% of patients.

Grade 3 or 4 serum chemistry abnormalities during treatment were reported in 33% of patients in the abiraterone acetate group and 25% of patients in the placebo group in study COU-AA-301. As previously noted, AEs reported in the hepatotoxicity SMQ were reported in 10% of patients in the COU-AA-301 abiraterone acetate group and 8% of patients in the placebo group. The most frequently reported Grade 3 or 4 serum chemistry abnormality in each group was ALP occurring in 18% of patients in the abiraterone acetate group and 13% of patients in the placebo group. Elevations in ALP were attributed to progressive disease in the bone. No other Grade 3 or 4 serum chemistry abnormality (including low potassium) occurred in greater than 7% of patients in the abiraterone acetate group or greater than 6% of patients in the placebo group.

In study COU-AA-301, shifts from Grade 0 or 1 or Grade 3 or 4 for low potassium occurred in 3.0% of patients in the abiraterone acetate group and 0.3% of patients in the placebo group. In the abiraterone acetate group, shifts from Grade 0 or 1 to Grade 3 or 4 occurred in 5.9% of patients for ALP, 0.9% of patients for ALT, and 1.0% of patients for AST. In the placebo group, such shifts occurred in 4.3% of patients for ALP, 0.3% of patients for ALT, and 0 patients for AST. Patients

beginning Study COU-AA-301 with normal transaminase concentrations infrequently experienced shifts to Grade 3 or 4. However, patients in both groups who began the study with Grade 1 or 2 liver transaminase concentrations (both AST and ALT) appeared to be at higher risk for a shift to higher grade. In the overall abiraterone acetate group, shifts from Grade 0 or 1 to Grade 3 or 4 occurred in 3% of patients for low potassium. Shifts from Grade 0 or 1 to Grade 3 or 4 occurred in 6% of patients for ALP, 1% of patients for ALT, and 1% of patients for AST.

Safety in special populations

Although higher incidences of AEs were observed in patients who were $\geq$ 75 years, the rates of Grade 3 or 4 AEs, SAEs, and AEs with an outcome of death was lower in the abiraterone acetate group compared with the placebo group.

The small proportion of non-white patients prevented any formal comparisons in the AE profile with respect to race.

In non-cancer patients with mild, moderate hepatic impairment compared to matched control patients, adverse events were reported in 8 (33%) patients (2 patients in the mild hepatic impairment cohort had AEs, 3 patients in the moderate impairment cohort and 3 patients in the normal hepatic function cohorts). However, limited safety conclusions can be drawn from this single dose study.

In non-cancer patients with end-stage renal disease (ESRD) and in matched control patients with normal renal function, 1 of 8 patients (13%) in the normal renal cohort had an AE (Grade 1 rhinorrhea). No patients in the ESRD cohort had an AE. Limited safety conclusions can be drawn from this single dose study.

Safety related to drug-drug interactions and other interactions

A phase I study was submitted in which the effect of food on the pharmacokinetics of abiraterone acetate in healthy male subjects was studied. Although food did not substantially change the t_{max} (rate of absorption), systemic exposure to abiraterone, as assessed by C_{max}, AUC_{0-t}, and AUC_{0-8}, increased with the administration of food compared to the fasted state. Compared to the fasted state, the geometric mean values for abiraterone C_{max} and AUC increased by approximately 7- and 5-fold, respectively, when administered with a low-fat meal, and by approximately 17- and 10-fold, respectively, when administered with a high-fat meal. The t1/2 of abiraterone was comparable between all treatments. The 90% CI for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} ratio estimates (high-fat meal/fasted, low-fat meal/fasted) were all outside the 80% to 125% equivalence range, indicating that food increased the relative bioavailability of abiraterone (data not shown).

Moreover, the results of a drug-drug interaction study of abiraterone acetate plus prednisone with dextromethorphan (substrate of CYP2D6 metbolism) and theophylline (substrate of CYP1A2 metabolism) were submitted (see Clinical Pharmacology section). No deaths, serious adverse events or adverse events leading to treatment discontinuation were reported in this study (data not shown).

Discontinuation due to adverse events

As noted under Participant flow in the pivotal study COU-AA-301, 12.4% of patients in the abiraterone arm and 17.8% of patients in the placebo arm discontinued treatment primarily due to adverse events.

Post marketing experience

Post-marketing experience is limited.

2.6.1. Discussion on clinical safety

The safety population baseline demographics and disease characteristics were well balanced between study arms in the pivotal Study COU-AA-301, which can overall be considered representative of the intended target population (mCRPC following docetaxel failure), although patients with poor performance status (ECOG 2-3) and non-white population is underrepresented.

Both in the abiraterone arm of the pivotal trial and in the overall abiraterone acetate group, the most frequently reported AEs were fatigue, back pain, nausea, and constipation, consistent with the natural history of mCRPC. In the overall abiraterone acetate group, the most frequently reported AEs were fatigue, nausea, back pain, arthralgia and peripheral oedema.

Compared with placebo and prednisone in Study COU-AA-301, treatment with abiraterone acetate and prednisone did not increase the incidence of Grade 3 or 4 AEs, SAEs, AEs leading to treatment discontinuation, or AEs with an outcome of death, indicating that these events were likely related to the patients' prostate cancer. Treatment-emergent SAEs more commonly reported in the AA group than in the placebo group of Study COU-AA-301 included cardiac disorders, vascular disorders, and infections and infestations (primarily due to an increase of urinary tract infections). The most common AEs with an outcome of death were disease progression events. The incidence of Grade 3 or 4 AEs, AEs leading to treatment discontinuation, and AEs leading to death was higher in the Study COU-AA-301 abiraterone acetate group compared with the pooled Phase 1/2 studies, possibly due to the more advanced stage of prostate cancer in the patient population of the pivotal study.

The most common adverse drug reactions observed in the overall abiraterone acetate group (n=1,070) were peripheral oedema, hypokalemia, urinary tract infection, and hypertension. Consistent with the pharmacologic mechanism of action of abiraterone, mineralocorticoid-related toxicities (based on the SMQ grouping), such as fluid retention/edema (31% versus 22%), hypokalemia (17% versus 8%), and hypertension (10% versus 8%) were observed more frequently for patients treated with abiraterone acetate and prednisone compared with those treated with placebo and prednisone, respectively, in Study COU-AA-301. However, when standardized for longer exposure time, only hypokalemia (47 events/100 P-Y versus 29 events/100 P-Y, respectively) and fluid retention/edema (71 events/100 P-Y versus 65 events/100 P-Y, respectively) were found to occur more frequently in the abiraterone group than in the placebo group (not hypertension). Urinary tract infection exposure-adjusted rate was also higher in abiraterone than in placebo-treated patients (24 events/100 P-Y and 18 events/100 P-Y, respectively). The mechanism involved in the higher observed incidence of urinary infections in the abiraterone group is unclear.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics (SmPC).

Co-administration of prednisone from the beginning of treatment and frequent electrolyte monitoring in Study COU-AA-301 appeared to decrease the incidence and severity of the AEs related to mineralocorticoid excess compared with some of the early stage studies which did not include the uniform administration of low-dose glucocorticosteroids. Consequently, the rates of fluid retention/edema, hypertension, and hypokalemia were all higher in pooled Phase 1/2 studies compared with Study COU-AA-301. Across all studies in patients with mCRPC, hypertension, hypokalemia, and peripheral oedema were most often Grade 1 or 2 non-SAEs, and they only

infrequently interfered with abiraterone acetate treatment, as evidenced by low rates of dose modifications/reductions, treatment discontinuations or deaths due to any of the 3 terms.

The incidence of cardiac events was slightly higher in the abiraterone acetate and prednisone group compared with the placebo and prednisone group (13% versus 11%, respectively) in Study COU-AA-301. The standardised (in P-Y) rates were also higher for the abiraterone acetate group. However, the rates of cardiac-related death were low and balanced in the 2 groups (1% of patients in each group) in Study COU-AA-301 and were similar to that of the early stage studies (1%). In addition, death due to myocardial infarction was infrequent in the 2 groups in Study COU-AA-301 (1 patient each) or in the pooled Phase ½ studies (2 [0.7%] patients).

Safety in patients with left ventricular ejection fraction < 50% or NYHA Class III or IV heart failure has not been established. Zytiga should be used with caution in patients with a history of cardiovascular disease. Before treatment hypertension must be controlled and hypokalaemia must be corrected. Caution is also required in treating patients whose underlying medical conditions might be compromised by increases in blood pressure, hypokalaemia, e.g., those on cardiac glycosides, or fluid retention, e.g., those with heart failure, severe or unstable angina pectoris, recent myocardial infarction or ventricular arrhythmia and those with severe renal impairment. Blood pressure, serum potassium and fluid retention should be monitored before treatment and at least monthly thereafter. This information is reflected in sections 4.4 and 4.8 of the SmPC.

As data from several randomised Phase 3 studies suggest that chronic ADTs are associated with QT interval prolongation, which may lead to the development of cardiac arrhythmias (Garnick, 2004), there were some concerns regarding the potential risk of AA in this regard. AA did not seem to have a major effect on the QT/QTc interval or to affect the ventricular repolarization to an extent that would require substantial risk-benefit considerations in patients with mCRPC. In addition, the trial COU-AA-006 was designed to specifically assess this issue. There were no notable differences between the MAA and the updated safety analysis in the overall AE profile in Study COU-AA-006. Cardiac AEs were rare (atrial fibrillation in 1 patient), and did not result in treatment discontinuation or abiraterone acetate dose modification or reduction. In addition, no patient had a maximum individual change in QTcF from baseline exceeding 30 msecs at post-dose time points, and only 1 patient had a maximum individual change in QTcB from baseline exceeding 30 msecs at a later time post-dose point.

Overall, there was a mild increase of AEs reported in the hepatotoxicity (LFT abnormalities) SMQ in the abiraterone group (10%) as compared to the placebo group (8%) in Study COU-AA-301, basically due to an increase of ALT (any grade: 3% versus 1%). However, after standardizing for the difference in duration of treatment exposure, a higher number of SMQ events/100 P-Y was in fact observed in the placebo group (33 events in the abiraterone acetate group and 42 events in the placebo group). Moreover, the incidence of clinically relevant elevations of liver transaminases or bilirubin (SAEs, grade 3-4 or AEs leading to treatment discontinuation) were not significantly different among study arms (Study COU-AA-301) and very low in any case (<1%). No AEs with an outcome of death were reported. Increases in hepatic enzymes occurring during treatment were managed with careful laboratory monitoring, treatment interruptions and retreatment only after return of the LFTs to baseline or Grade 1. Although no patients treated with abiraterone acetate were identified as having met all Hy's Law criteria, 2 cases of drug-induced liver injury were identified by the Applicant; 1 in the pivotal study and 1 in the early stage study, COU-AA-003. Hepatotoxicity is being managed as an identified risk in the Risk Management Plan.

Moreover, serum transaminase levels should be measured prior to starting treatment, every two weeks for the first three months of treatment, and monthly thereafter. If clinical symptoms or signs suggestive of hepatotoxicity develop, serum transaminases, in particular serum ALT, should be

measured immediately. If at any time the ALT rises above 5 times the upper limit of normal treatment should be interrupted immediately and liver function closely monitored. Re-treatment may take place only after return of liver function tests to the patient's baseline and at a reduced dose level.

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

Patients with active or symptomatic viral hepatitis were excluded from clinical trials; thus, there are no data to support the use of Zytiga in this population.

Zytiga is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients and in women who are or may potentially be pregnant. Abiraterone is not for use in women. There are no human data on the use of the medicine in pregnancy and this medicinal product is not for use in women of childbearing potential. Maternal use of a CYP17 inhibitor is expected to produce changes in hormone levels that could affect development of the foetus. Moreover, it is not known whether abiraterone or its metabolites are present in semen. A condom is required if the patient is engaged in sexual activity with a pregnant woman. If the patient is engaged in sex with a woman of childbearing potential, a condom is required along with another effective contraceptive method. Furthermore, it is not known if either abiraterone acetate or its metabolites are excreted in human milk. Finally, reproductive toxicology studies were not conducted with abiraterone acetate and no fertility data are available.

Caution is advised and monitoring for adrenocortical insufficiency should occur if patients are withdrawn from prednisone or prednisolone. If ZYTIGA is continued after corticosteroids are withdrawn, patients should be monitored for symptoms of mineralocorticoid excess. In patients on prednisone or prednisolone who are subjected to unusual stress, an increased dose of corticosteroids may be indicated before, during and after the stressful situation.

Decreased bone density may occur in men who are treated with Zytiga. The use of abiraterone in combination with glucocorticoid could increase this effect.

Zytiga contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine. The sodium content of this medicinal product is to be taken into consideration for patients on a controlled sodium diet.

There have been no reports of overdose during clinical studies. There is no specific antidote. In the event of an overdose, administration should be withheld and general supportive measures undertaken, including monitoring for arrhythmias, hypokalaemia and for signs and symptoms of fluid retention. Liver function should also be assessed.

The potential risk for drug-drug interactions is not fully elucidated. In particular, the possible effect of CYP3A4 inducers leading to a possible decrease of effect of abiraterone due to enhanced elimination is possible. As a consequence, the Applicant is conducting a drug-drug interaction study to evaluate the effect of a strong CYP3A4 inducer (ie, rifampicin) or a strong CYP3A4 inhibitor (ie, ketoconazole) on the pharmacokinetics of abiraterone after oral administration of abiraterone acetate. A relevant precaution was included in section 4.5 of the SmPC.

Caution is advised when ZYTIGA 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, flecanide, codeine,

oxycodone and tramadol (the latter three products requiring CYP2D6 to form their active analgesic metabolites).

2.6.2. Conclusions on the clinical safety

The safety profile of abiraterone acetate is considered acceptable and generally manageable with basic medical interventions (oral potassium supplements, diuretics and antihypertensive medication). Toxicities were generally mild, and resulted in infrequent dose reductions, dose interruptions, or discontinuations. In this regard it should be noted that the safety profile of abiraterone acetate is distinct from that typically induced by conventional cytotoxic agents, frequently associated with AEs that are potentially dose-limiting, debilitating, cumulative, or life-threatening. Indeed, AEs such as hypertension or hypokalemia are generally asymptomatic, and although fluid retention/oedema or urinary tract infections may be more disturbing to the patient, abiraterone does not induce toxicities such as myelosuppression, diarrhoea, mucositis, asthenia, alopecia, etc, which not only may be associated with higher risks of severe medical complications including death, but often have a major impact on the patient's quality of life which is particularly relevant in the context of non-curative therapy for an end-stage disease.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The applicant submitted a risk management plan.

Table 26: Summary of the risk management plan

Safety Concern	Agreed Pharmacovigilance Activities (routine and additional)	Agreed Risk Minimisation Activities (routine and additional)
Important identified risks:		
1) Hypertension 2) Hypokalaemia 3) Fluid retention/ oedema	Routine pharmacovigilance. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. <u>Additional</u> None	<u>Routine</u> 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. Additional guidance for the physician is also provided in Sections 4.2, 4.4, and 4.8 of the SmPC. <u>Additional</u> None

Safety Concern	Agreed Pharmacovigilance Activities (routine and additional)	Agreed Risk Minimisation Activities (routine and additional)
4) Hepatotoxicity	Routine pharmacovigilance. Targeted follow-up with reporter through a guided questionnaire to collect additional information related to this risk. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. <u>Additional</u> None.	<u>Routine</u> 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 transaminases before and during treatment). In addition, patients who develop severe hepatotoxicity (ALT 20 times the ULN) anytime while on therapy should be discontinued and patients should not be retreated (SmPC Section 4.2). SmPC Sections 4.2, 4.4, and 4.8 provide guidance for the physician. <u>Additional</u> None
5) Cardiac Disorders	Routine pharmacovigilance. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. <u>Additional</u> None	<u>Routine</u> The SmPC (Section 4.4) has precautions for treating patients at risk for cardiac issues and Section 4.8 has additional information for the physician on the cardiovascular effects. <u>Additional</u> None
Important potential risks:		
1) Osteoporosis	Routine pharmacovigilance. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. <u>Additional</u> None	<u>Routine</u> The SmPC (Section 4.4) and Package Leaflet provide information to the prescriber and patient about the potential for decreased bone density that may occur in men with mCRPC and that the use of abiraterone acetate in combination with a glucocorticoid could increase this effect. <u>Additional</u> None
2) Cataract	Routine pharmacovigilance. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. <u>Additional:</u> The mechanism of cataract formation in the rat will be further investigated in nonclinical studies.	<u>Routine</u> None <u>Additional</u> None

Safety Concern	Agreed Pharmacovigilance Activities (routine and additional)	Agreed Risk Minimisation Activities (routine and additional)
3) Drug-drug interaction (CYP2D6)	Routine pharmacovigilance. Relevant clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. 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
4) Increased exposure with food	Routine pharmacovigilance. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP. Additional Study 212082PCR2008: A Phase 2 open-label study to determine short-term safety of abiraterone acetate in fasting and fed states in subjects with mCRPC.	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. 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. Additional Study 212082PCR1004: A single-dose, pharmacokinetic trial in non-cancer subjects with severe hepatic impairment (Child-Pugh Class C).	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, so abiraterone acetate should be avoided in these patients (SmPC Section 4.2). Therefore, there are no data to support use in this patient population. Additional None

Safety Concern	Agreed Pharmacovigilance Activities (routine and additional)	Agreed Risk Minimisation Activities (routine and additional)
3) Use in patients with severe renal impairment	Routine pharmacovigilance. <u>Additional</u> None	<u>Routine</u> 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. <u>Additional</u> 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. <u>Additional</u> None	<u>Routine</u> 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 < 50% or NYHA Class III or IV heart failure has not been established. Before treatment, hypertension must be controlled and hypokalaemia must be corrected (SmPC Section 4.4). <u>Additional</u> None
5) Use in non-white patients	Routine pharmacovigilance. All ongoing clinical trial data are part of the Pharmacovigilance Plan, including long-term trial extensions and the EAP (with a focus on trials enrolling non-white subjects such as the trials in Asia). <u>Additional</u> COU-AA-301; COU-00-302 and 212082PCR3001: An integrated analysis of the safety data from these trials will be performed.	<u>Routine</u> The SmPC presents the baseline demographics of the COU-AA-301 trial population (SmPC Section 5.1). <u>Additional</u> None

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

Table 27: Additional pharmacovigilance activities

Description	Due date
The mechanism of cataract formation in the rat will be further investigated in the ongoing 2-year rat carcinogenicity study and in a 6-month carcinogenicity study in the transgenic Tg.rasH2 mouse.	2Q 2013 (rat) 3Q/4Q 2012 (mouse)

Description	Due date
Study 212082PCR2008; A Phase 2 open-label study to determine short-term safety of abiraterone acetate in fasting and fed states in subjects with mCRPC	28/02/2014
Study 212082PCR1004: A single-dose, pharmacokinetic trial in non-cancer subjects with severe hepatic impairment (Child-Pugh Class C).	30/04/2014
COU-AA-301; COU-00-302 and 212082PCR3001: An integrated analysis of the safety data from these trials will be performed.	3Q/2012

No additional risk minimisation activities were required beyond those included in the product information.

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

One pivotal trial was submitted in support of the efficacy of abiraterone acetate in combination with concomitant low dose glucocorticoid therapy in patients with advanced metastatic castrate refractory prostate cancer (mCRPC) in a population that had previously failed to 1 or 2 docetaxel-based regimens. Median overall survival was 14.8 months in the abiraterone group and 10.9 months in the placebo group. There was a 33% relative improvement in 12-month survival rate (60% in the abiraterone acetate group versus 45% in the placebo group). The study met therefore its primary endpoint at the pre-specified significance level (0.0141) required to cross the efficacy boundary for the interim analysis at the clinical cut-off (22 January 2010). Treatment with abiraterone acetate decreased the risk of death by 35% compared with placebo (HR=0.646; 95% CI: 0.543, 0.768; p<0.0001). The benefit in survival was confirmed in an updated analysis (cutoff of 20 September 2010, HR=0.740; 95%CI: 0.638, 0.859; p<0.0001), showing a median survival of 15.8 months for the AA group versus 11.2 months for the placebo group. Treatment effect on OS was robust after adjustment for stratification factors in multivariate analysis and was consistently favourable across all subgroups (ECOG, pain score, prior lines of chemotherapy, type of progression, age, visceral disease, baseline PSA, LDH or alkaline phosphatase, and geographical region).

This effect was further substantiated by results in the pre-specified secondary efficacy endpoints: time to biochemical or radiological disease progression was significantly increased, such as time to PSA progression [10.2 months versus 6.6 months in controls, HR=0.58, p<0.0001] or radiographic progression-free survival [5.6 months versus 3.6 months in controls, HR=0.673, p<0.0001]. PSA response rate was significantly greater in abiraterone treated patients compared to the placebo group (38% versus 10%, p<0.0001), also when only confirmed PSA responses were considered (29% versus 6%, p<0.0001), as was objective response rate in the subset of patients with baseline measurable disease (14% versus 3%, p<0.0001). Finally, symptom-related endpoints, such as pain palliation, time to pain progression, skeletal-related events, and quality of life scores also tended to favour abiraterone-treated patients over placebo-control ones.

Uncertainty in the knowledge about the beneficial effects

One limitation is the limited number of non-Caucasian patients in the pivotal clinical trial. Moreover, patients having received prior ketoconazol therapy were excluded from the study. Both issues are considered relevant information for prescribers which was reflected in the SmPC. Moreover, the lack of data in non-white patients is important missing information reflected in the RMP.

Risks

Unfavourable effects

The most frequently reported AEs reported in the pivotal trial were fatigue (44% and 43% in the abiraterone acetate and placebo groups, respectively), back pain (30% and 33%, respectively), nausea (30% and 32%, respectively), and constipation (26% and 31%, respectively), consistent with the natural history of mCRPC. In the overall abiraterone acetate group, the most frequently reported AEs were fatigue (44%), nausea (28%), back pain (27%), and arthralgia and edema peripheral (26%).

The most common adverse drug reactions observed in the overall abiraterone acetate group (n=1,070) were peripheral edema, hypokalemia, urinary tract infection, and hypertension. Consistent with the pharmacologic mechanism of action of abiraterone, mineralocorticoid-related toxicities (based on the SMQ grouping) such as fluid retention/edema (31% versus 22%), hypokalemia (17% versus 8%), and hypertension (10% versus 8%) were observed more frequently for patients treated with abiraterone acetate. Co-administration of prednisone from the beginning of treatment and frequent electrolyte monitoring in Study COU-AA-301 appeared to decrease the incidence and severity of the AEs related to mineralocorticoid excess compared with some of the early stage studies which did not include the uniform administration of low-dose glucocorticosteroids. Most of these events were Grade 1 or 2, non-SAEs (1% or less for each term, respectively), and infrequently interfered with abiraterone acetate treatment, as evidenced by low rates of dose modifications/reductions, treatment discontinuations or deaths due to any of the 3 terms (1% or less for each term, respectively).

In addition to the expected AEs due to increased mineralocorticoid activity, the following key safety risks have been identified:

The incidence of cardiac events was slightly higher in the abiraterone acetate and prednisone group with no differences in the rates of cardiac-related death (<1% of patients in each group).

There is a risk for increased urinary infections.

Finally, there was an increase for hepatotoxic events in relation to treatment with abiraterone (10% vs 8% in AA and placebo, respectively). Increments in hepatic enzymes occurring during treatment were managed with careful laboratory monitoring, treatment interruptions and retreatment only after return of the LFTs to baseline or Grade 1. Although no patients treated with abiraterone acetate were identified as having met all Hy's Law criteria, 2 cases of drug-induced liver injury were identified; 1 in the pivotal study and 1 in the early stage study, COU-AA-003. Hepatotoxicity is considered an identified risk for abiraterone therapy.

Uncertainty in the knowledge about the unfavourable effects

Overall the unfavourable effects were predictable and in keeping with the mechanism of action of abiraterone (mineralocorticoid excess) or the nature of the disease. However, the role of abiraterone

in hepatotoxicity is not fully understood. Increases in hepatic enzymes were observed during treatment with abiraterone and 2 patients (1 patient in the pivotal Study COU-AA-301 and 1 patient in Phase 2 Study COU-AA-003) were identified as potentially having met Hy's Law criteria. Routine and additional pharmacovigilance activities (see Table 27 above) are expected to provide further insight into the role of abiraterone in hepatotoxicity.

The potential risk for drug-drug interactions is not fully elucidated. In particular, the possible effect of CYP3A4 inducers leading to a possible decrease of effect of abiraterone due to enhanced elimination is possible. Ongoing interaction studies with inducers and inhibitors of CYP3A4 will elucidate the effect of CYP3A4 inhibition and especially of CYP3A4 induction on the pharmacokinetics of abiraterone.

Benefit-risk balance

Importance of favourable and unfavourable effects

Treatment with abiraterone showed an improvement in the median overall survival in a population with very few therapeutic alternatives. Results in key secondary endpoints supported the observed improvement in overall survival and measures of functional status and symptom-related endpoints also tended to favour abiraterone-treated patients over placebo-control ones. Abiraterone showed a clear antitumour effect in patients with advanced mCRPC that have failed prior docetaxel therapy. The results are considered to be mature, robust, consistent, and of clinical relevance.

The safety profile is considered acceptable and generally manageable with basic medical interventions (oral potassium supplements, diuretics and antihypertensive medication). Toxicities were generally mild, and resulted in infrequent discontinuations. In this regard it should be noted that the safety profile of abiraterone acetate is distinct from that typically induced by conventional cytotoxic agents, frequently associated with AEs that are potentially dose-limiting, debilitating, cumulative, or life-threatening. Indeed, AEs such as hypertension or hypokalemia are generally asymptomatic, and although fluid retention/edema or urinary tract infections may be more disturbing to the patient, abiraterone does not induce toxicities such as myelosuppression, diarrhoea, mucositis, asthenia, alopecia, etc, which may not only be associated with higher risks of severe medical complications including death, but often have a major impact on the patient's quality of life, which is particularly relevant in the context of non-curative therapy for an end-stage disease.

Benefit-risk balance

Overall, the efficacy of abiraterone has been demonstrated. The fact that this is an orally administered medicine is considered an additional advantage for this clinical setting. The adverse event profile is expected according to the mechanism of action of abiraterone and generally manageable with basic medical interventions.

Discussion on the benefit-risk balance

The benefit-risk balance for abiraterone in combination with prednisone or prednisolone for the treatment of metastatic advanced prostate cancer (castration resistant prostate cancer) in adult patients whose disease has progressed on or after a docetaxel-based chemotherapy regimen is considered positive. The favourable effects outweigh the negative effects and Zytiga is expected to be of major public health interest due to the poor prognosis of the target population that represents a high unmet medical need, while the novel mechanism of abiraterone may offer an alternative therapeutic option for this patient population.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Zytiga in combination prednisone or prednisolone in the treatment of metastatic castration resistant prostate cancer in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance and the fact that it is not authorised as a medicinal product within the European Union nor is it a salt, complex, isomer or mixture of isomers, or a derivative of an authorised substance, the CHMP considers that abiraterone acetate is to be qualified as a new active substance.

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