12 October 2017
EMA/816845/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Zytiga

International non-proprietary name: abiraterone acetate

Procedure No. EMEA/H/C/002321/II/0047

Note

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

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List of abbreviations

AA-P	abiraterone acetate plus low-dose prednisone and ADT
ADT	androgen deprivation therapy
AE	adverse event
AESI	Adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BFI	Brief Fatigue Inventory
BICR	blinded independent central review
BPI-SF	Brief Pain Inventory-Short Form
CRF	case report form (paper or electronic as appropriate for this study)
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	Evaluation of Drug Induced Serious Hepatotoxicity
EQ-5D-5L	EuroQoL
FACT-P	Functional Assessment of Cancer Therapy-Prostate
GCP	Good Clinical Practice
GnRH	gonadotrophin-releasing hormone
HR	hazard ratio
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IPCW	Inverse Probability censoring weighted
ITT	intent-to-treat
IWRS	interactive web response system
LFT	liver function test
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MedDRA	Medical Dictionary for Regulatory Activities
mHNPC	metastatic hormone-naive prostate cancer
miRNA	microRNA
MRI	magnetic resonance imaging
NCI	National Cancer Institute
NE	not evaluable
PFS2	progression-free survival 2
PRO	patient-reported outcome(s)
PRS	pain-related subscale
PSA	prostate-specific antigen
OS	overall survival
RECIST	Response Evaluation Criteria in Solid Tumors
rPFS	radiographic progression-free survival
SAE	serious adverse event
SOC	system organ class
ULN	upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International NV submitted to the European Medicines Agency on 5 April 2017 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSCP) in adult men in combination with androgen deprivation therapy (ADT) for Zytiga plus prednisone or pednisolone; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. The Risk Management Plan was updated in the light of the data submitted (version 14.2). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/0001/2015 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

Scientific advice was sought from the Committee for Medicinal Products for Human Use (CHMP) on 19 April 2012 (EMEA/H/SA/985/3/2012/II) and on 20 March 2014 (EMEA/H/SA/985/3/FU/1/2014/II) in relation to the pivotal study PCR3011 submitted in support of the present application.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Jorge Camarero Jiménez Co-Rapporteur: Robert James Hemmings

Timetable	Actual dates
Submission date	5 April 2017
Start of procedure:	22 April 2017
CHMP Rapporteur Assessment Report	26 June 2017
CHMP Co-Rapporteur Assessment Report	16 June 2017
PRAC Rapporteur Assessment Report	26 June 2017
Updated PRAC Rapporteur Assessment Report	30 June 2017
PRAC Outcome	6 July 2017
CHMP members comments	10 July 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	14 July 2017
Request for supplementary information (RSI)	20 July 2017
CHMP Rapporteur Assessment Report	13 September 2017
PRAC Rapporteur Assessment Report	14 September 2017
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	26 September 2017
PRAC Outcome	28 September 2017
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	6 October 2017
Opinion	12 October 2017

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Newly diagnosed high risk metastatic hormone sensitive prostate cancer

2.1.2. Epidemiology and risk factors, screening tools/prevention

Prostate cancer is the second most common cancer in men. An estimated 1.1 million men worldwide were diagnosed with prostate cancer in 2012, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases (759,000) occurring in more developed regions. In 2012, 420000 new cases were diagnosed and 101000 deaths estimated in Europe (Globocan, 2012).

The risk of clinically significant prostate cancer is related to age, ethnicity, family history, PSA level, free/total PSA ratio and findings on digital rectal examination (DRE) (Thompson IM, *et al*. 2006).

At diagnosis, patients may present with localised, regional or distant metastatic disease. Approximately 15-30% of newly diagnosed patients with prostate cancer have metastatic disease at the time of

diagnosis (Flamand 2008, Howard 2001, Jack 2009, Jonsson 2006, Norgaard 2010, Quaglia 2003). Prostate-specific antigen (PSA) testing has allowed earlier detection of prostate cancer.

2.1.3. Biologic features

Newly diagnosed prostate cancers are dependent upon androgen through activation of the androgen receptor. Androgens are a key factor in prostatic development, homeostasis and malignancy.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Patients with newly diagnosed metastatic hormone naïve prostate cancer (mHNPC) typically have a high disease burden, and the majority present with bone metastases (James 2015). Bone metastases are a major cause of morbidity and mortality, and therefore pose a substantial burden as they are associated with skeletal-related events, pain, and the need for radiation therapy or surgery to bone (Smith 2012).

The median survival for patients with mHNPC is variable (ranging from 13 months up to 75 months), and is dependent on the presence of high-risk prognostic features such as high PSA at diagnosis, high Gleason score, increased volume of metastatic disease, presence of bony symptoms (Milikan 2008) or presence of visceral metastasis (Gandaglia 2014).

As a guide to prognosis and therapy, localised disease is classified as low-, intermediate- or high-risk. Patients with intermediate- (T2b and/or GS7 and/or PSA10-20) or high-risk disease (⩾T2c or GS8-10 or PSA >20) should be staged for metastases (Cancer of the Prostate: ESMO Clinical Practice Guidelines).

The prostate cancer staging summary (7th edition of the AJCC/UICC Cancer Staging Handbook) is used for clinical staging (Cancer of the Prostate: ESMO Clinical Practice Guidelines).

2.1.5. Management

Hormone sensitive prostatic cancer (HSPC) responds to treatment that decreases androgen levels. In the hormone naïve setting the standard of care has historically been ADT (luteinizing hormone-releasing hormone [LHRH] agonist or surgical castration) with or without concurrent anti-androgens.

Recently, docetaxel-based chemotherapy has shown to provide significant benefit on OS when combined with ADT metastatic or locally advanced hormone-naïve disease (James *at al*, 2016; Sweeney *et al*, 2015) thus changing disease course (OS medians in the range of 50-60 months compared to medians around 32-45 months if treated with standard ADT) and treatment decisions in the metastatic castration-resistant setting.

The ESMO guideline recommends continuous androgen deprivation therapy (ADT) as first-line treatment of metastatic, hormone-naïve disease and ADT plus docetaxel as first-line treatment of metastatic, hormone-naïve disease in men fit enough for chemotherapy. Three phase III trials compared ADT alone versus ADT plus docetaxel in men with metastatic, hormone-naïve disease and showed a progression-free and/or overall survival benefit for the combination arm (Sweeney C, et al. 2014; Gravis G, et al. 2013, James ND, et al. 2015). Although the efficacy of docetaxel was positive, clinically significant toxicity was also noted (Gravis 2013, James 2016). The toxicities associated with docetaxel include myelosuppression (including febrile neutropenia), fatigue, alopecia, diarrhoea, neuropathy and peripheral oedema (Parker 2015, docetaxel package insert 2015).

About the product

Abiraterone acetate (ZYTIGA) is converted *in vivo* to abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α hydroxylase/C17,20 lyase (CYP17). This enzyme is expressed in and is required for androgen biosynthesis in testicular, adrenal and prostatic tumour tissues. CYP17 catalyses the conversion of pregnenolone and progesterone into testosterone precursors, DHEA and androstenedione, respectively, by 17α hydroxylation and cleavage of the C17,20 bond. CYP17 inhibition also results in increased mineralocorticoid production by the adrenals.

Treatment with ZYTIGA plus prednisone or pednisolone decreases serum testosterone to undetectable levels (using commercial assays) when given with LHRH analogues (or orchiectomy).

A marketing authorisation was granted by the European Commission on 5 September 2011 for ZYTIGA plus prednisone or prednisolone for the treatment of patients with metastatic castrate resistant prostate cancer (mCRPC) whose disease has progressed on or after a docetaxel-based chemotherapy regimen based on the pivotal Study COU-AA-301.

A Type II variation to extend the indication of ZYTIGA plus prednisone or prednisolone for the treatment of patients with mCRPC who are asymptomatic or mildly symptomatic after failure of ADT and in whom chemotherapy is not yet clinically indicated, based on pivotal Study COU-AA-302, was subsequently approved in the European Union (18 December 2012).

Zytiga plus prednisone or prednisolone is currently authorised in more than 100 countries worldwide (including the EU and US) for the treatment of men with mCRPC (exact wording of indications vary).

The applied and recommended indication is:

ZYTIGA plus prednisone or prednisolone is indicated for:

- *the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) (see SmPC section 5.1)*

The recommended dose is 1,000 mg (four 250 mg tablets) as a single daily dose that must not be taken with food. Taking the tablets with food increases systemic exposure to abiraterone (see SmPC sections 4.5 and 5.2).

For mHSPC, ZYTIGA is used with 5 mg prednisone or prednisolone daily.

Type of Application and aspects on development

Scientific advice was sought from the Committee for Medicinal Products for Human Use (CHMP) on 19 April 2012 (EMEA/H/SA/985/3/2012/II) and on 20 March 2014 (EMEA/H/SA/985/3/FU/1/2014/II) in relation to the pivotal study PCR3011 submitted in support of the present application.

Discussion points covered the key elements of the study, including sample size, inclusion of co-primary endpoints, and the statistical analysis plan. A brief summary of the conclusions of the advice are shown below.

<u>EMEA/H/SA/985/3/2012/II (April 2012)</u>

- The CHMP agreed that the proposed key inclusion exclusion criteria appear appropriate
- In order to minimise the risk of bias, the CHMP did not recommend an open-label trial
- The use of prednisone in the control group would be desirable
- There are no specific concerns regarding ADT as the reference
- A successful submission requires sufficiently mature data on overall survival (OS)

- Radiographic progression-free survival (rPFS) could be affected by the open-label nature of the trial and the company should make every effort to make rPFS as precise and robust as possible
- CHMP agreed that no new PK data would be required
- Results from a single pivotal study should be convincing and compelling

EMEA/H/SA/985/3/FU/1/2014/II (March 2014)

- The approach to amend the ongoing study to promote rPFS to co-primary endpoint with OS was agreed
- CHMP agreed that rPFS with a positive trend in OS, and support from secondary endpoints, would be considered a valid measure of clinical benefit
- The double blind design was expected to contribute to minimising bias
- CHMP agreed with the proposed secondary endpoints
- The proposed audit of a random sample of 160 scans could in principle be acceptable
- The proposed analysis plan was endorsed.

2.2. Non-clinical aspects

Apart from the environmental risk assessment, no new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

Table 1: Summary of main study results of ERA

Substance (INN / Invented Name): Abiraterone acetate/ Zytiga			
CAS-number (if available): 154229-19-3			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	5.12	Potential PBT YES
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.12	B
	BCF	903 (for low conc, 0.13 µg/L) 931 (for high conc, 1.3 µg/L	B
Persistence	DT_{50} or ready biodegradability	$DT_{50,}$ freshwater= 2.3 days	not P
Toxicity	NOEC or CMR	NOEC (fathead minnow partial life cycle) = 0.013 µg/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)	0.004	µg/L	> 0.01 threshold (N*)
Other concerns (e.g. chemical class)			N/A
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} > 22,387 Kg/L (log K_{oc} > 4.35)	List all values
Ready Biodegradability Test	OECD 301	12.56 %	Not readily

					biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 2.3 days $DT_{50, sediment}$ = ND $DT_{50, whole system}$ = 4.9 and 3.3 days % shifting to sediment = sediment-bound residue 28.2% and 22.1%			Evidence of primary biodegradation was observed for [^{14}C]abiraterone acetate in the aerobic water/sediment test samples.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**Value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	NOEC EC_{50}(72 h)	1000 > 1000	µg/L 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	21 days
Fish, Early Life Stage Toxicity Test/*Species*	Modified Partial Life-Cycle Exposure with Fathead Minnow (OECD 229)	NOEC	0.013	µg/L	*Pimephales promelas* (Fathead Minnow)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50}(3 h)	> 10^6	µg/L	NOEC(3 h) = 1000 mg/L
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	625 (for low conc, 0.13 µg/L) 576 (for high conc, 1.3 µg/L	µL/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 %
			903 (for low conc) 931 (for high conc)		With lipid normalisation of 5%
Aerobic and anaerobic transformation in soil	OECD 307	DT_{50} %CO_2	18 55.1 %	Days	Evolution of $^{14}CO_2$ (ultimate biodegradation) was 55.1% of the applied radioactivity accumulatively at Day 120. Metabolites identified were [^{14}C]abiraterone and dehydrogenated [^{14}C]abiraterone.
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	250	mg/kg	The nitrate production was inhibited by 3,9% on day 28. The empirical EC_{10}, EC_{25} and EC_{50} values for nitrogen transformation were estimated to be > 250 mg/kg dry soil

Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100 for all species	mg/kg	Bean (*Phaseolus vulgaris)* Oat *(Avena sativa)* Tomato *(Lycopersicon esculentum)*
Earthworm, Acute Toxicity Tests	OECD 207	LC_{50} NOEC	> 1000 500	mg/kg mg/kg	*Eisenia fetida* / 14 days
Collembola, Reproduction Test	ISO 11267	NOEC	1000 for mortality; 500 for re-production	mg/kg	*Folsomia candida* / 28 days
Sediment dwelling organism	OECD 218	NOEC	100	mg/kg	*Chironomus riparius* / 28 days

2.2.2. Discussion on non-clinical aspects

No new nonclinical pharmacology, pharmacokinetics and toxicology data were submitted in this application, which was considered acceptable by the CHMP.

An environmental risk assessment (ERA) was submitted to support the extension of the ZYTIGA plus prednisone or prednisolone indications to include the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT). Formerly, the MAH submitted an ERA that was assessed as part of the initial MA application for Zytiga 250 mcg tablets. An extended partial life cycle study with fathead minnow (Pimephales promelas) was subsequently submitted. The aim of this study was to assess the specific mode of action of abiraterone acetate for endocrine disrupting substances, according to the OECD recommendations. Within this study, an updated ERA report, the toxicity NOEC and $PEC_{SURFACEWATER}$ were refined. In the ERA submitted in the current application, the MAH has refined the $PEC_{SURFACEWATER}$.

2.2.3. Conclusion on the non-clinical aspects

Based on the result of the ratio $PEC_{surfacewater}/PNEC_{water}$, it is concluded that abiraterone acetate may represent a risk to organism populations in the aquatic environment.

Therefore, abiraterone acetate should be used according to the current precautions stated in the SmPC in order to minimise any potential risks to the environment (see SmPC sections 5.3 and 6.6.).

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Table of All Studies

StudyID EudraCT Number First Patient First Visit Completion date Study Status	Country(ies) Number of Centers	Phase Study Description/Design Study Population Primary Objective(s)	Total Number of Subjects	Study Drug(s): Formulation (Route of Administration) Dose Regimen Duration of Treatment	Number of Subjects Treated (by Treatment Group)	Type of Study Report Issue Date Document ID Number CTD Location of Report or Publication
Efficacy and Safety Controlled Studies						
212082PCR3011 Report 25 Jan 2013 CCO: 31 Oct 2016 Ongoing	AUS, ARG, BEL, BRA, BGR, CAN, CHL, CHN, COL, CZE, DEU, DNK, ESP, FIN, FRA, GBR, HUN, ISR, ITA, JPN, KOR, MEX, MYS, NLD, NZL, POL, PRT, ROU, RUS, TUR, UKR, SVK, SWE, ZAF 236[b]	Phase 3, multinational, randomized, double-blind, active-controlled, parallel-group study that evaluated whether abiraterone acetate in combination with low-dose prednisone and ADT is superior to ADT alone in improving rPFS and OS in subjects with mHNPC with high-risk prognostic factors	Planned: 1,200 Randomized: 1,209[a]	Tablets (Oral) Abiraterone acetate 1000 mg (administered as 4 x 250 mg tablets) once daily at least 1 hour before and 2 hours after a meal; prednisone 5 mg orally once daily; and LHRH agonist dosing to achieve and maintain subcastrate concentrations of testosterone (50 ng/dL or 1.7 nM) Abiraterone acetate-matching placebo 4 tablets once daily at least 1 hour before and 2 hours after a meal; prednisone-matching placebo 5 mg orally once daily; and LHRH agonist dosing to achieve and maintain subcastrate concentrations of testosterone (50 ng/dL or 1.7 nM) Duration: until disease progression, withdrawal of consent, unacceptable toxicity, or death	Abiraterone acetate (N=605)[a] Placebo (N=604)[a]	Full Report 13 Mar 2017 EDMS-ERI-138802756 5.3.5.1

2.3.2. Pharmacokinetics

No new data were provided with this submission, which was considered acceptable by the CHMP. The PK of abiraterone has been characterised in healthy volunteers as well as in patients with mCRPC who have progressed on or after treatment with docetaxel in Study COU-AA-301, and in chemotherapy-naïve patients who are asymptomatic or exhibit mild symptoms in the ongoing Study COU-AA-302. It is not expected that abiraterone PK in the newly diagnosed mHNPC patient population in Study 212082PCR3011 would deviate significantly from that observed in the latter 2 patient groups studied.

2.3.3. Pharmacodynamic

No new data were provided with this submission, which was considered acceptable by the CHMP.

The mechanism of action of abiraterone has been previously described (see SmPC section 5.1).

However, there remains a need to develop biomarker strategies to better understand and identify a priori, patients who will derive most benefit from abiraterone. The Clinical Study Report (CSR) and trial protocol of the main study (see under clinical efficacy) describes secondary objectives of identifying predictive markers of abiraterone response or resistance. Exploratory analysis of biomarker tumour samples collected from patients enrolled in this study is ongoing. Expression of response and resistance marker(s) will be correlated with rPFS. Although exploratory nature of this analysis is acknowledged, these data is of interest and the MAH is recommended to submit the results at the earliest opportunity for formal assessment (see letter of recommendations).

2.4. Clinical efficacy

2.4.1. Dose response study

No new dose responses studies were submitted with this application, which was considered acceptable by the CHMP. The dosing of ZYTIGA is in line with the two other approved prostate cancer indications; aside from the change in the recommended dose of prednisone from 10 mg daily to 5 mg daily.

2.4.2. Main study

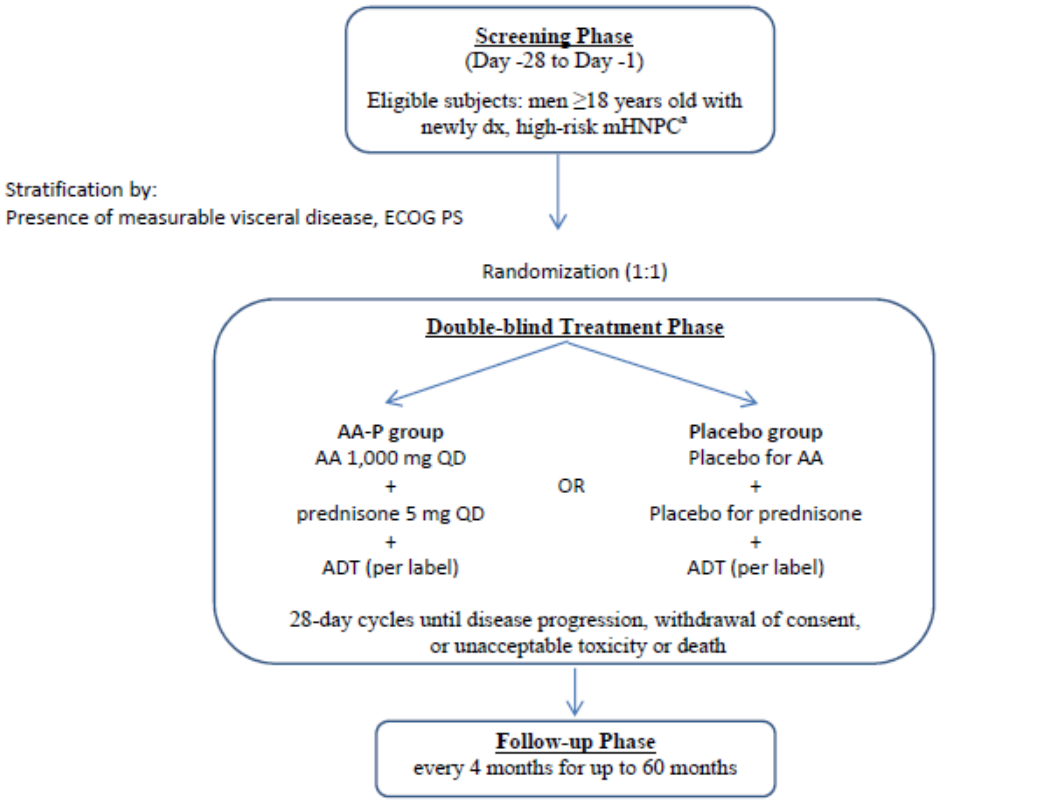
Study LATITUDE: A randomised, double-blind, comparative study of abiraterone acetate plus low dose prednisone plus androgen deprivation therapy (ADT) versus ADT alone in newly diagnosed subjects with high risk, metastatic hormone-naive prostate cancer (mHNPC)

Methods

This was a multinational, randomized, double-blind, active-controlled, parallel-group study of abiraterone acetate plus low-dose prednisone and ADT (AA-P group) compared with placebo and ADT (Placebo group) in subjects with newly diagnosed (within 3 months) mHNPC who had high-risk prognostic factors.

The study consisted of a Screening Phase of up to 28 days before randomization to establish eligibility and document baseline measurements, a Double-blind Treatment Phase (28-day treatment cycle), and a Follow-up Phase of up to 60 months to monitor survival status and subsequent prostate cancer therapy. An Open-label Extension Phase was also planned to allow all subjects to receive active study drug (AA-P) in the event of a positive study result at either the interim analyses or the final analysis.

Extension Phase will allow subjects to receive active drug (abiraterone acetate plus prednisone) for up to 3 years. A diagrammatic representation of the study design is presented below:



AA=abiraterone acetate; AA-P=abiraterone acetate plus low-dose prednisone and ADT; ADT=androgen deprivation therapy; dx=diagnosed; ECOG PS=Eastern Cooperative Oncology Group performance status; mHNPC=metastatic hormone-naïve prostate cancer; QD=once a day
[a] high risk=at least 2 of 3 risk factors (Gleason score ≥8, ≥3 lesions on bone scan, measurable visceral metastasis)

Study participants

The subjects selected for participation in this study were adult men (≥18 years) with high-risk, newly diagnosed mHNPC, who met the following acceptance criteria:

- Newly diagnosed metastatic prostate cancer with metastases within 3 months prior to randomization with histologically or cytologically confirmed adenocarcinoma of the prostate without neuroendocrine differentiation or small cell histology
- Distant metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI scan
- At least 2 of the following 3 high-risk prognostic factors:
    - (1) Gleason score ≥ 8,
    - (2) presence of ≥ 3 lesions on bone scan,
    - (3) presence of measurable visceral (excluding lymph node disease) metastasis on CT or MRI scan (according to RECIST 1.1 criteria)
- ECOG performance status grade of 0, 1, or 2

Subjects were not to be enrolled into the study if it were determined upon pre-study examination that they had significant cardiac, adrenal, or liver dysfunction; a malignancy other than prostate cancer or non-melanoma skin cancer within 5 years; or a significant laboratory abnormality. In addition, exclusions to participation were:

- Active infection or other medical condition that would make prednisone use contraindicated
- Any chronic medical condition requiring a higher systemic dose of corticosteroid than 5 mg prednisone per day
- Pathological findings consistent with small cell carcinoma of the prostate
- Known brain metastasis
- Prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer, except for up to 3 months of ADT or 1 course of palliative radiation or surgical therapy as outlined in the protocol.
- Uncontrolled hypertension (systolic blood pressure ≥160 mmHg or diastolic BP≥95 mmHg). Subjects with a history of hypertension are allowed provided blood pressure is controlled by anti-hypertensive treatment
- Active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction
- History of adrenal dysfunction
- Clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events or history of cardiac failure in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease
- Existing atrial fibrillation with or without pharmacotherapy. Other cardiac arrhythmia requiring pharmacotherapy
- Other malignancy (within 5 years), except non-melanoma skin cancer
- Administration of an investigational therapeutic or invasive surgical procedure (not including surgical castration) within 28 days of Cycle 1 Day 1 or currently enrolled in an investigational study
- Any condition or situation which, in the opinion of the investigator, would put the subject at risk, may confound study results, or interfere with the subject's participation in this study.

Treatments

- Abiraterone acetate (1,000 mg once daily) and low-dose prednisone (5 mg once daily) plus ADT (AA-P group) or
- Placebos of abiraterone acetate plus prednisone and ADT (Placebo group).

Selection of the ADT (LHRH agonist) was at the investigator's discretion, and dosing was consistent with the respective product labelling. Subjects could also have opted to undergo surgical castration in lieu of receiving ADT by LHRH analog.

Abiraterone acetate/placebo was to be taken on an empty stomach. No food was to be consumed for at least 2 hours before the dose of abiraterone acetate/placebo and for at least 1 hour after the dose of abiraterone acetate/placebo. Tablets were to be swallowed whole with water. If an abiraterone acetate/placebo dose was missed, it was to be omitted and not made up.

Prednisone/placebo 5 mg was to be taken orally once daily. It did not need to be taken at the same time as the abiraterone acetate/placebo dose. If the prednisone/placebo dose was missed, it was to be omitted and not made up.

The dose and frequency of administration of the LHRH agonist was to follow the prescribing information and was only to be adjusted if clinically indicated to achieve and maintain subcastrate concentrations of testosterone (<50 ng/dL or <1.7 nM).

Subjects were to receive treatment until documented disease progression, withdrawal of consent, dosing noncompliance, or unacceptable toxicity. Study drug was to be discontinued prior to documented radiographic progression if the investigator determined that the subject had experienced clinical progression. Treatment also was to have been discontinued due to dosing noncompliance, unacceptable toxicity, or subject choice.

Objectives

Primary Objective

The primary objective of the study was to determine whether abiraterone acetate plus prednisone in combination with androgen deprivation therapy (ADT) was superior to ADT alone in improving radiographic progression-free survival (rPFS) and overall survival (OS) in subjects with metastatic hormone-naive prostate cancer (mHNPC) with high-risk prognostic factors.

Secondary Objectives

The secondary objectives of the study were: (a) to evaluate the clinically relevant improvements as well as the safety of abiraterone acetate plus low-dose prednisone and ADT compared to ADT alone and (b) to identify microRNA (miRNA) and mRNA profiles predictive of abiraterone acetate response or resistance.

Outcomes / endpoints

Efficacy Analysis for the Co-Primary Endpoints: rPFS and Overall Survival

The co-primary endpoint of rPFS was defined as the time from randomization to the occurrence of radiographic progression or death from any cause. Radiographic progression included progression by bone scan (according to modified PCWG2) and progression of soft tissue lesions by CT or MRI (according to RECIST 1.1), both assessed by investigators. Subjects without radiographic progression or death were censored at the last disease assessment. Tumour measurements (CT or MRI and bone scans) were assessed at screening and then every 4 months starting with Cycle 5 in accordance with PCWG2 recommendations.

To assess any potential bias with the investigator-assessed radiographic progression, an audit plan was in place to randomly select at least 160 evaluable subjects for BICR. If a bias was present, a complete BICR of all subjects' scans would be performed.

The co-primary efficacy endpoint, OS, was measured from the date of randomization to the date of death (regardless of cause). Survival time of living subjects was censored on the last date the subject was known to be alive as of the cutoff date for the interim analysis.

Follow-up for survival was to occur every 4 months up to 60 months after subjects discontinued study drug.

Secondary endpoints

Endpoint	Description
Time to initiation of chemotherapy	The time interval from the date of randomization to the date of initiation of chemotherapy for prostate cancer. Subjects who have no chemotherapy administration at the time of analysis were censored at the last known alive date.
Time to subsequent therapy for prostate cancer	The time interval from the date of randomization to the date of initiation of subsequent therapy for prostate cancer. Subjects who have no subsequent therapy at the time of analysis were censored at the last known alive date. If a subject received a subsequent anti-prostate cancer therapy prior to the event, then subject was censored at the last assessment prior to the subsequent therapy.
Time to pain progression	The time interval from randomization to the first date a subject experiences a BPI-SF increase by ≥30% from baseline in the BPI-SF worst pain intensity (Item 3) observed at 2 consecutive evaluations ≥4 weeks apart. Subjects who have not experienced pain progression at the time of analysis were censored on the last known date a subject was known to have not progressed. Subjects with no on-study assessment or no baseline assessment were censored at date of randomization.
Time to skeletal-related event	Time from randomization to skeletal-related event (earliest one of the following): • Clinical or pathological fracture • Spinal cord compression • Palliative radiation to bone • Surgery to bone Subjects with no event were censored at the last known alive date.
Time to PSA progression	The time interval from the date of randomization to the date of the PSA progression as defined in the PCWG2 criteria. Subjects who have no PSA progression at the time of analysis were censored at the later of last known date of no progression and randomization.

BPI-SF=Brief Pain Inventory – Short Form; PCWG2=Prostate Cancer Working Group 2; PSA=prostate-specific antigen

Exploratory endpoints

PSA response rate	Proportion of subjects achieving a PSA decline ≥50% according to PCWG2 criteria.
PFS2	Time from randomization to second disease progression during follow-up post subsequent treatment or to death. Patients alive and for whom a second disease progression has not been observed were censored at the last time known to be alive and without second disease progression.
Patient-reported Outcome Measures (BPI-SF, FACT-P, BFI, EQ-5D-5L)	
Pain (BPI-SF)	BPI-SF Item 3 (Worst Pain Intensity), BPI-SF Item 4 (Least Pain Intensity), Item 5 (Average Pain Intensity), Item 6 (Pain Intensity Right Now), and Items 9A to 9G (Impact of Pain on Interference with Activities).
Functional status (FACT-P)	Physical Well-Being (PWB), Social/Family Well-Being (SFWB), Emotional Well-Being (EWB), Functional Well-being (FWB), Functional Assessment Cancer Therapy-General (FACT-G), Prostate Cancer Scale (PCS), Trial Outcome Index (TOI [PWB, SFWB, EWB, FWB), the FACT-P Total scale (FACT-G and PCS), and the FACT-P Pain Scale.
Fatigue (BFI)	Worst Fatigue (Item 3) and Fatigue Interference (Average of Items 4A-4F).
Quality-of-life (EQ-5D-5L)	Health State; EQ VAS score.
Time to first symptomatic local progression	Defined as occurrence of urethral obstruction or bladder outlet obstruction symptoms requiring a medical or surgical intervention. Subjects with no event were censored at the later of last dose date + 30 days or at randomization if the subject was never treated.
Prostate cancer-specific survival	Time from randomization to death date due to prostate cancer. Subjects alive or who died due to other reasons were censored at last date of known alive or death not due to prostate cancer.
Time to chronic opiate use	Time from randomization to new opioid analgesics use, or increased dose or frequency of existing opioid analgesics from Cycle 1 Day 1 for ≥3 weeks orally; 7 days parenterally (ie, non-oral formulation). Subjects with no event were censored at last dose + 30 days or at randomization if the subject is never treated.
Best overall response	Best overall response by RECIST 1.1 in subjects with measurable disease at baseline.
Castration Status	Castration level met based on testosterone values over time

BPI-SF=Brief Pain Inventory - Short Form; BFI=Brief Fatigue Inventory; EQ-5D-5L=EuroQol; FACT-P=Functional Assessment of Cancer Therapy – Prostate; PRO=patient-reported outcomes; PSA=prostate-specific antigen; PCWG2=Prostate Cancer Working Group 2; RECIST=Response Evaluation Criteria in Solid Tumors

Sample size

The overall level of significance for the study was 0.05, allocated between the 2 co-primary endpoints (0.001 for rPFS and 0.049 for OS). The timing of the first interim analysis was determined according to both rPFS and OS events required, so that the analysis would take place when the required number of events for both measures has been reached. Subjects were assigned randomly (1:1) to receive AA-P or Placebo (ADT alone).

It was assumed that failure would follow an exponential distribution with a constant hazard rate for both the rPFS and OS endpoints. It is estimated that 565 rPFS events would be required to provide at least 94% power in detecting a HR of 0.667 (median rPFS of 20 months for the ADT alone group versus 30 months for the AA-P group) at a 2-tailed level of significance of 0.001. Assuming a median OS of 33 months for the control group (placebo; ADT alone), a planned sample size of approximately 1,200 subjects provides 85% power to detect a HR of 0.81 (33 months versus 40.75 months, or >7 months of improvement) at a 2-tailed overall significance level of 0.049 and an enrollment duration of approximately 24 months over a total study duration of 78 months to obtain the required 852 death events.

Randomisation

Subjects were centrally randomized in a 1:1 ratio to receive either abiraterone acetate (1,000 mg once daily) and low-dose prednisone (5 mg once daily) plus ADT (AA-P group) or placebos of abiraterone acetate plus prednisone and ADT (Placebo group).

Prior to randomization, eligible subjects were stratified by presence of measurable visceral disease and ECOG performance status, and then randomly assigned in a 1:1 ratio to the active treatment (i.e., AA-P group) or control group (Placebo group). Randomization was facilitated by a centralized interactive web response system (IWRS).

Blinding (masking)

This was a double-blind study.

Randomization codes were maintained within the IWRS, which had the functionality to allow the investigator to break the blind for an individual subject. Investigators were instructed that under normal circumstances, the blind was not to be broken. Unblinding could have occurred in the following situations:

- If specific emergency treatment/course of action dictated knowing the treatment status of the subject
- If the subject discontinued from the study because of disease progression, and the investigator considered the information was essential to determine the next course of therapy
- In the event the IDMC recommended unblinding and crossing over of subjects to active treatment (abiraterone acetate)

It was recommended that the investigator contact the Sponsor or its designee if possible to discuss the particular situation before breaking the blind. In the event of unblinding, the Sponsor was to be notified as soon as possible, and the date, time, and reason for unblinding documented in the IWRS, eCRF, and source document. Subjects who had their treatment assignment unblinded were to be discontinued from the Double-blind Treatment Phase and entered into the Follow-up Phase.

Statistical methods

Unless otherwise specified, all continuous endpoints were summarized using descriptive statistics, which included the number of subjects with a valid measurement (n), mean, standard deviation, median, minimum, and maximum.

Time-to-event endpoints were analysed using Kaplan-Meier product limit methods to estimate the survival distributions and the median time-to- event. Inference for time-to-event endpoints were assessed using a stratified log-rank statistic as the primary analysis. The proportional hazard assumption was assessed graphically by plotting log (-log [estimated survival distribution function]) against log (survival time). The resulting graphs have approximately parallel lines when the assumption holds. If the proportional hazards assumption was reasonably met, then the HR was used as an estimate of treatment effect.

The rPFS and OS distribution, median rPFS and median OS, and the 95% confidence intervals were estimated using the Kaplan-Meier method. Statistical inference for OS was evaluated according to the group sequential testing design. The resulting statistic (stratified log-rank test statistic) was evaluated using East software to ensure that it was compared with the appropriate stopping boundary given the precise number of events observed at the time of the interim analysis.

A supportive analysis, using the Cox proportional hazards model, was performed. The score statistic, which is equivalent to a log-rank test statistic, was used to provide an adjusted estimate of the HR and corresponding 2-tailed 95% confidence interval.

Comparisons of secondary endpoints between treatment groups were conducted according to the Hochberg test procedure at an overall 2-sided 0.05 level of significance.

Estimates of the time-to-event endpoints were obtained using the Kaplan-Meier estimates of the survival distributions. Statistical inference was evaluated similarly as in the primary analysis, except that it was not evaluated using the group sequential testing design. The relative risk (AA-P:Placebo) for response rate was reported along with the associated 2 tailed 95% CIs. Statistical inference was evaluated using the Chi square statistic; the Fisher's exact test was used if the expected counts in some cells are small. Endpoints with change in scores used 2 independent t-test procedures. For PROs, a repeated measures model was used to estimate the mean PRO scores at each cycle.

Sensitivity analyses:

Sensitivity analyses on primary endpoints were performed to assess the robustness and consistency of the endpoints. The results from the analyses were not adjusted for multiplicity testing. In the event a large number of subjects crossover to abiraterone acetate plus prednisone or other life-extending subsequent therapies, additional sensitivity analyses were used in estimating the true treatment effect.

Subgroup Analysis for the Co-Primary Endpoints:

A non-stratified analysis on co-primary endpoints of rPFS and OS was performed. Subgroup analyses were planned for the co-primary endpoints (rPFS and OS) to investigate whether treatment effects were consistent within subgroups using a non-stratified univariate model. Each subgroup was analysed separately. The pre-planned subgroups were as follows: Age (<65, ≥ 65, ≥ 75), ECOG performance status grade (0/1 versus 2) at randomization, Gleason score (<8 versus ≥8), Number of baseline bone lesions (≤10 versus >10), Presence of visceral disease at randomization (Yes versus No), Baseline PSA was greater than the median baseline value (Yes versus No), LDH value was greater than the median baseline value (Yes versus No), Region (Eastern EU, Western EU, Asia Pacific, Rest of World)

The HR within each subgroup was estimated using a non-stratified Cox proportional hazard model. Results from these analyses were considered consistent with the primary analysis if the 95% confidence interval for the HR within the subgroup included the point estimate for the primary analysis.

Other exploratory analyses:

A post hoc multivariate analysis was conducted to evaluate the treatment effect when controlling for clinically meaningful factors (ECOG performance status scale, baseline serum PSA, baseline LDH, measurable visceral, bone metastasis at baseline and age) at baseline to estimate the HR for treatment effect. Then a Cox regression model was run with treatment and those factors as covariates.

A post hoc analysis of time to life-extending subsequent therapy for prostate cancer was conducted as done for the similar secondary endpoint, i.e., time to subsequent therapy for prostate cancer.

The strength of association between rPFS and OS was evaluated using Spearman's correlation coefficient, estimated through the Clayton copula,4 which takes censoring into account.

A non-stratified analysis of PSA response based on PCWG2 Criteria was conducted; the relative risk (95% CI) and p value were calculated based on confirmed responses. A PSA response was defined as a ≥ 50% decline from baseline according to PCWG2 criteria. For a PSA response to be confirmed, an additional central laboratory measurement obtained 4 or more weeks later had to show ≥ 50% decline from baseline.

To evaluate the treatment outcome following the subsequent therapy for prostate cancer, analysis of progression-free survival 2 (PFS2) was performed. PFS2 was defined as the time from randomization to the second disease progression during follow-up after the subsequent therapy, or to death from any cause. Patients alive and for whom a second progression had not been observed were censored at the last time known to be alive and without second disease progression.

Patient-reported outcome measures of BPI-SF, FACT-P, BFI, and the EQ-5D-5L were evaluated to assess treatment effect on pain, prostate cancer symptoms, functional status, and health-related quality of life. The analyses of these PRO outcomes are described in the PRO Statistical Analysis Plan in Appendix 9 (PRO).

In addition, other analyses were conducted to evaluate treatment effect: time to symptomatic local progression (i.e., occurrence of urethral obstruction or bladder outlet obstruction symptoms requiring medical or surgical intervention), prostate cancer-specific survival (i.e., time from randomization to death date due to prostate cancer), time to chronic opiate use (i.e., time from randomization to new opioid analgesics use, or increased dose or frequency of the existing opioid analgesics from Cycle 1 Day 1 for ≥ 3 weeks orally or 7 days parenterally), and best overall response as assessed by RECIST 1.1 Criteria (including complete response and partial response). Also, an evaluation of testosterone levels over time was conducted to determine if subjects' castration levels were met.

Planned Analyses

A single analysis was planned for the co-primary endpoint of rPFS, after ~565 rPFS events occurred. The OS endpoint incorporates the group sequential design by including 2 interim analyses and 1 final analysis with an alpha spending function calculated as Wang-Tsiatis power boundaries of shape parameter 0.2 (East software).

Analyses of the co-primary endpoint OS were planned to occur following ~426, ~554, and ~852 death events (corresponding to approximately 50%, approximately 65%, and 100% of the total events) using the ITT population (i.e., all subjects randomized into the study at the time of the interim analysis) (Table 2). The cumulative alpha spend was planned to be 0.011 and 0.022 for each of the 2 interim analyses, respectively. The exact significance levels were planned to be determined according to the observed

number of events at each interim analysis. It was expected that the first interim OS analysis would likely occur in conjunction with the rPFS analysis.

Table 2 - Planned Statistical Operating Characteristics for Overall Survival (Study 212082PCR3011)

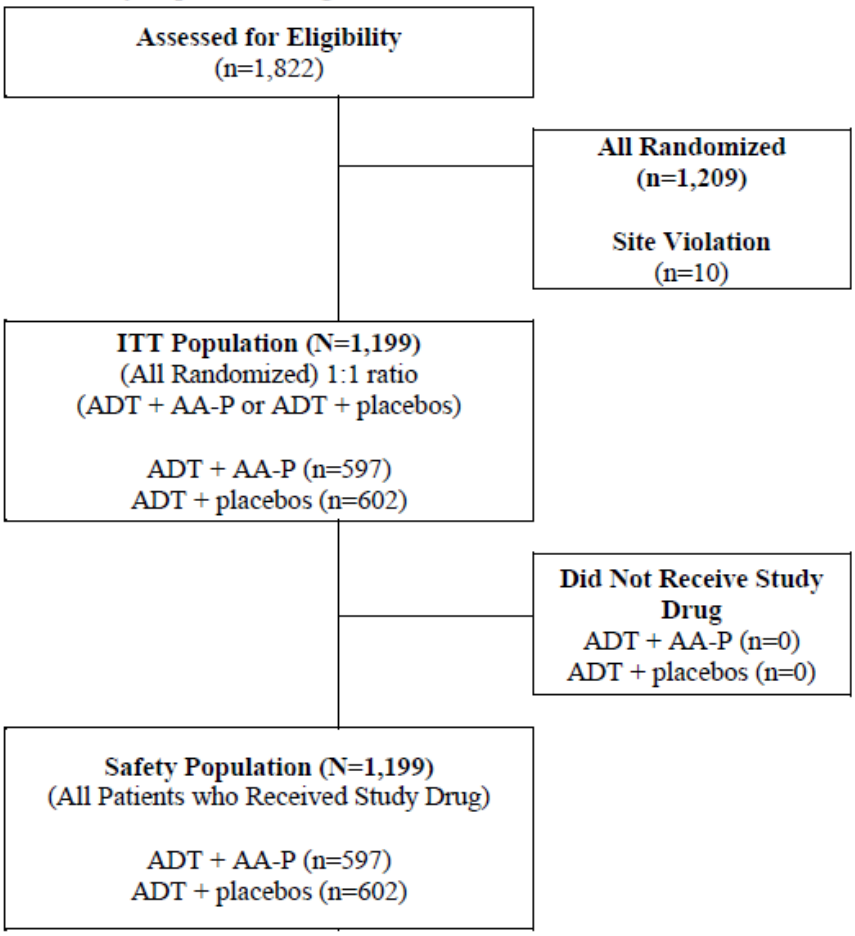
Variable	Analyses		
	Interim 1 (approximately 50% of Total Events)	**Interim 2** (approximately 65% of Total Events)	Final
Projected Observed OS Events	~426	~554	~852
Efficacy Boundary (HR)	0.78	0.81	0.87
Cumulative Stop Prob. Under (H_o)	0.011	0.022	0.049

HR=Hazard ratio; H_o=0% improvement; H_1=23% improvement; OS=overall survival

Results

Participant flow

The participant flow is shown below.



Note: AA-P = abiraterone acetate and prednisone; ADT=androgen deprivation therapy

Recruitment

From 12 February 2013 (first subject randomized) until 11 December 2014 (last subject randomized), 1,209 subjects were randomized at 236 sites in 34 countries in Europe, Asia, Australia, New Zealand, South Africa, Canada, and Latin America.

The clinical cutoff was 31 October 2016 (main analysis for rPFS and first IA for OS (48% of total events)).

Data from 10 subjects at Site 70139 were excluded (due to GMP non-compliance of the study site). The remaining 1,199 subjects comprise the ITT population. All ITT subjects who received at least 1 dose of study drug comprise the Safety population.

Table 3 - Primary Reason for Treatment Discontinuation; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Safety Population	597	602
Treatment discontinued	340 (57.0%)	490 (81.4%)
Treatment ongoing	257 (43.0%)	112 (18.6%)
Reasons for discontinuation		
Progressive disease	209 (35.0%)	369 (61.3%)
Adverse event	49 (8.2%)	31 (5.1%)
Withdrawal of consent	31 (5.2%)	41 (6.8%)
Death	26 (4.4%)	21 (3.5%)
Physician decision	11 (1.8%)	19 (3.2%)
Other	7 (1.2%)	5 (0.8%)
Noncompliance with study drug	4 (0.7%)	2 (0.3%)
Lost to follow-up	3 (0.5%)	2 (0.3%)

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74 subjects in the ITT population were unblinded during the study, 31 subjects in the AA-P group and 43 subjects in the Placebo group. The majority of subjects in the AA-P and Placebo groups were unblinded with the sponsor's approval, as permitted by the protocol, after disease progression (27 and 38, respectively) and a small number of subjects were unblinded for other unspecified reasons (4 and 5, respectively). No subjects were unblinded due to an adverse event.

Conduct of the study

Protocol amendments

The original protocol was amended 3 times. Amendments INT-1, and INT-2 were considered to be substantial and INT-3 was considered non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. Details of each amendment are included in the protocol.

Amendment INT-1 (27 November 2012; N=0 subjects enrolled)

The overall reason for the amendment was to address requests and recommendations from health authorities, investigators, and ethics committees. Major changes associated with this amendment are outlined below.

- Abiraterone acetate would be provided for a maximum of 3 years during the Open-label Extension Phase.
- PSA results would be made available to investigators and investigators would be notified if

testosterone levels did not fall below 50 ng/dL (or <1.7 nM; i.e., castrate levels). In these cases, the dose and frequency of LHRH agonist could be adjusted.

- The inclusion and exclusion criteria were updated to include all of the parameters utilized in the Child-Pugh classification for chronic liver disease. Inclusion Criterion 7 required a screening serum albumin of ⩾3 g/dL; Exclusion Criterion 7 excluded subjects with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction.
- Inclusion Criterion 5 (definition of high risk prognostic factor) specified that only CT or MRI scans were acceptable for measurement of visceral metastases.
- Exclusion Criterion 5 (prior therapy) revised the timing to allow for up to 3 months of ADT with LHRH agonists or orchiectomy with or without concurrent anti-androgens prior to Cycle 1 Day 1; and clarified that subjects may have had 1 course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 28 days prior to Cycle 1 Day 1 with all AEs associated with these procedures resolved at least to Grade 1 by Cycle 1 Day 1. Baseline echocardiograms were not required. Therefore, Exclusion Criterion 9 was revised to exclude subjects with clinically significant heart disease as evidenced by myocardial infarction, or arterial thrombotic events or history of cardiac failure in the past 6 months, severe or unstable angina, or New York Heart Association (NYHA) Class II-IV heart disease.
- To monitor for peripheral oedema throughout treatment, the requirement was added that weight be measured at all visits during the Double-blind Treatment Phase. Amendment INT-2 (18 April 2014; N=739 subjects enrolled)
- The overall reason for the amendment was to add rPFS as a co-primary endpoint with OS. Given that abiraterone acetate plus prednisone had already demonstrated a statistically significant survival benefit in patients with mCRPC who received prior chemotherapy, rPFS along with important secondary endpoints (e.g., time to subsequent chemotherapy, time to opiate use for cancer pain) and a strong trend in OS was considered a measure of clinical benefit to patients with newly diagnosed hormone-naïve high-risk metastatic prostate cancer. Therefore, rPFS was promoted from a secondary endpoint to a co-primary endpoint to provide an alternate measure of efficacy. Major changes associated with this amendment are outlined below.
- The planned sample size was changed from 1,270 to 1,200 subjects, the anticipated study enrollment duration was changed from 30 to 24 months, the total study duration was changed from 74 to 78 months to obtain the required number of final OS death events (n=852)
- A description of the statistical assumptions for the hypothesized rPFS HR was added, and the projections for the number of events needed for the 2 interim and final analyses were revised based on the change in α from 0.05 to 0.049 due to the addition of the rPFS co-primary endpoint
- Moved the endpoint “time to pain progression” from an exploratory to a secondary efficacy endpoint
- All CT, MRI, and bone scans will be sent to a central location for potential auditing Purposes Revised Exclusion Criterion 5.1: Anti-androgen use is allowed for up to 2 weeks after Cycle 1 Day 1 to adequately control tumour flare for subjects receiving LHRH agonist
- Revised Exclusion Criterion 10.1: to exclude subjects with existing atrial fibrillation with or without pharmacotherapy
- Removed the requirement for haematology assessments during the Open-label Extension Phase
- Frequency of liver function test (LFT) monitoring was increased to at least once per week for subjects with Grade 2 or 3 increases in alanine aminotransferase (ALT) or aspartate amino

transferase (AST)

- Defined conditions under which subjects were to be discontinued due to opioid use for cancer pain as the initiation of new opioid analgesics or increased dose or frequency of existing opioid analgesics for at least 3 weeks orally or 7 days parenterally

Amendment INT-3 (24 March 2016; N=1209 subjects enrolled)

The overall reason for the amendment was to revise the protocol language to accommodate for the time gap between the final rPFS and 1st interim analysis for OS. Therefore, the text was revised to clarify that the analysis of rPFS will occur at an estimated 565 rPFS events.

Protocol Deviations

Major protocol deviations for eligibility criteria not met are summarized in Table 4.

Note that 1 subject in the Placebo group in Table 5 (under "Subject did not meet inclusion or exclusion criteria") based on the Sponsor's assessment of eligibility is not included in Table 4, which is based on the investigator's assessment of eligibility from the eCRF.

Table 4 - Major Protocol Deviation for Eligibility Criteria Not Met; Intent-to-treat Population (Study 212082PCR3011)

TSIPD02: Major Protocol Deviation for Eligibility criteria not met; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo	Total
Analysis set: ITT population	597	602	1199
Total no. of subjects with a deviation of Eligibility criteria not met	11 (1.8%)	18 (3.0%)	29 (2.4%)
Active liver disease	2 (0.3%)	2 (0.3%)	4 (0.3%)
Cardiovascular disease	1 (0.2%)	8 (1.3%)	9 (0.8%)
Diagnosis of metastatic prostate cancer not within 3 months	1 (0.2%)	2 (0.3%)	3 (0.3%)
More than 5 mg prednisone per day for other condition	0	1 (0.2%)	1 (0.1%)
Not 2 high-risk prognostic factors	0	2 (0.3%)	2 (0.2%)
Not allowed prior therapies	3 (0.5%)	1 (0.2%)	4 (0.3%)
Other malignancy	3 (0.5%)	0	3 (0.3%)
Small cell carcinoma of prostate	1 (0.2%)	0	1 (0.1%)
Uncontrolled Hypertension	2 (0.3%)	2 (0.3%)	4 (0.3%)

Note: Percentages calculated with the number of subjects in each group as denominator.

Major protocol deviations identified during the study are summarized in Table 5.

Table 5 - Major Protocol Deviation; Intent-to-treat Population (Study 212082PCR3011)

TSIPD01: Major Protocol Deviation; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo	Total
Analysis set: ITT population	597	602	1199
Total no. subjects with a deviation	88 (14.7%)	64 (10.6%)	152 (12.7%)
Subject did not meet inclusion or exclusion criteria	11 (1.8%)	19 (3.2%)	30 (2.5%)
Subject did not withdraw as per protocol	7 (1.2%)	15 (2.5%)	22 (1.8%)
Subject received a disallowed concomitant treatment	29 (4.9%)	16 (2.7%)	45 (3.8%)
Subject received wrong treatment or incorrect dose	37 (6.2%)	14 (2.3%)	51 (4.3%)
Other	16 (2.7%)	5 (0.8%)	21 (1.8%)

Note: Percentages calculated with the number of subjects in each group as denominator.

The most common protocol deviation was having received the wrong treatment or the incorrect dose, i.e., dose interruptions or reductions were not performed correctly as per protocol guidelines for management of adverse events (6.2% for AA-P; 2.3% for Placebo). Only 3 subjects received the alternate treatment for 1 to 2 months (1 kit) over the duration of the study: 1 subject received active prednisone instead of placebo (1 month out of 13 months), 1 subject received placebo instead of active abiraterone acetate (1/2 month out of 26 months), and 1 subject received active abiraterone acetate instead of placebo (1 month out of 10 months).

Treatment compliance

Throughout the study, study sites maintained logs of the investigational tablets that were dispensed and returned. Compliance with study drug administration was to be assessed on Day 1 of Cycles 2 and 3, once a month from Cycles 4 to 13, then every 2 months until the end of study treatment.

Table 6 - Treatment Compliance; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Analysis set: safety population	597	602
Subjects Abiraterone Acetate/Placebo compliance level[a]		
n	595	601
75% or less	44 (7.4%)	12 (2.0%)
>75% through 80%	12 (2.0%)	10 (1.7%)
>80% through 85%	19 (3.2%)	14 (2.3%)
>85% through 90%	42 (7.0%)	36 (6.0%)
>90% through 95%	175 (29.3%)	153 (25.4%)
>95% through 100%	303 (50.8%)	376 (62.5%)
Subjects Prednisone or Prednisolone compliance level[a]		
n	595	601
75% or less	9 (1.5%)	6 (1.0%)
>75% through 80%	9 (1.5%)	4 (0.7%)
>80% through 85%	16 (2.7%)	13 (2.2%)
>85% through 90%	47 (7.9%)	42 (7.0%)
>90% through 95%	194 (32.5%)	167 (27.7%)
>95% through 100%	320 (53.6%)	369 (61.3%)

[a] Percent of doses (tablets) taken out of the protocol-specified dose (1000 mg/day for Abiraterone Acetate/Placebo and 5mg/day for Prednisone or Prednisolone).

Baseline data

The demographic and disease characteristics at study entry are presented in Table 7, Table 8 and Table 9.

Note that 1 Placebo subject's Gleason score was changed from 8 to 7 after randomization; this is the reason for 601 rather than 602 "subjects with high risk at screening" in Table 7.

Table 7 - Demographic Data; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo	Total
Analysis set: ITT population	597	602	1199
Age (years)			
N	597	602	1199
<65	221 (37.0%)	233 (38.7%)	454 (37.9%)
65-69	112 (18.8%)	134 (22.3%)	246 (20.5%)
70-74	141 (23.6%)	115 (19.1%)	256 (21.4%)
≥75	123 (20.6%)	120 (19.9%)	243 (20.3%)
Mean (SD)	67.3 (8.48)	66.8 (8.72)	67.1 (8.60)
Median	68.0	67.0	67.0
Range	(38; 89)	(33; 92)	(33; 92)
Sex			
N	597	602	1199
Male	597 (100.0%)	602 (100.0%)	1199 (100.0%)
Ethnicity			
N	597	602	1199
Hispanic or Latino	71 (11.9%)	72 (12.0%)	143 (11.9%)
Not Hispanic or Latino	499 (83.6%)	505 (83.9%)	1004 (83.7%)
Unknown	5 (0.8%)	9 (1.5%)	14 (1.2%)
Not reported	22 (3.7%)	16 (2.7%)	38 (3.2%)
Race			
N	597	602	1199
White	409 (68.5%)	423 (70.3%)	832 (69.4%)
Black or African American	15 (2.5%)	10 (1.7%)	25 (2.1%)
Asian	125 (20.9%)	121 (20.1%)	246 (20.5%)
American Indian or Alaska Native	1 (0.2%)	2 (0.3%)	3 (0.3%)
Native Hawaiian or other Pacific Islander	0	0	0
Other	43 (7.2%)	37 (6.1%)	80 (6.7%)
Unknown	1 (0.2%)	4 (0.7%)	5 (0.4%)
Not reported	3 (0.5%)	5 (0.8%)	8 (0.7%)
Weight (kg)			
N	597	602	1199
Mean (SD)	75.54 (14.650)	76.38 (14.595)	75.96 (14.622)
Median	74.40	75.05	75.00
Range	(43.0; 175.1)	(41.0; 131.6)	(41.0; 175.1)
Height (cm)			
N	596	598	1194
Mean (SD)	170.99 (7.923)	171.40 (7.933)	171.20 (7.928)
Median	171.00	171.90	171.00
Range	(114.0; 190.0)	(120.0; 198.0)	(114.0; 198.0)
Region			
N	597	602	1199
Eastern Europe	214 (35.8%)	217 (36.0%)	431 (35.9%)
Western Europe	155 (26.0%)	162 (26.9%)	317 (26.4%)
Asia	124 (20.8%)	121 (20.1%)	245 (20.4%)
Rest of World	104 (17.4%)	102 (16.9%)	206 (17.2%)

Table 8 - Baseline Disease Characteristics; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo	Total
Analysis set: ITT population	597	602	1199
Time from initial diagnosis to first dose (months)			
N	597	602	1199
Mean (SD)	1.8 (0.73)	1.9 (0.75)	1.9 (0.74)
Median	1.8	2.0	1.8
Range	(0; 3)	(0; 4)	(0; 4)
Histopathological grade			
N	595	601	1196
GX: Grade cannot be assessed	28 (4.7%)	30 (5.0%)	58 (4.8%)
G1: Well differentiated	13 (2.2%)	11 (1.8%)	24 (2.0%)
G2: Moderately differentiated	29 (4.9%)	36 (6.0%)	65 (5.4%)
G3: Poorly differentiated	246 (41.3%)	246 (40.9%)	492 (41.1%)
G4: Undifferentiated	57 (9.6%)	61 (10.1%)	118 (9.9%)
Unknown or not done	222 (37.3%)	217 (36.1%)	439 (36.7%)
Tumor Stage at Diagnosis			
N	596	601	1197
T0	0	1 (0.2%)	1 (0.1%)
T1	29 (4.9%)	25 (4.2%)	54 (4.5%)
T2	94 (15.8%)	113 (18.8%)	207 (17.3%)
T3	246 (41.3%)	254 (42.3%)	500 (41.8%)
T4	159 (26.7%)	128 (21.3%)	287 (24.0%)
TX	68 (11.4%)	80 (13.3%)	148 (12.4%)
Lymph Node Stage at Diagnosis			
N	596	600	1196
N0	152 (25.5%)	151 (25.2%)	303 (25.3%)
N1	280 (47.0%)	280 (46.7%)	560 (46.8%)
NX	164 (27.5%)	169 (28.2%)	333 (27.8%)
Metastasis Stage at Diagnosis			
N	597	602	1199
M1	597 (100.0%)	602 (100.0%)	1199 (100.0%)
Stage			
N	597	602	1199
IV	597 (100.0%)	602 (100.0%)	1199 (100.0%)
Gleason Score at Initial Diagnosis			
N	597	602	1199
<7	4 (0.7%)	1 (0.2%)	5 (0.4%)
7	9 (1.5%)	15 (2.5%)	24 (2.0%)
8	267 (44.7%)	281 (46.7%)	548 (45.7%)
9	280 (46.9%)	264 (43.9%)	544 (45.4%)
10	37 (6.2%)	41 (6.8%)	78 (6.5%)
Subjects with measurable disease at baseline			
N	597	602	1199
Yes	257 (43.0%)	271 (45.0%)	528 (44.0%)

	AA-P	Placebo	Total
Current Extent of Disease			
N	596	600	1196
Bone	580 (97.3%)	585 (97.5%)	1165 (97.4%)
Liver	32 (5.4%)	30 (5.0%)	62 (5.2%)
Lungs	73 (12.2%)	72 (12.0%)	145 (12.1%)
Node	283 (47.5%)	287 (47.8%)	570 (47.7%)
Prostate mass	151 (25.3%)	154 (25.7%)	305 (25.5%)
Viscera	18 (3.0%)	13 (2.2%)	31 (2.6%)
Soft tissue	9 (1.5%)	15 (2.5%)	24 (2.0%)
Other	2 (0.3%)	0	2 (0.2%)
Number of bone lesions at Screening(IWRS)			
N	597	602	1199
0	6 (1.0%)	7 (1.2%)	13 (1.1%)
1-2	5 (0.8%)	10 (1.7%)	15 (1.3%)
3-10	202 (33.8%)	208 (34.6%)	410 (34.2%)
11-20	109 (18.3%)	97 (16.1%)	206 (17.2%)
>20	275 (46.1%)	280 (46.5%)	555 (46.3%)
Subjects with high risk at Screening (IWRS)	597 (100.0%)	601 (99.8%)	1198 (99.9%)
GS≥8 + ≥3 bone lesions	573 (96.0%)	569 (94.7%)	1142 (95.3%)
GS≥8 + Measurable visceral	82 (13.7%)	87 (14.5%)	169 (14.1%)
≥3 bone lesions + Measurable visceral	84 (14.1%)	85 (14.1%)	169 (14.1%)
GS≥8 + ≥3 bone lesions + Measurable visceral	71 (11.9%)	70 (11.6%)	141 (11.8%)
Baseline Pain score (BPI-SF Item3)			
N	570	579	1149
0-1	284 (49.8%)	288 (49.7%)	572 (49.8%)
2-3	123 (21.6%)	137 (23.7%)	260 (22.6%)
≥4	163 (28.6%)	154 (26.6%)	317 (27.6%)
Mean (SD)	2.2 (2.45)	2.2 (2.40)	2.2 (2.42)
Median	2.0	2.0	2.0
Range	(0; 10)	(0; 10)	(0; 10)
ECOG performance status at baseline			
N	597	602	1199
0	326 (54.6%)	331 (55.0%)	657 (54.8%)
1	245 (41.0%)	255 (42.4%)	500 (41.7%)
2	26 (4.4%)	16 (2.7%)	42 (3.5%)

Note that 1 Placebo subject's Gleason score was changed from 8 to 7 after randomization; this is the reason for 601 rather than 602 "subjects with high risk at screening" in Table 7.

Table 9 - Baseline Disease-related Laboratory Parameters; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo	Total
Analysis set: ITT population	597	602	1199
Baseline PSA (ng/mL)			
N	595	600	1195
Mean (SD)	263.24 (791.440)	201.67 (647.807)	232.33 (723.252)
Median	25.43	23.05	23.85
Range	(0.0; 8775.9)	(0.1; 8889.6)	(0.0; 8889.6)
Baseline Hemoglobin (g/L)			
N	597	602	1199
Mean (SD)	130.52 (16.959)	131.57 (17.430)	131.05 (17.198)
Median	132.00	133.00	132.00
Range	(90.0; 175.0)	(89.0; 174.0)	(89.0; 175.0)
Baseline Lactate Dehydrogenase (U/L)			
N	591	595	1186
Mean (SD)	199.3 (133.11)	193.6 (104.22)	196.4 (119.47)
Median	177.0	176.0	177.0
Range	(73; 2634)	(67; 1444)	(67; 2634)

Prior Prostate Cancer Surgery/Therapies

Prior prostate cancer therapy and related information is summarized in Table 10.

Table 10 - Prior Prostate Cancer Surgery/Therapy and Related info; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo	Total
Analysis set: ITT population	597	602	1199
Subjects with Previous Prostate Cancer Therapy	560	560	1120
Surgery	22 (3.7%)	23 (3.8%)	45 (3.8%)
Radiotherapy	19 (3.2%)	26 (4.3%)	45 (3.8%)
Hormonal	559 (93.6%)	558 (92.7%)	1117 (93.2%)
GnRH Analog[a]	449 (75.2%)	450 (74.8%)	899 (75.0%)
Orchiectomy	73 (12.2%)	71 (11.8%)	144 (12.0%)
Anti-Androgens[b]	373 (62.5%)	371 (61.6%)	744 (62.1%)
Other[c]	7 (1.2%)	10 (1.7%)	17 (1.4%)
Time from GnRH Analog Start to First Dose (months)			
N	445	449	894
Mean (SD)	1.20 (0.722)	1.22 (0.736)	1.21 (0.729)
Median	1.08	1.08	1.08
Range	(0.1; 3.0)	(0.1; 3.5)	(0.1; 3.5)

[a] agonist or antagonist
[b] All anti-androgens were first generation antiandrogens (eg, bicalutamide, nilutamide, flutamide, cyproterone acetate).
[c] include estrogen and glucocorticoids

Concomitant Medications

As required by the protocol, all subjects were to have received GnRH analog or have had an orchiectomy. Since 144 (12%) subjects underwent an orchiectomy prior to randomization and another 12 (1.0%) subjects underwent orchiectomy after randomization, as expected the most common class of concomitant medication taken by subjects was endocrine therapy (89.6% and 90.0% of subjects in the AA-P and Placebo groups, respectively); specifically, GnRH agonists (also known as LHRH agonists) were taken by

87.9% of subjects in the AA-P group and 87.9% of subjects in the Placebo group. Degarelix was classified under other hormone antagonists and related agents and was received by 0.8% of subjects in the AA-P group and 0.5% of subjects in the Placebo group.

Subsequent therapy

A summary of subsequent therapies for prostate cancer is presented in Table 11.

Antineoplastic agents were administered as subsequent therapy for 18.3% of subjects in the AA-P group and 31.9% of subjects in the Placebo group. Anti-androgens (consisting of bicalutamide, enzalutamide, and flutamide) were administered to 11.6% of subjects in the AA-P group and 24.1% of subjects in the Placebo group. The most commonly administered subsequent therapy was docetaxel (17.8%, AA-P; 31.1%, Placebo), followed by bicalutamide (7.7%, AA-P; 14.0%, Placebo), enzalutamide (5.0%, AA-P; 12.6%, Placebo), and abiraterone acetate (1.7%, AA-P; 8.6%, Placebo).

Table 11 - Subsequent Therapy for Prostate Cancer; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Analysis set: ITT population	597	602
Total Number of Subjects with Subsequent Therapy	191 (32.0%)	322 (53.5%)
Total Number of Subjects with Subsequent Therapy (Systemic)	164 (27.5%)	296 (49.2%)
Antineoplastic Agents	109 (18.3%)	192 (31.9%)
Taxanes	107 (17.9%)	188 (31.2%)
Docetaxel	106 (17.8%)	187 (31.1%)
Cabazitaxel	11 (1.8%)	30 (5.0%)
Paclitaxel	0	1 (0.2%)
Other Antineoplastic Agents	7 (1.2%)	5 (0.8%)
Estramustine Phosphate Sodium	4 (0.7%)	2 (0.3%)
Estramustine	1 (0.2%)	0
Estramustine Phosphate	1 (0.2%)	3 (0.5%)
Olaparib	1 (0.2%)	0
Platinum Compounds	4 (0.7%)	7 (1.2%)
Carboplatin	3 (0.5%)	5 (0.8%)
Cisplatin	1 (0.2%)	1 (0.2%)
Oxaliplatin	0	1 (0.2%)
Anthracyclines And Related Substances	2 (0.3%)	3 (0.5%)
Doxorubicin	1 (0.2%)	0
Mitoxantrone Hydrochloride	1 (0.2%)	0
Mitoxantrone	0	3 (0.5%)
Monoclonal Antibodies	1 (0.2%)	0
Ipilimumab	1 (0.2%)	0
Podophyllotoxin Derivatives	1 (0.2%)	4 (0.7%)
Etoposide	1 (0.2%)	4 (0.7%)
Combinations Of Antineoplastic Agents	0	1 (0.2%)
Combinations Of Antineoplastic Agents	0	1 (0.2%)
Nitrogen Mustard Analogues	0	2 (0.3%)
Cyclophosphamide	0	2 (0.3%)
Protein Kinase Inhibitors	0	4 (0.7%)
Dovitinib	0	1 (0.2%)
Masitinib	0	3 (0.5%)
Pyrimidine Analogues	0	2 (0.3%)
Gemcitabine	0	1 (0.2%)
Uftoral	0	1 (0.2%)
Uncoded ATC Level 4	0	1 (0.2%)
Custirsen	0	1 (0.2%)
Endocrine Therapy	75 (12.6%)	183 (30.4%)
Anti-Androgens	69 (11.6%)	145 (24.1%)
Bicalutamide	46 (7.7%)	84 (14.0%)
Enzalutamide	30 (5.0%)	76 (12.6%)
Flutamide	4 (0.7%)	18 (3.0%)

	AA-P	Placebo
Other Hormone Antagonists And Related Agents	12 (2.0%)	53 (8.8%)
Abiraterone Acetate	10 (1.7%)	52 (8.6%)
Degarelix	2 (0.3%)	0
Abiraterone	0	1 (0.2%)
Estrogens	1 (0.2%)	6 (1.0%)
Ethinylestradiol	1 (0.2%)	6 (1.0%)
Progestogens	0	1 (0.2%)
Chlormadinone Acetate	0	1 (0.2%)
Corticosteroids For Systemic Use	19 (3.2%)	34 (5.6%)
Glucocorticoids	19 (3.2%)	34 (5.6%)
Prednisolone	9 (1.5%)	12 (2.0%)
Prednisone	7 (1.2%)	16 (2.7%)
Dexamethasone	3 (0.5%)	11 (1.8%)
Methylprednisolone	1 (0.2%)	1 (0.2%)
Drugs For Treatment Of Bone Diseases	11 (1.8%)	7 (1.2%)
Other Drugs Affecting Bone Structure And Mineralization	10 (1.7%)	7 (1.2%)
Denosumab	10 (1.7%)	7 (1.2%)
Bisphosphonates	1 (0.2%)	0
Zoledronic Acid	1 (0.2%)	0
Therapeutic Radiopharmaceuticals	11 (1.8%)	27 (4.5%)
Various Therapeutic Radiopharmaceuticals	11 (1.8%)	27 (4.5%)
Radium Ra 223 Dichloride	11 (1.8%)	27 (4.5%)
Sex Hormones And Modulators Of The Genital System	5 (0.8%)	10 (1.7%)
Synthetic Estrogens, Plain	4 (0.7%)	4 (0.7%)
Diethylstilbestrol	4 (0.7%)	3 (0.5%)
Hexestrol	0	1 (0.2%)
Antiandrogens, Plain	1 (0.2%)	6 (1.0%)
Cyproterone	1 (0.2%)	6 (1.0%)
All Other Therapeutic Products	3 (0.5%)	7 (1.2%)
Other Therapeutic Products	3 (0.5%)	7 (1.2%)
Investigational Drug	3 (0.5%)	7 (1.2%)
Immunostimulants	1 (0.2%)	0
Interleukins	1 (0.2%)	0
Interleukin-2	1 (0.2%)	0
Unspecified Herbal And Traditional Medicine	1 (0.2%)	1 (0.2%)
Uncoded ATC Level 4	1 (0.2%)	1 (0.2%)
Unspecified Herbal	1 (0.2%)	1 (0.2%)
Urologicals	1 (0.2%)	0
Testosterone-5-Alpha Reductase Inhibitors	1 (0.2%)	0
Finasteride	1 (0.2%)	0
Antimycotics For Systemic Use	0	2 (0.3%)
Imidazole Derivatives	0	2 (0.3%)
Ketoconazole	0	2 (0.3%)
Total Number of Subjects with Subsequent Surgery/Procedures	77 (12.9%)	121 (20.1%)

	AA-P	Placebo
Radiotherapy (To Bone)	67 (11.2%)	101 (16.8%)
Radiotherapy (Other Than Bone)	6 (1.0%)	17 (2.8%)
Surgery (To Bone)	5 (0.8%)	6 (1.0%)
Surgery (Other Than Bone)	4 (0.7%)	10 (1.7%)

Half as many subjects in the AA-P group (20.9%) received life-extending therapy (i.e., docetaxel, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide, sipuleucel-T, and radium-223) for prostate cancer compared with those in the Placebo group (40.9%); the most frequently used life-extending therapy was docetaxel (17.8%, AA-P and 31.1%, Placebo) followed by enzalutamide (5.0%,

AA-P and 12.6%, Placebo) and abiraterone acetate plus prednisone (1.7%, AA-P and 8.8%, Placebo) (Table 12). No subject received sipuleucel-T as subsequent therapy.

Table 12 - Life-extending Subsequent Therapy for Prostate Cancer; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Analysis set: ITT population	597	602
Subjects with Life-extending Subsequent Therapy	125 (20.9%)	246 (40.9%)
Docetaxel	106 (17.8%)	187 (31.1%)
Enzalutamide	30 (5.0%)	76 (12.6%)
Cabazitaxel	11 (1.8%)	30 (5.0%)
Radium Ra 223 Dichloride	11 (1.8%)	27 (4.5%)
Abiraterone	10 (1.7%)	53 (8.8%)

Note that one subject may have multiple Life-extending Subsequent Therapies.

Numbers analysed

Efficacy analyses were performed using the ITT population, which included 1,199 randomized subjects (597 subjects in the AA-P group and 602 subjects in the Placebo group).

Outcomes and estimation

Primary Efficacy Analysis

- Radiographic Progression-Free Survival

As of the cutoff date, among the 1,199 randomized subjects assessed by investigators, 593 (49.5%) subjects had radiographic progression or died: 239 (40.0%) in the AA-P group and 354 (58.8%) in the Placebo group. Radiographic PFS is presented in Table 13 and Figure 1.

Treatment with AA-P was statistically significant with a decreased risk of radiographic progression or death by 53% compared with Placebo (HR=0.466; 95% CI: 0.394, 0.550; p<0.0001). The median rPFS was 33.0 months in the AA-P group and was 14.8 months in the Placebo group.

The 24-month event-free rate was 61.1% for AA-P treatment and 34.7% for Placebo. The 36-month event-free rate was 47.1% for AA-P and 20.9% for Placebo.

The unstratified analysis of rPFS (HR=0.466; p<0.0001) was consistent with the stratified analysis.

Table 13 - Radiographic Progression-Free Survival - Stratified Analysis; Intent-to-treat Population (Study212082PCR3011)

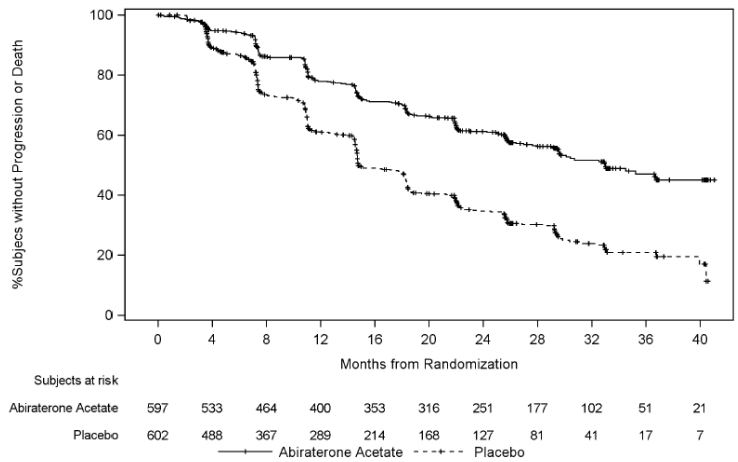
	AA-P	Placebo
Subjects randomized	597	602
Event	239 (40.0%)	354 (58.8%)
Censored	358 (60.0%)	248 (41.2%)
Time to Event (months)		
25th percentile (95% CI)	14.59 (11.47, 15.61)	7.43 (7.29, 10.58)
Median (95% CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)
75th percentile (95% CI)	NE (NE, NE)	30.36 (29.24, 39.95)
Range	(0.0+, 41.0+)	(0.0+, 40.6+)
6-month event-free rate (95% CI)	0.941 (0.918, 0.957)	0.867 (0.836, 0.892)
12-month event-free rate (95% CI)	0.779 (0.742, 0.812)	0.611 (0.567, 0.652)
18-month event-free rate (95% CI)	0.702 (0.661, 0.739)	0.476 (0.431, 0.520)
24-month event-free rate (95% CI)	0.611 (0.568, 0.652)	0.347 (0.303, 0.391)
30-month event-free rate (95% CI)	0.532 (0.483, 0.579)	0.250 (0.206, 0.296)
36-month event-free rate (95% CI)	0.471 (0.414, 0.526)	0.209 (0.162, 0.260)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.466 (0.394, 0.550)	

Note: += censored observation, NE=not estimable. The radiographic progression and death are considered in defining the rPFS event

[a] p value is from a log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or present).

[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA-P.

Figure 1 - Kaplan-Meier Plot of Radiographic Progression-free Survival; Intent-to-treat Population (Study 212082PCR3011)



- Overall Survival

At the time of main (only analysis planned) rPFS analysis a first IA on OS was performed (planned to be performed at approximately 50% of total events). The results of the first interim analysis of OS are presented in Table 14 and Figure 2.

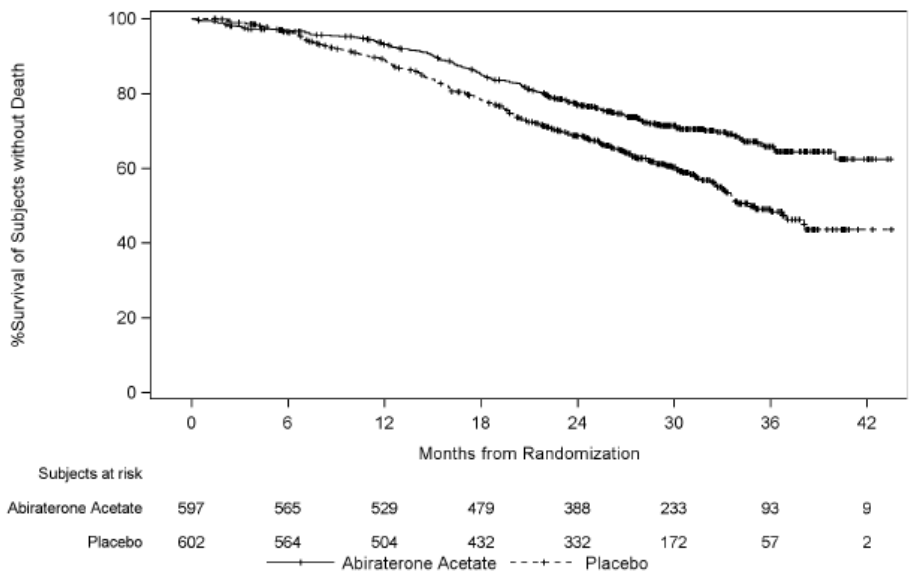
At the time of the data cutoff, 406 deaths were observed: 169 (28.3%) in the AA-P group and 237 (39.4%) in the Placebo group. The median follow-up time for all subjects was 30.4 months. The hazard ratio for OS was 0.621 (95% CI: 0.509, 0.756; p<0.0001), representing a 38% reduction in the risk of death; the median survival was not reached in the AA-P group and was 34.7 months in the Placebo group. The prespecified nominal statistical significance level based on the Wang-Tsiatis efficacy boundary with observed 406 events is 0.010.

Table 14 - Overall Survival, Stratified Analysis; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	169 (28.3%)	237 (39.4%)
Censored	428 (71.7%)	365 (60.6%)
Overall Survival (months)		
25th percentile (95% CI)	26.12 (22.74, 30.13)	19.75 (17.91, 21.82)
Median (95% CI)	NE (NE, NE)	34.73 (33.05, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1, 43.5+)	(1.4+, 43.5+)
12-month event-free rate (95% CI)	0.931 (0.908, 0.949)	0.892 (0.863, 0.914)
24-month event-free rate (95% CI)	0.769 (0.732, 0.802)	0.686 (0.646, 0.723)
36-month event-free rate (95% CI)	0.658 (0.608, 0.704)	0.492 (0.436, 0.546)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.621 (0.509, 0.756)	

Note:+= censored observation, NE = not estimable
[a]p value is from log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or present).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA-P.

Figure 2 - Kaplan-Meier Plot of Overall Survival; Intent-to-treat Population (Study 212082PCR3011)



On 12 January 2017, the IDMC reviewed trial data and recommended the study to be unblinded because of "compelling" clinical benefit. From that point cross-over of patients from Placebo to AA-P arm is allowed. A second interim analysis of OS is planned at approximately 554 (approximately 65 % of total events) events and a final analysis is planned at approximately 852 events (total events).

Sensitivity Analysis for Overall Survival

Subjects in the Placebo group received more life-extending subsequent therapy (20.9 % in AA-P and 40.9% in Placebo group (Table 12). A sensitivity analysis of OS conducted using the Inverse Probability censoring weight (IPCW) method, resulted in a statistically significant improvement in OS in favor of AA-P

(HR: 0.477; 95% CI: 0.3596, 0.6336, p<0.0001) after adjusting for subjects switching to other life-extending subsequent therapy.

A sensitivity analysis of OS conducted using a time-dependent Cox regression prior to subjects receiving subsequent anticancer therapy resulted in a statistically significant improvement in OS in favor of AA-P (HR: 0.573; 95% CI: 0.4453, 0.7369; p<0.0001).

A sensitivity analysis of OS conducted using censoring at the time of initiation of life-extending subsequent anticancer therapy resulted in a statistically significant improvement in OS in favour of AA-P (HR: 0.577; 95% CI: 0.449, 0.743; p<0.0001).

Secondary Efficacy Endpoints

- Time to Initiation of Chemotherapy

Time to initiation of chemotherapy was defined as the time interval from the date of randomization to the date of initiation of chemotherapy for prostate cancer. Initiation of chemotherapy was documented for 18.3% of subjects in the AA-P group and 31.7% of subjects in the Placebo group (Table 15 and Figure 3).

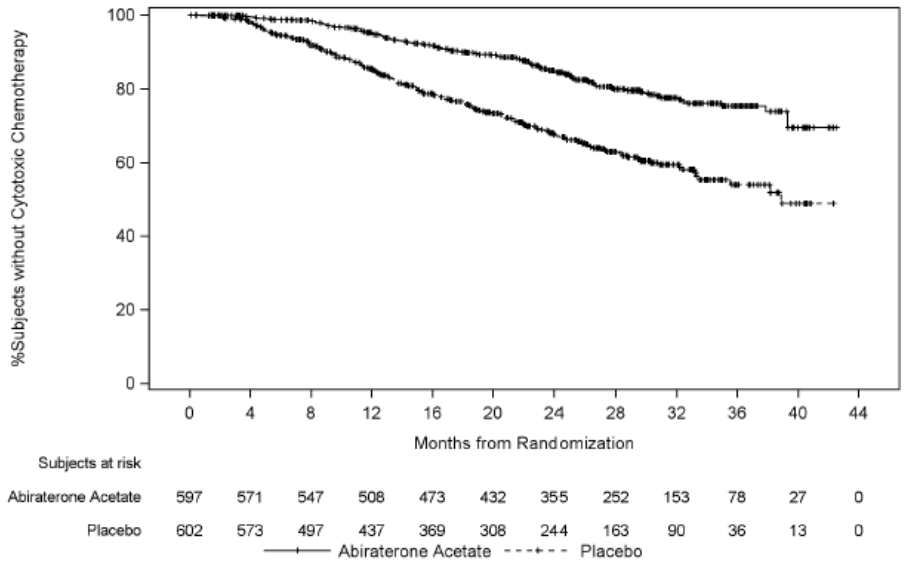
There was a 56% reduction in risk of initiation of chemotherapy (HR=0.443; 95% CI: 0.349, 0.561, p<0.0001). The median time to initiation of chemotherapy was not reached in the AA-P group and was 38.9 months in the Placebo group demonstrating that AA-P delayed the need for initiation of chemotherapy. The 36-month event free rate (i.e., percent of subjects for whom chemotherapy was not required at 3 years after initiation of study treatment) was 75.3% for AA-P versus 54.0% for Placebo.

Table 15 - Time to Initiation of Chemotherapy - Stratified Analysis; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	109 (18.3%)	191 (31.7%)
Censored	488 (81.7%)	411 (68.3%)
Time to Event (months)		
25th percentile (95% CI)	37.88 (29.86, NE)	18.63 (16.07, 21.55)
Median (95% CI)	NE (NE, NE)	38.90 (33.35, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.1+, 42.5+)	(1.4+, 42.3+)
6-month event-free rate (95% CI)	0.988 (0.975, 0.994)	0.945 (0.923, 0.961)
12-month event-free rate (95% CI)	0.951 (0.930, 0.966)	0.855 (0.823, 0.882)
18-month event-free rate (95% CI)	0.899 (0.871, 0.922)	0.764 (0.725, 0.798)
24-month event-free rate (95% CI)	0.850 (0.815, 0.878)	0.678 (0.634, 0.718)
30-month event-free rate (95% CI)	0.789 (0.747, 0.824)	0.605 (0.556, 0.651)
36-month event-free rate (95% CI)	0.753 (0.705, 0.795)	0.540 (0.476, 0.600)
42-month event-free rate (95% CI)	0.695 (0.611, 0.764)	0.489 (0.397, 0.574)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.443 (0.349, 0.561)	

Note: += censored observation, NE=not estimable.
[a] p value is from a log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or present).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA-P.

Figure 3 - Kaplan-Meier Plot of Time to Initiation of Chemotherapy; Intent-to-treat Population (Study 212082PCR3011)



- Time to Subsequent Therapy for Prostate Cancer

Time to subsequent therapy (all subsequent therapy for prostate cancer including hormonal therapy, chemotherapy, surgery, and radiation) is defined as the time interval from the date of randomization to the date of initiation of subsequent therapy for prostate cancer and is provided in Table 16 and Figure 4.

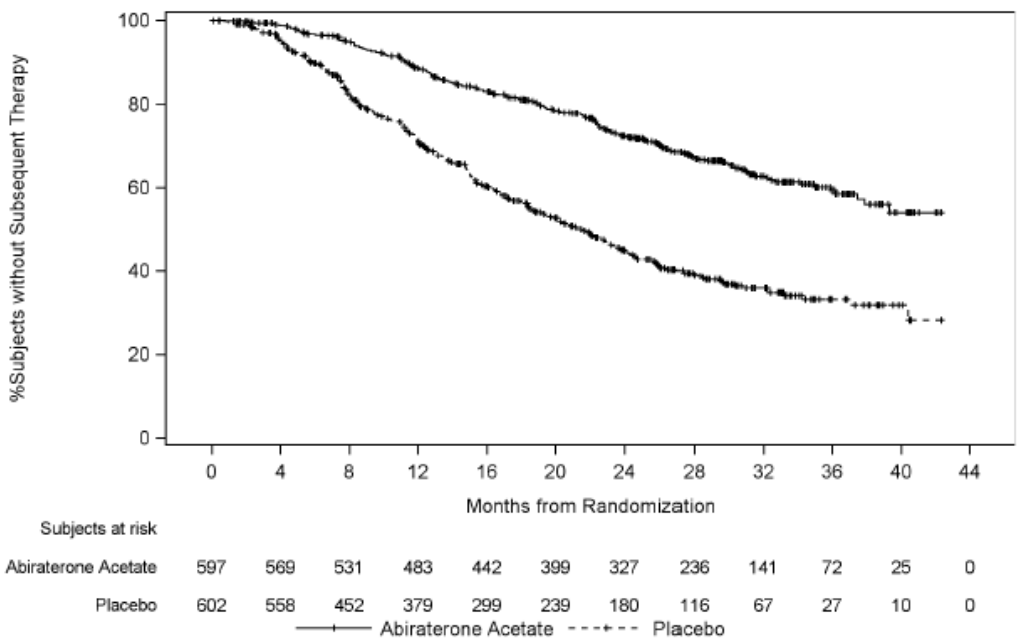
There were 32.0% of subjects in the AA-P group and 53.5% of subjects in the Placebo group who received subsequent therapy for prostate cancer. The median time to subsequent therapy was not reached in the AA-P group and was 21.6 months in the Placebo group (HR=0.415; 95% CI: 0.346, 0.497; p<0.0001), demonstrating that AA-P delayed the need for initiation of subsequent therapy.

Table 16 - Time to Subsequent Therapy for Prostate Cancer - Stratified Analysis; Intent-to-treat Population (Study 212082PCR3011)

	AA-P	Placebo
Subjects randomized	597	602
Event	191 (32.0%)	322 (53.5%)
Censored	406 (68.0%)	280 (46.5%)
Time to Event (months)		
25th percentile (95% CI)	22.47 (19.91, 25.23)	11.10 (9.30, 12.02)
Median (95% CI)	NE (37.88, NE)	21.55 (18.79, 23.62)
75th percentile (95% CI)	NE (NE, NE)	NE (40.41, NE)
Range	(0.1+, 42.3+)	(0.8, 42.3+)
6-month event-free rate (95% CI)	0.967 (0.949, 0.979)	0.898 (0.870, 0.919)
12-month event-free rate (95% CI)	0.886 (0.857, 0.910)	0.715 (0.675, 0.750)
18-month event-free rate (95% CI)	0.812 (0.776, 0.842)	0.566 (0.523, 0.607)
24-month event-free rate (95% CI)	0.724 (0.684, 0.760)	0.451 (0.406, 0.494)
30-month event-free rate (95% CI)	0.657 (0.612, 0.698)	0.369 (0.323, 0.414)
36-month event-free rate (95% CI)	0.593 (0.540, 0.642)	0.332 (0.283, 0.383)
42-month event-free rate (95% CI)	0.540 (0.468, 0.607)	0.283 (0.205, 0.366)
p value[a]	< 0.0001	
Hazard ratio (95% CI)[b]	0.415 (0.346, 0.497)	

Note: += censored observation, NE=not estimable.
[a] p value is from a log-rank test stratified by ECOG PS score(0/1 or 2) and visceral (absent or present).
[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors AA-P.

Figure 4 - Kaplan-Meier Plot of Time to Subsequent Therapy for Prostate Cancer; Intent-to-treat Population (Study 212082PCR3011)



- Time to Life-Extending Subsequent Therapy for Prostate Cancer

The time to life-extending subsequent therapy (i.e., docetaxel, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide, sipuleucel-T, and radium-223) was analysed; a summary of life-extending therapy received during the study is provided in Table 12 of this report.

There were 20.9% of subjects in the AA-P group and 40.9% of subjects in the Placebo group who

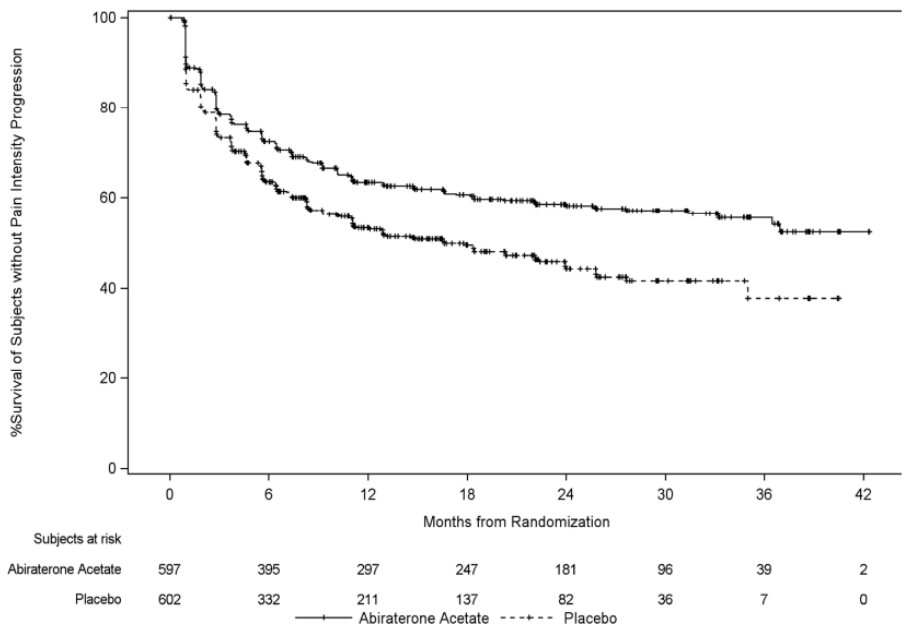
received life-extending subsequent therapy (i.e., docetaxel, cabazitaxel, abiraterone acetate plus prednisone, enzalutamide, sipuleucel-T, and radium-223).

The median time to life-extending subsequent therapy was not reached in the AA-P group and was 29.5 months in the Placebo group, demonstrating that AA-P delayed the need for initiation of life-extending subsequent therapy (HR=0.365; 95% CI: 0.294, 0.454; p<0.0001). The 36-month event-free rate was 70.1% for AA-P and 43.3% for Placebo.

- Time to Pain Progression

Time to pain progression was defined as the time interval from randomization to the first date a subject experiences a ≥30% increase from baseline in the BPI-SF worst pain intensity (Item 3) observed at 2 consecutive evaluations ≥4 weeks apart. Time to pain progression is presented in Figure 5. Pain progression was documented for 39.0% of subjects in the AA-P group and 48.0% of subjects in the Placebo group. There was a 31% reduction in risk of pain progression (HR=0.695; 95% CI: 0.583, 0.829; p<0.0001). The median time to pain progression was not reached in the AA-P group and was 16.6 months in the Placebo group. The 36-month event-free rate (i.e., the percent of subjects without pain progression at 3 years after initiation of study treatment) was 55.5% for AA-P versus 37.9% for Placebo.

Figure 5 - Kaplan-Meier Plot of Time to Pain Progression (BPI3); Intent-to-treat Population (Study 212082PCR3011)



Sensitivity Analysis for Time to Pain Progression

In a population of subjects who have no or minimal pain, a 2-point increase in time to pain intensity progression may be more clinically relevant. Therefore, an analysis for time to worst pain intensity progression (2-point increase) was conducted. A 2-point increase in time to pain intensity progression was defined as the time interval from randomization to the first date a subject experienced an increase by 2 points from baseline in the BPI-SF worst pain intensity item (Item 3) observed at 2 consecutive evaluations ⩾4 weeks apart.

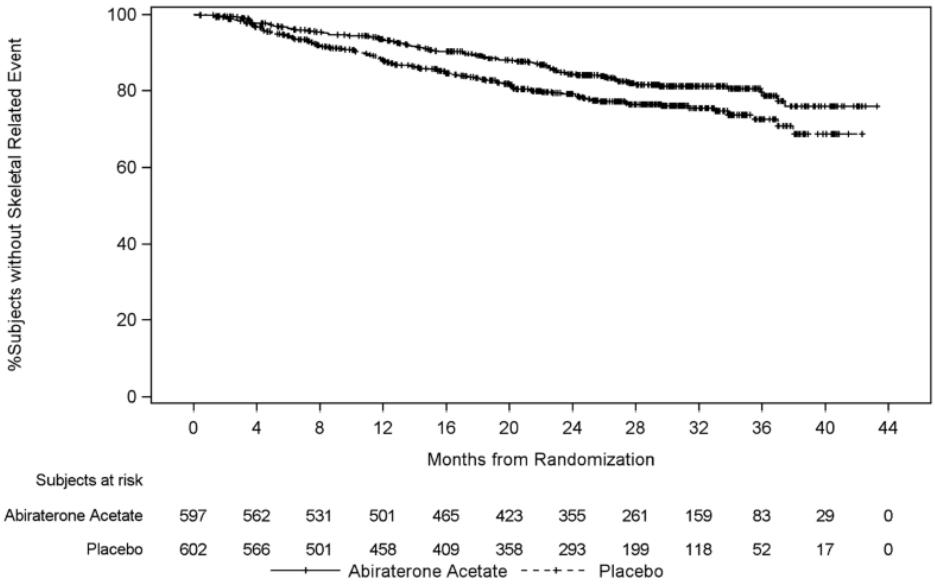
Treatment with AA-P reduced the risk of worst pain intensity progression (2-point increase) by 37% compared with placebo; the median time to pain progression (2-point increase) was not reached in either

treatment group (HR=0.631; 95% CI: 0.517, 0.770; p<0.0001). The 36 –month event-free rate was 64.9% in the AA-P group compared with 51.2% in the Placebo group.

- Time to Skeletal-related Event

Time to skeletal-related event was defined as the earliest of the following: clinical or pathological fracture, spinal cord compression, palliative radiation to bone, or surgery to bone. There was a 30% reduction in the risk of skeletal-related event (HR=0.703; 95% CI: 0.539, 0.916; p=0.0086). The 25th percentile time to skeletal-related event was not reached for the AA-P group and was 33.0 months for Placebo. A Kaplan-Meier plot of time to skeletal-related event is presented in Figure 6.

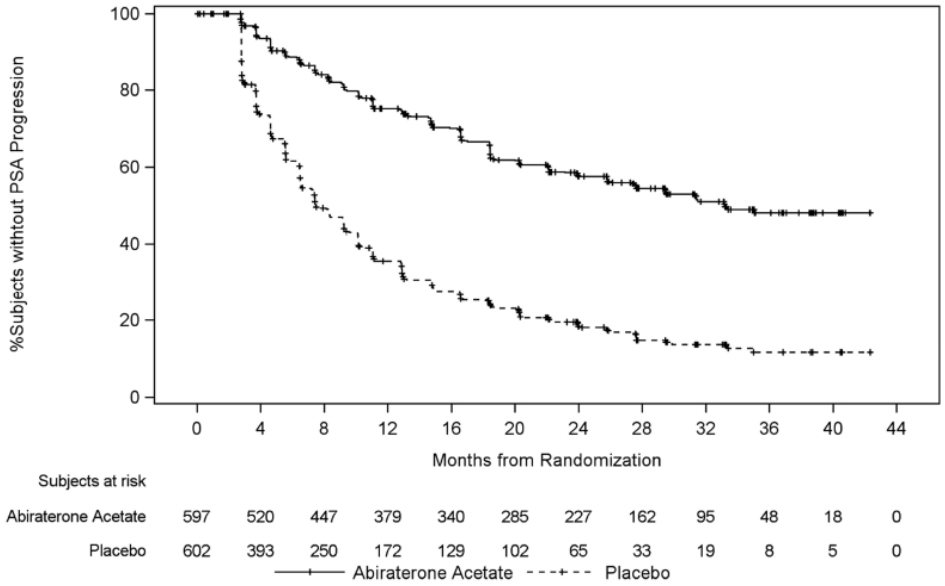
Figure 6 - Kaplan-Meier Plot of Time to Skeletal-related Event; Intent-to-treat Population (Study 212082PCR3011)



- Time to PSA Progression (by PCWG2 Criteria)

Time to PSA progression was defined as the time interval from the date of randomization to the date of PSA progression, according to PCWG2 criteria. Prostate-specific antigen progression was documented for 40.4% of subjects in the AA-P group and 72.1% of subjects in the Placebo group (Figure 7). Treatment with AA-P statistically significantly decreased the risk of PSA progression by 70% compared with Placebo (HR=0.299; 95% CI: 0.255, 0.352; p<0.0001). The median time to PSA progression was 33.2 months in the AA-P group and 7.4 months in the Placebo group, a delay in PSA progression by >25 months in the AA-P group compared with the Placebo group.

Figure 7- Kaplan-Meier Plot of PSA Progression; Intent-to-treat population



Exploratory Efficacy Endpoints Analyses

Exploratory analyses included PSA response rate, progression-free survival following subsequent therapy (PFS2), PRO measures (BPI-SF, FACT-P, BFI, and EQ-5D-DL), time to symptomatic local progression, prostate cancer-specific survival, time to chronic opiate use, and best overall response. Castration status is also included in this section.

PSA Response Rate

A confirmed PSA response was observed in 91.0% of subjects in the AA-P group and 66.8% of subjects in the Placebo group (relative risk=1.362; p<0.0001).

Progression-free Survival Following Subsequent Therapy (PFS2)

Progression-free survival following subsequent therapy (PFS2) was defined as the time from randomization to the second disease progression during follow-up after systemic subsequent therapy, or death from any cause.

Among the 164 (27.5%) subjects in the AA-P group and 296 (49.2%) subjects in the Placebo group that received systemic subsequent therapy, 98/164 (59.8%) and 183/296 (61.8%) experienced PFS2 events, respectively. The median PFS2 was longer with initial AA-P treatment (27.8 months) compared with initial Placebo treatment (23.9 months), but did not reach statistical significance (HR=0.819; 95% CI=0.638, 1.051; p=0.1162). Note that PFS2 was based on investigator-assessed progression (clinical/radiographic/PSA progression), after first subsequent therapy, and this progression was not based on a protocol-defined criterion definition.

Patient-Reported Outcome (PRO) Measures: BPI-SF, FACT-P, BFI, EQ-5D-5L

PRO data for the BPI-SF, FACT-P, BFI, and EQ-5D-5L were collected at baseline, every month from Cycle 2 to Cycle 13, every 2 months thereafter until radiographic or clinical progression of disease, and at the end of study treatment visit. In addition, EQ-5D-5L data were collected further, i.e., every 4 months for a total of 12 months after treatment discontinuation.

- Brief Pain Inventory – Short Form

The BPI-SF was used to measure subjects' self-assessment of pain experienced during the study. The cumulative compliance rate for completion of the BPI-SF was greater than 95.0% through Cycle 13 and 90.0% or greater thereafter (through Cycle 47); compliance rates were similar across the treatment groups.

- Time to Event Analysis on BPI-SF

The results for BPI-SF Worst Pain Intensity (BPI-SF Item 3, a secondary efficacy endpoint, titled "Time to Pain Progression") and the corresponding sensitivity analysis utilising a 2-point scale are presented under secondary endpoints subheading (see above).

Time to BPI-SF pain interference progression (Combined scale of Items 9A through 9G, Impact of Pain on Interference with Activities) showed that treatment with AA-P significantly reduced the risk of pain interference progression by 33% compared with treatment with Placebo (HR=0.671; 95% CI: 0.561, 0.803; p<0.0001). The median time to BPI-SF pain interference progression was not reached in the AA-P group and was 18.4 months in the Placebo group.

Time to BPI-SF average pain progression (average of BPI-SF Items 3, 4, 5, and 6) showed that the median time to BPI-SF average pain progression was not reached in either treatment group; HR=0.896; 95% CI: 0.691, 1.162; p=0.4057. It should be noted that the majority of subjects in this analysis were censored (80.6%, AA-P group; 81.1%, Placebo).

- Repeated Measures Analysis on BPI-SF

Change from baseline using the repeated measures mixed-effect model was conducted for BPI-SF worst pain intensity, pain interference and average pain progression. Significant differences were observed as early as Cycle 2 through Cycle 33 for all BPI measures, except for Cycle 3 for BPI-SF average pain progression and Cycle 25 for BPI-SF pain interference, with lower mean scores for AA-P indicative of less pain intensity, interference, and progression.

- FACT-P

The FACT-P is a prostate-specific PRO instrument used to measure prostate cancer symptoms, functional status, and health-related quality of life.

Time to Event Analysis: The results for the FACT-P Total Score showed that treatment with AA-P statistically significantly delayed the time to health-related quality of life degradation by 15% (HR=0.853; 95% CI: 0.736, 0.989; p=0.0322) (Mod5.3.5.1\PCR3011\Sec5.4.3.2.1). The median time to deterioration in FACT-P (Total Score) was 12.9 months in the AA-P group and 8.3 months in the Placebo group.

The results for the FACT-P Pain-related Subscale (PRS) showed that treatment with AA-P statistically significantly delayed the time to pain-related symptoms by 24% (HR=0.760; 0.659, 0.876; p=0.0001). The median time to degradation in FACT-P PRS was 10.2 months in the AA-P group and 6.5 months in the Placebo group.

A summary of the FACT-P Total Score and subscale score results is presented in Table 17. Results for the majority of subscales of the FACT-P were consistent with a delay of degradation of functional status and health-related quality-of-life for the AA-P group compared with the Placebo group. The other FACT-P subscales showed a statistically significant decrease in the risk of worsening function for subjects in the AA-P group compared with the Placebo group (PCS, p=0.0025; other subscales, p=0.0001), except for the FACT-P subscales of Functional Assessment Cancer Therapy-General (FACT-G), Social/Family Well-Being (SFWB), Emotional Well-Being (EWB), and Functional Well-Being (FWB).

The FACT-P endpoints showed a consistent pattern of delays in pain and prostate cancer symptom

progression, as well as degradation of functional status, and health-related quality of life in subjects treated with AA-P compared with Placebo.

Table 17 - Summary of FACT-P Total Score and Subscale Score Results (Study PCR3011: ITT Population)

FACT-P Subscale	Median (95% CI) Time to Progression (months)		Hazard ratio of AA-P/Placebo (95% CI)	p value
	AA-P	Placebo		
FACT-P (Total Score)	12.91 (9.03, 16.59)	8.34 (7.36, 11.10)	0.853 (0.736, 0.989)	0.0322
FACT-P Subscales:				
PRS	10.18 (8.31, 14.78)	6.47 (5.55, 7.46)	0.760 (0.659, 0.876)	0.0001
PCS	8.31 (6.47, 11.07)	5.55 (4.60, 7.33)	0.808 (0.701, 0.930)	0.0025
TOI	18.43 (14.36, 22.64)	9.23 (7.43, 11.17)	0.734 (0.630, 0.854)	0.0001
FACT-G	12.91 (9.33, 18.43)	8.31 (7.36, 11.07)	0.868 (0.747, 1.007)	0.0584
PWB	14.36 (10.15, 18.20)	7.43 (6.51, 9.20)	0.750 (0.648, 0.869)	0.0001
SFWB	3.78 (2.89, 4.70)	5.49 (4.60, 6.44)	1.064 (0.923, 1.226)	0.3810
EWB	16.13 (10.18, 20.70)	10.15 (8.31, 14.82)	0.923 (0.791, 1.078)	0.3056
FWB	7.36 (5.55, 9.23)	5.45 (3.78, 6.41)	0.894 (0.776, 1.029)	0.1089

EWB=Emotional Well-Being; FACT-G=Functional Assessment of Cancer Therapy-General; FACT-P=Functional Assessment of Cancer Therapy-Prostate; FWB=Functional Well-Being; PCS=Prostate Cancer Subscale; PRS=Pain-related Subscale; PWB=Physical Well-Being; SFWB=Social/Family Well-Being; TOI=Total Outcome Index
Source: Mod5.3.5.1\PCR3011\Table25

Repeated Measures Analysis: Change from baseline using repeated measures mixed effect model was conducted for FACT-P total score and all subscales. Significant differences were observed favouring AA-P versus placebo as early as Cycle 2 for the FACT-P PRS, as early as Cycle 4 for PWB, and as early as Cycle 5 for the FACT-P Total, PCS, TOI, FACT-G through Cycle 33.

Clear numeric separation was observed for FWB with significant differences as early as Cycle 3 and then for the majority of the cycles (except Cycle 4, Cycle 11, and Cycle 33). Numeric differences were observed between groups for EWB with some of these differences being significant. No differences were observed between AA-P versus placebo for the SFWB.

- BFI

The BFI instrument was used to evaluate fatigue.

Time to Event Analysis: For time to BFI worst fatigue intensity progression (Item 3), treatment with AA-P significantly delayed the time to BFI worst fatigue interference progression by 35% (HR=0.652; 95% CI: 0.527, 0.805; p=0.0001); the median time to BFI worst fatigue intensity progression was not reached in either the AA-P or Placebo group.

For time to BFI fatigue interference progression (average of Items 4A-4F), treatment with AA-P significantly delayed the time to BFI fatigue interference progression by 41% (HR=0.594; 95% CI: 0.470, 0.750; p<0.0001); the median time to BFI fatigue interference progression was not reached in either the AA-P or Placebo group.

Repeated Measures Analysis: Change from baseline using the repeated measures mixed-effect model was conducted for BFI worst fatigue intensity and BFI fatigue interference scales. Significant differences between groups were observed in both BFI worst fatigue intensity and fatigue interference as early as Cycle 5 through Cycle 33, except for Cycles 17 and 27 for BFI worst fatigue intensity.

- EQ-5D-5L

The EQ-5D-5L questionnaires were used to measure mobility, self-care, usual activities, pain, discomfort, and anxiety/depression and health-related quality of life. A summary of the health states from the five dimensions and the VAS score for overall health status over time are presented in. Changes from baseline on the VAS were all positive for subjects treated with AA-P and were numerically greater than those from

the Placebo group.

Time to Symptomatic Local Progression

Time to symptomatic local progression, defined as the occurrence of urethral obstruction or bladder outlet obstruction symptoms requiring medical or surgical intervention (e.g., transurethral resection of the prostate, nephrostomy tube insertion, bladder catheter insertion) is presented in Mod5.3.5.1\PCR3011\Sec5.4.4. Overall, only a small number of subjects experienced such an event, 33 (5.5%) subjects in AA-P group and 37 (6.1%) subjects in Placebo group. The analysis of time to symptomatic local progression favoured treatment with AA-P compared with Placebo (HR=0.683; 95% CI: 0.426, 1.097; p=0.1126); the median time to symptomatic local progression was not reached in either treatment group. Note that the majority of subjects in this analysis were censored (94.5%, AA-P; 93.9%, Placebo) as only 5.8% of subjects across both treatment groups experienced symptomatic local progression.

Prostate Cancer-specific Survival

Prostate cancer-specific survival, defined as the time from randomization to death date due to prostate cancer, is summarized in Mod5.3.5.1\PCR3011\Sec5.4.5. Subjects who were alive or who died due to other reasons were censored at last date of known alive or death not due to prostate cancer. Death due to prostate cancer occurred less frequently in the AA-P group (122 [20.4%] events) as compared to the Placebo group (194 [32.2%] events). A statistically significant improvement in prostate cancer-specific OS was observed for the AA-P group compared with the Placebo group (HR=0.547; 95% CI: 0.436, 0.687; p<0.0001).

Time to Chronic Opiate Use

Time to chronic opiate use was defined as the time from randomization to new opioid analgesics use, or increased dose or frequency of the existing opioid analgesics (from Cycle 1 Day 1 for ⩾3 weeks orally or 7 days parenterally [for non-oral formulations]). Subjects with no event were censored at the last dose + 30 days. A slightly lower percentage of subjects in the AA-P group compared with those in the Placebo group received chronic opioid analgesics (20.8% vs. 22.8%) and received this medication much later (24-month event free rate: 80.0% vs. 71.3%). A 29% reduction in risk of requiring chronic opioid use was observed (HR=0.706; 95% CI: 0.553, 0.902; p=0.0051). The median time to chronic opioid analgesic use was not reached in either treatment group. It should be noted that the majority of subjects in this analysis were censored (79.2%, AA-P group; 77.2%, Placebo group) as less than 25% of subjects across both treatment groups received chronic use of opioid analgesics.

Best Overall Response

Best overall response in subjects with measurable disease at baseline (257 subjects in AA-P group and 271 in Placebo group), as assessed by RECIST 1.1. A higher percentage of subjects in the AA-P group compared with those in the Placebo group achieved a complete or partial response. Complete response was observed in 59 (23.0%) subjects in the AA-P group and 41 (15.1%) subjects in the Placebo group. Partial response was observed in 147 (57.2%) subjects in the AA-P group and 137 (50.6%) subjects in the Placebo group, while stable disease was observed in 34 (13.2%) and 50 (18.5%) subjects, respectively.

The unstratified analysis of objective response rate favored treatment with AA-P over Placebo (relative risk=1.220, p=0.0002) and was consistent with the stratified analysis.

Castration Status

Castration level for testosterone <0.50 ng/mL (<1.70 nmol/L) was attained for the majority of subjects at baseline (61.2% for AA-P group and 61.8% for Placebo group). Overtime the majority of subjects in the

AA-P and Placebo groups were below the castration level (Cycle 3, Day 1: 95.3% and 92.5%, Cycle 6, Day 1: 96.6% and 93.8%, End of Treatment: 96.4% and 93.8%, respectively). As a result, subjects on AA-P treatment as well as those who received Placebo treatment received adequate castration treatment for prostate cancer.

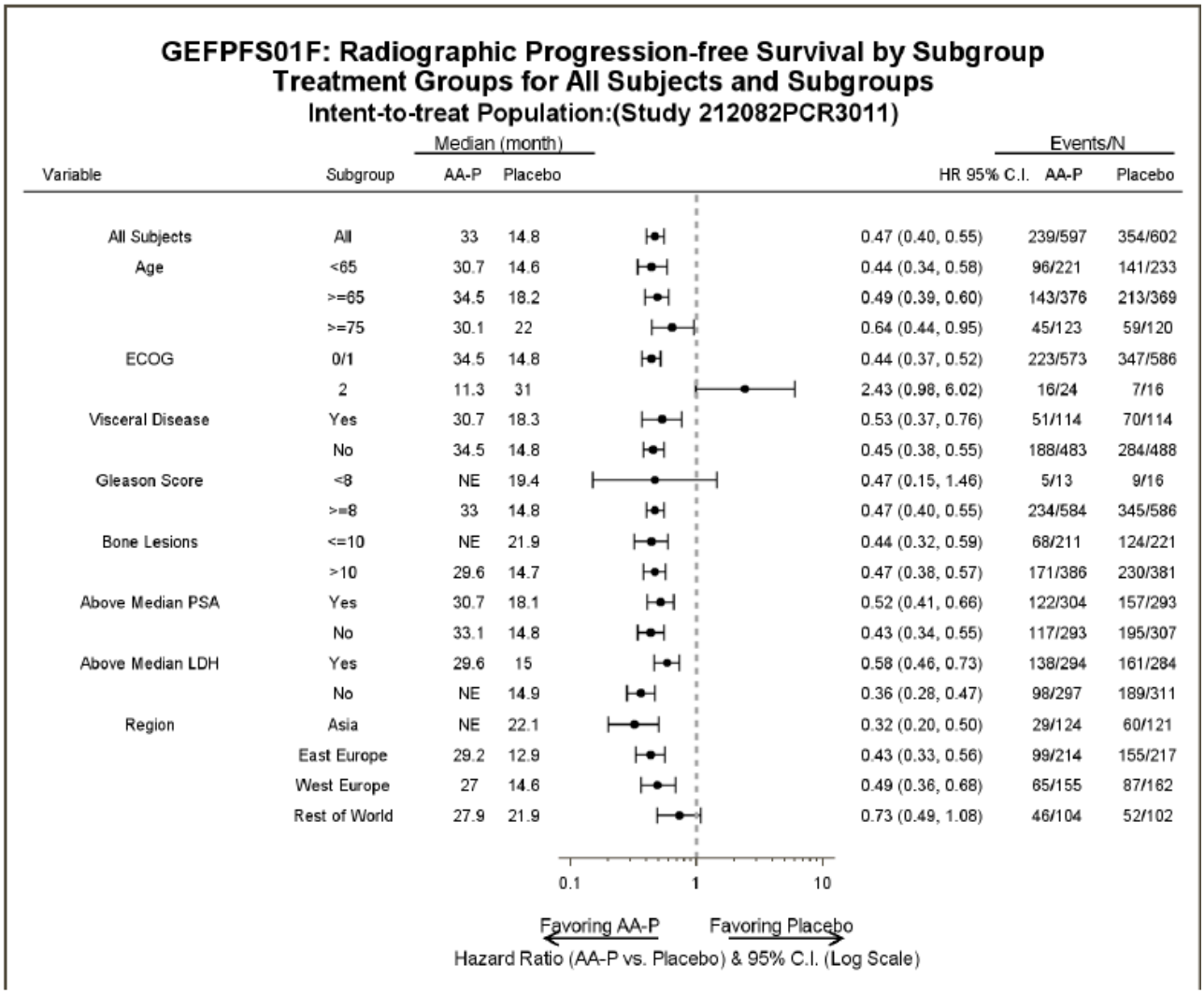
Ancillary analyses

Radiographic Progression-Free Survival

- Subgroup Analyses of Radiographic Progression-free Survival

Subgroup analyses of rPFS are presented in Figure 8. The treatment effect of AA-P on rPFS was favourable and consistent with the overall study population (HR<1.0; ranging from 0.32-0.73), except for the subgroup of ECOG score of 2.

Figure 8 - Radiographic Progression-free Survival by Subgroup Treatment Groups for All Subjects and Subgroups; Intent-to-treat Population: (Study 212082PCR3011)

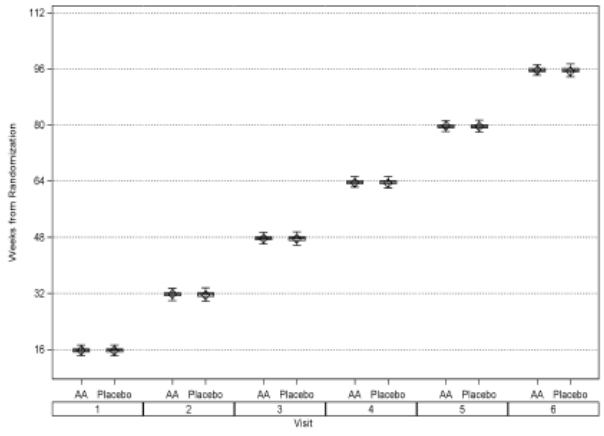


Symmetry of Time of Tumour and Bone Assessments

The timing of tumour and bone scan assessments through 96 weeks after randomization is presented below. Tumour and bone scan assessments were to be performed every 16 weeks. The timing of assessments in both treatment groups adhered closely to the visit schedule specified in the protocol. No

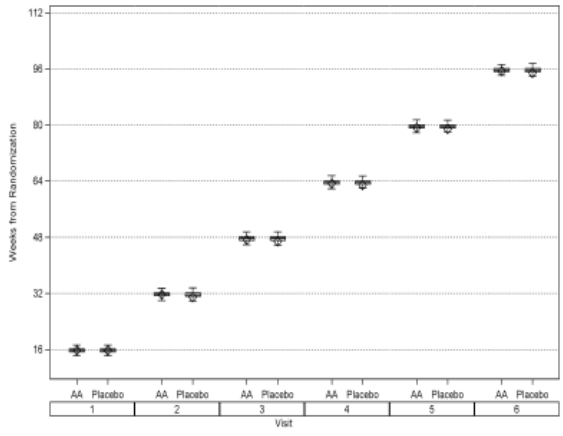
differences in the timings of the assessments were noted between the treatment groups.

GEFPFS02A: Boxplot of Tumor Assessment Time; Intent-to-treat Population (Study 212082PCR3011)



The boxplots represent: 25th percentile (bottom), median (line within), mean (dot), 75th percentile (top)
Lines extending from boxplots extend to 1.5 x inner quartile range

GEFPFS02B: Boxplot of Bone Assessment Time; Intent-to-treat Population (Study 212082PCR3011)



The boxplots represent: 25th percentile (bottom), median (line within), mean (dot), 75th percentile (top)
Lines extending from boxplots extend to 1.5 x inner quartile range

Radiographic Review by Audit Plan

An audit was performed based on a random sample of 202 evaluable subjects, i.e., subjects who had both a baseline and at least 1 post-baseline disease assessment (100 in AA-P group and 102 in Placebo group) to compare the investigators' assessments with that of the BICR.

The results are as follows:

Early discrepancy rates (EDR) (AA-P) – EDR (Placebo) was 10.1%, which is greater than - 10%, and

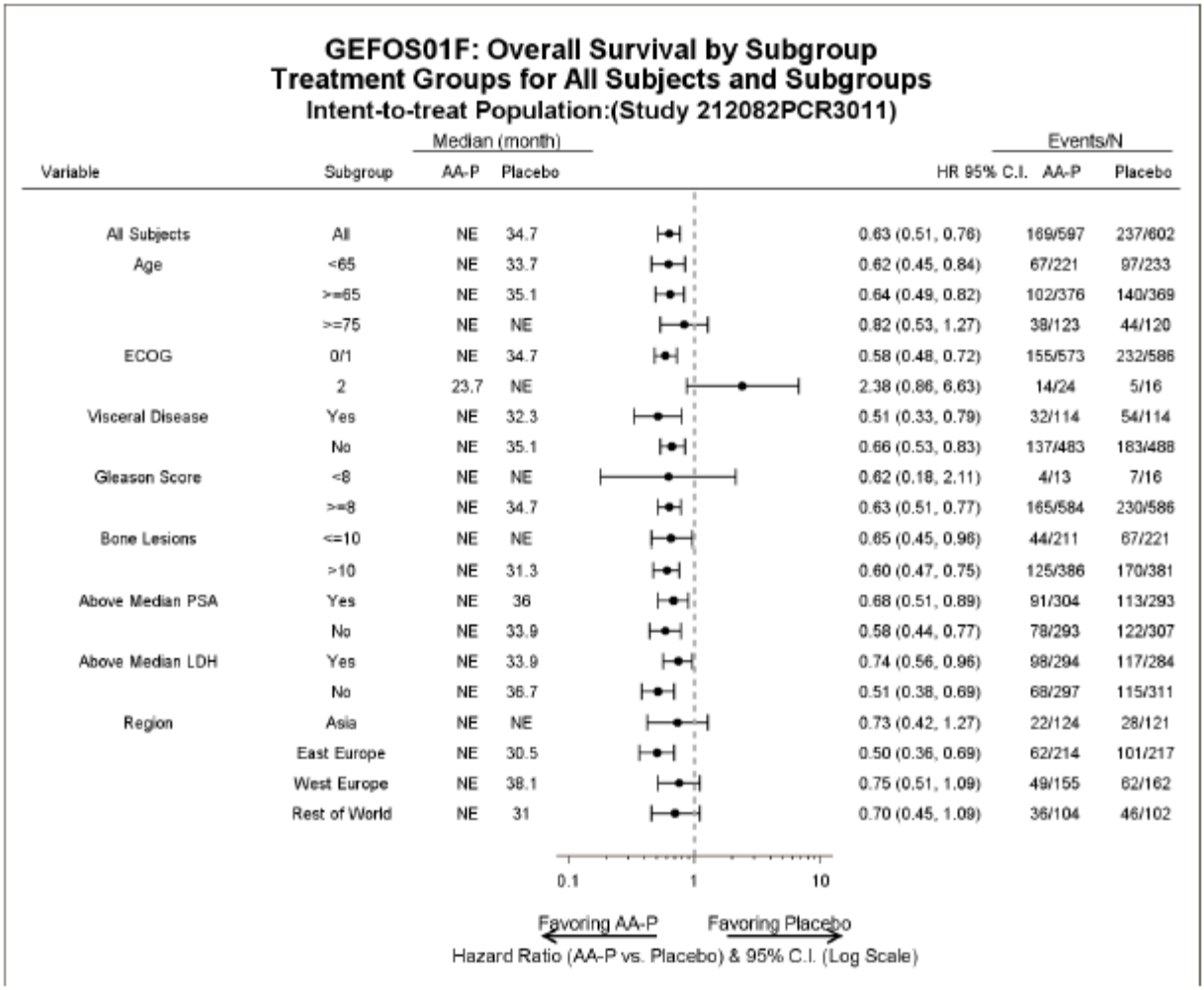
Late discrepancy rates (LDR) (AA-P) – LDR (Placebo) was -12.4%, which is less than 10%.

The IDMC reviewed the results and concluded no bias favouring the AA-P group.

Overall survival

- Subgroup Analyses of Overall Survival

The subgroup analyses of OS are presented in the figure below. The point estimates of the treatment effect of AA-P on OS were favourable for all subgroups (HR<1.0; ranging from 0.50-0.82) and consistent with the overall study results, except for the subgroup of ECOG score of 2.



- Multivariate Analysis of Overall Survival

A multivariate analysis was conducted for OS to evaluate the treatment effect when controlling for potential prognostic factors. After adjusting for these prognostic factors, the results remain supportive of the primary analysis (Table 18).

Table 18 - Overall Survival – Non stratified Proportional Hazards Model (Multivariate Analysis); Intent-to-treat Population (Study 212082PCR3011)

	Model Fit		Hazard Ratio	
	Coeff(SE)	p-value	Estimate	95% C.I.
Treatment (AA-P vs. Placebo)	-0.49 (0.101)	< 0.0001	0.610	0.610 (0.500, 0.744)
Age	-0.00 (0.006)	0.5242	0.996	0.996 (0.985, 1.008)
ECOG score (0,1 vs. 2)	-0.34 (0.238)	0.1591	0.715	0.715 (0.449, 1.140)
Log(Baseline Serum PSA) (ng/mL)	-0.03 (0.023)	0.2106	0.972	0.972 (0.929, 1.016)
Log(Baseline Lactate Dehydrogenase) (IU/L)	1.01 (0.139)	< 0.0001	2.751	2.751 (2.096, 3.611)
Measurable Visceral (Yes vs. No)	0.17 (0.102)	0.0973	1.185	1.185 (0.970, 1.448)
Baseline Gleason Score	0.13 (0.075)	0.0767	1.142	1.142 (0.986, 1.322)
Bone Lesions at baseline (<=10 vs. >10)	-0.55 (0.115)	< 0.0001	0.578	0.578 (0.462, 0.724)

Model dependent variable is overall survival, expressed as months from date of randomization to date of death from any cause.
If the hazard ratio < 1, then result favors the first level of the parameter (as listed above).
Subjects who are not deceased at time of analysis are censored on the last date subject was known to be alive or lost to follow-up.

Association of Radiographic Progression-free Survival and Overall Survival

The strength of association between rPFS and OS was evaluated using Spearman's correlation coefficient estimated through the Clayton copula (Burzykowski 2001) which takes censoring into account. A positive

association between the 2 endpoints was observed, with the estimated value of the coefficient equal to 0.820.

Summary of main study

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

Table 19 - Summary of Efficacy for trial 212082PCR3011

Title: LATITUDE, A Randomized, Double-blind, Comparative Study of Abiraterone Acetate Plus Low dose Prednisone Plus Androgen Deprivation Therapy (ADT) Versus ADT Alone in Newly Diagnosed Subjects With High Risk, Metastatic Hormone-Naive Prostate Cancer(mHNPC)			
Study identifier	Protocol 212082PCR3011; Phase 3; EudraCT Number: 2012-002940-26		
Design	Randomized, Double-blind		
	Duration of screening phase: Duration of treatment phase: Duration of follow-up phase: Duration of Extension phase:		Up to 28 days before randomization 28-day treatment cycles Up to 60 months to monitor OS status and subsequent prostate cancer therapy Open-label cross-over allowed (if positive IA)
Hypothesis	Superiority		
Treatments groups	AA-P group		AA 1000 mgQD + prednisone 5 mg QD+ADT until DP, withdrawal consent or unacceptable tox. or death toxicity; n=597
	Placebo group		Placebo for AA + Placebo for prednisone+ADT until DP, withdrawal consent or unacceptable tox. or death toxicity; n=602
Endpoints and definitions	Co-Primary endpoint	**rPFS & OS**	rPFS: time from randomization to the occurrence of radiographic progression (bone scan PCWG2 or soft tissue RECIST 1.1. both by investigators) or death from any cause. Audit plan on a random sample by BICR. OS: time from randomization to the date of death (regardless of cause).
	Secondary:	Time to initiation of chemotherapy	Time from randomization to initiation of chemotherapy for prostate cancer.
	Secondary:	Time to subsequent therapy for prostate cancer	Time from randomization to initiation of subsequent therapy for prostate cancer.
	Secondary:	Time to pain progression	Time from randomization to the first date a subject experiences a BPI-SF increase by ≥30% from baseline in the BPI-SF worst pain intensity (Item 3) observed at 2 consecutive evaluations ≥4 weeks apart.
	Secondary:	Time to skeletal-related event	Time from randomization to skeletal-related event (earliest one of the following): Clinical or pathological fracture, Spinal cord compression, Palliative radiation to bone, Surgery to bone.
	Secondary:	Time to PSA progression	Time from randomization to the date of the PSA progression (PCWG2 criteria).
Database lock	31 Oct 2016 (clinical cut-off for investigator-assessed rPFS and the first interim analysis of OS)		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat			
Descriptive statistics and estimate variability	Treatment group	AA-P	Placebo group	
	Number of subject	597	602	
	rPFS **Median (months)**	**33.02**	**14.78**	
	(95% CI)	**(29.57, NE)**	**(14.69, 18.27)**	
	OS **Median (months)**	**NE**	**34.73**	
	(95% CI)	**(NE, NE)**	**(33.05, NE)**	
	Time to initiation of chemotherapy Median (months)	NE	38.90	
	(95% CI)	(NE, NE)	(33.35, NE)	
	Time to subsequent therapy for PC	NE	21.55	
	(95% CI)	(37.88, NE)	(18.79, 23.62)	
	Time to pain progression	NE	16.62	
	(95% CI)	(36.47, NE)	(11.07, 23.95)	
	Time to skeletal-related event	NE	NE	
	(95% CI)	(NE, NE)	(NE, NE)	
	Time to PSA progression	33.18	7.43	
	(95% CI)	(27.63, NE)	(7.20, 9.20)	

Effect estimate per comparison	Co->Primary **rPFS**	Comparison groups	<1 favors AA-P.
		Hazard ratio	**0.466**
		(95% CI)	**(0.394, 0.550)**
		P-value	< 0.0001
	Co->Primary **OS**	Comparison groups	<1 favors AA-P. (33.8% events; 48% of 852 deaths included in the final analysis)
		Hazard ratio	**0.621**
		(95% CI)	**(0.509, 0.756)**
		P-value	< 0.0001
	Secondary: Time to initiation of chemotherapy Median (months)	Comparison groups	<1 favors AA-P.
		Hazard ratio	0.443
		(95% CI)	(0.349, 0.561)
		P-value	<0.0001
	Secondary: Time to subsequent therapy for PC	Comparison groups	<1 favors AA-P.
		Hazard ratio	0.415
		(95% CI)	(0.346, 0.497)

		P-value	<0.0001
	Time to pain progression	Comparison groups	<1 favors AA-P.
		Hazard ratio	0.695
		(95% CI)	(0.583, 0.829)
		P-value	<0.0001
	Time to skeletal-related event	Comparison groups	
		Hazard ratio	0.703
		(95% CI)	(0.539, 0.916)
		P-value	0.0086
	Time to PSA progression	Comparison groups	
		Hazard ratio	0.299
		(95% CI)	(0.255, 0.352)
		P-value	<0.0001
Notes	Exploratory efficacy endpoints included PRO measures (BPI-SF, FACT-P, BFI, EQ-5D-5L) , prostate cancer-specific OS, PSA response rate, BOR, PFS2, time to symptomatic local progression and time to chronic opiate use.		

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

A cross trial comparison was provided and is summarised below.

Study PCR3011 & comparison Studies (STAMPEDE, CHAARTED, GETUG-AFU 15): Study	Study population, previous treatment entry criteria & treatment
STAMPEDE	Hormone Naïve Prostate Cancer: • Newly diagnosed metastatic disease (mHNPC) • Newly diagnosed node positive disease • Newly diagnosed, high-risk locally advanced disease (at least 2 of: Stage T3/4, PSA≥40ng/ml, or Gleason score=8-10) • Previously treated with radical surgery or radiotherapy (or both) and relapsing with at least 1 of: PSA≥4ng/ml and increasing with doubling time <6months, PSA≥20ng/ml;N+ or; M+ disease Prior chemotherapy and long-term ADT were not allowed. Anti-androgens were allowed to cover tumour flare. Adjuvant treatment was allowed but must have been completed at least 12 mo before entering the trial (with a duration no longer than 12 mo). Treatment: ADT+ZA+Doc, ADT+Doc, ADT+ZA, or ADT
CHAARTED	mHNPC • Stratified by high-volume vs. low-volume Prior docetaxel was not allowed. Adjuvant ADT was allowed if the duration was 24 mo or less, but must have been completed at least 12 mo before entering the trial. Treatment: ADT+ Doc or ADT
GETUG-AFU 15	mHNPC • Retrospectively stratified by high-volume vs. low-volume Prior chemotherapy for metastatic disease was not allowed. Prior chemotherapy or ADT, or both, were allowed in the neoadjuvant or adjuvant setting or in case of isolated PSA increase, but the treatment must have been discontinued at least 12 mo before inclusion. Treatment: ADT+ Doc or ADT
PCR3011	mHNPC • All subjects were newly diagnosed and high-risk Prior ADT up to 3 months before start of trial was allowed. Treatment: ADT+AA-P or ADT
ADT: androgen deprivation therapy; Doc: docetaxel (6 cycles in STAMPEDE and CHAARTED; 9 cycles in GETUG-AFU 15); ZA: zolendronic acid; AA-P: Abiraterone Acetate+Prednisone	

Table 20: Study PCR3011 and Comparison Studies (STAMPEDE, CHAARTED, GETUG-AFU 15): Efficacy Results

Study	Treatment Group	Number of Subjects	Overall Survival	Hazard Ratio (95%)	Median Follow-Up
STAMPEDE	HNPC (all subjects)				43 mo
	ADT+Doc	592	81 mo	0.78 (0.66-0.93) p=0.006	
	ADT Alone	1184	71 mo		
	mHNPC (subset)				
	ADT+Doc	362	60 mo	**0.76 (0.62-0.92) p=0.005**	
	ADT Alone	724	45 mo		
CHAARTED	mHNPC (all subjects)				
	ADT+Doc	397	57.6 mo	0.61 (0.47-0.80) p<0.001	28.9 mo
	ADT Alone	393	44.0 mo		
	High-Volume mHNPC (subset)				
	ADT+Doc	263	49.2 mo	**0.60 (0.45-0.81) p<0.001**	29.2 mo
	ADT Alone	250	32.2 mo		
GETUG-AFU 15	mHNPC (all subjects)				83.9 mo
	ADT+Doc	192	62.1 mo	0.88 (0.68-1.14) p=0.3	
	ADT Alone	193	48.6 mo		
	High-Volume mHNPC (subset)				
	ADT+Doc	92	39.8 mo	0.78 (0.56-1.09) p=0.14	
	ADT Alone	91	35.1 mo		
PCR3011	High-Risk mHNPC (all subjects)				
	ADT+AA-P	602	NR	**0.621 (0.509, 0756) p<0.0001**	30.4 mo
	ADT Alone	597	34.7 mo		

[1]Results are not significant; NR=not reached
Gravis 2016, James 2016, Sweeney 2015

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Abiraterone acetate plus prednisone or prednisolone is currently indicated for the treatment of patients with mCRPC (see SmPC section 4.1 for detailed indications). The new claimed indication for abiraterone acetate plus prednisone or prednisolone is for an earlier setting of metastatic prostate cancer, prior to development of castration resistant disease. In the hormone naïve setting the standard of care has historically been ADT (luteinizing hormone-releasing hormone [LHRH] agonist or surgical castration) with or without concurrent anti-androgens. Recently, docetaxel-based chemotherapy has shown to provide significant benefit on OS when combined with ADT metastatic or locally advanced hormone-naïve disease (James *et al*, 2016; Sweeney *et al*, 2015) thus changing disease course (OS medians in the range of 50-60 months compared to medians around 32-45 months if treated with standard ADT) and treatment decisions in the metastatic castration-resistant setting.

In support of the present application, the MAH submitted the results of study LATITUDE (PCR3011) which is phase 3, randomized, double-blind trial in which AA (1000 mg once daily) plus low dose prednisone (5 mg) administered add-on to ADT was compared to ADT alone (placebo group) in subjects with newly diagnosed (within 3 months prior to randomization) mHNPC with high-risk prognostic factors. High-risk is defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥ 8 of primary tumor; (2) presence of 3 or more lesions on bone scan; (3) presence of measurable visceral (excluding lymph node

disease) metastasis. The term mHNPC refers to either metastatic hormone naïve prostate cancer or metastatic hormone sensitive prostate cancer as the study population included those subjects that may have never received hormonal therapy (naïve) as well as subjects who received up to 3 months of hormonal therapy but were still responsive to treatment (sensitive). Newly diagnosed patients in this first-line setting could have received previous prostate cancer therapy not more than three months prior to randomization consisting of LHRH analogues or orchiectomy with or without concurrent antiandrogens or one course of palliative radiation or surgical therapy to treat symptoms. Prior chemotherapy, radiation therapy or surgery were not allowed out of these exceptions.

The MAH has provided a statement regarding GCP compliance for the main study. However, GCP-non-compliance was detected at one investigative site during a sponsor conducted audit which led to the exclusion of 10 patients from the ITT population. The MAH implemented a number of tools to ensure the robustness and integrity of the clinical trial data. Aside from the non-compliant GCP site, no major study conduct issues are identified.

Stratification according to ECOG status (0, 1 vs. 2) and presence of measurable visceral metastases (yes vs. no excluding lymph node metastases) was performed. The prednisone dose proposed to be administered together with AA was lower than that to be used in the castration resistant setting in an attempt to reduce long-term toxicity of higher doses of corticosterioids, which is acceptable.

Although ADT is considered an appropriate comparator, based on the recent results of the large STAMPEDE and CHAARTED trials, ADT plus docetaxel (6 cycles) is currently considered an alternative for some patients based on the significant benefit shown in terms of OS in metastatic or locally advanced hormone-naïve disease (James at al., 2016; Sweeney et al, 2015). In this sense, a head to head comparison vs. docetaxel would have been also informative.

In terms of choice of endpoints, the use of rPFS along with OS as co-primary endpoint is acceptable, seeing as rPFS would provide a faster endpoint to observe the benefit from this approach, whereas OS can indeed offer most valuable information about the benefit in the long-run, with important facts regarding the right sequence. PFS2 is also endorsed with the objective in mind of exploring cross-resistance phenomena.

The primary analysis of rPFS was based on the investigator-assessment of progression. To confirm the absence of investigator bias, a radiology review by independent assessors was planned on a sample of at least 160 evaluable subjects. The proposal for an audit plan in a representative sample was reviewed and accepted by the SAWP.

Demographic characteristics are considered consistent with that of a population newly diagnosed mPC, nevertheless as also previously observed in trials in the castration resistant setting the number of patients with ECOG PS=2 is limited and black race patients are underrepresented. This has been adequately reflected in section 5.1 of the SmPC.

Median time from diagnosis to first dose was 1.8 and 2.0 months for AA-P and Placebo arms respectively. All patients had metastatic disease at diagnosis with a 97.4% having bone metastases (46.3% >20 bone lesions) and 47.7% having node involvement. The trial population can be considered representative of a high-risk population as defined by the company, most patients has a Gleason score ≥8 (Gleason score=8 in 45.7%; =9 in 45.4% and =10 in 6.5% of patients). The majority of patients (95.3%) presented with (Gleason score ≥8+≥3 bone lesions) and an additional 11.8% had (Gleason score ≥8+≥3 bone lesions+ Measurable visceral disease). 14.1% presented with (Gleason score ≥8+ Measurable visceral) and a minority complied with the 3 criteria to be considered high risk (14.1% had both +≥3 bone lesions+ Measurable visceral disease without a Gleason score ≥8).

Baseline pain score was ≥4 for 27.6% of patients. PSA level at baseline was similar between the treatment groups (median: 25.43 ng/mL, AA-P; 23.05 ng/mL, Placebo).

Regarding prior therapies for prostate cancer, the majority of patients had received previous therapies (no more than 3 months prior to randomization) only 79 patients had not received any prior therapy.

Importantly, significant amendments to study protocol were introduced by means of two important protocol amendments and an additional amendment that introduced minor changes. Main changes pertained to the inclusion of rPFS as co-primary endpoint with OS (the previously planned single primary endpoint) and also changes on the definition of "high-risk" population. The company informed about changes introduced by the first two protocol amendments which affected, among others, two of the main aspects of trial design in a follow-up scientific advice (EMEA/H/SA/985/3/FU/1/2014/II): the primary efficacy endpoint (INT-2) and key characteristics of study population (INT-1). According to SA letter, the definition of high risk patients changed in a manner that could potentially lead to bias in trial population. Initially high risk patients were those with Gleason score of ≥8 and/or presence of cancer-related bone pain (defined as BPI-SF score ≥4 in the worst pain over the last 24 hours or requirement for the use of opioid analgesics to treat cancer-related pain associated with distant metastases). This was subsequently modified and according to the new definition Gleason score >8 was not mandatory anymore and a patient could be considered as high risk with visceral disease and bone metastasis. Although pain may not be so directly related to survival, high Gleason score together with presence of bone pain and poor performance status seem to be the most important prognosis factors for a shorter life expectancy. In spite of the methodological concerns related to a change in the target population made during the conduct of the trial, no concerns were raised by the SAWP given the status of enrolment at the time of review.

Protocol deviations were reported in 12.7% of trial population (14.7% in AA-P arm vs. 10.6% in Placebo arm) being most of them due to subjects receiving disallowed concomitant treatments, wrong treatment or incorrect dose of due to non-compliance with eligibility criteria. Numbers are small and thus there is no impact on study outcomes is foreseen.

Efficacy data and additional analyses

The primary efficacy analysis in support of this application was performed at the data cut-off of 31-oct-2016. This was the only planned analysis for rPFS and the first IA planned for OS, two additional analyses one IA and one final were planned OS.

Cross-over of patients progressing on placebo arm to AA-P was recommended by the IDMC after the cut-off date for the efficacy analyses presented in this report, thus no impact of cross over on efficacy endpoints is present for the time being.

With 49.45% (593/1199) of the total events, results in terms of rPFS based on investigator assessment showed a median rPFS of 33.02 months (95%CI: 29.57, NE) for the AA-P arm which represents a 18-months increase compared to the Placebo arm, 14.78 months (95%CI: 14.69, 18.27). The addition of AA-P to backbone ADT therapy decreased the risk of radiographic progression or death (rPFS) by 53% compared with ADT alone (HR=0.466; 95% CI: 0.394, 0.520; p<0.0001) which is considered clinically relevant for the target population.

The fact that the analysis of time of tumour and bone assessments shows symmetry between study arms is reassuring. An audit plan was planned by the company to randomly review a subset of evaluable subjects (n=202) concluding the lack of bias in the investigator assessment, with an agreement rate around 90% between investigators' and BICR assessments. There was no evidence of investigator bias in the assessment of rPFS based on thresholds for the late and early discrepancy rates of -10% for EDR and 10% for LDR. The discrepancy rates were 10.1% for EDR and -12.4% for LDR.

Results in terms of the co-primary endpoint OS at the time of the first interim analysis are immature (33.9% event). An update on OS data is expected to be available at the time of the 2nd preplanned IA (1Q 2018). In spite of the low rate of events, a statistically significant result shows an early marked result in favour of AA-P (HR=0.621; 95% CI: 0.509, 0.756; p<0.0001). The use of subsequent therapies known

to have impact on patient´s survival was almost 2-fold higher in the placebo arm, which is in line with what can be expected based on primary results. Although the magnitude of the impact that subsequent therapies have in OS results cannot be completely elucidated, the company performed different sensitivity analyses all supporting primary analysis.

Subgroup analyses for both co-primary endpoints showed consistent results in all subgroups analysed but for patients with ECOG-PS=2. Although the limited number of patients with ECOG PS=2 (n=40) precludes from drawing firm conclusions, section 5.1 of SmPC has been revised to reflect this observation.

Main secondary endpoints which indirectly reflect the quality of life of patients were: Time to initiation of chemotherapy, Time to subsequent therapy for prostate cancer, Time to pain progression, Time to SRE, Time to PSA progression. All showed statistically significant results in favour of AA-P arm with medians not reached in any of the endpoints in the AA-P arm but for time to PSA progression (median AA-P arm 33.2 months vs. 7.4 placebo arm).

Additional exploratory endpoints also favoured AA-P arm. A PSA response was observed in 91% of patients in AA-P arm vs. 66.8% in placebo arm. PROs consistently favoured AA-P arm.

A trend for longer PFS2 was observed in the AA-P arm (27.8 months and 23.9 months) with a HR<1 but not reaching statistical significance, which is to some extent expectable given the limited number of patients that received subsequent therapies in the AA-P arm (27.5% vs.49.2% in placebo arm).

Overall, in spite of the immaturity of the results submitted in terms of OS, a marked and statistically significant difference is observed in favour of AA-P arm. An increase in rPFS of the observed magnitude (18-month increase in median rPFS) together with evidence of positive result in terms of OS and improvement in the quality of life of patients as pointed out by results of secondary endpoints is deemed clinically compelling for the proposed setting.

Apart from issues related to the comparator arm, the main uncertainty of this assessment is related to treatment sequencing. The lack of mature OS data appears critical when it comes to answering the question whether early initiation of AA-P is better than its use in later lines appears. The impact of the use of abiraterone acetate plus prednisone administered to mHNPC patients rather than in the castration-resistant setting on the development of cross-resistances and on the overall survival and overall patient´s benefit could not be evaluated based on available data.

Despite a clear benefit is observed in terms of main efficacy endpoints, it is highly unlikely that unbiased OS data can be obtained because of the noise that cross-over of patients will have in future analyses. An exploratory analysis of OS according to the different treatment sequences received by patients after progression in trial PCR3011 i.e. chemotherapy followed by hormonal therapy or vice versa, was requested in order to try to depict treatment sequencing after abiraterone acetate use in the hormone naïve setting. Given the limited data available no reliable conclusions on best treatment sequencing can be drawn.

Overall, it seems challenging to assess the impact that early initiation of AA-P may have on cross-resistance development. Although PFS2 results appear to point out in a positive direction, further data is needed. Efficacy analysis in the subset of patients that received enzalutamide as subsequent therapy to abiraterone acetate plus prednisone compared to those patients who did not was also submitted. Although a 2.7 months difference is observed between those patients who received subsequent enzalutamide and those who did not, the exploratory nature of the analysis and the limited number of subjects (n=30) that received enzalutamide as subsequent therapy after discontinuation of AA-P limits drawing any firm conclusion. Updated PFS2 data is expected to be submitted by the company at the time of the second IA on OS (1Q 2018) and these data might shed some light on cross-resistance development (see letter of recommendations). Additionally, exploratory data from biomarker analysis (currently ongoing) is expected to be provided by the company as soon as available (see letter of

recommendations).

As part of the application, the Applicant presented descriptive data across relevant trials to contextualise the results seen in study PCR3011 to current clinical standard of care. In similar populations of prostate cancer patients, statistically significant improvements in OS were observed with the addition of docetaxel to ADT, in both the STAMPEDE study (HR: 0.76, p=0.005) and the CHAARTED study (HR: 0.60, p<0.001). Based on this data, the ADT + docetaxel combination is considered to be the standard of care for mHNPC patients eligible for chemotherapy (and referenced in the current ESMO guideline on prostate cancer; 2015). Comparable survival results are seen in study PCR3011, when abiraterone acetate + prednisone was added to ADT (HR: 0.62, p<0.0001). The utility of more effective blockage of the androgen-receptor axis has also been explored in the STAMPEDE study; 1:1 randomisation ADT alone or ADT + abiraterone acetate + prednisone (n= 1917, multi-stage, multi-arm platform design study - published recently as James et al., 2017; New England Journal of Medicine). With a median follow up of 40 months, the HR for OS was 0.63 (0.52-0.76) and the HR for treatment-failure events 0.29 (0.25-0.34).

2.4.4. Conclusions on the clinical efficacy

Results from trial PCR3011 show a statistically significant and clinically relevant result in terms of both rPFS and OS. The magnitude of the observed effect is considered of clinical relevance with a 18-month increase the median rPFS together with an already positive outcome in terms of OS despite the immaturity of survival data. Secondary endpoints consistently supported primary efficacy outcomes, indirectly reflecting improvement in the quality of life of patients.

2.5. Clinical safety

Introduction

Summary of known safety profile of abiraterone as described in the current SmPC

The most common adverse reactions seen with abiraterone are peripheral oedema, hypokalaemia, hypertension and urinary tract infection. Other important adverse reactions include cardiac disorders, hepatotoxicity, fractures, and allergic alveolitis. Abiraterone may cause hypertension, hypokalaemia and fluid retention as a pharmacodynamic consequence of its mechanism of action. In clinical studies, mineralocorticoid adverse reactions were seen more commonly in patients treated with abiraterone acetate plus prednisone or prednisolone than in patients treated with placebo: hypokalaemia 21% vs.11%, hypertension 16% vs. 11% and fluid retention (peripheral oedema) 26% vs. 20%, respectively. In patients treated with abiraterone acetate plus prednisone or prednisolone, CTCAE (version 3.0) Grades 3 and 4 hypokalaemia and CTCAE (version 3.0). Grades 3 and 4 hypertension were observed in 4% and 2% of patients, respectively. Mineralocorticoid reactions generally were able to be successfully managed medically. Concomitant use of a corticosteroid reduces the incidence and severity of these adverse reactions.

Patient exposure

Integrated safety population

Safety data from a total of 3,993 subjects are included in the integrated safety population: 2,230 AA subjects and 1,763 Placebo subjects. The safety population includes subjects from Study PCR3011 in the

mHNPC population as well as subjects from 4 previous Phase 3 registration studies in the mCRPC population (Studies COU-AA-302 + ABI-PRO-3002 and COU-AA-301 + ABI-PRO-3001).

This summary of clinical safety incorporates data from the 5 randomized phase 3 clinical studies, in which a total of 2,230 subjects were treated with AA 1,000 mg once daily plus prednisone/prednisolone 5 mg once or twice daily. Only the safety data from the double-blind phase was included for Studies ABI-PRO-3001 and PCR3011; Studies COU-AA-301, COU-AA-302, and ABI-PRO-3002 include all unblinded safety data. For all 5 studies, all subjects received and remained on a stable regimen of ADT (LHRH analogs [LHRH agonists in Study PCR3011] or had surgical castration).

Studies COU-AA-301 and ABI-PRO-3001 were grouped together because these 2 studies enrolled mCRPC patients whose disease had progressed on or after docetaxel therapy; Studies COU-AA-302 and ABI-PRO-3002 were grouped together because these 2 studies enrolled asymptomatic or mildly symptomatic chemotherapy- naïve patients.

COU-AA-301+ ABI-PRO-3001[a]		COU-AA-302+ ABI-PRO-3002[a]		PCR3011[b]		Combined	
AA (N=934)	Placebo (N=465)	AA (N=699)	Placebo (N=696)	AA (N=597)	Placebo (N=602)	AA (N=2230)	Placebo (N=1763)

AA=abiraterone acetate; ADT= luteinizing hormone-releasing hormone or surgical castration
[a] Studies COU-AA-301, ABI-PRO-3001, COU-AA-302, and ABI-PRO-3002: AA=AA + prednisone 10 mg/day; Placebo= placebo + prednisone 10 mg/day
[b] Studies PCR3011: AA=AA + prednisone 5 mg/day + ADT; Placebo=Placebo (AA)+ Placebo (prednisone)+ ADT

The ADR analyses were generated from the 'integrated safety population – all clinical studies' dataset and are presented below.

Combined Randomized Studies[c]		Pooled Phase 1/2 Studies	All Clinical Studies[a]	
AA (N=2230)	Placebo (N=1763)	AA (N=429)	AA (N=2659)	Placebo (N=1763)

AA=abiraterone acetate; ADT= luteinizing hormone-releasing hormone or surgical castration
[a] Studies COU-AA-301, ABI-PRO-3001, COU-AA-302, and ABI-PRO-3002: AA=AA + prednisone 10 mg/day; Placebo= placebo + prednisone 10 mg/day
Study PCR3011: AA=AA + prednisone 5 mg/day + ADT; Placebo=Placebo (AA)+ Placebo (prednisone)+ ADT

The 'integrated safety population – Phase 3 studies' and the 'integrated safety population – all clinical studies' datasets include any subject who received at least 1 dose of abiraterone acetate or placebo during the study.

All subjects in both treatment groups (the AA group and the placebo group) of Studies COU-AA-301, ABI-PRO-3001, COU-AA-302, and ABI-PRO-3002 received concurrent 10 mg prednisone/prednisolone. Subjects in the AA treatment group of Study PCR3011 received abiraterone acetate plus 5 mg prednisone and no prednisone in the placebo group.

Extent of exposure

In all of the Phase 3 studies included in the summary, the median treatment duration was longer in the AA-P group compared with the placebo group: Study PCR3011 (AA-P: 24.0 months, Placebo: 14.3 months), COU-AA-302 and ABI-PRO-3002 (AA-P: 10.8 months, Placebo: 5.9 months), COU-AA-301 + ABI-PRO-3001 (AA-P: 7.4 months, Placebo: 3.7 months).

In study 212082PCR3011, the median total treatment duration was 24 months (25 cycles, [treatment cycle 28 days]) in the AA-P group and 14 months (15 cycles) in the placebo group. A majority of

subjects, 91.8% of subjects in the AA-P group and 86.0% of subjects in the placebo group, received ≥6 cycles of study drug; 54.4% and 29.7% of subjects, respectively, received ≥24 cycles.

Table 21: Extent of exposure, cumulative summary; integrated safety population – Phase 3 studies

	COU-AA-301 +ABI-PRO-3001		COU-AA-302 +ABI-PRO-3002		PCR3011		Combined	
	AA	Placebo	AA	Placebo	AA	Placebo	AA	Placebo
Subjects treated	934	465	699	696	597	602	2230	1763
Total treatment duration (months)								
N	934	465	699	696	597	602	2230	1763
Mean (SD)	9.01 (6.619)	5.92 (5.448)	13.12 (9.568)	9.39 (8.257)	22.31 (11.511)	16.09 (10.502)	13.86 (10.564)	10.77 (9.432)
Median	7.39	3.65	10.84	5.93	23.98	14.28	11.01	7.23
Range	(0.2; 25.6)	(0.1; 24.9)	(0.3; 34.9)	(0.1; 32.4)	(0.1; 43.0)	(0.7; 42.6)	(0.1; 43.0)	(0.1; 42.6)
Total number of cycles started								
N	934	465	699	696	597	602	2230	1763
Mean (SD)	10.0 (7.22)	6.6 (5.91)	14.6 (10.39)	10.5 (8.97)	24.2 (12.34)	17.4 (11.18)	15.2 (11.37)	11.8 (10.10)
Median	8.0	4.0	12.0	7.0	25.0	15.0	12.0	8.0
Range	(1; 28)	(1; 27)	(1; 38)	(1; 36)	(1; 47)	(1; 47)	(1; 47)	(1; 47)

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Adverse events

Overall safety profile

Table 22: Overall Safety Profile; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Analysis set: safety population	597	602
Number of subjects with treatment-emergent adverse events(a)	558 (93.5%)	557 (92.5%)
Drug-related(b)	336 (56.3%)	269 (44.7%)
Number of subjects with Grade 3-4 treatment-emergent adverse event(a)	374 (62.6%)	287 (47.7%)
Drug-related(b)	162 (27.1%)	67 (11.1%)
Number of subjects with treatment-emergent serious adverse events(a)	165 (27.6%)	146 (24.3%)
Drug-related(b)	29 (4.9%)	12 (2.0%)
Grade 3-4	142 (23.8%)	116 (19.3%)
Number of subjects with treatment-emergent adverse events leading to treatment discontinuation(c)	73 (12.2%)	61 (10.1%)
Drug-related(b)	21 (3.5%)	11 (1.8%)
Number of subjects with treatment-emergent adverse events leading to death	28 (4.7%)	24 (4.0%)
Drug-related(b)	3 (0.5%)	3 (0.5%)
All deaths within 30 days of last dose	40 (6.7%)	37 (6.1%)
Adverse event	27 (4.5%)	20 (3.3%)
Death due to prostate cancer	11 (1.8%)	16 (2.7%)
Natural causes	1 (0.2%)	0
Unknown	1 (0.2%)	1 (0.2%)
(a) Does not include Grade 5 events. (b) Adverse events reported as possible, probable or very likely related to AA-P/Pbo or Prednisone/Pbo or both (c) Discontinuation for AA-P/Pbo or Prednisone/Pbo or both		

Table 23: Overall Safety Profile; Integrated Safety Population-Phase 3 Studies

	COU-AA-301 +ABI-PRO-3001		COU-AA-302 +ABI-PRO-3002		PCR3011		Combined	
	AA	Placebo	AA	Placebo	AA	Placebo	AA	Placebo
Subjects treated	934	465	699	696	597	602	2230	1763
Treatment-emergent adverse events (TEAEs)[a]	919 (98.4%)	456 (98.1%)	641 (91.7%)	638 (91.7%)	558 (93.5%)	557 (92.5%)	2118 (95.0%)	1651 (93.6%)
Drug-related[b]	618 (66.2%)	306 (65.8%)	460 (65.8%)	432 (62.1%)	336 (56.3%)	269 (44.7%)	1414 (63.4%)	1007 (57.1%)
Grade 3-4 TEAEs	524 (56.1%)	260 (55.9%)	293 (41.9%)	268 (38.5%)	374 (62.6%)	287 (47.7%)	1191 (53.4%)	815 (46.2%)
Drug-related[b]	146 (15.6%)	46 (9.9%)	127 (18.2%)	80 (11.5%)	162 (27.1%)	67 (11.1%)	435 (19.5%)	193 (10.9%)
Serious TEAEs[a]	355 (38.0%)	186 (40.0%)	194 (27.8%)	157 (22.6%)	165 (27.6%)	146 (24.3%)	714 (32.0%)	489 (27.7%)
Drug-related[b]	59 (6.3%)	22 (4.7%)	55 (7.9%)	29 (4.2%)	29 (4.9%)	12 (2.0%)	143 (6.4%)	63 (3.6%)
Grade 3-4	306 (32.8%)	158 (34.0%)	160 (22.9%)	132 (19.0%)	142 (23.8%)	116 (19.3%)	608 (27.3%)	406 (23.0%)
Drug-related grade 3-4	52 (5.6%)	19 (4.1%)	48 (6.9%)	21 (3.0%)	29 (4.9%)	9 (1.5%)	129 (5.8%)	49 (2.8%)
TEAEs leading to treatment discontinuation[c]	172 (18.4%)	100 (21.5%)	63 (9.0%)	61 (8.8%)	73 (12.2%)	61 (10.1%)	308 (13.8%)	222 (12.6%)
Drug-related[b]	30 (3.2%)	14 (3.0%)	30 (4.3%)	17 (2.4%)	21 (3.5%)	11 (1.8%)	81 (3.6%)	42 (2.4%)
TEAEs leading to death	114 (12.2%)	70 (15.1%)	25 (3.6%)	22 (3.2%)	28 (4.7%)	24 (4.0%)	167 (7.5%)	116 (6.6%)
Drug-related[b]	4 (0.4%)	3 (0.6%)	2 (0.3%)	3 (0.4%)	3 (0.5%)	3 (0.5%)	9 (0.4%)	9 (0.5%)
All deaths within 30 days of last dose	106 (11.3%)	63 (13.5%)	22 (3.1%)	15 (2.2%)	40 (6.7%)	37 (6.1%)	168 (7.5%)	115 (6.5%)
Underlying disease	68 (7.3%)	42 (9.0%)	8 (1.1%)	4 (0.6%)	11 (1.8%)	16 (2.7%)	87 (3.9%)	62 (3.5%)
Adverse events[d]	5 (0.5%)	7 (1.5%)	2 (0.3%)	3 (0.4%)	27 (4.5%)	20 (3.3%)	34 (1.5%)	30 (1.7%)
Other	29 (3.1%)	14 (3.0%)	11 (1.6%)	7 (1.0%)	1 (0.2%)	0	41 (1.8%)	21 (1.2%)
Unknown	4 (0.4%)	0	1 (0.1%)	1 (0.1%)	1 (0.2%)	1 (0.2%)	6 (0.3%)	2 (0.1%)

[a] Grade 5 events are not included.
[b] Adverse events reported to be possibly related, probably related, very likely related, or related to abiraterone acetate/placebo or prednisone/prednisolone are classified as drug-related. Adverse events with missing relationship are not considered as drug-related AEs.
[c] Discontinuation of study medication includes discontinuation of AA/placebo or prednisone/prednisolone or both.
[d] Death reason of "Adverse events" were not collected separately in COU-AA-301 and COU-AA-302.

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Treatment-emergent Adverse Events

Adverse events were coded and reported according to standard methods. Treatment-emergent adverse events (TEAEs) were defined as any AEs occurring or worsening in severity, on or after the first dose and within 30 days after the last dose of study treatment. Investigators were required to assess the relatedness of all TEAEs.

To assess the effect of the longer duration of exposure in the AA-P group, an analysis standardising for the difference in treatment duration was performed for all reported AEs and reported as number of events per 100 patient-years (P-Y) of exposure (time on treatment). More than 1 event per subject may be included in this rate. This differs from the other AE analyses in which rates are calculated on the basis of the number of subjects who experience an event. A subject is counted only once in these analyses, irrespective of whether multiple events occur.

Table 24: Treatment-emergent Adverse Events Reported in at Least 5% of Subjects in Either Treatment Group; Safety Population (Study 212082PCR3011)

	AA-P					Placebo				
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4
Analysis set: safety population	597					602				
Total number of subjects with a treatment-emergent adverse event	558 (93.5%)	45 (7.5%)	139 (23.3%)	342 (57.3%)	32 (5.4%)	557 (92.5%)	75 (12.5%)	195 (32.4%)	265 (44.0%)	22 (3.7%)
System organ class										
Preferred term										
Musculoskeletal and connective tissue disorders	297 (49.7%)	125 (20.9%)	117 (19.6%)	55 (9.2%)	0	319 (53.0%)	117 (19.4%)	130 (21.6%)	72 (12.0%)	0
Back pain	110 (18.4%)	55 (9.2%)	41 (6.9%)	14 (2.3%)	0	123 (20.4%)	61 (10.1%)	43 (7.1%)	19 (3.2%)	0
Arthralgia	89 (14.9%)	48 (8.0%)	35 (5.9%)	6 (1.0%)	0	86 (14.3%)	40 (6.6%)	31 (5.1%)	15 (2.5%)	0
Bone pain	74 (12.4%)	24 (4.0%)	29 (4.9%)	20 (3.4%)	0	88 (14.6%)	29 (4.8%)	42 (7.0%)	17 (2.8%)	0
Pain in extremity	65 (10.9%)	39 (6.5%)	19 (3.2%)	7 (1.2%)	0	69 (11.5%)	39 (6.5%)	18 (3.0%)	12 (2.0%)	0
Musculoskeletal pain	25 (4.2%)	18 (3.0%)	3 (0.5%)	4 (0.7%)	0	41 (6.8%)	25 (4.2%)	10 (1.7%)	6 (1.0%)	0
Vascular disorders	275 (46.1%)	59 (9.9%)	89 (14.9%)	126 (21.1%)	1 (0.2%)	204 (33.9%)	61 (10.1%)	78 (13.0%)	64 (10.6%)	1 (0.2%)
Hypertension	219 (36.7%)	21 (3.5%)	77 (12.9%)	121 (20.3%)	0	133 (22.1%)	14 (2.3%)	59 (9.8%)	59 (9.8%)	1 (0.2%)
Hot flush	92 (15.4%)	74 (12.4%)	18 (3.0%)	0	0	75 (12.5%)	58 (9.6%)	16 (2.7%)	1 (0.2%)	0
Investigations	232 (38.9%)	61 (10.2%)	102 (17.1%)	62 (10.4%)	7 (1.2%)	203 (33.7%)	79 (13.1%)	76 (12.6%)	45 (7.5%)	2 (0.3%)
Alanine aminotransferase increased	98 (16.4%)	41 (6.9%)	24 (4.0%)	31 (5.2%)	2 (0.3%)	77 (12.8%)	48 (8.0%)	21 (3.5%)	8 (1.3%)	0
Aspartate aminotransferase increased	87 (14.6%)	35 (5.9%)	26 (4.4%)	25 (4.2%)	1 (0.2%)	68 (11.3%)	39 (6.5%)	20 (3.3%)	9 (1.5%)	0
Weight increased	54 (9.0%)	10 (1.7%)	38 (6.4%)	6 (1.0%)	0	51 (8.5%)	18 (3.0%)	27 (4.5%)	6 (1.0%)	0
Blood lactate dehydrogenase increased	39 (6.5%)	14 (2.3%)	14 (2.3%)	10 (1.7%)	1 (0.2%)	30 (5.0%)	8 (1.3%)	11 (1.8%)	9 (1.5%)	0
Infections and infestations	223 (37.4%)	90 (15.1%)	102 (17.1%)	29 (4.9%)	2 (0.3%)	162 (26.9%)	67 (11.1%)	76 (12.6%)	17 (2.8%)	2 (0.3%)
Urinary tract infection	42 (7.0%)	17 (2.8%)	19 (3.2%)	6 (1.0%)	0	22 (3.7%)	7 (1.2%)	10 (1.7%)	5 (0.8%)	0
Upper respiratory tract infection	40 (6.7%)	23 (3.9%)	16 (2.7%)	1 (0.2%)	0	28 (4.7%)	20 (3.3%)	7 (1.2%)	1 (0.2%)	0
Nasopharyngitis	39 (6.5%)	29 (4.9%)	10 (1.7%)	0	0	36 (6.0%)	26 (4.3%)	10 (1.7%)	0	0
Metabolism and nutrition disorders	223 (37.4%)	66 (11.1%)	59 (9.9%)	90 (15.1%)	8 (1.3%)	157 (26.1%)	61 (10.1%)	54 (9.0%)	39 (6.5%)	3 (0.5%)
Hypokalaemia	122 (20.4%)	31 (5.2%)	29 (4.9%)	57 (9.5%)	5 (0.8%)	22 (3.7%)	7 (1.2%)	7 (1.2%)	7 (1.2%)	1 (0.2%)
Hyperglycaemia	75 (12.6%)	28 (4.7%)	20 (3.4%)	26 (4.4%)	1 (0.2%)	68 (11.3%)	31 (5.1%)	19 (3.2%)	18 (3.0%)	0
Decreased appetite	21 (3.5%)	12 (2.0%)	7 (1.2%)	2 (0.3%)	0	32 (5.3%)	20 (3.3%)	8 (1.3%)	4 (0.7%)	0
Gastrointestinal disorders	199 (33.3%)	109 (18.3%)	70 (11.7%)	16 (2.7%)	4 (0.7%)	195 (32.4%)	113 (18.8%)	68 (11.3%)	14 (2.3%)	0
Constipation	62 (10.4%)	44 (7.4%)	16 (2.7%)	2 (0.3%)	0	67 (11.1%)	49 (8.1%)	15 (2.5%)	3 (0.5%)	0
Nausea	41 (6.9%)	26 (4.4%)	12 (2.0%)	3 (0.5%)	0	40 (6.6%)	24 (4.0%)	14 (2.3%)	2 (0.3%)	0
Vomiting	37 (6.2%)	22 (3.7%)	12 (2.0%)	3 (0.5%)	0	36 (6.0%)	25 (4.2%)	9 (1.5%)	2 (0.3%)	0
Diarrhoea	30 (5.0%)	22 (3.7%)	6 (1.0%)	2 (0.3%)	0	41 (6.8%)	29 (4.8%)	11 (1.8%)	1 (0.2%)	0
Abdominal pain	24 (4.0%)	16 (2.7%)	8 (1.3%)	0	0	31 (5.1%)	19 (3.2%)	9 (1.5%)	3 (0.5%)	0
General disorders and administration site conditions	191 (32.0%)	113 (18.9%)	52 (8.7%)	26 (4.4%)	0	206 (34.2%)	103 (17.1%)	64 (10.6%)	37 (6.1%)	2 (0.3%)
Fatigue	77 (12.9%)	47 (7.9%)	20 (3.4%)	10 (1.7%)	0	86 (14.3%)	47 (7.8%)	25 (4.2%)	14 (2.3%)	0
Oedema peripheral	56 (9.4%)	38 (6.4%)	16 (2.7%)	2 (0.3%)	0	53 (8.8%)	33 (5.5%)	17 (2.8%)	3 (0.5%)	0
Nervous system disorders	127 (21.3%)	66 (11.1%)	26 (4.4%)	32 (5.4%)	3 (0.5%)	114 (18.9%)	57 (9.5%)	22 (3.7%)	31 (5.1%)	4 (0.7%)
Headache	45 (7.5%)	36 (6.0%)	7 (1.2%)	2 (0.3%)	0	30 (5.0%)	24 (4.0%)	5 (0.8%)	1 (0.2%)	0
Respiratory, thoracic and mediastinal disorders	98 (16.4%)	58 (9.7%)	27 (4.5%)	13 (2.2%)	0	66 (11.0%)	36 (6.0%)	15 (2.5%)	13 (2.2%)	2 (0.3%)
Cough	37 (6.2%)	30 (5.0%)	7 (1.2%)	0	0	16 (2.7%)	16 (2.7%)	0	0	0
Blood and lymphatic system disorders	78 (13.1%)	27 (4.5%)	25 (4.2%)	21 (3.5%)	5 (0.8%)	107 (17.8%)	33 (5.5%)	39 (6.5%)	33 (5.5%)	2 (0.3%)
Anaemia	54 (9.0%)	21 (3.5%)	18 (3.0%)	12 (2.0%)	3 (0.5%)	85 (14.1%)	21 (3.5%)	37 (6.1%)	26 (4.3%)	1 (0.2%)
Psychiatric disorders	65 (10.9%)	39 (6.5%)	25 (4.2%)	1 (0.2%)	0	50 (8.3%)	32 (5.3%)	16 (2.7%)	2 (0.3%)	0
Insomnia	31 (5.2%)	22 (3.7%)	8 (1.3%)	1 (0.2%)	0	30 (5.0%)	23 (3.8%)	7 (1.2%)	0	0

Treatment emergent adverse events with toxicity grade of grade 3 or 4

Grade 3 or 4 AEs were reported in 62.6% of subjects in the AA-P group and 47.7% of subjects in the Placebo group.

Table 25: Treatment-emergent Grade 3-4 Adverse Events Reported in at Least 1% of Subjects in Either Treatment Group, by system organ class and preferred term; Safety Population (Study 212082PCR3011)

	AA-P			Placebo		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Analysis set: safety population	597			602		
Total number of subjects with a treatment-emergent adverse event	374 (62.6%)	342 (57.3%)	32 (5.4%)	287 (47.7%)	265 (44.0%)	22 (3.7%)
System organ class						
Preferred term						
Vascular disorders	127 (21.3%)	126 (21.1%)	1 (0.2%)	65 (10.8%)	64 (10.6%)	1 (0.2%)
Hypertension	121 (20.3%)	121 (20.3%)	0	60 (10.0%)	59 (9.8%)	1 (0.2%)
Metabolism and nutrition disorders	98 (16.4%)	90 (15.1%)	8 (1.3%)	42 (7.0%)	39 (6.5%)	3 (0.5%)
Hypokalaemia	62 (10.4%)	57 (9.5%)	5 (0.8%)	8 (1.3%)	7 (1.2%)	1 (0.2%)
Hyperglycaemia	27 (4.5%)	26 (4.4%)	1 (0.2%)	18 (3.0%)	18 (3.0%)	0
Hyperkalaemia	7 (1.2%)	5 (0.8%)	2 (0.3%)	9 (1.5%)	9 (1.5%)	0
Investigations	69 (11.6%)	62 (10.4%)	7 (1.2%)	47 (7.8%)	45 (7.5%)	2 (0.3%)
Alanine aminotransferase increased	33 (5.5%)	31 (5.2%)	2 (0.3%)	8 (1.3%)	8 (1.3%)	0
Aspartate aminotransferase increased	26 (4.4%)	25 (4.2%)	1 (0.2%)	9 (1.5%)	9 (1.5%)	0
Blood lactate dehydrogenase increased	11 (1.8%)	10 (1.7%)	1 (0.2%)	9 (1.5%)	9 (1.5%)	0
Weight increased	6 (1.0%)	6 (1.0%)	0	6 (1.0%)	6 (1.0%)	0
Musculoskeletal and connective tissue disorders	55 (9.2%)	55 (9.2%)	0	72 (12.0%)	72 (12.0%)	0
Bone pain	20 (3.4%)	20 (3.4%)	0	17 (2.8%)	17 (2.8%)	0
Back pain	14 (2.3%)	14 (2.3%)	0	19 (3.2%)	19 (3.2%)	0
Pain in extremity	7 (1.2%)	7 (1.2%)	0	12 (2.0%)	12 (2.0%)	0
Arthralgia	6 (1.0%)	6 (1.0%)	0	15 (2.5%)	15 (2.5%)	0
Musculoskeletal pain	4 (0.7%)	4 (0.7%)	0	6 (1.0%)	6 (1.0%)	0
Muscular weakness	3 (0.5%)	3 (0.5%)	0	7 (1.2%)	7 (1.2%)	0
Nervous system disorders	35 (5.9%)	32 (5.4%)	3 (0.5%)	35 (5.8%)	31 (5.1%)	4 (0.7%)
Spinal cord compression	12 (2.0%)	12 (2.0%)	0	10 (1.7%)	7 (1.2%)	3 (0.5%)
Infections and infestations	31 (5.2%)	29 (4.9%)	2 (0.3%)	19 (3.2%)	17 (2.8%)	2 (0.3%)
Pneumonia	10 (1.7%)	9 (1.5%)	1 (0.2%)	3 (0.5%)	3 (0.5%)	0
Urinary tract infection	6 (1.0%)	6 (1.0%)	0	5 (0.8%)	5 (0.8%)	0
Renal and urinary disorders	30 (5.0%)	29 (4.9%)	1 (0.2%)	29 (4.8%)	28 (4.7%)	1 (0.2%)
Urinary retention	10 (1.7%)	10 (1.7%)	0	8 (1.3%)	8 (1.3%)	0
Haematuria	6 (1.0%)	6 (1.0%)	0	3 (0.5%)	3 (0.5%)	0

	AA-P			Placebo		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Blood and lymphatic system disorders	26 (4.4%)	21 (3.5%)	5 (0.8%)	35 (5.8%)	33 (5.5%)	2 (0.3%)
Anaemia	15 (2.5%)	12 (2.0%)	3 (0.5%)	27 (4.5%)	26 (4.3%)	1 (0.2%)
General disorders and administration site conditions	26 (4.4%)	26 (4.4%)	0	39 (6.5%)	37 (6.1%)	2 (0.3%)
Fatigue	10 (1.7%)	10 (1.7%)	0	14 (2.3%)	14 (2.3%)	0
Asthenia	4 (0.7%)	4 (0.7%)	0	7 (1.2%)	7 (1.2%)	0
General physical health deterioration	4 (0.7%)	4 (0.7%)	0	6 (1.0%)	6 (1.0%)	0

Note: Table does not include Grade 5 events.
The 'Number of subjects with a Grade 3 or 4 treatment emergent adverse event' and system organ class rows are based on all subjects. Preferred terms reported are events occurring in at least 1% of subjects in either treatment group.
Worst toxicity is reported for recurring events of different non-missing toxicity grades for each subject.

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Adverse Events of Special Interest (AESI) (study 212082PCR3011)

Based on previous experience and the known mechanism of action of abiraterone, adverse events of special interest were highlighted in the clinical study report. These include cardiac disorders, events related to mineralocorticoid excess (hypertension, hypokalaemia, and fluid retention/oedema), hepatotoxicity, cataract, osteoporosis, rhabdomyolysis/myopathy, allergic alveolitis and drug-drug interactions (CYP2D6) and food effect.

Events related to mineralocorticoid excess: Fluid retention/oedema

Fluid retention/ oedema were reported in 12.4% of subjects in the AA-P group and 11.3% of subjects in the placebo group. Peripheral oedema accounted for most of these events (9.4% vs. 8.8%). Most were Grade 1 or 2; no Grade 4 events were reported. No subject had fluid retention/ oedema events with an outcome of death. Treatment discontinuation was rare for fluid retention/ oedema. After standardising for

the difference in duration of treatment exposure, an excess of 2.3 fluid retention/oedema events/100 P Y (for all grades) was observed in the placebo group (9.3 in the AA-P group and 11.6 in the placebo group).

Events related to mineralocorticoid excess: Hypokalaemia

Hypokalaemia were reported in 20.4% of subjects in the AA-P group and 3.7% of subjects in the Placebo (Grade 3; 9.5% vs. 1.2%). Hypokalaemia rarely led to treatment discontinuation, dose reduction or interruption. After standardising for the difference in duration of treatment exposure, an excess of 17.6 hypokalaemia events/100 P-Y was observed in the AA-P group (23.2 in the AA-P group and 5.6 in the placebo group).

Events related to mineralocorticoid excess: Hypertension

Hypertension was reported in 38.5% of subjects in the AA-P group and 23.9% of subjects in the Placebo group. Grade 3 events were reported in 20.9% of subjects in the AA-P group and 10.3% of subjects in the Placebo group. Hypertension SAEs were reported in 5 (0.8%) subjects in the AA-P group and 3 (0.5%) subjects in the Placebo group. After standardising for the difference in duration of treatment exposure, an excess of 20.2 hypertension events/100 P-Y (for all grades) was observed in the AA-P group (57.5 in the AA-P group and 37.3 in the Placebo group). Potentially consequential events resulting from hypertension were rare; the incidence of death due to cardiac disorders and cerebrovascular accident was low and similar between both treatment groups.

Hepatotoxicity

Hepatotoxicity was reported in 22.4% of AA-P group and 18.1% of placebo group. The most frequently reported individual hepatotoxicity AE were ALT increased (16.4% vs. 12.8%), AST increased (14.6% vs. 11.3%), hyperbilirubinaemia (2.8% vs. 0.5%), hepatic enzyme increased (1.2% vs. 0.3%), and blood alkaline phosphatase increased (0.3% vs. 1.2%). Grade 3 events were reported in 7.7% of subjects in the AA-P group and 3.3% of subjects in the Placebo group. SAEs were reported in 1.2% of subjects in the AA-P group and none in the Placebo group. Grade 3 or 4 hepatotoxicity was observed in 8.4% of patients treated with ZYTIGA plus prednisone in Study 3011.

Adverse events leading to dose reduction or interruption in the AA-P and Placebo groups were most frequently reported for AST increased (5.4% vs. 1.7%) and ALT increased (5.2% vs. 1.8%). After standardising for the difference in duration of treatment exposure, an excess of 8.5 hepatotoxicity events/100 P-Y (for all grades) was observed in the AA-P group (45.2 in the AA-P group and 36.7 in the Placebo group).

Ten patients who received ZYTIGA plus prednisone were discontinued because of hepatotoxicity; two had Grade 2 hepatotoxicity, six had Grade 3 hepatotoxicity, and two had Grade 4 hepatotoxicity. No patient died of hepatotoxicity in Study 3011.

In the 3011 trial, patients with baseline ALT and AST > 2.5 X ULN, bilirubin > 1.5 X ULN or those with active or symptomatic viral hepatitis or chronic liver disease; ascites or bleeding disorders secondary to hepatic dysfunction were excluded.

Cardiac disorders

Cardiac disorders were reported in 12.4% of subjects in AA-P group and 7.8% of subjects in the placebo group; arrhythmias (6.7% versus 3.3%), ischemic heart disease (3.2% versus 1.2%), cardiac disorders-other causes (2.2% versus 3.3%), and cardiac failure (3.0% versus 1.2%). Grade 3 events were reported 2.5% in the AA-P and 1.0% of subjects in the placebo groups. Grade 4 events were reported in 0.8% of subjects in the AA-P group and no subjects in the placebo group. Grade 5 events were reported in 2.0% of subjects in the AA-P group and 1.5% of subjects in the placebo group. SAES were reported in 3.5% of subjects in the AA-P group and 0.7% of subjects in the placebo group. After standardising for the

difference in duration of treatment exposure, there was no difference in cardiac disorder events/100 P-Y (for all grades) (9.5 in the AA-P group and 9.4 in the Placebo group).

Cataract

Cataract events were reported in 2.7% of subjects in the AA-P group and 1.3% of subjects in the Placebo group. Grade 3 cataract events were reported in 5 (0.8%) subjects in the AA-P group and 1 (0.2%) subject in the Placebo group. After standardising for the difference in duration of treatment exposure, an excess of 0.8 cataracts/ 100 P-Y (for all grades) was observed in the AA-P group (1.9 vs. and 1.1).

Osteoporosis (including osteoporosis-related fractures)

Osteoporosis, events were reported in 5.4% of subjects in the AA-P group and 4.2% of subjects in the placebo group; osteoporosis/osteopenia (4.2% versus 2.8%) and fractures (1.3% in both treatment groups). Grade 3 osteoporosis and osteoporosis-related fractures were reported in 1.2% of subjects in the AA-P and 2.2% of subjects in the placebo group. After standardising for the difference in duration of treatment exposure, a slight increase of 0.3 osteoporosis events/100 P-Y (for all grades) was observed in the AA-P group (3.5 in the AA-P group and 3.2 in the Placebo group).

Rhabdomyolysis /myopathy

Rhabdomyolysis/ myopathy was not reported for any subject in the AA-P group and in 1 (0.2%) subject in the placebo group with Grade 1 myopathy.

Allergic Alveolitis

No events of allergic alveolitis were observed in either treatment group.

Adverse events of clinical importance

Adverse events of clinical importance were described as anaemia, diarrhoea, sexual dysfunction, thrombocytopenia, dyspepsia, urinary tract infection, haematuria, and adrenal insufficiency. These events were reported in a total of 28.3% of subjects in the AA-P group and 28.1% of subjects in the placebo group.

Anaemia

Anaemia was reported in 9.2% of subjects in the AA-P group and 14.3% of subjects in the placebo group.

Grade 3 anaemia was reported in 2.0% vs. 4.3% of subjects. SAE were reported in 1.0% of subjects in each groups. After standardising for the difference in duration of treatment exposure, an excess of 10 anaemia events/100 P-Y (for all grades) was observed in the placebo group (7.2 in the AA-P group and 17.2 in the placebo group).

Diarrhoea

Diarrhoea was reported in 5.0% of subjects in the AA-P group and 6.8% of subjects in the placebo group. Grade 3 diarrhoea; 0.3% vs. 0.2%. After standardising for the difference in duration of treatment exposure, an excess (almost doubling) of 3.1 diarrhoea events/100 P-Y (for all grades) was observed in the Placebo group (3.3 in the AA-P group and 6.4 in the placebo group).

Sexual dysfunction

Sexual dysfunction, decreased libido, and impotence events were reported in 16 (2.7%) subjects in the AA-P group and 5 (0.8%) subjects in the placebo group. Erectile dysfunction accounted for most of these events. After standardising for the difference in duration of treatment exposure, a doubling of sexual dysfunction events/100 P-Y (for all grades) was observed in the AA-P group (1.7) compared to the placebo group (0.7).

Thrombocytopenia

Thrombocytopenia was reported in 3.4% of subjects in the AA-P group and 3.3% of subjects in the Placebo group. Grade 3 thrombocytopenia was reported in no subject in the AA-P group and 1.0% of subjects in the Placebo group. After standardising for the difference in duration of treatment exposure, thrombocytopenia events/100 P-Y (for all grades) were similar (3.9 in the AA-P group and 3.7 in the Placebo group).

Dyspepsia

Dyspepsia was reported in 2.8% of subjects in the AA-P group and 2.0% of subjects in the Placebo group. After standardising for the difference in duration of treatment exposure, an increase of 0.6 dyspepsia events/100 P-Y (for all grades) was observed in the AA-P group (2.1 in the AA-P group and 1.5 in the Placebo group).

Urinary tract infection

Urinary tract infection was reported in 7.2% of subjects in the AA-P group and 3.7% of subjects in the placebo group (Grade 3; 1.0% vs. 0.8%). After standardising for the difference in duration of treatment exposure, an excess of 1.7 urinary tract infection events/100 P-Y (for all grades) was observed in the AA-P group (5.2 in the AA-P group and 3.5 in the placebo group).

Haematuria

Haematuria was reported in 4.5% of subjects in the AA-P group and 3.2% of subjects in the placebo group. After standardising for the difference in duration of treatment exposure, an increase of 0.3 haematuria events/100 P-Y (for all grades) was observed in the AA-P group (3.0 in the AA-P group and 2.7 in the Placebo group). 6 (1.0%) subjects in the AA-P group and 3 (0.5%) subjects in the Placebo group had Grade 3 event.

Adverse Events of Special Interest (combined phase 3 trials)

Table 26: Treatment-emergent Adverse Events of Special interest by toxicity grade, integrated safety population-Phase 3 studies (combined phase 3 trials)

	Combined											
	AA						Placebo					
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Subjects treated	2230						1763					
Total no. subjects with a treatment-emergent adverse event of special interest	1435 (64.3%)	456 (20.4%)	438 (19.6%)	464 (20.8%)	50 (2.2%)	24 (1.1%)	889 (50.4%)	340 (19.3%)	301 (17.1%)	211 (12.0%)	16 (0.9%)	20 (1.1%)
Adverse Event of Special Interest MedDRA Preferred Term												
Fluid retention/oedema	514 (23.0%)	344 (15.4%)	138 (6.2%)	29 (1.3%)	1 (<0.1%)	0	303 (17.2%)	198 (11.2%)	85 (4.8%)	18 (1.0%)	1 (0.1%)	1 (0.1%)
Oedema peripheral	430 (19.3%)	302 (13.5%)	108 (4.8%)	18 (0.8%)	0	0	251 (14.2%)	166 (9.4%)	75 (4.3%)	10 (0.6%)	0	0
Pleural effusion	28 (1.3%)	15 (0.7%)	10 (0.4%)	2 (0.1%)	1 (<0.1%)	0	17 (1.0%)	6 (0.3%)	5 (0.3%)	5 (0.3%)	0	1 (0.1%)
Peripheral swelling	26 (1.2%)	21 (0.9%)	5 (0.2%)	0	0	0	20 (1.1%)	15 (0.9%)	3 (0.2%)	2 (0.1%)	0	0
Joint swelling	20 (0.9%)	13 (0.6%)	6 (0.3%)	1 (<0.1%)	0	0	11 (0.6%)	7 (0.4%)	3 (0.2%)	1 (0.1%)	0	0
Localised oedema	12 (0.5%)	9 (0.4%)	3 (0.1%)	0	0	0	10 (0.6%)	5 (0.3%)	4 (0.2%)	1 (0.1%)	0	0
Fluid retention	11 (0.5%)	5 (0.2%)	6 (0.3%)	0	0	0	7 (0.4%)	5 (0.3%)	1 (0.1%)	1 (0.1%)	0	0
Generalised oedema	10 (0.4%)	4 (0.2%)	3 (0.1%)	3 (0.1%)	0	0	4 (0.2%)	2 (0.1%)	1 (0.1%)	0	1 (0.1%)	0
Lymphoedema	9 (0.4%)	4 (0.2%)	3 (0.1%)	2 (0.1%)	0	0	5 (0.3%)	3 (0.2%)	2 (0.1%)	0	0	0
Ascites	7 (0.3%)	2 (0.1%)	3 (0.1%)	2 (0.1%)	0	0	2 (0.1%)	2 (0.1%)	0	0	0	0
Local swelling	7 (0.3%)	3 (0.1%)	2 (0.1%)	2 (0.1%)	0	0	6 (0.3%)	3 (0.2%)	3 (0.2%)	0	0	0
Oedema	6 (0.3%)	6 (0.3%)	0	0	0	0	4 (0.2%)	4 (0.2%)	0	0	0	0
Joint effusion	3 (0.1%)	0	3 (0.1%)	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Bone swelling	2 (0.1%)	2 (0.1%)	0	0	0	0	0	0	0	0	0	0
Hydrothorax	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Swelling	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Bone marrow oedema	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Brain oedema	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Implant site oedema	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Injection site oedema	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Mouth swelling	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Muscle oedema	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Pericardial effusion	1 (<0.1%)	1 (<0.1%)	0	0	0	0	2 (0.1%)	1 (0.1%)	1 (0.1%)	0	0	0
Fluid overload	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Hypervolaemia	0	0	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Testicular swelling	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Hypertension	486 (21.8%)	115 (5.2%)	206 (9.2%)	164 (7.4%)	1 (<0.1%)	0	280 (15.9%)	62 (3.5%)	129 (7.3%)	88 (5.0%)	1 (0.1%)	0
Hypertension	470 (21.1%)	109 (4.9%)	201 (9.0%)	160 (7.2%)	0	0	268 (15.2%)	59 (3.3%)	123 (7.0%)	85 (4.8%)	1 (0.1%)	0
Blood pressure increased	15 (0.7%)	6 (0.3%)	6 (0.3%)	3 (0.1%)	0	0	9 (0.5%)	1 (0.1%)	5 (0.3%)	3 (0.2%)	0	0
Hypertensive crisis	4 (0.2%)	0	0	3 (0.1%)	1 (<0.1%)	0	2 (0.1%)	0	0	2 (0.1%)	0	0
Blood pressure fluctuation	1 (<0.1%)	0	0	1 (<0.1%)	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Diastolic hypertension	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Retinopathy hypertensive	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Secondary hypertension	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Essential hypertension	0	0	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Metabolic syndrome	0	0	0	0	0	0	2 (0.1%)	1 (0.1%)	0	1 (0.1%)	0	0
Orthostatic hypertension	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Primary hyperaldosteronism	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Hypokalaemia	406 (18.2%)	210 (9.4%)	70 (3.1%)	113 (5.1%)	13 (0.6%)	0	142 (8.1%)	99 (5.6%)	18 (1.0%)	24 (1.4%)	1 (0.1%)	0
Hypokalaemia	405 (18.2%)	210 (9.4%)	70 (3.1%)	112 (5.0%)	13 (0.6%)	0	142 (8.1%)	99 (5.6%)	18 (1.0%)	24 (1.4%)	1 (0.1%)	0
Blood potassium decreased	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Hepatotoxicity	360 (16.1%)	128 (5.7%)	102 (4.6%)	116 (5.2%)	14 (0.6%)	0	239 (13.6%)	126 (7.1%)	63 (3.6%)	44 (2.5%)	4 (0.2%)	1 (0.1%)

	Combined											
	AA						Placebo					
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Hepatic function abnormal	131 (5.9%)	35 (1.6%)	43 (1.9%)	48 (2.2%)	5 (0.2%)	0	67 (3.8%)	34 (1.9%)	14 (0.8%)	15 (0.9%)	4 (0.2%)	0
Alanine aminotransferase increased	127 (5.7%)	62 (2.8%)	27 (1.2%)	35 (1.6%)	3 (0.1%)	0	96 (5.4%)	65 (3.7%)	23 (1.3%)	8 (0.5%)	0	0
Aspartate aminotransferase increased	117 (5.2%)	59 (2.6%)	27 (1.2%)	30 (1.3%)	1 (<0.1%)	0	89 (5.0%)	56 (3.2%)	23 (1.3%)	10 (0.6%)	0	0
Hyperbilirubinaemia	49 (2.2%)	28 (1.3%)	12 (0.5%)	9 (0.4%)	0	0	19 (1.1%)	11 (0.6%)	3 (0.2%)	4 (0.2%)	1 (0.1%)	0
Hypoalbuminaemia	20 (0.9%)	9 (0.4%)	10 (0.4%)	1 (<0.1%)	0	0	21 (1.2%)	7 (0.4%)	13 (0.7%)	1 (0.1%)	0	0
Blood alkaline phosphatase increased	15 (0.7%)	4 (0.2%)	3 (0.1%)	6 (0.3%)	2 (0.1%)	0	20 (1.1%)	8 (0.5%)	4 (0.2%)	8 (0.5%)	0	0
Hepatic enzyme increased	7 (0.3%)	2 (0.1%)	4 (0.2%)	1 (<0.1%)	0	0	3 (0.2%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	0	0
Hepatomegaly	6 (0.3%)	3 (0.1%)	2 (0.1%)	1 (<0.1%)	0	0	2 (0.1%)	1 (0.1%)	1 (0.1%)	0	0	0
Gamma-glutamyltransferase increased	5 (0.2%)	1 (<0.1%)	1 (<0.1%)	3 (0.1%)	0	0	3 (0.2%)	2 (0.1%)	0	1 (0.1%)	0	0
Jaundice	4 (0.2%)	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	2 (0.1%)	1 (0.1%)	0	1 (0.1%)	0	0
Liver disorder	3 (0.1%)	3 (0.1%)	0	0	0	0	3 (0.2%)	2 (0.1%)	0	0	0	1 (0.1%)
Liver function test abnormal	3 (0.1%)	0	1 (<0.1%)	2 (0.1%)	0	0	0	0	0	0	0	0
Blood bilirubin increased	2 (0.1%)	0	2 (0.1%)	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Hepatic pain	2 (0.1%)	2 (0.1%)	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Hepatic steatosis	2 (0.1%)	2 (0.1%)	0	0	0	0	2 (0.1%)	2 (0.1%)	0	0	0	0
Hepatotoxicity	2 (0.1%)	0	0	0	2 (0.1%)	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Hypertransaminasaemia	2 (0.1%)	0	1 (<0.1%)	0	1 (<0.1%)	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Liver injury	2 (0.1%)	2 (0.1%)	0	0	0	0	3 (0.2%)	3 (0.2%)	0	0	0	0
Transaminases increased	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Abnormal faeces	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Cholestasis	1 (<0.1%)	0	1 (<0.1%)	0	0	0	3 (0.2%)	0	1 (0.1%)	2 (0.1%)	0	0
Drug-induced liver injury	1 (<0.1%)	0	1 (<0.1%)	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Hepatitis toxic	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Hepatobiliary disease	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Hepatocellular injury	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Ischaemic hepatitis	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Jaundice cholestatic	1 (<0.1%)	0	0	1 (<0.1%)	0	0	1 (0.1%)	0	0	0	0	0
Liver tenderness	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Varices oesophageal	1 (<0.1%)	1 (<0.1%)	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Hepatic encephalopathy	0	0	0	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Hepatosplenomegaly	0	0	0	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Liver palpable	0	0	0	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Ocular icterus	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Cardiac Disorders	346 (15.5%)	127 (5.7%)	92 (4.1%)	82 (3.7%)	20 (0.9%)	24 (1.1%)	219 (12.4%)	98 (5.6%)	68 (3.9%)	29 (1.6%)	6 (0.3%)	18 (1.0%)
Arrhythmia	212 (9.5%)	94 (4.2%)	57 (2.6%)	39 (1.7%)	7 (0.3%)	14 (0.6%)	123 (7.0%)	57 (3.2%)	35 (2.0%)	18 (1.0%)	1 (0.1%)	12 (0.7%)
Atrial fibrillation	57 (2.6%)	11 (0.5%)	29 (1.3%)	13 (0.6%)	4 (0.2%)	0	35 (2.0%)	10 (0.6%)	16 (0.9%)	8 (0.5%)	1 (0.1%)	0
Tachycardia	43 (1.9%)	31 (1.4%)	9 (0.4%)	2 (0.1%)	0	0	18 (1.0%)	11 (0.6%)	7 (0.4%)	0	0	0
Palpitations	30 (1.3%)	24 (1.1%)	6 (0.3%)	0	0	0	15 (0.9%)	15 (0.9%)	0	0	0	0
Syncope	28 (1.3%)	5 (0.2%)	5 (0.2%)	18 (0.8%)	0	0	19 (1.1%)	7 (0.4%)	3 (0.2%)	9 (0.5%)	0	0
Ventricular extrasystoles	13 (0.6%)	12 (0.5%)	1 (<0.1%)	0	0	0	6 (0.3%)	5 (0.3%)	1 (0.1%)	0	0	0
Loss of consciousness	12 (0.5%)	4 (0.2%)	4 (0.2%)	4 (0.2%)	0	0	2 (0.1%)	2 (0.1%)	0	0	0	0
Bradycardia	9 (0.4%)	8 (0.4%)	1 (<0.1%)	0	0	0	7 (0.4%)	5 (0.3%)	1 (0.1%)	0	1 (0.1%)	0
Cardio-respiratory arrest	8 (0.4%)	0	0	1 (<0.1%)	0	7 (0.3%)	2 (0.1%)	0	0	0	0	2 (0.1%)
Sinus tachycardia	8 (0.4%)	6 (0.3%)	1 (<0.1%)	0	0	0	7 (0.4%)	4 (0.2%)	2 (0.1%)	1 (0.1%)	0	0

	Combined											
	AA						Placebo					
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Atrial flutter	6 (0.3%)	1 (<0.1%)	2 (0.1%)	1 (<0.1%)	2 (0.1%)	0	4 (0.2%)	1 (0.1%)	3 (0.2%)	0	0	0
Supraventricular extrasystoles	6 (0.3%)	5 (0.2%)	1 (<0.1%)	0	0	0	4 (0.2%)	4 (0.2%)	0	0	0	0
Supraventricular tachycardia	6 (0.3%)	0	3 (0.1%)	3 (0.1%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Cardiac arrest	4 (0.2%)	0	0	0	0	4 (0.2%)	5 (0.3%)	0	0	0	0	5 (0.3%)
Heart rate increased	4 (0.2%)	3 (0.1%)	0	1 (<0.1%)	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Arrhythmia supraventricular	3 (0.1%)	3 (0.1%)	0	0	0	0	4 (0.2%)	2 (0.1%)	2 (0.1%)	0	0	0
Sudden death	3 (0.1%)	0	0	0	0	3 (0.1%)	5 (0.3%)	0	0	0	0	5 (0.3%)
Atrial tachycardia	1 (<0.1%)	1 (<0.1%)	0	0	0	0	3 (0.2%)	0	3 (0.2%)	0	0	0
Supraventricular tachyarrhythmia	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Ventricular arrhythmia	1 (<0.1%)	1 (<0.1%)	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Ventricular tachycardia	1 (<0.1%)	0	0	0	1 (<0.1%)	0	0	0	0	0	0	0
Other cardiac disorders	81 (3.6%)	39 (1.7%)	30 (1.3%)	11 (0.5%)	1 (<0.1%)	0	74 (4.2%)	44 (2.5%)	24 (1.4%)	5 (0.3%)	1 (0.1%)	0
Chest pain	46 (2.1%)	23 (1.0%)	17 (0.8%)	5 (0.2%)	1 (<0.1%)	0	55 (3.1%)	30 (1.7%)	21 (1.2%)	3 (0.2%)	1 (0.1%)	0
Cardiac disorder	14 (0.6%)	3 (0.1%)	7 (0.3%)	4 (0.2%)	0	0	9 (0.5%)	5 (0.3%)	2 (0.1%)	2 (0.1%)	0	0
Conduction disorder	4 (0.2%)	2 (0.1%)	2 (0.1%)	0	0	0	0	0	0	0	0	0
Sinus bradycardia	4 (0.2%)	3 (0.1%)	1 (<0.1%)	0	0	0	3 (0.2%)	3 (0.2%)	0	0	0	0
Bundle branch block left	3 (0.1%)	2 (0.1%)	1 (<0.1%)	0	0	0	2 (0.1%)	2 (0.1%)	0	0	0	0
Electrocardiogram QT prolonged	3 (0.1%)	2 (0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Atrioventricular block	2 (0.1%)	1 (<0.1%)	0	1 (<0.1%)	0	0	2 (0.1%)	1 (0.1%)	0	1 (0.1%)	0	0
Atrioventricular block first degree	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Cardiomyopathy	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Mitral valve disease	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Sinus arrhythmia	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Hypertrophic cardiomyopathy	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Left ventricular hypertrophy	0	0	0	0	0	0	2 (0.1%)	2 (0.1%)	0	0	0	0
Wandering pacemaker	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Ischaemic Heart Disease	73 (3.3%)	19 (0.9%)	17 (0.8%)	23 (1.0%)	8 (0.4%)	6 (0.3%)	39 (2.2%)	12 (0.7%)	11 (0.6%)	9 (0.5%)	3 (0.2%)	4 (0.2%)
Angina pectoris	38 (1.7%)	19 (0.9%)	12 (0.5%)	6 (0.3%)	1 (<0.1%)	0	14 (0.8%)	7 (0.4%)	5 (0.3%)	2 (0.1%)	0	0
Myocardial infarction	14 (0.6%)	0	1 (<0.1%)	5 (0.2%)	5 (0.2%)	3 (0.1%)	7 (0.4%)	0	1 (0.1%)	2 (0.1%)	2 (0.1%)	2 (0.1%)
Coronary artery disease	11 (0.5%)	2 (0.1%)	3 (0.1%)	5 (0.2%)	0	1 (<0.1%)	4 (0.2%)	1 (0.1%)	1 (0.1%)	2 (0.1%)	0	0
Myocardial ischaemia	7 (0.3%)	1 (<0.1%)	2 (0.1%)	4 (0.2%)	0	0	10 (0.6%)	4 (0.2%)	1 (0.1%)	4 (0.2%)	0	1 (0.1%)
Acute myocardial infarction	6 (0.3%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	4 (0.2%)	0	2 (0.1%)	1 (0.1%)	1 (0.1%)	0
Acute coronary syndrome	4 (0.2%)	0	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	1 (0.1%)	0	0	0	0	1 (0.1%)
Troponin I increased	2 (0.1%)	0	0	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0
Angina unstable	1 (<0.1%)	1 (<0.1%)	0	0	0	0	4 (0.2%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	0	0
Arteriosclerosis coronary artery	1 (<0.1%)	1 (<0.1%)	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Coronary artery stenosis	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Electrocardiogram ST segment depression	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0

	Combined											
	AA						Placebo					
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Electrocardiogram T wave inversion	1 (<0.1%)	1 (<0.1%)	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Ischaemic cardiomyopathy	1 (<0.1%)	0	0	1 (<0.1%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Troponin increased	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Cardiac Failure	57 (2.6%)	11 (0.5%)	14 (0.6%)	22 (1.0%)	6 (0.3%)	4 (0.2%)	15 (0.9%)	6 (0.3%)	4 (0.2%)	2 (0.1%)	1 (0.1%)	2 (0.1%)
Cardiac failure	17 (0.8%)	3 (0.1%)	6 (0.3%)	4 (0.2%)	3 (0.1%)	1 (<0.1%)	5 (0.3%)	2 (0.1%)	2 (0.1%)	0	0	1 (0.1%)
Cardiac failure congestive	15 (0.7%)	2 (0.1%)	1 (<0.1%)	8 (0.4%)	2 (0.1%)	2 (0.1%)	2 (0.1%)	1 (0.1%)	0	0	1 (0.1%)	0
Ejection fraction decreased	8 (0.4%)	1 (<0.1%)	3 (0.1%)	4 (0.2%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Pulmonary oedema	7 (0.3%)	3 (0.1%)	3 (0.1%)	1 (<0.1%)	0	0	2 (0.1%)	1 (0.1%)	0	1 (0.1%)	0	0
Cardiac failure acute	3 (0.1%)	0	0	3 (0.1%)	0	0	1 (0.1%)	0	0	0	0	1 (0.1%)
Left ventricular dysfunction	3 (0.1%)	0	2 (0.1%)	1 (<0.1%)	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Orthopnoea	3 (0.1%)	1 (<0.1%)	2 (0.1%)	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Diastolic dysfunction	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Dyspnoea paroxysmal nocturnal	2 (0.1%)	2 (0.1%)	0	0	0	0	0	0	0	0	0	0
N-terminal prohormone brain natriuretic peptide increased	2 (0.1%)	0	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0
Acute pulmonary oedema	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Cardiac failure chronic	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Cardiogenic shock	1 (<0.1%)	0	0	0	1 (<0.1%)	0	0	0	0	0	0	0
Cardiomegaly	1 (<0.1%)	1 (<0.1%)	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Cardiopulmonary failure	1 (<0.1%)	0	0	0	1 (<0.1%)	0	0	0	0	0	0	0
Cor pulmonale	1 (<0.1%)	0	0	1 (<0.1%)	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Pulmonary congestion	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Right ventricular failure	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Venous pressure jugular increased	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Osteoporosis including osteoporosis-related fractures	149 (6.7%)	49 (2.2%)	64 (2.9%)	30 (1.3%)	5 (0.2%)	0	91 (5.2%)	25 (1.4%)	41 (2.3%)	21 (1.2%)	3 (0.2%)	0
Osteoporosis/osteopenia	110 (4.9%)	41 (1.8%)	45 (2.0%)	20 (0.9%)	3 (0.1%)	0	68 (3.9%)	22 (1.2%)	27 (1.5%)	16 (0.9%)	3 (0.2%)	0
Rib fracture	44 (2.0%)	22 (1.0%)	21 (0.9%)	1 (<0.1%)	0	0	22 (1.2%)	13 (0.7%)	8 (0.5%)	1 (0.1%)	0	0
Spinal compression fracture	16 (0.7%)	5 (0.2%)	8 (0.4%)	2 (0.1%)	1 (<0.1%)	0	11 (0.6%)	2 (0.1%)	5 (0.3%)	4 (0.2%)	0	0
Osteoporosis	14 (0.6%)	7 (0.3%)	7 (0.3%)	0	0	0	10 (0.6%)	3 (0.2%)	4 (0.2%)	3 (0.2%)	0	0
Wrist fracture	8 (0.4%)	2 (0.1%)	5 (0.2%)	1 (<0.1%)	0	0	2 (0.1%)	0	2 (0.1%)	0	0	0
Hip fracture	6 (0.3%)	0	1 (<0.1%)	4 (0.2%)	1 (<0.1%)	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Osteopenia	6 (0.3%)	4 (0.2%)	2 (0.1%)	0	0	0	5 (0.3%)	4 (0.2%)	1 (0.1%)	0	0	0
Femur fracture	5 (0.2%)	0	0	5 (0.2%)	0	0	3 (0.2%)	1 (0.1%)	0	2 (0.1%)	0	0
Lumbar vertebral fracture	3 (0.1%)	2 (0.1%)	0	1 (<0.1%)	0	0	2 (0.1%)	0	0	1 (0.1%)	1 (0.1%)	0
Radius fracture	3 (0.1%)	0	1 (<0.1%)	1 (<0.1%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Thoracic vertebral fracture	3 (0.1%)	2 (0.1%)	1 (<0.1%)	0	0	0	5 (0.3%)	0	2 (0.1%)	2 (0.1%)	1 (0.1%)	0
Bone loss	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Cervical vertebral fracture	2 (0.1%)	0	0	2 (0.1%)	0	0	0	0	0	0	0	0
Osteoporotic fracture	2 (0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Spinal fracture	2 (0.1%)	0	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0
Femoral neck fracture	1 (<0.1%)	0	0	1 (<0.1%)	0	0	2 (0.1%)	0	0	1 (0.1%)	1 (0.1%)	0
Fracture	1 (<0.1%)	0	0	1 (<0.1%)	0	0	4 (0.2%)	1 (0.1%)	1 (0.1%)	2 (0.1%)	0	0

	Combined											
	AA						Placebo					
	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Ilium fracture	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Kyphosis	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Pelvic fracture	1 (<0.1%)	0	0	1 (<0.1%)	0	0	2 (0.1%)	0	2 (0.1%)	0	0	0
Pubis fracture	1 (<0.1%)	0	0	1 (<0.1%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Bone metabolism disorder	0	0	0	0	0	0	1 (0.1%)	1 (0.1%)	0	0	0	0
Fractured sacrum	0	0	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Fractures PT grouping	50 (2.2%)	12 (0.5%)	24 (1.1%)	12 (0.5%)	2 (0.1%)	0	29 (1.6%)	6 (0.3%)	16 (0.9%)	6 (0.3%)	0	0
Tooth fracture	14 (0.6%)	7 (0.3%)	7 (0.3%)	0	0	0	7 (0.4%)	3 (0.2%)	4 (0.2%)	0	0	0
Foot fracture	6 (0.3%)	0	5 (0.2%)	1 (<0.1%)	0	0	4 (0.2%)	2 (0.1%)	2 (0.1%)	0	0	0
Upper limb fracture	5 (0.2%)	1 (<0.1%)	3 (0.1%)	0	1 (<0.1%)	0	2 (0.1%)	0	2 (0.1%)	0	0	0
Humerus fracture	4 (0.2%)	1 (<0.1%)	1 (<0.1%)	2 (0.1%)	0	0	4 (0.2%)	0	2 (0.1%)	1 (0.1%)	0	0
Stress fracture	4 (0.2%)	3 (0.1%)	0	1 (<0.1%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Ankle fracture	3 (0.1%)	0	0	3 (0.1%)	0	0	3 (0.2%)	0	2 (0.1%)	1 (0.1%)	0	0
Hand fracture	3 (0.1%)	0	3 (0.1%)	0	0	0	0	0	0	0	0	0
Scapula fracture	3 (0.1%)	1 (<0.1%)	1 (<0.1%)	1 (<0.1%)	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Tibia fracture	3 (0.1%)	0	2 (0.1%)	1 (<0.1%)	0	0	2 (0.1%)	0	1 (0.1%)	1 (0.1%)	0	0
Traumatic fracture	3 (0.1%)	1 (<0.1%)	0	2 (0.1%)	0	0	0	0	0	0	0	0
Patella fracture	2 (0.1%)	0	2 (0.1%)	0	0	0	0	0	0	0	0	0
Facial bones fracture	1 (<0.1%)	0	1 (<0.1%)	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Fibula fracture	1 (<0.1%)	0	1 (<0.1%)	0	0	0	2 (0.1%)	1 (0.1%)	1 (0.1%)	0	0	0
Jaw fracture	1 (<0.1%)	0	1 (<0.1%)	0	0	0	0	0	0	0	0	0
Skull fracture	1 (<0.1%)	0	0	0	1 (<0.1%)	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Ulna fracture	1 (<0.1%)	0	0	1 (<0.1%)	0	0	0	0	0	0	0	0
Lower limb fracture	0	0	0	0	0	0	2 (0.1%)	0	0	2 (0.1%)	0	0
Cataract (SMQ Lens disorders)	65 (2.9%)	37 (1.7%)	14 (0.6%)	14 (0.6%)	0	0	53 (3.0%)	40 (2.3%)	7 (0.4%)	6 (0.3%)	0	0
Cataract	29 (1.3%)	7 (0.3%)	9 (0.4%)	13 (0.6%)	0	0	20 (1.1%)	10 (0.6%)	4 (0.2%)	6 (0.3%)	0	0
Vision blurred	27 (1.2%)	25 (1.1%)	1 (<0.1%)	1 (<0.1%)	0	0	25 (1.4%)	22 (1.2%)	3 (0.2%)	0	0	0
Visual acuity reduced	8 (0.4%)	3 (0.1%)	5 (0.2%)	0	0	0	7 (0.4%)	7 (0.4%)	0	0	0	0
Visual impairment	6 (0.3%)	4 (0.2%)	2 (0.1%)	0	0	0	5 (0.3%)	5 (0.3%)	0	0	0	0
Lenticular opacities	1 (<0.1%)	1 (<0.1%)	0	0	0	0	0	0	0	0	0	0
Cataract operation complication	0	0	0	0	0	0	1 (0.1%)	0	0	1 (0.1%)	0	0
Colour blindness acquired	0	0	0	0	0	0	1 (0.1%)	0	1 (0.1%)	0	0	0
Rhabdomyolysis/myopathy	11 (0.5%)	7 (0.3%)	2 (0.1%)	2 (0.1%)	0	0	8 (0.5%)	4 (0.2%)	4 (0.2%)	0	0	0
Myopathy	11 (0.5%)	7 (0.3%)	2 (0.1%)	2 (0.1%)	0	0	8 (0.5%)	4 (0.2%)	4 (0.2%)	0	0	0

Note: A subject who had events with missing toxicity grade is counted in the total column but not listed separately.

Adverse Drug Reactions

The ADR analysis was conducted using AE data from 14 clinical studies (N=4,422): 5 Phase 3 randomized studies (N=3,993) ((COU-AA-301, ABI-PRO-3001, COU-AA-302, ABI-PRO-3002, and PCR3011) and 9 Phase 1/2 single arm studies (N=429) (Studies 006, 015, PCR2007, 001/001EXT, 002, 003/003EXT, 004, BMA, and BE). Based upon this analysis of 14 clinical studies, the preferred terms of Fatigue and Hyperglycemia met the pre-specified ADR criteria: 1% (AA vs placebo) and 5 events per 100 P-Y between group difference (AA vs placebo).

Review of the AE data for the preferred term of Fatigue from the 5 Phase 3 studies combined (N=3,993) and from Study PCR3011 alone (N=1,199) did not meet the pre-defined ADR criteria. In fact, in Study PCR3011, there was a lower incidence of Fatigue in the AA group (12.9%) compared with the Placebo group (14.3%), and lower to that seen in the mCRPC studies.

Review of the AE data for the PT of Hyperglycemia from the 5 Phase 3 studies combined (N=3,993) and from Study PCR3011 alone (N=1,199) did not meet the pre-defined ADR criteria. In the 5 Phase 3 studies combined, 8.9% of subjects in the AA group and 7.8% of subjects in the Placebo group reported AEs of Hyperglycemia. In Study PCR3011, Hyperglycemia was reported by 12.6% of subjects in the AA group and 11.3% of subjects in the Placebo group. For the 5 Phase 3 studies combined and for Study PCR3011, the criterion for a between group difference (AA vs Placebo) of ≥5 events per 100 P-Y was not met.

Serious adverse event / deaths / other significant events

Serious adverse events

Serious adverse events were reported in 27.6% of subjects in the AA-P group and 24.3% of subjects in the placebo group. Commonly reported SAEs were pneumonia (1.8% versus 0.3%), spinal cord compression (1.7% versus 1.8%), urinary retention (1.5% versus 1.7%), urinary tract infection (1.2% versus 0.8%), haematuria (1.0% versus 0.5%), back pain (0.8% versus 1.7%), bone pain (0.7% versus 1.0%) and anaemia (1.0% versus 1.0%).

Table 27: Treatment-emergent Serious Adverse Events Reported in at Least 2 Subjects in Either Treatment Group; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Musculoskeletal and connective tissue disorders	19 (3.2%)	29 (4.8%)
Gastrointestinal disorders	13 (2.2%)	10 (1.7%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (2.0%)	7 (1.2%)
Metabolism and nutrition disorders	10 (1.7%)	2 (0.3%)
Vascular disorders	10 (1.7%)	9 (1.5%)
Blood and lymphatic system disorders	8 (1.3%)	9 (1.5%)
Injury, poisoning and procedural complications	8 (1.3%)	15 (2.5%)
General disorders and administration site conditions	6 (1.0%)	13 (2.2%)
Respiratory, thoracic and mediastinal disorders	6 (1.0%)	12 (2.0%)
Investigations	4 (0.7%)	3 (0.5%)

Deaths

As of the cutoff date (31st October 2016), 40 (6.7%) subjects in the AA-P group and 37 (6.1%) subjects in the placebo group died during treatment or within 30 days after the last dose. 11 (1.8%) subjects in the AA-P group and 16 (2.7%) subjects in the placebo group died due to prostate cancer. 27 (4.5%) subjects in the AA-P group and 20 (3.3%) subjects in the placebo group died within 30 days of the last dose due to AEs. 28 (4.7%) subjects in the AA-P group and 24 (4.0%) subjects in the placebo group had an AE with an outcome of death.

Table 28: Treatment-emergent Adverse Events Leading to Death; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Total number of subjects with a treatment-emergent adverse event leading to death	28 (4.7%)	24 (4.0%)
Cardiac disorders	10 (1.7%)	6 (1.0%)
Gastrointestinal disorders	3 (0.5%)	0

General disorders and administration site conditions	3 (0.5%)	6 (1.0%)
Infections and infestations	5 (0.8%)	5 (0.8%)
Injury, poisoning and procedural complications	2 (0.3%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	0	1 (0.2%)
Nervous system disorders	4 (0.7%)	4 (0.7%)
Psychiatric disorders	0	1 (0.2%)
Renal and urinary disorders	0	1 (0.2%)
Respiratory, thoracic and mediastinal disorders	3 (0.5%)	1 (0.2%)

Laboratory findings

Shifts from Grade 0 or 1 to Grade 3 or 4 for ALT and AST were observed in 6.4% and 4.5% of subjects in the AA-P group and in 1.3% and 1.5% of subjects in the placebo group. Shifts from Grade 0 or 1 to Grade 3 or 4 for low potassium were observed in 9.6% of subjects in the AA-P group and 1.3% of subjects in the Placebo group. Shifts from Grade 0 or 1 to Grade 3 or 4 for fasting serum glucose (high) were observed in 4.4% of subjects in the AA-P group and 2.6% of subjects in the placebo group.

Safety in special populations

Higher incidences of AEs were generally observed in subjects with advanced age, higher baseline ECOG performance status, lower baseline haemoglobin and higher baseline LDH. These findings were also observed in the previous abiraterone acetate studies.

Safety related to drug-drug interactions and other interactions

There were no reports of new drug-drug interaction TEAEs in study PCR3011.

Discontinuation due to adverse events

For the subjects who discontinued treatment in the AA-P group (57.0%) and Placebo group (81.4%), progressive disease was the primary reason for discontinuation (35.0% in the AA-P group, 61.3% in the Placebo group). Adverse events that led to treatment discontinuation were reported in 73 (12.2%) subjects in the AA-P group and 61 (10.1%) subjects in the Placebo group. The most frequently reported AEs leading to treatment discontinuation (reported in ≥1% of subjects in either the AA-P or Placebo group) were Spinal cord compression (0.8% versus 1.0%) and Bone pain (0.5% versus 1.0%). Notably, there were only rare cases of discontinuation for the preferred terms of hypokalaemia (0.3% in the AA-P group versus 0 in the Placebo group), Hypertension (0.5% in the AA-P group versus 0 in the Placebo group)/Blood pressure increased (0 in the AA-P group and 0.2% in the Placebo group), and in the cardiac disorders SOC (1.2% in the AA-P group and 0.3% in the Placebo group).

Table 29: Primary Reason for Treatment Discontinuation; Safety Population (Study 212082PCR3011)

	AA-P	Placebo
Safety Population	597	602
Treatment discontinued	340 (57.0%)	490 (81.4%)
Treatment ongoing	257 (43.0%)	112 (18.6%)
Reasons for discontinuation		
Progressive disease	209 (35.0%)	369 (61.3%)
Adverse event	49 (8.2%)	31 (5.1%)
Withdrawal of consent	31 (5.2%)	41 (6.8%)
Death	26 (4.4%)	21 (3.5%)
Physician decision	11 (1.8%)	19 (3.2%)
Other	7 (1.2%)	5 (0.8%)

Noncompliance with study drug	4 (0.7%)	2 (0.3%)
Lost to follow-up	3 (0.5%)	2 (0.3%)

Dose interruptions, reductions, or other modifications

Adverse events leading to dose reduction or interruption were reported for 32.2% of subjects in the AA-P group and 17.4% of subjects in the placebo group. The most frequently reported AEs leading to reduction or interruption of treatment were hypokalaemia (8.2% versus 0.7%), hypertension (7.0% versus 2.5%), AST increased (5.4% versus 1.7%) and ALT increased (5.2% versus 1.8%).

Post marketing experience

The first marketing approval for abiraterone acetate plus prednisone was on 28 April 2011 in the United States. Based on the 71,418,529 grams distributed worldwide, the estimated post-marketing exposure for abiraterone acetate from launch to 31st October 2016 is 71,418,529 person-days or 10,202,646 person-weeks or 2,380,618 person-months or 195,667 person-years. No new ADRs have been detected for abiraterone from post-marketing data.

2.5.1. Discussion on clinical safety

Abiraterone plus prednisone or prednisolone has been authorised in the EU since September 2011. Special warnings and precautions for use include hypertension, hypokalaemia, fluid retention and cardiac failure due to mineralocorticoid excess, hepatotoxicity and hepatic impairment, corticosteroid withdrawal and coverage of stress situations. These and other adverse events were considered to be adverse events of special interest in the clinical trial protocol.

Treatment emergent AEs were reported in 93.5% of subjects in the AA-P group and 92.5% of subjects in the placebo group. The most frequently reported events in ≥20% of AA-P subjects were hypertension (36.7% versus 22.1%), hypokalaemia (20.4% versus 3.7%) and back pain (18.4% versus 20.4%). No new safety signal has been identified. The incidence of Grade 3-4 AEs was higher in the AA-P group compared to placebo, (63% vs. 48%). The most frequently reported events were related to mineralocorticoid excess and included hypertension (20.3% vs. 10.0%) and hypokalaemia (10.4% vs. 1.3%).

A higher incidence of hypertension and hypokalemia was observed in the hormone sensitive population (study 3011). Hypertension was reported in 36.7% of patients in the hormone sensitive population (study 3011) compared to 11.8% and 20.2% in studies 301 and 302, respectively. Hypokalemia was observed in 20.4% of patients in the hormone sensitive population (study 3011) compared to 19.2% and 14.9% in 301 and 302, respectively.

The number of subjects with drug-related treatment-emergent adverse events was higher in the AA-P group compared to the placebo group, 56.3% vs. 44.7% and for grade 3-4 events 27.1% vs. 11.1%. In a cross trial comparison, the safety profile of abiraterone plus prednisone was broadly consistent with that observed to the previous mCRPC Phase III studies, with the exception of Grade 3-4 drug-related adverse events (COU-AA-301: 15.6%, COU-AA-302: 18.2% and PCR3011: 27.1%). The Applicant proposes this may be due to a higher incidence of hypertension compared with the previous studies and this difference may be attributed to the use of more stringent criteria to determine Grade 3 hypertension. However, it cannot be excluded that a lower dose of prednisone (5 mg in the PCR3011 vs. 10 mg in the mCRPC studies) did not impact the incidence of hypertension in the pivotal study. Taking into account that adverse events (including hypertension) were generally manageable and the benefits outweigh the risks for the claimed indication, no concerns arise.

Based on previous experience and the known mechanism of action of abiraterone, adverse events of special interest were highlighted in the CSR. These include cardiac disorders, events related to mineralocorticoid excess (hypertension, hypokalaemia, and fluid retention/oedema), hepatotoxicity, cataract, osteoporosis, rhabdomyolysis/myopathy, allergic alveolitis and drug-drug interactions (CYP2D6) and food effect. Consistent with the mechanism of action of abiraterone and previous clinical experience, mineralocorticoid-related toxicities were reported commonly in abiraterone treated subjects.

Hepatotoxicity is a well-known abiraterone adverse reaction and was observed in the study. The current section 4.2 of the SmPC contains detailed guidance regarding emerging patient hepatotoxicity and drug interruptions, dose reduction and drug discontinuation. No further changes to the hepatotoxicity section are proposed on the basis of the data derived from study PCR3011.

The incidence and severity of adverse events was higher in the subgroups of patients with baseline ECOG2 performance status grade and also in elderly patients (≥75 years) (see SmPC section 4.8).

Deaths within 30 days of last dose were similar between arms, 6.7% vs. 6.1%. Marginally more serious adverse events were reported in the AA-P group vs. placebo, 27.6% vs. 24.3%. Adverse events leading to dose reduction or interruption were reported for 32.2% of subjects in the AA-P group and 17.4% of subjects in the placebo group.

The reported AEs leading to dose reduction or interruption are well known events and listed in section 4.4 of the SmPC. More subjects in the placebo group discontinued treatment, 81.4% (61.3% for disease progression) vs. 57.0% (35.0% for disease progression).

The abiraterone plus prednisone group received therapy for almost twice as long as subjects in the placebo group (24 vs. 14 months). To assess the effect of the longer duration of exposure an analysis was conducted and reported as the number of events per 100 patient-years (P-Y) of exposure. When standardising for exposure (events per 100 P-Y), the rate of adverse events was lower for the AA-P group (484) compared with the placebo group (530). The following events (Grades 1 - 4) were observed at an excess of 5 or more events/100 P-Y in the AA-P group compared with the placebo group: hypertension (53.1 vs 34.6) and hypokalaemia (23.2 vs 5.6). The following events were observed at an excess of 5 or more events/100 P-Y in the placebo group: anaemia (7.1 vs 17.0), back pain (13.8 vs 21.3), arthralgia (12.3 vs 18.1) and bone pain (9.1 vs 14.0).

The Applicant states no new ADR has been identified in the post marketing data to date. Although it cannot be excluded that a lower dose of prednisone did not impact the incidence of hypertension in the pivotal study, adverse events (including hypertension) were generally manageable and the benefits outweigh the risks for the claimed indication.

The product information has been updated to reflect revised frequencies of adverse drug reactions based on the integrated Safety Population (see SmPC section 4.8). No new ADRs were included based on the review of the available safety data which is considered acceptable. No changes are warranted to the list of safety concerns and pharmacovigilance plan (see RMP).

2.5.2. Conclusions on clinical safety

The risks associated with abiraterone plus prednisone treatment in the mHNPC population are concordant with the known toxicities previously observed and described in the approved mCRPC population, and appear clinically manageable to the majority of patients.

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in

the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 14.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 14.2 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Hepatotoxicity Cardiac disorders Osteoporosis including osteoporosis-related fractures Rhabdomyolysis/Myopathy Allergic alveolitis Increased exposure with food
Important potential risks	Anaemia Cataract Drug-drug interaction (CYP2D6)
Missing information	Use in patients with active or symptomatic viral hepatitis Use in patients with moderate/severe hepatic impairment and chronic liver disease Use in patients with severe renal impairment 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%

There was no change to the list of safety concerns as a result of the new indications, which was considered acceptable.

Pharmacovigilance plan

The Pharmacovigilance Plan remains unchanged. There are no ongoing and planned studies in the PhV development plan. Routine pharmacovigilance remains sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risks		
Hepatotoxicity	Prior to treatment with ZYTIGA, serum transaminases should be measured, and then every 2 weeks for the first 3 months *of treatment and monthly thereafter* (SmPC Section 4.2).	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	SmPC Sections 4.2 and 4.4 contain recommendations for dosing and monitoring of liver function if hepatotoxicity develops. The SmPC (Section 4.8) lists hepatitis fulminant and acute hepatic failure as rare adverse drug reactions, based on rare postmarketing reports of acute liver failure and hepatitis fulminant, some with fatal outcome. SmPC Section 4.8 also describes clinical trial liver function test findings.	
Cardiac disorders	SmPC Section 4.4 advises that caution is required in treating patients with a history of cardiovascular disease and provides information for assessing cardiac function and for correcting, controlling, and monitoring signs and symptoms of cardiac disorders before and during treatment. Cardiovascular adverse reactions are provided in SmPC Section 4.8.	None
Osteoporosis including Osteoporosis-related fractures	SmPC Section 4.4 provides information about the potential for decreased bone density in men with metastatic advanced prostate cancer. The use of ZYTIGA plus a glucocorticoid could increase this effect. SmPC Section 4.8 provides information about fractures.	None
Rhabdomyolysis/myopathy	SmPC Section 4.4 provides information about skeletal muscle effects and recommends caution in patients concomitantly treated with drugs known to be associated with myopathy/rhabdomyolysis. SmPC Section 4.8 lists myopathy and rhabdomyolysis.	None
Allergic alveolitis	The SmPC Section 4.8 lists allergic alveolitis as a rare adverse drug reaction	None
Increased exposure with food	The SmPC specifies that ZYTIGA must not be taken with food, should be taken at least 2 hours after eating, and no food for at least 1 hour after taking ZYTIGA (SmPC Sections 4.2, 4.5, and 5.2). The product packaging provides instructions for correct	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administration in relation to food.	
Important Potential Risks		
Anaemia	SmPC Section 4.4 provides information about the potential for anaemia.	None
Cataract	The MAH considers that language in the SmPC is not warranted at this time.	
Drug-drug interaction (CYP2D6)	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 and with such products, a dose reduction should be considered (SmPC Section 4.5).	None
Missing Information		
Use in patients with active or symptomatic viral hepatitis	Patients with active or symptomatic hepatitis were excluded from clinical trials (SmPC Section 4.4).	None
Use in patients with moderate/severe hepatic impairment and chronic liver disease	There are no data on the clinical safety of ZYTIGA in patients with pre-existing moderate or severe liver damage and no dose adjustment can be predicted. Use of ZYTIGA in patients with moderate hepatic impairment is described in SmPC Sections 4.2, 4.4, 5.2 and is contraindicated in patients with severe hepatic impairment (SmPC Sections 4.2, 4.3, 4.4, and 5.2).	None
Use in patients with severe renal impairment	There is no clinical experience in patients with prostate cancer and severe renal impairment. Caution is advised in these patients (SmPC Section 4.2).	None
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%	ZYTIGA should be used with caution in patients with a history of cardiovascular disease (SmPC Section 4.4). SmPC Section 4.4 provides information for assessing cardiac function and for correcting, controlling, and monitoring signs and symptoms of cardiac disorders before and during treatment.	None

The risk minimisation measures remain unchanged.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable considering the changes to the package leaflet are minimal.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The claimed indication is: Zytiga is indicated with prednisone or prednisolone for the treatment of adult men with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in combination with androgen deprivation therapy (ADT).

Prostate cancer is an androgen driven malignancy. Approximately 15-30% of patients have metastatic disease at the time of diagnosis, typically presenting high disease burden and bone metastases in its majority. After standard ADT therapy, most patients will develop castration-resistant disease.

The median survival for patients with mHNPC is variable (ranging from 13 months up to 75 months), and is dependent on the presence of high-risk prognostic features such as high PSA at diagnosis, high Gleason score, increased volume of metastatic disease, presence of bony symptoms (Milikan 2008) or presence of visceral metastasis (Gandaglia 2014).

3.1.2. Available therapies and unmet medical need

In the hormone naïve setting the standard of care has historically been ADT (luteinizing hormone-releasing hormone [LHRH] agonist or surgical castration) with or without concurrent anti-androgens.

Recently, docetaxel-based chemotherapy in addition to standard ADT is considered an alternative based on the significant benefit shown in terms of OS in metastatic or locally advanced hormone-naïve disease (James *et al*, 2016; Sweeney *et al*, 2015) (OS medians in the range of 50-60 months compared to medians around 32-45 months if treated with standard ADT) thus changing disease course and treatment decisions in the metastatic castration-resistant setting. Although docetaxel plus standard ADT is currently recommended for patients candidates to chemotherapy, significant toxicities are associated to docetaxel therapy (ESMO guideline).

3.1.3. Main clinical studies

Efficacy data in support of this application were provided from trial PCR3011: A phase 3, randomized, double-blind trial in which AA (1000 mg once daily) plus low dose prednisone (5 mg) administered add-on to ADT was compared to ADT alone in subjects with newly diagnosed (within 3 months prior to randomization) mHNPC with high-risk prognostic factors.

High-risk is defined as having at least 2 of the following 3 risk factors: (1) Gleason score of ≥ 8 of primary tumor; (2) presence of 3 or more lesions on bone scan; (3) presence of measurable visceral (excluding lymph node disease) metastasis.

3.2. Favourable effects

Results from trial PCR3011 study in the efficacy target population of patients at the cut-off date of 31-oct-2016 included the main analysis planned for rPFS (investigator assessed) and the first interim analysis for OS (2 IA planned plus 1 final analysis).

The outcome from one of the two co-primary endpoints of the trial (rPFS & OS) shows a statistically significant and clinically relevant increase of 18 months in median rPFS (median 33.2 months in the AA-P arm vs. 14.78 placebo arm; HR=0.466; 95% CI: 0.394, 0.520; p<0.0001). OS data though immature (event rate 33.9%) already reached statistical significance (median not reached in AA-P arm vs. 34.73 months) pointing towards an effect of clinical relevance. These results are supported by several sensitivity and subgroup analyses.

Secondary endpoints were included to provide additional evidence of clinical benefit, in particular delaying the course of the disease, and to show consistency with the primary endpoints. Treatment with AA-P delayed the need for initiation of chemotherapy (HR=0.443; p<0.0001), delayed the time to initiation of all subsequent therapy (HR=0.415; p<0.0001), delayed the time to pain progression (HR=0.695; p<0.0001), delayed the time to skeletal-related event (HR=0.703; p=0.0086) and delayed the time to PSA progression (HR=0.299; p<0.0001). Thus, the secondary efficacy endpoints demonstrated favourable benefit of AA-P compared to the placebo group, supporting the primary analysis.

Exploratory analyses included PSA response rate, progression-free survival following subsequent therapy (PFS2), PRO measures, time to symptomatic local progression, prostate-cancer-specific survival, time to chronic opiate use, and best overall response and were also favourable for AA-P treatment.

3.3. Uncertainties and limitations about favourable effects

Although promising results are shown in terms of OS, more mature data are needed in order to confirm these findings. Updated OS data will be available at the time of the 2nd preplanned IA, this is 1Q 2018 (see letter of recommendations). However, it can be anticipated that the cross-over of patients (allowed after results of main analysis of rPFS and 1st IA on OS) will unavoidably confound results.

The main drawbacks of the trial relate to the ADT comparator arm, which is not considered the only alternative anymore for all mHNPC patients and as such it is not possible to put the findings in context of current clinical practice. Furthermore, the premature unblinding of trial preclude definitive conclusion about the place of AA-P in therapeutic. Based on the available, it is not possible to evaluate whether early initiation of AA is better than its use in later lines and additionally how the introduction of AA in the mHNPC setting will impact not only cross-resistance to subsequent hormonal therapy but also patient's benefit and long-term overall survival throughout entire course of the disease. Regarding the development of cross-resistances, data on PFS2 point out in the right direction as there appears to be a trend for longer PFS2 in the AA-P arm however data are still too immature with low percentage of events.

Although the limited sample size of the subgroups of patients with an ECOG-PS of 2 is acknowledged, a consistent negative effect is observed in rPFS and OS results (PFS HR=2.43; OS HR=2.38). The SmPC has been updated to reflect that the treatment effect of AA-P on rPFS and OS across the pre-specified subgroups was favourable and consistent with the overall study population, except for the subgroup of ECOG score of 2.

3.4. Unfavourable effects

Abiraterone plus prednisone or prednisolone has been authorised in the EU since September 2011. The Applicant states no new ADR has been identified in the post marketing period to date.

The abiraterone plus prednisone group received therapy for almost twice as long as subjects in the placebo group (24 vs. 14 months). To assess the effect of the longer duration of exposure an analysis was conducted and reported as the number of events per 100 patient-years (P-Y) of exposure. When standardising for exposure (events per 100 P-Y), the rate of adverse events was lower for the AA-P group (484) compared with the placebo group (530).

Without adjustment for treatment duration, the number of subjects with drug-related treatment-emergent adverse events was higher in the AA-P group compared to the placebo group, 56.3% vs. 44.7% and for grade 3-4 events 27.1% vs. 11.1%. In a cross trial comparison, the safety profile of abiraterone plus prednisone was broadly consistent with that observed to the previous mCRPC Phase III studies, with the exception of Grade 3-4 drug-related adverse events (COU-AA-301: 15.6%, COU-AA-302: 18.2% and PCR3011: 27.1%).

Treatment emergent AEs were reported in 93.5% of subjects in the AA-P group and 92.5% of subjects in the placebo group. The most frequently reported events in ≥20% of AA-P subjects were hypertension (36.7% versus 22.1%), hypokalaemia (20.4% versus 3.7%) and back pain (18.4% versus 20.4%). No new safety signal has been identified. The incidence of Grade 3-4 AEs was higher in the AA-P group compared to placebo (63% vs. 48%). The most frequently reported events were related to mineralocorticoid excess and included hypertension (20.3% vs. 10.0%) and hypokalaemia (10.4% vs. 1.3%). A higher incidence of hypertension and hypokalemia was observed in the hormone sensitive population (study 3011).

Hepatotoxicity is a well-known abiraterone adverse reaction and was observed in the study. It was reported in 22.4% of AA-P group and 18.1% of placebo group. The most frequently reported individual hepatotoxicity AE were ALT increased (16.4% vs. 12.8%), AST increased (14.6% vs. 11.3%), hyperbilirubinaemia (2.8% vs. 0.5%), hepatic enzyme increased (1.2% vs. 0.3%), and blood alkaline phosphatase increased (0.3% vs. 1.2%).

Deaths within 30 days of last dose were similar between arms, 6.7% vs. 6.1%. Marginally more serious adverse events were reported in the AA-P group vs. placebo, 27.6% vs. 24.3%.

Adverse events leading to dose reduction or interruption were reported for 32.2% of subjects in the AA-P group and 17.4% of subjects in the placebo group. The reported AEs leading to dose reduction or interruption are well known events and listed in section 4.4 of the SmPC. More subjects in the placebo group discontinued treatment, 81.4% (61.3% for disease progression) vs. 57.0% (35.0% for disease progression).

3.5. Uncertainties and limitations about unfavourable effects

There are no uncertainties and limitations about unfavourable effects.

3.6. Effects Table

Table 30 - Effects Table for Zytiga in the treatment of newly diagnosed mHNPC patients with at least 2 high-risk prognostic factors (data cut-off: 31 October 2016).

Effect	Short Description	Unit	Abiraterone plus prednisone (plus SOC)	Placebo (plus SOC)	Uncertainties/ Strength of evidence	References
Favourable Effects						
rPFS	rPFS investigator-assessed per PCWG2 or RECIST 1.1 Co-primary	month (95%CI)	33.02 (29.57, NE)	14.78 (14.69, 18.27)	Main analysis with 49.5% of events	
OS	Co-primary	month	NE (NE, NE)	34.73 (33.05, NE)	1st IA with 33.9% of events HR (95% CI): 0.621 (0.509, 0.756)	
Time to chemotherapy	Secondary		NE (NE, NE)	38.9 (33.4, NE)	HR (95% CI): 0.443 (0.349, 0.561)	
Time to subs therapy			NE (37.9, NE)	21.6 (18.8, 23.6)	HR (95% CI): 0.415 (0.346, 0.497)	
Time to Pain progression			NE (36.5, NE)	16.6 (11.1, 24.0)	HR (95% CI): 0.695 (0.583, 0.829)	
Time to SRE			NE (NE, NE)	NE (NE, NE)	HR (95% CI): 0.703 (0.539, 0.916)	
Time to PSA pregression			33.2 (27.6, NE)	7.4 (7.2, 9.2)	HR (95% CI):.299 (0.255, 0.352)	
Unfavourable Effects						
TEAEs	overall incidence	%	93,5 %	92,5 %		
G3-4 TEAEs	Incidence	%	62,6 %	47,7 %		
Serious TEAEs	Incidence	%	27,6 %	24,3 %		

TEAEs leading to discontinuation TEAEs leading to death	idem	% % %	12,2 % 4.7%	10,1 % 4.0%		
Hypertension		%	36,7 %	22,1 %		
hypokalemia			20,4 %	3,7 %		
ALT increase/ AST increase		%	16.4 % / 14.6%	12.8% / 11.3%		
Cardiac disorders		%	12,4 %	7,8 %		

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Abiraterone acetate plus prednisone as add-on therapy to standard ADT has shown a clinically relevant increase in terms of rPFS. Although results are rather immature, OS data shows an early marked result in favour of AA-P. These results are consistently supported by favourable results in terms of main secondary endpoints which are considered to indirectly reflect the quality of life of patients.

Even though results are considered *per se* compelling to conclude about superiority of AA-P vs. ADT alone in the proposed target population of mHNPC patients with high-risk characteristics, some uncertainties mainly related to the ADT comparator arm, which is not considered the only alternative for all mHNPC patients, as well as the premature unblinding of trial preclude from definitive concluding about the place in therapeutic of AA-P.

Acknowledging the limitations of cross trial comparison, the beneficial effects of abiraterone + prednisone + ADT observed in the PCR3011 study appear to be at least as effective as the current docetaxel + ADT combination standard of care with the added patient advantage of abiraterone acetate being an oral formulation,. Importantly, for an application based on a single pivotal study, the beneficial results seen in the PCR3011 study have recently been replicated in the STAMPEDE study.

Updated OS data with longer follow-up is expected to be provided, however this will not totally clarify the question whether it is better to challenge the mPC with AA-P at an early stage or whether on the contrary, it is better to delay AA-P administration to the castration-resistant setting. Despite the uncertainties about the right sequence, there is no doubt that abiraterone plus prednisone can prolong the survival in patients with mCRPC, as previously shown in other studies. In summary, abiraterone plus prednisone treatment appears to offer a valuable option for patients newly diagnosed with high risk

metastatic hormone sensitive prostate cancer (mHSPC) delaying the progression disease and likely increasing the life expectancy.

Updated PFS2 data is expected to be submitted by the company at the time of the second IA on OS. Additionally, exploratory data from biomarker analysis is expected to be provided by the company as soon as available (see letter of recommendations).

The safety profile of abiraterone plus prednisone is well characterised. In this new setting, no new unexpected events have been reported. The overall safety profile of abiraterone plus prednisone in the treatment of adult men with newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) and in combination with androgen deprivation therapy (ADT) is consistent with that known in the already authorized conditions for use. Concomitant medications and the underlying condition may explain an important portion of the observed AEs. Although it cannot be excluded that a lower dose of prednisone did not impact the incidence of hypertension in the pivotal study, adverse events (including hypertension) were generally manageable and the benefits outweigh the risks for the claimed indication.

Overall, the safety profile is considered manageable and well tolerated, based on the frequencies of SAEs, AE leading to treatment discontinuation and AES leading to death, with no major differences over placebo.

3.7.2. Balance of benefits and risks

Results from trial PCR3011 showed a clinically relevant and significant advantage for patients with mHNPC whereas the safety profile of abiraterone acetate plus prednisone remains manageable and consistent with the already authorised conditions of use. Considering all favourable and unfavourable effects, the benefit-risk balance is considered positive.

3.8. Conclusions

The overall B/R of ZYTIGA plus prednisone or prednisolone for the treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT) is positive.

4. Recommendations

Outcome

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

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include treatment of newly diagnosed high risk metastatic hormone sensitive prostate cancer (mHSCP) in adult men in combination with androgen deprivation therapy (ADT) for Zytiga plus prednisone or prednisolone; as a consequence, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC are

updated. The Package Leaflet is updated in accordance. The Risk Management Plan was updated in the light of the data submitted (version 14.2). In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).