23 February 2023
EMA/126335/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Akeega

International non-proprietary name: niraparib / abiraterone acetate

Procedure No. EMEA/H/C/005932/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

AA	abiraterone acetate
AAP	abiraterone acetate plus prednisone or prednisolone
ACTH	adrenocorticotrophic hormone
ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AML	acute myeloid leukemia
API	Active pharmaceutical ingredient
AR	Assessment report
AR	androgen receptor
AST	aspartate aminotransferase
ATM	ataxia telangiectasia mutated gene
AUC	area under the plasma concentration-time curve
AUC0-24h	AUC from time 0 to 24 hours
AUC0-24h,ss	AUC from time 0 to 24 hours at steady state
AUC0-8h	AUC from time 0 to 8 hours
AUC0-∞	AUC from time 0 to infinity
AUClast	AUC from time 0 to infinity
BA	bioavailability
BCF	bioconcentration factor
BCRP	Breast Cancer Resistance Protein
BCS	Biopharmaceutics classification system
BCS	biopharmaceutical classification system
BE	bioequivalence
BICR	blinded independent central review
BID	bis in die, twice a day
BPI-SF	Brief Pain Inventory-Short Form
BRCA	breast cancer gene (BRCA1 or 2)
BRCA1mut	mutated breast cancer gene 1
BRIP1	BRCA1 interacting protein C terminal helicase 1
BSEP	Bile Salt Export Pump
CAS	Chemical Abstract Service
Cavg	average drug concentration
CC50	cell growth by 50%
CCO	clinical cutoff
CDK12	cyclin-dependent kinase 12
CE	carboxylesterase
CFU	colony-forming-unit
CFU-GM	colony-forming-unit haematopoietic
CFU-MK	colony-forming-unit megakaryocyte
CHEK2	checkpoint kinase 2
CI	confidence interval
CIPC	Critical in-process controls

CL/F	apparent oral clearance
Cmax	maximum plasma concentration
Cmax,ss	maximum plasma concentration at steady state
CoA	Certificate of analysis
COVID-19	Coronavirus Disease-2019
CPP	Critical process parameter
CQA	Critical quality attribute
CRCL	creatinine clearance
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
Ctrough	plasma concentration at the end of a dosing interval
Ctrough,ss	plasma concentration at the end of a dosing interval at steady state
CV	coefficient of variation
CYP	cytochrome
CYP17	17 α-hydroxylase/C17,20-lyase
D1	duration of zero-order drug release
DAT	Dopamine Transporter
DDI	drug-drug interaction
DDR	DNA damage repair
DHEA	dehydroepiandrosterone
DLT	dose-limiting toxicities
DMSO	Dimethylsulfoxide
DNA	deoxyribonucleic acid
DRD	DNA-repair gene defects
DSB	double-strand break
DSC	differential scanning calorimetry
DT	dissipation time
EBRT	external beam radiation therapy
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eDISH	evaluation of Drug Induced Serious Hepatotoxicity
EMA	European Medicines Agency
E-R	exposure-response
ERA	Environmental Risk Assessment
ESRD	end-stage renal disease
eTMF	electronic trial master file
EU	European Union
F1	apparent oral bioavailability
FACT-P	Functional Assessment of Cancer Therapy-Prostate questionnaire
FANCA	Fanconi anemia complementation group A
FDC	fixed-dose combination
FDC	niraparib/abiraterone acetate fixed-dose combination
FDC+P	niraparib/abiraterone acetate fixed-dose combination plus prednisone
FOIA	Freedom of Information Act
Fpen	percentage of market penetration

FT-IR	Fourier-transform infrared spectroscopy
GC	gas chromatography
GCP	good clinical practices
GLP	good laboratory practices
GMP	good manufacturing practices
GMR	geometric mean ratio
GnRH	gonadotropin-releasing hormone
HDAC2	histone deacetylase 2
hERG	human ether-à-go-go-related gene
HGSOC	High Serous Ovarian Cancer
HPLC	High-performance liquid chromatography
HR	hazard ratio
HRQoL	health-related quality of life
HRR	homologous recombination repair
ICH	International Council for Harmonisation
ICP-MS	Inductively-coupled plasma mass spectrometry
ICP-OES	Inductively-coupled plasma optical emission spectrometry
ILS	Increased Life Span
INN	International Non-proprietary name
IPC	In process control
IR	Infrared spectroscopy
ISS	Integrated Safety Summary
ITT	intent-to-treat
IV	IV intravenous
IWRS	interactive web response system
KA	first-order absorption rate constant
KM	Kaplan-Meier
Koc	adsorption/desorption coefficient based on organic carbon content
Kow	partition coefficient octanol/water (= Pow)
LC-MS	liquid chromatography–mass spectrometry
LC-MS/MS	liquid chromatography tandem mass spectrometry
LH	luteinizing hormone
LLOQ	lower limit of quantification
LOQ	(1) limit of quantification, (2) list of questions
LS	low strength
M1	niraparib major metabolite
M10	niraparib glucuronide metabolite
MAAs	manufacturing authorisation applications
MACE	major adverse cardiovascular events
MAH	Marketing Authorization Holder
MATE	multidrug and toxin extrusion protein
mCRPC	metastatic castration-resistant prostate cancer
mCSPC	metastatic castration-sensitive prostate cancer
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic hormone sensitive prostate cancer
MTD	maximum tolerated dose
NET	norepinephrine transporter

nira+AAP	niraparib + abiraterone acetate plus prednisone
NMR	1H nuclear magnetic resonance spectroscopy
NMT	not more than
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NONMEM	nonlinear mixed-effects modeling
NSCLC	non-small cell lung cancer
OAT	organic anion transporter
OATP1B1	organic anion transporting polypeptide 1B1
OCT	organic cation transporter
OECD	Organization for Economic Co-operation and Development
ORR	objective response rate
OS	overall survival
PALB2	partner and localizer of BRCA2
PARPi	poly (adenosine diphosphate-ribose) polymerase inhibitor
PBMC	peripheral blood mononuclear cells
PBO	placebo
PBT	Persistence, Bioaccumulation and Toxicity
PD	pharmacodynamic(s)
PDX	patient-derived xenograft
PE	polyethylene
PEC	predicted environmental concentration
P-gp	P-glycoprotein
PK	pharmacokinetics
PNEC	predicted no effect concentration
PopPK	population PK
PRES	posterior reversible encephalopathy syndrome
PRO	patient-reported outcome(s)
PSA	prostate specific antigen
PSD	particle size distribution
PVC	polyvinyl chloride
PVdC	polyvinylidene chloride
Q	quartile
QC	quality control
QD	once daily
QP	Qualified Person
QT	time from ECG Q wave to the end of the T wave corresponding to electrical systole
QTc	corrected QT
QTcF	QT interval corrected with Fridericia’s formula
QTPP	quality target product profile
RBC	red blood cells
RH	relative humidity
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
RRT	relative retention time
RS	regular strength
SAC	single-agent combination
SAE	serious adverse event

SAP	statistical analysis plan
SCE	summary of clinical efficacy
SCS	summary of clinical safety
SD	standard deviation
SLS	sodium lauryl sulfate
SmPC	Summary of Product Characteristics
SOC	system organ class
SSB	single-strand binding
t1/2	terminal elimination half-life
TANK-1	tankyrase-1 (or PARP5a)
TCC	time to initiation of cytotoxic chemotherapy
TEAE	treatment-emergent adverse event
TGI	tumour growth inhibition
tmax	time to reach the maximum plasma concentration
TPSA	time to PSA progression
TSE	transmissible spongiform encephalopathies
TSP	time to symptomatic progression
TTC	threshold of toxicological concern
UGT	uridine 5'-diphospho-glucuronosyltransferase
ULN	upper limit of normal
USPI	United States prescribing information
UV	ultraviolet
VCaP	vertebral cancer of the prostate
Vd/F	apparent volume of distribution
vPARP	vault PARP (or PARP4)
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Janssen-Cilag International N.V. submitted on 28 April 2022 an application for marketing authorisation to the European Medicines Agency (EMA) for AKEEGA, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 20 May 2021.

The applicant applied for a fixed-dose combination (FDC) of niraparib plus abiraterone acetate in combination with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who are positive for homologous recombination repair (HRR) gene alterations (germline and/or somatic).

Legal basis

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for new fixed combination products.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0244/2020 on the granting of a (product-specific) waiver.

Similarity

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

Applicant's request for consideration

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004. The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the fact that despite the positive results of the pivotal Phase 3 study (MAGNITUDE), in which a statistically significant gain in radiographic progression free survival (rPFS) was observed in the randomized patient population, it was unclear that the proposed combination of niraparib + abiraterone would address an unmet need in the applied indication. Granting accelerated assessment was therefore not considered justified.

Scientific advice

The applicant did seek scientific advice from the CHMP on:

- 26 July 2018 (EMEA/H/SA/3872/1/2018/HTA/II) regarding the development of niraparib in combination with AAP as a treatment for prostate cancer and the design of the pivotal Phase 3 study (64091742PCR3001).
- 27 February 2020 (EMEA/H/SA/4392/1/2020/III) regarding the following quality and clinical aspects:
  - The proposed Phase 1 open-label, multicenter, randomised, and sequential design BE/BA study (study 67652000PCR1001): the overall 2-stage design to demonstrate BE between the regular-strength FDC and single agents to support MAA; the use of testosterone as a supplemental pharmacodynamic endpoint to support bioequivalence; the proposed statistical assumptions and approach to demonstrate BE; the overall design of the single parallel group study with a low-strength formulation to support an MAA for the low-strength FDC.
  - The requirement for stand-alone food-effect studies for the FDC.
- 20 May 2021 (EMA/SA/0000056554) regarding the proposed approach and method for dissolution testing of both drug substances.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Blanca Garcia-Ochoa Co-Rapporteur: Ingrid Wang

The application was received by the EMA on	28 April 2022
The procedure started on	19 May 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	10 August 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	22 August 2022
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	15 September 2022
The applicant submitted the responses to the CHMP consolidated List of Questions on	16 October 2022
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 November 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	01 December 2022
The CHMP agreed on a list of outstanding issues <in writing and/or in an oral explanation> to be sent to the applicant on	15 December 2022

The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 January 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	16 February 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to AKEEGA on	23 February 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The Applicant applied for a fixed-dose combination (FDC) of niraparib plus abiraterone acetate for the treatment, in combination with prednisone or prednisolone, of adult patients with metastatic castration-resistant prostate cancer (mCRPC) who are positive for homologous recombination repair (HRR) gene alterations (germline and/or somatic).

The finally agreed indication for Akeega is, in combination with prednisone or prednisolone, for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations in whom chemotherapy is not clinically indicated.

2.1.2. Epidemiology and risk factors

Worldwide, prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men, accounting for 1.4 million new cancer cases and 375,304 cancer deaths in 2020 (IARC 2020). In Europe, prostate cancer is the most common cancer in men, with 473,344 new cases, representing 20.2% of all cancers in men, and 108,088 (10%) of cancer deaths in 2020 (IARC 2020).

The incidence of prostate cancer correlates with age, with the average age at the time of diagnosis being 66 years (Rawla 2019). Of note, prostate cancer is more common in Black men compared with White or Hispanic men.

The main prostate cancer risk factors are advanced age, ethnicity, genetic factors and family history. Other factors that have been associated with prostate cancer include diet, obesity and physical inactivity.

2.1.3. Biologic features

The oncogenesis of prostate cancer is associated with complex interactions between inherent germline susceptibility, acquired somatic gene alterations, and microenvironmental and macroenvironmental factors (Sandhu 2021).

DNA damage response (DDR) genes have a key role in prostate cancer. The estimated prevalence of inherited DDR mutations in men with metastatic prostate cancer is approximately 12%, and these mutations are most commonly in BRCA1, BRCA2, ATM, CHEK2, RAD51D, and PALB2 (Pritchard 2016) Prostate cancers arising in patients with germline BRCA2 mutations often have more aggressive clinicopathological features and worse clinical outcomes (Castro et al 2013). However, the prognostic value of other germline mutations in DDR genes is not currently known. Somatic aberrations in DDR genes (most frequently, BRCA2, ATM, BRCA1, CHEK2, CDK12, and PALB2) occur in approximately 23% of metastatic prostate cancers (Robinson 2015). Mutations in the BRCA (BRCA1 and/or BRCA2) are the most prevalent homologous recombination repair (HRR) gene mutations in mCRPC (with BRCA2 more prevalent than BRCA1) with ATM the second most frequently mutated gene in mCRPC (Robinson 2015).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

At the time of diagnosis, the majority of patients have localised disease. Patients diagnosed at an early stage are amenable to curative therapy, however advanced stages are life-threatening. Patients who present with metastatic disease at initial presentation typically have cancers with a more aggressive biology and have a shorter overall survival compared with patients who develop metastatic recurrence years after the initial diagnosis of primary prostate cancer. For patients diagnosed with metastatic disease, the 5-year survival rate is 30% (American Cancer Society 2021, Siegel 2021).

Metastatic castration resistant prostate cancer is predominantly characterised by bone pain, fatigue, and urinary dysfunction (Gater 2011). Bone is the predominant site of disseminated prostate cancer, and pain is the most common manifestation of bone metastases. Around 90% of patients with mCRPC have bone metastases, which leads to significant morbidity, including pain and skeletal-related events such as spinal cord compression and pathological fractures, which require interventions such as bone surgery or radiation therapy.

2.1.5. Management

Prostate cancers are dependent on androgen-mediated signalling for their growth and survival. Thus, for many decades, initial treatment for metastatic prostate cancer has been surgical castration by bilateral orchiectomy or chemical castration with androgen deprivation therapy [ADT] (Crawford 1989, Eisenberger 1998, Sharifi 2010). Of note, androgen pathway inhibitors (i.e., abiraterone, enzalutamide or apalutamide) and docetaxel, in combination with ADT, have shown to be beneficial in this context. However, even if there is an initial benefit with ADT, resistance to ADT, inevitably occurs.

Treatment options for patients with mCRPC include abiraterone acetate (plus prednisone or prednisolone) and enzalutamide for chemotherapy naïve patients who are asymptomatic or mildly symptomatic and in whom chemotherapy is not yet clinically indicated (ESMO 2020; NCCN 2022). For symptomatic patients or patients with signs of rapid progression or visceral metastases despite lack of symptoms, initial use of docetaxel may be preferred. The radionuclide radium-223 may be used in patients with bone-predominant symptomatic metastatic CRPC.

Patients with HRR gene alterations who have not received therapy for mCRPC (first line treatment for mCRPC) are currently managed in the same manner as other patients with mCRPC who do not harbour an HRR alteration. The PARP pathway has been identified as a potential drug target in prostate cancers that have HRR gene alterations. In this context, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors represent a novel, targeted therapeutic approach toward the treatment of men with prostate cancer and HRR gene alterations.

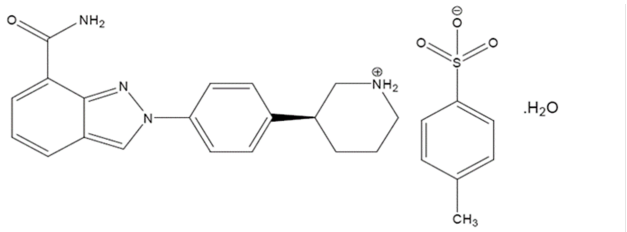
Recently, two PARP inhibitors, olaparib and rucaparib, were approved for the treatment of men with mCRPC. Olaparib is approved for the treatment of mCRPC in patients with deleterious HRR mutations (US) or BRCA mutations (EU) who had progressed after prior treatment with enzalutamide or AAP and in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated. Rucaparib is approved, only in the US, for mCRPC patients with deleterious BRCA mutation who had received previous treatment with an AR-targeted therapy and a taxane-based chemotherapy.

2.2. About the product

Akeega is a **fixed-dose combination** (FDC) of the individual drug substances niraparib and abiraterone acetate as film-coated tablets.

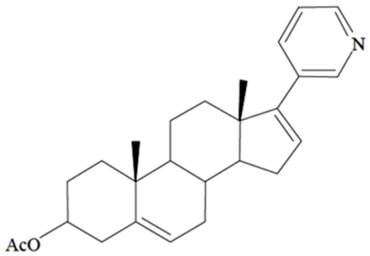
Niraparib is an orally available, highly selective PARPi, with activity against PARP-1 and PARP-2 DNA-repair polymerases. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death.

In the EU niraparib (Zejula) is approved as monotherapy for (1) the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response to platinum-based chemotherapy; and for (2) the maintenance treatment of adult patients with advanced epithelial (International Federation of Gynecology and Obstetrics [FIGO] Stages III and IV) high grade ovarian, fallopian tube or primary peritoneal cancer who are in response following completion of first-line platinum-based chemotherapy.



Abiraterone acetate is a prodrug of 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.

In the EU abiraterone acetate (Zytiga) is approved with prednisone or prednisolone for (1) the treatment of newly diagnosed high risk metastatic hormone-sensitive prostate cancer (mHSPC) in adult men in combination with androgen deprivation therapy (ADT); (2) the treatment of mCRPC in adult men who are asymptomatic or mildly symptomatic after failure of ADT in whom chemotherapy is not yet clinically indicated; and (3) the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel based chemotherapy regimen.



The FDC is formulated in two strengths:

- 100 mg/500 mg film-coated tablets ('regular-strength'). Each film-coated tablet contains 100 mg of niraparib (as tosylate monohydrate) and 500 mg of abiraterone acetate.
- 50 mg/500 mg film-coated tablets ('low-strength'). Each film-coated tablet contains 50 mg of niraparib (as tosylate monohydrate) and 500 mg of abiraterone acetate.

Initially claimed indication and recommendation for use:

Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with prostate cancer, who have progressed to metastatic castration resistant prostate cancer (mCRPC), and are positive for homologous recombination repair (HRR) gene alterations (germline and/or somatic).

The recommended starting dose of Akeega is 200 mg/1,000 mg (two 100 mg niraparib/500 mg abiraterone acetate tablets), as a single daily dose at approximately the same time every day.

Akeega is used with 10 mg prednisone or prednisolone daily.

Akeega is for oral use. The tablets must be taken as a single dose, once daily on an empty stomach. Akeega must be taken at least two hours after eating and food must not be eaten for at least one hour after taking Akeega.

2.3. Type of application and aspects on development

The prostate cancer clinical development program includes the following studies: 64091742PCR1001 (BEDIVERE), 64091742PCR2002 (QUEST), 64091742PCR2001 (GALAHAD), 64091742PCR3001 (MAGNITUDE), 67652000PCR3002 (AMPLITUDE), and 67652000PCR1001 (BA/BE Study), which are respectively referred to in this document.

The safety and efficacy of niraparib and abiraterone acetate plus prednisone are supported by the clinical studies conducted in the mCRPC population (MAGNITUDE, QUEST, BEDIVERE, the BA/BE Study, and GALAHAD), and are included in this submission.

The pivotal study to the proposed indication is study 64091742PCR3001 (MAGNITUDE), a Phase 3, randomised, placebo-controlled, multicenter, double-blind study to assess the efficacy and safety of niraparib in combination with abiraterone acetate plus prednisone (AAP) in men with mCRPC who previously received no prior treatment for mCRPC except for ≤4 months of AAP.

The applicant received Scientific advice from the CHMP on 26 July 2018, 27 February 2020 and 20 May 2021. For further information see section 1.1

A pre-submission meeting with the Rapporteurs was held on 10 January 2022.

2.4. Quality aspects

2.4.1. Introduction

The finished product is a fixed dose combination presented as film-coated tablets containing niraparib tosylate monohydrate equivalent to 50 or 100 mg niraparib and 500 mg of abiraterone acetate

Other ingredients are:

Tablet core (both strengths): colloidal anhydrous silica, crospovidone, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate.

Film-coating (100 mg / 500 mg strength): iron oxide red (E172), iron oxide yellow (E172), sodium lauryl sulfate, glycerol monocaprylocaprate, polyvinyl alcohol, talc, and titanium dioxide (E171)

Film-coating (50 mg / 500 mg strength): iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172), sodium lauryl sulfate, glycerol monocaprylocaprate, polyvinyl alcohol, talc, and titanium dioxide (E171)

The product is available in PVdC/PE/PVC foil blister with an aluminium push-through foil sealed inside a cardboard wallet as described in section 6.5 of the SmPC.

2.4.2. Active substance

The quality information for the active substances niraparib tosylate monohydrate and abiraterone acetate is mainly the same as the information provided in the previously approved marketing authorisation (MAs) for the mono-component products. The active substances information includes resubmission of data from the niraparib (Zejula) and abiraterone acetate (Zytiga) MAs. Changes to the active substances sections in the dossier compared to the active substance information in the previously approved mono-component MAs are highlighted in the dossier.

Niraparib tosylate monohydrate

General information

The chemical name of niraparib tosylate monohydrate is 2-[4-(3S)-3-piperidinylphenyl]-2H-indazole-7-carboxamide,4-methylbenzenesulfonate hydrate corresponding to the molecular formula $C_{26}H_{30}N_4O_5S$. It has a relative molecular mass of 510.61 and the following structure:

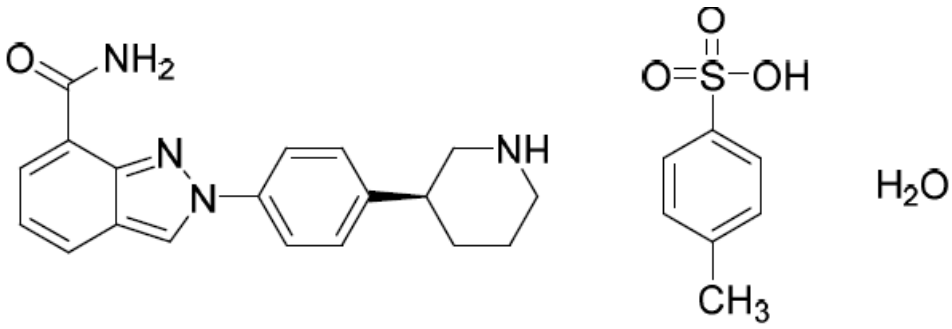


Figure 1: Niraparib tosylate monohydrate structure

The chemical structure was elucidated by a combination of nuclear magnetic resonance spectroscopy (NMR), liquid chromatography mass spectrometry (LC/MS), and single crystal X-ray crystallography with confirmatory data from elemental analysis, Fourier transform infra-red (FT-IR) spectroscopy, and ultraviolet (UV) spectroscopy The solid state properties of the active substance were measured by thermogravimetric-FTIR analysis (TGA-FTIR).

Niraparib exhibits stereoisomerism due to the presence of a single chiral centre. The stereochemistry originates and is controlled in the synthesis.

Niraparib tosylate monohydrate is a non-hygroscopic white to off white powder, highly soluble in aqueous media over the pH range from 1.2 – 6.8. It is classified as a class I compound according to the BCS.

Only one crystalline form is observed for niraparib tosylate monohydrate (designated as niraparib tosylate monohydrate Form 1.

Manufacture, characterisation and process controls

Niraparib tosylate monohydrate is manufactured by two manufacturing sites.

Niraparib tosylate monohydrate is synthesized in 6 main steps using two commercially available, well defined starting materials with acceptable specifications The manufacturing process is fully described and is in line with the currently approved process for the mono-component product (Zejula). 1Based on the results of the comprehensive process development program conducted and process purging studies, stages have been designated as critical steps in the niraparib commercial process. Stages of the commercial process were shown to have no critical process parameters (CPPs) or in-process controls/critical in-process controls (IPCs/CIPCs) and are not considered critical steps.

Genotoxic impurities may be generated from the proposed commercial process. The levels are well controlled by the process and it has been demonstrated that they are not a safety concern.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. There have been three slightly different variations of the same synthetic route to manufacture niraparib tosylate monohydrate active substance. The synthetic approaches for Processes I to III all employ the same carbon-carbon bond and carbon-hetero bond formation steps. The order of some chemical transformations has varied between processes, as has the selection of isolated intermediates. Changes introduced have been presented in sufficient detail and have been justified. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process. Active substance batches manufactured using Process III were used in clinical studies, as primary stability batches, and for commercial product.

The manufacturing process has been developed using a combination of traditional and enhanced approach to pharmaceutical development, in line with ICH Q11 Guideline. The early development work in establishing the commercial route for niraparib synthesis primarily used the traditional approach to screen and select reagents, solvents, catalysts, and reaction temperature, as well as to optimize the process for early stage production. When appropriate, an enhanced approach, such as the use of statistical design of experiment and one variable at a time (OVAT) studies has been conducted to understand the sensitivity of the process to various parameters and ensure that the process is robust across the defined normal operating ranges (NORs), proven acceptable ranges (PARs) and critical process parameters (CPPs). Although aspects of enhanced approach to pharmaceutical development have been used, no design space or regulatory flexibility is applied for.

The active substance is packaged in a low-density polyethylene (LDPE) inner liner in an LDPE outer bag. Both liner and bag are appropriately closed and placed in a closed plastic drum. The container closure system has been evaluated in ongoing stability studies under both accelerated (40 °C/75% RH) and long-term (25 °C/60% RH) storage conditions. The available stability data indicate that the container closure system is suitable to storage of niraparib tosylate monohydrate. All primary packaging material complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

The active substance specification includes tests for appearance (visual), identification (FT-IR, HPLC), identification of toluene sulfonic acid (HPLC), assay (HPLC), chromatographic purity (HPLC), chiral purity (Chiral HPLC), residual solvents (GC), water content (KF), elemental impurities (ICP-MS), particle size (laser diffraction), solid form (Ph. Eur.) and residue on ignition / sulfated ash (Ph. Eur.).

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (n=49 pilot and commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturers stored in the intended commercial package for up to 48 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, assay, individual and total impurities, water content, chiral impurity, particle size, and solid form. The analytical methods used were the same as for release and were stability indicating.

Samples from all active substance batches placed on stability at the long-term stability condition (25 °C/60% RH) and the accelerated stability condition (40 °C/75% RH) remained within the commercial acceptance criteria for attributes at all timepoints tested. No apparent change occurred for any attribute during up to 48 months of storage at the long-term condition or during up to 6 months of storage at the accelerated condition.

Photostability testing following the ICH guideline Q1B was performed on 2 batches. No detectable degradation was observed for niraparib tosylate monohydrate exposed to light stress conditions over the duration of the study.

Results as solid to heat, light and as solution to acid, base and hydrogen peroxide forced degradation conditions were provided. None of the impurities observed during the forced degradation studies have been shown to increase during the accelerated, intermediate and long-term stability studies, using the same stability indicating method. These studies demonstrate the stability indicating nature of the HPLC method.

The stability results indicate that the active substance manufactured by the proposed supplier(s) is sufficiently stable. The stability results justify the proposed retest period without storage conditions in the proposed container.

Abiraterone acetate

General information

The chemical name of abiraterone acetate is (3β)-17-(3-pyridinyl) androsta-5,16-dien-3-yl acetate corresponding to the molecular formula $C_{26}H_{33}NO_2$. It has a relative molecular weight of 391.55 and the following structure:

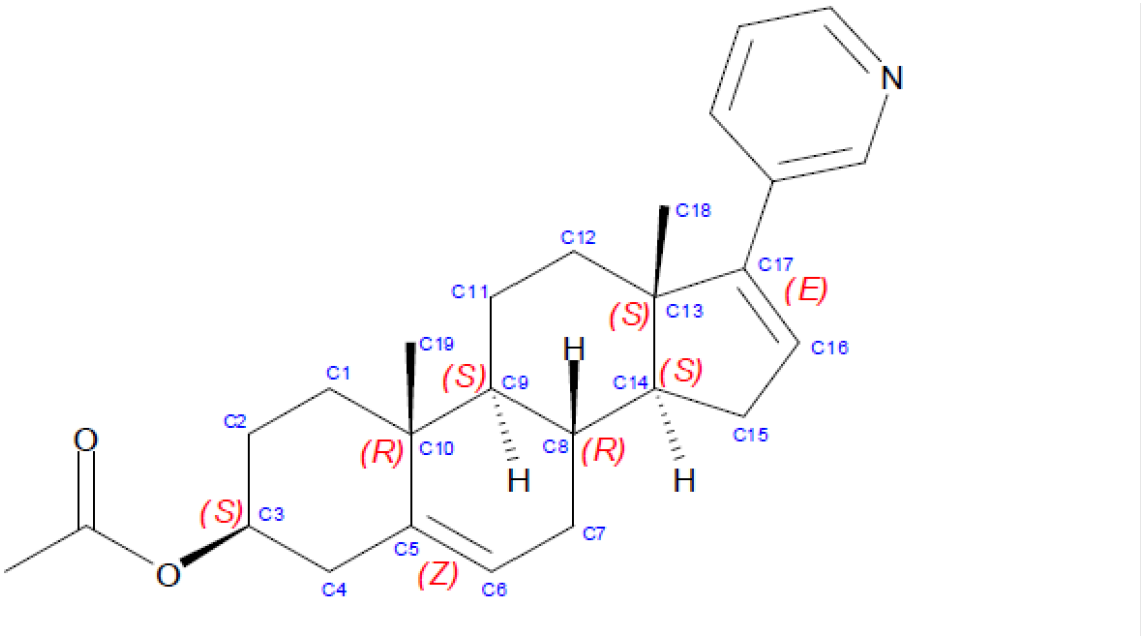


Figure 2: Abiraterone acetate structure

The chemical structure of *a*biraterone acetate was elucidated by a combination of high-resolution mass spectrometry (MS), elemental analysis, infrared (IR) spectroscopy, and nuclear magnetic resonance (NMR) spectroscopy. Ultraviolet (UV) spectroscopy data is added only to complement the spectral data set. Optical rotation is added to demonstrate the chirality of the compound.

Abiraterone acetate is a non-hygroscopic white to off-white powder practically insoluble in aqueous media over a wide range of pH values and very slightly soluble in 0.1 N HCl solution.

Abiraterone acetate exhibits stereoisomerism due to the presence of 6 chiral centers (3S, 8R, 9S, 10R, 13S, 14S) and 2 centers of geometrical isomerism (5Z and 16E). Abiraterone acetate is produced as a single enantiomer with its stereochemical elements introduced via the synthesis starting material acetate which is an enantiomerically pure material. The diastereomeric purity does not alter during the chemical synthesis.

Polymorphism has been observed for abiraterone acetate. The majority of polymorph screening experiments resulted in Form A.

Manufacture, characterisation and process controls

Abiraterone acetate is manufactured by one manufacturing site.

Abiraterone acetate is synthesized in 4 steps from one well defined starting material with acceptable specification. The critical steps and controls in the active substance manufacture have been identified taking into account critical quality attributes of the active substance and a pre-determined set of principles. Process steps 1 to 3 were identified as being critical in terms of the impact on the impurity

profile. The fate of the impurities has been extensively investigated using spiking studies and was supported with data from a large number of batches. Critical process parameters are adequately defined and justified.

2Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.
The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The active substance is packaged in an antistatic, low-density polyethylene (LDPE) bag that has been flushed with an inert gas and secured appropriately with a twist-tie or equivalent which complies with the EC directive 2002/72/EC and EC 10/2011 as amended.

Specification

Abiraterone acetate specification includes tests for appearance (visual), identification (IR), assay (HPLC), chromatographic purity (HPLC), residual solvents (GC), water content (KF), palladium (ICP-MS), residue on ignition / sulfated ash (Ph. Eur.), loss on drying (Ph. Eur.), and particle size (laser diffraction)

Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and (non-compendial methods) appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis data (n=28 pilot and commercial scale batches) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data from 3 commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package for up to 24 months under long term conditions (25 ºC / 75% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested*:* appearance, assay, water content and chromatographic purity. The analytical methods used were the same as for release and were stability indicating.

Available stability data indicate that abiraterone acetate remains stable during storage at the different storage conditions, when stored in the proposed container closure system. No stability related changes are observed in the assay values and no significant degradation is observed in any of the long-term storage and accelerated conditions.

Photostability testing following the ICH guideline Q1B was performed on 1 batch. No detectable degradation was observed for abiraterone acetate exposed to light stress conditions over the duration of the study.

A forced degradation study under extreme stress conditions was performed on the active substance in solution. The forced degradation study included testing the effects of photolysis, thermal oxidative, thermal acidic, neutral, and alkaline conditions on the active substance. In addition, the study was

conducted to demonstrate that the HPLC analytical purity method is stability indicating. The Stress In solution stability study shows that all major degradation products are separated from each other and none of them co-elute. The final HPLC test method is stability-indicating.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period without storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

Description of the product and Pharmaceutical development

The strength 100 mg/500 mg is presented as orange, oval, film-coated tablets (22 mm x 11 mm), debossed with "N 100 A" on one side, and plain on the other side.

The strength 50 mg/500 mg is presented as yellowish orange to yellowish brown, oval, film-coated tablets (22 mm x 11 mm), debossed with "N50 A" on one side, and plain on the other side.

The aim of the finished product development was to combine niraparib and abiraterone acetate in an oral fixed dose film-coated tablet that is bioequivalent to the combined administration of both commercially available single agent formulations i.e., niraparib 100 mg capsule and abiraterone acetate 250 mg uncoated tablet. The rationale to develop a fixed-dose combination (FDC) instead of using two single component finished products was to reduce the pill burden.

The physicochemical properties of the active substances that can influence the performance of the finished product and its manufacturability () are identified and discussed.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards except Opadry which complies with In house specifications. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

The granulation process were used as the starting point for the development of the FDC film-coated tablet.

To avoid potential dust formation and to differentiate tablet formulations by color, a film-coat was applied to the tablets.

The proposed QC dissolution method was optimized for medium pH, type and concentration of surfactant and the paddle rotation speed**.**Discriminatory power is sufficiently justified using batches with meaningful changes compared to the applied finished product: particle size distribution (PSD) of both active substances, tablet hardness, stability changes and film-coating weight gain.

Bioequivalence study was performed showing bioequivalence between the fixed-dose combination and the niraparib and abiraterone acetate co-administered as single agents at steady state under modified fasted conditions.

A Quality by Design (QbD) approach is followed for the manufacturing process development. Finished product quality target product profile (QTPP) and critical quality attributes (CQAs) are defined following ICH Q8 and with sufficient justification. A risk assessment is performed in order to establish critical process parameters (CPPs) and their ranges; the risk assessment is not detailed, but is assured to be in line with ICH Q9. Critical control points (CCPs) are defined as control limits or ranges for a CPP, a CMA of an active substance or excipient, or a critical in-process control (CIPC). However, design space is not claimed by the applicant.

The primary packaging is PVdC/PE/PVC foil blister with an aluminum push-through foil. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The finished product is manufactured by one manufacturing site.The finished product is manufactured using granulation of the niraparib tosylate monohydrate and abiraterone acetate as active substances, followed by blending with the extragranular excipients, compression, and film-coating

The manufacturing process consists of 10 main steps: preparation of binder solution, preblending, granulation and drying, screening, initial blending, final blending, compression, preparation coating suspension, film coating and packaging.

3

Process validation data are not provided. However, since the manufacturing process is standard according to the Annex II of the Guideline on process validation, this can be accepted. A process validation scheme on three consecutive batches and according to the Annex I of this guideline has been presented for each strength. The in-process controls are adequate for this pharmaceutical form.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: appearance (visual), identification active substances (HPLC, UV), assay active substances (HPLC), chromatography purity (HPLC), uniformity of dosage units (HPLC), dissolution of the active substances (Ph. Eur.), microbial purity (Ph. Eur.).

Taking into account the toxicologically qualified status, the acceptance criterion in the commercial niraparib tosylate monohydrate, and the limited release and stability data that are currently available, the proposed acceptance criterion is considered appropriate and adequately justified.

Taking into account acceptance criteria for the impurities in the commercial active substance abiraterone acetate, the toxicological qualification levels, and the limited release and stability data that are currently available, the proposed acceptance criteria for these impurities are considered appropriate and adequately justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data using a validated ICP-MS method was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for testing has been presented.

Batch analysis results are provided for a number pilot and commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data from 3 commercial scale batches per strength of the finished product stored for up to 6 months under 5 ºC, for up to 18 months under long term conditions (25 ºC / 60% RH and 30 ºC/75%), for up to 6 months under accelerated conditions (40 ºC / 75% RH) and for up 6 months under stress conditions (50 ºC) according to the ICH guidelines were provided. The batches of the finished product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for appearance, assay, chromatographic purity, dissolution, water content, and microbial purity. The analytical procedures used are stability indicating.

No substantial stability related changes were observed during storage of the drug product at the different storage conditions. All results are well within specification. The currently available stability data indicate that the finished product is chemically and physically stable under light ICH conditions, for at least 6 months at 5 ºC, for at least 18 months at 25 °C/60% RH and 30 ºC/75% RH, for at least 6 months at 40 ºC/75% RH, and for at least 3 months at 50 ºC upon storage in the proposed commercial packaging.

Forced degradation studies under extreme stress conditions were performed to test the effects of thermal acidic, thermal alkaline oxidative, neutral, dry heat, humid heat, and metal ions conditions on the finished product in solution, as well as the effect of light on the solid finished product as per ICH Q1B Guideline. These studies were also conducted to demonstrate that the finished product UHPLC chromatographic purity methods are stability indicating.

The finished product is stable under neutral, heat, heat/humidity and metal ions conditions. The finish product is prone to minor degradation under oxidative conditions and when exposed to light at ICH conditions. The finished product is unstable under acidic and alkaline conditions.

In conclusion, the UHPLC test methods are specific and stability indicating and are suitable for analysis of stability samples.

Based on available stability data, the proposed shelf-life of 30 months without storage conditions as stated in the SmPC (section 6.3) are acceptable.

Adventitious agents

It is confirmed that the lactose is produced from milk from healthy animals in the same condition as those used to collect milk for human consumption and that the lactose has been prepared without the use of ruminant material other than calf rennet according to the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents Via Human and veterinary medicinal products.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

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

The applicant has applied QbD principles in the development of the active substances and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendations for future quality development

Not applicable

2.5. Non-clinical aspects

2.5.1. Introduction

The combination of niraparib/abiraterone acetate (AA) is presented as a fixed-dose combination (200 mg/1000 mg, respectively), in which the monotherapies have been previously characterized in their original MAA (EMEA/H/C/004249 and EMEA/H/C002321).

From a non-clinical point of view, the Applicant based the development of this FDC on the preclinical data generated for the monocomponents. In line with ICH S9 guidance, only two additional nonclinical pharmacology studies were conducted with the combination.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Primary pharmacodynamics of niraparib from approved package showed the inhibition of PARP-1 and PARP-2 in the nanomolar range. In the case of abiraterone*, in vitro* studies showed the inhibition of CYP17αhydroxylase.

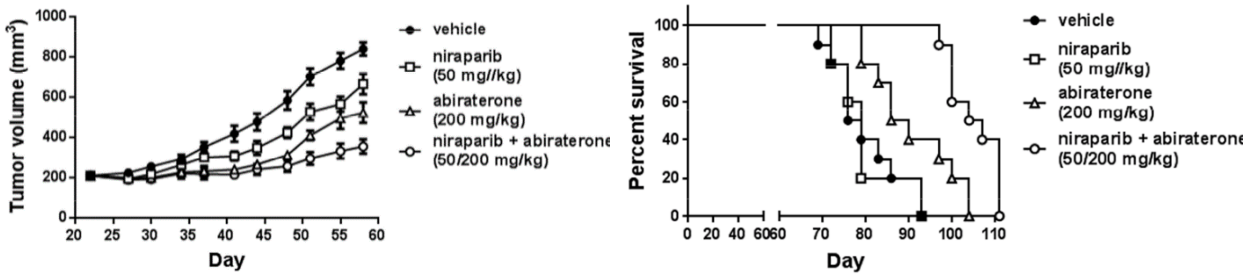
***In vivo* combination studies**

With regards to the combination of niraparib (PARP inhibitor) and abiraterone acetate (androgen biosynthesis inhibitor), the Applicant conducted two *in vivo* studies conducted in two xenograft tumor models (BRCA1/2 wild type VCaP and BRCA2 mutant LuCaP).

- Efficacy of Niraparib Alone or in Combination with Abiraterone Acetate in the VCaP Prostate Xenograft model in Mice

The anti-tumour efficacy of the combination (with AA) and niraparib alone was investigated in the BRCA2-wt VCaP xenograft model (DD18026 study). VCaP tumours harbour no known mutations in homologous recombination genes. The results of the study revealed that niraparib/AA combination inhibited tumour growth and increased survival compared with animals dosed either agent as monotherapy (Figure 3).

Figure 3. Effect of Niraparib and/or Abiraterone in Castrated Male Mice Bearing VCaP Tumours on Tumour Volume (left) and Survival (right)

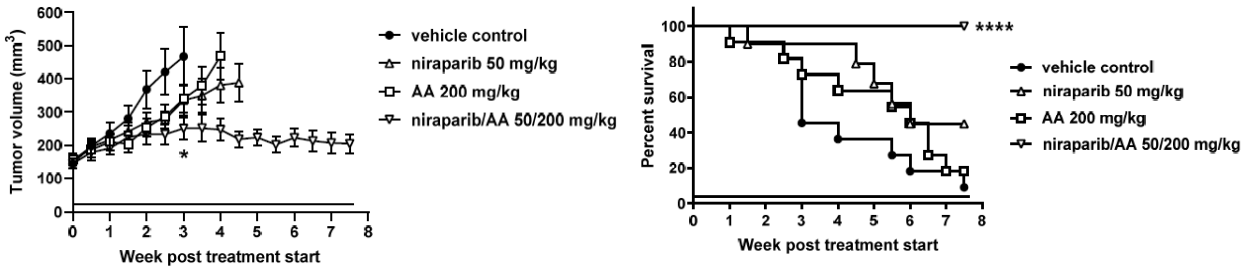


- Efficacy of Niraparib Monotherapy and Combination Treatment with Abiraterone Acetate in Mice Bearing BRCA2 Mutant Prostate Cancer Xenografts

The other *in vivo* study combination was conducted in the LuCaP 174.1 BRCA2-mutant PDX model (DD21076 study). Treatment with niraparib induced 89% TGI at Week 5, compared with the vehicle control group. At week 9.5, niraparib treatment resulted in sustained tumour regressions in 10 of 10 mice and induced at least 58% ILS and a significant increase in survival (p=0.0002) compared with the control group. This study demonstrates that in certain, highly sensitive BRCA2 deficient models, niraparib has potent single-agent anti-tumour efficacy.

In LuCaP 96 CR BRCA2-mutant PDX, niraparib and AA were tested alone or in combination. Over the course of the study, tumours in the vehicle control group grew progressively, more slowly in the niraparib or AA groups, and in the combination group remained static or decreased in volume (Figure 4, left). Survival after 7.5 weeks of treatment indicated that niraparib and AA treatments each induced an ILS of 100% compared with the control group. All 10 mice in the niraparib + AA treatment group survived to the end of the study, for an ILS of at least 150% and a significant increase in survival (p<0.0001) compared with the vehicle control group (Figure 4).

Figure 4. Effect of Niraparib, AA, or the Combination on the Growth of LuCaP 96CR BRCA2-mutant Tumours (left) and Survival (right)



2.5.2.2. Secondary pharmacodynamic studies

Secondary pharmacodynamic assays for niraparib as monotherapy have been previously analysed in the original dossier. Initial *in vitro* studies showed a potential action of niraparib on brain monoamines

(dopamine and norepinephrine). Follow-up studies revealed that niraparib did not occupy DAT in striatum (PET study) at relevant exposure levels. In a second in vivo study, niraparib did not exert a psychostimulant effect on mice. No secondary pharmacodynamics assays for abiraterone acetate were conducted, which is supported due to the selectivity and mechanism of action proposed.

Regarding the combination, no secondary pharmacodynamic studies were conducted, which is in line with ICH S9 and guideline on the non-clinical development of fixed-dose combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).

2.5.2.3. Safety pharmacology programme

Safety pharmacology studies were conducted separately, and no combination study was carried out. This is in line with guideline ICH S9. Summary of safety pharmacology for single agents is provided below.

Niraparib

In vitro cardiovascular safety

In a GLP-compliant hERG (human Ether-à-go-go-Related Gene) assay, (3000-09-004), hERG current inhibition was 11.0% at 3 µM, 37.9% at 10 µM, 69.3% at 30 µM, and 91.4% at 100 µM versus 0.78% using vehicle control. The IC50 for the inhibitory effect of niraparib tosylate monohydrate on hERG potassium current was 15.2 µM.

In vivo cardiovascular safety

In a non-GLP study in anesthetised dogs (TT-07-5300), niraparib (1, 3, or 10 mg/kg) increased the heart rate in a dose-dependent fashion (+5%, +9%, and +17%). A dose-independent increase (+16%, +21%, or 20%) in mean arterial pressure was observed from 1 mg/kg. There was no effect on QT/QTc, blood flow or PR up to and including the highest dose of 10 mg/kg (peak average plasma concentration measured during infusion in dogs was 15.3 µM).

In a GLP study in conscious telemeterized beagle dogs (3, 6, and 15 mg/kg of niraparib), no changes were noted in heart rate, pulse pressure, ECG parameters (PR, QRS, QT, and QTc intervals), or body temperature up to 24 hours post-dose. When adjusted for baseline, a statistically significant increase in blood pressure (mean arterial pressure, systolic pressure, and diastolic pressure) was noted in female dogs at 15 mg/kg. For male dogs, a statistically significant increase was observed only in systolic pressure at the interval of 4 to 5 hours post-dose.

In the 1-month and 3-month GLP toxicity studies in dogs, niraparib was administered at the highest doses of 15 and 12 mg/kg/day, respectively. No drug-related ECG abnormalities were observed.

Central Nervous System Safety

Niraparib (100 mg/kg single dose) had no effect in mice on neurological function, including general behaviour, neural reflexes, or spontaneous activity during the 24-h post-dose period and no effect on thermoregulation (TT-07-5362, non-GLP).

Single oral administration of niraparib at doses of 5, 10, and 30 mg/kg to male and female rats had no effect on any qualitative and quantitative FOB parameters up to 24 h post-dose (6901661, GLP).

Respiratory Safety

No niraparib-related (10, 50, and 100 mg/kg) effects were noted on any of the respiratory parameters (tidal volume, respiratory rate, and derived minute volume) up to 24 hours post-dose (6901248, GLP).

Abiraterone Acetate

In Vitro Cardiovascular Safety

Abiraterone inhibited the hERG potassium current at 10 and 27 µM by 2% and 6%, respectively. Due to this modest level of inhibition at the highest concentration, which was close to the limits of solubility for the compound, the IC50 for abiraterone could not be determined. Abiraterone acetate inhibited the hERG potassium current at 1.3, 3, 10 and 27 µM by 2, 10, 38 and 84%, respectively. The IC50 for the inhibitory effect of AA on hERG potassium current was 12.2 µM (071018.DPC).

In Vivo Cardiovascular Safety

The administration of AA at dose levels up to 2,000 mg/kg had no effect on the hemodynamic and the electrocardiographic intervals (RR, PR, QRS, QT and QTc) in male cynomolgus monkeys following a 24-h monitoring period. In addition, no overt arrhythmias/abnormalities were found on inspection of the ECG tracings over the 24-h recording period (692409, GLP).

Central Nervous System Safety

Behavioural assessment in rats (TOX9587, GLP) revealed a slight decrease in alertness and a decreased pinna reflex at 40 and 400 mg/kg. Peak observations were observed at 3 h post-dosing on Day 0 and absent at the 24-h post-dosing observation. In addition, a slight increase in incidence for reacting to touch escape was noticed at 400 mg/kg at 24 hours post-dosing. There were no neurologic or autonomic abnormalities and no signs of general toxicity. The observed behavioural changes noticed at 40 and 400 mg/kg were considered of minor clinical relevance.

Respiratory Safety

Lower tidal volume was observed in rats given 750 mg/kg but not in animals dosed at 2,000 mg/kg. No other significant changes in respiratory parameters were observed (8210847, GLP).

Gastric Irritation

There were no treatment-related effects in the gastrointestinal tract and the internal viscera in male mice administered AA at 800 mg/kg at gross observations (1632-1, GLP).

2.5.2.4. Pharmacodynamic drug interactions

The potential PD interactions are shown in the primary pharmacodynamics section (*in vivo* combination studies).

2.5.3. Pharmacokinetics

The non-clinical PK package presented for this procedure relied on the documentation previously assessed for the approval of the single agents. Assessment for the combination was made based on the review of metabolism, enzymes/transporters involved in the metabolism or disposition and *in vitro* drug-drug interaction potential of individual single agents.

The analytical methods for non-clinical study samples were previously assessed in the individual dossiers, in line with Guideline on bioanalytical methods validation (EMA/CHMP/EWP/192217/2009 Rev. 1 Corr. 2).

Consistent with guideline on non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005), the applicant has submitted non-clinical studies, ADME-related

parameters and data for mono-components of the FDC. These data were previously assessed in the original dossiers, and no further assessment is considered necessary.

2.5.4. Toxicology

The toxicological profile of the combination was based on the previous studies conducted with the individual components. In line with ICH S9 guidance, no combination toxicology studies is required for the proposed FDC. Previous findings are summarized below.

2.5.4.1. Single dose toxicity

No single dose studies were conducted with niraparib. No mortality was observed after single dose administration of abiraterone acetate in mice or rats up to 2000 mg/Kg or 400 mg/kg, respectively.

2.5.4.2. Repeat dose toxicity

Niraparib: the target organs of toxicity reported were bone marrow (hypocellularity, decrease of RBC, WBC and platelets) and testes (hypospermatogenesis considered as a pharmacological effect of PARP inhibition). They were observed in both rat and dog species, in a dose-dependent fashion and were reversible after a free-drug period. Other toxicological findings noted in rats were cardiac arterial hypertrophy and an increased amount of trabecula in the bone, without reversibility. NOAEL values were established at 10 mg/kg/day and 4.5 mg/kg/day for rats and dogs, respectively.

AA: the most significant findings were attributed to the interference of steroid metabolism (androgen biosynthesis inhibitor), producing toxicity in reproductive system, adrenal glands, liver, pituitary (rats only), and male mammary glands. Also, RBC parameter was affected in studies in mice and rats, with evidence of extramedullary haematopoiesis in the spleen in mice, although no microscopic changes were correlated in bone marrow. In this regard, haematological changes were also observed in monkeys. Liver of the nonclinical species was also affected in long-term toxicity studies, and the findings were not fully reversed after a 4-week recovery period. Similarly, cataracts were observed in chronic studies in rats (potential species-specific effect cannot be ruled out), which were not considered reversible.

Overlapping toxicities from the individual components were identified, namely effects on testes and RBC. In terms of interspecies comparison, safety margins of the FDC were presented on the base of the individual data for monotherapies.

2.5.4.3. Genotoxicity

Niraparib was not mutagenic in a bacterial reverse mutation assay (Ames) test but was clastogenic in an in vitro mammalian chromosomal aberration assay and in an in vivo rat bone marrow micronucleus assay. This clastogenicity is consistent with genomic instability resulting from the primary pharmacology of niraparib and indicates potential for genotoxicity in humans. AA and abiraterone was without genotoxic potential in a standard battery of studies.

2.5.4.4. Carcinogenicity

No carcinogenic studies were performed with niraparib.

A six-month carcinogenicity study in the transgenic (Tg.rasH2) mouse and a 2-year carcinogenicity study in rat were conducted with AA. These studies were submitted and assessed in a previous procedure for AA (EMEA/H/C/002321/II/0012). A brief summary of both studies is presented below.

In Tg.rasH2 mice (TOX10088), AA was administered orally (gavage) once daily for 6 months at 0 (vehicle), 125, 375 or 750 mg/kg/day (25/sex/group).Treatment of Tg.rasH2 mice with AA at daily oral doses up to 750 mg/kg for 6 months did not increase the incidence of neoplastic lesions.

In a 2-year carcinogenicity study in Crl:CD(SD) rats (TOX9619), AA was administered orally (gavage) once daily for 2 years (65/sex/group) at 0 (demineralized water), 0 (vehicle), 5, 15 or 50 mg/kg/day for male rats, and 0 (demineralized water), 0 (vehicle), 15, 50 or 150 mg/kg/day for female rats.

Histopathological examination revealed an increase in the incidence of testicular interstitial (Leydig) cell adenomas in all test article-treated male groups; in addition, two males given 50 mg/kg/day and one male given 15 mg/kg/day had testicular interstitial cell carcinomas.

Oral administration of AA to rats for 2 years was associated with an increase in the incidence of testicular interstitial (Leydig) cell adenomas in all treated male groups and with interstitial cell carcinomas in 1 and 2 rats at 15 and 50 mg/kg/day, respectively. These findings were a sequential response of the pharmacological action of the test article, which inhibits testosterone production, and are considered rat-specific as the interstitial cells of rats possess significantly higher number of LH receptors than humans (Alison 1994 and Clegg 1997). The occurrence of testicular tumours had no impact on overall survival in treated male groups. Overall survival was higher than vehicle control for all treated female groups and there was a concomitant dose-dependent reduction in the incidence of pituitary adenomas and mammary tumours.

2.5.4.5. Reproductive and developmental toxicity

No reproductive toxicology studies were performed with niraparib. Given the potential teratogenicity and foetal mortality because of its mechanism of action (inhibition of PARP-1 and PARP-2), the absence of these studies with niraparib is justified and in line with ICH S9.

In male rats, AA administration revealed effects on male fertility (reduced organ weights of the reproductive system, sperm counts, sperm motility, altered sperm morphology and decreased fertility), with reversibility observed after 16 weeks recovery. In female rats, AA caused increased incidence of irregular or extended estrous cycles and pre-implantation loss. No differences in mating, fertility, and litter parameters were observed. Effects were reversible after 4 weeks from the last AA administration. Findings in fertility are consistent with pharmacological activity (anti-androgenic effect).

In an embryo-foetal development study in rats, AA had adverse developmental effects on foetuses (increased post implantation loss and resorptions and decreased number of live foetuses; foetal developmental delay; decreased foetal body weight; and decreased foetal ano-genital distance).

In a non-GLP study in juvenile rats, AA findings were consistent with those observed in adult animals (histopathological changes in the liver, pituitary, ovaries, and the male reproductive tract of the juvenile rats). Sexual maturation was also affected in males. It is noted that the effects observed were attributed to the androgen inhibition.

2.5.4.6. Toxicokinetic data

2.5.4.7. Local Tolerance

No local tolerance (oral gavage) studies were conducted with niraparib. In the case of AA, no treatment-related effects were reported in the gastrointestinal tract after oral administration.

2.5.5. Other Toxicity studies

The major metabolites of niraparib and AA were identified in nonclinical species and can be considered as evaluated in the studies conducted. Information for qualified impurities was also included in the non-clinical part.

Additional toxicity studies were performed with the mono-components of the FDC. In the case of mechanistic assay, AA administration resulted in decreased testosterone levels and increased in LH levels, which are in line with the pharmacological activity of AA. Also, the potential phototoxicity of niraparib and AA were investigated, and the results indicated no evidence for cutaneous or ocular phototoxicity

2.5.6. Ecotoxicity/environmental risk assessment

Data of the single agents are presented below.

Table 1 Summary of main study results

Substance (INN/Invented Name): Niraparib/Zejula			
CAS-number (if available): 1038915-60-4			
PBT assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	-0.6 - 2.1	not B
	BCF		
Persistence	DT50 (at 12ºC)	$DT50_{water}$: 2.3-14 days $DT50_{sediment}$: 742-996 days >>180 days $DT50_{system}$: 329-478 days >>180 days	vP
Toxicity	NOEC (fish)	NOEC = 0.032 mg/L	not T
PBT-statement:	Niraparib is considered to be not PBT nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{SURFACEWATER,}$ refined	0.0645 (Fpen: 4.3/10,000)	µg/L	> 0.01 threshold: Y
PEC $_{SURFACEWATER,}$ default	1.5	µg/L	> 0.01 threshold: Y
Other concerns (e.g. chemical class)	-	–	N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	*Sludge:* KFoc 1,597-3,483 L/kg *Soil:* KFoc 34,073-173,972 L/kg	K_{OC} for sludge is below the trigger for Tier B assessment (>10,000 L/kg).

Ready Biodegradability Test	QSAR models of BIOWIN v4.10 of EpiSuite				Not readily biodegradable
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	*Schoonrewoerdsewiel*: DT50, water = 1.1 DT50, sediment = 349 DT50, whole system = 225 % shifting to sediment = 94-99% *Emperor Lake:* DT50, water = 6.5 DT50, sediment = 469 DT50, whole system = 155 % shifting to sediment = 75-91%			>10% shifting to sediment: Y A sediment toxicity test is triggered (Tier B).
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/ *Pseudokirchneriella subcapitata*	OECD 201	NOEC	1,000	µg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	320	µg/L	
Fish, Early Life Stage Toxicity Test/ *Pimephales promelas*	OECD 210	NOEC	32	µg/L	Lowest NOEC in long-term studies, used for PNEC calculations
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10 EC50	44,000 210,000	µg/L	
Phase IIb Studies					
Sediment dwelling organisms / *Chironomus riparius*	OECD 218	NOEC	3374	mg/kg dwt	
Derived PNEC values for Niraparib					
	NOEC	AF	PNEC		
$PNEC_{surfacewater}$	NOEC fish	10	3.2 µg/L		
$PNEC_{microorganism}$	NOEC respiration inhibition	10	3200 µg/L		
$PNEC_{groundwater}$	NOEC Daphnia reproduction test	10	32 µg/L		
$PNEC_{sediment}$	NOEC	100	33.7 mg/Kg DWT		

Substance (INN/Invented Name): Abiraterone acetate / Zytiga			
CAS-number (if available): 154229-19-3			
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	5.12	
	BCF	903 (for low conc, 0.13 µg/L) 931 (for high conc, 1.3 µg/L)	not B
Persistence	DT50 (at 12ºC)	$DT50_{water}$: 4.6 d $DT50_{soil}$: 38.2 d $DT50_{system}$: 7.0-10 d	not P
Toxicity	NOEC (fish)	NOEC = 0.000013mg/L	T
PBT-statement:	Abiraterone acetate is considered to be not PBT nor vPvB		
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)			(Y/N)

Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} > 22,387 kg/L (log K_{oc} > 4.35)	HPLC-method
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 (72h) EC_{50} (72h)	1000 > 1000	µg/L	*Pseudokirchneriella subcapitata*. NOEC value is the same for both measures of growth (biomass and growth rate)
Daphnia sp. Reproduction Test	OECD 211	NOEC	0.47	µg/L	21 days
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC	0.013	µg/L	*Pimphales promelas* (Fathead Minnow)
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} (3h)	> 10^6	µg/L	NOEC (3h) = 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	L/kg	%lipids: Percent lipids at steady state (wet weight tissue basis) low 3.46% and high 3.76 % Percent lipids at steady state (dry weight tissue basis) low 19.65 % and high 22.74 %
			903 (for low conc) 931 (for high conc)		With lipid normalisation of 5%
Aerobic and anaerobic transformation in soil	OECD 307	DT50 %CO_2	18 55.1%	Days	Evolution of $^{14}CO2$ (ultimate biodegradation) was 55.1% of the applied radioactivity accumulatively at Day 120. Metabolites identified were: [^{14}C]abiraterone

					and dehydrogenated [^{14}C]abiraterone. One soil (Sandy loam)
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 Sandy loam soil
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	100 for all species	mg/ kg	Bean *(Phaseolus vulgaris)* Oat *(Avena sativa)* Tomato *(Lycopersicon esculentum)*
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	>1000 500	mg/ kg	*Eisenia fetida* / 14 days
Collembola, Reproduction Test	ISO 11267	NOEC	1000 for mortality 500 for reproducti on	mg/ kg	*Folsomia candida* / 28 days
Sediment dwelling organism	OECD 218	NOEC	100	mg/ kg	*Chironomus riparius* / 28 days

2.5.7. Discussion on non-clinical aspects

This is a FDC of niraparib and AA in which individual components are already approved in the EU. The Applicant has designed the strategy for this MAA based on ICH S9, in which no additional studies with the combination are required.

In this context, the only new non-clinical studies submitted in the nonclinical part of the dossier have been two PD studies. Based on these studies the combination showed decreasing tumour volumes and increasing survival with the combination as compared with single-agent treatments in BRCA-related tumour models (BRCA1 and BRCA2 wild type VCaP and BRCA2 mutant LuCaP).

By referring to literature data and in vivo data showing effect of niraparib and other PARP inhibitors on HRD mutated, wt-BRCA models (not comprising prostate), it is suggested that niraparib may provide clinical benefit to prostate cancer patients with BRCA-1- and BRCA-2-mutation positive, and BRCA wild-type, HRD positive tumors. However, while additive effects of niraparib and abiraterone acetate were demonstrated in an animal model with BRCA2 mutation positive castrate resistant prostate tumours, no data have been presented supporting beneficial effect of the combination in castrate resistant tumour models harbouring other HR mutations than BRCA2. Thus, while the nonclinical data have demonstrated pharmacodynamic effects of niraparib and abiraterone on mCRPC with BRCA mutations, there are no nonclinical data supportive of effect on mCRPC with non-BRCA mutations.

It is noted that proposed dose levels of each component do not exceed the maximum approved dose levels given as monotherapy in clinical practice. Safety margins of the FDC were presented on the base of the individual data for monotherapies, which is considered adequate given the absence of potential interactions between the mono-components of the combination. No major clinical DDIs are expected between the two mono-components. Primary metabolic pathways involved in the metabolism of niraparib and AA are mediated by esterases with subsequent metabolism via phase II enzymatic pathways (glucuronidation or sulfate conjugation). For both drugs, CYPs pathways play a minimal role in the metabolic elimination and are unlikely to be induced or inhibited by major CYP DDIs. Drug transporter substrate and inhibition profiles suggests unlikely interaction between the two drugs.

Considering the mechanism of actions proposed for niraparib and AA (PARP inhibition and CYP17 inhibition), the combination niraparib/AA could affect fertility. This is also indicated by findings in animal studies where niraparib-related decreased spermatogenesis was observed in both rats and dogs, and AA reduced male fertility was observed in rats. This is adequately addressed in SmPC sections 4.6 and 5.3.

Considering that mono-components are well characterized, and given that both are approved in the EU, no further assessment has been considered necessary from a non-clinical point of view.

ERA

Niraparib is considered to be very persistent (vP), but it is considered to be a not-PBT and not-vPvB substance. The BCF values for abiraterone acetate have been revised and updated to 903 (low dose) and 931 (high dose), and Abiraterone Acetate is still considered to be a non-bioaccumulative substance.

Niraparib and Abiraterone DT50 Persistence values have been normalised to 12 ºC using Arrhenius Equation to reflect environmental temperatures in Europe. Niraparib final values of DT50 remain over the 180 days triggering threshold (according to REACH Annex XIII Criteria), so Niraparib is still considered to be a very persistent substance. Updated Abiraterone final values of DT50 remain below the corresponding triggering thresholds (40 days for water and total system and 120 days for soil compartment, according to REACH Annex XIII), so it is still considered to be a non-persistent substance.

For niraparib, a Phase I and Phase II Tier A-Tier B analysis (for toxicity study with sediment-dwelling organisms) was carried out and all risk quotients were below the threshold values.

Regarding abiraterone acetate, a Phase I and Phase II Tier A-Tier B were carried out. All risk quotients were under the triggering threshold except the surface water one, which was above 1 (8.23 µg/L).

Considering the above data, niraparib tosylate monohydrate and its metabolites are not considered to pose a risk for the environment, but abiraterone acetate and/or its metabolites may represent a risk to the organism population in aquatic environment, following prescribed usage in patients.

2.5.8. Conclusion on the non-clinical aspects

The non-clinical aspects of Akeega (niraparib/AA) have been summarised in this document.

Considering that mono-components are well characterized and given that both niraparib and abiraterone Acetate are approved in the EU, only two new PD studies were submitted in the nonclinical part of the dossier, and no further assessment is considered necessary from a non-clinical point of view. Overall, the nonclinical part of the dossier is considered approvable.

Based on the ERA, abiraterone acetate and/or its metabolites may represent a risk to the organism population in aquatic environment, therefore, abiraterone acetate should be used according to the current precautions stated in the SmPC to minimise any potential risks to the environment.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

As claimed by the Applicant, the clinical trials were performed in accordance with GCP. The Applicant has also 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**

Objective of Study	Study (Status)	Study Design	Study Population/Treatment Regimens	Subjects Treated or Planned
Studies included in the current submission				
Pivotal efficacy & safety of niraparib and AAP combination therapy; Primary ADR data	64091742PCR3001 MAGNITUDE (ongoing)	Phase 3, randomized, placebo-controlled, multicenter, double-blind study to assess the efficacy and safety of niraparib in combination with AAP in men with mCRPC who previously received no prior treatment for mCRPC except for ≤4 months of AAP Cohort 1 provides the pivotal efficacy and safety data for combination treatment with niraparib & AAP Cohort 3 will provide a description of the clinical experience with the FDC tablet	Cohort 1: subjects with HRR gene alterations Randomized to niraparib 200 mg and AAP (1,000 mg/10 mg) or placebo and AAP daily as SAC	423
			Cohort 2: subjects with no HRR gene alterations Randomized to niraparib 200 mg and AAP (1,000 mg/10 mg) or placebo and AAP daily as SAC	246[1]
			Cohort 3: subjects with HRR gene alterations Non-randomized, open-label treatment with niraparib/AA (200 mg/1,000 mg) as FDC tablet plus prednisone (10 mg) daily	95
Relative BA and supportive safety of the FDC and SAC of niraparib and AA	64091742PCR2002 QUEST[2] (ongoing)	Phase 1b/2, open-label dose-selection and dose-expansion study to evaluate the safety and antitumor effect of niraparib in combination with other agents for the treatment of men with mCRPC who progressed on 1 prior line of novel AR-targeted therapy for mCRPC[4] Combination 2 evaluated the efficacy and safety of niraparib and AAP combination therapy Combination 3 evaluated the relative BA and safety of niraparib/AA administered as FDC tablet or SAC Subjects with or without HRR gene alterations were enrolled	Combination 2 Niraparib 200 mg and AAP (1,000 mg/10 mg) daily as SAC	24
			Combination 3 PK Assessment Phase: single dose of niraparib 200 mg and AA 1,000 mg given as a FDC tablet or SAC on Day 1 followed by PK sampling through Day 8, with subsequent Extension	68

AA=abiraterone acetate; AAP=abiraterone acetate plus prednisone; ADR=adverse drug reaction; AR=androgen receptor; BA=bioavailability; BE=bioequivalence; BRCA=breast cancer gene; DNA-deoxyribonucleic acid; FDC=fixed-dose combination; HRR=homologous recombination repair; LS=low-strength; mCRPC=metastatic castration-resistant prostate cancer; MOA=mechanism of action; OS=overall survival; PK=pharmacokinetic; RP2D=recommended Phase 2 dose; rPFS=radiographic progression-free survival; RS=regular-strength; RR=response rate; SAC=single-agent combination; SAE=serious adverse event

Note: HRR gene alterations included BRCA1, BRCA2, cyclin-dependent kinase 12 (CDK-12), Fanconi anemia complementation Group A gene (FANCA), partner and localizer of BRCA2 gene (PALB2), checkpoint kinase 2 gene (CHEK2), BRCA1 interacting protein C-terminal Helicase 1 gene (BR1P1), histone deacetylase 2 gene (HDAC2), and ataxia telangiectasia mutated gene (ATM)

[1]In MAGNITUDE Cohort 2, results from a pre-specified futility analysis suggested no clinical benefit, and no further patients were subsequently enrolled. In total, 247 subjects were randomized, and 246 subjects were treated.
[2]QUEST is set up as a platform-like study to evaluate different combination regimens with niraparib. Other niraparib combination regimens in the QUEST and BEDIVERE studies are not part of the MAA, so are not included in the table.
[3]In BA/BE Study, up to 120 subjects will be enrolled in order to ensure at least 96 subjects evaluable for BE.
[4]In QUEST Combination 3 and the BA/BE Study, entry criteria allowed previous treatment for mCRPC and only limited safety data was collected in the Extension (SAEs in QUEST Combination 3; SAEs, grade 3 or higher AEs, AEs leading to dose modification and withdrawal in the BA/BE Study).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The clinical pharmacology program for the FDC (fixed-dose combination) of niraparib/ abiraterone acetate (AA) plus prednisone is based on the development of the two single agents used in combination. Pharmacokinetics (PK) bridging from the SAC (single-agent combination) to the FDC tablets were submitted to support the approval of niraparib/AA FDC plus prednisone for the treatment of adults who have progressed to mCRPC and are positive for HRR gene alterations.

The FDC biopharmaceutic development program consisted of:

- an initial relative BA study (QUEST Combination 3) in which two different fixed-dose formulations FDC1 (FDC1-RS and LS) and FDC2 (FDC2-RS) were tested
- a formal BE study for FDC-RS and relative BA for FDC-LS (BA/BE Study)
- an *in silico* evaluation of BE for the FDC-LS tablets.

Additionally, subjects were dosed in a separate cohort of the Phase 3 Study MAGNITUDE to gain clinical experience with the FDC-RS and FDC-LS tablet formulations.

Niraparib RP2D (recommended Phase 2 dose) when administered in combination with an AR-targeted therapy was investigated in a phase 1b dose-escalation study (BEDIVERE). Other analyses included a population PK (PopPK) analysis based on data pooled from the five clinical studies (Table 19) in the mCRPC population and an exposure-response (E-R) analysis based on the primary efficacy and selected safety endpoints of the pivotal Phase 3 study (MAGNITUDE).

In addition to the above studies clinical pharmacology studies conducted as part of the registration package of the respective monotherapy submissions for niraparib and AA, were also included in this submission to provide comprehensive clinical pharmacology package for the niraparib/AA FDC.

Analytical Methods: Bioanalytical methods were developed and validated to support the quantification of niraparib, major niraparib metabolite M1, AA, and abiraterone in plasma

Absorption

Niraparib

Study PR-30-5015-C: based on the results from in vitro using bidirectional cell permeability assays in Caco-2 cells and LLC-PK1 cells, niraparib was predicted to be a highly permeable drug with limited efflux transport. Niraparib showed relatively high oral absolute BA (F approximately 73%) after administration of a single oral dose of 300 mg niraparib given as 3×100 mg capsules in subjects with cancer.

Absolute BA for a 200 mg dose is not available. However, up to a dose of 200 mg, due to its high solubility and permeability, niraparib is considered to be a biopharmaceutical classification system Class I compound and the PK of niraparib is approximately dose proportional (study **PN001**), thus the absolute BA is predicted to be similar at a 200 mg dose. Following oral dosing, the tmax occurs within 5 hours.

Abiraterone

In vitro, both abiraterone and AA were found to have low apparent permeability in Caco-2 cell monolayers and not to be substrates of P-gp. Based on its low solubility and permeability, AA is a biopharmaceutical classification system Class IV compound. These physicochemical properties of AA and the rapid conversion to abiraterone systemically, resulted in comparable plasma abiraterone concentration-time profiles across studies when given alone or in combination with niraparib.

Abiraterone is rapidly absorbed. The absolutely bioavailability is not known, although the bioavailability from the commercial tablet in the fasted state is unlikely to be higher than 10%, as the bioavailability can be increased by 10-fold in the fed state.

Influence of food

No formal food effect study with the FDC tablets was conducted.

Niraparib

Based on results from the food effect study of niraparib as single agent (Study **PR-30-5011-C2-FE**), food has no clinically relevant effect on niraparib BA and thus can be taken with or without food.

Abiraterone

Food increases the BA of abiraterone (Studies **COU-AA-009**, **212082PCR1005**, and **212082PCR2008**) and thus AA is recommended to be administered under modified fasting conditions (SmPC section 4.2).

Distribution

Niraparib

In the ADME Study **PR-30-5015-C** after administration of a single oral dose of 300 mg niraparib given as 3×100 mg capsules in subjects with cancer, the Vd/F was 1,220 L, indicating an extensive tissue distribution of niraparib. In the PopPK analysis of niraparib in the combination with AA, the central and peripheral Vd/F were 386 and 731 L, respectively in subjects with mCRPC. Niraparib was moderately protein bound to human plasma (83.0%) in vitro.

Abiraterone acetate

The plasma protein binding of 14C-abiraterone in human plasma is 98.8% to 99.9% (*in vitro* studies **8202266**, **FK7603**, **FK7448**). Based on popPK analysis (abiraterone as single agent), the central and peripheral Vd/F were 5,630 L and 17400 L, suggesting that abiraterone extensively distributes to peripheral tissues. In the PopPK analysis of abiraterone when given in combination with niraparib, the central and peripheral Vd/F were 7,052 L and 18,722 L, respectively in subjects with mCRPC.

Elimination

Niraparib

In the ADME Study **PR-30-5015-C** after administration of a single oral dose of 300 mg 14C-radioactive niraparib given as 3×100 mg capsules in six subjects with cancer, a mean measured total of 86.2%

(range: 71.1-91.0%) of the radioactive dose was recovered in urine and faecal samples collected daily from 0 to 504 hours (21 days) post-dose. Total radioactivity recovered in the urine accounted for 47.5% (range: 33.4-60.2%) and in the faeces for 38.8% (range: 28.3-47.0%) of the dose. Therefore, the overall recovery in the excreta following the continuous collection up to 21 days was virtually complete, suggestive of minimal long-term retention of niraparib or its metabolites. Moreover, hepatobiliary clearance and renal excretion are the major routes of elimination in humans.

Abiraterone

Following oral administration of 14C-AA, approximately 88% of the radioactive dose was recovered in faeces and approximately 5% in urine (study **COU-AA-007**). The major compounds present in faeces were unchanged AA and abiraterone (approximately 55% and 22% of the administered dose, respectively). The mean t1/2 of abiraterone in plasma was approximately 15 hours based on data from healthy subjects. The average t½ of abiraterone when given in combination with niraparib, calculated based on PopPK based estimated values of clearance, intercompartmental clearance, and central and peripheral volume of distribution, was approximately 19.7 hours in subjects with mCRPC, which is consistent with observed t1/2 of abiraterone monotherapy.

- **Metabolism**

Data generated regarding the metabolism of niraparib and abiraterone, when niraparib and AA were administered as monotherapy, were used to support the niraparib/AA combination. No new studies of metabolism were conducted during the development of the combination.

Niraparib

Niraparib is metabolised primarily via the amide hydrolysis pathway, catalysed by carboxylesterases to form a major inactive metabolite (M1), followed by the uridine 5'-diphospho-glucuronosyltransferases-mediated glucuronidation and the other minor secondary pathway (ie, methylation). Exposure to M1 in plasma appears to be comparable to that of the parent compound with terminal elimination half-life (t1/2) analogous to that of the parent.

Abiraterone

Following oral administration of 14C-AA as capsules, AA is hydrolysed to abiraterone, which then undergoes metabolism including sulfation, hydroxylation, and oxidation primarily in the liver. The majority of circulating radioactivity (approximately 92%) is found as abiraterone and its metabolites. Of 15 detectable metabolites, there are two main metabolites (inactive), abiraterone sulfate and N-oxide abiraterone sulfate, each representing approximately 43% of total radioactivity.

Dose proportionality and time dependencies

Niraparib

Niraparib exhibited linear PK and dose-proportional exposure (AUC and Cmax). Moreover, the consistent tmax and t1/2 across the range of doses evaluated (30-400 mg) suggest overall dose independent absorption and clearance. Following repeat administrations of the daily recommended dose of 300 mg, niraparib accumulation on Day 21 was consistent for both AUC and Cmax (approximately 2 folds) (**Study PN001**).

Abiraterone

Comparison of abiraterone exposure after administration of the 500 mg and 250 mg doses to the reference dose of 1,000 mg showed that abiraterone exposure was slightly greater than dose proportional (**Study COA-AA-016**).

Summary of Mean (±SD) Pharmacokinetic Parameters for Abiraterone
(Study COU-AA-016: Full PK Data Analysis Set)

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

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

Bioequivalence

Bioequivalence of the 100/500 mg niraparib/AA FDC tablet to the SAC is supported by Study 67652000PCR1001 (hereafter referred to as BA/BE Study).

Bioequivalence of the 50/500 mg Tablet to the SAC is claimed by the results from the relative BA assessments and additional analyses comparing FDC-LS to SAC in the BA/BE Study as well as supplemental *in silico* BE studies based on a PopPK model.

Initial relative BA study, Niraparib plus AA (64091742PCR2002, QUEST Combination 3)

Study QUEST was a Phase 1b-2, multicenter, open-label study to evaluate niraparib in combination with other anticancer agents in subjects with mCRPC with or without HRR gene alterations.

Combination 3 of this study was a partly randomised (Cohort 1 only), parallel group study to determine the PK and safety of three FDC tablet formulations of niraparib plus AA in 68 subjects with mCRPC.

The primary objective was to determine the relative BA of two FDC-RS tablet formulations of niraparib and AA compared with niraparib and AA co-administered as SAC under fasting conditions in subjects with mCRPC. A secondary objective was to evaluate the PK of a FDC-LS tablet formulation.

Serial blood samples were collected at pre-dose and up to 168h post-dose. Study design and results are given in the Tables below.

Overall, given the comparable niraparib exposures seen with FDC1-RS and FDC2-RS but higher abiraterone exposures for FDC2-RS compared to FDC1-RS, the FDC1 (RS and LS) formulation was chosen for further clinical development.

Table 2. Overview of QUEST study design

Cohort	Treatment Arm	Number of Subjects	PK Assessment Phase (Fasting Conditions) [a] Study Days 1-8	Extension Phase [b] (Modified Fasting Conditions) [c] (C1D1 until EOT) C1D1=Study Day 8 After 168 h PK Sample
1	A	17	Single dose 200 mg niraparib/1,000 mg AA as SAC	niraparib 200 mg QD AA 1,000 mg QD prednisone 5 mg bid as SAC or AA 1,000 mg QD prednisone 5 mg bid as SAC [d]
	B	17	Single dose 200 mg niraparib/1,000 mg AA as FDC1-RS tablets (G010)	
2	C	17	Single dose 200 mg niraparib/1,000 mg AA as FDC2-RS tablets (G012)	
3	D	17	Single dose 100 mg niraparib/1,000 mg AA as FDC1-LS tablets (G009)	

AA=abiraterone acetate; bid=twice a day; C1D1=Cycle 1 Day 1; EOT=end of treatment; FDC=fixed-dose combination; HRR=homologous recombination repair; LS=low strength; PK=pharmacokinetic(s); QD=once daily; RS=regular strength; SAC=single-agent combination.

[a] Subjects fasted from food and fluids (excluding noncarbonated water) for ≥10 hours before dosing. Intake of water was allowed until 2 hours before study drug intake.

[b] Subjects continued treatment until disease progression, withdrawal of consent, loss to follow-up, lack of clinical benefit in the opinion of the investigator, or if sponsor ended the study.

[c] Modified fasting conditions defined as study drug intake on empty stomach only: intake ≥1 hour before or ≥2 hours after a meal.

[d] Subjects received niraparib+AA or AA alone QD, each in combination with 5 mg prednisone (or prednisolone) bid, during the extension phase at the investigator's discretion guided by HRR gene alteration status.

Note: Treatments A and B were randomly assigned, whereas subjects were assigned to Treatments C and D.

Table 3: PK Parameters of Niraparib in Plasma After Single-dose Administration of 100 mg or 200 mg Niraparib With 1,000 mg AA in Subjects With mCRPC (64091742PCR2002)

Parameter	Mean±SD; t_{max}: Median (Range)			
	Cohort 1A Niraparib+AA, SAC	Cohort 1B Niraparib+AA, FDC1-RS	Cohort 2 Niraparib+AA, FDC2-RS	Cohort 3 Niraparib+AA, FDC1-LS
N	16	16 [a]	17	17 [b]
C_{max}, ng/mL	428 (189)	398 (160)	417 (176)	193 (65.3)
t_{max}, h	2.00 (1.50-8.02)	2.02 (1.50-7.92)	3.00 (1.50-6.00)	2.00 (1.50-4.03)
$AUC_{0\text{-}168h}$, ng.h/mL	14,672 (7,346)	11,862 (4,973)	13,321 (5,843)	5,214 (1,769)
C_{max}/dose, ng/mL	NA	NA	NA	385 (131)
$AUC_{0\text{-}168h}$/dose, ng.h/mL	NA	NA	NA	10,428 (3,538)

-=not present; AA=abiraterone acetate; $AUC_{0\text{-}168h}$=area under the plasma concentration-time curve from time 0 to 168 hours; $AUC_{0\text{-}168h}$/dose=dose-normalized $AUC_{0\text{-}168h}$ for niraparib; C_{max}=maximum plasma concentration; C_{max}/dose=dose-normalized C_{max} for niraparib; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; NA=not applicable; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination; SD=standard deviation; t_{max}=time to reach the maximum plasma concentration.

[a] N=15 for $AUC_{0\text{-}168h}$.

[b] N=16 for $AUC_{0\text{-}168h}$ and $AUC_{0\text{-}168h}$/dose.

Note: Dose normalized to 200 mg.

Cohort 1A: 200 mg niraparib/1,000 mg AA as SAC.

Cohort 1B: 200 mg niraparib/1,000 mg AA as FDC1-RS (G010).

Cohort 2: 200 mg niraparib/1,000 mg AA as FDC2-RS (G012).

Cohort 3: 100 mg niraparib/1,000 mg AA as FDC1-LS (G009).

Table 4: Statistical Analysis of PK Parameters of Niraparib After Single-dose Administration of 100 mg or 200 mg Niraparib With 1,000 mg AA in Subjects With mCRPC (64091742PCR2002)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Cohort 1A Niraparib+AA, SAC (Reference)	Cohort 1B Niraparib+AA, FDC1-RS (Test)			
N	16	16			
C_{max}, ng/mL	390	366	93.96	71.78-123.00	47.2
AUC_{0-168h}, ng.h/mL [a]	13,120	10,911	83.16	62.91-109.95	48.2
	Cohort 1A Niraparib+AA, SAC (Reference)	Cohort 2 Niraparib+AA, FDC2-RS (Test)			
N	16	17			
C_{max}, ng/mL	390	386	98.98	76.50-128.07	45.8
AUC_{0-168h}, ng.h/mL	13,120	12,045	91.81	68.76-122.57	52.0
	Cohort 1A Niraparib+AA, SAC (Reference)	Cohort 3 Niraparib+AA, FDC1-LS (Test)			
N	16	17			
C_{max}/dose, ng/mL	390	361	92.78	72.18-119.26	44.5
AUC_{0-168h}/dose, ng.h/mL [b]	13,120	9,934	75.72	59.24-96.79	42.7

AA=abiraterone acetate; AUC_{0-168h}=area under the plasma concentration-time curve from time 0 to 168 hours; AUC_{0-168h}/dose=dose-normalized AUC_{0-168h} for niraparib; CI=confidence interval; C_{max}=maximum plasma concentration; C_{max}/dose=dose-normalized C_{max} for niraparib; CV=coefficient of variation; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination.

[a] N=15 for test.

[b] N=16 for test.

Note: Dose normalized to 200 mg.

Cohort 1A: 200 mg niraparib/1,000 mg AA as SAC.

Cohort 1B: 200 mg niraparib/1,000 mg AA as FDC1-RS (G010).

Cohort 2: 200 mg niraparib/1,000 mg AA as FDC2-RS (G012).

Cohort 3: 100 mg niraparib/1,000 mg AA as FDC1-LS (G009).

Table 5: PK Parameters of Abiraterone in Plasma After Single-dose Administration of 1,000 mg AA With 100 mg or 200 mg Niraparib in Subjects With mCRPC (64091742PCR2002)

Parameter	Mean±SD; t_{max}: Median (Range)			
	Cohort 1A Niraparib+AA, SAC	Cohort 1B Niraparib+AA, FDC1-RS	Cohort 2 Niraparib+AA, FDC2-RS	Cohort 3 Niraparib+AA, FDC1-LS
N	16	16 [a]	17	17 [b]
C_{max}, ng/mL	145 (127)	154 (120)	181 (184)	180 (162)
t_{max}, h	2.49 (1.47-8.00)	1.74 (1.00-9.92)	2.00 (1.50-6.00)	1.52 (1.00-3.00)
AUC_{0-168h}, ng.h/mL	836 (698)	846 (808)	1,108 (1,240)	832 (728)

AA=abiraterone acetate; AUC_{0-168h}=area under the plasma concentration-time curve from time 0 to 168 hours; C_{max}=maximum plasma concentration; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination; SD=standard deviation; t_{max}=time to reach the maximum plasma concentration.

[a] N=15 for AUC_{0-168h}.

[b] N=16 for AUC_{0-168h}.

Note: Cohort 1A: 200 mg niraparib/1,000 mg AA as SAC.
Cohort 1B: 200 mg niraparib/1,000 mg AA as FDC1-RS (G010).
Cohort 2: 200 mg niraparib/1,000 mg AA as FDC2-RS (G012).
Cohort 3: 100 mg niraparib/1,000 mg AA as FDC1-LS (G009).

Table 6: Statistical Analysis of PK Parameters of Abiraterone After Single-dose Administration of 1,000 mg AA With 100 mg or 200 mg Niraparib in Subjects With mCRPC (64091742PCR2002)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Cohort 1A Niraparib+AA, SAC (Reference)	Cohort 1B Niraparib+AA, FDC1-RS (Test)			
N	16	16			
C_{max}, ng/mL	82.6	112	135.14	68.26-267.54	162.9
AUC_{0-168h}, ng.h/mL [a]	516	596	115.53	60.14-221.92	146.1
	Cohort 1A Niraparib+AA, SAC (Reference)	Cohort 2 Niraparib+AA, FDC2-RS (Test)			
N	16	17			
C_{max}, ng/mL	82.6	124	150.72	77.46-293.24	160.0
AUC_{0-168h}, ng.h/mL	516	760	147.24	79.85-271.53	138.8
	Cohort 1A Niraparib+AA, SAC (Reference)	Cohort 3 Niraparib+AA, FDC1-LS (Test)			
N	16	17			
C_{max}, ng/mL	82.6	132	160.01	83.47-306.74	153.9
AUC_{0-168h}, ng.h/mL [b]	516	656	127.09	70.20-230.06	128.8

AA=abiraterone acetate; AUC_{0-168h}=area under the plasma concentration-time curve from time 0 to 168 hours; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; RS=regular strength; SAC=single-agent combination.

[a] N=15 for test.

[b] N=16 for test.

Note: Cohort 1A: 200 mg niraparib/1,000 mg AA as SAC.
Cohort 1B: 200 mg niraparib/1,000 mg AA as FDC1-RS (G010).
Cohort 2: 200 mg niraparib/1,000 mg AA as FDC2-RS (G012).
Cohort 3: 100 mg niraparib/1,000 mg AA as FDC1-LS (G009).

- **Niraparib plus AA (67652000PCR1001, BA/BE Study)**

Study design

This was an open-label, randomised, multi-centre study with a sequential design to assess the BE of a regular-strength (RS) FDC tablet formulation of niraparib/AA versus the single agent combination (SAC) formulation of niraparib and AA at steady state and to assess the relative BA of a low-strength (LS) FDC tablet formulation of niraparib/AA versus the SAC formulation of niraparib and AA after single dose administration in subjects with metastatic castration resistant prostate cancer (mCRPC).

Table 7: Study Design with Treatment Sequences for Randomisation Scheme (Study 67652000PCR1001)

Sequence Number	Number of Subjects	Treatment Phase			
		PK Assessment Phase[a] (modified fasting)[c]			Extension Phase[b] (modified fasting)[c]
		Relative BA for LS FDC	BE for RS FDC via 2-way cross over		
		Period 1 SINGLE DOSE	Period 2 MULTIPLE DOSE	Period 3 MULTIPLE DOSE	MULTIPLE DOSE
		1-week run-in with single dose on Study Day -7	C1D1-C1D11	C1D12-C1D22	(C1D23-Cycle X)
		Study Days -7 to -1[d]	Study Days 1 to 11	Study Days 12 to 22	≥Study Day 23
1	30	Treatment A 100 mg niraparib/ 1,000 mg AA as SAC[e]	Treatment B 200 mg niraparib/ 1,000 mg AA as SAC[f]	Treatment D 200 mg niraparib/ 1,000 mg AA as RS FDC tablets[g]	Chronic treatment with 1,000 mg AA QD plus 5 mg prednisone/prednisolone BID and niraparib 200 mg QD as SAC OR Chronic treatment with 1,000 mg AA QD plus 5 mg prednisone/prednisolone BID as SAC
2	30	Treatment A 100 mg niraparib/ 1,000 mg AA as SAC[e]	Treatment D 200 mg niraparib/ 1,000 mg AA as RS FDC tablets[g]	Treatment B 200 mg niraparib/ 1,000 mg AA as SAC[f]	
3	30	Treatment C 100 mg niraparib/ 1,000 mg AA as LS FDC tablets[h]	Treatment B 200 mg niraparib/ 1,000 mg AA as SAC[f]	Treatment D 200 mg niraparib/ 1,000 mg AA as RS FDC tablets[g]	
4	30	Treatment C 100 mg niraparib/ 1,000 mg AA as LS FDC tablets[h]	Treatment D 200 mg niraparib/ 1,000 mg AA as RS FDC tablets[g]	Treatment B 200 mg niraparib/ 1,000 mg AA as SAC[f]	

Key: AA = abiraterone acetate; BA = bioavailability; BE = bioequivalence; BID = twice daily; C = cycle; D = day; FDC = fixed-dose combination; HRR = homologous recombination repair; LS = low-strength; PK = pharmacokinetics; QD = once daily; RS = regular-strength; SAC = single agent combination.

a. During repeated dosing (Periods 2 and 3), all subjects received niraparib and AA QD in combination with 5 mg prednisone (or prednisolone) BID.

b. During the Extension Phase, subjects received niraparib and AA or AA alone QD, each in combination with 5 mg prednisone (or prednisolone) BID at the discretion of the investigator as guided by HRR gene alteration status. Subjects continued treatment until disease progression, withdrawal of consent, loss to follow-up, lack of clinical benefit in the opinion of the investigator, start of subsequent anticancer therapy, or until sponsor ended the study.

c. Modified fasting defined as study treatment intake on an empty stomach only: intake at least 1 hour before or at least 2 hours after a meal.

d. Study Day -1 was followed by Study Day 1. Study Day -7 could also start on Study Days -6, -5, or -4.

e. Single agents were given as 1×100-mg niraparib capsule and 4×250-mg AA tablets as a single dose.

f. Single agents were given as 2×100-mg niraparib capsules and 4×250-mg AA tablets as a QD dose.

g. RS FDC given as 2×FDC tablets (100 mg niraparib/500 mg AA) as a QD dose.

h. LS FDC given as 2×FDC tablets (50 mg niraparib/500 mg AA) as a single dose.

Objective and endpoints

Table 8: Objectives and Endpoints (Study 67652000PCR1001)

Objectives	Endpoints
Primary	
To determine the BE of an RS FDC tablet formulation of niraparib and AA with respect to niraparib and AA co-administered as single agents at steady state under modified fasted conditions in subjects with mCRPC (Periods 2 and 3).	PK parameters ($C_{max,ss}$, $AUC_{0\text{-}24h,ss}$, and test-to-reference ratios for these parameters) of niraparib and AA at steady state.
Secondary	
To determine the relative BA of an LS FDC tablet formulation of niraparib and AA with respect to niraparib and AA co-administered as single agents after a single dose administration under modified fasted conditions in subjects with mCRPC (Period 1).	PK parameters (C_{max}, $AUC_{0\text{-}72h}$, and test-to-reference ratios for these parameters) of niraparib and AA after a single dose.
To compare the PD of AA (serum testosterone levels) following multiple dose administration of an RS FDC tablet formulation of niraparib and AA to the PD of AA following niraparib and AA co-administered as single agents (Periods 2 and 3).	PD parameter (serum testosterone levels and test-to-reference ratio) at steady state.
To assess the safety of niraparib in combination with AAP in subjects with mCRPC.	Incidence and severity of AEs and clinical laboratory safety.

Key: AA = abiraterone acetate; AAP = abiraterone acetate plus prednisone (or prednisolone); AE = adverse event; $AUC_{0\text{-}24h,ss}$ = area under the plasma concentration-time curve from time 0 to 24 hours at steady state; $AUC_{0\text{-}72h}$ = area under the plasma concentration-time curve from time 0 to 72 hours postdosing; BA = bioavailability; BE = bioequivalence; C_{max} = maximum observed analyte concentration; $C_{max,ss}$ = maximum observed analyte concentration at steady state; FDC = fixed-dose combination; LS = low-strength; mCRPC = metastatic castration-resistant prostate cancer; PD = pharmacodynamics; PK = pharmacokinetics; RS = regular-strength.

Statistical approaches to establish BE

The primary PK parameters for the statistical analysis were Cmax,ss and AUC0-24h,ss.

A linear mixed-effect model that included treatment, period, and treatment sequence as fixed effects, and subject within sequence as a random effect, was used to estimate the least square means and intrasubject variance. Data were log-transformed prior to analysis. Point estimates and 90% CIs for the GMRs of Cmax,ss and AUC0-24h,ss between the test (Treatment D) and reference (Treatment B) formulations for niraparib and abiraterone were obtained. As a secondary analysis, an ANOVA model that included treatment, period, sequence, and subject within sequence as fixed effects was applied in the statistical analysis for the BE assessment. No random effect was included in this model.

Statistical Analysis of Relative BA

The primary PK parameters for statistical analysis were Cmax and AUC0-72h of niraparib and abiraterone. An ANOVA model with treatment as fixed effect was applied to the log-transformed PK parameters and the results were presented in original scale after antilog transformation.

Additional Paired Data Analysis to Assess the Comparability of Abiraterone Exposures between the FDC-LS and SAC Formulation

To further assess the relative BA of the FDC-LS formulation versus SAC within the same subjects, based on the high inter-subject variability observed for FDC-LS in the initial analysis, comparing exposures between Treatment groups C and A, an additional subgroup analysis using single sequence data (extracted data for Treatments C and B based on treatment sequences CBD and CDB) was performed for abiraterone as abiraterone PK at the dose of 1,000 mg is shown to be linear and stationary.

For Cmax comparison, since Treatment C was a single-dose design, abiraterone Cmax,ss for this group was calculated using nonparametric superposition method and popPK model derived accumulation ratios.

For AUC comparison abiraterone AUC0-∞ was calculated for Treatment C, which was compared with the observed AUC0-24h,ss from Treatment B.

A linear mixed-effect model that included treatment as fixed effect and subject as a random effect was used to estimate the least square means and intrasubject variance. The point estimate and 90% CIs for the GMRs of Cmax,ss and AUC (AUC0-∞ for Treatment C and AUC0-24h,ss for Treatment B) between the test (Treatment C) and reference (Treatment B) formulations for abiraterone were obtained.

Results

Niraparib (FDC-RS BE Assessment)

Table 9: PK Parameters of Niraparib at Steady State After Multiple-dose Administrations of 200 mg Niraparib and 1,000 mg AA Given as SAC (Treatment B, Current Commercial Formulation) or Given as FDC-RS (Treatment D) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Mean±SD; $t_{max,ss}$: Median (Range)	
	Treatment B: SAC Formulation	Treatment D: FDC-RS Formulation
Periods 2 and 3		
N	118 [a]	122 [b]
$C_{trough,ss}$, ng/mL	425 (186)	434 (184)
$C_{max,ss}$, ng/mL	808 (265)	831 (270)
$t_{max,ss}$, h	3.00 (0.00-10.00)	3.00 (1.00-8.00)
$AUC_{0-24h,ss}$, ng.h/mL	13,581 (5,147)	13,616 (4,854)
Ratio $C_{max,ss}$	-	1.05 (0.25)
Ratio $AUC_{0-24h,ss}$	-	1.03 (0.24)

-=not calculated; AA=abiraterone acetate; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours postdose at steady state; $C_{max,ss}$=maximum plasma concentration at steady state; $C_{trough,ss}$=observed trough analyte concentration at steady state; FDC=fixed-dose combination; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination; SD=standard deviation; $t_{max,ss}$=time to reach the maximum plasma concentration at steady state.

[a] N=117 for $C_{trough,ss}$ and $AUC_{0-24h,ss}$.

[b] N=121 for $C_{trough,ss}$ and $AUC_{0-24h,ss}$, N=117 for Ratio $C_{max,ss}$ and N=116 for Ratio $AUC_{0-24h,ss}$.

Table 10: Statistical Analysis of PK Parameters of Niraparib at Steady State After Multiple-dose Administrations of 200 mg Niraparib and 1,000 mg AA Given as SAC (Treatment B, Current Commercial Formulation) or Given as FDC-RS (Treatment D) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Treatment B: SAC (Reference)	Treatment D: FDC-RS (Test)			
Primary analysis					
N	117 [a]	117 [a]			
$C_{trough,ss}$, ng/mL	389	405	104.22	99.34-109.33	22.2
$C_{max,ss}$, ng/mL	771	791	102.59	99.18-106.12	15.7
$AUC_{0-24h,ss}$, ng.h/mL	12,781	12,916	101.06	97.91-104.31	14.6

AA=abiraterone acetate; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours postdose at steady state; CI=confidence interval; $C_{max,ss}$=maximum observed analyte concentration at steady state; $C_{trough,ss}$=observed trough analyte concentration at steady state; CV=coefficient of variation; FDC=fixed-dose combination; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination.

[a] N=116 for $AUC_{0-24h,ss}$.

Abiraterone (FDC-RS BE Assessment)

Table 11: PK Parameters of Abiraterone at Steady State After Multiple-dose Administrations of 200 mg Niraparib and 1,000 mg AA Given as SAC (Treatment B, Current Commercial Formulation) or Given as FDC-RS (Treatment D) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Mean±SD; $t_{max,ss}$: Median (Range)	
	Treatment B: SAC Formulation	Treatment D: FDC-RS Formulation
Periods 2 and 3		
N	118 [a]	122 [b]
$C_{trough,ss}$, ng/mL	9.54 (7.48)	9.37 (6.31)
$C_{max,ss}$, ng/mL	158 (96.5)	151 (88.8)
$t_{max,ss}$, h	2.00 (1.00-4.00)	1.50 (0.98-9.90)
$AUC_{0-24h,ss}$, ng.h/mL	768 (546)	707 (414)
Ratio $C_{max,ss}$	-	1.20 (0.99)
Ratio $AUC_{0-24h,ss}$	-	1.04 (0.55)

AA=abiraterone acetate; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours postdose at steady state; $C_{max,ss}$=maximum plasma concentration at steady state; $C_{trough,ss}$=observed trough analyte concentration at steady state; FDC=fixed-dose combination; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination; SD=standard deviation; $t_{max,ss}$=time to reach the maximum plasma concentration at steady state.

[a] N=117 for $C_{trough,ss}$ and $AUC_{0-24h,ss}$.

[b] N=121 for $C_{trough,ss}$ and $AUC_{0-24h,ss}$, N=117 for Ratio $C_{max,ss}$ and N=116 for Ratio $AUC_{0-24h,ss}$.

Table 12: Statistical Analysis of PK Parameters of Abiraterone at Steady State After Multiple-dose Administrations of 200 mg Niraparib and 1,000 mg AA Given as SAC (Treatment B, Current Commercial Formulation) or Given as FDC-RS (Treatment D) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Treatment B: SAC (Reference)	Treatment D: FDC-RS (Test)			
Primary analysis					
N	117 [a]	117 [a]			
$C_{trough,ss}$, ng/mL	7.66	7.63	99.72	93.90-105.90	28.1
$C_{max,ss}$, ng/mL	129	124	96.67	87.59-106.69	48.0
$AUC_{0-24h,ss}$, ng.h/mL	632	590	93.33	86.91-100.23	33.6

AA=abiraterone acetate; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours postdose at steady state; CI=confidence interval; $C_{max,ss}$=maximum observed analyte concentration at steady state; $C_{trough,ss}$=observed trough analyte concentration at steady state; CV=coefficient of variation; FDC=fixed-dose combination; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); RS=regular strength; SAC=single-agent combination.

[a] N=116 for $AUC_{0-24h,ss}$.

Based on the 90% CIs of Cmax,ss and AUC0-24h,ss for niraparib and abiraterone, the FDC-RS formulation met the BE criteria (CI% within 80.00-125.00) versus the reference SAC formulation.

Niraparib (FDC-LS Relative BA Assessment)

Table 13: PK Parameters of Niraparib After Single-dose Administration of 100 mg Niraparib and 1,000 mg AA Given as SAC (Treatment A, Current Commercial Formulation) or as FDC-LS (Treatment C) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001: PK Analysis Set)

Parameter	Mean±SD; t_{max}: Median (Range)	
	Treatment A: SAC Formulation	Treatment C: FDC-LS Formulation
N	67 [a]	67 [a]
C_{max}, ng/mL	239 (170)	211 (147)
t_{max}, h	2.00 (1.48-48.00)	2.00 (0.50-6.00)
AUC_{0-72h}, ng.h/mL	4,619 (2,223)	4,065 (1,664)
$AUC_{0-\infty}$, ng.h/mL	6,080 (2,456)	4,578 (1,881)

AA=abiraterone acetate; AUC_{0-72h}=area under the plasma concentration-time curve from time 0 to 72 hours postdose; $AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 to infinity; C_{max}=maximum plasma concentration; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); SAC=single-agent combination; SD=standard deviation; t_{max}=time to reach the maximum plasma concentration.

[a] N=66 for AUC_{0-72h} and N=25 for $AUC_{0-\infty}$.

[b] N=25 for $AUC_{0-\infty}$.

The inter-subject variabilities (CV%) for Cmax and AUC0-72h were 56.2% and 41.8%, respectively.

Table 14: Statistical Analysis of the PK Parameters of Niraparib After Single-dose Administration of 100 mg Niraparib and 1,000 mg AA Given as SAC (Treatment A, Current Commercial Formulation) or Given as FDC-LS (Treatment C) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001: PK Analysis Set)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Treatment A: SAC (Reference)	Treatment C: FDC-LS (Test)			
N	67 [a]	67			
C_{max}, ng/mL	202	183	90.88	78.22-105.59	56.2
AUC_{0-72h}, ng.h/mL	4,197	3,782	90.11	80.31-101.12	41.8

AA=abiraterone acetate; AUC_{0-72h}=area under the plasma concentration-time curve from time 0 to 72 hours postdose; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); SAC=single-agent combination.

[a] N=66 for AUC_{0-72h}.

Abiraterone (FDC-LS Relative BA Assessment)

Table 15: PK Parameters of Abiraterone After Single-dose Administration of 100 mg Niraparib and 1,000 mg AA Given as SAC (Treatment A, Current Commercial Formulation) or Given as FDC-LS (Treatment C) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Mean±SD; t_{max}: Median (Range)	
	Treatment A: SAC Formulation	Treatment C: FDC-LS Formulation
N	67 [a]	67 [b]
C_{max}, ng/mL	132 (95.3)	185 (134)
t_{max}, h	1.89 (1.00-6.00)	1.50 (0.97-4.08)
AUC_{0-72h}, ng.h/mL	672 (435)	853 (590)
$AUC_{0-\infty}$, ng.h/mL	709 (464)	896 (611)

AA=abiraterone acetate; AUC_{0-72h}=area under the plasma concentration-time curve from time 0 to 72 hours postdose; $AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 to infinity; C_{max}=maximum plasma concentration; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); SAC=single-agent combination; SD=standard deviation; t_{max}=time to reach the maximum plasma concentration.

[a] N=66 for AUC_{0-72h} and N=58 for $AUC_{0-\infty}$.

[b] N=65 for $AUC_{0-\infty}$.

Table 16: Statistical Analysis of PK Parameters of Abiraterone After Single-dose Administration of 100 mg Niraparib and 1,000 mg AA Given as SAC (Treatment A, Current Commercial Formulation) or Given as FDC-LS (Treatment C) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Treatment A: SAC (Reference)	Treatment C: FDC-LS (Test)			
N	67 [a]	67			
C_{max}, ng/mL	108	143	132.62	108.35-162.32	80.4
AUC_{0-72h}, ng.h/mL	562	685	121.93	101.09-147.07	72.9

AA=abiraterone acetate; AUC_{0-72h}=area under the plasma concentration-time curve from time 0 to 72 hours postdose; CI=confidence interval; C_{max}=maximum plasma concentration; CV=coefficient of variation; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); SAC=single-agent combination.

[a] N=66 for AUC_{0-72h}.

The inter-subject variabilities (%CV) in the PK parameters for Cmax and AUC0-72h were 80.4% and 72.9%, respectively.

Based on the 90% CIs of single dose Cmax and AUC0-72h for niraparib and abiraterone, the FDC-LS formulation did not meet the BE criteria versus the reference SAC formulation for niraparib Cmax and abiraterone Cmax and AUC0-72h.

Abiraterone (Additional exploratory statistical evaluation to assess the comparability between the FDC-LS and SAC formulations)

Based on the additional paired analysis, 90% CI of the GMRs for estimated abiraterone Cmax,ss and AUC (AUC0-∞ for FDC-LS or AUC0-24h,ss for SAC) between FDC-LS and SAC were within the 80.00% to 125.00% BE criteria (Table below).

Table 17: Statistical Analysis of PK Parameters of Abiraterone After Single-dose Administration of 200 mg Niraparib and 1,000 mg AA Given as SAC (Treatment B, Current Commercial Formulation) or 100 mg Niraparib and 1,000 mg AA Given as FDC-LS (Treatment C) Under Modified Fasting Conditions in Subjects With mCRPC (67652000PCR1001)

Parameter	Geometric Mean		Geometric Mean Ratio (%)	90% CI	CV (%)
	Treatment B: SAC (Reference)	Treatment C: FDC-LS (Test)			
N	57 [a]	57 [a,]			
C_{max}, ng/mL [b]	146	147 [b]	100.54	85.41-118.34	55.8
C_{max}, ng/mL [c]	146	155 [c]	105.84	89.57-125.07	57.3
AUC, ng.h/mL [d]	688	706	102.58	86.51-121.64	56.8

AA=abiraterone acetate; AUC=area under the plasma concentration-time curve; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours postdose at steady state; $AUC_{0-\infty}$=area under the plasma concentration-time curve from time 0 to infinity; CI=confidence interval; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum observed analyte concentration at steady state; CV=coefficient of variation; FDC=fixed-dose combination; LS=low strength; mCRPC=metastatic castration-resistant prostate cancer; N=maximum number of subjects with data; PK=pharmacokinetic(s); SAC=single-agent combination.

[a] N=54 for AUC.

[b] $C_{max,ss}$ is simulated using nonparametric superposition.

[c] $C_{max,ss}$ is computed by C_{max} single dose multiplied by individual population PK derived accumulation ratios. Complete summary table of the statistical results comparing the PK of abiraterone by this method between Treatment B and C is provided in TABPK35a in Appendix 9. The detailed statistical results are provided in TABPK36a in Appendix 9. Individual PK parameters are listed in TABPK37a in Appendix 9.

[d] AUC is parameter $AUC_{0-24h,ss}$ for Treatment B and parameter $AUC_{0-\infty}$ for Treatment C.

In silico BE assessment for the FDC-LS

PopPK simulations of 1000 replicates of the BA/BE study design (conducted as a 2-way steady state cross-over PK assessment phase in Periods 2 and 3, ie, the BE assessment phase for FDC versus SAC) with a sample size of N=120 were performed. The Day 11 and Day 22 individual exposure parameters AUC0-24h,ss and Cmax,ss for FDC-LS and/or SAC for both niraparib and abiraterone were calculated from the simulated data using NCA. The probability of demonstrating BE for FDC-LS compared with SAC was calculated as the proportion of simulated clinical trial replicates in which BE criteria (90% CI of estimated GMR within the 80% to 125% range) were met for both AUC0-24h,ss and Cmax,ss for both niraparib and abiraterone.

The abiraterone pre-final PPK model, which included effects of FDC-LS on KA (20% decrease versus SAC) and D1 (34% decrease versus SAC) was used for the simulated BE assessment of FDC-LS. BE criteria would simultaneously be met in 96.4% for all four exposure parameters.

Table 18: Summary of Estimated GMR and 90% CIs for Niraparib and Abiraterone AUC0-24h,ss and Cmax,ss for the Simulated BE Trials of FDC-LS vs Single Agents (PopPK prefinal model)

Compound	Exposure Parameter	GMR and 90% CI	Mean	SD	5th%	Median	95th%
Niraparib	AUC ratio	5th percentile CI	86.3	2.5	82.4	86.3	90.5
		GMR point estimate	88.2	2.54	84.3	88.3	92.4
		95th percentile CI	90.2	2.6	86.2	90.2	94.6
	Cmax ratio	5th percentile CI	86	2.78	81.5	86	90.7
		GMR point estimate	88.7	2.88	84.1	88.7	93.7
		95th percentile CI	91.5	2.98	86.7	91.5	96.7
Abiraterone	AUC ratio	5th percentile CI	95.6	2.65	91.4	95.6	100
		GMR point estimate	100	2.75	95.6	100	105
		95th percentile CI	105	2.89	100	105	109
	Cmax ratio	5th percentile CI	90.9	5.12	82.8	90.9	99.3
		GMR point estimate	98.7	5.51	90.1	98.7	108
		95th percentile CI	107	5.98	97.6	107	117

AUC=area under the concentration-time curve; $AUC_{0-24,ss}$=area under the concentration-time curve during 24 hours after dosing at steady state; BE=bioequivalence; CI=confidence interval; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum plasma concentration at steady state; FDC-LS=low strength fixed-dose combination; GMR=geometric means ratio; vs=versus.

Pharmacokinetics in target population

Population PK analysis

PK modelling was performed using Nonlinear mixed-effects modelling software NONMEM (ICON plc, Version 7.3) and the first-order conditional estimation with interaction estimation method. The PopPK analysis was based on 9935 niraparib plasma PK samples from 916 subjects and 6289 abiraterone plasma PK samples from 954 subjects, obtained in the five clinical studies described in the Table below.

Table 19: Overview of Studies Included in the PPK and E-R Analyses

Study Number	Study Title and Design (including doses administered)	Brief Description of PK Data (including number of subjects with PK samples, rich or sparsely sampled)
64091742PCR1001 BEDIVERE	A safety and PK study of niraparib plus androgen receptor-targeted therapy (apalutamide or AAP) in men with metastatic castration-resistant prostate cancer Phase 1b, open-label, dose-selection, and dose-expansion study to determine the safety and RP2D of niraparib in combination with AR-targeted therapy in men with mCRPC previously treated with ≥1 line of taxane-based chemotherapy and ≥1 line of AR-targeted therapy Subjects with or without HRR gene alterations were enrolled. **Only the data from the niraparib+AAP combination are included in the PPK evaluation.** Doses: Niraparib 200 mg and AAP (1000 mg/10 mg) orally Niraparib 300 mg and AAP (1000 mg/10 mg) orally Dose Schedule: DLT period: Every day for 1 cycle (Cycle 1) Dose-expansion period: Every day for all cycles A cycle was 4 weeks	24 subjects Rich PK sampling: 1 h, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 24 h on Cycles 1 and 2 Day 1, predose on Cycles 2, 3, and then every 3 cycles on Day 1
67652000PCR1001 FDC BA/BE Study	An open-label, randomized study to assess the relative bioavailability and bioequivalence of FDC formulations of niraparib plus AA compared with niraparib and AA coadministered as single agents in men with prostate cancer Subjects with mCRPC with or without HRR gene alterations were enrolled.	135 subjects Rich PK sampling: predose, 30 min, 1 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 10 h, 24 h, 48 h, 72 h on Days -7 to -1 (Period 1); predose, 30 min, 1 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 10 h on

Study Number	Study Title and Design (including doses administered)	Brief Description of PK Data (including number of subjects with PK samples, rich or sparsely sampled)
	Subjects were randomly assigned to 1 of 4 treatment sequences (ABD, ADB, CBD, or CDB) over 3 periods and treated as follows: Period 1 (Days -7 to -1): single-dose relative-BA assessment of SAC vs FDC-LS formulation of niraparib/AA Treatment A: niraparib 100 mg and AA 1000 mg as SAC Treatment C: niraparib 100 mg/AA 1000 mg as FDC-LS Periods 2 and 3 (Days 1 to 11 and Days 12 to 23): multiple-dose, 2-way cross-over BE assessment of SAC vs FDC-RS formulation of niraparib/AA Treatment B: niraparib 200 mg and AAP (1000 mg/10 mg) daily as SAC Treatment D: niraparib 200 mg/AA 1000 mg as FDC-RS plus prednisone 10 mg daily	Days 11 and 22 (Periods 2 and 3, respectively)
64091742PCR2001 GALAHAD	A Phase 2 efficacy and safety study of niraparib in men with metastatic castration-resistant prostate cancer and DNA-repair anomalies Non-randomized, single-arm open-label monotherapy study to assess the safety and efficacy of niraparib in subjects with measurable mCRPC previously treated with ≥1 line of taxane-based chemotherapy and ≥1 line of AR-targeted therapy and who have either biallelic DNA-repair anomalies in BRCA (BRCA1 or BRCA2) or germline BRCA Niraparib 300 mg daily	289 subjects Sparse PK sampling: predose, 1 h to 3 h, and 4 h to 6 h postdose on Cycles 1 and 2 Day 1; predose on Cycle 1 Day 15 and on Day 1 of Cycles 3, 4, 5, and 7
64091742PCR2002 QUEST	A Phase 1b-2 study of niraparib combination therapies for the treatment of metastatic castration-resistant prostate cancer Open-label dose-selection and dose-expansion study to evaluate the safety and antitumor effect of niraparib in combination with other agents for the treatment of men with mCRPC who progressed on 1 prior line of novel AR-targeted therapy for mCRPC Combination 2 evaluated the safety and efficacy of niraparib and AAP combination therapy. No PK samples were collected. Combination 3 evaluated the safety and relative BA of niraparib/AA administered as FDC or SAC. Only the data from the combination 3 will be included in the PPK evaluation.	Cohort 1: 34 subjects Cohort 3: 17 subjects Rich PK sampling: predose, 30 min, 2 h, 1 h 30 min, 2 h, 3 h, 4 h, 6 h, 8 h, 10 h, 24 h, 48 h, 72 h, 168 h postdose

Study Number	Study Title and Design (including doses administered)	Brief Description of PK Data (including number of subjects with PK samples, rich or sparsely sampled)
	Subjects with or without HRR gene alterations were enrolled. Combination 3 PK assessment phase: single dose of niraparib 200 mg and AA 1000 mg given as an FDC (Cohort 1, Treatment Group B) or a SAC (Cohort 2, Treatment Group A) on Day 1; single dose of niraparib 100 mg and AA 1000 mg given as an FDC (Cohort 3, Treatment Group C) on Day 1	
64091742PCR3001 MAGNITUDE	A Phase 3 randomized, placebo-controlled, double-blind study of niraparib in combination with AAP vs AAP for treatment of subjects with metastatic prostate cancer Multicenter study to assess the efficacy and safety of niraparib in combination with AAP in subjects with mCRPC who previously received no prior treatment for mCRPC except <4 months of AAP Cohorts 1 and 2 provided the pivotal efficacy and safety data for combination treatment with niraparib and AAP Cohort 3 evaluated the clinical experience with the FDC formulation Cohort 1: subjects with HRR gene alterations Randomized to niraparib 200 mg (or placebo) and AAP (1000 mg/10 mg) daily as SAC Cohort 2: subjects with no HRR gene alterations Randomized to niraparib 200 mg (or placebo) and AAP (1000 mg/10 mg) daily as SAC Cohort 3: subjects with HRR gene alterations Non-randomized, open-label treatment with niraparib/AA (200 mg/1000 mg) as FDC plus prednisone (10 mg) daily	Cohort 1: 423 subjects Cohort 2: 246 subjects Cohort 3: 95 subjects Sparse PK sampling: • Niraparib: predose and 1 to 3 h postdose on Cycle 2 Day 1, predose on Cycle 3 Day 1, predose or ≥3 h postdose on Cycles 4 to 7 Abiraterone: predose on Cycles 2 and 3

AA=abiraterone; AAP=abiraterone acetate plus prednisone; AR=androgen receptor; BA=bioavailability; BE=bioequivalence; BRCA=breast cancer gene; DLT=dose-limiting toxicity; FDC=fixed-dose combination; FDC-LS=low strength fixed-dose combination; FDC-RS=regular strength fixed-dose combination; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; PK=pharmacokinetic(s); PPK=population pharmacokinetic(s); RP2D=recommended Phase 2 dose; SAC=single-agent combination; vs=versus.

Niraparib PPK model

A PPK model of niraparib, previously developed in subjects with ovarian cancer (**TESA-PMX-NIRAPARIB-1391**, dated 02.09.2019), was used as the starting point for structural model development on the current analysis dataset. The effects of FDC-RS and -LS formulations compared with single-agent niraparib capsule formulation were introduced on the absorption parameters KA, D1, and F1 in the base model prior to covariate testing. The final niraparib model is given below.

Final model:

Table 20: Parameter Estimates of the Niraparib Final PPK Model (CJNJ-67652000)

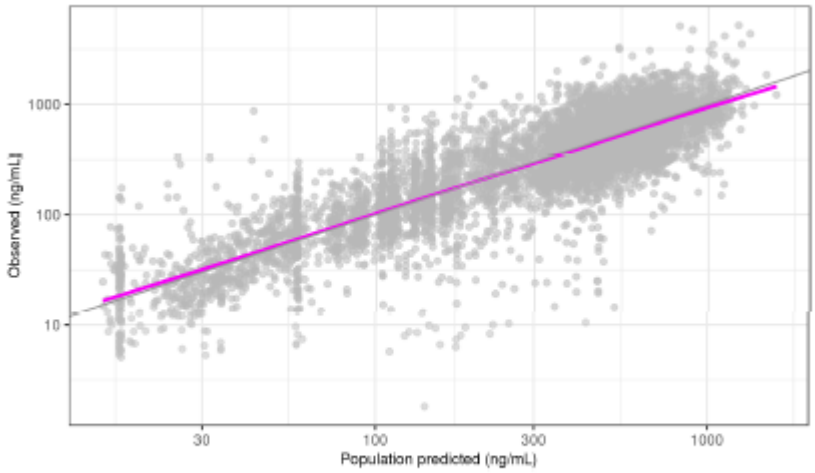
Parameter	Estimate	Std. Err.	RSE%	Transformed Estimate (%)[a]	Shrinkage (%)[b]
KA (1/h)	0.834	0.0539	6	-	-
CL (L/h)	16.7	0.370	2	-	-
V2 (L)	386	16.6	4	-	-
V3 (L)	731	36.8	5	-	-
Q (L/h)	60.5	3.71	6	-	-
D1 (h)	1.33	0.0428	3	-	-
F1 single-agent capsule	1 (fixed)	-	-	-	-
FDC-LS on D1 (vs SAC)	-0.118	0.0550	47	89	-
FDC-LS on F1 (vs SAC)	-0.131	0.0272	21	88	-
CRCL on CL	0.305	0.0351	12	81	-
HRR-negative on CL (vs HRR-positive BRCA1 or BRCA2)	-0.115	0.0253	22	88	-
HRR-positive non-BRCA on CL (vs HRR-positive BRCA1 or BRCA2)	-0.0792	0.0270	34	92	-
Other races on KA (vs white race)	-0.359	0.0581	16	64	-
Hispanic/Latino race on KA (vs white race)	-0.334	0.0865	26	67	-
Asian race on Q (vs white race)	-0.389	0.151	39	61	-
Asian race on V3 (vs white race)	0.483	0.154	32	148	-
IIV KA	0.364	0.0513	14	66	47
IIV CL	0.0683	0.00777	11	27	26
IIV V2	0 (fixed)	-	-	-	-
IIV V3	0.184	0.0249	14	45	50
IIV Q	0 (fixed)	-	-	-	-
IIV D1	0.530	0.0604	11	84	42
IIV F1	0.103	0.00864	8	33	20
Residual error rich PK sampling	0.0478	0.00303	6	22	-
Residual error sparse PK sampling	0.117	0.00758	6	35	-

BRCA=breast cancer gene; CL=oral clearance; CRCL=creatinine clearance; D1=duration of zero-order drug release; F1=apparent oral bioavailability; FDC-LS=low strength fixed-dose combination; HRR=homologous recombination repair; IIV=interindividual variability; KA=first-order absorption rate constant; PK=pharmacokinetic(s); PPK=population pharmacokinetic(s); Q=intercompartmental clearance; RSE=residual standard error; SAC=single-agent combination; Std. err.=standard error; vs=versus; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

[a] Transformed estimates shown in relative percentage scale and calculated as follows: for the effects of FDC-LS on D1 and F1, 100×exp(estimate) where estimate represents the untransformed estimate as returned by NONMEM; for the other categorical covariate effects, 100×(1+estimate); for the effect of CRCL on CL, 100×0.5^{estimate} (ie, halving of CRCL compared with the median value of the analysis dataset 90.24 mL/min); for IIV and residual error, 100×sqrt(exp(var)-1), where var represents the variance estimate for the log-normally distributed random effects and residual errors as returned by NONMEM.

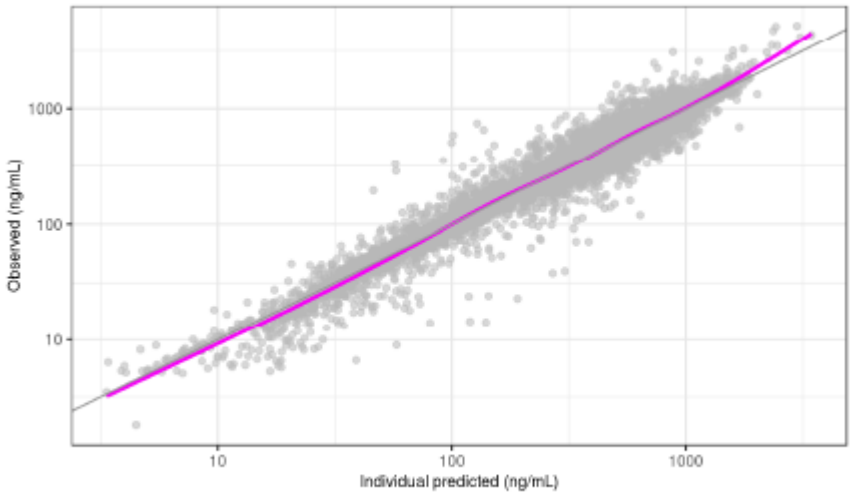
[b] Subjects who did not have observations and hence had estimated random effects equal to 0 were removed from shrinkage calculation.

Figure 38: Observations vs Population Predictions for the Niraparib Final PPK Model



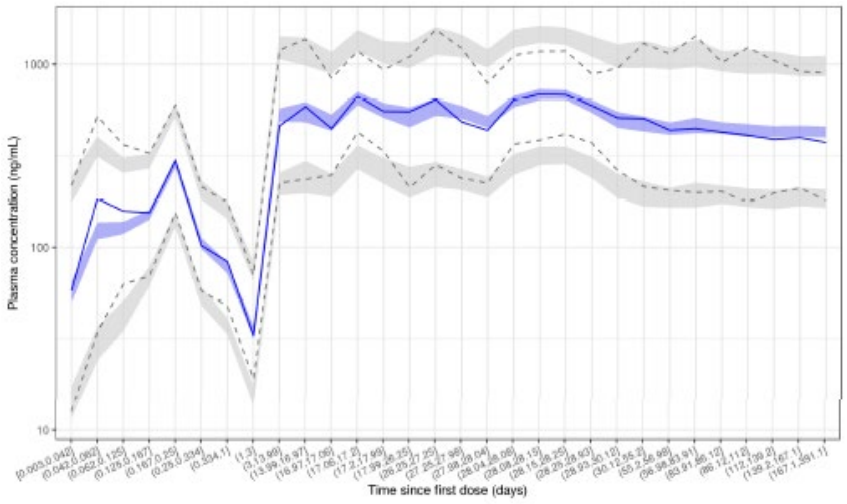
PPK=population pharmacokinetic(s).
Note: The smoothing line is applied to data points with population prediction ≥15 ng/mL, 122 data points (out of total 9907, ie. 1.23%) not shown for reasons of readability.

Figure 41: Observations vs Individual Predictions for the Niraparib Final PPK Model



PPK=population pharmacokinetic(s).

Figure 5: Prediction-corrected Visual Predictive Check for the Niraparib Final PPK Model

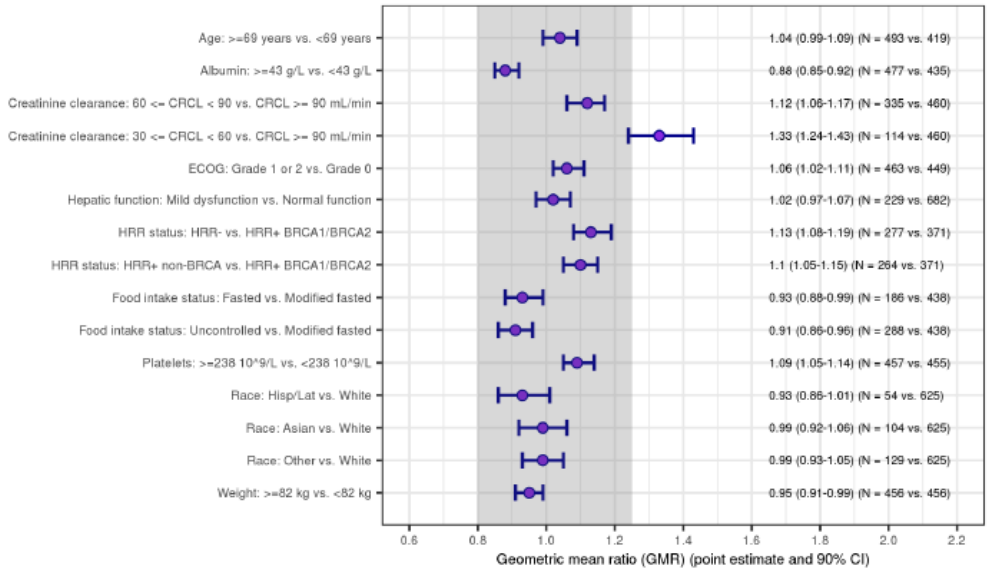


PPK=population pharmacokinetic(s).

Impact of covariates

The impact/clinical relevance of statistically significant covariates and non-included covariates was investigated using forest plots showing the distributions of individual niraparib post-hoc exposure metrics across covariates (Figures below).

Figure 6: Forest Plot of AUC0-24h,ss Based on the Niraparib Final PPK Model



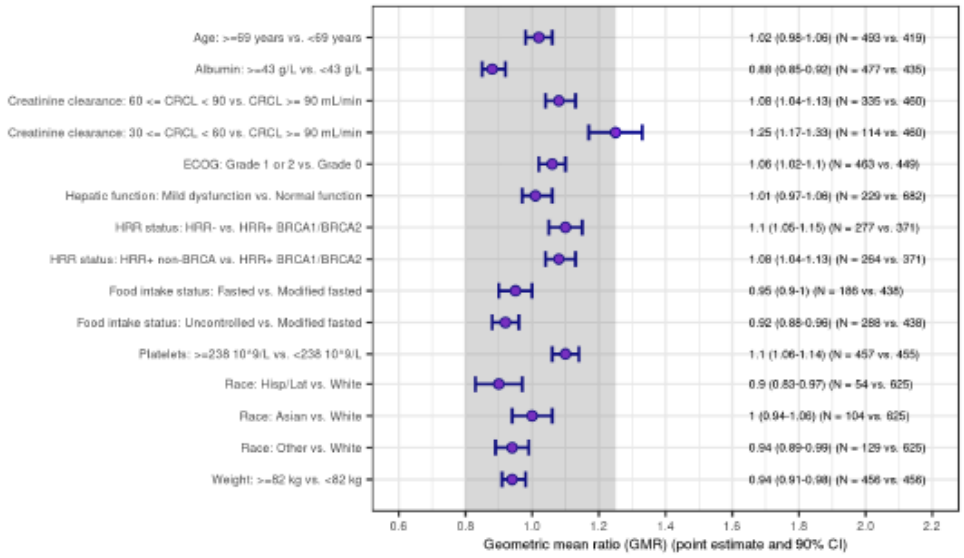
$AUC_{0\text{-}24h,ss}$=area under the concentration-time curve during 24 hours after dosing at steady state; BRCA=breast cancer gene; CI=confidence interval; CRCL=creatinine clearance; ECOG=Eastern Cooperative Oncology Group Performance Status; GMR=geometric mean ratio; Hisp/Lat=Hispanic/Latino race; HRR=homologous recombination repair; mod.=moderate; N=number of subjects (excluding subjects who did not have observations in the analysis dataset); vs=versus.

The gray band represents the 80% to 125% range.

GMR (90% CI) for creatinine clearance 15 ≤ CRCL <30 vs CRCL ≥90 mL/min was 1.63 (1.16-2.31) based on N=3 vs 460, not shown on the plot for readability reasons.

GMR (90% CI) for moderate hepatic dysfunction (based on National Cancer Institute criteria) vs normal function was 1.04 (0.58-1.88) based on N=1 vs 682, not shown on the plot for readability reasons.

Figure 7: Forest Plot of Cmax,ss Based on the Niraparib Final PPK Model



$C_{max,ss}$=maximum plasma concentration during a dosing interval at steady state; BRCA=breast cancer gene; CI=confidence interval; CRCL=creatinine clearance; ECOG=Eastern Cooperative Oncology Group Performance Status; GMR=geometric mean ratio; Hisp/Lat=Hispanic/Latino race; HRR=homologous recombination repair; mod.=moderate; N=number of subjects (excluding subjects who did not have observations in the analysis dataset); vs=versus.

The gray band represents the 80% to 125% range.

GMR (90% CI) for creatinine clearance 15 ≤ CRCL <30 vs CRCL ≥90 mL/min was 1.54 (1.13-2.10) based on N=3 vs 460, not shown on the plot for readability reasons.

GMR (90% CI) for moderate hepatic dysfunction (based on National Cancer Institute criteria) vs normal function was 1.05 (0.62-1.79) based on N=1 vs 682, not shown on the plot for readability reasons.

Abiraterone PPK model

External evaluation:

An external model evaluation was performed to verify the predictive performance of the previously developed PPK model on the current analysis dataset.

Model update:

A model update was then performed to obtain improved residual plots and to assess the effect of FDC-RS and FDC-LS formulations on the abiraterone absorption parameters.

Table 21: Summary of Key Model Runs to Develop the Abiraterone PPK Model

Run Number	Based on Run	Description	Fixed Effects	Random Effects	Minimization	Covariance Step	OFV	ΔOFV
Prev	-	External evaluation of previous model	KA, CL, V2, V3, Q, D1, F1	KA, CL, D1, F1	-	-	2317.112	-
01	Prev	Re-estimation of all parameters (including different RUV for sparse vs rich) with same IIV for fasted and modified fasted for KA, D1, F1	KA, CL, V2, V3, Q, D1, F1	KA, CL, D1, F1	Successful	Successful	1716.222	-600.890
02	01	FDC-RS (FORM=3) and FDC-LS (FORM=4) added on KA, D1, F1	KA, CL, V2, V3, Q, D1, F1	KA, CL, D1, F1	Successful	Successful	1640.990	-75.232
03a	02	FDC-LS on F1 removed	KA, CL, V2, V3, Q, D1, F1	KA, CL, D1, F1	Successful	Successful	1640.995	0.005
04a	**03a**	**FDC-LS on KA and D1 removed**	**KA, CL, V2, V3, Q, D1, F1**	**KA, CL, D1, F1**	**Successful**	**Successful**	**1648.029**	**7.034**

CL=oral clearance; D1=duration of zero-order drug release; F1=apparent oral bioavailability; FDC-LS=low strength fixed-dose combination; FDC-RS=regular strength fixed-dose combination; IIV: interindividual variability; KA=first-order absorption rate constant; OFV= objective function value; Q=intercompartmental clearance; RUV=residual unexplained variability; vs=versus; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

Note: Bold font identifies the final model.

The parameters of the "pre-final" model (ie, run 03a), which is used in the simulated BE assessment for FDC-LS, are summarised in Table 22.

Table 22: Parameter Estimates of the Abiraterone Pre-Final PPK Model

Parameter	Estimate	Std. Err.	RSE%	Transformed Estimate (%)[a]	Shrinkage (%)[b]
KA fasted state (1/h)	3.63	0.414	11	-	-
KA modified fasted state (1/h)	1.33	0.303	23	-	-
CL (L/h)	1675	71.5	4	-	-
V2 (L)	7039	358	5	-	-
V3 (L)	18723	1061	6	-	-
Q (L/h)	1223	71.2	6	-	-
D1 (h)	1.09	0.147	13	-	-
F1 single-agent tablet fasted state	1 (fixed)	-	-	-	-
F1 single-agent tablet modified fasted state	1.08	0.0648	6	-	-
FDC-RS on KA (vs SAC)	0.405	0.146	36	150	-
FDC-RS on D1 (vs SAC)	0.163	0.144	88	118	-
FDC-RS on F1 (vs SAC)	-0.075	0.036	48	93	-
FDC-LS on KA (vs SAC)	-0.228	0.227	100	80	
FDC-LS on D1 (vs SAC)	-0.417	0.372	89	66	
IIV KA	0.503	0.0911	18	81	58
IIV CL	0.0574	0.0113	20	24	45
IIV V2	0 (fixed)	-	-	-	-
IIV V3	0 (fixed)	-	-	-	-
IIV Q	0 (fixed)	-	-	-	-
IIV D1	0.296	0.0886	30	59	72
IIV F1	0.375	0.0381	10	67	26
Residual error rich PK sampling	0.299	0.0169	6	59	-
Residual error sparse PK sampling	0.477	0.0427	9	78	-

BE=bioequivalence; CL=oral clearance; D1=duration of zero-order drug release; F1=apparent oral bioavailability; FDC-LS=low strength fixed-dose combination; FDC-RS=regular strength fixed-dose combination; IIV=interindividual variability; KA=first-order absorption rate constant; NONMEM=nonlinear mixed-effects modeling software; PK=pharmacokinetic(s); PPK=population pharmacokinetic(s); Q=intercompartmental clearance; RSE=residual standard error; SAC=single-agent combination; Std. err.=standard error; vs=versus; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

[a] Transformed estimates shown in relative percentage scale and calculated as follows: for the effects of FDC-RS on KA, D1, and F1, and of FDC-LS on KA and D1, 100×exp(estimate) where estimate represents the untransformed estimate as returned by NONMEM; for IIV and residual error, 100×sqrt(exp(var)-1), where var represents the variance estimate for the log-normally distributed random effects and residual errors as returned by NONMEM.

[b] Subjects who did not have observations and hence had estimated random effects equal to 0 were removed from shrinkage calculation.

Table 23: Parameter Estimates of the Abiraterone Final PPK Model

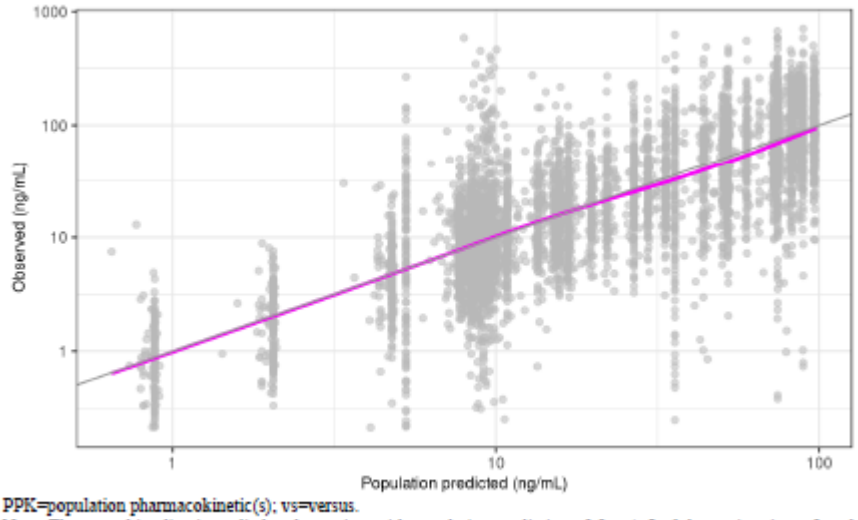
Parameter	Estimate	Std. Err.	RSE%	Transformed Estimate (%)[a]	Shrinkage (%)[b]
KA fasted state (1/h)	3.19	0.173	5	-	-
KA modified fasted state (1/h)	1.32	0.126	10	-	-
CL (L/h)	1673	79	5	-	-
V2 (L)	7052	379	5	-	-
V3 (L)	18722	1124	6	-	-
Q (L/h)	1224	78.3	6	-	-
D1 (h)	0.875	0.0632	7	-	-
F1 single-agent tablet fasted state	1 (fixed)	-	-	-	-
F1 single-agent tablet modified fasted state	1.08	0.0654	6	-	-
FDC-RS on KA (vs SAC)	0.510	0.0843	17	167	-
FDC-RS on D1 (vs SAC)	0.358	0.0728	20	143	-
FDC-RS on F1 (vs SAC)	-0.0749	0.0354	47	93	-
IIV KA	0.453	0.0717	16	76	58
IIV CL	0.0579	0.0111	19	24	45
IIV V2	0 (fixed)	-	-	-	-
IIV V3	0 (fixed)	-	-	-	-
IIV Q	0 (fixed)	-	-	-	-
IIV D1	0.315	0.103	33	61	72
IIV F1	0.374	0.0381	10	67	26
Residual error rich PK sampling	0.3	0.0172	6	59	-
Residual error sparse PK sampling	0.479	0.0426	9	78	-

CL=oral clearance; D1=duration of zero-order drug release; F1=apparent oral bioavailability; FDC-RS=regular strength fixed-dose combination; IIV=interindividual variability; KA=first-order absorption rate constant; NONMEM=nonlinear mixed-effects modeling software; PK=pharmacokinetic(s); PPK=population pharmacokinetic(s); Q=intercompartmental clearance; RSE=residual standard error; SAC=single-agent combination; Std. err.=standard error; vs=versus; V2=volume of distribution of the central compartment; V3=volume of distribution of the peripheral compartment.

[a] Transformed estimates shown in relative percentage scale and calculated as follows: for the effects of FDC-RS on KA, D1, and F1, 100×exp(estimate) where estimate represents the untransformed estimate as returned by NONMEM; for IIV and residual error, 100×sqrt(exp(var)-1), where var represents the variance estimate for the log-normally distributed random effects and residual errors as returned by NONMEM.

[b] Subjects who did not have observations and hence had estimated random effects equal to 0 were removed from shrinkage calculation.

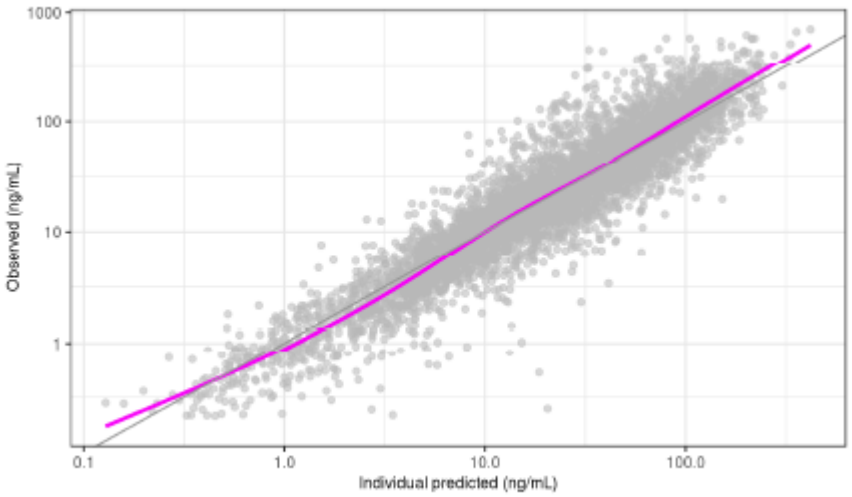
Figure 69: Observations vs Population Predictions for the Abiraterone Final PPK Model



PPK=population pharmacokinetic(s); vs=versus.

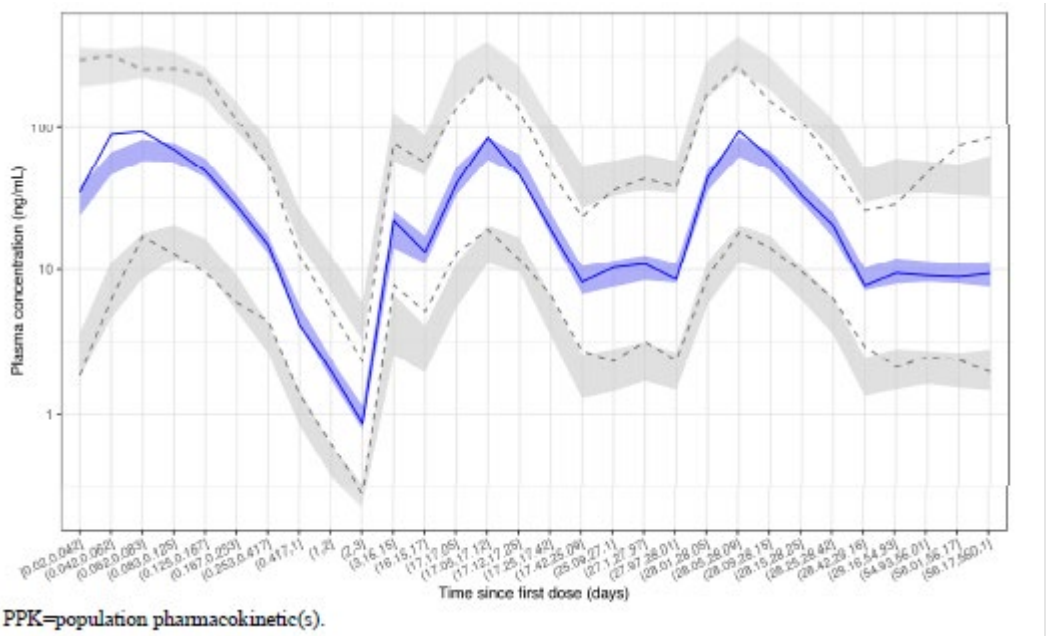
Note: The smoothing line is applied to data points with population prediction ≥0.2 ng/mL, 6 data points (out of total 6,289, ie, 0.1%) not shown for reasons of readability.

Figure 72: Observations vs Individual Predictions for the Abiraterone Final PPK Model



PPK=population pharmacokinetic(s); vs=versus.

Figure 8: Prediction-corrected Visual Predictive Check for the Abiraterone Final PPK Model

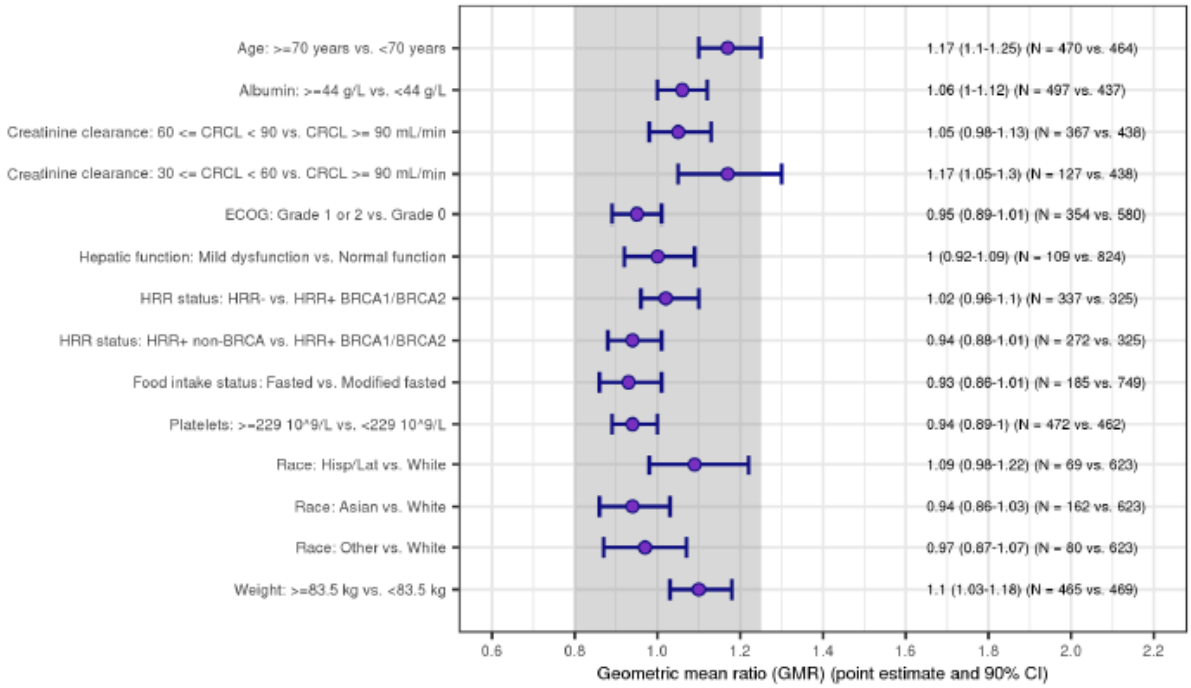


PPK=population pharmacokinetic(s).

Impact of covariates:

The impact/clinical relevance of statistically significant covariates and non-included covariates were investigated using forest plots showing the distributions of individual abiraterone post-hoc exposure metrics across covariates (Figures below). Forest plots showing the model-predicted impact on steady state exposure metrics ($AUC_{0\text{-}24h}$, C_{max} and C_{trough}) based on the final model fixed effect parameters for abiraterone and niraparib have also been provided.

Figure 9: Forest Plot of AUC0-24h,ss Based on the Abiraterone Final PPK Model



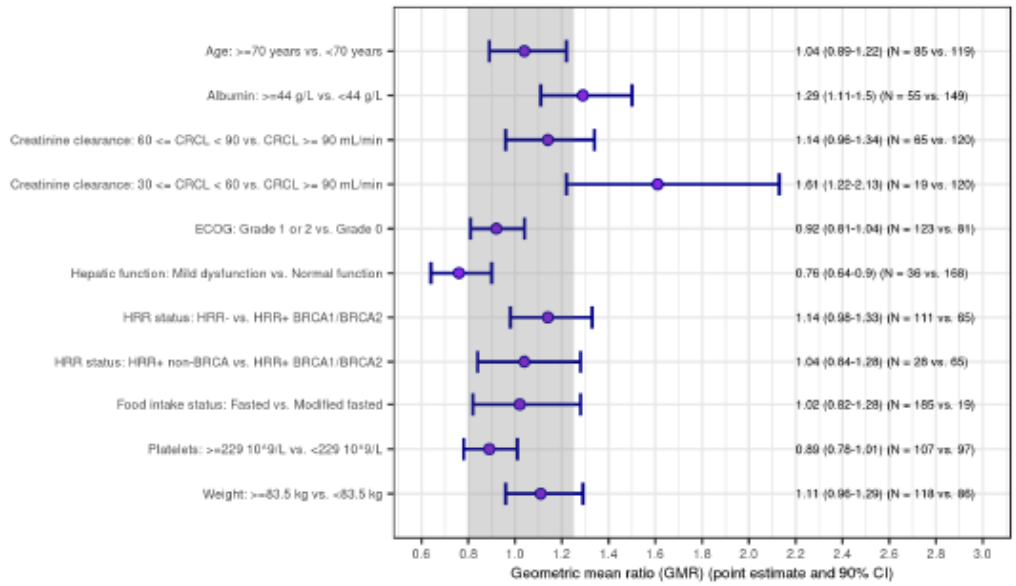
$AUC_{0\text{-}24h,ss}$=area under the concentration-time curve during 24 hours after dosing at steady state; BRCA=breast cancer gene; CI=confidence interval; CRCL=creatinine clearance; ECOG=Eastern Cooperative Oncology Group Performance Status; GMR=geometric mean ratio; Hisp/Lat=Hispanic/Latino race; HRR=homologous recombination repair; mod.=moderate; N=number of subjects (excluding subjects who did not have observations in the analysis dataset); vs=versus.

The gray band represents the 80% to 125% range.

GMR (90% CI) for creatinine clearance 15 ≤ CRCL <30 vs CRCL ≥90 mL/min was 1.12 (0.60-2.07) based on N=2 vs 438, not shown on the plot for readability reasons.

GMR (90% CI) for moderate hepatic dysfunction (based on National Cancer Institute criteria) vs normal function was 1.56 (0.66-3.71) based on N=1 vs 824, not shown on the plot for readability reasons.

Figure 10: Forest Plot of Cmax,ss Based on the Abiraterone Final PPK Model



BRCA=breast cancer gene; CI=confidence interval; $C_{max,ss}$=maximum plasma concentration during a dosing interval at steady state; CRCL=creatinine clearance; ECOG=Eastern Cooperative Oncology Group Performance Status; GMR=geometric mean ratio; Hisp/Lat=Hispanic/Latino race; HRR=homologous recombination repair; mod.=moderate; N=number of subjects (excluding subjects who did not have observations in the analysis dataset); vs=versus.

The gray band represents the 80% to 125% range.

GMR (90% CI) for Hispanic/Latino race vs white race was 1.27 (0.67-2.4) based on N=2 vs 189, GMR (90% CI) for Asian race vs white race was 1.42 (0.76-2.67) based on N=2 vs 189, and GMR (90% CI) for other races vs white race was 0.46 (0.34-0.61) based on N=11 vs 189, not shown on the plot for readability reasons.

Special populations

- ***Impaired renal function***

There is no formal study of niraparib/AA combo (as SAC or FDC) in subjects with renal impairment. Results from mono component studies and popPK analyses including combination therapy data are presented below.

Niraparib

There was no formal study of niraparib in subjects with renal impairment.

In the pooled PopPK dataset from subjects with mCRPC, 50% of the subjects had normal renal function (CRCL ≥90 mL/minute; N=462/916), 37% of the subjects had mild dysfunction (CRCL 60-<90 mL/minute; N=337/916), 12% of the subjects had moderate dysfunction (CRCL 30-<60 mL/minute; N=114/916), and 3 of the subjects had severe dysfunction (CRCL <30 mL/minute).

In the popPK niraparib model analysis, CRCL was identified as a covariate on CL/F (estimated exponent 0.305, which translates into a ~29% reduction in CL/F in a subject with CRCL 30 mL/min compared to the reference subject with CLCR 90.24 mL/min.

Abiraterone

Systemic exposure to abiraterone was not increased in subjects with end-stage renal disease compared with matched control subjects with normal renal function in study **COU-AA-012**.

Table 24: PK Parameters of Abiraterone in Plasma From Stage I (COU-AA-012)

Parameter	Mean (SD), t_{max}: Median (Range)	
	ESRD N=8	Normal Renal Function N=8
C_{max}, ng/mL	50.2 (37.7)	104 (124)
t_{max}, h	3.0 (1.0-6.0)	1.5 (1.0-4.0)
AUC_{last}, ng.h/mL	305 (267)	485 (513)
$AUC_{0-\infty}$, ng.h/mL	315 (265)	497 (523)
$t_{1/2}$, h	16.0 (2.00)	19.0 (4.08)
CL/F, L/h	5,060 (3,034)	3,168 (1,638)
Vd/F, L	118,926 (74,377)	80,346 (32,619)
	Ratio of Geometric Means (Test/Reference) % (90% CI)	
	N=8	
C_{max}, ng/mL	53.1 (26.77-105.21)	
AUC_{last}, ng.h/mL	62.8 (32.41-121.71)	
$AUC_{0-\infty}$, ng.h/mL	65.0 (34.25-123.21)	

$AUC_{0-\infty}$=area under the plasma concentration-time curve extrapolated to infinite time; AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of the last quantifiable concentration; CI=confidence interval; CL/F=apparent oral clearance; C_{max}=maximum plasma concentration; ESRD=end-stage renal disease; N=maximum number of subjects with data; PK=pharmacokinetic(s); SD=standard deviation; $t_{1/2}$=terminal elimination half-life; t_{max}=time to reach the maximum plasma concentration; Vd/F=apparent volume of distribution.

In a previous popPK analysis in subjects with mCRPC who received abiraterone, renal function (mild/moderate impairment) was not identified as a significant covariate on abiraterone PK.

In the current PopPK dataset consisting of subjects with mCRPC, 47% of the subjects had normal renal function (CRCL ≥90 mL/minute; N=447/954), 40% of the subjects had mild dysfunction (CRCL 60-<90 mL/minute; N=378/954), 13% of the subjects had moderate dysfunction (CRCL 30-<60 mL/minute; N=127/954), and two of the subjects had severe dysfunction (CRCL <30 mL/minute). Renal function (CRCL) was not re-investigated as a covariate in the current popPK model analysis.

- ***Impaired hepatic function***

There is no formal study of niraparib/AA combo (as SAC or FDC) in subjects with hepatic impairment. All clinical trials investigating the combination therapy (niraparib and abiraterone) excluded subjects with moderate or severe hepatic impairment.

Niraparib

Study **3000-01-003**: The area under the plasma concentration-time curve from time 0 to infinity (AUC0-∞) in subjects with moderate hepatic impairment was 1.56 times the niraparib AUC0-∞ in subjects with normal hepatic function following administration of a single 300 mg dose whereas moderate hepatic impairment did not have an effect on niraparib Cmax or on niraparib protein binding.

In the pooled niraparib PopPK dataset from subjects with mCRPC, the majority of patients (74.7%, 684/916) had normal hepatic function, and 25.2% (231/916) and 01.1% (1/916) had mild and moderate hepatic impairment, respectively (National Cancer Institute criteria). Hepatic impairment was not identified as a significant covariate on niraparib pharmacokinetics in the popPK model analysis.

Abiraterone

Systemic exposure to abiraterone after a single 1,000 mg oral dose of AA increased by approximately 11% and 260% in subjects with mild and moderate pre-existing hepatic impairment, respectively, compared with subjects with normal hepatic function (study **COU-AA-011**). Systemic exposures to abiraterone after the administration of a 125 mg suspension of AA in subjects with severe hepatic impairment were 358% (for Cmax), 756% (for AUC from time 0 to the time of the last quantifiable

concentration), and 697% (for AUC0-∞) of dose-normalised exposures reported in subjects with normal hepatic function after the administration of a 2,000 mg suspension of AA (study **212082PCR1004**).

The fraction of free drug increased by 80% in subjects with severe hepatic impairment compared to subjects with normal hepatic function.

In the pooled abiraterone PopPK dataset from subjects with mCRPC, the majority of patients (87.9%, 684/954) had normal hepatic function, and 25.2% (114/954) and 01.1% (1/954) had mild and moderate hepatic impairment, respectively (National Cancer Institute criteria). Mild hepatic impairment was not investigated as a covariate in the abiraterone popPK model analysis.

- ***Gender***

All clinical pharmacology data for the combination were derived from male subjects.

Race

Niraparib

In the studied patient population (n=916), 68.7% (n=629) was white (not Hispanic or Latino), 5.9% (n=54) was white (Hispanic or Latino), 11.4% (n=104) was Asian, 2.2% (n=20) was black, other or unknown was 11.5 % (n=105), while Native Hawaiian or Other Pacific Islander accounted for 0.2% (n=2) and American Indian or Alaskan Native accounted for 0.2% (n=2).

Based on the PopPK analysis with pooled PK data from subjects with mCRPC, other races (ie, races other than white, Asian, or Hispanic/Latino), and Hispanic/Latino race, were identified as covariates on first-order absorption rate constant (36% decrease versus white race and 33% decrease versus white race, respectively), as well as Asian race on intercompartmental clearance (39% decrease versus white race), and on volume of distribution of the peripheral compartment (48% increase versus white race).

Abiraterone

In a previous PopPK analysis in subjects with mCRPC who received abiraterone, the potential effects of race/ethnicity on the pharmacokinetics of abiraterone were not formally investigated as subjects were primarily white males (>75%).

In the currently studied patient population (n=954), 67.2% (n=641) was white (not Hispanic or Latino), 7.2% (n=69) was white (Hispanic or Latino), 17.1% (n=163) was Asian, 1.2% (n=11) was black, other or unknown was 6.8% (n=65), while Native Hawaiian or Other Pacific Islander accounted for 0.2% (n=2) and American Indian or Alaskan Native accounted for 0.3% (n=3). Race was not investigated as a covariate in the current popPK model analysis.

- ***Weight***

Niraparib

Based on the current PopPK analysis, body weight (43-165 kg) did not have a clinically relevant impact on the exposure to niraparib.

Abiraterone

Based on previous popPK modelling using data from single agent therapy, body weight (56-135 kg) did not have a clinically relevant impact on the exposure of abiraterone. In the current popPK analysis body weight (46-165 kg) was not re-investigated as a covariate.

- ***Elderly***

The summary table with the distribution of subjects included in the PK analysis dataset across different sub-groups of age (18-64, 65-74, 75-84, and 85+ years) is shown in Table 25 for niraparib and in

Table 26 for abiraterone, where table rows for "controlled" studies include subjects from MAGNITUDE study Cohorts 1 and 2, while table rows for "uncontrolled" studies include subjects from studies BEDIVERE, GALAHAD (for niraparib only), QUEST, MAGNITUDE Cohort 3, and the BA/BE study.

Table 25:Summary of subjects by study type and age groups for niraparib

Study type	Age 18-64 years	Age 65-74 years	Age 75-84 years	Age 85+ years
Controlled	81 (8.8%)	149 (16.3%)	88 (9.6%)	9 (1%)
Uncontrolled	179 (19.5%)	282 (30.8%)	114 (12.4%)	14 (1.5%)

Table 26:Summary of subjects by study type and age group for abiraterone

Study type	Age 18-64 years	Age 65-74 years	Age 75-84 years	Age 85+ years
Controlled	168 (17.6%)	304 (31.9%)	168 (17.6%)	16 (1.7%)
Uncontrolled	95 (10%)	140 (14.7%)	56 (5.9%)	7 (0.7%)

Pharmacokinetic interaction studies

Pharmacokinetic drug interaction studies with the FDC have not been performed.

Potential for DDI for the FDC is based on information that were generated as part of the development programs for niraparib and abiraterone as single entities. No new DDI is expected when niraparib and AA are given in combination.

The exposures of niraparib and abiraterone are apparently not impacted to a great extent when given in combination compared with when given alone based on comparison with historical data generated with single entities (Table 27,Table 28).

Table 27: Across-study Summary of PK of Niraparib After Single and Multiple Dose Administration of 200 and 100 mg Niraparib Given as 100 mg Capsules in Subjects With Cancer (PN001, 64091742PCR1001, 64091742PCR2002, 67652000PCR1001)

Dosing	Study	Dose (mg)	t_{max}, h		C_{max}, ng/mL		AUC_{0-24h}, ng.h/mL
			N	Median (Range)	Mean (SD)	N	Mean (SD)
Single	PN001	200[a]	6	3.0 (2.0-4.1)	563 (329)	6	6,621 (4,344)
	PN001	100[a]	5	3.3 (3.0-4.0)	300 (142)	5	3,203 (1,289)
	64091742PCR1001[b]	200	4	3.26 (3.00-4.00)	379 (194)	3	5,139 (1,629)
	67652000PCR1001[c]	100	67	2.00 (1.48-48.00)	239 (170)	66	4,619 (2,223)[d]
Multiple	PN001	200[a]	5	4.0 (2.0-6.0)	964 (854)	5	16,736 (16,157)
	PN001	100[a]	3	2.0 (1.5-3.0)	513 (262)	3	7,417 (3,585)
	64091742PCR1001[b]	200	11	4.00 (2.00-6.35)	985 (409)	10	17,745 (9,380)
	67652000PCR1001[b]	200	118	3.00 (0.00-10.00)[e]	808 (265)[f]	117	13,581 (5,147)[g]

AA=abiraterone acetate; AUC=area under the plasma concentration-time curve; AUC_{0-24h}=area under the plasma concentration-time curve from time 0 to 24 hours; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours at steady state; AUC_{0-72h}=area under the plasma concentration-time curve from time 0 to 72 hours; C_{max}=maximum plasma concentration; $C_{max,ss}$=maximum plasma concentration at steady state; N=maximum number of subjects with data; PK=pharmacokinetic(s); SD=standard deviation; t_{max}=time to reach the maximum plasma concentration; $t_{max,ss}$=time to reach the maximum plasma concentration at steady state.

[a] C_{max} and AUC are dose normalized from 210 mg to 200 mg or 110 mg to 100 mg as applicable; AUC and C_{max} values were converted from nM to ng/mL using niraparib molecular weight of 320.39.
[b] 200 mg niraparib given as 100 mg capsules in combination with 1,000 mg AA given as 250 mg tablets.
[c] 100 mg niraparib given as a 100 mg capsule in combination with 1,000 mg AA given as 250 mg tablets.
[d] AUC_{0-72h}.
[e] $t_{max,ss}$.
[f] $C_{max,ss}$.
[g] $AUC_{0-24h,ss}$.

Table 28: Across-study Summary of PK of Abiraterone After Single and Multiple Dose Administration of 1,000 mg AA Given as 250 mg Tablets in Subjects With Prostate Cancer (212082PCR2008, 64091742PCR2002, 67652000PCR1001, 64091742PCR1001)

Dosing	Study	t_{max}, h		C_{max}, ng/mL	AUC_{0-24h}, ng.h/mL		Note
		N	Median (Range)	Mean (SD)	N	Mean (SD)	
Single	COU-AA-006	33	2 (1-4)	182 (254)	33	675 (725)	
	67652000PCR1001[a]	67	1.89 (1.00-6.00)	132 (95.3)	66	672 (435)[b]	
Multiple	COU-AA-006	33	2 (1-6)	226 (178)	33	993 (639)	
	212082PCR2008	15	2.0 (0.5-6.0)	182 (145)	15	970 (541)	Analysis of meal ≥1 h after dose
	64091742PCR1001[a]	3	1.35 (1.00-2.00)	137 (69.4)	3	712 (140)	
	67652000PCR1001[a]	118	2.00 (1.00-4.00)[c]	158 (96.5)[d]	117	768 (546)[e]	

AA=abiraterone acetate; AUC_{0-24h}=area under the plasma concentration-time curve from time 0 to 24 hours; $AUC_{0-24h,ss}$=area under the plasma concentration-time curve from time 0 to 24 hours at steady state; AUC_{0-72h}=area under the plasma concentration-time curve from time 0 to 72 hours; C_{max}=maximum observed concentration; $C_{max,ss}$=maximum plasma concentration at steady state; N=maximum number of subjects with data; PK=pharmacokinetic(s); SD=standard deviation; t_{max}=time to reach the maximum plasma concentration; $t_{max,ss}$=time to reach the maximum plasma concentration at steady state.

[a] 1,000 mg AA was given as 250 mg tablets in combination with 200 mg niraparib given as 100 mg capsules.
[b] AUC_{0-72h}.
[c] $t_{max,ss}$.
[d] $C_{max,ss}$.
[e] $AUC_{0-24h,ss}$.

2.6.2.2. Pharmacodynamics

Mechanism of action

Niraparib in combination with abiraterone acetate

Niraparib is an orally available, highly selective PARPi, with activity against PARP-1 and PARP-2 DNA-repair polymerases. In vitro studies have shown that niraparib-induced cytotoxicity may involve inhibition of PARP enzymatic activity and increased formation of PARP-DNA complexes resulting in DNA damage, apoptosis and cell death. Abiraterone acetate is a prodrug of abiraterone, an androgen biosynthesis inhibitor. Specifically, abiraterone selectively inhibits the enzyme 17α-hydroxylase/C17,20-lyase (CYP17).

Approximately 15-20% of subjects with mCRPC have HRR gene alterations. The HRR gene alterations may act as be a second oncogenic driver, which could be amenable to treatment with a PARP inhibitor. For such subjects, antitumor activity with a PARP inhibitor has been demonstrated in Study 64091742PCR2001 (hereafter referred to as GALAHAD).

Primary and Secondary pharmacology

- ***Primary pharmacology***

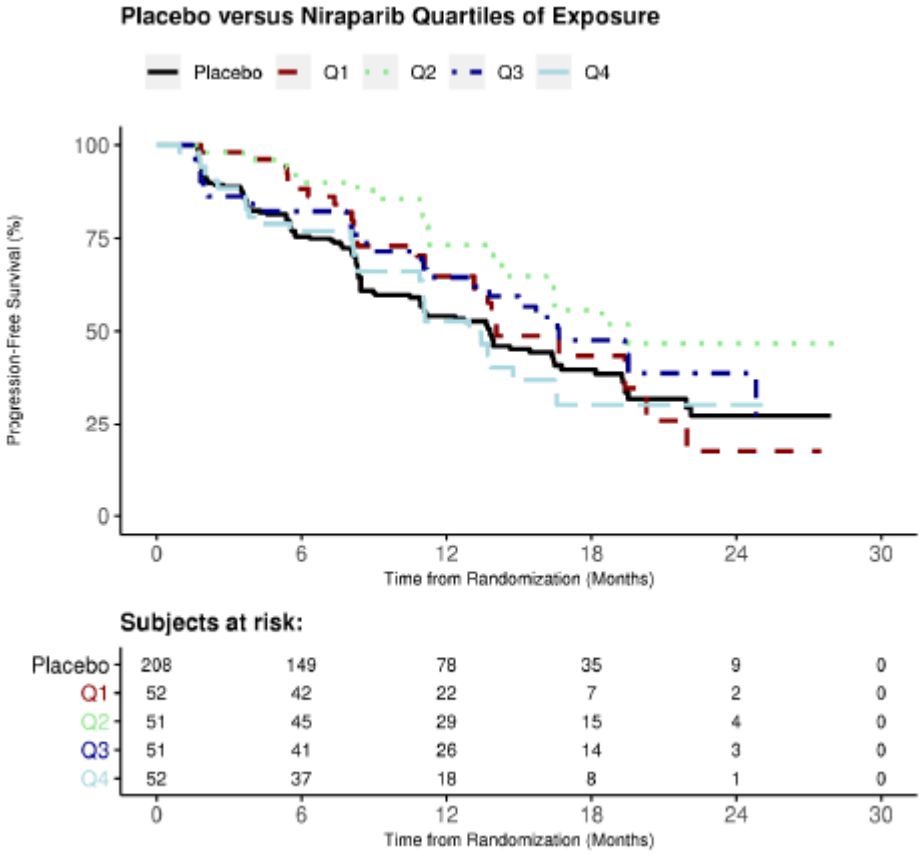
The E-R evaluations were based on data from the MAGNITUDE study, Cohort 1 and 2, cohorts with a double-blind placebo-controlled design. For efficacy, only data from subjects with HRR gene alteration (Cohort 1) were included, while for safety, data from subjects with or without HRR gene alteration (Cohort 1 and 2) were considered. The primary efficacy endpoint was rPFS, defined as the time interval from the date of randomization to the first date of radiographic progression as assessed by Blinded Independent Central Review or death due to any cause, whichever occurred first.

Efficacy evaluation

Univariate Kaplan-Meier Analysis

Univariate Kaplan-Meier analyses to explore the influence of the prognostic factors as well as niraparib exposure metrics on the efficacy endpoint.

Figure 11: Kaplan-Meier Plot of Radiographic Progression-free Survival by Central Review: Influence of Niraparib Exposure Metrics – Cohort 1, All HRR Randomised Analysis Set (Subjects with PK Parameters, N=414)



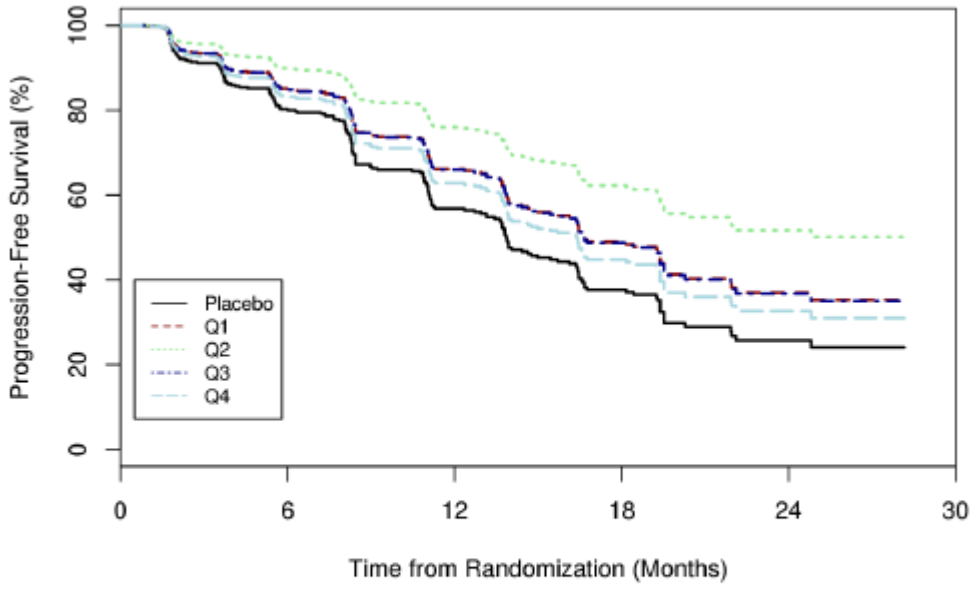
HRR=homologous recombination repair; PK=pharmacokinetic(s); Q=quartile.

Multivariate Analysis

Multivariate Cox regression analysis was conducted in a stepwise manner.

A multivariate Cox regression analysis with niraparib Cavg categorised by quartiles adjusted for the significant prognostic factors (baseline prostate-specific antigen, lactate dehydrogenase, alkaline phosphatase, and presence of visceral disease [yes versus no]) was conducted. No E-R relationship was observed.

Figure 12: Predicted Survival for Radiographic Progression-free Survival in Placebo and Q1 to Q4 of Niraparib Cavg, Adjusted for the Significant Prognostic Factors



ALP=alkaline phosphatase; C_{avg}=average drug concentration; LDH=lactate dehydrogenase; PSA=prostate-specific antigen; Q1=lowest exposure quartile; Q2=second exposure quartile; Q3=third exposure quartile; Q4=highest exposure quartile.
The predicted survival profiles are drawn for a typical subject with mean PSA, LDH and ALP values, and no visceral disease at baseline.

The key safety endpoints included in the exposure-safety analysis were selected based on observed adverse events with an occurrence higher than 10% and severity of Grade 3 or higher and a statistically significant difference between the incidences in the niraparib plus AAP group versus the placebo plus AAP group. Preselected safety endpoints (grouped term) for the analysis included:

- Haematological toxicity (including thrombocytopenia, anaemia, and/or neutropenia)
- Nausea
- Hypertension
- Hypokalemia
- Fluid retention/edema
- Hepatotoxicity

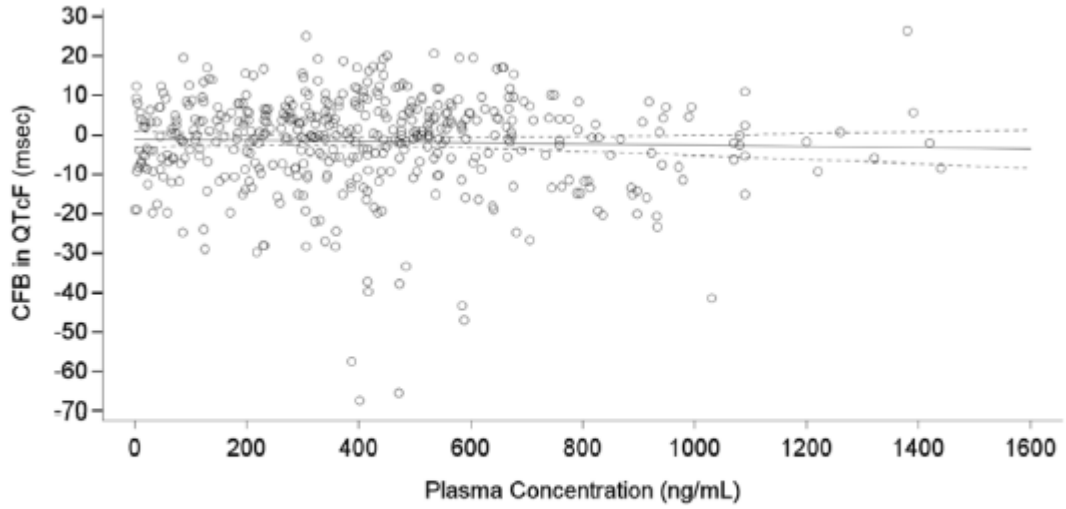
- ***Secondary pharmacology***

Niraparib (PR-30-5011-C1-CARDIAC) (Monotherapy Study, Previously Submitted)

Evaluation of potential effect of niraparib on QT/QTc in patients with cancer.

The relationship between niraparib plasma concentration and change from baseline in the QTcF interval was explored graphically and analysed using a linear mixed-effects model. No exposure-related positive trends were observed in mean QTcF or mean changes from baseline (ΔQTcF) versus time since dosing. No statistically significant correlation between ΔQTcF and the concentration of circulating niraparib in subjects was detected (estimated slope: 0.0049, 95% CI: -0.0020, 0.0117).

Figure 13: **Correlation Between the QTc Change From Baseline and the Plasma Concentration in the QTc and Food Effect Subject Subsets (PR-30-5011-C1-CARDIAC)**



CFB=change from baseline; CI=confidence interval; QTc=QT interval corrected for heart rate; QTcF=QT interval corrected for heart rate using Fridericia's formula.

Note: Regression line (95% CI): Intercept=-2.2, Slope=0.0049(-0.0020, 0.0117), p=0.164 for the slope of CFB in QTc against plasma concentration, which are calculated from a mixed effects model with a fixed effect for plasma concentration and random effect for subject.

Source: Mod5.3.5.4/PR-30-5011-C1-CARDIAC/Fig7

Abiraterone (COU-AA-006) (Monotherapy Study, Previously Submitted)

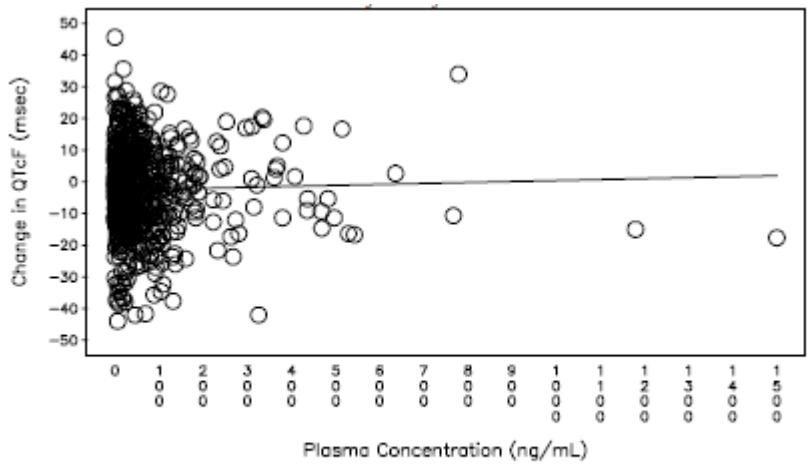
A QT/QTc and multi-dose PK study of AA (CB7630) plus prednisone in patients with mCRPC.

The relationship between QTcF and the corresponding abiraterone concentrations were evaluated by applying a linear mixed effects model. The expected changes from baseline in the QTcF intervals (and corresponding 95% confidence intervals) were also presented.

In addition the change in QTc was plotted vs. corresponding abiraterone concentrations and Cmax for abiraterone.

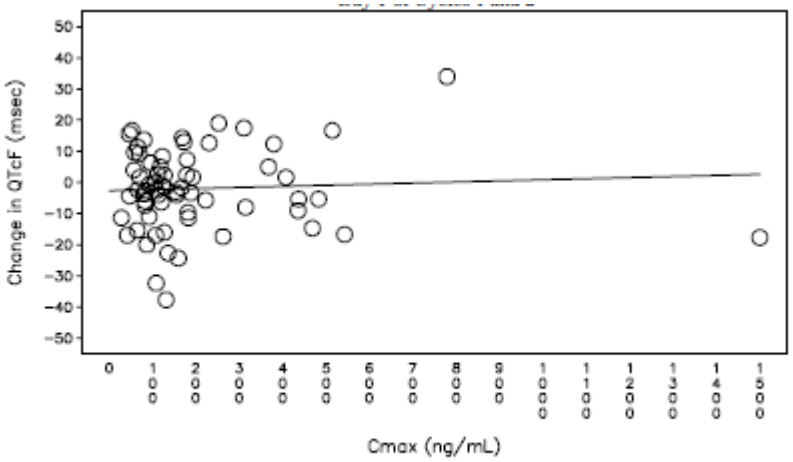
The individual change from baseline in QTcF interval and corresponding abiraterone plasma concentrations exhibited no apparent relationship as shown in Figure 14 and Figure 15.

Figure 14: **Scatter Plot of Plasma Concentration of Abiraterone versus Change From Baseline in QTcF Day 1 of Cycles 1 and 2**



The reference line was based on a linear mixed effects model with Intercept=-2.7015 (p-value=0.0214) and Slope=0.0031 (p-value=0.4737).
PROD\RE459 [F_ECG_5_1.rtf], 05OCT2010 11:16.

Figure 15: **Scatter Plot of Abiraterone Cmax versus Change From Baseline in QTcF Day 1 of Cycles 1 and 2**



The reference line was based on a linear mixed effects model with Intercept=-2.7289 (p-value=0.2642) and Slope=0.0036 (p-value=0.6149).
PROD\RE459 [F_ECG_5_3.rtf], 05OCT2010 11:16.

- ***Relationship between plasma concentration and effect***

Exposure-Response analysis

Exposure metrics:

For the E-R analyses, niraparib and abiraterone average exposure up to the time of the first event (ie, progression or death for efficacy, adverse event for safety endpoints), censoring, or end of the treatment was considered:

- Efficacy: steady-state Cavg (ie, AUC0-24h,ss/24) up to the time of the event of interest
- Safety: steady-state AUC0-24h and Cmax up to the time of the event of interest

The relationship between AUC0-24h,ss and Cmax,ss exposure metrics was investigated via scatterplots and linear regression. The correlation between the metrics was high (R^2>0.98) for both niraparib and

abiraterone. Therefore, the exposure metrics used for the safety E-R analysis was AUC0-24h up to the time of the event or end of treatment.

Exposure-efficacy analysis

Univariate Kaplan-Meier analyses on the primary population for E-R analysis were performed to explore the influence of niraparib exposure on rPFS. Niraparib Cavg exposure metrics were categorised by quartiles and an additional category included the subjects randomised to placebo plus AAP.

As summarised in Table 29, no consistent exposure-response relationship was observed in the niraparib plus AAP group. Cavg group Q2 appeared to have a slightly longer median rPFS when compared with other exposure quartile groups, however, none of the groups was statistically different than the lowest quartile (Q1) group.

Table 29: Summary of Radiographic Progression-free Survival by Central Review (Univariate Kaplan- Meier Analysis): Influence of the Niraparib Exposure Metrics – Cohort 1, All HRR Randomized Analysis Set (Subjects With PK Parameters) (N=414)

Niraparib + AAP Group	N	Number of Events (%)	Median rPFS (Months)	HR (95%CI)	p-value
Q1	52	24 (46.2)	14.1		
Q2	51	20 (39.2)	19.5	0.619 (0.341,1.13)	0.116
Q3	51	26 (51)	16.7	0.894 (0.51,1.57)	0.695
Q4	52	29 (55.8)	12.9	1.32 (0.766,2.27)	0.318
Both groups					
Placebo	208	114 (54.8)	13.8		
Q1	52	24 (46.2)	14.1	0.818 (0.526,1.27)	0.373
Q2	51	20 (39.2)	19.5	0.522 (0.324,0.841)	0.00751
Q3	51	26 (51)	16.7	0.752 (0.49,1.15)	0.192
Q4	52	29 (55.8)	12.9	1.07 (0.708,1.61)	0.756

AA-P=abiraterone acetate plus prednisone; CI=confidence interval; HR=hazard ratio; HRR=homologous recombination repair; N=number of subjects; PK=pharmacokinetic(s); Q=quartile; rPFS=radiographic progression-free survival.

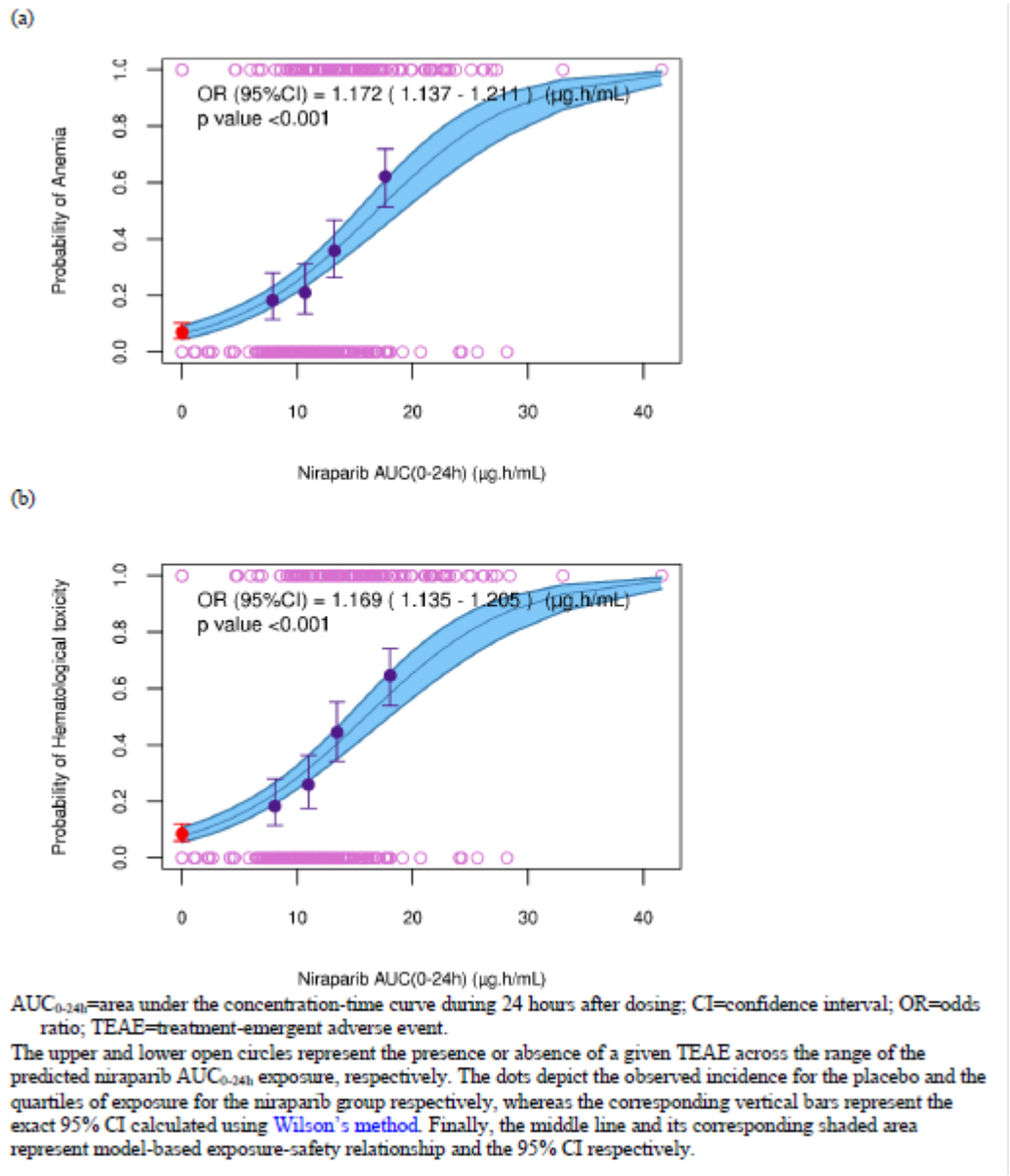
Exposure-safety analysis

First, the exploratory analysis consisted in checking that the pre-selected safety endpoints met the pre-defined criteria for E-R analysis, ie, Grade 3 or higher, overall incidence ≥10% and difference between the incidences in the niraparib plus AAP group versus placebo plus AAP group statistically significant.

Based on the exploratory analysis, the safety endpoints included in the E-R analysis were anaemia and haematological toxicity as combined class of events.

The results showed that the probability of experiencing Grade 3 to 4 anaemia increases with increasing niraparib exposure (Figure 16 a). Similar results were observed with haematological toxicity as combined class of events (Figure 16 b).

Figure 16: **Logistic Regression Representing the Probability of Experiencing Grade 3 or Higher Anaemia (a) and Haematological Toxicity (b) as a Function of Niraparib AUC0-24h - Cohorts 1 and 2, All HRR Randomised Analysis Set (Subjects with PK Parameters, N=655)**



AUC_{0-24h}=area under the concentration-time curve during 24 hours after dosing; CI=confidence interval; OR=odds ratio; TEAE=treatment-emergent adverse event.

The upper and lower open circles represent the presence or absence of a given TEAE across the range of the predicted niraparib AUC_{0-24h} exposure, respectively. The dots depict the observed incidence for the placebo and the quartiles of exposure for the niraparib group respectively, whereas the corresponding vertical bars represent the exact 95% CI calculated using Wilson's method. Finally, the middle line and its corresponding shaded area represent model-based exposure-safety relationship and the 95% CI respectively.

2.6.3. Discussion on clinical pharmacology

The validation of the analytical methods used for the determination of abiraterone and abiraterone acetate (PBRL-RD-1350/JJP567XL-115673-B/BA10183) and of niraparib and M1 in human plasma samples, is considered correct according to EMEA/CHMP/EWP/192217/2009 Rev.1 Corr.2.

The analysis of study samples is considered to have been overall correctly conducted.

Bioequivalence

To bridge the applied formulations to efficacy and safety data obtained with single agent formulations in MAGNITUDE cohort 1 (efficacy and safety, target population) and cohort 2 (safety population), the Applicant conducted a BE/BA study comparing the PK following administration of single agent

formulations and the regular and low strength fixed-dose combinations. Currently EU approved single agent formulations (*i.e.* niraparib [Zejula] 100 mg capsules and abiraterone [Zytiga] 250 mg tablets) were used in both the BA/BE study and in Magnitude cohort 1 and 2.

Regular strength tablet (FDC-RS)

The BE study design for assessing bioequivalence of FDC-RS vs SAG is acceptable and in accordance with the EMA BE guidline (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Sample size calulations, based on inter-individual variability (IIV) from single agent studies and an overall power of at least 80%, appears acceptable. Up to 120 patients were to be enrolled to account for potentially greater IIV due to modified fasting conditions and potential non-evaluability and ensure at least 96 BE evaluable subjects (protocol amendement 2, 19. April 2021).

Based on niraparib and abiraterone half-lifes (50±15 h and 15h, respectively) and QD dosing, steady state is expected to be achieved within the second PK assessment period (*i.e.* 11 days). The PK assessment phase was, according to the Applicant, kept to a minimum due to the potential heamatological effect of niraparib in HRR negative patients.

Primary PK parameters (Cmax, AUC24,ss) and statistical methods used to investigate bioequivalence for FDC-RS are acceptable. Originally, a two-stage design in accordance with the EMA BE guideline was originally planned, however "to increase the probability of success in the final BE analysis", the interim analysis was not further pursued (Protocol amendment 2 19. April 2021).

With respect to niraparib, BE was demonstrated for FDC-RS vs SAC. Point estimates were 1.03 and 1.01 for Cmax,ss and AUC0-24h,ss, respectively, the 90% CIs were within the prespecified acceptance limits (80.00-125.00%), and IIVs for the primary BE PK parameters were low (~15-16%). Abiraterone Cmax,ss and AUC0-24h,ss geometric mean ratios and corresponding 90% CI intervals (*i.e.* 96.67 [90%CI 87.59, 106.69] and 93.33 [90%CI 86.91, 100.23]) were also within the acceptance limits when FDC-RS was compared with SAC, although the upper bound 90% CI for AUC0-24h,ss was just above 100. IIVs for primary BE PK parameters were ~34-48%.

In summary, bioequivalence between the regular-strength fixed-dose combination tablets and the single agents of niraparib and abiraterone acetate has been adequately demonstrated.

Low strength tablet (FDC-LS)

The lower strenght tablet was developed to accommodate dose reductions of niraparib. No formal evaluation of BE between the lower strength of niraparib/abiraterone fixed-dose tablets (FDC-LS) and SAC was attempted. Instead, relative bioavailability of FDC-LS versus SAC following a single dose was investigated using a parallel design which was not in accordance with the scientific advice provided (EMEA/H/SA/4392/1/2020/III). The rationale for chosing a parallel design (*i.e.* biowaiver criteria) is not supported.

In parallel design studies, the treatment groups should be comparable in all known variables that may affect the pharmacokinetics of the active substance. This is an essential pre-requisite to give validity to the results from such studies. Although, according to the Applicant, no differences in demographics or disease characteristics between treatment sequences were apparent, the study design did not account for inter-subject differences as patients were randomly assigned to treatment sequences 1 to 4.

For the FDC-LS formulation following a single dose of niraparib/abiraterone 100 mg/1000 mg, lower bound 90%CI of niraparib Cmax (78.22) was not within the general BE acceptance limits, and lower bound 90%CI for AUC0-72h was borderline (80.31). Geometric mean ratios of niraparib Cmax and AUC0-72h were 90.88% and 90.11%, respectively. With respect to abiraterone, GMR (90%CI) for

Cmax and AUC0-72h were 132.62 (108.35-162.32) and 121.93 (101.09-147.07), and 90CI% intervals did not contain 100.

Thus, the relative BA assessment indicated non-bioequivalence between FDC-LS tablets and SAC.The apparent increased abiraterone exposure represent a potential safety concern with the FDC-LS as abiraterone is already given at the maximum recommended dose (1000 mg) according to the proposed posology. However, it is still unclear whether these BA results are related to high interindividual variability or represent actual formulation effects.

Due to the high IIV in GMR observed for abiraterone FDC-LS vs SAC, the Applicant presented additional post hoc investigations of paired single-sequence data which showed that 90% CI of the GMRs for estimated abiraterone Cmax,ss and AUC (AUC0-∞ for FDC-LS or AUC0-24h,ss for SAC) between FDC-LS and SAC were within the 80.00% to 125.00% BE criteria.

In addition, the Applicant conducted a model-based assessment to predict whether the FDC-LS formulation was bioequivalent with the single agents. The simulation of a cross-over design with the pre-final PopPK model of abiraterone, which included the covariate effects of LS-FDC on KA and D1, while accounting for their large RSE, showed a probability of showing BE of 96.4%.Considering the unfeasibility to conduct an experimental BE study, the submitted modelling and simulation exercise could be used in this specific case to support the post hoc analysis conducted with sequence 3 and 4 of the submitted BA/BE study. However, a level of uncertainty still remains regarding the potential higher exposure of abiraterone with the LS-FDC, which has been communicated in section 4.2 and 5.2 of the currently proposed SmPC.

Food effects

The impact of food effects has not been characterised with the FDC of niraparib and abiraterone. The effect of food has only been assessed in food effects studies where niraparib or abiraterone were administered as monotherapy. Studies with abiraterone showed a significant increase in the exposure of abiraterone when administered with food. Based on that data, MAGNITUDE, QUEST combination 3 and BA/BE studies were conducted under modified fasting conditions. A statement that Akeega should be taken under modified fasting conditions is included in the SmPC section 4.2.

Distribution

The SmPC includes the data of apparent volume of distribution (Vc/F) of both molecules niraparib and abiraterone. Both active principles show a high distribution to peripheral tissues and the large protein binding (>80%) explains the large apparent volume of distribution in the central compartment for niraparib (386L) and abiraterone (7052 L).

Elimination

PopPK analysis has been used to inform the SmPC section 5.2. The niraparib and abiraterone models were overall able to describe central tendency in the studied population of mCRPC patients.

Dose proportionality

Niraparib administered as monotherapy showed linear PK and dose-proportional exposure across the range of doses evaluated (30-400 mg).

The dose proportionality of abiraterone between 250 and 1000 mg has been demonstrated, based on the estimated Cmax, AUClast and AUCinf ratios between the highest dose (1000 mg) and the lower doses (250, 500 and 750 mg).

Niraparib co-administered with AAP

After multiple dose administration of 200 mg and 300 mg of niraparib plus AAP, no conclusions on dose proportionality could be drawn; for the majority of subjects receiving 200 mg niraparib trough values were only available for one treatment cycle and for subjects receiving 300 mg niraparib the data were very limited (**Study BEDIVERE**).

Population PK modelling

The niraparib and abiraterone popPK models are used to support the current application with:

- a description of pharmacokinetics and its variability;
- the identification of significant covariates (extrinsic and intrinsic factors) and
- an estimate of exposures for ER analysis.

The PopPK models were also used to simulate bioequivalence for the FDC-LS formulation (see above).

When used for bioequivalence simulation, the popPK models are of high regulatory impact as they are then the key source of evidence in the absence of an adequately designed confirmative bioequivalence study. The descriptive use of the model to inform the SmPC is considered of low to medium impact.

The popPK analysis was based on a pooled dataset from five Studies, which includes data of niraparib as monotherapy and niraparib and AA in combination, all in subjects with metastatic prostate cancer [reference to Table popPK dataset in section 2.6.2.1]. M1 method for handling BLQ-data is considered acceptable as niraparib and abiraterone BLQs were <3.9% and <1.9%, respectively.

Niraparib PPK model

The base PopPK model of niraparib was a 2-compartment model with linear elimination and sequential zero and first-order absorption. Although the structural definition of the popPK model of niraparib in monotherapy was a 3-compartment model, the use of 2-compartment PK model seems adequate based on the statistical performance and the modelling strategy implemented.

The covariate analysis included a full covariate model with backward elimination of non-statistically significant covariates. The strategy is endorsed due to the moderate-to-high eta-shrinkage observed in several PK parameters of the base model.

The effects of FDC-RS and FDC-LS formulation were tested on the absorption parameters (Ka, D1, F1). Due to very large RSEs values on the effects of FDC-RS on Ka and F1 and of FDC-LS on D1, only FDC-LS on D1 and FDC-LS on F1 (RSEs<50 %) were retained in the final model. The strategy of covariate selection seems adequate, although it leads to unexpected PK relationships, such as differences for the FDC at low strength on F1 and D1, but not on Ka. The impact on bioavailability (F1) and duration of zero-order absorption (D1) of the low strength is difficult to understand, since it may be linked to differences in the soluble fraction and transit time, leading the ~11-12% difference on F1 and D1 vs the regular strength. However, the impact in terms of exposure metrics of those differences is unknown.

Inter-individual variability (IIV) on Ka, Vp and D1 in the final model was high (66%, 44% and 83% respectively) and the added covariate effects explained only a small part of the observed variability. The final model included the following statistically significant covariate effects: FDC-LS on D1 and F1; other races and Hispanic/latino race on Ka; CRCL, HRR-negative and HRR-positive non-BRCA on CL; Asian race on Q and Vp.

The pcVPCs of the final popPK model demonstrates the adequacy of the mathematical framework to characterise the central tendency across the different studies. A slight underprediction at initial sampling times in the FDC1-LS data is observed, which may explain the large IIV on Ka and D1 due to deficiencies in the characterisation of the absorption phase.

The clinical relevance of statistically significant covariates and non-included covariates was assessed over exposure metrics (AUC0-24h,ss and Ctrough,ss), suggesting that clinically relevant changes in exposure (>20%) are expected in patients with moderate renal impairment with the proposed dosing regimen.

Abiraterone PPK model

The popK model was a 2-compartment disposition model with zero-order input in a depot compartment followed by first-order absorption in a series of transit compartments and finally into the central compartment, and first-order elimination as previously developed in subjects with mCRPC. No covariates were included in the final model, and the relatively high IIV (61-76%) observed in absorption PK parameters could thus not be explained. The overall model performance (pcVPC) suggests that the final popPK model of abiraterone slightly over-predicts the inter-individual random effects, since prediction intervals of the 5^{th} and 95^{th} percentiles are above and below the corresponding experimental percentiles.

Special populations

Impaired renal function

Niraparib

It has been previously shown that hepatobiliary clearance and renal excretion are the major routes of elimination of niraparib in humans. No formal dedicated PK study was performed to investigate the effect of renal impairment on niraparib PK as monotherapy.

Based on the population PK modelling, CrCl was identified as a significant covariate in the final niraparib PopPK model (patients with prostate cancer).

Abiraterone

In a previous dedicated study (abiraterone monotherapy), systemic exposure to abiraterone did not increase in subjects with end-stage renal disease on dialysis

Based on the Abiraterone PopPK analysis, CrCl was not included as a covariate in the final model. The recommendations for use of niraparib+abiraterone in patients with mild, moderate and severe renal impairment appear appropriate from a PK and safety perspective based on current knowledge.

Hepatic impairment

The recommendations for use of niraparib+abiraterone in patients with mild, moderate and severe hepatic impairment appear appropriate from a PK and safety perspective based on current knowledge.

Race

Race was identified as a covariate in the niraparib popPK analysis, but the expected impact on exposure is small. In a previous abiraterone popPK analysis in subjects with mCRPC (primarily white males), race was not formally investigated as a significant covariate. Race was not re-investigated as a covariate in the current popPK analysis, despite the increased number of patients with race other than white in the current patient population (including 17.1% Asians). A new covariate search would have been useful to formally investigate the effect of Asian vs White ethnic origin on abiraterone PK, however, the issue was not further pursued

Weight

The Applicant conducted a model-based approach using a forest plot analysis in order to assess the impact of body weight over the exposure metrics (Ctrough,ss, Cmax, ss and AUC0-24,ss) comparing patients with weights ≥ 82 kg versus patients with weights ≤82 kg for niraparib and comparing patients with weights ≥ 83.5 kg versus patients with weights ≤83.5 kg for abiraterone. The clinical relevance analysis stratified by body-weight quartiles did not suggest any relevant change in exposure metrics for niraparib nor abiraterone.

Elderly

Niraparib

Based on the population PK modelling, age was not identified as a significant covariate in the final niraparib PopPK model. The Applicant conducted a model-based approach using a forest plot analysis in order to assess the impact age over the exposure metrics (Ctrough,ss, Cmax, ss and AUC0-24,ss) comparing patients aged ≥ 69 years versus patients <69 years. No relevant changes were found.

Abiraterone

Based on previous population PK modelling, age was not identified as a significant covariate. Age was not re-investigated as a covariate in the current popPK analysis. The Applicant conducted a model-based approach using a forest plot analysis in order to assess the impact age over the exposure metrics (Ctrough,ss, Cmax, ss and AUC0-24,ss). AUCss 24h changed 10-25% and Cmin 12-20% when comparing patients aged ≥ 70 years versus patients <70 years.

Section 5.2 adequately describes the effects of intrinsic factors on PK of niraparib and abiraterone as single agents as well as recommendations for use of the FDC in special populations.

Pharmacokinetics interactions studies

No formal characterisation of the interaction effects of niraparib and abiraterone on different enzymatic pathways have been conducted for the FDC formulation. Recommendations for the FDC formulation have been incorporated based on the previous evidence on the in vivo interactions of each component as monotherapy, which is considered acceptable.

Overall, no major differences in exposure were observed for niraparib and abiraterone at multiple dose regimen between monotherapy and combination, suggesting that the metabolic pathways may not be altered due to the simultaneous co-administration of niraparib or abiraterone. Minor differences could be observed, especially on Cmax, after single dose administration between monotherapy and combination therapy, which may be more related on changes in the dissolution/absorption process of each drug rather than differences in the metabolic profile.

Secondary pharmacology: QTc prolongation

No clinically relevant QTc prolongation was identified for niraparib and abiraterone as monotherapy. The results suggest that niraparib and abiraterone exposure is not statistically linked to changes in QT/QTc prolongation. No additional information was provided regarding the effect of combination therapy of niraparib and abiraterone on QT/QTc prolongation. However, no clinically relevant changes in QT/QTc interval prolongation are expected for the combination therapy based on previous evidence as monotherapy of each active principle.

Exposure-Response analysis

The exposure-response analysis was based on data from the MAGNITUDE study. The objective was to explore the relationship between niraparib exposure and the efficacy and safety endpoints.

Exposure-efficacy

Only subjects with HRR gene alteration (Cohort 1) were included. The efficacy outcome used was rPFS. Cavg derived from the PPK analysis was used as the measure of exposure. The Kaplan-Meier analysis identified a statistically significant improvement in the niraparib plus AAP group with a reduction in the risk of rPFS compared to the placebo plus AAP group. When the exposure of niraparib was categorised by quartiles, no statistically significant exposure-efficacy relationship could be established.

In the HRR+ non-BRCA subgroup, the treatment with Nira+AAP showed no benefit compared to placebo, with a HR of 0.986 (95% CI: 0.675, 1.442, p=0.94).

During the assessment additional E-R analyses based on exposure metrics (AUC0-24h,ss) associated with the first dose were submitted. In the non-stratified univariate Kaplan-Meier analysis with niraparib exposure categorised by quartiles, no clear exposure-response relationship was evident, but the median rPFS was apparently shorter in the highest exposure quartile (Q4). This was also the case in the multivariate analysis adjusted for significant prognostic factors (baseline PSA, baseline LDH, baseline ALP and presence of visceral disease). No clear E-R relationship could be seen in subgroup univariate analyses for subjects with BRCA gene alteration and non-BRCA gene alterations. The reason for the seemingly poorer outcome observed in Q4 for exposure metrics based on both average daily dose and first dose is not known and could not, based on available data, be interpreted as a result of the higher exposure per se. The analyses were exploratory and should be interpreted with caution. There was a small number of patients (~50) in each exposure quartile. A relatively narrow exposure range was studied as all patients received the same starting dose, and there is uncertainty in the estimated individual exposure metrics as a consequence of sparse sampling and eta-shrinkage. Also, the analyses across quartiles may have been influenced by other unbalanced prognostic factors not accounted for.

Exposure-safety

Subjects enrolled in Cohorts 1 and 2 from MAGNITUDE study were included. AUC0-24h up to the time of the event or end of treatment was used as the exposure metric. The key safety endpoints included were selected based on an occurrence higher than 10% and a severity grade 3 of higher, therefore only anaemia was included. Statistically significant relationships between AUC0-24h of niraparib and anaemia and haematological toxicity were established, suggesting that patients at the third and fourth quartiles would show a 40% and 60% probability, respectively, of developing anaemia or haematological toxicity.

The Applicant has used steady-state exposure metrics (Cavg or AUC0-24h) derived based on the post-hoc estimates from the final PopPK models scaled by the average daily dose up to the time of the first event of interest (rPFS event, end of treatment, or censoring date). While the use of time-variant exposure accounts for dose modifications, bias may be introduced in the ER analyses because exposure (independent variable) will no longer be independent of the response (dependent variable). During the assessment, the Applicant has submitted additional E-R analyses based on exposure metrics (AUC0-24h,ss) associated with the first dose. The results were similar to those previously reported using exposure metrics based on average dose and demonstrated an increasing risk of anaemia and haematological toxicity with increasing niraparib exposure. However, the analyses were exploratory and should be interpreted with caution.

2.6.4. Conclusions on clinical pharmacology

The clinical pharmacology documentation is considered adequate. The pharmacokinetic properties of niraparib and abiraterone as a fixed-dose combination have been characterised using several clinical studies in healthy subjects and cancer patients, and bioequivalence has been demonstrated for the

FDC-RS compared to SAC. An uncertainty still remains regarding the potential higher exposure of abiraterone with the LS-FDC, which is adequately communicated in the SmPC.

The exposure-response relationship of niraparib in patients with metastatic prostate cancer has been conducted evaluating exposure metrics with several response endpoints. No statistically significant relationship was established between niraparib exposure and PFS, indicating that differences in exposure are not expected to predict differences in efficacy at the proposed dose. A positive and steep exposure-safety relationship has been established between niraparib AUC0-24h and haematological toxicity, suggesting that patients above the median exposure would show a probability >40% of developing haematological safety events.

2.6.5. Clinical efficacy

2.6.5.1. Dose response studies

The dose of niraparib (200 mg once daily) was selected based on data from the completed Phase 1b **Study 64091742PCR1001 (BEDIVERE)**. This was a Phase 1b, multicenter, open-label, dose-selection study with dose expansion that enrolled adult subjects with mCRPC, with or without DNA-repair anomalies, who received at least 1 line of prior taxane-based chemotherapy and 1 line of androgen receptor (AR)-targeted therapy. The primary objectives were to evaluate the safety and to establish the recommended Phase 2 dose (RP2D) of niraparib, when administered in combination with an AR-targeted therapy. The secondary objectives were to evaluate the PK of niraparib in combination with apalutamide or abiraterone acetate and the PK of apalutamide and abiraterone acetate in combination with niraparib.

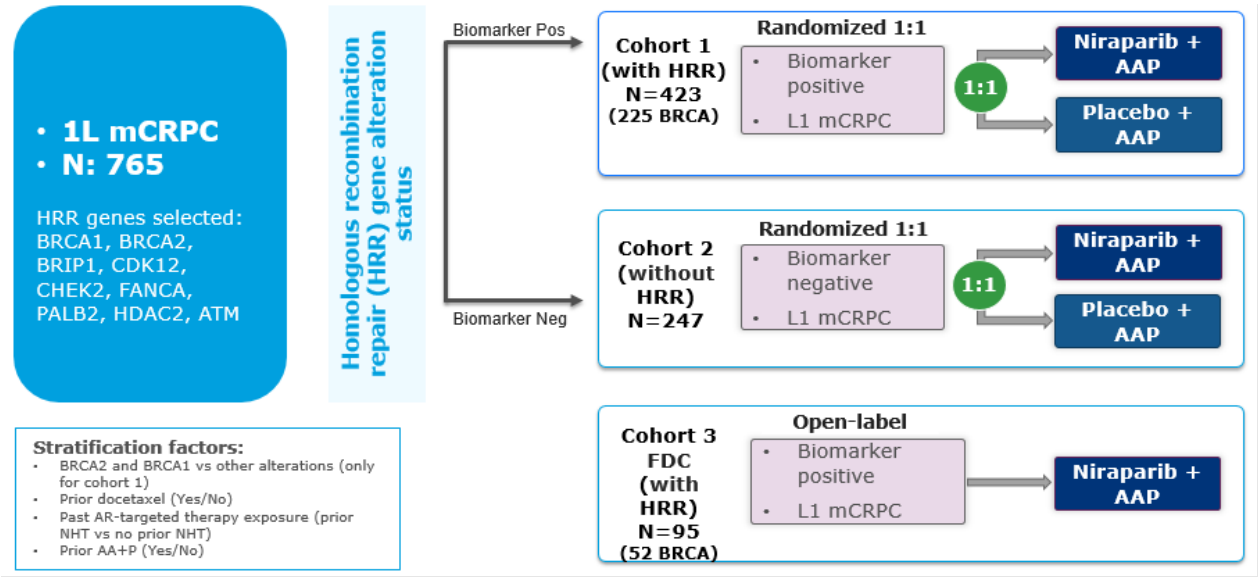
The study was comprised of a standard 3+3 dose selection (Part 1), followed by a dose expansion (Part 2) once a recommended Phase 2 dose (RP2D) of niraparib in combination with AAP was determined. Only two dose levels (the 200-mg and 300-mg doses) of niraparib were tested. A total of 33 subjects were enrolled and treated, 6 into the niraparib+apalutamide group and 27 into the niraparib+AAP group. During the DLT period, 4 subjects were enrolled into the 200-mg niraparib+AAP cohort, and 8 subjects were enrolled into the 300-mg niraparib+AAP cohort. An additional 15 subjects were subsequently enrolled into the expansion cohort. In the niraparib+AAP group, no subjects in the 200-mg cohort experienced a DLT. One subject (12.5%) in the 300-mg cohort experienced 2 DLTs of fatigue and gamma-glutamyltransferase (GGT) increased. Two additional subjects in the 300-mg cohort experienced Grade 4 neutropenia at Cycle 2 Day 1, which contributed to the selection of the 200-mg cohort as the MTD for nira+AAP. Comparable exposures of niraparib between the 2 doses when coadministered with AAP were observed.

Based on all these data, niraparib 200 mg was chosen as dose for use in combination with AAP.

2.6.5.2. Main study

Study MAGNITUDE (64091742PRC3001): a phase 3, randomized, placebo-controlled, double-blind study of niraparib in combination with abiraterone acetate and prednisone versus abiraterone acetate and prednisone for treatment of subjects with metastatic prostate cancer

Figure 17. Study design MAGNITUDE



Subjects were prospectively screened for HRR alterations and then enrolled into either Cohort 1 (presence of HRR gene alterations) or Cohort 2 (absence of HRR gene alterations). After completion of enrolment into Cohort 1 and 2, a separate open-label cohort (Cohort 3) was enrolled for subjects with HRR gene alterations to obtain clinical experience with the FDC tablet formulation of niraparib and AA. Subjects in Cohort 3 were enrolled under the same inclusion/exclusion criteria and underwent the same study procedures as Cohort 1, except that subjects in Cohort 3 received open-label niraparib/AA as a FDC tablet plus prednisone instead of niraparib, AA, and prednisone as single agents

The study consisted of a Pre-screening phase to assess biomarker eligibility prior to other screening evaluations, a Screening Phase, a Treatment Phase, an Extension Phase, and a Follow-up Phase.

Methods

- **Study Participants**

Key inclusion criteria

1. Had HRR gene alteration status (as identified by the Sponsor's required assays or local testing for HRR gene alteration) as follows:

   a. Cohort 1: positive for HRR gene alteration. Alterations in breast cancer (BRCA)1, BRCA2, cyclin-dependent kinase 12 (CDK12), ataxia telangiectasia mutated gene (ATM), Fanconi anaemia complementation group A (FANCA), partner and localizer of BRCA2 (PALB2), checkpoint kinase 2 (CHEK2), BRCA1 interacting protein C-terminal helicase 1 (BRIP1), and histone deacetylase 2 (HDAC2) genes

   b. Cohort 2: not positive for HRR gene alteration (i.e., no HRR gene alteration). Negative for alterations in the genes listed for Cohort 1.

   c. Cohort 3: positive for HRR gene alteration. Same gene alterations as listed for Cohort 1

2. Had metastatic disease documented by positive bone scan or metastatic lesions on CT or MRI.
3. Had metastatic prostate cancer in the setting of castrate levels of testosterone ≤50 ng/dL on a gonadotropin releasing hormone analog (GnRHa) or bilateral orchiectomy as evidenced by PSA progression or radiographic progression.
4. Were able to continue GnRHa during the study if not surgically castrate.
5. Had ECOG Performance Score Grade of 0 or 1.
6. Had score of ≤3 on the BPI-SF Question #3 (worst pain in last 24 hours).
7. Clinical laboratory values at Screening:
    a. ANC ≥1.5 x 10^9 /L.
    b. Haemoglobin ≥9.0 g/dL, independent of transfusions for at least 30 days.
    c. Platelet count ≥100 x 10^9 /L.

Key exclusion criteria

1. Had prior treatment with a PARP inhibitor.
2. Had systemic therapy (i.e., novel second generation AR targeted therapy such as enzalutamide, apalutamide, or darolutamide; taxane-based chemotherapy, or more than 4 months of abiraterone acetate plus prednisone [AAP] prior to randomization) in the mCRPC setting; or AAP outside of the mCRPC setting.
3. Subjects who had received 2 to 4 months of AAP prior to randomization for the treatment of mCRPC should have had no evidence of progression by PSA (per PCWG3) during screening. These potential subjects were required to have 2 PSA values during the Pre-screening and Screening Phases. The second PSA value was to be within 2 weeks of randomization and PSA rise was thought to be due to flare, the Investigator was to confirm that there was no radiographic progression.
4. Had presence of uncontrolled hypertension (persistent systolic BP ≥160 mmHg or diastolic BP ≥100 mmHg). Subjects with a history of hypertension were allowed, if BP was controlled to within these limits by anti-hypertensive treatment.
5. Subjects who are receiving opioid analgesics at the time of screening.
6. Subjects who had the following ≤28 days prior to randomization:
    a) A transfusion (platelets or red blood cells).
    b) Hematopoietic growth factors.
    c) An investigational agent for prostate cancer.
    d) Major surgery (Sponsor should be consulted regarding what constitutes major surgery).
    e) Radiation therapy

Treatments

Subjects in Cohorts 1 and 2 were randomized in a 1:1 ratio to receive either 200 mg niraparib, 1,000 mg AA, and 10 mg prednisone (nira+AAP) and or matching placebo, 1,000 mg AA, and 10 mg prednisone (PBO+AAP) daily. Subjects in Cohort 3 received 200 mg niraparib/1,000 mg AAP (referred to hereafter as FDC) and 10 mg prednisone daily (FDC+P).

Background therapy with a GnRHa for patients who had not previously undergone surgical castration was mandatory to maintain castrate concentrations of testosterone (≤50 ng/dL). The choice of GnRHa was at the discretion of the investigator.

Two FDC tablet formulations were available to treat subjects in Cohort 3. The regular strength FDC formulation was designed for the full-dose regimen of 200 mg niraparib and 1,000 mg of AA (plus prednisone) daily, comprised of 2 tablets, each containing 100 mg niraparib and 500 mg AA. Prednisone was given separately. For subjects who required a dose reduction of niraparib, a low strength formulation containing 50 mg niraparib and 500 mg AA was available, with 2 tablets taken daily (plus prednisone) to achieve a total daily dose of niraparib 100 mg and AA 1,000 mg. Subjects who required a dose interruption of either agent, or who required a dose reduction of AA were allowed to take single agent medications to comprise the dose prescribed by the investigator in accordance with the protocol.

Subjects took daily treatment orally on a continuous basis. Treatment began at Cycle 1 Day 1 in the treatment phase and continued in 28-day cycles until the study drug was discontinued.

Objectives

Table 30. Objectives and endpoints

Objectives	Endpoints/Assessments
Primary	
• To evaluate the effectiveness of niraparib plus AAP compared to AAP plus placebo	• rPFS by BICR.
Secondary	
• To assess the clinical benefit of niraparib plus AAP compared to AAP plus placebo	• TCC • TSP • OS
• To characterize the PK of niraparib when given with AAP and abiraterone trough levels	• Observed plasma concentrations of niraparib and abiraterone and estimated population PK and exposure parameters for niraparib
• To characterize the safety profile of niraparib when given with AAP compared to AAP with placebo	• Incidence and severity of AEs • Clinical laboratory test results
Other	
• To evaluate other efficacy assessments and determine the clinical benefit of niraparib plus AAP compared to AAP plus placebo	• Time to PSA progression based on PCWG3 criteria • PFS2 • Time to pain progression As described in the SAP, additional endpoints evaluated were: • Objective response rate • Duration of response • PSA response rate • Time to first subsequent anti-cancer therapy
• To evaluate subject experience with disease-related symptoms • To evaluate overall health-related quality of life • To evaluate subject experience regarding treatment-related symptoms and tolerability	• PROs as assessed by the BPI-SF, the FACT-P, the EQ-5D-5L and PRO-CTCAE[a]
• To characterize the medical resource utilization profile of subjects treated with niraparib plus AAP compared to AAP plus placebo	• Medical resource utilization data associated with medical encounters
• To evaluate relationship between niraparib exposure, efficacy and safety measures, and exploratory response biomarkers	• Parameters describing exposure-response with efficacy (eg, rPFS by BICR), safety (eg, AEs), and response biomarker (eg, PSA) endpoints

Key: AAP=abiraterone acetate plus prednisone; AE=adverse event; BICR=blinded independent central review; BPI-SF=brief pain inventory-short form; EQ-5D-5L=EuroQol 5 Dimension 5 Level; FACT-P=functional assessment of cancer therapy-prostate; OS=overall survival; PK=pharmacokinetics; PCWG3=Prostate Cancer Working Group 3; PFS=progression-free survival; PFS2=PFS on first subsequent therapy; PRO=patient-reported outcomes; PRO-CTCAE=patient-reported outcome(s) Common Terminology Criteria for Adverse Events; PSA=prostate-specific antigen; rPFS=radiographic progression-free survival; SAP=statistical analysis plan; TCC=time to initiation of cytotoxic chemotherapy; TSP=time to symptomatic progression.
[a] PRO-CTCAE assessments will only be done in the United States and in English.

Outcomes/endpoints

Primary endpoint

The primary endpoint was radiographic progression-free survival (rPFS), as assessed by BICR and defined as the time from the date of randomization to the date of radiographic progression or death, whichever occurred first.

Radiographic progression is determined by first occurrence of progression by bone scan (according to PCWG3 criteria) or progression of soft tissue lesions by CT or MRI (according to RECIST 1.1 criteria), both assessed by BICR.

Secondary endpoints

- Time to initiation of cytotoxic chemotherapy (TCC) defined as the time from the date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer.
- Time to symptomatic progression (TSP) defined as the time from the date of randomization to the date of the first of any of the following:
  - The use of external beam radiation therapy (EBRT) for skeletal symptoms;
  - The need for tumour-related orthopaedic surgical intervention;
  - Other cancer-related procedures (e.g. nephrostomy insertion, bladder catheter insertion, EBRT, or surgery for tumour symptoms other than skeletal);
  - Cancer-related morbid events (e.g., fracture [symptomatic and/or pathologic], cord compression, urinary obstructive events); or
  - Initiation of the new anti-cancer therapy for cancer pain.
- Overall survival (OS) defined as the time from the date of randomization to the date of death from any cause.

Other efficacy endpoints

- Time to PSA progression (TPSA) defined as the time from the date of randomization to the first date of documented PSA progression, according to PCWG3 criteria.

  There will be a PSA progression when after decline from baseline: PSA increase ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value ≥ 3 weeks later (ie, a confirmed rising trend); And when no decline from baseline: PSA increase ≥25% and ≥ 2 ng/mL from baseline beyond 12 weeks.
- Progression-free survival 2 (PFS2), defined as the time from randomization to the date of first progression (radiographic, clinical, or PSA progression) on the first subsequent therapy or death from any cause, whichever occurred first.
- Time to pain progression defined as the time from the date of randomization to the date of the first observation of pain progression (an increase by at least 2 points from baseline in BPI-SF worst pain intensity [item 3] observed at 2 consecutive evaluations ≥3 weeks apart).

Sample size

Cohort 1: Approximately 400 subjects with mCRPC and HRR gene alterations were to be randomized 1:1 to receive nira+AAP or PBO+AAP to provide 87% power in detecting a HR of 0.65 in subjects with mCRPC and HRR gene alterations at a 2-tailed level of significance of 0.05. Assuming approximately 50% of subjects in Cohort 1 belong to the BRCA subgroup, with the proposed sample size approximately 102 rPFS events are planned to be observed in the BRCA subgroup to provide 93% power to detect a HR of 0.5 at a 2-tailed level of significance of 0.05.

Cohort 2: Approximately 600 subjects with mCRPC and no HRR gene alteration were to be randomized 1:1 to receive nira+AAP or PBO+AAP if futility was not met.

Cohort 3: Approximately 100 subjects with HRR gene alterations were to be enrolled into Cohort 3, 50% of whom had BRCA alterations.

Randomisation and Blinding (masking)

Subjects were randomly assigned in **a 1:1 ratio to receive either** nira+AAP or PBO+AAP. Randomization was performed across all study sites using the interactive web response system (IWRS). Subjects were stratified by past taxane-based chemotherapy exposure (yes versus no), past AR targeted therapy exposure (prior novel anti-androgen therapy, such as enzalutamide, apalutamide, darolutamide versus no prior novel anti-androgen therapy), and prior AAP use (yes versus no). For Cohort 1, stratification by gene alteration group (i.e., BRCA1 or BRCA2 versus all other HRR gene alterations) was also performed. Cohort 3 was open label and not randomized.

Cohorts 1 and 2 are conducted in double-blind fashion. Cohort 3 is open label, although the independent central imaging reviewers remain blinded to which cohort the subjects are assigned

Statistical methods

The following analysis populations were used in the evaluation of safety and efficacy:

- **Randomized Analysis Set** for Cohort 1: Randomized subjects in Cohort 1 were used in efficacy analysis for Cohort 1.
- **Safety Analysis Set**: The safety analysis set included all randomized subjects who received at least 1 dose of study treatment in Cohort 1 or Cohort 2. The safety analysis set was used for evaluating safety. Safety analysis was performed separately by Cohort.
- **FDC Analysis Set**: All subjects who were enrolled into Cohort 3 will be used for baseline and demographic data analysis, and their clinical experience will be described. All subjects who received at least 1 dose of study treatment in Cohort 3 will be evaluated for safety.

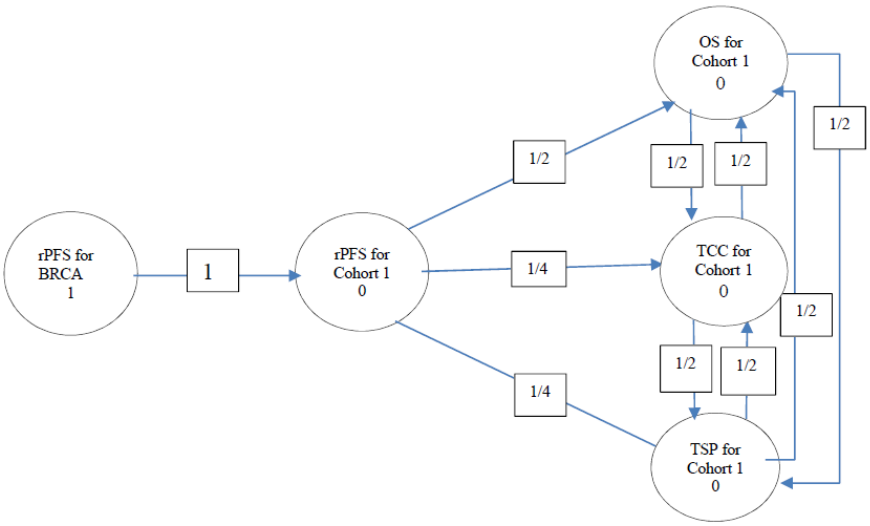
Efficacy analyses

The final analysis of the primary endpoint rPFS was performed when approximately 220 rPFS events were observed in Cohort 1 and approximately 102 rPFS events were observed in the BRCA subgroup within Cohort 1. Pre-specified sensitivity analyses were performed in accordance with the SAP.

Efficacy analysis began by testing rPFS in the BRCA subgroup of Cohort 1 using a 2-sided alpha level of 0.05. If significance was met in the BRCA subgroup, then rPFS in all of Cohort 1 was to be tested, also at a 2-sided alpha level of 0.05 based on the pre-defined testing hierarchy. If rPFS in Cohort 1 was significant, then the secondary endpoints were to be tested using group sequential method with 2 interim analyses and the final analysis. After testing for the primary endpoint of rPFS in the BRCA subgroup and Cohort 1, alpha of 0.05 was split between the secondary endpoints, which were analysed for all of Cohort 1 with an alpha of 0.025 allocated to OS and an alpha of 0.0125 allocated to TCC and TSP separately. The alpha for the secondary endpoints was further subdivided between the 2 planned interim analyses and the final analysis. For the secondary endpoints, the O'Brien-Fleming (OBF) boundaries as implemented by the Lan-DeMets alpha spending method were utilized, and interim boundary cut-offs were calculated using the information fraction for the OS endpoint.

The boundary for significance for TCC and TSP at the IA1 was 0.0001 and for OS 0.0005. The IA2 and the final analysis will be performed when approximately 170 OS events and 246 OS events have been observed, respectively.

Figure 18. Graphical Approach for Testing Key Efficacy Endpoints



Futility analysis for Cohort 2

A non-binding futility analysis was planned for Cohort 2 after approximately 200 subjects were enrolled and approximately 125 composite progression events had been observed; where composite progression events were the first of either radiographic progression, PSA progression, or death. Enrolment in this cohort was held after 247 subjects had been enrolled. The quantitative decision criterion for evaluating futility was derived based on the estimated HR using the composite progression events through a Cox proportional-hazard model. Cohort 2 would be considered futile if the observed HR for time to composite progression events was greater than or equal to 1.

The pre-planned futility analysis for Cohort 2 was performed on 13 August 2020, assessing data from 233 subjects with 113 composite progression events observed. With a HR=1.087 for the composite progression endpoint, the pre-specified criteria for futility of HR >1 was met, and futility was declared for this cohort. Based upon the IDMC recommendation, the Sponsor permanently halted enrolment in Cohort 2, and this cohort was unblinded.

Results

Participant flow

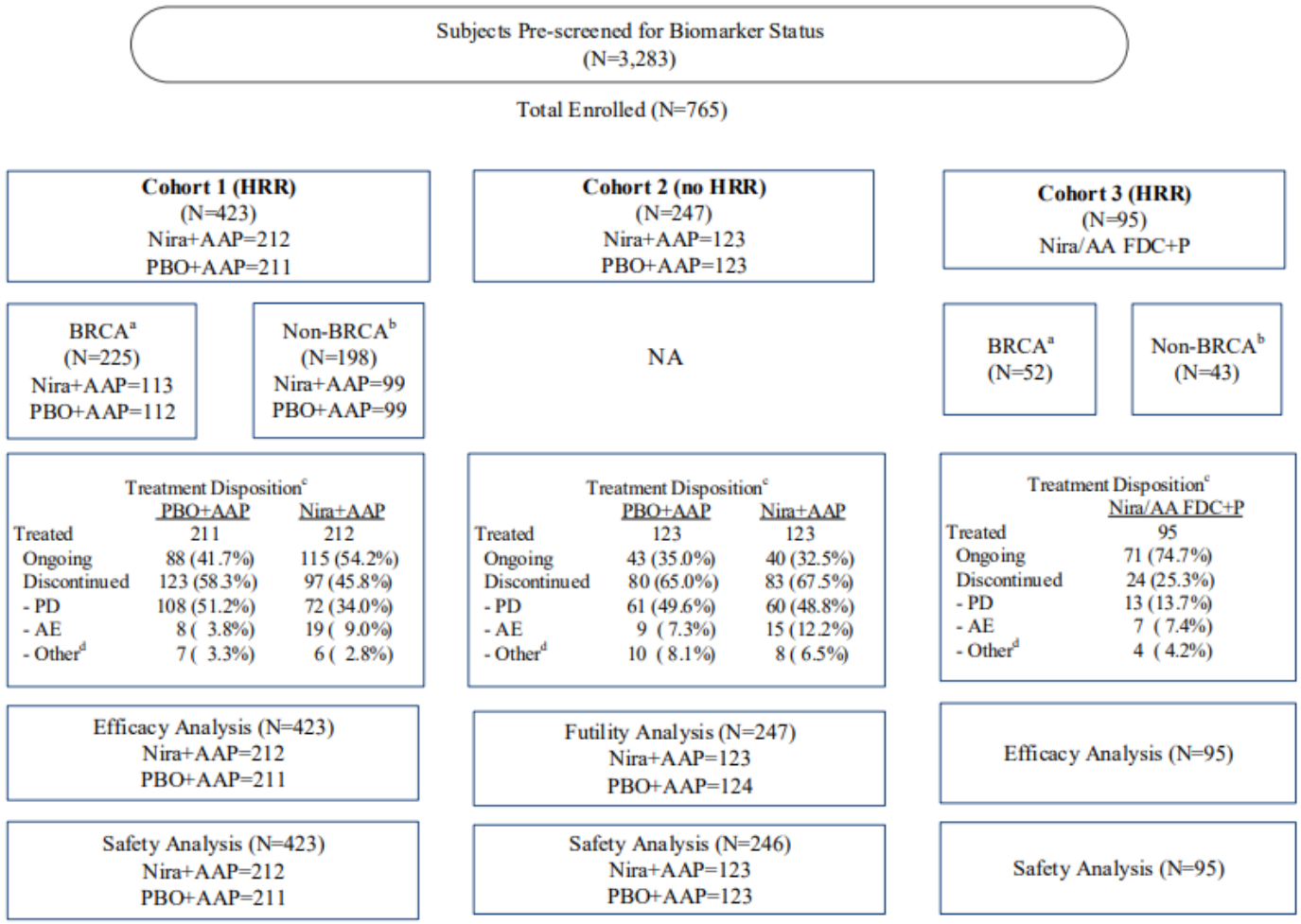
A total of 3,283 subjects screened for eligibility for the MAGNITUDE Study.

During the pre-screening process, 2,337 subjects failed pre-screening and did not proceed to study screening. The primary reason for pre-screen failure was subjects testing negative for HRR gene alterations after Cohort 2 (non-HRR) had been closed to enrolment. Of the 946 subjects who entered screening, **765 subjects** were enrolled in the study: 423 subjects in Cohort 1, 95 subjects in Cohort 3, and 247 subjects in Cohort 2.

A total of **423 subjects** with HRR gene alterations were randomized into **Cohort 1**: 212 into the nira+AAP group and 211 into the PBO+AAP group. All subjects received at least 1 dose of study drug and were included in the Safety Analysis Set.

A total of **95 subjects** were enrolled into **Cohort 3**, all of whom received at least 1 dose of study drug and were included in the Safety Analysis Set.

Figure 19. Participant flow chart for MAGNITUDE



AA=abiraterone acetate; AE=adverse event; BRCA=breast cancer gene; HRR=homologouos recombination repair; Nira=niraparib; PA-IA1=final analysis of the primary endpoint of radiographic progression-free survival and first interim analysis of secondary endpoints; PBO=placebo; PD=progressive disease

[a] Includes BRCA1, BRCA2 single or co-occurring gene alterations

[b] Includes BRIP1, FANCA, CHEK2, HDAC2, ATM, CDK12, PALB2 single or co-occurring gene alterations

[c] As of the clinical cutoff date for PA-IA1 (08 October 2021).

[d] Includes subject refused further study treatment, physician decision, non-compliance with study drug

Nira/PBO+AAP=niraparib 200 mg or PBO and AA 1,000 mg plus prednisone 10 mg daily as single-agent combination

Nira/AA FDC+P=niraparib 200 mg/AA 1,000 mg as a fixed-dose combination plus prednisone 10 mg daily

Patient disposition

Table 31. Treatment Disposition; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: Safety	211	212	423
Subjects ongoing	88 (41.7%)	115 (54.2%)	203 (48.0%)
Discontinued study treatment	123 (58.3%)	97 (45.8%)	220 (52.0%)
Reason for discontinuation			
Progressive disease	108 (51.2%)	72 (34.0%)	180 (42.6%)
Adverse event	8 (3.8%)	19 (9.0%)	27 (6.4%)
Adverse event - COVID-19 related	1 (0.5%)	7 (3.3%)	8 (1.9%)
Subject refused further study treatment	5 (2.4%)	6 (2.8%)	11 (2.6%)
Physician decision	2 (0.9%)	0	2 (0.5%)

Key: AAP = abiraterone acetate plus prednisone.

Table 32. Treatment Disposition; Cohort 3 Safety Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: safety	95
Subjects ongoing	71 (74.7%)
Discontinued study treatment	24 (25.3%)
Reason for discontinuation	
Progressive disease	13 (13.7%)
Adverse event	7 (7.4%)
Subject refused further study treatment	3 (3.2%)
Physician decision	1 (1.1%)

Key: AA = abiraterone acetate, FDC = fixed dose combination.

Recruitment

The first subject signed informed consent on 05 February 2019 and the last subject signed informed consent on 22 June 2021. During this time, 765 subjects were enrolled in the study: 423 subjects into Cohort 1, 247 subjects into Cohort 2, and 95 subjects into Cohort 3.

Subjects were enrolled across 26 countries: Argentina (7 sites); Australia (11 sites); Belgium (5 sites); Brazil (19 sites); Bulgaria (1 site); Canada (5 sites); China (10 sites); Czech Republic (5 sites); France (9 sites); Germany (3 sites); Hungary (7 sites); Italy (9 sites); Malaysia (6 sites); Mexico (3 sites); Netherlands (4 sites); Poland (9 sites); Portugal (1 site); Russian Federation (16 sites); South Korea (14 sites); Spain (11 sites); Sweden (2 sites); Taiwan (8 sites); Turkey (10 sites); Ukraine (11 sites); United Kingdom (4 sites); United States (15 sites).

Conduct of the study

There were **6 global amendments** to the original protocol (22 October 2018). The first protocol amendment was adopted after subject enrolment began. A summary of the changes included in each global amendment is provided below.

Global Amendment 1 (10 April 2019) included the following changes:

- Clarified collection of BPI-SF #3 assessments during the screening period,
- Added PRO-CTCAE assessments for subjects in the US,
- Modified text regarding MDS/AML evaluation to clarify that the tests, as clinically indicated, were to be done locally and not centrally, and
- Implemented administrative changes based on local regulations, and some minor editorial changes.

Global Amendment 2 (30 September 2019) included the following changes:

- Changed the secondary endpoints of the study and minor editorial changes. The secondary endpoints of time-to-chronic opioid use and time-to-pain progression were removed and replaced with time-to symptomatic progression.
- Changed collection of pain using the BPI-SF #3 from daily collection on a handheld device, to monthly collection on a site tablet, or by using interview mode.

Global Amendment 3 (12 February 2020) included the following changes:

- Stopped enrolment of subjects with ATM mutations into Cohort 1 and added that at least 50% of subjects randomized into Cohort 1 were to have BRCA mutations.

Global Amendment 4 (03 July 2020) included the Following Changes:

- Updated the statistical analysis of the study to specify that subjects with BRCA1 or 2 gene alterations (the BRCA subgroup) of Cohort 1 were to be analysed first. If statistical significance was reached in the BRCA subgroup, then the entire population of subjects with HRR gene alterations (Cohort 1) was to be tested. If statistical significance in Cohort 1 was reached and futility had not been met in Cohort 2, then the combined population of Cohort 1 and Cohort 2 (ITT population) was to be tested. Otherwise, if futility analysis was met, the ITT analysis was not to be performed.
- Enrolled a new Cohort of subjects (Cohort 3) who would receive niraparib/AA FDC tablet formulation plus prednisone with the objective of describing the clinical experience with the FDC tablets in subjects with mCRPC and HRR gene alterations.
- An additional biomarker, CDK12, was added to the panel of genes that determined eligibility for Cohorts 1 and 3, and the wording "DRD" was updated to "HRR gene alteration" given that subjects whose tumours had mutations in genes outside of the DNA-repair pathway could be included for enrolment.

Global Amendment 5 (29 January 2021) Included the Following Changes:

- Revised safety monitoring and guidance based on updates to the niraparib core safety information.
- Clarified the procedures for subjects moving into the Extension Phase (open-label or long term), and the limited data collection phase for Cohort 2 subjects remaining on treatment.

Global Amendment 6 (30 September 2021) Included the Following Changes:

- Aligned with the SAP, the analysis approach for testing secondary endpoints (OS, TCC, and TSP) in Cohort 1 was updated to a group sequential method, and a second interim analysis, hereafter referred to as IA2, was added.

Protocol deviations

All protocol deviations of eligibility criteria and those deviations that could impact subject safety or primary endpoints were considered major protocol deviations. Major protocol deviations were identified in 16 subjects overall: 6 (2.8%) subjects in the nira+AAP group and 10 (4.7%) subjects in the PBO+AAP group.

Table 33. Summary of Subjects with Major Protocol Deviations; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: randomized	211	212	423
Subjects with major protocol deviations	10 (4.7%)	6 (2.8%)	16 (3.8%)
Entered but did not satisfy criteria	4 (1.9%)	1 (0.5%)	5 (1.2%)
Received a disallowed concomitant treatment	2 (0.9%)	3 (1.4%)	5 (1.2%)
Received wrong treatment or incorrect dose	1 (0.5%)	2 (0.9%)	3 (0.7%)
Other	3 (1.4%)	0	3 (0.7%)
Other – COVID-19	1 (0.5%)	0	1 (0.2%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Subjects may appear in more than one category.

Baseline data

Cohort 1

Demographic characteristics

Table 34. Summary of Demographics; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: randomized	211	212	423
Age, years			
N	211	212	423
Mean (SD)	68.6 (8.17)	69.2 (8.79)	68.9 (8.49)
Median	69.0	69.0	69.0
Range	(43; 88)	(45; 100)	(43; 100)
< 65	62 (29.4%)	61 (28.8%)	123 (29.1%)
≥ 65-74	100 (47.4%)	88 (41.5%)	188 (44.4%)
≥ 75	49 (23.2%)	63 (29.7%)	112 (26.5%)
Sex			
N	211	212	423
Male	211 (100.0%)	212 (100.0%)	423 (100.0%)
Race			
N	211	212	423
American Indian or Alaska Native	1 (0.5%)	1 (0.5%)	2 (0.5%)
Asian	41 (19.4%)	29 (13.7%)	70 (16.5%)
Black or African American	0	5 (2.4%)	5 (1.2%)
White	153 (72.5%)	160 (75.5%)	313 (74.0%)
Unknown	16 (7.6%)	17 (8.0%)	33 (7.8%)
Ethnicity			
N	211	212	423
Hispanic or Latino	25 (11.8%)	26 (12.3%)	51 (12.1%)
Not Hispanic or Latino	169 (80.1%)	166 (78.3%)	335 (79.2%)
Not reported	17 (8.1%)	20 (9.4%)	37 (8.7%)
Weight, kg			
N	211	212	423
Mean (SD)	85.2 (17.92)	84.4 (17.26)	84.8 (17.57)
Median	84.1	82.2	83.0
Range	(46; 161)	(49; 150)	(46; 161)
Height, cm			
N	210	212	422
Mean (SD)	172.3 (8.05)	171.5 (7.80)	171.9 (7.93)
Median	172.0	171.0	172.0
Range	(150; 200)	(152; 196)	(150; 200)

Key: AAP = abiraterone acetate plus prednisone.
Note: N's for each parameter reflect non-missing values.

Disease characteristics

Table 35. Summary of Prostate Cancer Baseline Clinical Disease Characteristics; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: randomized	211	212	423
Time from initial diagnosis to randomization (years)			
N	211	212	423
Mean (SD)	3.86 (3.632)	3.66 (3.584)	3.76 (3.605)
Median	2.26	2.40	2.30
Range	(0.5; 17.2)	(0.5; 26.6)	(0.5; 26.6)
Time from mCRPC to first dose (years)			
N	211	212	423
Mean (SD)	0.49 (0.635)	0.43 (0.409)	0.46 (0.534)
Median	0.27	0.31	0.29
Range	(0.0; 5.1)	(0.0; 2.8)	(0.0; 5.1)
Tumor stage at initial diagnosis			
N	211	212	423
T0	1 (0.5%)	1 (0.5%)	2 (0.5%)
T1	16 (7.6%)	15 (7.1%)	31 (7.3%)
T2	43 (20.4%)	33 (15.6%)	76 (18.0%)
T3	93 (44.1%)	93 (43.9%)	186 (44.0%)
T4	34 (16.1%)	31 (14.6%)	65 (15.4%)
Unknown	24 (11.4%)	39 (18.4%)	63 (14.9%)
Lymph node stage at initial diagnosis			
N	211	212	423
N0	80 (37.9%)	80 (37.7%)	160 (37.8%)
N1	83 (39.3%)	74 (34.9%)	157 (37.1%)
NX	33 (15.6%)	37 (17.5%)	70 (16.5%)
Unknown	15 (7.1%)	21 (9.9%)	36 (8.5%)
Metastasis stage at initial diagnosis			
N	211	212	423
M0	97 (46.0%)	76 (35.8%)	173 (40.9%)
M1	106 (50.2%)	127 (59.9%)	233 (55.1%)
Unknown	8 (3.8%)	9 (4.2%)	17 (4.0%)
Gleason Score at initial diagnosis			
N	210	211	421
<7	16 (7.6%)	17 (8.1%)	33 (7.8%)
7	46 (21.9%)	40 (19.0%)	86 (20.4%)
3+4	14 (6.7%)	15 (7.1%)	29 (6.9%)
4+3	31 (14.8%)	25 (11.8%)	56 (13.3%)
Unknown	1 (0.5%)	0	1 (0.2%)
>=8	142 (67.6%)	144 (68.2%)	286 (67.9%)
Unknown	6 (2.9%)	10 (4.7%)	16 (3.8%)
Prior Prostate Cancer Therapy			
N	211	212	423
Hormonal therapy	201 (95.3%)	204 (96.2%)	405 (95.7%)
Radiotherapy	91 (43.1%)	90 (42.5%)	181 (42.8%)
Surgery	138 (65.4%)	133 (62.7%)	271 (64.1%)
Prior novel AR targeted therapy	5 (2.4%)	8 (3.8%)	13 (3.1%)
Past taxane-based chemotherapy	44 (20.9%)	41 (19.3%)	85 (20.1%)
AAP	48 (22.7%)	50 (23.6%)	98 (23.2%)

Other	57 (27.0%)	51 (24.1%)	108 (25.5%)
ECOG Performance Status Score at baseline			
N	211	212	423
0	146 (69.2%)	130 (61.3%)	276 (65.2%)
1	65 (30.8%)	82 (38.7%)	147 (34.8%)
Extent of Disease at study entry[a]			
N	211	212	423
Bone	170 (80.6%)	183 (86.3%)	353 (83.5%)
Bone only	85 (40.3%)	78 (36.8%)	163 (38.5%)
Visceral	39 (18.5%)	51 (24.1%)	90 (21.3%)
Liver	13 (6.2%)	18 (8.5%)	31 (7.3%)
Lung	18 (8.5%)	27 (12.7%)	45 (10.6%)
Adrenal Gland	7 (3.3%)	3 (1.4%)	10 (2.4%)
Other	9 (4.3%)	10 (4.7%)	19 (4.5%)
Soft tissue	15 (7.1%)	6 (2.8%)	21 (5.0%)
Nodal[b]	95 (45.0%)	113 (53.3%)	208 (49.2%)
Pelvic	58 (27.5%)	72 (34.0%)	130 (30.7%)
Non-pelvic	69 (32.7%)	76 (35.8%)	145 (34.3%)
Prostate[c]	3 (1.4%)	2 (0.9%)	5 (1.2%)
Number of bone lesions at study entry			
N	211	212	423
<=10 lesions[d]	128 (60.7%)	127 (59.9%)	255 (60.3%)
> 10 lesions	83 (39.3%)	85 (40.1%)	168 (39.7%)
BPI-SF pain score (item 3)			
N	211	210	421
0	103 (48.8%)	108 (51.4%)	211 (50.1%)
1 to 3	86 (40.8%)	88 (41.9%)	174 (41.3%)
> 3	22 (10.4%)	14 (6.7%)	36 (8.6%)
Mean (SD)	1.25 (1.709)	1.13 (1.659)	1.19 (1.683)
Median	1.00	0.00	0.00
Range	(0.0; 9.0)	(0.0; 10.0)	(0.0; 10.0)
PSA at initial diagnosis (ug/L)			
N	184	192	376
Mean (SD)	340.34 (1129.890)	222.76 (613.271)	280.30 (904.450)
Median	40.89	41.50	41.07
Range	(0.1; 12080.0)	(0.1; 5211.0)	(0.1; 12080.0)

Key: AAP = abiraterone acetate plus prednisone.
[a]Subjects having multiple lesions within each category are counted only once in the category, but may be represented on more than one category.
[b]Includes lymph nodes not specified as pelvic or non-pelvic.
[c]Prostate local recurrence/progression
[d]Includes subjects with no bone lesion
Note: Pain score data for 2 subjects were collected but were not transmitted before database lock. They are not included in analyses.

HRR gene alterations

Cohort 1 included 229 (54.1%) subjects with BRCA1 or BRCA2 gene alterations, either singly or with another co-occurring mutation, and 194 (45.8%) subjects with Other HRR gene alterations. The BRCA and Other HRR subgroups were based on Interactive Web Response System (IWRS) classification. All subjects who had a BRCA gene alteration, whether singly or as part of a co-occurring alteration, were considered part of the BRCA subgroup. Of note, 4 subjects who were randomized/stratified into the Other HRR subgroup were later found to have co-occurring BRCA gene alterations and were kept as per their original stratification in the primary and secondary analyses.

Table 36. Frequency of Subjects with Gene Alterations; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: randomized	211	212	423
Single Gene Alterations			
ATM	42 (19.9%)	43 (20.3%)	85 (20.1%)
BRCA1	4 (1.9%)	12 (5.7%)	16 (3.8%)
BRCA2	88 (41.7%)	86 (40.6%)	174 (41.1%)
BRIP1	4 (1.9%)	4 (1.9%)	8 (1.9%)
CDK12	8 (3.8%)	5 (2.4%)	13 (3.1%)
CHEK2	20 (9.5%)	18 (8.5%)	38 (9.0%)
FANCA	6 (2.8%)	5 (2.4%)	11 (2.6%)
HDAC2	3 (1.4%)	2 (0.9%)	5 (1.2%)
PALB2	4 (1.9%)	8 (3.8%)	12 (2.8%)
Subtotal single gene alterations	179 (84.8%)	183 (86.3%)	362 (85.6%)
Co-occurring Gene Alterations			
ATM/BRCA1	1 (0.5%)	1 (0.5%)	2 (0.5%)
ATM/BRCA2	5 (2.4%)	3 (1.4%)	8 (1.9%)
BRCA1/BRCA2	2 (0.9%)	2 (0.9%)	4 (0.9%)
BRCA1/CDK12	0	1 (0.5%)	1 (0.2%)
BRCA1/CHEK2	0	2 (0.9%)	2 (0.5%)
BRCA1/PALB2	0	1 (0.5%)	1 (0.2%)
BRCA2/CDK12	2 (0.9%)	1 (0.5%)	3 (0.7%)
BRCA2/CHEK2	10 (4.7%)	2 (0.9%)	12 (2.8%)
BRCA2/FANCA	2 (0.9%)	1 (0.5%)	3 (0.7%)
BRCA2/PALB2	1 (0.5%)	0	1 (0.2%)
BRCA2/CDK12/CHEK2/HDAC2	0	1 (0.5%)	1 (0.2%)
BRCA2/CDK12/CHEK2/PALB2	0	1 (0.5%)	1 (0.2%)
Subtotal BRCA Co-occurring	23 (10.9%)	16 (7.5%)	39 (9.2%)
ATM/BRIP1	0	1 (0.5%)	1 (0.2%)
ATM/CDK12	1 (0.5%)	2 (0.9%)	3 (0.7%)
ATM/CHEK2	1 (0.5%)	2 (0.9%)	3 (0.7%)
ATM/PALB2	1 (0.5%)	1 (0.5%)	2 (0.5%)
CDK12/CHEK2	3 (1.4%)	2 (0.9%)	5 (1.2%)
CHEK2/FANCA	2 (0.9%)	4 (1.9%)	6 (1.4%)
CHEK2/PALB2	0	1 (0.5%)	1 (0.2%)
ATM/CDK12/PALB2	1 (0.5%)	0	1 (0.2%)
Subtotal non-BRCA Co-occurring	9 (4.3%)	13 (6.1%)	22 (5.2%)

AAP=abiraterone acetate plus prednisone; ATM=ataxia telangiectasia mutated gene; BRCA=breast cancer gene; BRIP1=BRCA1 interacting protein C terminal helicase 1; CDK12=cyclin-dependent kinase 12; CHEK2=checkpoint kinase 2; FANCA=Fanconi anemia complementation group A gene; HDAC2=histone deacetylase 2; HRR=homologous recombination repair; PALB2=partner and localizer of BRCA2

Key: AAP = abiraterone acetate plus prednisone.

Prior prostate cancer therapies

All subjects had prior ADT by either bilateral orchiectomy (14.7%) or by GnRHa therapy (85.3%). Most subjects (95.7%) received prior hormonal therapy.

Table 37. Summary of Prior Prostate Cancer Related Therapies; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: randomized	211	212	423
Previous prostate cancer therapy			
N	211	212	423
Surgery or radiotherapy	166 (78.7%)	167 (78.8%)	333 (78.7%)
Surgery only	75 (35.5%)	77 (36.3%)	152 (35.9%)
Radiotherapy only	28 (13.3%)	34 (16.0%)	62 (14.7%)
Both surgery and radiotherapy	63 (29.9%)	56 (26.4%)	119 (28.1%)
Orchidectomy	30 (14.2%)	32 (15.1%)	62 (14.7%)
Hormonal therapy	201 (95.3%)	204 (96.2%)	405 (95.7%)
Novel AR targeted therapy	5 (2.4%)	8 (3.8%)	13 (3.1%)
Taxane chemotherapy	44 (20.9%)	41 (19.3%)	85 (20.1%)
AAP	48 (22.7%)	50 (23.6%)	98 (23.2%)
Other	57 (27.0%)	51 (24.1%)	108 (25.5%)
Dexamethasone	3 (1.4%)	4 (1.9%)	7 (1.7%)
Estramustine	2 (0.9%)	0	2 (0.5%)
Investigational Drug	1 (0.5%)	2 (0.9%)	3 (0.7%)
Ipilimumab	0	1 (0.5%)	1 (0.2%)
Prednisolone	13 (6.2%)	12 (5.7%)	25 (5.9%)
Prednisone	36 (17.1%)	33 (15.6%)	69 (16.3%)
Sipuleucel-T	4 (1.9%)	2 (0.9%)	6 (1.4%)

Key: AAP = abiraterone acetate plus prednisone.
Subjects having multiple therapies/surgeries are counted only once.

Subsequent anti-cancer therapies

Table 38. Summary of Selected Subsequent Therapy for Prostate Cancer for Subjects who Discontinued Treatment; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:subjects discontinued treatment	123	97
Number of subjects with selected subsequent therapy for prostate cancer	78 (63.4%)	46 (47.4%)
Chemotherapy	58 (47.2%)	39 (40.2%)
Docetaxel	46 (37.4%)	26 (26.8%)
Cabazitaxel	15 (12.2%)	11 (11.3%)
Carboplatin	5 (4.1%)	6 (6.2%)
Carboplatin;etoposide	0	1 (1.0%)
Cisplatin	2 (1.6%)	1 (1.0%)
Etoposide	0	1 (1.0%)
Carboplatin;docetaxel	2 (1.6%)	0
Estramustine	1 (0.8%)	0
Mitoxantrone	2 (1.6%)	0
Vinorelbine	1 (0.8%)	0
Other	13 (10.6%)	11 (11.3%)
Investigational drug	6 (4.9%)	4 (4.1%)
Radium	1 (0.8%)	2 (2.1%)
Radium ra 223	3 (2.4%)	2 (2.1%)
Durvalumab	0	1 (1.0%)
Imaradenant	0	1 (1.0%)
Lutetium (lu 177)	1 (0.8%)	1 (1.0%)
Sipuleucel-t	0	1 (1.0%)
Investigational antineoplastic drugs	1 (0.8%)	0
Nivolumab	1 (0.8%)	0
Novel AR targeted therapy	10 (8.1%)	10 (10.3%)
Enzalutamide	10 (8.1%)	10 (10.3%)
PARPi	13 (10.6%)	1 (1.0%)
Olaparib	10 (8.1%)	1 (1.0%)
Niraparib	2 (1.6%)	0
Rucaparib	1 (0.8%)	0
Talazoparib	1 (0.8%)	0

Key: AAP = abiraterone acetate plus prednisone.
Note: Recurrent medications are counted only once per subject.

Cohort 3

Table 39.Summary of Demographics; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Age, years	
N	95
Mean (SD)	69.2 (8.99)
Median	70.0
Range	(47; 90)
< 65	25 (26.3%)
≥ 65-74	48 (50.5%)
≥ 75	22 (23.2%)
Sex	
N	95
Male	95 (100.0%)
Race	
N	95
American Indian or Alaska Native	1 (1.1%)
Asian	14 (14.7%)
Black or African American	3 (3.2%)
White	70 (73.7%)
Unknown	7 (7.4%)
Ethnicity	
N	95
Hispanic or Latino	12 (12.6%)
Not Hispanic or Latino	77 (81.1%)
Not reported	6 (6.3%)
Weight, kg	
N	95
Mean (SD)	84.2 (14.22)
Median	82.0
Range	(52; 134)
Height, cm	
N	95
Mean (SD)	173.1 (7.19)
Median	173.0
Range	(157; 190)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: N's for each parameter reflect non-missing values.

Table 40. Summary of Prostate Cancer Baseline Clinical Disease Characteristics; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Time from initial diagnosis to randomization (years)	
N	95
Mean (SD)	3.84 (4.388)
Median	2.21
Range	(0.5; 24.8)
Time from mCRPC to first dose (years)	
N	95
Mean (SD)	0.40 (0.470)
Median	0.27
Range	(0.0; 4.0)
Tumor stage at initial diagnosis	
N	95
T1	5 (5.3%)
T2	17 (17.9%)
T3	34 (35.8%)
T4	21 (22.1%)
Unknown	18 (18.9%)
Lymph node stage at initial diagnosis	
N	95
N0	30 (31.6%)
N1	41 (43.2%)
NX	14 (14.7%)
Unknown	10 (10.5%)
Metastasis stage at initial diagnosis	
N	95
M0	36 (37.9%)

M1	56 (58.9%)
Unknown	3 (3.2%)
Gleason Score at initial diagnosis	
N	95
<7	3 (3.2%)
7	20 (21.1%)
3+4	8 (8.4%)
4+3	11 (11.6%)
Unknown	1 (1.1%)
>=8	71 (74.7%)
Unknown	1 (1.1%)
Prior Prostate Cancer Therapy	
N	95
Hormonal therapy	89 (93.7%)
Radiotherapy	47 (49.5%)
Surgery	56 (58.9%)
Prior novel AR targeted therapy	3 (3.2%)
Past taxane-based chemotherapy	21 (22.1%)
AAP	26 (27.4%)
Other	26 (27.4%)
ECOG Performance Status Score at baseline	
N	95
0	73 (76.8%)
1	22 (23.2%)
Extent of Disease at study entry[a]	
N	94
Bone	81 (86.2%)
Bone only	45 (47.9%)
Visceral	13 (13.8%)
Liver	5 (5.3%)
Lung	10 (10.6%)
Other	3 (3.2%)
Soft tissue	1 (1.1%)
Nodal[b]	44 (46.8%)
Pelvic	22 (23.4%)
Non-pelvic	31 (33.0%)
Prostate[c]	1 (1.1%)
Number of bone lesions at study entry	
N	95
<=10 lesions[d]	57 (60.0%)
> 10 lesions	38 (40.0%)
BPI-SF pain score (item 3)	
N	94
0	50 (53.2%)
1 to 3	37 (39.4%)
> 3	7 (7.4%)
Mean (SD)	1.03 (1.418)
Median	0.00
Range	(0.0; 6.0)

	Niraparib/AA FDC Plus Prednisone
PSA at initial diagnosis (ug/L)	
N	80
Mean (SD)	516.52 (1367.115)
Median	44.59
Range	(0.2; 8101.0)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
[a]Subjects having multiple lesions within each category are counted only once in the category, but may be represented on more than one category.
[b]Includes lymph nodes not specified as pelvic or non-pelvic.
[c]prostate local recurrence/progression
[d]includes subjects with no bone lesion
Note: Pain score data for 1 subject was collected but was not transmitted before database lock. Hence this subject is not included in analyses.

Table 41. Frequency of Subjects with Gene Alterations; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Single Gene Alterations	
BRCA1	8 (8.4%)
BRCA2	35 (36.8%)
CDK12	17 (17.9%)
CHEK2	14 (14.7%)
FANCA	5 (5.3%)
HDAC2	1 (1.1%)
PALB2	3 (3.2%)
Subtotal single gene alterations	83 (87.4%)
Co-occurring Gene Alterations	
BRCA1/BRCA2	2 (2.1%)
BRCA1/CDK12	1 (1.1%)
BRCA1/CHEK2	1 (1.1%)
BRCA2/CHEK2	2 (2.1%)
BRCA2/PALB2	1 (1.1%)
ATM/BRCA2/CHEK2	1 (1.1%)
BRCA2/CHEK2/PALB2	1 (1.1%)
Subtotal BRCA Co-occurring	9 (9.5%)
ATM/CDK12	1 (1.1%)
ATM/CHEK2	1 (1.1%)
ATM/FANCA	1 (1.1%)
Subtotal non-BRCA Co-occurring	3 (3.2%)

Key: AA = abiraterone acetate, FDC = fixed dose combination.

Numbers analysed

Table 42. Datasets analysed

	Cohort 1		Cohort 2		Cohort 3
	PBO+AAP	Nira+AAP SAC	PBO+AAP	Nira+AAP SAC	Nira+AAP FDC
Planned	~200	~200	~300	~300	~100
Enrolled	423 across both groups		247 across both groups		95
Randomized	211	212	124	123	N/A
Randomized Analysis Set	211	212	124	123	-
FDC Analysis Set	-	-	-	-	95
Safety Analysis Set	211	212	124	123	95

Key: AAP=abiraterone acetate plus prednisone; FDC=fixed-dose combination; N/A=not applicable; Nira=niraparib; PBO=placebo; SAC=single-agent combination.

Outcomes and estimation

Cohort 1

Primary endpoint

This primary analysis of the rPFS primary efficacy endpoint by BICR was performed after 217 rPFS events had been observed in the All HRR population, with 109 rPFS events observed in the BRCA subgroup, which met the minimum requirement for rPFS events needed per the SAP.

The CCO for this analysis was **08 October 2021**, at which time the median duration of survival follow-up for all subjects in Cohort 1 was 18.6 months.

All HRR population

Table 43. Summary of Radiographic Progression-Free Survival by Central Review – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Event	117 (55.5%)	100 (47.2%)
Censored	94 (44.5%)	112 (52.8%)
Time to event (months)		
25th percentile (95% CI)	5.72 (4.27, 8.21)	8.97 (8.05, 11.04)
Median (95% CI)	13.70 (10.91, 16.39)	16.46 (13.83, 19.38)
75th percentile (95% CI)	NE (19.52, NE)	NE (24.80, NE)
Range	(0.3, 27.9+)	(0.0+, 28.2+)
6-months event free rate (95% CI)	0.743 (0.678, 0.797)	0.846 (0.789, 0.888)
12-months event free rate (95% CI)	0.533 (0.459, 0.602)	0.640 (0.566, 0.705)
18-months event free rate (95% CI)	0.392 (0.314, 0.468)	0.450 (0.368, 0.529)
24-months event free rate (95% CI)	0.269 (0.182, 0.364)	0.348 (0.257, 0.441)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.0217
Hazard ratio (95% CI) [b]		0.729 (0.556,0.956)

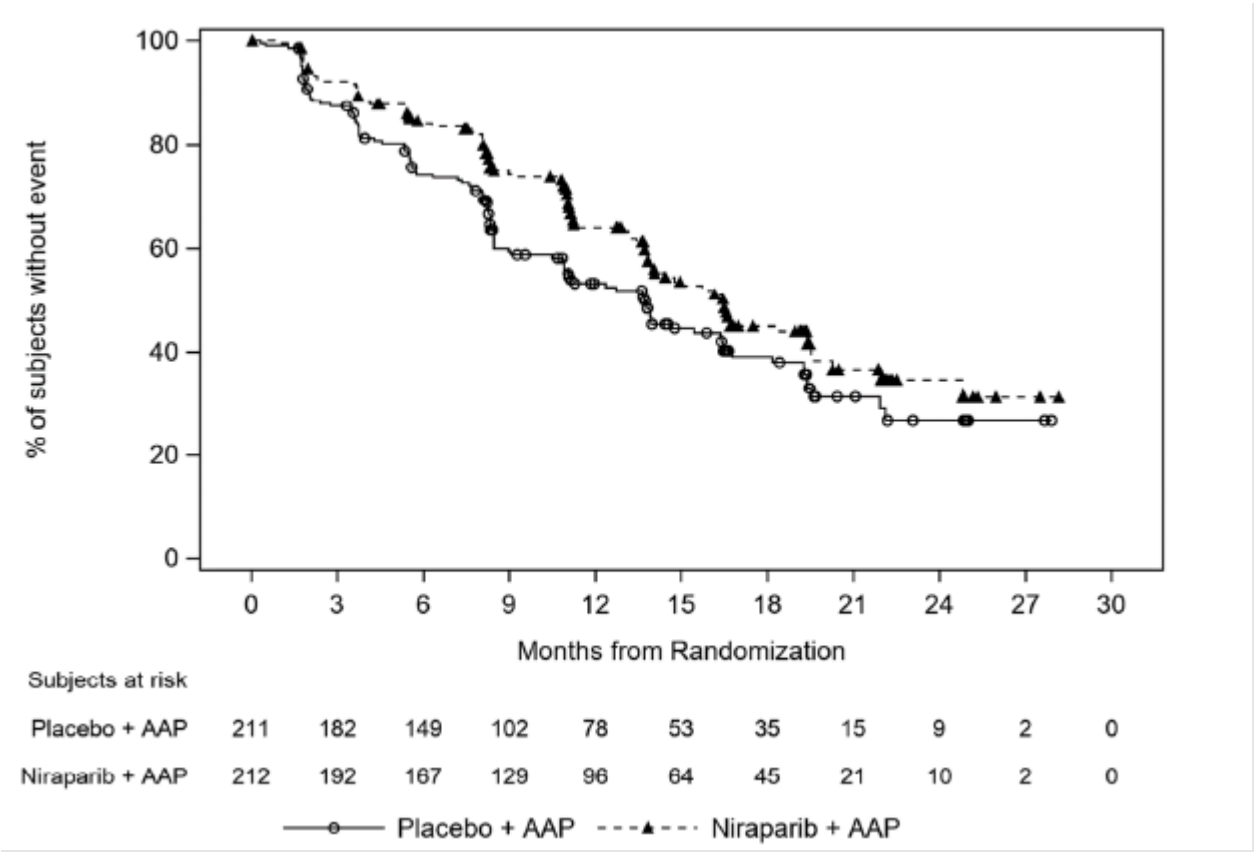
Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Table 44. Reasons for Event/Censored in the Analysis of Radiographic Progression-Free Survival by Central Review; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Event[a]	117 (55.5%)	100 (47.2%)
Radiographic progression	109 (51.7%)	84 (39.6%)
Death	8 (3.8%)	16 (7.5%)
Censored[a]	94 (44.5%)	112 (52.8%)
Permanently censored	15 (7.1%)	15 (7.1%)
No post baseline assessments	0	2 (0.9%)
No radiographic progression or death observed prior to any new systemic anti-cancer therapy received	12 (5.7%)	11 (5.2%)
2 consecutive missing scans	1 (0.5%)	1 (0.5%)
Withdrew Consent to Remain on Study	1 (0.5%)	1 (0.5%)
Lost to Follow-up	1 (0.5%)	0
No PD or Death Observed by Study Discontinuation	0	0
Still at Risk	79 (37.4%)	97 (45.8%)
On treatment by cutoff	76 (36.0%)	89 (42.0%)
Discontinued treatment by cutoff	3 (1.4%)	8 (3.8%)

Key: AAP = abiraterone acetate plus prednisone.
[a] The censoring reasons and event types are mutually exclusive.

Figure 20. Kaplan-Meier Plot of Radiographic Progression-Free Survival by Central Review; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)



BRCA subgroup

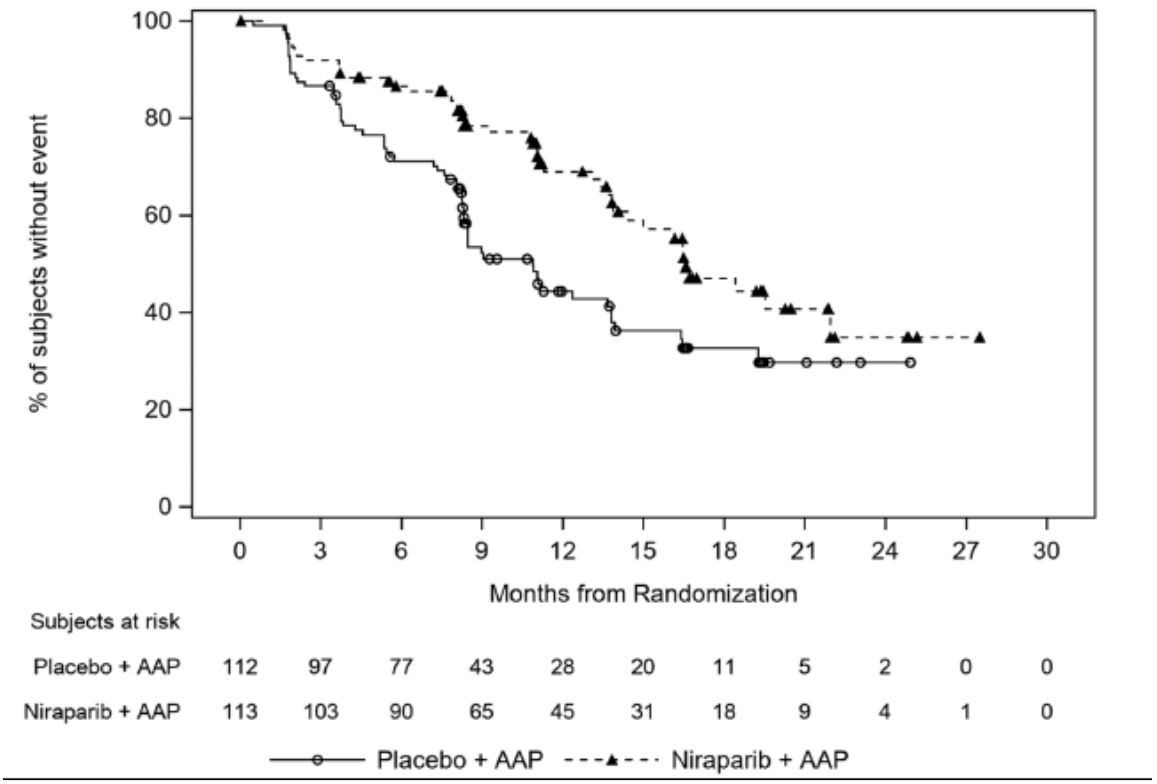
A statistically significant and clinically meaningful benefit of nira+AAP treatment was observed in subjects with BRCA 1 or BRCA2 gene alterations (by IWRS stratification), with a HR for rPFS of 0.533 (95% CI: 0.361, 0.789; p=0.0014).

Table 45. Summary of Radiographic Progression-Free Survival by Central Review – Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	112	113
Event	64 (57.1%)	45 (39.8%)
Censored	48 (42.9%)	68 (60.2%)
Time to event (months)		
25th percentile (95% CI)	5.36 (3.58, 8.05)	10.87 (8.05, 13.44)
Median (95% CI)	10.87 (8.31, 13.80)	16.56 (13.86, NE)
75th percentile (95% CI)	NE (16.39, NE)	NE (21.95, NE)
Range	(0.5, 24.9+)	(0.0+, 27.5+)
6-months event free rate (95% CI)	0.711 (0.617, 0.786)	0.865 (0.786, 0.916)
12-months event free rate (95% CI)	0.444 (0.341, 0.542)	0.690 (0.584, 0.775)
18-months event free rate (95% CI)	0.327 (0.224, 0.433)	0.470 (0.344, 0.587)
24-months event free rate (95% CI)	0.297 (0.192, 0.410)	0.349 (0.199, 0.503)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.0014
Hazard ratio (95% CI) [b]		0.533 (0.361,0.789)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 21. Kaplan-Meier Plot of Radiographic Progression-Free Survival by Central Review; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)



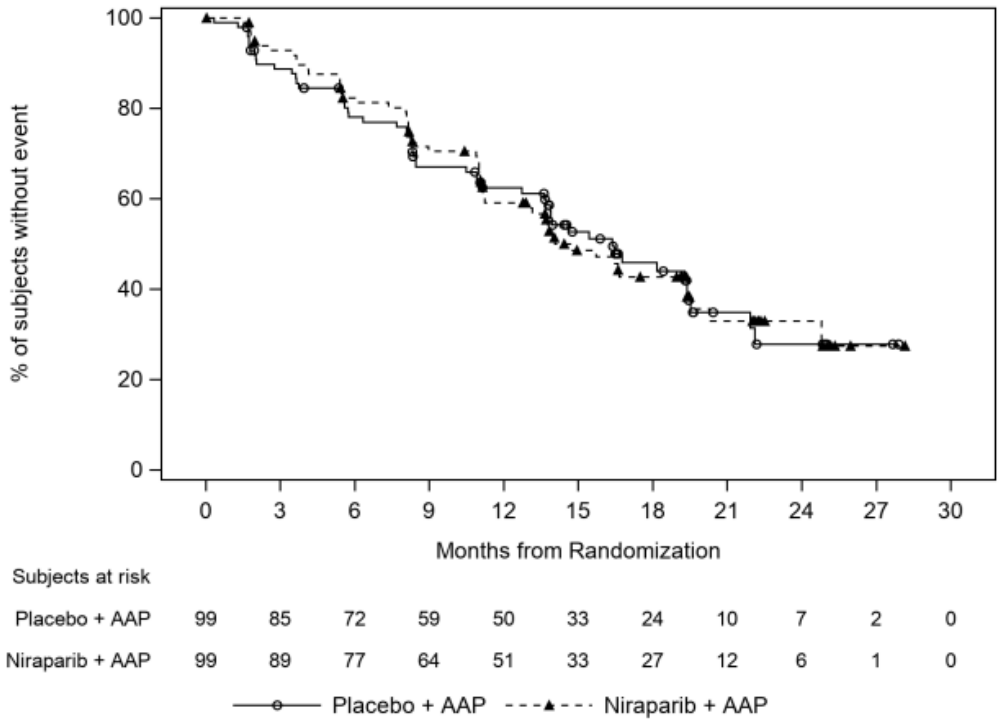
Non-BRCA subgroup

Table 46. Summary of Radiographic Progression-free Survival by Central Review – Stratified Analysis; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	99	99
Event	53 (53.5%)	55 (55.6%)
Censored	46 (46.5%)	44 (44.4%)
Time to event (months)		
25th percentile (95% CI)	8.08 (5.52, 10.48)	8.15 (5.45, 11.01)
Median (95% CI)	16.36 (13.63, 19.38)	14.75 (11.17, 19.38)
75th percentile (95% CI)	NE (19.52, NE)	NE (19.52, NE)
Range	(0.3, 27.9+)	(0.0+, 28.2+)
6-months event free rate (95% CI)	0.780 (0.683, 0.851)	0.823 (0.731, 0.886)
12-months event free rate (95% CI)	0.624 (0.517, 0.714)	0.591 (0.484, 0.684)
18-months event free rate (95% CI)	0.459 (0.344, 0.566)	0.427 (0.318, 0.531)
24-months event free rate (95% CI)	0.279 (0.159, 0.412)	0.329 (0.215, 0.448)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.9437
Hazard ratio (95% CI) [b]		0.986 (0.675,1.442)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 22*. Kaplan-Meier Plot of Radiographic Progression-free Survival by Central Review; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001)*



The MAA was based on the final analysis for the primary endpoint of rPFS. With an additional 8.1 months of median follow-up, the rPFS analysis was updated at the time of the second interim analysis

(IA2). While not formally assessed, the results shown in Table 47 demonstrate consistency in rPFS benefit with niraparib +AAP in all HRR cohort and the BRCA subgroup.

Table 47 Primary endpoint Results: rPFS by BICR for cohort 1 at PA-IA1 and IA2 (allHRR and BRCA)

rPFS Analysis	n (events)	PBO+AAP median (mos)	nira+AAP median (mos)	HR (95% CI)	p-value (log-rank test)
All HRR					
PA-IA1	423 (217)	13.70	16.46	0.729 (0.556, 0.956)	0.0217[a]
Update at IA2	423 (264)	13.67	16.66	0.760 (0.595, 0.972)	0.0280[b]
BRCA Subgroup					
PA-IA1	225 (109)	10.87	16.56	0.533 (0.361, 0.789)	0.0014[a]
Update at IA2	225 (135)	10.87	19.52	0.553 (0.392, 0.782)	0.0007[b]

[a] statistically significant
[b] nominal p-value

Secondary endpoints

The initial submission was based on the final analysis for the primary endpoint of rPFS which coincided with the first interim analysis for the secondary endpoints (PA-IA1). Since the initial submission the MAGNITUDE study accrued the required number of events to trigger the pre-specified second interim analysis for the secondary endpoints (IA2). All of the secondary endpoints (TSP, TCC, and OS) were formally statistically assessed at IA2. These results are presented below, with a clinical cut-off **17 June 2022**.

- **Time to initiation of cytotoxic chemotherapy (TCC)**

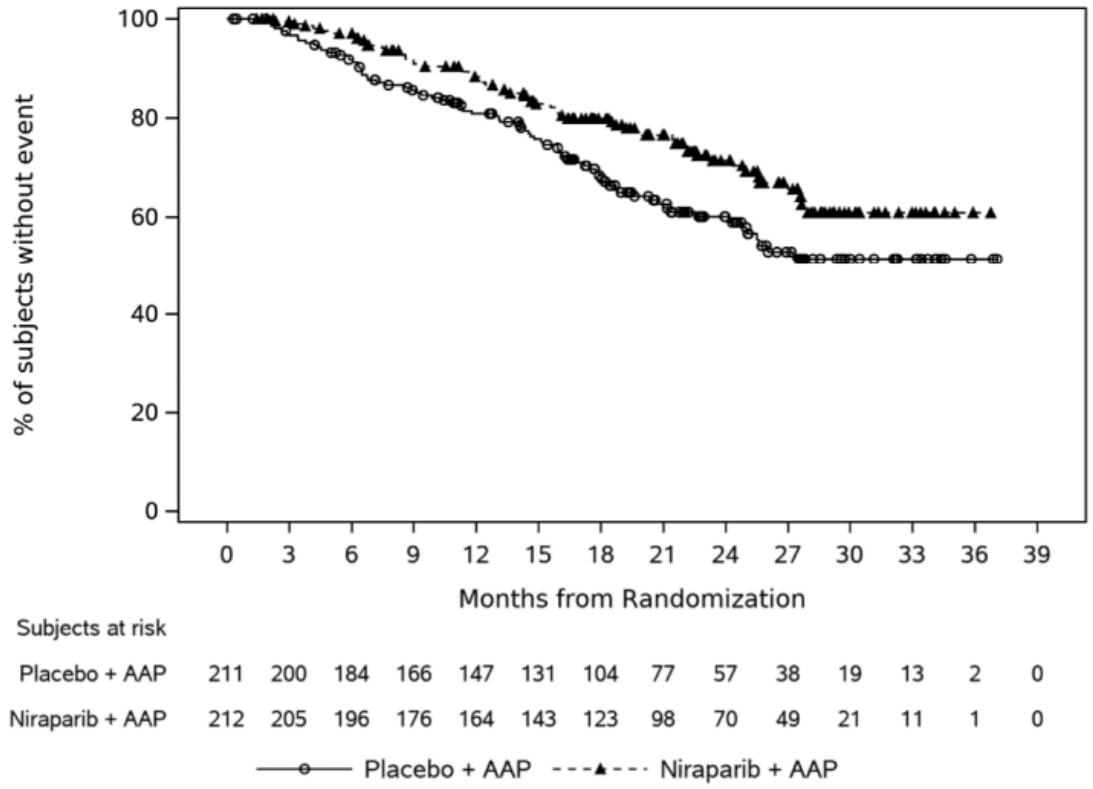
All HRR population

Table 48. Summary of Time to Initiation of Cytotoxic Chemotherapy – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	211	212
Event	77 (36.5%)	57 (26.9%)
Censored	134 (63.5%)	155 (73.1%)
Time to event (months)		
25th percentile (95% CI)	15.24 (11.79, 17.91)	21.49 (15.93, 25.63)
Median (95% CI)	NE (24.80, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3+, 37.1+)	(1.4+, 36.8+)
6-months event free rate (95% CI)	0.917 (0.870, 0.948)	0.971 (0.936, 0.987)
12-months event free rate (95% CI)	0.809 (0.747, 0.857)	0.883 (0.829, 0.920)
18-months event free rate (95% CI)	0.684 (0.611, 0.747)	0.799 (0.734, 0.849)
24-months event free rate (95% CI)	0.600 (0.520, 0.671)	0.714 (0.636, 0.777)
30-months event free rate (95% CI)	0.515 (0.424, 0.598)	0.608 (0.510, 0.692)
p-value [a]		0.0206
Hazard ratio (95% CI) [b]		0.666 (0.471,0.942)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 23. Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



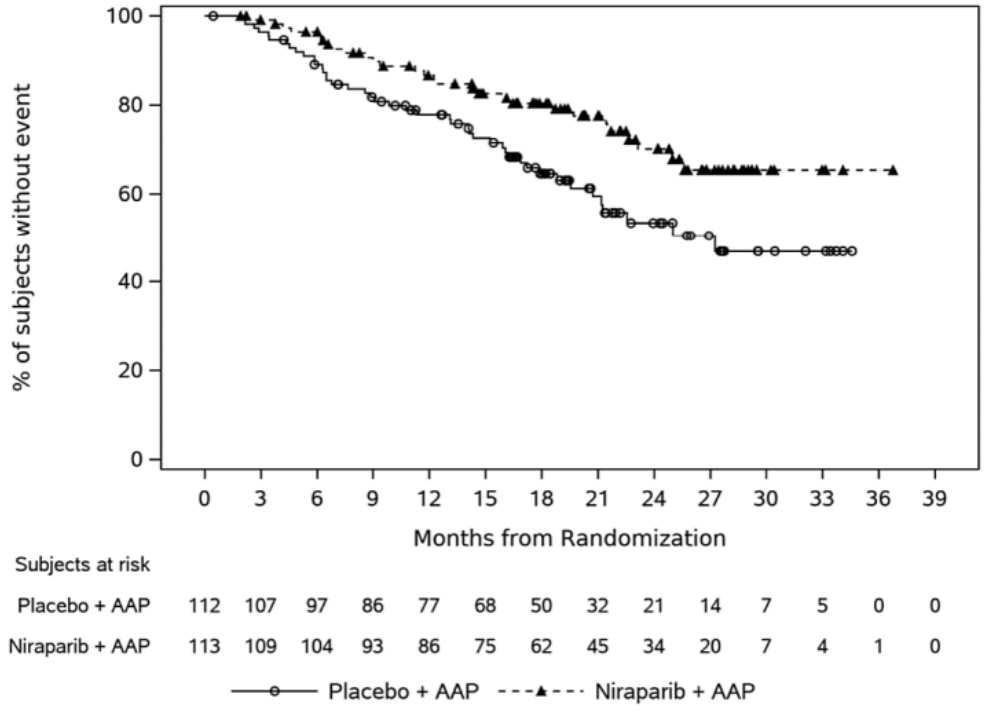
BRCA subgroup

Table 49. Summary of Time to Initiation of Cytotoxic Chemotherapy – Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	112	113
Event	44 (39.3%)	28 (24.8%)
Censored	68 (60.7%)	85 (75.2%)
Time to event (months)		
25th percentile (95% CI)	14.09 (8.57, 17.22)	21.49 (14.52, NE)
Median (95% CI)	27.27 (20.73, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.5+, 34.6+)	(1.9+, 36.8+)
6-months event free rate (95% CI)	0.891 (0.817, 0.937)	0.964 (0.906, 0.986)
12-months event free rate (95% CI)	0.778 (0.687, 0.846)	0.867 (0.786, 0.919)
18-months event free rate (95% CI)	0.645 (0.542, 0.731)	0.804 (0.712, 0.869)
24-months event free rate (95% CI)	0.534 (0.414, 0.640)	0.700 (0.583, 0.791)
30-months event free rate (95% CI)	0.468 (0.333, 0.592)	0.654 (0.525, 0.755)
p-value [a]		0.0152
Hazard ratio (95% CI) [b]		0.558 (0.346,0.900)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 24. Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



Key: AAP = abiraterone acetate plus prednisone.

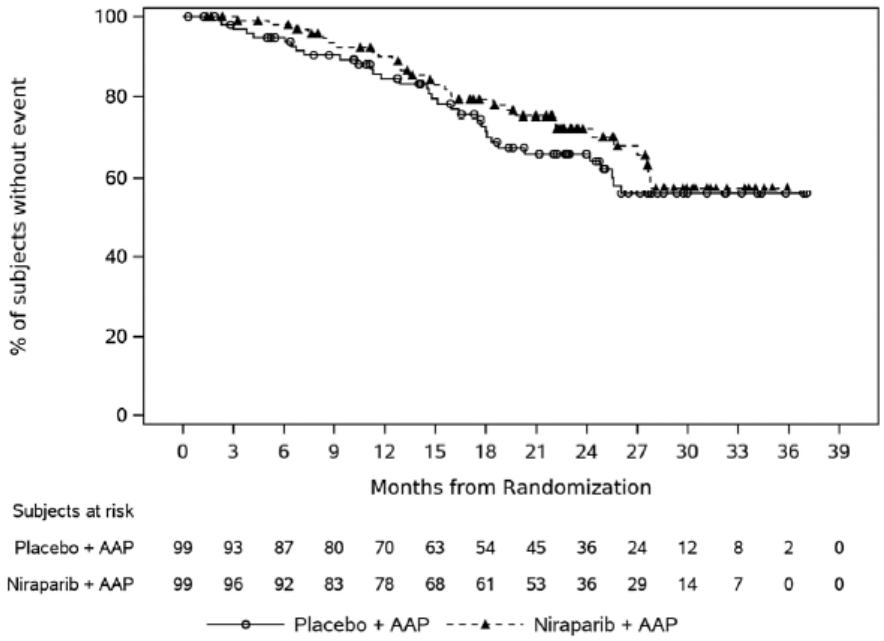
Non-BRCA subgroup

Table 50. Summary of Time to Initiation of Cytotoxic Chemotherapy – Stratified Analysis; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	99	99
Event	33 (33.3%)	29 (29.3%)
Censored	66 (66.7%)	70 (70.7%)
Time to event (months)		
25th percentile (95% CI)	17.51 (12.91, 24.18)	21.98 (14.62, 27.60)
Median (95% CI)	NE (25.49, NE)	NE (27.60, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3+, 37.1+)	(1.4+, 35.9+)
6-months event free rate (95% CI)	0.948 (0.879, 0.978)	0.979 (0.918, 0.995)
12-months event free rate (95% CI)	0.845 (0.751, 0.905)	0.900 (0.817, 0.947)
18-months event free rate (95% CI)	0.729 (0.620, 0.812)	0.793 (0.691, 0.864)
24-months event free rate (95% CI)	0.660 (0.546, 0.753)	0.723 (0.611, 0.807)
30-months event free rate (95% CI)	0.558 (0.430, 0.669)	0.574 (0.431, 0.694)
p-value [a]		0.4365
Hazard ratio (95% CI) [b]		0.817 (0.491,1.360)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 25. Kaplan-Meier Plot of Time to Initiation of Cytotoxic Chemotherapy; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



-
  - **Time to symptomatic progression (TSP)**

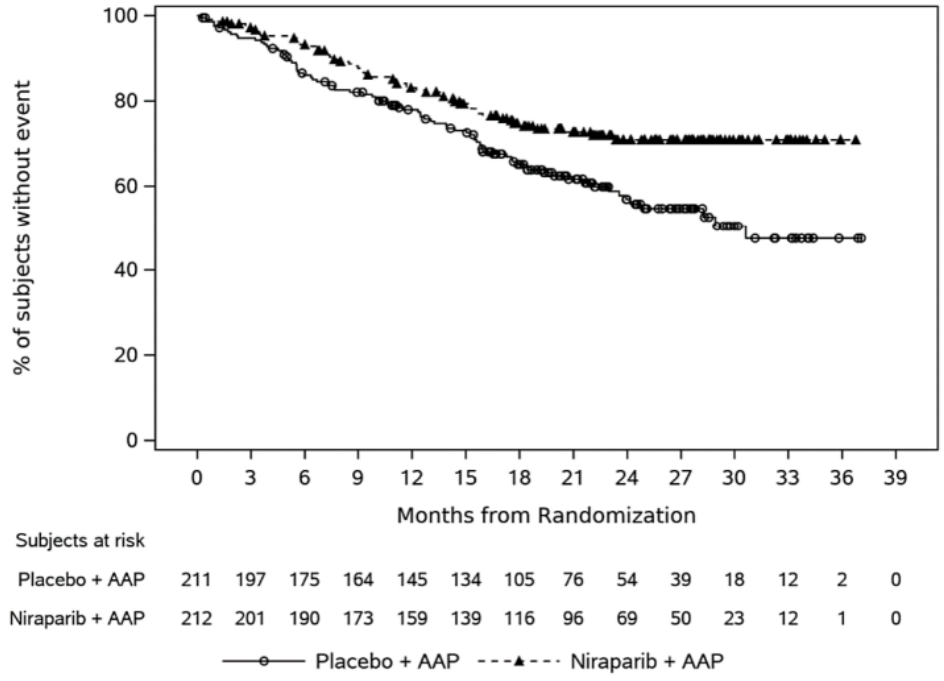
All HRR population

Table 51. Summary of Time to Symptomatic Progression – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	211	212
Event	83 (39.3%)	54 (25.5%)
Censored	128 (60.7%)	158 (74.5%)
Time to event (months)		
25th percentile (95% CI)	13.24 (9.79, 15.90)	17.68 (13.77, NE)
Median (95% CI)	30.62 (23.56, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3, 37.1+)	(0.2, 36.8+)
6-months event free rate (95% CI)	0.860 (0.805, 0.900)	0.932 (0.889, 0.959)
12-months event free rate (95% CI)	0.779 (0.716, 0.830)	0.831 (0.772, 0.876)
18-months event free rate (95% CI)	0.651 (0.578, 0.714)	0.740 (0.672, 0.797)
24-months event free rate (95% CI)	0.568 (0.488, 0.641)	0.709 (0.635, 0.770)
30-months event free rate (95% CI)	0.505 (0.410, 0.593)	0.709 (0.635, 0.770)
p-value [a]		0.0029
Hazard ratio (95% CI) [b]		0.596 (0.422,0.841)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 26. Kaplan-Meier Plot of Time to Symptomatic Progression; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



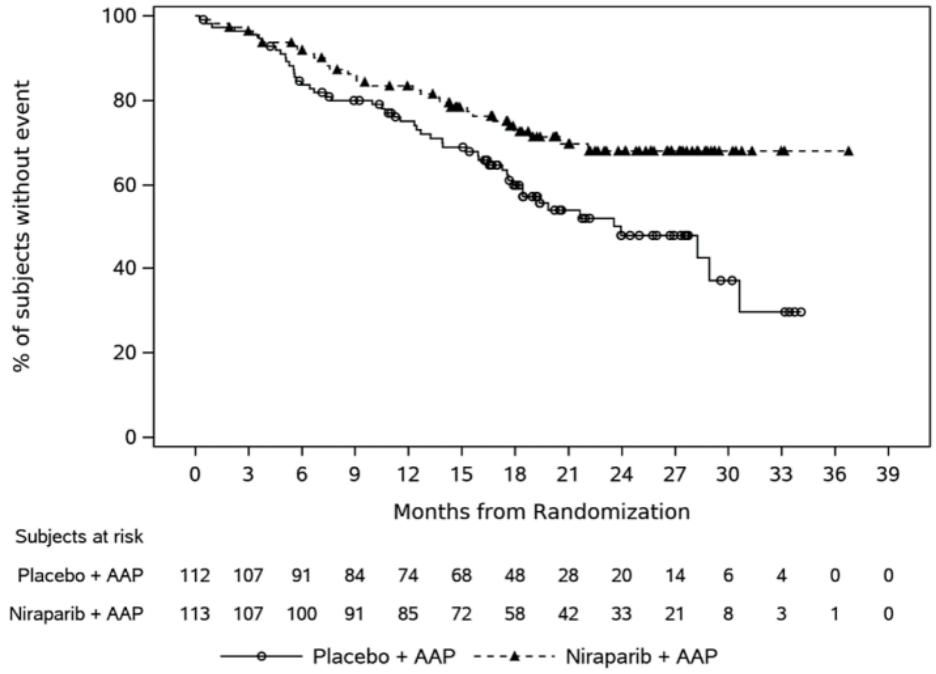
BRCA subgroup

Table 52. Summary of Time to Symptomatic Progression – Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	112	113
Event	51 (45.5%)	31 (27.4%)
Censored	61 (54.5%)	82 (72.6%)
Time to event (months)		
25th percentile (95% CI)	12.32 (6.44, 15.93)	17.68 (9.56, NE)
Median (95% CI)	23.56 (17.91, 30.62)	NE (NE, NE)
75th percentile (95% CI)	NE (28.91, NE)	NE (NE, NE)
Range	(0.3, 34.1+)	(0.2, 36.8+)
6-months event free rate (95% CI)	0.837 (0.754, 0.894)	0.919 (0.850, 0.957)
12-months event free rate (95% CI)	0.751 (0.657, 0.822)	0.834 (0.750, 0.892)
18-months event free rate (95% CI)	0.599 (0.496, 0.688)	0.727 (0.628, 0.803)
24-months event free rate (95% CI)	0.478 (0.361, 0.585)	0.680 (0.573, 0.766)
30-months event free rate (95% CI)	0.372 (0.220, 0.524)	0.680 (0.573, 0.766)
p-value [a]		0.0071
Hazard ratio (95% CI) [b]		0.544 (0.347,0.853)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 27. Kaplan-Meier Plot of Time to Symptomatic Progression; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



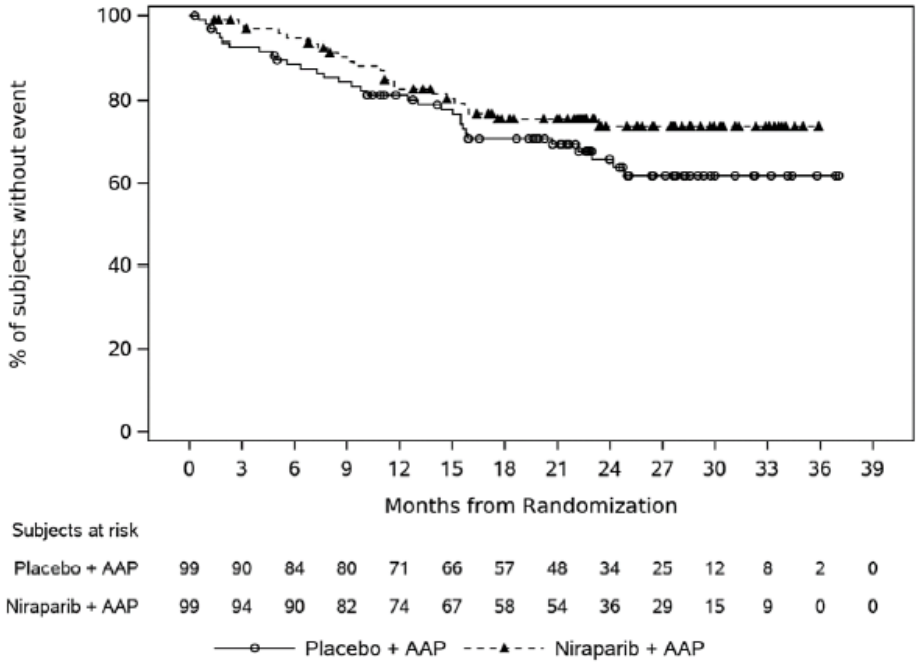
Non-BRCA subgroup

Table 53. Summary of Time to Symptomatic Progression – Stratified Analysis; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cut-off 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	99	99
Event	32 (32.3%)	23 (23.2%)
Censored	67 (67.7%)	76 (76.8%)
Time to event (months)		
25th percentile (95% CI)	15.47 (9.26, 22.97)	23.36 (11.70, NE)
Median (95% CI)	NE (24.80, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3+, 37.1+)	(0.2, 35.9+)
6-months event free rate (95% CI)	0.887 (0.804, 0.936)	0.948 (0.880, 0.978)
12-months event free rate (95% CI)	0.813 (0.719, 0.878)	0.827 (0.733, 0.890)
18-months event free rate (95% CI)	0.707 (0.602, 0.789)	0.755 (0.652, 0.832)
24-months event free rate (95% CI)	0.658 (0.544, 0.749)	0.736 (0.628, 0.818)
30-months event free rate (95% CI)	0.618 (0.498, 0.717)	0.736 (0.628, 0.818)
p-value [a]		0.1591
Hazard ratio (95% CI) [b]		0.681 (0.398,1.166)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Table 54. Kaplan-Meier Plot of Time to Symptomatic Progression; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



- **Overall survival (OS)**

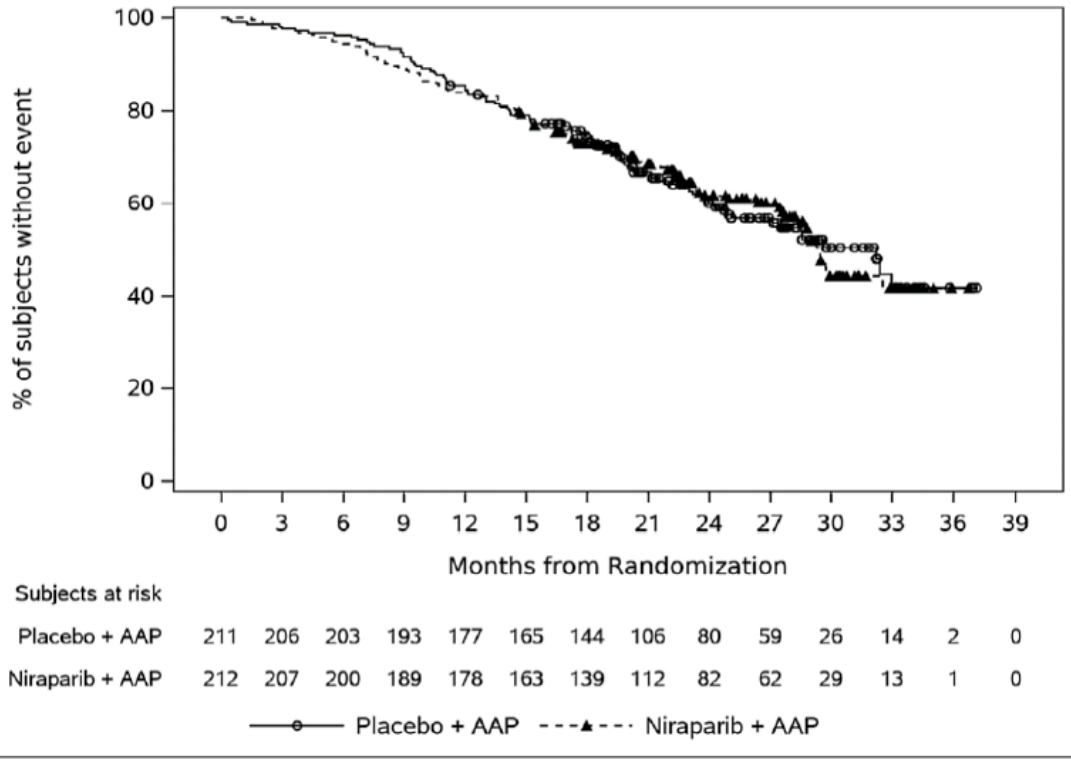
All HRR population

Table 55. Summary of Overall Survival – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Event	89 (42.2%)	90 (42.5%)
Censored	122 (57.8%)	122 (57.5%)
Time to event (months)		
25th percentile (95% CI)	17.91 (14.06, 20.01)	16.79 (13.77, 20.47)
Median (95% CI)	32.20 (24.87, NE)	29.31 (27.70, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3, 37.1+)	(1.5, 36.8+)
6-months event free rate (95% CI)	0.962 (0.926, 0.981)	0.943 (0.902, 0.967)
12-months event free rate (95% CI)	0.844 (0.787, 0.886)	0.840 (0.783, 0.883)
18-months event free rate (95% CI)	0.741 (0.676, 0.795)	0.729 (0.663, 0.784)
24-months event free rate (95% CI)	0.598 (0.522, 0.665)	0.616 (0.541, 0.682)
30-months event free rate (95% CI)	0.502 (0.413, 0.584)	0.444 (0.350, 0.535)
p-value [a]		0.9480
Hazard ratio (95% CI) [b]		1.010 (0.751,1.357)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 28. Kaplan-Meier Plot of Overall Survival; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



Key: AAP = abiraterone acetate plus prednisone.

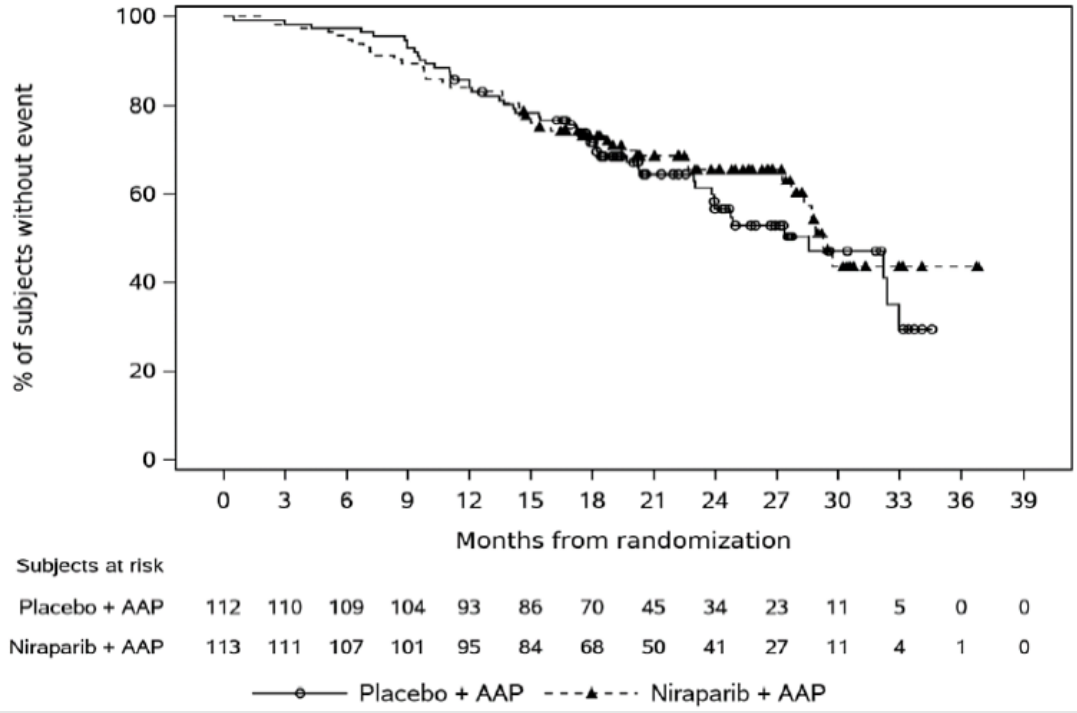
BRCA subgroup

Table 56. Summary of Overall Survival – Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	112	113
Event	49 (43.8%)	43 (38.1%)
Censored	63 (56.3%)	70 (61.9%)
Time to event (months)		
25th percentile (95% CI)	17.22 (12.12, 20.24)	15.97 (12.09, 22.67)
Median (95% CI)	28.55 (23.82, 32.95)	29.27 (27.70, NE)
75th percentile (95% CI)	NE (32.39, NE)	NE (NE, NE)
Range	(0.5, 34.6+)	(1.9, 36.8+)
6-months event free rate (95% CI)	0.973 (0.919, 0.991)	0.947 (0.886, 0.976)
12-months event free rate (95% CI)	0.839 (0.757, 0.895)	0.841 (0.759, 0.897)
18-months event free rate (95% CI)	0.717 (0.622, 0.792)	0.732 (0.640, 0.805)
24-months event free rate (95% CI)	0.566 (0.455, 0.663)	0.656 (0.554, 0.741)
30-months event free rate (95% CI)	0.470 (0.341, 0.588)	0.435 (0.284, 0.578)
p-value [a]		0.5505
Hazard ratio (95% CI) [b]		0.881 (0.582,1.335)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 29: Kaplan-Meier Plot of Overall Survival; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



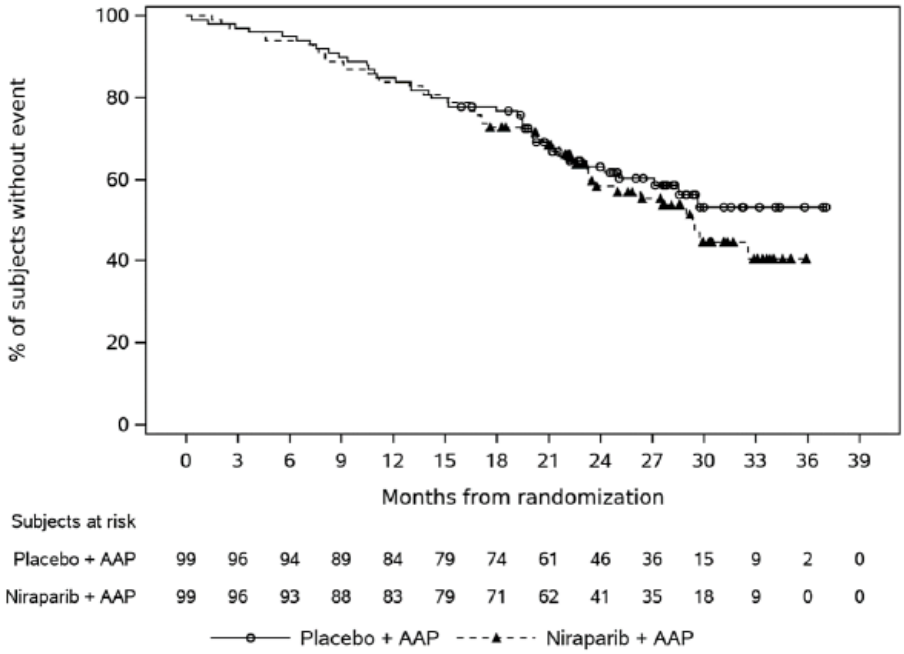
Non-BRCA subgroup

Table 57. Summary of Overall Survival – Stratified Analysis; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	99	99
Event	40 (40.4%)	47 (47.5%)
Censored	59 (59.6%)	52 (52.5%)
Time to event (months)		
25th percentile (95% CI)	19.38 (12.16, 21.55)	17.08 (11.17, 21.95)
Median (95% CI)	NE (25.07, NE)	29.31 (23.33, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3, 37.1+)	(1.5, 35.9+)
6-months event free rate (95% CI)	0.949 (0.883, 0.979)	0.939 (0.870, 0.972)
12-months event free rate (95% CI)	0.848 (0.761, 0.906)	0.838 (0.750, 0.898)
18-months event free rate (95% CI)	0.767 (0.671, 0.839)	0.727 (0.628, 0.804)
24-months event free rate (95% CI)	0.632 (0.525, 0.721)	0.584 (0.475, 0.678)
30-months event free rate (95% CI)	0.532 (0.407, 0.642)	0.445 (0.322, 0.561)
p-value [a]		0.4846
Hazard ratio (95% CI) [b]		1.162 (0.761,1.774)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 30. Kaplan-Meier Plot of Overall Survival; Cohort 1 Non-BRCA Randomized Analysis Set (Study 64091742PCR3001) - IA2 Clinical Cutoff 17 June 2022



Other efficacy endpoints

Updated data were provided for time to PSA progression, PFS2 and time to pain progression based on a 2IA (data cut-off 17 June 2022). Results of other efficacy endpoints presented below are based on the 1IA (08 October 2021).

- **Time to PSA progression**

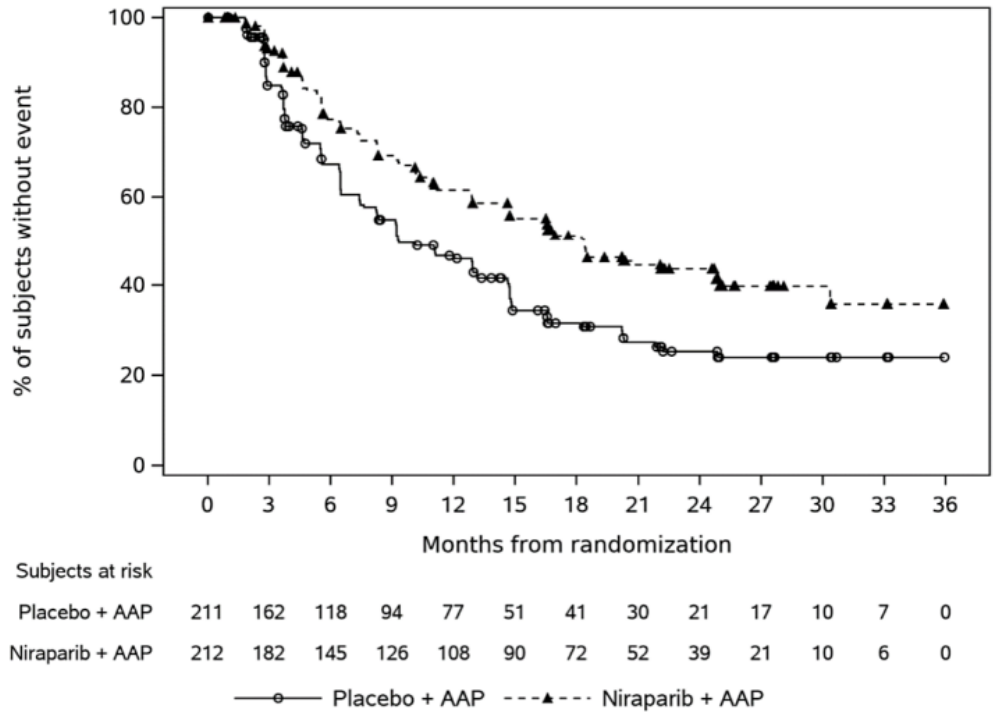
In the All HRR population (Cohort 1), substantial prolongation was observed in TPSA in subjects treated with nira+AAP group compared to the PBO+AAP group at IA2 (median 18.37 months nira+AAP vs 9.33 months PBO+AAP). The HR for the TPSA was 0.602 (95% CI: 0.462, 0.785); nominal p=0.0002.

Table 58. Summary of Time to PSA Progression– Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Event	129 (61.1%)	104 (49.1%)
Censored	82 (38.9%)	108 (50.9%)
Time to event (months)		
25th percentile (95% CI)	4.63 (3.71, 5.55)	7.29 (5.55, 9.20)
Median (95% CI)	9.33 (8.21, 13.14)	18.37 (14.72, 24.80)
75th percentile (95% CI)	24.87 (16.59, NE)	NE (NE, NE)
Range	(0.0+, 35.9+)	(0.0+, 35.9+)
6-months event free rate (95% CI)	0.673 (0.601, 0.735)	0.773 (0.707, 0.826)
12-months event free rate (95% CI)	0.466 (0.391, 0.537)	0.615 (0.541, 0.680)
18-months event free rate (95% CI)	0.315 (0.246, 0.387)	0.512 (0.436, 0.582)
24-months event free rate (95% CI)	0.253 (0.185, 0.326)	0.437 (0.360, 0.511)
30-months event free rate (95% CI)	0.240 (0.173, 0.314)	0.398 (0.317, 0.478)
p-value [a]		0.0002
Hazard ratio (95% CI) [b]		0.602 (0.462,0.785)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 31. Kaplan-Meier Plot of Time to PSA Progression; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)



Key: AAP = abiraterone acetate plus prednisone.

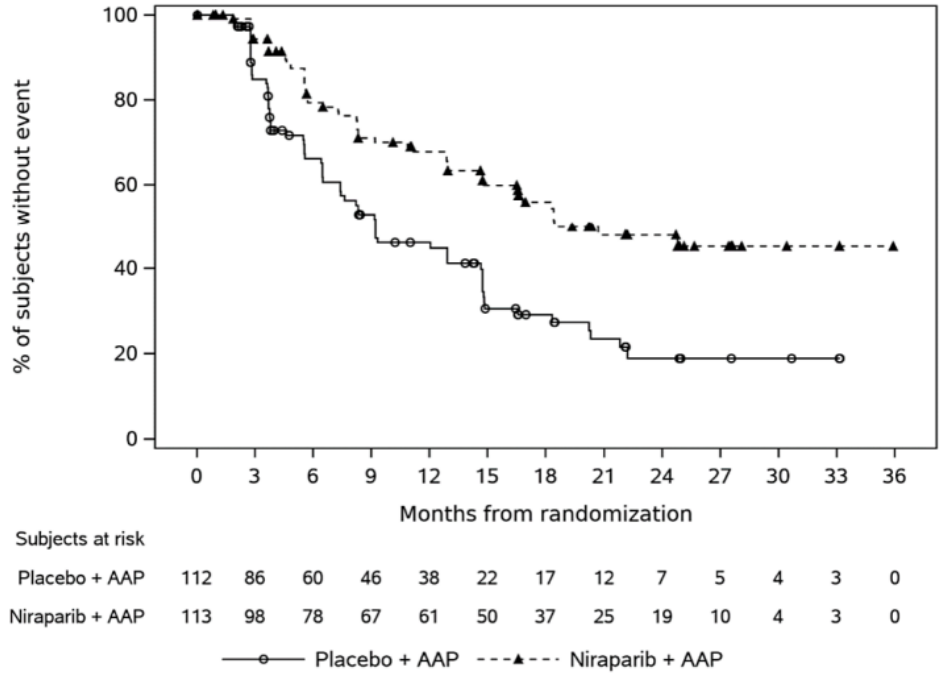
A substantial treatment effect was observed in TPSA in the BRCA subgroup at IA2, with nearly a doubling in median TSPA in the nira+AAP group (18.43 months) as compared with the PBO+AAP group (9.23 months) with an HR=0.478 (95% CI: 0.328, 0.696); nominal p=<0.0001.

Table 59. Summary of Time to PSA Progression– Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	112	113
Event	70 (62.5%)	48 (42.5%)
Censored	42 (37.5%)	65 (57.5%)
Time to event (months)		
25th percentile (95% CI)	3.78 (3.65, 5.59)	8.28 (5.55, 12.88)
Median (95% CI)	9.23 (7.39, 14.65)	18.43 (14.78, NE)
75th percentile (95% CI)	20.30 (14.75, NE)	NE (NE, NE)
Range	(0.0+, 33.2+)	(0.0+, 35.9+)
6-months event free rate (95% CI)	0.662 (0.559, 0.746)	0.793 (0.701, 0.860)
12-months event free rate (95% CI)	0.460 (0.357, 0.558)	0.678 (0.576, 0.760)
18-months event free rate (95% CI)	0.291 (0.198, 0.390)	0.559 (0.451, 0.653)
24-months event free rate (95% CI)	0.188 (0.102, 0.294)	0.479 (0.367, 0.583)
30-months event free rate (95% CI)	0.188 (0.102, 0.294)	0.452 (0.336, 0.562)
p-value [a]		<.0001
Hazard ratio (95% CI) [b]		0.478 (0.328,0.696)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 32. Kaplan-Meier Plot of Time to PSA Progression; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)



Key: AAP = abiraterone acetate plus prednisone.

- **Progression free survival 2 (PFS2)**

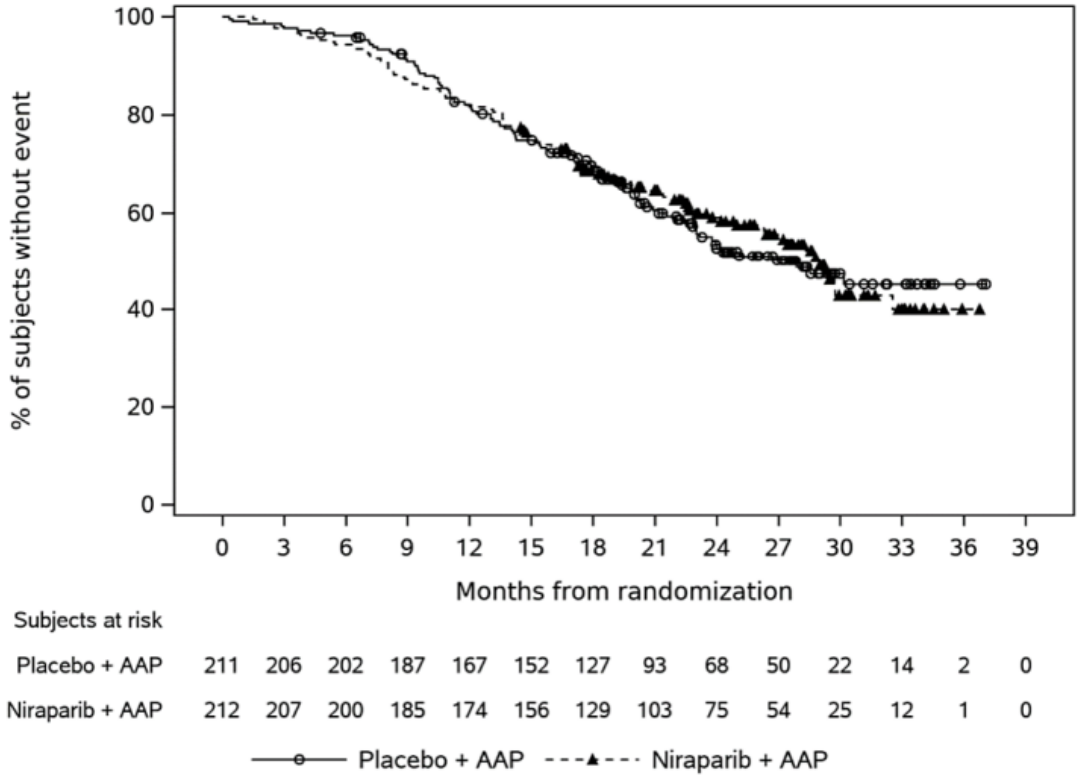
All HRR population

Table 60. Summary of Progression-free Survival 2– Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Event	94 (44.5%)	95 (44.8%)
Censored	117 (55.5%)	117 (55.2%)
Time to event (months)		
25th percentile (95% CI)	14.26 (12.16, 17.97)	14.98 (13.14, 17.58)
Median (95% CI)	27.86 (22.83, NE)	28.94 (24.97, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3, 37.1+)	(1.5, 36.8+)
6-months event free rate (95% CI)	0.962 (0.926, 0.981)	0.943 (0.902, 0.967)
12-months event free rate (95% CI)	0.817 (0.757, 0.863)	0.821 (0.762, 0.866)
18-months event free rate (95% CI)	0.691 (0.622, 0.750)	0.685 (0.617, 0.743)
24-months event free rate (95% CI)	0.528 (0.451, 0.599)	0.591 (0.517, 0.657)
30-months event free rate (95% CI)	0.473 (0.390, 0.552)	0.429 (0.334, 0.520)
p-value [a]		0.8018
Hazard ratio (95% CI) [b]		0.964 (0.723,1.285)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 33. Kaplan-Meier Plot of Progression-free Survival 2; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)



Key: AAP = abiraterone acetate plus prednisone.

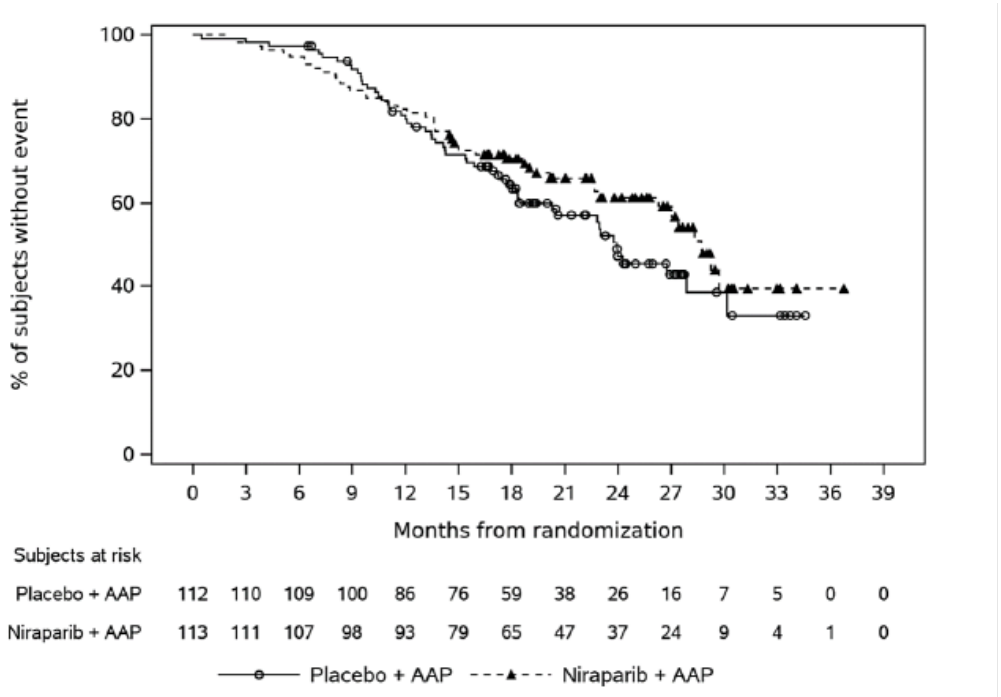
BRCA Subgroup

Table 61. Summary of Progression-free Survival 2– Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	112	113
Event	54 (48.2%)	47 (41.6%)
Censored	58 (51.8%)	66 (58.4%)
Time to event (months)		
25th percentile (95% CI)	13.70 (11.04, 17.22)	14.72 (11.04, 20.14)
Median (95% CI)	23.95 (18.43, 30.16)	28.71 (26.28, NE)
75th percentile (95% CI)	NE (30.16, NE)	NE (29.70, NE)
Range	(0.5, 34.6+)	(1.9, 36.8+)
6-months event free rate (95% CI)	0.973 (0.919, 0.991)	0.947 (0.886, 0.976)
12-months event free rate (95% CI)	0.799 (0.711, 0.863)	0.823 (0.739, 0.882)
18-months event free rate (95% CI)	0.645 (0.546, 0.728)	0.705 (0.611, 0.780)
24-months event free rate (95% CI)	0.471 (0.359, 0.575)	0.613 (0.507, 0.702)
30-months event free rate (95% CI)	0.385 (0.256, 0.512)	0.394 (0.245, 0.540)
p-value [a]		0.2293
Hazard ratio (95% CI) [b]		0.785 (0.528,1.166)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 34. Kaplan-Meier Plot of Progression-free Survival 2; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)



- **Time to initiation of subsequent therapy**

Table 62. Time to Subsequent Therapy – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	211	212
Event	78 (37.0%)	46 (21.7%)
Censored	133 (63.0%)	166 (78.3%)
Time to event (months)		
25th percentile (95% CI)	12.81 (10.09, 14.52)	18.56 (14.82, 22.60)
Median (95% CI)	21.19 (17.84, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.3+, 29.0+)	(1.4+, 28.2+)
6-months event free rate (95% CI)	0.888 (0.836, 0.924)	0.961 (0.924, 0.981)
12-months event free rate (95% CI)	0.756 (0.687, 0.811)	0.848 (0.788, 0.892)
18-months event free rate (95% CI)	0.584 (0.498, 0.660)	0.767 (0.692, 0.827)
24-months event free rate (95% CI)	0.434 (0.323, 0.540)	0.642 (0.523, 0.738)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.0002
Hazard ratio (95% CI) [b]		0.499 (0.344,0.722)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Table 63. Time to Subsequent Therapy – Non-stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	112	113
Event	49 (43.8%)	25 (22.1%)
Censored	63 (56.3%)	88 (77.9%)
Time to event (months)		
25th percentile (95% CI)	9.82 (6.28, 13.14)	19.71 (12.22, 21.42)
Median (95% CI)	17.81 (14.29, 21.19)	NE (21.42, NE)
75th percentile (95% CI)	NE (21.19, NE)	NE (NE, NE)
Range	(0.5+, 27.1+)	(1.9, 27.6+)
6-months event free rate (95% CI)	0.837 (0.754, 0.894)	0.955 (0.895, 0.981)
12-months event free rate (95% CI)	0.694 (0.593, 0.774)	0.841 (0.753, 0.900)
18-months event free rate (95% CI)	0.465 (0.340, 0.580)	0.789 (0.683, 0.863)
24-months event free rate (95% CI)	0.289 (0.143, 0.453)	0.521 (0.307, 0.697)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.0004
Hazard ratio (95% CI) [b]		0.427 (0.263,0.692)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a nonstratified log-rank test
[b]Hazard ratio is from nonstratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

- **Time to Pain Progression**

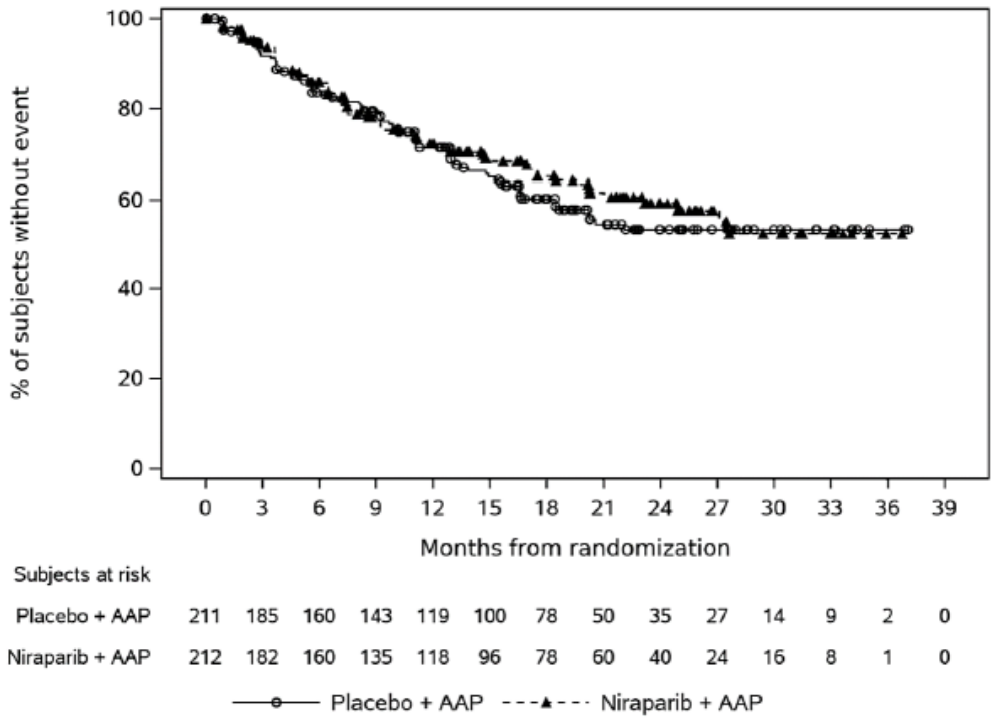
All HRR Population

Table 64. Summary of Time to Pain Progression – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	211	212
Event	79 (37.4%)	71 (33.5%)
Censored	132 (62.6%)	141 (66.5%)
Time to event (months)		
25th percentile (95% CI)	10.18 (8.11, 12.94)	11.01 (7.43, 14.85)
Median (95% CI)	NE (18.60, NE)	NE (24.90, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.0+, 37.1+)	(0.0+, 36.8+)
6-months event free rate (95% CI)	0.836 (0.778, 0.881)	0.858 (0.801, 0.900)
12-months event free rate (95% CI)	0.713 (0.643, 0.772)	0.722 (0.651, 0.781)
18-months event free rate (95% CI)	0.602 (0.525, 0.671)	0.651 (0.574, 0.718)
24-months event free rate (95% CI)	0.534 (0.450, 0.611)	0.592 (0.507, 0.666)
30-months event free rate (95% CI)	0.534 (0.450, 0.611)	0.525 (0.419, 0.620)
p-value [a]		0.4981
Hazard ratio (95% CI) [b]		0.894 (0.647,1.236)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 35. Kaplan-Meier Plot of Time to BPI-SF Worst Pain Intensity Progression; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)



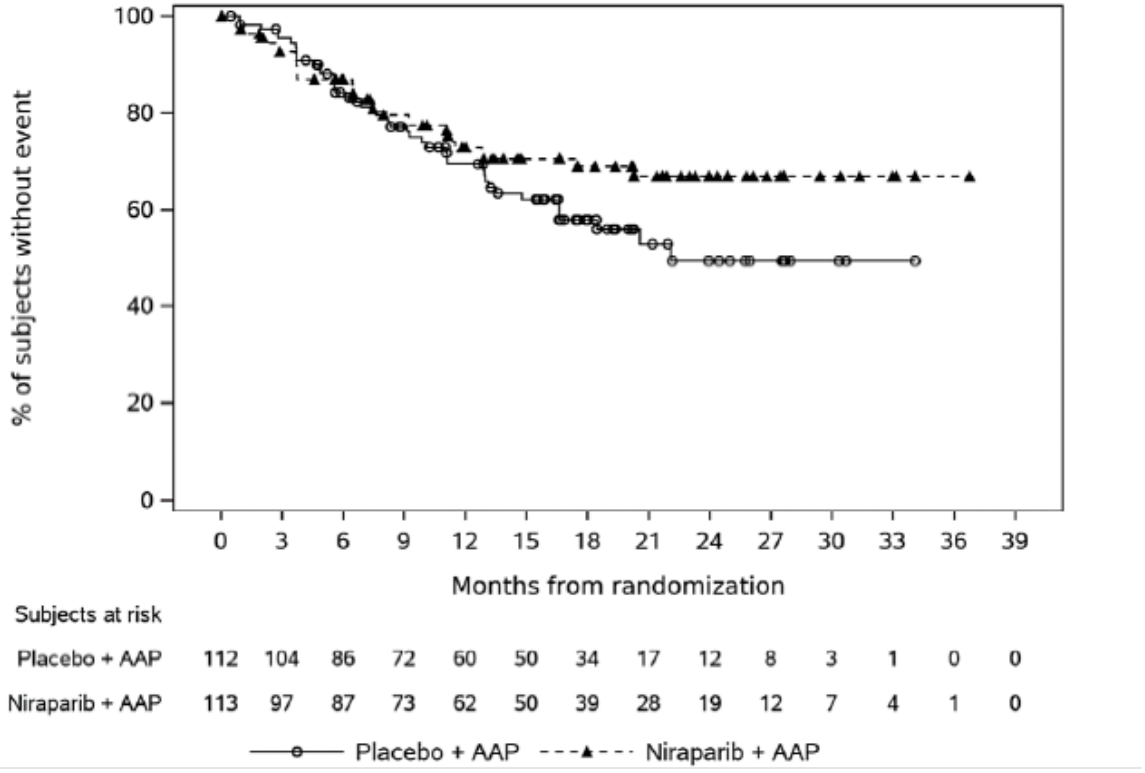
BRCA Subgroup

Table 65. Summary of Time to Pain Progression – Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	112	113
Event	43 (38.4%)	31 (27.4%)
Censored	69 (61.6%)	82 (72.6%)
Time to event (months)		
25th percentile (95% CI)	9.86 (6.14, 12.98)	11.27 (6.54, NE)
Median (95% CI)	22.11 (16.59, NE)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)	NE (NE, NE)
Range	(0.5+, 34.1+)	(0.0+, 36.8+)
6-months event free rate (95% CI)	0.842 (0.758, 0.899)	0.869 (0.789, 0.920)
12-months event free rate (95% CI)	0.694 (0.593, 0.775)	0.729 (0.629, 0.806)
18-months event free rate (95% CI)	0.579 (0.470, 0.674)	0.689 (0.584, 0.773)
24-months event free rate (95% CI)	0.494 (0.362, 0.613)	0.669 (0.559, 0.758)
30-months event free rate (95% CI)	0.494 (0.362, 0.613)	0.669 (0.559, 0.758)
p-value [a]		0.1338
Hazard ratio (95% CI) [b]		0.701 (0.439,1.118)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Figure 36. Kaplan-Meier Plot of Time to Pain Progression; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)



- **Objective Response Rate (ORR)**

Table 66. Summary of Objective Response Rate Based on RECIST Version 1.1 Criteria in Subjects with Measurable Disease at Baseline; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Number of subjects with measurable disease at baseline[a]	82	92
Responder	23 (28.0%)	55 (59.8%)
Non-responder	59 (72.0%)	37 (40.2%)
p-value[b]		< 0.001
Relative Risk (95% CI)[c]		2.131 (1.450,3.132)
Best Overall Response		
Complete Response (CR)	9 (11.0%)	20 (21.7%)
Partial Response (PR)	14 (17.1%)	35 (38.0%)
Stable Disease (SD)	41 (50.0%)	25 (27.2%)
Progressive Disease (PD)	13 (15.9%)	8 (8.7%)
Not Evaluable (NE)	5 (6.1%)	4 (4.3%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Response is a CR or PR. CR and PR do not have to be confirmed.
[a]No progression by PCWG3.
[b]p-value is from chi square test.
[c]Relative Risk >1 favors active treatment.
Note: Percent of Responder/Non-responder is based on the number of subjects with measurable disease at baseline.

Table 67. Summary of Objective Response Rate Based on RECIST Version 1.1 Criteria in Subjects with Measurable Disease at Baseline; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	112	113
Number of subjects with measurable disease at baseline[a]	48	56
Responder	15 (31.3%)	29 (51.8%)
Non-responder	33 (68.8%)	27 (48.2%)
p-value[b]		0.035
Relative Risk (95% CI)[c]		1.657 (1.015,2.705)
Best Overall Response		
Complete Response (CR)	7 (14.6%)	10 (17.9%)
Partial Response (PR)	8 (16.7%)	19 (33.9%)
Stable Disease (SD)	24 (50.0%)	18 (32.1%)
Progressive Disease (PD)	8 (16.7%)	6 (10.7%)
Not Evaluable (NE)	1 (2.1%)	3 (5.4%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Response is a CR or PR. CR and PR do not have to be confirmed.
[a]No progression by PCWG3.
[b]p-value is from chi-square test.
[c]Relative Risk >1 favors active treatment.
Note: Percent of Responder/Non-responder is based on the number of subjects with measurable disease at baseline.

Table 68. Summary of objective response rate based on RECIST v1.1 criteria in subjects with measurable disease at baseline; Cohort 1 Non-BRCA Randomised Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	99	99
Number of subjects with measurable disease at baseline[a]	34	36
Responder	8 (23.5%)	26 (72.2%)
Non-responder	26 (76.5%)	10 (27.8%)
p-value[b]		< 0.001
Relative Risk (95% CI)[c]		3.069 (1.620,5.815)
Best Overall Response		
Complete Response (CR)	2 (5.9%)	10 (27.8%)
Partial Response (PR)	6 (17.6%)	16 (44.4%)
Stable Disease (SD)	17 (50.0%)	7 (19.4%)
Progressive Disease (PD)	5 (14.7%)	2 (5.6%)
Not Evaluable (NE)	4 (11.8%)	1 (2.8%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Response is a CR or PR. CR and PR do not have to be confirmed.
[a]No progression by PCWG3.
[b]p-value is from chi-square test.
[c]Relative Risk >1 favors active treatment.
Note: Percent of Responder/Non-responder is based on the number of subjects with measurable disease at baseline.

- **Duration of response**

In the All HRR population, the median duration of response for subjects with a CR or PR as assessed by BICR among subjects with measurable disease at baseline was prolonged in the nira+AAP group; median 11.07 months in the nira+AAP group compared to 8.67 months in the PBO+AAP group.

Results in the BRCA subgroup were consistent with the All HRR population, with a longer duration of response observed in the nira+AAP group compared the PBO+AAP group.

- **PSA response**

Table 69. Summary of PSA Response Rate - Nonstratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: randomized	211	212
Subjects with PSA Response	143 (67.8%)	163 (76.9%)
Confirmed	131 (62.1%)	156 (73.6%)
Unconfirmed	12 (5.7%)	7 (3.3%)
p-value [a]		0.011
Relative Risk (95% CI)[b]		1.185 (1.038,1.353)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is based on confirmed response from chi-square test.
[b]Relative Risk is based on confirmed response. Relative Risk >1 favors active treatment.

Cohort 3

As of the CCO of 17 June 2022 for IA2, the Cohort 3 median duration of study treatment was 12.8 months. Survival follow-up for Cohort 3 was also of short duration (13.8 months) at IA2. As there was no separate hypothesis for Cohort 3 only descriptive statistics for key efficacy endpoints are provided. Median follow up time was of 5.5 months for rPFS.

Table 70. Summary of Radiographic Progression-free Survival by Central Review – Nonstratified Analysis; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Event	31 (32.6%)
Censored	64 (67.4%)
Time to event (months)	
25th percentile (95% CI)	8.15 (3.75, 11.10)
Median (95% CI)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)
Range	(0.0+, 16.4+)
6-months event free rate (95% CI)	0.769 (0.668, 0.843)
12-months event free rate (95% CI)	0.639 (0.525, 0.732)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: + = censored observation, NE = not estimable

Table 71. Summary of Time to Initiation of Cytotoxic Chemotherapy – Nontratified Analysis; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Event	14 (14.7%)
Censored	81 (85.3%)
Time to event (months)	
25th percentile (95% CI)	NE (12.25, NE)
Median (95% CI)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)
Range	(0.5+, 16.8+)
6-months event free rate (95% CI)	0.955 (0.885, 0.983)
12-months event free rate (95% CI)	0.853 (0.755, 0.914)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: + = censored observation, NE = not estimable

Table 72. Summary of Time to Symptomatic Progression – Nonstratified Analysis; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Event	14 (14.7%)
Censored	81 (85.3%)
Time to event (months)	
25th percentile (95% CI)	NE (12.25, NE)
Median (95% CI)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)
Range	(0.5+, 16.8+)
6-months event free rate (95% CI)	0.955 (0.885, 0.983)
12-months event free rate (95% CI)	0.853 (0.755, 0.914)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: + = censored observation, NE = not estimable

Table 73. Summary of Overall Survival – Nonstratified Analysis; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Event	17 (17.9%)
Censored	78 (82.1%)
Time to event (months)	
25th percentile (95% CI)	NE (11.24, NE)
Median (95% CI)	NE (NE, NE)
75th percentile (95% CI)	NE (NE, NE)
Range	(0.5, 16.8+)
6-months event free rate (95% CI)	0.916 (0.839, 0.957)
12-months event free rate (95% CI)	0.825 (0.730, 0.889)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: + = censored observation, NE = not estimable

Table 74. Summary of PSA Response Rate; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Subjects with PSA Response	70 (73.7%)
Confirmed	66 (69.5%)
Unconfirmed	4 (4.2%)

Key: AA = abiraterone acetate, FDC = fixed dose combination.

Table 75. Summary of Time to PSA Progression; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Event	33 (34.7%)
Censored	62 (65.3%)
Time to event (months)	
25th percentile (95% CI)	7.39 (3.71, 9.30)
Median (95% CI)	NE (11.10, NE)
75th percentile (95% CI)	NE (NE, NE)
Range	(0.0+, 16.6+)
6-months event free rate (95% CI)	0.770 (0.663, 0.847)
12-months event free rate (95% CI)	0.592 (0.473, 0.693)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: + = censored observation, NE = not estimable

Table 76. Summary of Objective Response Rate Based on RECIST Version 1.1 Criteria in Subjects with Measurable Disease at Baseline - Nonstratified Analysis; Cohort 3 Enrolled Analysis Set (Study 64091742PCR3001)

	Niraparib/AA FDC Plus Prednisone
Analysis set: enrolled	95
Number of subjects with measurable disease at baseline[a]	32
Responder	13 (40.6%)
Non-responder	19 (59.4%)
Best Overall Response	
Complete Response (CR)	8 (25.0%)
Partial Response (PR)	5 (15.6%)
Stable Disease (SD)	12 (37.5%)
Progressive Disease (PD)	5 (15.6%)
Not Evaluable (NE)	2 (6.3%)

Key: AA = abiraterone acetate, FDC = fixed dose combination.
Note: Response is a CR or PR. CR and PR do not have to be confirmed.
[a]No progression by PCWG3.
Note: Percent of Responder/Non-responder is based on the number of subjects with measurable disease at baseline.

Ancillary analyses

Sensitivity analyses

An evaluation of the concordance between independent-BICR and **investigator-assessed rPFS** showed agreement in 88.2% of events in the nira+AAP group and 86.7% of events in the PBO+AAP group.

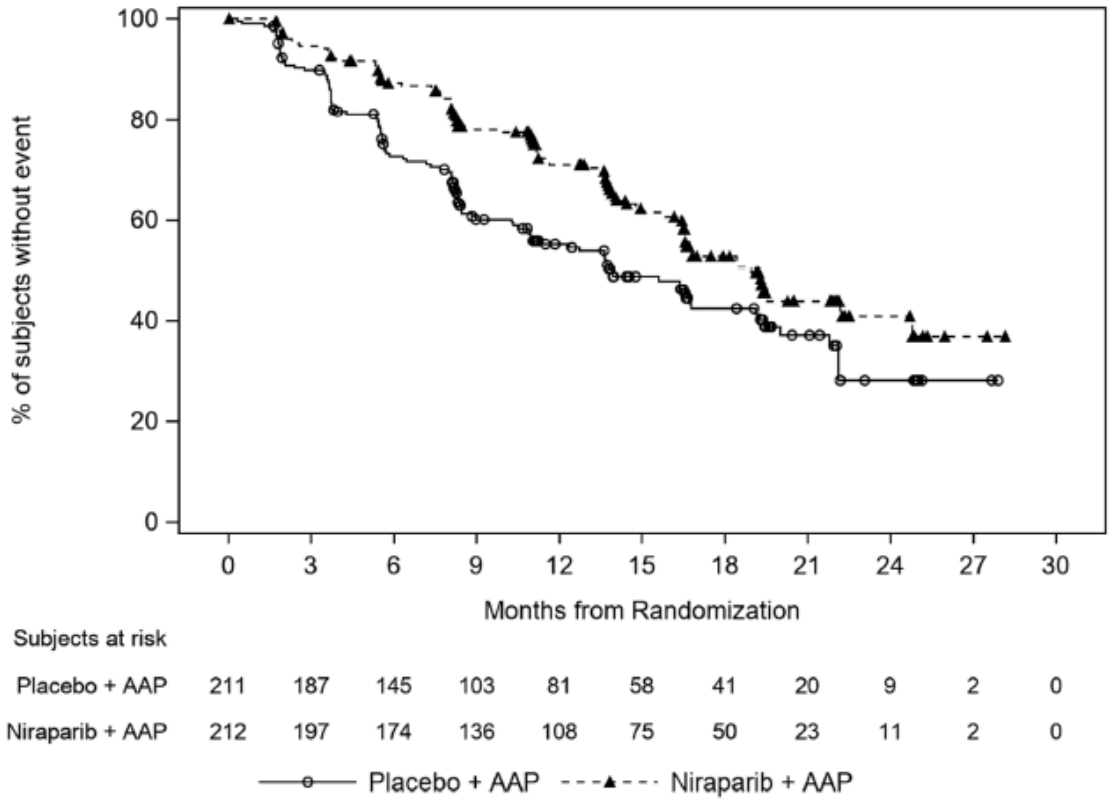
Table 77. Summary of Radiographic Progression-Free Survival by BICR and Investigator Review in All HRR Population (Stratified Analysis)

	PBO+AAP (N=211) Median (months)	nira+AAP (N=212) Median (months)	HR (95% CI) (Stratified Cox model)	P-value (stratified log-rank test)
BICR	13.70	16.46	0.729 (0.556,0.956)	0.0217
Investigator	13.90	18.96	0.644 (0.486,0.855)	0.0022*

AAP=abiraterone acetate plus prednisone; BICR=blind independent central review; CI=confidence interval; HR=hazard ratio; HRR=homologous recombination repair; N=number; nira=niraparib; PBO=placebo; rPFS=radiographic progression-free survival

* nominal p-value

Figure 37. Kaplan-Meier Plot of Radiographic Progression-free Survival by Investigator Review; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)



A stratified analysis of rPFS by BICR in the All HRR population performed **without censoring for subsequent therapy** was consistent with the primary analysis.

Table 78. Summary of Radiographic Progression-free Survival by Central Review Not Censored For Subsequent Therapy – Stratified Analysis; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	211	212
Event	119 (56.4%)	105 (49.5%)
Censored	92 (43.6%)	107 (50.5%)
Time to event (months)		
25th percentile (95% CI)	5.72 (4.27, 8.21)	8.44 (8.05, 11.04)
Median (95% CI)	13.67 (10.87, 16.36)	16.13 (13.80, 18.43)
75th percentile (95% CI)	NE (19.38, NE)	NE (21.95, NE)
Range	(0.3, 27.9+)	(0.0+, 28.2+)
6-months event free rate (95% CI)	0.744 (0.679, 0.798)	0.846 (0.789, 0.888)
12-months event free rate (95% CI)	0.526 (0.452, 0.594)	0.630 (0.556, 0.695)
18-months event free rate (95% CI)	0.386 (0.309, 0.462)	0.430 (0.350, 0.508)
24-months event free rate (95% CI)	0.266 (0.180, 0.359)	0.332 (0.244, 0.423)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.0302
Hazard ratio (95% CI) [b]		0.745 (0.571,0.973)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

As patients with CDK12 alterations were initially enrolled into Cohort 2, a pre-planned sensitivity analysis including those 14 **subjects with CDK12 gene alterations** from Cohort 2 with all Cohort 1 subjects was performed. While the results (by BICR) showed a statistically significant benefit for treatment with nira+AAP with a HR of 0.745; 95% CI: 0.572, 0.970; nominal p=0.0282 for rPFS, with a median rPFS of 15.70 months for the nira+AAP group and 13.67 months for the PBO+AAP group, the inclusion of these 14 subjects weakened the positive results slightly.

Analyses of rPFS in the BRCA Subgroup by investigator

An evaluation of the concordance between independent-BICR and investigator-assessed rPFS showed agreement in 89.4% of events in the nira+AAP group and 87.5% of events in the PBO+AAP group.

Table 79. Summary of rPFS by BICR and Investigator Review in BRCA Subgroup (Stratified Analysis) Cohort 1 (Study 64091742PCR3001)

	PBO+AAP (N=211) Median (months)	nira+AAP (N=212) Median (months)	HR (95% CI) (Stratified Cox model)	P-value (stratified log-rank test)
BICR	10.87	16.56	0.533 (0.361,0.789)	0.0014
Investigator	12.35	19.25	0.499 (0.334,0.748)	0.0006*

AAP=abiraterone acetate plus prednisone; BRCA=breast cancer gene; BICR=blind independent central review; CI=confidence interval; HR=hazard ratio; nira=niraparib; PBO=placebo; rPFS=radiographic progression-free survival
* nominal p-value

Figure 38. Kaplan-Meier Plot of Radiographic Progression-free Survival by Investigator Review; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

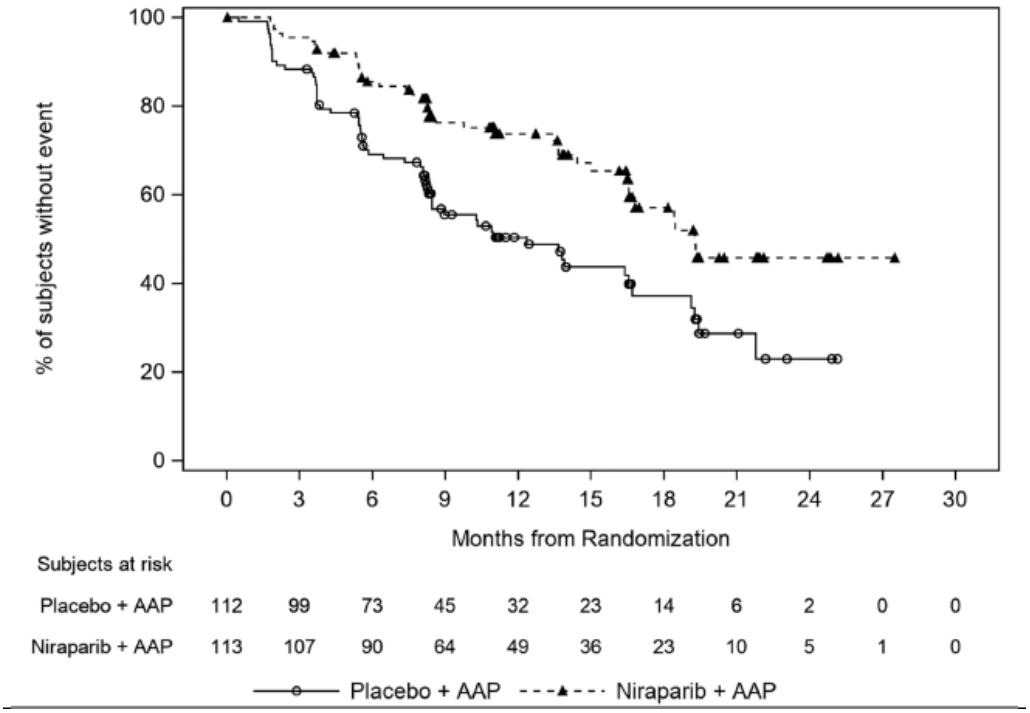


Table 80. Summary of Radiographic Progression-free Survival by Central Review Not Censored For Subsequent Therapy – Stratified Analysis; Cohort 1 BRCA Randomized Analysis Set (Study 64091742PCR3001)

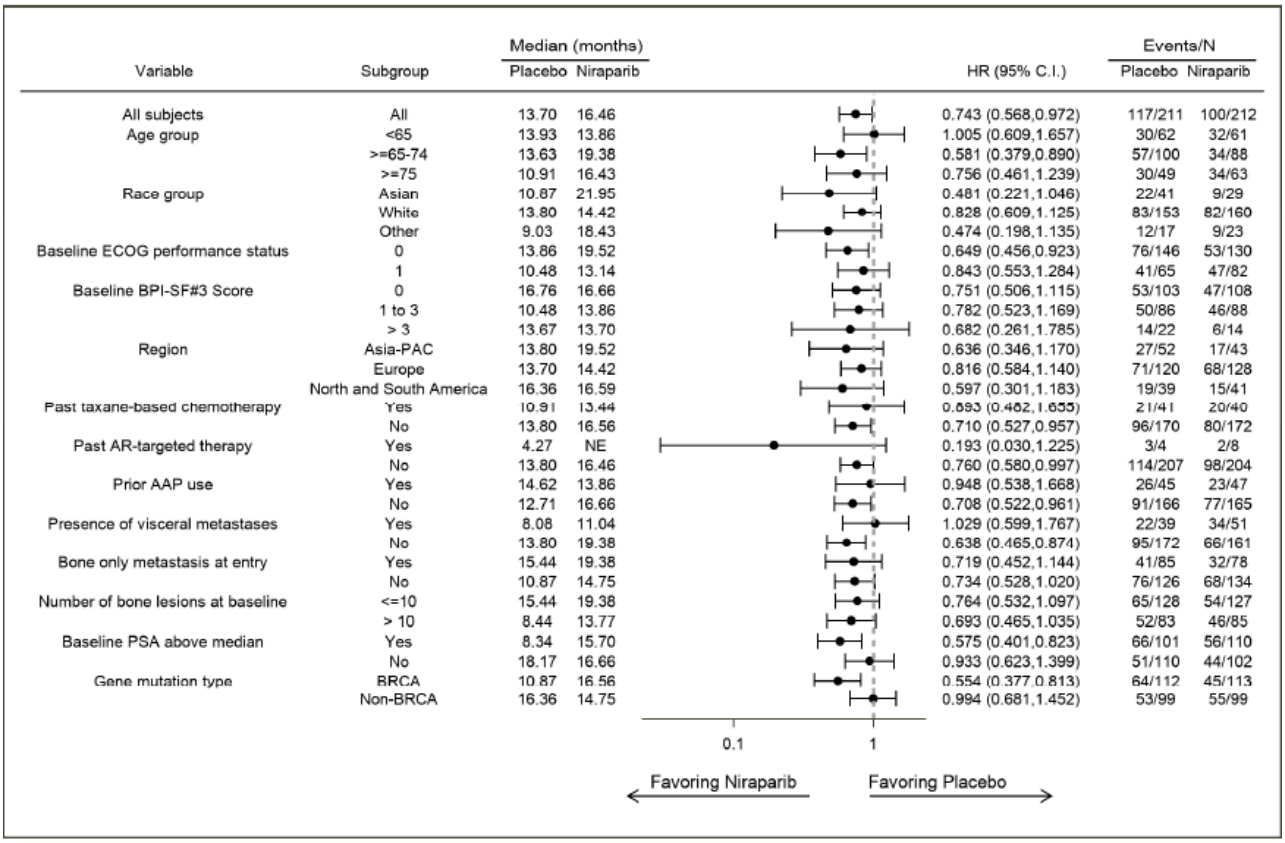
	Placebo + AAP	Niraparib + AAP
Analysis set:randomized	112	113
Event	65 (58.0%)	48 (42.5%)
Censored	47 (42.0%)	65 (57.5%)
Time to event (months)		
25th percentile (95% CI)	5.36 (3.58, 8.05)	10.87 (7.85, 13.44)
Median (95% CI)	10.87 (8.31, 13.80)	16.56 (13.86, 21.95)
75th percentile (95% CI)	NE (16.39, NE)	NE (19.52, NE)
Range	(0.5, 24.9+)	(0.0+, 27.5+)
6-months event free rate (95% CI)	0.713 (0.619, 0.787)	0.865 (0.787, 0.917)
12-months event free rate (95% CI)	0.437 (0.335, 0.535)	0.686 (0.581, 0.770)
18-months event free rate (95% CI)	0.322 (0.221, 0.427)	0.437 (0.313, 0.555)
24-months event free rate (95% CI)	0.292 (0.188, 0.404)	0.324 (0.184, 0.473)
30-months event free rate (95% CI)	NE (NE, NE)	NE (NE, NE)
p-value [a]		0.0021
Hazard ratio (95% CI) [b]		0.554 (0.378,0.812)

Key: AAP = abiraterone acetate plus prednisone.
[a]p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).
[b]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment.
Note: + = censored observation, NE = not estimable

Subgroup analyses

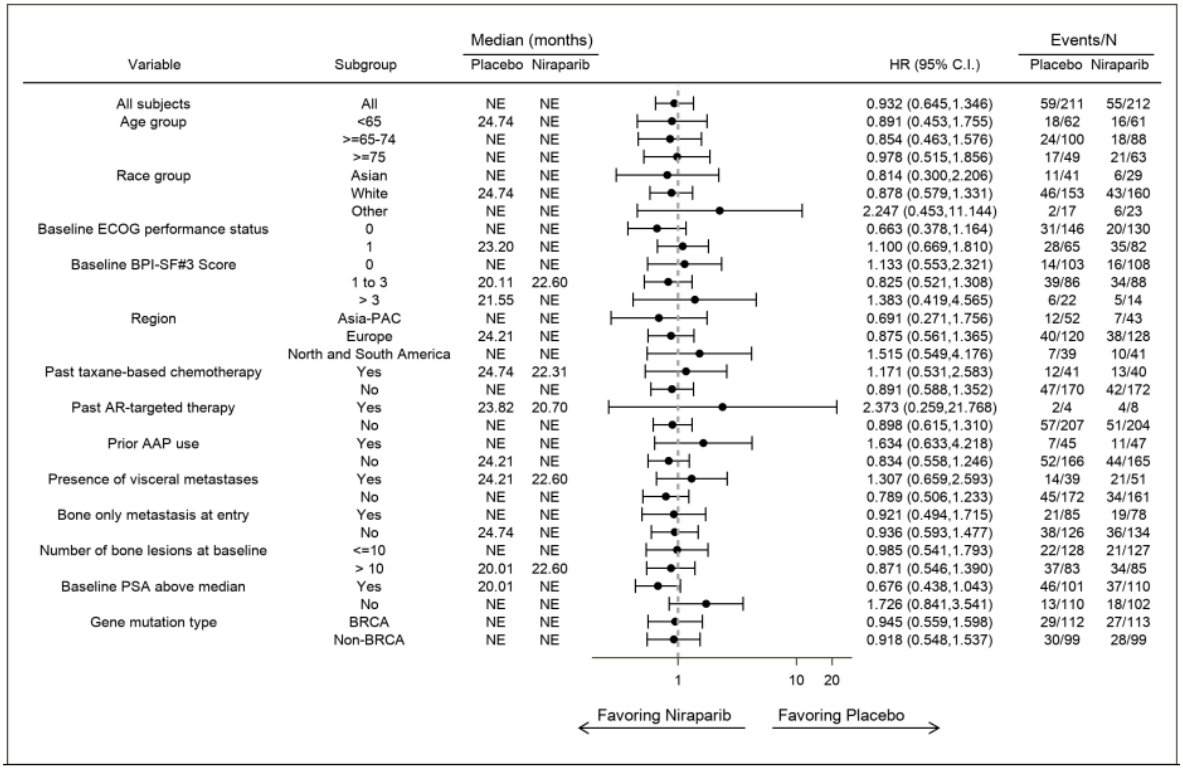
Cohort 1

Table 81. Forest Plot of Radiographic Progression-Free Survival by Central Review for Subgroups Defined by Baseline Clinical Disease Characteristics; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001)



Key: AAP = abiraterone acetate plus prednisone.
Note: Gene Mutation categories pertain to IWRS stratification by Gene alteration

. Forest Plot of Overall Survival for Subgroups Defined by Baseline Clinical Disease Characteristics; Cohort 1 All HRR Randomized Analysis Set (Study 64091742PCR3001) – 1IA



Key: AAP = abiraterone acetate plus prednisone. Note: Gene Mutation categories pertain to IWRS stratification by Gene Alteration

Analysis of efficacy endpoints by gene alteration

Table 82. Key efficacy endpoints for Cohort 1 by gene alteration – IA2

Gene	Treatment group	rPFS (Primary Analysis) N(events)	rPFS (Primary Analysis) HR(95% CI)	rPFS N(events)	rPFS HR(95% CI)	TCC N(events)	TCC HR(95% CI)	TSP N(events)	TSP HR(95% CI)	OS N(events)	OS HR(95% CI)
Non-BRCA Co-Occurring	**PBO+AAP**	**9(6)**	**2.436**	**9(6)**	**2.436**	**9(2)**	**3.489**	**9(4)**	**0.574**	**9(3)**	**3.858 (1.063,14.000)**
	nira+AAP	**13(12)**	**(0.872,6.801)**	**13(12)**	**(0.872,6.801)**	**13(6)**	**(0.657,18.536)**	**13(3)**	**(0.128,2.582)**	**13(12)**	
HRR-Fanconi (PALB2, BRIP1, FANCA)	**PBO+AAP**	**14(11)**	**0.578**	**14(11)**	**0.677**	**14(5)**	**0.726**	**14(6)**	**0.612**	**14(8)**	**0.705 (0.263,1.890)**
	nira+AAP	**17(8)**	**(0.231,1.448)**	**17(10)**	**(0.285,1.606)**	**17(6)**	**(0.221,2.390)**	**17(5)**	**(0.185,2.019)**	**17(8)**	
PALB2	PBO+AAP	4(4)	0.585	4(4)	0.541	4(1)	0.563	4(2)	0.217	4(3)	0.460 (0.101,2.082)
	nira+AAP	8(5)	(0.154,2.222)	8(6)	(0.144,2.032)	8(3)	(0.049,6.405)	8(1)	(0.019,2.419)	8(4)	
BRIP1	PBO+AAP	4(3)	0.232	4(3)	0.437	4(0)	NE (NE)	4(1)	1.137	4(3)	0.401 (0.065,2.471)
	nira+AAP	4(1)	(0.024,2.261)	4(2)	(0.072,2.651)	4(2)		4(2)	(0.097,13.269)	4(3)	
FANCA	PBO+AAP	6(4)	1.066	6(4)	0.734	6(4)	0.417	6(3)	1.225	6(2)	1.414 (0.088,22.822)
	nira+AAP	5(2)	(0.176,6.439)	5(2)	(0.133,4.057)	5(1)	(0.043,4.027)	5(2)	(0.172,8.739)	5(1)	
HRR-associated (CHEK2 +HDAC2)	**PBO+AAP**	**23(12)**	**0.643**	**23(14)**	**0.774**	**23(7)**	**0.761**	**23(7)**	**0.546**	**23(12)**	**0.632 (0.257,1.554)**
	nira+AAP	**20(8)**	**(0.261,1.581)**	**20(12)**	**(0.356,1.684)**	**20(6)**	**(0.255,2.271)**	**20(4)**	**(0.159,1.876)**	**20(8)**	
CHEK2	PBO+AAP	20(10)	0.660	20(11)	0.865	20(7)	0.491	20(6)	0.482	20(10)	0.664 (0.252,1.753)
	nira+AAP	18(7)	(0.250,1.747)	18(11)	(0.372,2.009)	18(4)	(0.143,1.687)	18(3)	(0.120,1.938)	18(7)	
HDAC2	PBO+AAP	3(2)	0.712	3(3)	0.712	3(0)	NE (NE)	3(1)	0.707	3(2)	0.440 (0.038,5.131)
	nira+AAP	2(1)	(0.063,8.022)	2(1)	(0.063,8.022)	2(2)		2(1)	(0.042,11.786)	2(1)	
ATM	PBO+AAP	42(21)	1.114	42(25)	1.255	42(16)	0.467	42(11)	0.788	42(14)	1.132 (0.557,2.300)
	nira+AAP	43(26)	(0.625,1.985)	43(32)	(0.738,2.134)	43(9)	(0.206,1.058)	43(9)	(0.326,1.901)	43(17)	
CDK12	PBO+AAP	16(7)	1.315	16(10)	0.890	16(6)	1.317	16(5)	1.053	16(9)	1.302 (0.445,3.809)
	nira+AAP	11(7)	(0.433,3.992)	11(7)	(0.336,2.357)	11(5)	(0.381,4.557)	11(4)	(0.281,3.943)	11(6)	

Key: AAP=abiraterone acetate plus prednisone; ATM=ataxia telangiectasia mutated gene; BRCA=breast cancer gene; BRIP1=BRCA1 interacting protein C-terminal helicase 1; CDK12=cyclin-dependent kinase 12; CHEK2=checkpoint kinase 2; CI=confidence interval; FANCA=Fanconi anemia complementation group A gene; HDAC2=histone deacetylase 2; HR=hazard ratio; HRR=homologous recombination repair; N=number; NE=not estimable; nira=niraparib; ORR=objective response rate; OS=overall survival; PALB2=partner and localizer of BRCA2; PBO=placebo; PSA= prostate-specific antigen; rPFS=radiographic progression-free survival; RR=risk ratio; TCC=time to initiation of cytotoxic chemotherapy; TPSA=time to PSA progression; TSP=time to symptomatic progression
Note: Non-estimable HRs are due to few or no events.

Summary of main efficacy results

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 83. Summary of efficacy for trial 64091742PCR3001 (MAGNITUDE)

Title: A Phase 3 Randomized, Placebo-controlled, Double-blind Study of Niraparib in Combination with Abiraterone Acetate and Prednisone Versus Abiraterone Acetate and Prednisone for Treatment of Subjects with Metastatic Prostate Cancer			
Study identifier	64091742PCR3001 (MAGNITUDE); 2017-003364-12; NCT03748641		
Design	Phase 3, randomized, placebo-controlled, multicentre, double-blind study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Pre-screening Phase for biomarker evaluation only, a Screening Phase, a Treatment Phase, a Follow-up Phase Not applicable Not applicable
Hypothesis	Superiority Niraparib and AAP will demonstrate improved rPFS compared to placebo and AAP in subjects with treatment-naive mCRPC and homologous recombination repair (HRR) gene alterations or in subjects with a prespecified subset of HRR		
Treatments groups:	PBO + AAP		placebo and abiraterone acetate plus prednisone (AAP) (1,000 mg/10 mg) daily as single-agent combination, 211 patients randomized
	Nira + AAP		niraparib 200 mg and abiraterone acetate plus prednisone (AAP) (1,000 mg/10 mg) daily as single-agent combination, 212 patients randomized
Endpoints and definitions	Cohort 1 - Primary endpoint	rPFS (as assessed by BICR)	Radiographic progression-free survival, as assessed by blinded independent central review: defined as the time from the date of randomization to the date of radiographic progression or death, whichever occurs first
	Cohort 1 - Secondary endpoint	TCC	Time-to-initiation of cytotoxic chemotherapy: defined as the time from date of randomization to the date of initiation of cytotoxic chemotherapy for prostate cancer.
	Cohort 1 - Secondary endpoint	TSP	Time-to-symptomatic progression: defined as the time from the date of randomization to the time of the first of any of the following: • The use of EBRT for skeletal symptoms. • The need for tumour-related orthopaedic surgical intervention • Other cancer-related procedures (for example: nephrostomy insertion, bladder

			catheter insertion, EBRT, or surgery for tumour symptoms other than skeletal). • Cancer-related morbid events (for example: fracture [symptomatic and/or pathologic, cord compression, urinary obstructive events). Initiation of a new systemic anti-cancer therapy because of cancer pain.
	Cohort 1 - Secondary endpoint	OS	Overall survival: defined as the time from date of randomization to date of death from any cause.
Database lock	DCO: 8 October 2021. The data presented below are for the final analysis of rPFS and interim analysis for the secondary endpoints of TCC, TSP and OS.		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Cohort 1 – BRCA 1/2 subgroup		
Descriptive statistics and estimate variability	Treatment group	PBO + AAP	Nira + AAP
	N	112	113
	Median rPFS by BICR (months)	10.87	16.56
Effect estimate per comparison	Primary endpoint: rPFS by BICR	Comparison groups	Nira + AAP vs PBO + AAP
		Hazard ratio [a]	0.533
		95% CI	0.361, 0.789
		P-value [b,c]	0.0014
Analysis population and time point description	Cohort 1 - all HRR population		
Descriptive statistics and estimate variability	Treatment group	PBO + AAP	Nira + AAP
	N	211	212
	Median rPFS by BICR (months)	13.70	16.46
Effect estimate per comparison	Primary endpoint: rPFS rPFS by BICR	Comparison groups	Nira + AAP vs PBO + AAP
		Hazard ratio [a]	0.729
		95% CI	0.556, 0.956
		P-value [b,c]	0.0217
Notes	[a]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment. [b]p-value is from a log-rank test stratified by stratification factors. [c]p-value is statistically significant. Stratification factors included in stratified analysis are: past taxane-based chemotherapy exposure (yes versus no), and prior AAP use (yes versus no) for BRCA 1/2 subgroup, and added gene alteration group (BRCA1 or BRCA2 versus all other HRR) for all HRR population. BICR=blind independent central review		
Analysis description	**Secondary analysis**		

Analysis population and time point description	Cohort 1 - all HRR population		
Descriptive statistics and estimate variability	Treatment group	PBO + AAP	Nira + AAP
	N	211	212
	Median TCC (months)	25.99	Not estimable
	Median TSP (months)	Not estimable	Not estimable
	Median OS (months)	Not estimable	Not estimable
Effect estimate per comparison	Secondary endpoint: TCC	Comparison groups	Nira + AAP vs PBO + AAP
		Hazard ratio [a]	0.588
		95% CI	0.389, 0.889
		P-value [b]	0.0108
	Secondary endpoint: TSP	Comparison groups	Nira + AAP vs PBO + AAP
		Hazard ratio [a]	0.686
		95% CI	0.474, 0.993
		P-value [b]	0.0444
	Secondary endpoint: OS	Comparison groups	Nira + AAP vs PBO + AAP
		Hazard ratio [a]	0.938
		95% CI	0.648, 1.358
		P-value [b]	0.7333
Notes	[a]Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favors niraparib + AAP treatment. [b]p-value is from a log-rank test stratified by stratification factors. p value is not statistically significant. Stratification factors included in stratified analysis are: past taxane-based chemotherapy exposure (yes versus no), and prior AAP use (yes versus no) for BRCA 1/2 subgroup, and added gene alteration group (BRCA1 or BRCA2 versus all other HRR) for all HRR population.		

2.6.5.3. Clinical studies in special populations

A summary of subjects enrolled in controlled and non-controlled prostate cancer trials of niraparib (200 mg) and AA (1,000 mg) plus prednisone/prednisolone in subjects with mCRPC by age group is provided in the table below. The only study to evaluate subjects in first-line mCRPC was MAGNITUDE. All other studies (QUEST, BEDIVERE, BA/BE) evaluated subjects receiving second-line or higher treatment for mCRPC.

Table 84. Summary of Niraparib Controlled and Non-controlled Prostate Cancer Trials by Age Group; Magnitude Cohort 1,2,3, QUEST Combination 2,3, BA/BE and BEDIVERE

	Age <65	Age 65- 74	Age 75- 84	Age >= 85
Controlled Trials[a]	171 (25.5%)	308 (46.0%)	173 (25.8%)	18 (2.7%)
Non-Controlled Trials[b]	100 (29.2%)	163 (47.7%)	69 (20.2%)	10 (2.9%)

[a]Controlled - Magnitude Cohort 1 and Cohort 2 randomized subjects. N=670.
[b]Non-controlled - QUEST Combination 2,3, BEDIVERE subjects who received 200 mg of niraparib, Magnitude Cohort 3, BA/BE. N=342.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

The Applicant has partnered with Foundation Medicine Inc. (FMI) and Agilent - Resolution Bioscience (RB) to develop two companion diagnostic assays (CDx), one tissue (FMI) and one plasma based (RB), to identify HRR gene alterations in patients who may be eligible for therapy. Both assays are next generation sequencing based in vitro diagnostic devices. The FMI FoundationOne CDx (F1CDx) diagnostic assay is CE-marked under the IVD Directive 98/79/EC (IVDD) and according to the Applicant is legally placed on the market. The Resolution Bioscience HRD diagnostic assay RB is also CE-marked under IVDD. These assays were used in the selection of patients for niraparib in the clinical studies within this application.

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

This application is mainly based on the pivotal Phase 3 **Study 64091742PRC3001 (MAGNITUDE)**, a randomized, double-blind, placebo-controlled, multi-center study that evaluated the efficacy and safety of niraparib in combination with AA and prednisone daily (nira+AAP) compared with placebo plus AAP (pbo+AAP) daily in subjects with mCRPC who had not received prior systemic therapy in the mCRPC setting.

The study consisted of three cohorts. In Cohort 1 and Cohort 2 patients were randomised (1:1) to receive either nira+AAP (as monocomponents) or pbo+AAP. Cohort 1 included patients with HRR gene alterations while Cohort 2 included patients without HRR gene alterations. Both cohorts were double-blind. There was a third cohort, Cohort 3, to assess the FDC of nira+AAP. This was open-label and enrolled patients with HRR gene alterations. In the context of the currently applied indication, the most relevant one is **Cohort 1**. Cohort 3 is planned to provide evidence on efficacy and safety of the FDC.

Determination of HRR gene alteration status was required before randomisation (pre-screening). The panel of genes tested for inclusion in Cohort 1 was based on its higher frequency in prostate cancer and the biological plausibility to show benefit with the combination of niraparib and AAP.

The comparator AA is considered appropriate in the context of asymptomatic/mildly symptomatic men with chemotherapy-naïve mCRPC since AAP is one of the SoC therapies in this setting and it is in fact one of the components of the FDC. The choice of the comparator was agreed during a scientific advice (SA) procedure in 2018 (EMEA/H/SA/3872/1/2018/HTA/II). However, the comparator would not be appropriate for patients with visceral metastases and/or asymptomatic disease.

The design of the MAGNITUDE trial seems to be adapted to the indication in asymptomatic/mildly symptomatic mCRPC patients with or without visceral metastases, who may have received chemotherapy in the hormone sensitive setting only.

All patients enrolled in the study were asymptomatic or mildly symptomatic at screening as required by the protocol of the study. However, at baseline (Cycle 1 Day 1), there were 36 (8.6%) patients with a BPI>3, that can be considered symptomatic. Efficacy data in the subgroup of patients with visceral metastasis and/or symptomatic disease who had not received prior chemotherapy, and in whom chemotherapy would therefore have been the most relevant comparator (i.e., instead of abiraterone), were provided during the assessment. Based on the submitted data no apparent differences in rPFS were observed between treatment arms neither in the HRR population (HR 0.958; 95% CI: 0.594, 1.547), nor in the subgroup of BRCA mutated patients (HR 1.007; 95% CI: 0.501,2.023). In the OS analysis, data suggested no benefit and possibly a trend in disfavour of study treatment (HR 1.274; 95% CI: 0.720,2.255) which seems more evident in the subgroup of patients with BRCA mutations (HR 2.172; 95% CI: 0.971,4.855). However, the interpretation of these results is limited by the low number of study subjects involved and by the arbitrary subgroups based on multiple factors. In any case, mCRPC patients in whom chemotherapy is clinically indicated are excluded from treatment with nira+AAP by the indication wording.

Patients received 200 mg niraparib + 1000 mg AA + 10 mg prednisone in the nira+AAP arm and matching placebo plus AA and prednisone at the same doses in the pbo+AAP arm. The selected dose for abiraterone is the recommended dose in the currently approved indications of Zytiga. With regards to niraparib, a dose of 200 mg was chosen based on the results of the Phase 1 study 64091742PCR1001 (BEDIVERE) in which doses of 200 mg and 300 mg of niraparib were tested in combination with abiraterone 1000 mg+ prednisone 10 mg. Since DLTs were reported with the 300 mg dose, while not with the 200 mg dose, and no significant differences in exposure were observed between both doses, the 200 mg dose was finally chosen as the RP2D for niraparib when administered in combination with abiraterone plus prednisone.

Background therapy with a GnRHa was mandatory for patients who had not previously undergone surgical castration. If, during the study, either study drug was permanently discontinued due to toxicity, the other study drug (niraparib/placebo or AA) could be continued. In the same way also in Cohort 3 (FDC cohort), the use of the single agent medications was allowed in case of discontinuation of one of the drugs and if a dose reduction of AA was required (currently not reflected in the PI). Nevertheless, it is not believed that these adjustments of mono-components have impacted the efficacy outcome. It is noted that the proposed FDC allow limited flexibility in terms of dosing and management of treatment-related toxicities by dose modification.

In Cohort 1 randomisation was stratified by past exposure to taxane-based chemotherapy, AR targeted therapy, prior AAP use (yes or no) and by gene alteration group (i.e., BRCA1 or BRCA2 versus all other HRR gene alterations).

The primary endpoint of the study was rPFS as assessed by BICR according to RECIST 1.1. for soft tissues and PCWG3 criteria to assess changes in bone. OS was a secondary endpoint of the study. Other (key) secondary endpoints were time to initiation of cytotoxic chemotherapy (TCC) and time to symptomatic progression (TSP). Other efficacy endpoints were time to PSA progression (TPSA), PFS2, time to pain progression, ORR, duration of response, PSA response rate and time to first-subsequent anticancer therapy. Overall, the primary and secondary endpoints are considered adequate. Even if OS would be the preferred primary endpoint, rPFS is also acceptable as agreed during the above mentioned SA procedure. The importance of collecting OS data and the need to provide sufficiently mature OS data at the time of submission was however also highlighted by the CHMP at that time. The fact that rPFS is assessed by a BIRC is reassuring.

Statistical methods

A multiple testing procedure was employed across the primary endpoint of rPFS and the key secondary endpoints to preserve the family-wise type I error rate at the 2-sided 5% level. The primary endpoint was initially tested in the BRCA subgroup and if statistically significant then in the all Cohort 1 population. Since no interim analyses have been performed for the first 2 comparisons of the hierarchy (i.e., rPFS for BCRA and rPFS for Cohort 1), the full 5% of alpha was considered. Overall, the approach is considered acceptable.

Two interim analyses and one final analysis for the secondary endpoints of TCC, TSP and OS were considered approximately when 100, 170 and 246 OS events had been observed. The Lan-DeMets alpha spending function with the O'Brien-Fleming approach is considered acceptable. The approach to control the overall type I error through different interim analyses is also endorsed.

The hypothesis for the estimation of the sample size in the different cohorts can be considered acceptable.

Conduct of the study

There have been 6 global amendments of the original version of the protocol (dated 22 Oct 2018). Of these, Amendment 4 and Amendment 6 are considered the most relevant ones. Of note, with Amendment 3 enrolment of subjects with ATM alterations was stopped, according to the Applicant due to external data that suggested limited benefit in these patients, but no further information has been provided in this regard.

With protocol amendment 4 (dated 3 Jul 2020) the statistical analysis plan was modified and the BRCA mutated population became the primary efficacy population (i.e. population to be analysed first). Further, an additional biomarker (CKK12) was added to the panel of genes and Cohort 3 was included. Regarding amendment 6 (dated 30 Sep 2021), the analysis testing for the secondary endpoints was changed and a 2nd IA was added. Justification on the reason/s that motivated all these changes provided by the Applicant was acknowledged.

The number of major protocol deviations was low and balanced between treatment arms so it is unlikely that these deviations could have had an impact on the reported results.

Efficacy data and additional analyses

Cohort 1

At the time of the DCO for the primary analysis (8 October 2021), 48% of patients were ongoing treatment (54% in the nira+AAP arm and 42% in the pbo+AAP arm). The main reason for treatment discontinuation in both treatment arms was disease progression (34% and 51%, respectively).

Baseline characteristics

Patients included in the study had a median age of 69 years (range: 43, 100). Most of them were White (74%) and had an EOCG PS of 0 or 1. Around half of the patients was diagnosed in a metastatic stage and 68% had a Gleason score ≥8 at initial diagnosis. Testosterone levels (median) at baseline were 1.21 (range: 0.1, 3.1) which suggest that some patients do not have castrate levels of testosterone (i.e. ≤50 ng/dL ≈ 1.74 nmol/L). According to the Applicant there were 7 patients with testosterone levels >50 ng/dL as per central laboratory (6 in the control arm and 1 in the experimental arm) but who had testosterone castrate levels as per local laboratory and therefore they did not violate the inclusion criteria. Considering the low number of patients, it appears unlikely this may have had an impact on the results.

At study entry most patients had bone metastases (83.5%), 21.3% had visceral metastases and 49.2% nodal metastases. Of note, the proportion of patients with visceral metastasis was slightly higher in the nira+AAP arm (24.1% vs 18.5%). BFI-SF pain score was 0 in 50% of patients and 1 to 3 in 41.3% of patients, as per the inclusion criteria. However, pain scores were reassessed at Cycle 1 Day 1, at which time 36 (8.6%) subjects had a pain score>3. Overall baseline characteristics were comparable between BRCA and non-BRCA subgroups. Of note, patients in the BRCA-mutated subgroup were slightly younger and a higher proportion of patients had received prior taxane-based chemotherapy and AAP. No other relevant differences have been observed.

All patients included in Cohort 1 had a HRR gene alteration. There were 229 (54.1%) patients with BRCA1 or BRCA2 gene alteration, of which 39 had co-occurring gene alterations. Regarding other HRR gene alterations, ATM was the most common (85 [20.1%]). With Amendment 3 of the protocol, patients with ATM alteration were no longer included in the study. Information on whether these mutations were somatic or germline was not available since the assays used in the study were not able to distinguish between germline and somatic mutations.

Regarding concomitant treatment, more than half of patients received analgesics in both treatment arm, including opioids but the number of patients that received opioids was low and comparable between treatment arms.

Use of antihypertensive was higher in the nira+AAP arm, which is not unexpected taking into account the added toxicity of both niraparib and AAP. Approximately 29% of patients received drugs for treatment of bone disorders (including bisphosphonates and denosumab). Of note, the proportion of patients that received denosumab was almost double in the nira+AAP arm (15% vs 8%).

At the cut-off date among patients who had discontinued study treatment (97 in the nira+AAP arm and 123 in the pbo+AAP arm), 47% and 63% had received subsequent treatment, mainly chemotherapy. Of note, 13 patients in the pbo+AAP arm received subsequent treatment with a PARPi while only 1 in the nira+AAP arm.

Outcomes

As per the SAP, the **primary endpoint** rPFS, was assessed first in patients with a BRCA1/2 mutation (n=225) and if statistically significant then in the overall population (All HRR population; n=423)

In the All HRR population the combination of nira+AAP demonstrated a statistically significant improvement in **rPFS** (BICR assessment) compared with pbo+AAP (**HR 0.729; 95% CI: 0.556, 0.956**), with a median rPFS of 16.46 months in the nira+AAP arm and 13.70 months in the pbo+AAP arm. At the time of DCO for the primary analysis (8 Oct 2021) the number of censored patients was 53% in the nira+AAP arm and 44.5% in the pbo+AAP arm. While the total number of rPFS events was higher in the placebo arm, there was a notable unbalance in the number of early deaths, which may disfavour treatment with nira+AAP (16 deaths vs 8 deaths in the placebo arm, with only a few subjects censored, which correspond to approx. 4%-points). A discussion of this apparent imbalance, and any crossings of the survival curves (violation of proportional hazard assumption), was requested. After examining the reasons for the deaths that occurred during the first six months of treatment, no discernible pattern was found. Regarding proportional hazards no firm conclusions could be drawn.

Despite radiological progression 52 (24.5%) patients in the niraparib arm and 66 (31.3%) patients in the placebo arm continued treatment beyond soft tissue disease progression. Median (range) treatment duration after progression was 2.91 (0.1, 12.0) months and 1.99 (0.0, 16.5) months, in the niraparib and placebo arm, respectively. Further, there were 29 (13.3%) patients in the niraparib arm and 39 (18.5%) in the placebo arm that continued treatment beyond bone progression, with a median (range) treatment exposure of 4.60 (0.9, 13.0) and 3.81 (0.5, 10.3) months, respectively. Of note, bone progression required to be confirmed ≥6 weeks after the initial scan. The proportion of patients that

received treatment beyond progression was comparable between treatment arms, although treatment exposure beyond progression was slightly longer in the niraparib arm.

A sensitivity analysis of rPFS by the investigator was overall consistent with the primary analysis (HR 0.644; 95% CI: 0.486, 0.855). Sensitivity analyses including patients CDK12 and without censoring for subsequent therapy were also consistent with the primary analysis.

In the BRCA subgroup, the benefit of nira+AAP over pbo+AAP in terms of rPFS (BICR) was higher than in the overall population (HR 0.533; 95% CI: 0.361, 0.789). Median rPFS was 16.56 months in the nira+AAP arm and 10.87 months in the pbo+AAP arm.

While a clear benefit was observed in BRCA mutated patients, the effect of the addition of niraparib to AAP was less clear in non-BRCA patients, in whom no apparent benefit was observed for rPFS (HR 0.994; 95% CI: 0.681, 1.452). Median rPFS in this subgroup of patients was of 14.75 months in the nira+AAP arm and 16.36 months in the pbo+AAP arm and no separation of the KM curves was observed. Moreover, OS data in the non-BRCA subgroup based on the 2IA suggested a potential detrimental effect with nira+AAP compared with placebo+AAP (HR 1.162; 95% CI: 0.761, 1.774), with median OS of 29.31 months in the nira+AAP arm and not reached in the placebo+APP, although statistical significance was not reached. The reported results posed concerns on the potential benefit of nira+AAP in patients with non-BRCA mutations, which represented a heterogeneous subgroup of patients with different type of HRR gene alterations. An analysis of efficacy data by gene alteration in the non-BRCA subgroup was provided. However, the interpretation of results was hampered by the small size of the subgroups. Moreover, no preclinical data have been presented supporting beneficial effect of the combination of nira+AAP in castrate resistant tumour models harbouring other HRR alterations than BRCA. As a result, the indication was restricted to the population with a BRCA mutation, in whom a clear benefit was observed (see the finally agreed indication below).

Key **secondary endpoints** included TCC, TSP and OS. Results presented at the time of submission, based on the first interim analysis (IA), showed a trend in favour of the nira+AAP arm for TCC and TSP in the HRR population although statistical significance was not reached. Regarding OS in the overall population, with 55 (25.9%) events in the nira+AAP arm and 59 (28.0%) in the pbo+AAP arm and a median follow-up of 18.6 months, no statistically significant differences were observed between treatment arms (HR 0.938; 95% CI: 0.648, 1.358); p=0.7333. The median OS was not reached in either treatment group and overlapping KM curves were observed. Results in the key secondary endpoint in the BRCA subgroup, were overall consistent with the observed in the overall population.

Updated efficacy data of these secondary endpoints based on the 2IA (DCO 17 June 2022). showed a statistically significant improvement in TSP with nira+AAP over placebo+AAP in the HRR population (HR 0.596; 95% CI: 0.422, 0.841; p=0.0029). Median TSP was not reached for nira+AAP and was of 30.62 months for placebo+AAP. Results were consistent in the subgroup of BRCA-mutated patients (HR 0.544; 95% CI: 0.347, 0.853).

For TCC, positive results in favour of the nira+AAP arm were shown (HR 0.666; 95% CI 0.471, 0.942; p=0.0206), although statistical significance was not reached. Median TCC was not reached in either treatment arm. An improvement in TCC was seen in the BRCA subgroup favouring treatment with nira+AAP (HR 0.558; 95% CI: 0.346, 0.900; nominal p=0.0152).

At the time of the 2IA the number of OS events in the HRR population was of 90 (42.5%) in the nira+AAP arm and 89 (42.2%) in the placebo arm, with a high number of patients censored (around 57% in both treatment arms). Median follow-up was 26.8 months. In the HRR population no differences were observed between treatment arms (HR 1.010; 95% CI: 0.751, 1.357) with longer median OS reported in the placebo arm (29.31 months nira+AAP vs. 32.2 months placebo+AAP). In the subgroup of BRCA-mutated patients (n=225), with 38.1% events in the nira+AAP arm and 43.8% in the placebo+AAP arm,

a trend in favour of the nira+AAP was observed, although statistical significance was not reached (HR 0.881; 95% CI: 0.582, 1.335). Median OS was 29.27 months in the nira+AAP arm and 28.55 in the placebo+AAP arm. Median follow-up was 24.80 months. The final analysis is expected to be submitted as Post approval efficacy study in 1Q 2024 **(PAES).**

With regards to other secondary endpoints, at 1IA, positive results in favour of the experimental arm were observed in TPSA (HR 0.569; 95% CI: 0.425, 0.760), with a median of 18.51 months in the nira+AAP arm vs 9.33 months in the pbo+AAP arm. ORR was also higher in patients treated with nira+AAP compared with pbo+AAP (59.8% vs 28.0%, respectively). However, no statistically significant differences between treatment arms were observed in PFS2 (HR 0.990; 95% CI: 0.698, 1.403) and time to initiation of subsequent therapy (HR 0.871; 95% CI: 0.614, 1.237),

Updated efficacy data provided for TPSA, PFS2 and TTPP for both HRR population and BRCA population showed a delay in TPSA in the nira+AAP group compared with placebo+AAP (HR 0.602; 95% CI: 0.462, 0.785), with a median TPSA of 18.33 months in the nira+AAP arm vs 9.33 months in the placebo+AAP arm. The improvement was higher in the subgroup of BRCA-mutated patients (HR 0.478; 95% CI: 0.328, 0.696). No differences were observed between treatment arms in the HRR population for PFS2 (HR 0.964; 95% CI: 0.723, 1.285). In the BRCA-mutated subgroup, the effect on PFS2 was more pronounced, although statistical significance was not reached (HR 0.785; 95% CI: 0.528, 1.166). Consistent with PA-IA1, a trend towards prolongation in TTPP was observed with nira+AAP in the HRR population (HR 0.894; 95% CI: 0.647, 1.236) and the BRCA subgroup (HR 0.701; 95% CI: 0.439, 1.118), although results were not statistically significant.

With regards to the **subgroup analysis**, no apparent benefit appears to be derived from nira+AAP treatment over pbo+AAP in HRR population for patients <65 years, patients with visceral metastases and patients who received prior AAP treatment. However, due to the small number of patients included in these subgroups results should be interpreted with caution.

Cohort 3

The patient population included in *Cohort 3* was overall comparable with patients enrolled in Cohort 1 except for a lower proportion of patients with ECOG 1 (23%) and patients with visceral metastases (14%).

Results of key efficacy endpoints have been provided. However, at the time of the DCO, with a median follow-up of 5.5 months, data were immature with high censoring. Submission of 1-year efficacy data from Cohort 3 showed that primary endpoint and secondary endpoints were comparable to Cohort 1. However, as data were still immature (35-45% maturity in rPFS and 20-25% in OS) the Applicant is recommended to submit the efficacy data (i.e., rPFS by BICR, TSP, TCC and OS) post-approval **(PAM-REC)**.

Biomarker

Blood and tumour tissue were required to be collected for determination of HRR gene alterations using one tissue and one plasma assay. Both next generation sequencing based in vitro diagnostic devices. Information regarding clinical and analytical validation of biomarker tests was provided. Moreover, information on the concordance of HRR gene alteration status between tumour DNA and plasma ctDNA was provided. Discordances between tissue and ctDNA assays were observed. Of the number of patients tested (n=423), 291 and 277 were HRR positive as determined by tumour and ctDNA, respectively.

The description of primary endpoint and relevant secondary endpoints according to central biomarker analytic method (tissue vs ctDNA), including K-M plots, has been provided. Trends in primary and secondary endpoints are considered comparable in both biomarker methods to overall findings, with

most convincing data in the BRCA subgroup. A notable resemblance in numbers was seen between tissue-based and ctDNA-based assays, since discordances between the tests are expected. The clinical validity of the test of ctDNA will be determined when the survival data are mature. This strategy is according to SA [EMA/CHMP/SAWP/481577/2018] and considered acceptable.

According to the protocol, exploratory biomarker assays may be performed (where allowed by local regulations) to better define changes in tumour status over time. Results of these exploratory analyses should be provided once available (PAM-**REC)**.

The indication has been restricted to patients with BRCA 1/2 mutations.

2.6.7. Conclusions on the clinical efficacy

In the study MAGNITUDE, the combination of niraparib + AAP showed a statistically significant improvement in rPFS (BICR) compared with AAP alone in patients with mCRPC with HRR gene alterations (Cohort 1). An improvement in TSP and TCC was observed, although the latter did not reach statistical significance. Regarding (interim) OS data, although still relatively immature, no statistically significant differences were observed between treatment arms. Results appeared to be driven by patients with BRCA 1/BRCA 2 mutations. In the subgroup of non-BRCA patients no apparent benefit in terms of rPFS and potential detrimental effect in OS was observed. Consequently, the indication has been restricted to patients with BRCA 1/2 mutations and to those 'in whom chemotherapy is not clinically indicated'. The final indication is (in combination with prednisone or prednisolone) for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations in whom chemotherapy is not clinically indicated.

2.6.8. Clinical safety

The clinical safety profile of the niraparib/AA fixed-dose combination + prednisone was established from the MAGNITUDE study Cohort 1.

Cohort 1 provides the pivotal safety data and Cohort 3 provides a description of the clinical experience with the FDC tablet (DCO was 08-Oct-2021).

Additionally, supportive safety data were provided from the Combined Single Agent Combination (SAC) Group (niraparib and abiraterone acetate plus prednisone single-agent combination), where data were integrated from studies MAGNITUDE Cohorts 1 and 2, QUEST Combination 2, and BEDIVERE. As different combinations and dosages were tested in these studies, safety data were only integrated from subjects whose starting dose was the intended registration dose of 200 mg niraparib and 1,000 mg AA plus 10 mg prednisone as SAC. Additional supportive safety data for the FDC tablets was provided from MAGNITUDE Cohort 3 to allow for a comparison to SAC.

Safety data includes 473 subjects who received combination therapy with niraparib and abiraterone acetate plus prednisone: 378 subjects received individual products, referred to as niraparib and AAP single-agent combination (nira+AAP SAC) and 95 subjects received niraparib/AA fixed-dose combination tablets plus prednisone (FDC+P).

During the procedure the Applicant submitted updated safety data based on the most recent DCO (17 June 2022). Unless otherwise specified, all the safety data mentioned in the assessment report refer to the initial DCO (08 October 2021), which was overall in line with the safety data from the initial submission. Tables with the updated safety data are included after the tables provided in the initial assessment.

Table 85. Overview of the clinical study data included in the Summary of Clinical Safety (SCS):

Study		Study Design	Study Population	Treatment (daily)	Number of Subjects	CCO Date
MAGNITUDE 64091742PCR3001	Cohort 1	Phase 3, randomized, placebo-controlled, multicenter, double-blind study to assess the efficacy and safety of niraparib in combination with AAP	Men with mCRPC who previously received no prior treatment for mCRPC except ≤4 months of AAP (**with** HRR gene alterations)	Niraparib 200 mg and AAP (1,000 mg/10 mg) as SAC	212	08 Oct 2021
				Placebo and AAP (1,000 mg/10 mg)	211	
	Cohort 2[1]		Men with mCRPC who previously received no prior treatment for mCRPC except ≤4 months of AAP (**without** HRR gene alterations)[1]	Niraparib 200 mg and AAP (1,000 mg/10 mg) as SAC	123[2]	18 Sep 2020[3] (subjects without CDK-12) 08 Oct 2021[4] (subjects with CDK-12)
	Cohort 3	Non-randomized and open-label	Men with mCRPC who previously received no prior treatment for mCRPC except ≤4 months of AAP (**with** HRR gene alterations)	Niraparib/AA (200 mg/1,000 mg) as FDC tablet plus P (10 mg)[5]	95	08 Oct 2021
QUEST[5,6] 64091742PCR2002	Combination 2	Phase 1b/2, open-label dose-selection and dose-expansion study to evaluate the safety and antitumor effect of niraparib in combination with other agents	Men with mCRPC who progressed on 1 prior line of novel AR-targeted therapy for mCRPC (**with** HRR gene alterations)	Niraparib 200 mg and AAP (1,000 mg/10 mg) as SAC	24	29 Mar 2021

Study	Study Design	Study Population	Treatment (daily)	Number of Subjects	CCO Date
BEDIVERE[6] 64091742PCR1001	Phase 1b, open-label, dose-selection and dose-expansion study to determine the safety and RP2D of niraparib in combination with AR-targeted therapy	Men with mCRPC previously treated with ≥1 line of taxane-based chemotherapy and ≥1 line of AR-targeted therapy (**with or without** HRR gene alterations)	Niraparib 200 mg and AAP (1,000 mg/10 mg) as SAC	19	16 Jul 2019 (final data)

AA=abiraterone acetate; AAP=abiraterone acetate plus prednisone; AR=androgen receptor; CCO=clinical cutoff; FDC=fixed-dose combination; HRR=homologous recombination repair; mCRPC=metastatic castration-resistant prostate cancer; P=prednisone; RP2D=recommended Phase 2 dose; SAC=single-agent combination; SCS= Summary of Clinical Safety

Note: HRR gene alterations included BRCA1, BRCA2, cyclin-dependent kinase 12 (CDK-12), Fanconi anemia complementation Group A gene (FANCA), partner and localizer of BRCA2 gene (PALB2), checkpoint kinase 2 gene (CHEK2), BRCA1 interacting protein C-terminal Helicase 1 gene (BR1P1), histone deacetylase 2 gene (HDAC2), and ataxia telangiectasia mutated gene (ATM)

[1] MAGNITUDE Cohort 2 included 247 subjects: 233 subjects without HRR gene alterations (117 in the nira+AAP arm and 116 in the PBO+AAP arm) plus 14 subjects with CDK-12 gene alterations (6 in the nira+AAP arm and 8 in the PBO+AAP arm).

[2] The SCS only included data from 123 subjects in the nira+AAP arm of MAGNITUDE Cohort 2. Data from the additional 124 subjects who received PBO+AAP in the control arm of MAGNITUDE Cohort 2 were not included in the SCS.

[3] The nira+AAP arm of MAGNITUDE Cohort 2 included 117 subjects without any HRR gene alterations who were unblinded based upon results from a pre-specified futility analysis that suggested no clinical benefit, with a CCO date of 18 Sep 2020.

[4] The nira+AAP arm of MAGNITUDE Cohort 2 also included 6 subjects with CDK-12 gene alterations who were not unblinded at the time of the pre-specified futility analysis and had a later CCO date of 08 Oct 2021.

[5] Combination therapy with the niraparib/AA FDC tablet, instead of the individual components, reduced the pill burden from 6 to 2 tablets plus prednisone.

[6] QUEST and BEDIVERE evaluated different combination regimens with niraparib. Combination regimens (other than niraparib and AAP) from these studies are not included in the SCS. Additionally, 8 subjects in BEDIVERE who received niraparib and AAP combination therapy (but with a niraparib dose of 300 mg, instead of 200 mg) are not included in the SCS.

2.6.8.1. Patient exposure

Table 86. Treatment Disposition; Integrated Safety

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety	211	212	378	95
Subjects with treatment ongoing	88 (41.7%)	115 (54.2%)	191 (50.5%)	71 (74.7%)
Subjects discontinued from treatment	123 (58.3%)	97 (45.8%)	187 (49.5%)	24 (25.3%)
Reason for termination				
Progressive disease	108 (51.2%)	72 (34.0%)	128 (33.9%)	13 (13.7%)
Adverse event	8 (3.8%)	19 (9.0%)	37 (9.8%)	7 (7.4%)
Subject refused further study treatment	5 (2.4%)	6 (2.8%)	12 (3.2%)	3 (3.2%)
Physician decision	2 (0.9%)	0	5 (1.3%)	1 (1.1%)
Withdrawal by subject	0	0	4 (1.1%)	0
Non-Compliance with study drug	0	0	1 (0.3%)	0
Duration of study treatment (months)[a]				
N	211	212	378	95
Mean (SD)	12.7 (6.74)	13.9 (6.91)	12.1 (6.51)	5.3 (2.06)
Median	12.1	13.8	12.2	5.4
Range	(0; 29)	(0; 29)	(0; 29)	(0; 9)

[a] Treatment duration is defined as the duration from the date of the first dose of study drug to the date of last dose of study drug+1 divided by 30.4375.
Key: AAP = abiraterone acetate plus prednisone

Table 87. Treatment Disposition; Integrated Safety (for BRCA and HRR) Analysis Set– IA2 Clinical Cutoff 17 June 2022.

	MAGNITUDE Cohort 1 (SAC)				Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE		MAGNITUDE Cohort 3 FDC	
	BRCA		All HRR		BRCA	All	BRCA	All HRR
	Placebo + AAP	Niraparib + AAP	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety (for BRCA and HRR)	112	113	211	212	130	378	52	95
Subjects with treatment ongoing	29 (25.9%)	47 (41.6%)	57 (27.0%)	74 (34.9%)	51 (39.2%)	147 (38.9%)	30 (57.7%)	56 (58.9%)
Subjects discontinued from treatment	83 (74.1%)	66 (58.4%)	154 (73.0%)	138 (65.1%)	79 (60.8%)	231 (61.1%)	22 (42.3%)	39 (41.1%)
Reason for termination								
Progressive disease	76 (67.9%)	47 (41.6%)	135 (64.0%)	98 (46.2%)	56 (43.1%)	157 (41.5%)	14 (26.9%)	26 (27.4%)
Adverse event	4 (3.6%)	14 (12.4%)	11 (5.2%)	27 (12.7%)	16 (12.3%)	45 (11.9%)	5 (9.6%)	8 (8.4%)
Adverse event - COVID-19 related	0	5 (4.4%)	1 (0.5%)	10 (4.7%)	5 (3.8%)	11 (2.9%)	0	0
Subject refused further study treatment	2 (1.8%)	4 (3.5%)	6 (2.8%)	10 (4.7%)	4 (3.1%)	16 (4.2%)	2 (3.8%)	4 (4.2%)
Physician decision	1 (0.9%)	0	2 (0.9%)	1 (0.5%)	2 (1.5%)	6 (1.6%)	1 (1.9%)	1 (1.1%)
Death	0	0	0	0	0	0	0	0
Death - COVID-19 related	0	0	0	0	0	0	0	0
Other	0	1 (0.9%)	0	2 (0.9%)	1 (0.8%)	2 (0.5%)	0	0
Other - COVID-19 related	0	0	0	0	0	0	0	0

Key: AAP = abiraterone acetate plus prednisone, FDC=fixed-dose combination
Note: Combined SAC Group (All) = 212 (MAGNITUDE Cohort 1) + 123 (MAGNITUDE Cohort 2) + 19 (Bedivere) + 24 (QUEST2) = 378
Note: Combined SAC Group (BRCA) = 113 (MAGNITUDE Cohort 1) + 0 (MAGNITUDE Cohort 2) + 0 (Bedivere) + 17 (QUEST2) = 130
[TSIDS01_HRR_BRCA.RTF] [JNJ-64091742/Z_SCS/DBR_PCR3001SCS/RE_PCR3001SCSIA2/PROD/TSIDS01_HRR_BRCA.SAS] 09NOV2022, 08:33

Table 88. Summary of Exposure to Study Agent; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: safety	211	212	423
Duration of study treatment (months)[a]			
N	211	212	423
Mean (SD)	12.7 (6.74)	13.9 (6.91)	13.3 (6.85)
Median	12.1	13.8	12.8
Range	(0; 29)	(0; 29)	(0; 29)
Duration of study treatment (months)[a]			
0 - <3 months	16 (7.6%)	16 (7.5%)	32 (7.6%)
3 - <6 months	29 (13.7%)	14 (6.6%)	43 (10.2%)
6 - <9 months	15 (7.1%)	24 (11.3%)	39 (9.2%)
9 - <12 months	44 (20.9%)	34 (16.0%)	78 (18.4%)
12 - <15 months	31 (14.7%)	28 (13.2%)	59 (13.9%)
15 - <18 months	28 (13.3%)	28 (13.2%)	56 (13.2%)
18 - <21 months	21 (10.0%)	31 (14.6%)	52 (12.3%)
21 - <24 months	14 (6.6%)	21 (9.9%)	35 (8.3%)
24 - <27 months	9 (4.3%)	13 (6.1%)	22 (5.2%)
27 - <30 months	4 (1.9%)	3 (1.4%)	7 (1.7%)
30 - <33 months	0	0	0
Total numbers of cycles			
N	211	212	423
Mean (SD)	13.9 (7.07)	15.1 (7.32)	14.5 (7.21)
Median	13.0	15.0	13.0
Range	(1; 31)	(1; 31)	(1; 31)
Total numbers of cycles			
≥1 cycle	211 (100.0%)	212 (100.0%)	423 (100.0%)
≥3 cycles	204 (96.7%)	202 (95.3%)	406 (96.0%)
≥6 cycles	177 (83.9%)	190 (89.6%)	367 (86.8%)
≥9 cycles	162 (76.8%)	172 (81.1%)	334 (79.0%)
≥12 cycles	134 (63.5%)	142 (67.0%)	276 (65.2%)
≥15 cycles	96 (45.5%)	114 (53.8%)	210 (49.6%)
≥18 cycles	61 (28.9%)	78 (36.8%)	139 (32.9%)
≥21 cycles	43 (20.4%)	61 (28.8%)	104 (24.6%)
≥24 cycles	19 (9.0%)	27 (12.7%)	46 (10.9%)
≥27 cycles	11 (5.2%)	14 (6.6%)	25 (5.9%)
≥30 cycles	2 (0.9%)	2 (0.9%)	4 (0.9%)

Key: AAP = abiraterone acetate plus prednisone.
[a] Treatment duration is defined as the duration from the date of the first dose of study drug to the date of last dose of study drug+1 divided by 30.4375.

For information regarding baseline demographic and disease characteristics, please refer to clinical efficacy of this assessment report.

Table 89. Summary of Exposure to Study Agent; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001) – IA2 Clinical Cut-off 17 June 2022

	Placebo + AAP	Niraparib + AAP	Total
Analysis set: safety	211	212	423
Duration of study treatment (months)[a]			
N	211	212	423
Mean (SD)	15.5 (9.16)	17.5 (9.30)	16.5 (9.27)
Median	15.2	17.9	16.6
Range	(0; 37)	(0; 37)	(0; 37)
Duration of study treatment (months)[a]			
0 - <3 months	16 (7.6%)	16 (7.5%)	32 (7.6%)
3 - <6 months	29 (13.7%)	14 (6.6%)	43 (10.2%)
6 - <9 months	11 (5.2%)	18 (8.5%)	29 (6.9%)
9 - <12 months	25 (11.8%)	18 (8.5%)	43 (10.2%)
12 - <15 months	23 (10.9%)	18 (8.5%)	41 (9.7%)
15 - <18 months	30 (14.2%)	23 (10.8%)	53 (12.5%)
18 - <21 months	23 (10.9%)	23 (10.8%)	46 (10.9%)
21 - <24 months	11 (5.2%)	22 (10.4%)	33 (7.8%)
24 - <27 months	14 (6.6%)	22 (10.4%)	36 (8.5%)
27 - <30 months	14 (6.6%)	21 (9.9%)	35 (8.3%)
30 - <33 months	4 (1.9%)	7 (3.3%)	11 (2.6%)
33 - <36 months	9 (4.3%)	8 (3.8%)	17 (4.0%)
36 - <39 months	2 (0.9%)	2 (0.9%)	4 (0.9%)
Total number of cycles			
N	211	212	423
Mean (SD)	16.8 (9.67)	18.7 (9.74)	17.8 (9.75)
Median	17.0	19.0	17.0
Range	(1; 40)	(1; 40)	(1; 40)
Total number of cycles			
>1 cycle	211 (100.0%)	212 (100.0%)	423 (100.0%)
>3 cycles	204 (96.7%)	202 (95.3%)	406 (96.0%)
≥6 cycles	177 (83.9%)	190 (89.6%)	367 (86.8%)
≥9 cycles	162 (76.8%)	173 (81.6%)	335 (79.2%)
≥12 cycles	146 (69.2%)	157 (74.1%)	303 (71.6%)
>15 cycles	124 (58.8%)	141 (66.5%)	265 (62.6%)
>18 cycles	92 (43.6%)	117 (55.2%)	209 (49.4%)
≥21 cycles	73 (34.6%)	101 (47.6%)	174 (41.1%)
≥24 cycles	50 (23.7%)	71 (33.5%)	121 (28.6%)
≥27 cycles	37 (17.5%)	49 (23.1%)	86 (20.3%)
>30 cycles	26 (12.3%)	30 (14.2%)	56 (13.2%)
>33 cycles	14 (6.6%)	14 (6.6%)	28 (6.6%)
≥36 cycles	10 (4.7%)	10 (4.7%)	20 (4.7%)
≥39 cycles	2 (0.9%)	2 (0.9%)	4 (0.9%)

Key: AAP = abiraterone acetate plus prednisone.
[a] Treatment duration is defined as the duration from the date of the first dose of study drug to the date of last dose of study drug+1 divided by 30.4375.

[TSIEX01_HRR.RTF] [JNJ-64091742/PCR3001/DBR_IA2/RE_IA2/PROD/TSIEX01.SAS] 13JUL2022, 16:37

2.6.8.2. Adverse events

Table 90. Overall Safety Profile; Integrated Safety

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
Analysis set: Integrated safety	Placebo + AAP 211	Niraparib + AAP 212	Niraparib + AAP 378	Niraparib + AAP 95
Subjects with 1 or more:				
AEs	199 (94.3%)	210 (99.1%)	371 (98.1%)	89 (93.7%)
Related AEs [a]	116 (55.0%)	162 (76.4%)	304 (80.4%)	67 (70.5%)
AEs leading to death [b]	7 (3.3%)	12 (5.7%)	18 (4.8%)	4 (4.2%)
Serious AEs	52 (24.6%)	76 (35.8%)	145 (38.4%)	21 (22.1%)
Related serious AEs[a]	6 (2.8%)	24 (11.3%)	53 (14.0%)	5 (5.3%)
AEs leading to discontinuation of study agent[c]	13 (6.2%)	23 (10.8%)	47 (12.4%)	9 (9.5%)
Grade 3 or 4 AEs	98 (46.4%)	142 (67.0%)	260 (68.8%)	46 (48.4%)
COVID-19 AEs[d]	9 (4.3%)	14 (6.6%)	17 (4.7%)	0
COVID-19 SAEs[d]	5 (2.4%)	10 (4.7%)	11 (3.1%)	0

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination
[a] An AE is categorized as related if assessed by the investigator as related to any of the study drugs. For Quest and Bedivere, an AE is categorized as related if assessed by the investigator as possibly, probably or very likely related to study agent. For Magnitude, an AE is categorized as related is assessed by the investigator as related.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.
[d] Bedivere subjects are excluded for the calculation of COVID-19 related AEs.

Table 91. Overall Safety Profile; Integrated Safety (for BRCA and HRR) Analysis Set– IA2 Clinical Cutoff 17 June 2022

	MAGNITUDE Cohort 1 (SAC)				Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE		MAGNITUDE Cohort 3 FDC	
	BRCA		All HRR		BRCA	All	BRCA	All HRR
	Placebo + AAP	Niraparib + AAP	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety (for BRCA and HRR)	112	113	211	212	130	378	52	95
Subjects with 1 or more:								
AEs	109 (97.3%)	112 (99.1%)	203 (96.2%)	211 (99.5%)	129 (99.2%)	372 (98.4%)	51 (98.1%)	91 (95.8%)
Related AEs [a]	73 (65.2%)	86 (76.1%)	121 (57.3%)	165 (77.8%)	103 (79.2%)	307 (81.2%)	41 (78.8%)	71 (74.7%)
AEs leading to death [b]	4 (3.6%)	10 (8.8%)	9 (4.3%)	20 (9.4%)	10 (7.7%)	26 (6.9%)	2 (3.8%)	4 (4.2%)
Serious AEs	28 (25.0%)	46 (40.7%)	61 (28.9%)	93 (43.9%)	55 (42.3%)	163 (43.1%)	16 (30.8%)	29 (30.5%)
Related serious AEs[a]	3 (2.7%)	13 (11.5%)	8 (3.8%)	26 (12.3%)	17 (13.1%)	56 (14.8%)	3 (5.8%)	5 (5.3%)
AEs leading to discontinuation of study agent[c]	6 (5.4%)	17 (15.0%)	15 (7.1%)	32 (15.1%)	19 (14.6%)	56 (14.8%)	6 (11.5%)	12 (12.6%)
Grade 3 or 4 AEs	57 (50.9%)	77 (68.1%)	104 (49.3%)	153 (72.2%)	90 (69.2%)	272 (72.0%)	31 (59.6%)	54 (56.8%)
COVID-19 AEs[d]	10 (8.9%)	15 (13.3%)	16 (7.6%)	29 (13.7%)	15 (11.5%)	32 (8.9%)	11 (21.2%)	12 (12.6%)
COVID-19 SAEs[d]	4 (3.6%)	9 (8.0%)	7 (3.3%)	18 (8.5%)	9 (6.9%)	19 (5.3%)	0	0

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination
[a] An AE is categorized as related if assessed by the investigator as related to any of the study drugs. For Quest and Bedivere, an AE is categorized as related if assessed by the investigator as possibly, probably or very likely related to study agent. For Magnitude, an AE is categorized as related is assessed by the investigator as related.
[b] AEs leading to death are based on AE outcome of Fatal.
[c] An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.
[d] Bedivere subjects are excluded for the calculation of COVID-19 related AEs.
Note: Combined SAC Group (All) = 212 (MAGNITUDE Cohort 1) + 123 (MAGNITUDE Cohort 2) + 19 (Bedivere) + 24 (QUEST2) = 378
Note: Combined SAC Group (BRCA) = 113 (MAGNITUDE Cohort 1) + 0 (MAGNITUDE Cohort 2) + 0 (Bedivere) + 17 (QUEST2) = 130

Table 92. Overall Summary of Treatment-emergent Adverse Events; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set:safety	211	212
Subjects with 1 or more:		
AEs	199 (94.3%)	210 (99.1%)
Related AEs [a]	116 (55.0%)	162 (76.4%)
Niraparib/Placebo related AEs	84 (39.8%)	146 (68.9%)
Abiraterone acetate related AEs	84 (39.8%)	110 (51.9%)
AEs leading to death [b]	7 (3.3%)	12 (5.7%)
Serious AEs	52 (24.6%)	76 (35.8%)
Related serious AEs [a]	6 (2.8%)	24 (11.3%)
Niraparib/Placebo related serious AEs	5 (2.4%)	21 (9.9%)
Abiraterone acetate related serious AEs	2 (0.9%)	10 (4.7%)
AEs leading to discontinuation of study agent [c]	13 (6.2%)	23 (10.8%)
AEs leading to discontinuation of Niraparib/Placebo	10 (4.7%)	23 (10.8%)
AEs leading to discontinuation of Abiraterone acetate	12 (5.7%)	19 (9.0%)
Grade 3 or 4 AEs	98 (46.4%)	142 (67.0%)
COVID-19 AEs	9 (4.3%)	14 (6.6%)
COVID-19 SAEs	5 (2.4%)	10 (4.7%)
COVID-19 non-serious AEs	5 (2.4%)	5 (2.4%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event
[a]An AE is categorized as related if assessed by the investigator as related to niraparib, abiraterone acetate or prednisone.
[b]AEs leading to death are based on AE outcome of Fatal.
[c]An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.

Common adverse events

Table 93. Treatment-emergent Adverse Events with Frequency of at Least 5% in Any Group by System Organ Class and Preferred Term; Integrated Safety

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety	211	212	378	95
Subjects with 1 or more AEs	199 (94.3%)	210 (99.1%)	371 (98.1%)	89 (93.7%)
System organ class Preferred term				
Gastrointestinal disorders	96 (45.5%)	125 (59.0%)	239 (63.2%)	50 (52.6%)
Constipation	29 (13.7%)	65 (30.7%)	118 (31.2%)	23 (24.2%)
Nausea	29 (13.7%)	50 (23.6%)	99 (26.2%)	25 (26.3%)
Vomiting	14 (6.6%)	28 (13.2%)	64 (16.9%)	8 (8.4%)
Dyspepsia	6 (2.8%)	13 (6.1%)	21 (5.6%)	6 (6.3%)
Diarrhoea	8 (3.8%)	10 (4.7%)	25 (6.6%)	6 (6.3%)
Abdominal pain	12 (5.7%)	9 (4.2%)	15 (4.0%)	2 (2.1%)
Abdominal distension	1 (0.5%)	8 (3.8%)	15 (4.0%)	7 (7.4%)
Dry mouth	3 (1.4%)	6 (2.8%)	15 (4.0%)	5 (5.3%)
Blood and lymphatic system disorders	59 (28.0%)	119 (56.1%)	212 (56.1%)	41 (43.2%)
Anaemia	43 (20.4%)	98 (46.2%)	177 (46.8%)	37 (38.9%)
Thrombocytopenia	18 (8.5%)	45 (21.2%)	86 (22.8%)	11 (11.6%)
Neutropenia	12 (5.7%)	29 (13.7%)	54 (14.3%)	8 (8.4%)
Leukopenia	5 (2.4%)	22 (10.4%)	32 (8.5%)	3 (3.2%)
Lymphopenia	4 (1.9%)	19 (9.0%)	30 (7.9%)	2 (2.1%)
General disorders and administration site conditions	78 (37.0%)	111 (52.4%)	197 (52.1%)	31 (32.6%)
Fatigue	35 (16.6%)	56 (26.4%)	105 (27.8%)	16 (16.8%)
Asthenia	19 (9.0%)	33 (15.6%)	57 (15.1%)	12 (12.6%)
Oedema peripheral	18 (8.5%)	20 (9.4%)	35 (9.3%)	0
Pyrexia	12 (5.7%)	13 (6.1%)	18 (4.8%)	1 (1.1%)
Musculoskeletal and connective tissue disorders	107 (50.7%)	97 (45.8%)	163 (43.1%)	27 (28.4%)
Back pain	44 (20.9%)	31 (14.6%)	59 (15.6%)	7 (7.4%)
Arthralgia	20 (9.5%)	28 (13.2%)	41 (10.8%)	5 (5.3%)
Bone pain	24 (11.4%)	21 (9.9%)	29 (7.7%)	5 (5.3%)
Pain in extremity	14 (6.6%)	10 (4.7%)	19 (5.0%)	4 (4.2%)
Musculoskeletal chest pain	11 (5.2%)	4 (1.9%)	11 (2.9%)	1 (1.1%)
Vascular disorders	65 (30.8%)	93 (43.9%)	160 (42.3%)	24 (25.3%)
Hypertension	44 (20.9%)	66 (31.1%)	117 (31.0%)	15 (15.8%)
Hot flush	15 (7.1%)	15 (7.1%)	24 (6.3%)	4 (4.2%)
Metabolism and nutrition disorders	71 (33.6%)	92 (43.4%)	169 (44.7%)	31 (32.6%)
Decreased appetite	13 (6.2%)	30 (14.2%)	69 (18.3%)	13 (13.7%)
Hypokalaemia	20 (9.5%)	29 (13.7%)	48 (12.7%)	10 (10.5%)
Hyperglycaemia	18 (8.5%)	21 (9.9%)	39 (10.3%)	5 (5.3%)
Hyperkalaemia	12 (5.7%)	18 (8.5%)	27 (7.1%)	5 (5.3%)
Hyponatraemia	5 (2.4%)	4 (1.9%)	9 (2.4%)	7 (7.4%)
Infections and infestations	55 (26.1%)	84 (39.6%)	131 (34.7%)	14 (14.7%)
Urinary tract infection	13 (6.2%)	20 (9.4%)	33 (8.7%)	4 (4.2%)
Respiratory, thoracic and mediastinal disorders	37 (17.5%)	70 (33.0%)	119 (31.5%)	13 (13.7%)
Dyspnoea	12 (5.7%)	34 (16.0%)	53 (14.0%)	6 (6.3%)

Cough	10 (4.7%)	15 (7.1%)	28 (7.4%)	2 (2.1%)
Investigations	59 (28.0%)	69 (32.5%)	125 (33.1%)	23 (24.2%)
Blood alkaline phosphatase increased	14 (6.6%)	21 (9.9%)	32 (8.5%)	5 (5.3%)
Blood creatinine increased	8 (3.8%)	19 (9.0%)	23 (6.1%)	7 (7.4%)
Weight decreased	5 (2.4%)	19 (9.0%)	48 (12.7%)	7 (7.4%)
Aspartate aminotransferase increased	20 (9.5%)	11 (5.2%)	16 (4.2%)	4 (4.2%)
Alanine aminotransferase increased	22 (10.4%)	10 (4.7%)	16 (4.2%)	2 (2.1%)
Nervous system disorders	48 (22.7%)	66 (31.1%)	119 (31.5%)	23 (24.2%)
Dizziness	12 (5.7%)	24 (11.3%)	42 (11.1%)	3 (3.2%)
Headache	19 (9.0%)	17 (8.0%)	26 (6.9%)	7 (7.4%)
Renal and urinary disorders	47 (22.3%)	52 (24.5%)	88 (23.3%)	15 (15.8%)
Haematuria	8 (3.8%)	14 (6.6%)	24 (6.3%)	1 (1.1%)
Injury, poisoning and procedural complications	41 (19.4%)	35 (16.5%)	67 (17.7%)	10 (10.5%)
Fall	26 (12.3%)	11 (5.2%)	23 (6.1%)	4 (4.2%)
Psychiatric disorders	20 (9.5%)	35 (16.5%)	56 (14.8%)	9 (9.5%)
Insomnia	8 (3.8%)	22 (10.4%)	36 (9.5%)	3 (3.2%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

[TSFAE03_SCS_EU1.RTF] [JNJ-64091742/PCR3001/DBR_CSR/RE_EUREG/PROD/TSFAE03_SCS_EU1.SAS] 23SEP2022, 00:10

Table 94. Treatment-emergent Adverse Events with Frequency of at Least 5% in Any Group by System Organ Class and Preferred Term; IA2 Clinical Cutoff 17 June 2022, Integrated

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety	211	212	378	95
Subjects with 1 or more AEs	203 (96.2%)	211 (99.5%)	372 (98.4%)	91 (95.8%)
System organ class Preferred term				
Gastrointestinal disorders	100 (47.4%)	133 (62.7%)	247 (65.3%)	57 (60.0%)
Constipation	33 (15.6%)	70 (33.0%)	124 (32.8%)	27 (28.4%)
Nausea	31 (14.7%)	52 (24.5%)	101 (26.7%)	29 (30.5%)
Vomiting	16 (7.6%)	31 (14.6%)	67 (17.7%)	12 (12.6%)
Dyspepsia	8 (3.8%)	14 (6.6%)	22 (5.8%)	8 (8.4%)
Diarrhoea	9 (4.3%)	13 (6.1%)	30 (7.9%)	7 (7.4%)
Abdominal pain	12 (5.7%)	11 (5.2%)	17 (4.5%)	8 (8.4%)
Abdominal pain upper	7 (3.3%)	11 (5.2%)	16 (4.2%)	3 (3.2%)
Abdominal distension	1 (0.5%)	8 (3.8%)	15 (4.0%)	7 (7.4%)
Dry mouth	3 (1.4%)	6 (2.8%)	15 (4.0%)	5 (5.3%)
Blood and lymphatic system disorders	66 (31.3%)	128 (60.4%)	222 (58.7%)	47 (49.5%)
Anaemia	48 (22.7%)	106 (50.0%)	186 (49.2%)	40 (42.1%)
Thrombocytopenia	20 (9.5%)	49 (23.1%)	91 (24.1%)	17 (17.9%)
Neutropenia	15 (7.1%)	32 (15.1%)	57 (15.1%)	12 (12.6%)
Leukopenia	5 (2.4%)	23 (10.8%)	33 (8.7%)	6 (6.3%)
Lymphopenia	4 (1.9%)	22 (10.4%)	33 (8.7%)	5 (5.3%)
General disorders and administration site conditions	86 (40.8%)	122 (57.5%)	209 (55.3%)	41 (43.2%)
Fatigue	40 (19.0%)	63 (29.7%)	112 (29.6%)	20 (21.1%)
Asthenia	21 (10.0%)	35 (16.5%)	60 (15.9%)	15 (15.8%)
Oedema peripheral	18 (8.5%)	20 (9.4%)	35 (9.3%)	2 (2.1%)
Pyrexia	14 (6.6%)	16 (7.5%)	21 (5.6%)	4 (4.2%)
Musculoskeletal and connective tissue disorders	114 (54.0%)	107 (50.5%)	174 (46.0%)	37 (38.9%)
Back pain	47 (22.3%)	36 (17.0%)	65 (17.2%)	9 (9.5%)
Arthralgia	23 (10.9%)	32 (15.1%)	45 (11.9%)	9 (9.5%)
Bone pain	24 (11.4%)	23 (10.8%)	31 (8.2%)	5 (5.3%)
Pain in extremity	15 (7.1%)	12 (5.7%)	22 (5.8%)	6 (6.3%)
Muscular weakness	4 (1.9%)	10 (4.7%)	19 (5.0%)	2 (2.1%)
Spinal pain	11 (5.2%)	5 (2.4%)	7 (1.9%)	5 (5.3%)
Musculoskeletal chest pain	11 (5.2%)	4 (1.9%)	12 (3.2%)	1 (1.1%)
Infections and infestations	68 (32.2%)	99 (46.7%)	147 (38.9%)	31 (32.6%)
Urinary tract infection	18 (8.5%)	22 (10.4%)	36 (9.5%)	4 (4.2%)
COVID-19	11 (5.2%)	21 (9.9%)	23 (6.1%)	10 (10.5%)
Pneumonia	11 (5.2%)	14 (6.6%)	23 (6.1%)	3 (3.2%)
Metabolism and nutrition disorders	73 (34.6%)	99 (46.7%)	177 (46.8%)	43 (45.3%)
Decreased appetite	15 (7.1%)	33 (15.6%)	72 (19.0%)	16 (16.8%)
Hypokalaemia	21 (10.0%)	29 (13.7%)	48 (12.7%)	12 (12.6%)
Hyperglycaemia	18 (8.5%)	25 (11.8%)	44 (11.6%)	9 (9.5%)
Hyperkalaemia	12 (5.7%)	18 (8.5%)	27 (7.1%)	7 (7.4%)
Hyponatraemia	7 (3.3%)	5 (2.4%)	11 (2.9%)	7 (7.4%)
Vascular disorders	68 (32.2%)	97 (45.8%)	164 (43.4%)	35 (36.8%)
Hypertension	47 (22.3%)	70 (33.0%)	121 (32.0%)	24 (25.3%)
Hot flush	15 (7.1%)	16 (7.5%)	25 (6.6%)	5 (5.3%)

Safety

Respiratory, thoracic and mediastinal disorders	43 (20.4%)	76 (35.8%)	125 (33.1%)	18 (18.9%)
Dyspnoea	14 (6.6%)	38 (17.9%)	57 (15.1%)	7 (7.4%)
Cough	11 (5.2%)	18 (8.5%)	31 (8.2%)	4 (4.2%)
Investigations	64 (30.3%)	74 (34.9%)	132 (34.9%)	31 (32.6%)
Blood alkaline phosphatase increased	16 (7.6%)	23 (10.8%)	34 (9.0%)	5 (5.3%)
Weight decreased	7 (3.3%)	22 (10.4%)	52 (13.8%)	10 (10.5%)
Blood creatinine increased	9 (4.3%)	19 (9.0%)	25 (6.6%)	9 (9.5%)
Aspartate aminotransferase increased	21 (10.0%)	13 (6.1%)	18 (4.8%)	5 (5.3%)
Alanine aminotransferase increased	22 (10.4%)	11 (5.2%)	17 (4.5%)	2 (2.1%)
Blood lactate dehydrogenase increased	6 (2.8%)	11 (5.2%)	12 (3.2%)	3 (3.2%)
Nervous system disorders	55 (26.1%)	72 (34.0%)	125 (33.1%)	29 (30.5%)
Dizziness	13 (6.2%)	27 (12.7%)	45 (11.9%)	3 (3.2%)
Headache	19 (9.0%)	20 (9.4%)	30 (7.9%)	10 (10.5%)
Renal and urinary disorders	55 (26.1%)	58 (27.4%)	95 (25.1%)	20 (21.1%)
Haematuria	11 (5.2%)	16 (7.5%)	26 (6.9%)	1 (1.1%)
Urinary retention	9 (4.3%)	10 (4.7%)	15 (4.0%)	5 (5.3%)
Injury, poisoning and procedural complications	47 (22.3%)	42 (19.8%)	74 (19.6%)	19 (20.0%)
Fall	29 (13.7%)	16 (7.5%)	28 (7.4%)	6 (6.3%)
Psychiatric disorders	23 (10.9%)	38 (17.9%)	59 (15.6%)	11 (11.6%)
Insomnia	8 (3.8%)	24 (11.3%)	38 (10.1%)	5 (5.3%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination, IA2 = Interim Analysis 2
Note: Preferred terms with less than 5% frequency were removed. If the frequency of all preferred terms under a system organ category is less than 5% and the frequency of this system organ category term is greater than or equal to 5%, then that system organ category term will also be removed.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

Treatment related adverse events

Table 95. TEAEs Considered as Related to Niraparib/PBO by the Investigator Reported in ⩾ 5% of Subjects; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

TEAE PT	Placebo + AAP (N=211)	Niraparib + AAP (N=212)
	TEAE considered related to PBO	TEAE considered related to Niraparib
Anaemia	19 (9.0%)	76 (35.8%)
Thrombocytopenia	9 (4.3%)	37 (17.5%)
Nausea	12 (5.7%)	36 (17.0%)
Fatigue	12 (5.7%)	35 (16.5%)
Neutropenia	6 (2.8%)	23 (10.8%)
Constipation	9 (4.3%)	22 (10.4%)
Hypertension	10 (4.7%)	17 (8.0%)
Decreased Appetite	6 (2.8%)	16 (7.5%)
Vomiting	3 (1.4%)	15 (7.1%)
Leukopenia	1 (0.5%)	15 (7.1%)
Dyspnoea	3 (1.4%)	12 (5.7%)
Asthenia	9 (4.3%)	12 (5.7%)

Key: AAP=abiraterone acetate plus prednisone; N=number; PBO=placebo; PT=preferred term; TEAE=treatment-emergent adverse event

Table 96. TEAEs Considered as Related to Niraparib/PBO by the Investigator Reported in ≥5% of Subjects; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001) – IA2 Clinical Cutoff 17 June 2022

Table 64 of the Day 180 AR: TEAEs Considered as Related to Niraparib/PBO by the Investigator Reported in ≥5% of Subjects; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001) – IA2 Clinical Cutoff 17 June 2022

TEAE PT	Placebo + AAP (N=211)	Niraparib + AAP (N=212)
	TEAE considered related to PBO	TEAE considered related to Niraparib
Anaemia	21 (10.0%)	82 (38.7%)
Thrombocytopenia	9 (4.3%)	39 (18.4%)
Nausea	12 (5.7%)	37 (17.5%)
Fatigue	15 (7.1%)	37 (17.5%)
Neutropenia	6 (2.8%)	25 (11.8%)
Constipation	10 (4.7%)	25 (11.8%)
Hypertension	11 (5.2%)	18 (8.5%)
Decreased Appetite	7 (3.3%)	17 (8.0%)
Vomiting	3 (1.4%)	16 (7.5%)
Leukopenia	1 (0.5%)	16 (7.5%)
Dyspnoea	3 (1.4%)	11 (5.2%)
Asthenia	10 (4.7%)	14 (6.6%)

Key: AAP=abiraterone acetate plus prednisone; N=number; PBO=placebo; PT=preferred term; TEAE=treatment-emergent adverse event

Grade 3 or 4 adverse events

Grade 3-4 TEAEs occurred in 67% of the nira+AAP arm and 46% of the PBO+AAP arm in MAGNITUDE Cohort 1, 69% of the Combined SAC Group, and 48% of MAGNITUDE Cohort 3.

Table 97. Most Frequently Reported Grade 3 or 4 Treatment-Emergent Adverse Events (Preferred Term)

Event	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
SOC of Blood and Lymphatic System Disorders				
Grade 3	8.5%	26%	32%	19%
Grade 4	0.5%	6.6%	5.8%	1.1%
Grade 3 or 4	9.0%	33%	38%	20%
Anemia (preferred term)				
Grade 3	7.6%	28%	30%	18%
Grade 4	0	1.4%	1.1%	0
Grade 3 or 4	7.6%	30%	32%	18%
Neutropenia (preferred term)				
Grade 3	1.4%	5.2%	6.1%	3.2%

Event	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Grade 4	0	1.4%	1.9%	1.1%
Grade 3 or 4	1.4%	6.6%	7.9%	4.2%
Thrombocytopenia (preferred term)				
Grade 3	2.4%	2.8%	5.0%	4.2%
Grade 4	0	3.8%	3.2%	1.1%
Grade 3 or 4	2.4%	6.6%	8.2%	5.3%
SOC of Vascular Disorders				
Grade 3	14%	17%	17.5%	12%
Grade 4	0	0	0.3%	0
Grade 3 or 4	14%	17%	18%	12%
Hypertension (preferred term)				
Grade 3	12%	15%	16%	9.5%
Grade 4	0	0	0	0
Grade 3 or 4	12%	15%	16%	9.5%
SOC of General Disorders and Administration Site Conditions				
Grade 3	6.6%	6.1%	9.3%	3.2%
Grade 4	0	0.5%	0.5%	0
Grade 3 or 4	6.6%	6.6%	9.8%	3.2%
Fatigue (preferred term)				
Grade 3	4.3%	3.3%	5.3%	0
Grade 4	0	0	0	0
Grade 3 or 4	4.3%	3.3%	5.3%	0
SOC of Investigations				
Grade 3	9.5%	8.0%	7.9%	4.2%
Grade 4	0.5%	0.9%	0.5%	0
Grade 3 or 4	10%	9.0%	8.5%	4.2%
Increased Blood Alkaline Phosphatase (preferred term)				
Grade 3	2.4%	4.2%	3.7%	0
Grade 4	0	0.9%	0.5%	0
Grade 3 or 4	2.4%	5.2%	4.2%	0

Source: Mod5.3.5.3/ISS/TSFAE05 (Grade 3 or 4)
Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Frequently reported TEAEs of Grade 3 or 4 TEAEs defined as >5% of subjects in either arm of MAGNITUDE Cohort 1, Combined SAC Group, or MAGNITUDE Cohort 3. SOCs included for frequently reported TEAEs (>5%).

Table 98. Most Frequently Reported Grade 3 or 4 Treatment-Emergent Adverse Events (Preferred Term) – IA2 Clinical Cutoff 17 June 2022

Event	MAGNITUDE Cohort 1				Combined SAC Group		MAGNITUDE Cohort 3	
	BRCA		All HRR		BRCA	All	BRCA	All HRR
	PBO+AAP	nira+AAP SAC	PBO+AAP	nira+AAP SAC	nira+AAP SAC	nira+AAP SAC	FDC+P	FDC+P
	(n=112)	(n=113)	(n=211)	(n=212)	(n=130)	(n=378)	(n=52)	(n=95)
SOC of Blood and Lymphatic System Disorders								
Grade 3	11 (9.8%)	26 (23.0%)	21 (10.0%)	58 (27.4%)	35 (26.9%)	125 (33.1%)	14 (26.9%)	23 (24.2%)
Grade 4	1 (0.9%)	9 (8.0%)	2 (0.9%)	14 (6.6%)	10 (7.7%)	22 (5.8%)	1 (1.9%)	1 (1.1%)
Grade 3 or 4	12 (10.7%)	35 (31.0%)	23 (10.9%)	72 (34.0%)	45 (34.6%)	147 (38.9%)	15 (28.8%)	24 (25.3%)
Anemia (preferred term)								
Grade 3	10 (8.9%)	29 (25.7%)	18 (8.5%)	61 (28.8%)	38 (29.2%)	117 (31.0%)	15 (28.8%)	21 (22.1%)
Grade 4	0	3 (2.7%)	0	3 (1.4%)	3 (2.3%)	4 (1.1%)	0	0
Grade 3 or 4	10 (8.9%)	32 (28.3%)	18 (8.5%)	64 (30.2%)	41 (31.5%)	121 (32.0%)	15 (28.8%)	21 (22.1%)
Thrombocytopenia (preferred term)								
Grade 3	3 (2.7%)	4 (3.5%)	5 (2.4%)	8 (3.8%)	8 (6.2%)	21 (5.6%)	2 (3.8%)	6 (6.3%)
Grade 4	0	5 (4.4%)	0	8 (3.8%)	6 (4.6%)	12 (3.2%)	1 (1.9%)	1 (1.1%)
Grade 3 or 4	3 (2.7%)	9 (8.0%)	5 (2.4%)	16 (7.5%)	14 (10.8%)	33 (8.7%)	3 (5.8%)	7 (7.4%)
Neutropenia (preferred term)								
Grade 3	2 (1.8%)	7 (6.2%)	4 (1.9%)	11 (5.2%)	10 (7.7%)	23 (6.1%)	1 (1.9%)	4 (4.2%)
Grade 4	1 (0.9%)	1 (0.9%)	1 (0.5%)	3 (1.4%)	1 (0.8%)	7 (1.9%)	1 (1.9%)	1 (1.1%)
Grade 3 or 4	3 (2.7%)	8 (7.1%)	5 (2.4%)	14 (6.6%)	11 (8.5%)	30 (7.9%)	2 (3.8%)	5 (5.3%)
Lymphopenia (preferred term)								
Grade 3	1 (0.9%)	5 (4.4%)	1 (0.5%)	8 (3.8%)	6 (4.6%)	16 (4.2%)	1 (1.9%)	2 (2.1%)
Grade 4	0	1 (0.9%)	1 (0.5%)	1 (0.5%)	1 (0.8%)	1 (0.3%)	0	0
Grade 3 or 4	1 (0.9%)	6 (5.3%)	2 (0.9%)	9 (4.2%)	7 (5.4%)	17 (4.5%)	1 (0.9%)	2 (2.1%)
SOC of Vascular Disorders								
Grade 3	19 (17.0%)	16 (14.2%)	29 (13.7%)	37 (17.5%)	17 (13.1%)	68 (18.0%)	12 (23.1%)	17 (17.9%)
Grade 4	0	1 (0.9%)	0	1 (0.5%)	1 (0.8%)	2 (0.5%)	0	0
Grade 3 or 4	19 (17.0%)	17 (15.0%)	29 (13.7%)	38 (17.9%)	18 (13.8%)	70 (18.5%)	12 (23.1%)	17 (17.9%)
Hypertension (preferred term)								
Grade 3	17 (15.2%)	15 (13.3%)	26 (12.3%)	33 (15.6%)	15 (11.5%)	61 (16.1%)	11 (21.2%)	14 (14.7%)
Grade 4	0	0	0	0	0	0	0	0
Grade 3 or 4	17 (15.2%)	15 (13.3%)	26 (12.3%)	33 (15.6%)	15 (11.5%)	61 (16.1%)	11 (21.2%)	14 (14.7%)
SOC of General Disorders and Administration Site Conditions								
Grade 3	6 (5.4%)	11 (9.7%)	16 (7.6%)	17 (8.0%)	12 (9.2%)	39 (10.3%)	2 (3.8%)	3 (3.2%)
Grade 4	0	0	0	1 (0.5%)	0	2 (0.5%)	0	0
Grade 3 or 4	6 (5.4%)	11 (9.7%)	16 (7.6%)	18 (8.5%)	12 (9.2%)	41 (10.8%)	2 (3.8%)	3 (3.2%)
Fatigue (preferred term)								
Grade 3	4 (3.6%)	4 (3.5%)	11 (5.2%)	8 (3.8%)	5 (3.8%)	21 (5.6%)	0	0
Grade 4	0	0	0	0	0	0	0	0
Grade 3 or 4	4 (3.6%)	4 (3.5%)	11 (5.2%)	8 (3.8%)	5 (3.8%)	21 (5.6%)	0	0
SOC of Investigations								
Grade 3	13 (11.6%)	11 (9.7%)	22 (10.4%)	19 (9.0%)	12 (9.2%)	32 (8.5%)	3 (5.8%)	5 (5.3%)
Grade 4	1 (0.9%)	1 (0.9%)	1 (0.5%)	2 (0.9%)	1 (0.8%)	2 (0.5%)	0	0
Grade 3 or 4	14 (12.5%)	12 (10.6%)	23 (10.9%)	21 (9.9%)	13 (10.0%)	34 (9.0%)	3 (5.8%)	5 (5.3%)
Increased Blood Alkaline Phosphatase (preferred term)								
Grade 3	4 (3.6%)	6 (5.3%)	5 (2.4%)	10 (4.7%)	7 (5.4%)	15 (4.0%)	0	0
Grade 4	0	1 (0.9%)	0	2 (0.9%)	1 (0.8%)	2 (0.5%)	0	0
Grade 3 or 4	4 (3.6%)	7 (6.2%)	5 (2.4%)	12 (5.7%)	8 (6.2%)	17 (4.5%)	0	0
SOC of Metabolism and Nutrition Disorders								
Grade 3	9 (8.0%)	8 (7.1%)	13 (6.2%)	16 (7.5%)	10 (7.7%)	31 (8.2%)	4 (7.7%)	7 (7.4%)
Grade 4	2 (1.8%)	2 (1.8%)	3 (1.4%)	3 (1.4%)	2 (1.5%)	5 (1.3%)	2 (3.8%)	2 (2.1%)
Grade 3 or 4	11 (9.8%)	10 (8.8%)	16 (7.6%)	19 (9.0%)	12 (9.2%)	36 (9.5%)	6 (11.5%)	9 (9.5%)
Hypokalemia								
Grade 3	6 (5.4%)	2 (1.8%)	7 (3.3%)	7 (3.3%)	2 (1.5%)	11 (2.9%)	2 (3.8%)	3 (3.2%)
Grade 4	0	1 (0.9%)	0	1 (0.5%)	1 (0.8%)	2 (0.5%)	2 (3.8%)	2 (2.1%)
Grade 3 or 4	6 (5.4%)	3 (2.7%)	7 (3.3%)	8 (3.8%)	3 (2.3%)	13 (3.4%)	4 (7.7%)	5 (5.3%)

Source: Attachment TSFAE05_IA2_ISS (All HRR) and Attachment TSFAE05_BRCA_IA2_ISS (BRCA)
Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE

Frequently reported TEAEs of Grade 3 or 4 TEAEs defined as >5% of subjects in either arm of MAGNITUDE Cohort 1, Combined SAC Group, or MAGNITUDE Cohort 3. SOCs included for frequently reported TEAEs (>5%).

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Serious adverse events occurred in 76 subjects in the nira+AAP arm (35.8%) and 52 subjects in the PBO+AAP arm (24.6%) in MAGNITUDE Cohort 1.

Table 99. Treatment-emergent Serious Adverse Events with Frequency of at Least 1% in Any Group by System Organ Class and Preferred Term

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety	211	212	378	95
Subjects with 1 or more SAEs	52 (24.6%)	76 (35.8%)	145 (38.4%)	21 (22.1%)
System organ class Preferred term				
Infections and infestations	14 (6.6%)	24 (11.3%)	33 (8.7%)	6 (6.3%)
Pneumonia	4 (1.9%)	7 (3.3%)	11 (2.9%)	2 (2.1%)
COVID-19	1 (0.5%)	6 (2.8%)	7 (1.9%)	0
COVID-19 pneumonia	2 (0.9%)	4 (1.9%)	4 (1.1%)	0
Urinary tract infection	2 (0.9%)	2 (0.9%)	4 (1.1%)	2 (2.1%)
Urosepsis	1 (0.5%)	2 (0.9%)	4 (1.1%)	0
Abscess oral	0	0	0	1 (1.1%)
Septic shock	0	0	0	1 (1.1%)
Blood and lymphatic system disorders	4 (1.9%)	17 (8.0%)	37 (9.8%)	3 (3.2%)
Anaemia	2 (0.9%)	12 (5.7%)	31 (8.2%)	2 (2.1%)
Thrombocytopenia	0	4 (1.9%)	6 (1.6%)	0
Neutropenia	0	3 (1.4%)	3 (0.8%)	1 (1.1%)
Cardiac disorders	8 (3.8%)	10 (4.7%)	17 (4.5%)	2 (2.1%)
Myocardial infarction	3 (1.4%)	3 (1.4%)	4 (1.1%)	1 (1.1%)
Acute myocardial infarction	1 (0.5%)	0	0	1 (1.1%)
Renal and urinary disorders	11 (5.2%)	9 (4.2%)	18 (4.8%)	2 (2.1%)
Urinary retention	2 (0.9%)	4 (1.9%)	4 (1.1%)	0
Haematuria	1 (0.5%)	3 (1.4%)	5 (1.3%)	1 (1.1%)
Calculus bladder	0	2 (0.9%)	2 (0.5%)	1 (1.1%)
Acute kidney injury	2 (0.9%)	1 (0.5%)	3 (0.8%)	1 (1.1%)
General disorders and administration site conditions	5 (2.4%)	7 (3.3%)	17 (4.5%)	0
Fatigue	1 (0.5%)	2 (0.9%)	4 (1.1%)	0
Respiratory, thoracic and mediastinal disorders	3 (1.4%)	7 (3.3%)	14 (3.7%)	4 (4.2%)
Pulmonary embolism	1 (0.5%)	4 (1.9%)	8 (2.1%)	3 (3.2%)
Dyspnoea	0	3 (1.4%)	5 (1.3%)	0
Pleural effusion	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Respiratory failure	0	0	1 (0.3%)	1 (1.1%)
Metabolism and nutrition disorders	3 (1.4%)	6 (2.8%)	15 (4.0%)	1 (1.1%)
Dehydration	0	2 (0.9%)	5 (1.3%)	0
Hypokalaemia	1 (0.5%)	2 (0.9%)	3 (0.8%)	1 (1.1%)
Nervous system disorders	2 (0.9%)	6 (2.8%)	13 (3.4%)	2 (2.1%)
Dizziness	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Lumbar radiculopathy	0	0	0	1 (1.1%)
Gastrointestinal disorders	4 (1.9%)	5 (2.4%)	14 (3.7%)	4 (4.2%)
Diarrhoea	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Abdominal mass	0	0	0	1 (1.1%)
Colitis ischaemic	0	0	0	1 (1.1%)
Ileus	0	0	0	1 (1.1%)
Inguinal hernia	1 (0.5%)	0	0	1 (1.1%)
Vomiting	0	0	4 (1.1%)	0

Musculoskeletal and connective tissue disorders	3 (1.4%)	5 (2.4%)	12 (3.2%)	1 (1.1%)
Back pain	1 (0.5%)	2 (0.9%)	4 (1.1%)	1 (1.1%)
Vascular disorders	3 (1.4%)	4 (1.9%)	6 (1.6%)	1 (1.1%)
Hypovolaemic shock	0	0	0	1 (1.1%)
Injury, poisoning and procedural complications	8 (3.8%)	3 (1.4%)	7 (1.9%)	4 (4.2%)
Femoral neck fracture	1 (0.5%)	1 (0.5%)	2 (0.5%)	1 (1.1%)
Ankle fracture	0	0	0	1 (1.1%)
Femur fracture	0	0	1 (0.3%)	1 (1.1%)
Humerus fracture	0	0	0	1 (1.1%)
Road traffic accident	0	0	0	1 (1.1%)
Endocrine disorders	0	0	0	1 (1.1%)
Adrenal insufficiency	0	0	0	1 (1.1%)

Key: AAP = abiraterone acetate plus prednisone, SAE = serious adverse event, FDC=fixed-dose combination
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

[TSFAE15_SCS_EU1.RTF] [JNJ-64091742/PCR3001/DBR_CSR/RE_EUREG/PROD/TSFAE15_SCS_EU1.SAS] 23SEP2022, 00:10

Table 100. Treatment-emergent Serious Adverse Events with Frequency of at Least 1% in Any Group by System Organ Class and Preferred Term, IA2 Clinical Cutoff 17 June 2022, Integrated Safety

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
Analysis set: Integrated safety	Placebo + AAP 211	Niraparib + AAP 212	Niraparib + AAP 378	Niraparib + AAP 95
Subjects with 1 or more SAEs	61 (28.9%)	93 (43.9%)	163 (43.1%)	29 (30.5%)
System organ class Preferred term				
Infections and infestations	18 (8.5%)	36 (17.0%)	45 (11.9%)	7 (7.4%)
COVID-19	3 (1.4%)	10 (4.7%)	11 (2.9%)	0
Pneumonia	4 (1.9%)	9 (4.2%)	13 (3.4%)	2 (2.1%)
COVID-19 pneumonia	2 (0.9%)	8 (3.8%)	8 (2.1%)	0
Urinary tract infection	2 (0.9%)	2 (0.9%)	4 (1.1%)	2 (2.1%)
Urosepsis	1 (0.5%)	2 (0.9%)	4 (1.1%)	1 (1.1%)
Lower respiratory tract infection	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Septic shock	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Abscess oral	0	0	0	1 (1.1%)
Blood and lymphatic system disorders	6 (2.8%)	17 (8.0%)	38 (10.1%)	4 (4.2%)
Anaemia	3 (1.4%)	12 (5.7%)	32 (8.5%)	2 (2.1%)
Thrombocytopenia	0	4 (1.9%)	6 (1.6%)	0
Neutropenia	1 (0.5%)	3 (1.4%)	3 (0.8%)	1 (1.1%)
Leukopenia	0	0	1 (0.3%)	1 (1.1%)
Cardiac disorders	9 (4.3%)	15 (7.1%)	22 (5.8%)	2 (2.1%)
Acute myocardial infarction	2 (0.9%)	3 (1.4%)	3 (0.8%)	1 (1.1%)
Myocardial infarction	3 (1.4%)	3 (1.4%)	4 (1.1%)	1 (1.1%)
Atrial fibrillation	1 (0.5%)	2 (0.9%)	4 (1.1%)	0
General disorders and administration site conditions	6 (2.8%)	10 (4.7%)	20 (5.3%)	0
Fatigue	2 (0.9%)	2 (0.9%)	4 (1.1%)	0
Renal and urinary disorders	13 (6.2%)	9 (4.2%)	18 (4.8%)	5 (5.3%)
Urinary retention	2 (0.9%)	4 (1.9%)	4 (1.1%)	1 (1.1%)
Haematuria	2 (0.9%)	3 (1.4%)	5 (1.3%)	1 (1.1%)
Calculus bladder	0	2 (0.9%)	2 (0.5%)	1 (1.1%)
Acute kidney injury	2 (0.9%)	1 (0.5%)	3 (0.8%)	1 (1.1%)
Hydronephrosis	2 (0.9%)	0	1 (0.3%)	1 (1.1%)
Urinary tract obstruction	2 (0.9%)	0	1 (0.3%)	1 (1.1%)
Gastrointestinal disorders	5 (2.4%)	8 (3.8%)	18 (4.8%)	4 (4.2%)
Diarrhoea	0	2 (0.9%)	3 (0.8%)	1 (1.1%)
Vomiting	0	1 (0.5%)	5 (1.3%)	0
Abdominal mass	0	0	0	1 (1.1%)
Colitis ischaemic	0	0	0	1 (1.1%)
Ileus	0	0	0	1 (1.1%)
Inguinal hernia	2 (0.9%)	0	0	1 (1.1%)
Respiratory, thoracic and mediastinal disorders	5 (2.4%)	8 (3.8%)	15 (4.0%)	5 (5.3%)
Dyspnoea	1 (0.5%)	4 (1.9%)	6 (1.6%)	0
Pulmonary embolism	2 (0.9%)	4 (1.9%)	8 (2.1%)	4 (4.2%)
Pleural effusion	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Respiratory failure	0	0	1 (0.3%)	1 (1.1%)
Metabolism and nutrition disorders	5 (2.4%)	7 (3.3%)	17 (4.5%)	3 (3.2%)
Dehydration	0	2 (0.9%)	5 (1.3%)	1 (1.1%)
Hyperglycaemia	0	2 (0.9%)	4 (1.1%)	0
Hypokalaemia	1 (0.5%)	2 (0.9%)	3 (0.8%)	1 (1.1%)
Hypoglycaemia	1 (0.5%)	0	1 (0.3%)	1 (1.1%)

Nervous system disorders	5 (2.4%)	7 (3.3%)	14 (3.7%)	3 (3.2%)
Dizziness	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Lumbar radiculopathy	0	0	0	1 (1.1%)
Transient ischaemic attack	0	0	1 (0.3%)	1 (1.1%)
Musculoskeletal and connective tissue disorders	4 (1.9%)	6 (2.8%)	13 (3.4%)	1 (1.1%)
Back pain	1 (0.5%)	2 (0.9%)	4 (1.1%)	1 (1.1%)
Injury, poisoning and procedural complications	8 (3.8%)	5 (2.4%)	9 (2.4%)	7 (7.4%)
Femur fracture	0	2 (0.9%)	3 (0.8%)	2 (2.1%)
Femoral neck fracture	1 (0.5%)	1 (0.5%)	2 (0.5%)	1 (1.1%)
Ankle fracture	0	0	0	1 (1.1%)
Fall	1 (0.5%)	0	0	1 (1.1%)
Hand fracture	0	0	0	1 (1.1%)
Humerus fracture	0	0	0	1 (1.1%)
Road traffic accident	0	0	0	1 (1.1%)
Vascular disorders	3 (1.4%)	5 (2.4%)	7 (1.9%)	1 (1.1%)
Hypovolaemic shock	0	0	0	1 (1.1%)
Endocrine disorders	0	0	0	1 (1.1%)
Adrenal insufficiency	0	0	0	1 (1.1%)

Key: AAP = abiraterone acetate plus prednisone, SAE = serious adverse event, FDC=fixed-dose combination, IA2 = interim analysis 2
Note: Preferred terms with less than 1% frequency were removed. If the frequency of all preferred terms under a system organ category is less than 1% and the frequency of this system organ category term is greater than or equal to 1%, then that system organ category term will also be removed.
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
[TSFAE15_SCSIA2_EU1.RTF] [JNJ-64091742/PCR3001/DBR_CSR/RE_EUREG/PROD/TSFAE15_SCSIA2_EU1.SAS] 13FEB2023, 05:01

Deaths

On-study treatment deaths were defined as a death occurring within 30 days of the last dose of study drug.

As of the DCO date, 19 subjects (9%) in each treatment group had died while on treatment or within 30 days of the last dose of study drug in Cohort 1. The most common cause of death on study treatment was progressive disease, with 12 deaths in the PBO+AAP group and 8 in the nira+AAP group.

Of note, 12 subjects (5.7%) in the nira+AAP group and 7 subjects (3.3%) in the PBO+AAP group had TEAEs leading to death. The most common AE leading to death within 30 days of last dose of study drug was COVID-19.

In addition to older age and prostate cancer, almost all patients who died due to COVID-19 had co-morbidities and no patients had documentation that they were immunized to COVID-19. At the last recording of haematological lab values, none of the patients had clinically relevant leukopenia, neutropenia, or lymphopenia with the exception of one subject (in the PBO+AAP group), who had anaemia at the time of death due to COVID-19.

According to the subject narratives presented in the SCS, only one of the non-COVID-19 related deaths in the niraparib/AAP arm was attributed to a TEAE of niraparib (pneumonia) by the investigators.

Table 101. Summary of Deaths During Treatment; Cohort 1 All HRR Safety Analysis Set (Study64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: safety	211	212
Deaths during treatment	19 (9.0%)	19 (9.0%)
Adverse event	7 (3.3%)	11 (5.2%)
Related to study agent	0	1 (0.5%)
Relationship unknown	0	0
Progressive disease	12 (5.7%)	8 (3.8%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Related includes deaths that were related to study agent.

Table 102. Summary of Deaths During Treatment; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001) – IA2 Clinical Cutoff 17 June 2022

	Placebo + AAP	Niraparib + AAP
Analysis set: safety	211	212
Deaths during treatment	23 (10.9%)	29 (13.7%)
Adverse event	9 (4.3%)	19 (9.0%)
Related to study agent	1 (0.5%)	1 (0.5%)
Relationship unknown	0	0
Progressive disease	14 (6.6%)	10 (4.7%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Related includes deaths that were related to study agent.

Table 103. Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Integrated Safety

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety	211	212	378	95
Subjects with 1 or more AEs leading to death	7 (3.3%)	12 (5.7%)	18 (4.8%)	4 (4.2%)
Infections and infestations	2 (0.9%)	7 (3.3%)	8 (2.1%)	2 (2.1%)
COVID-19	0	4 (1.9%)	5 (1.3%)	0
COVID-19 pneumonia	0	2 (0.9%)	2 (0.5%)	0
Pneumonia	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Septic shock	0	0	0	1 (1.1%)
Suspected COVID-19	2 (0.9%)	0	0	0
Cardiac disorders	3 (1.4%)	2 (0.9%)	5 (1.3%)	0
Cardio-respiratory arrest	0	1 (0.5%)	1 (0.3%)	0
Cor pulmonale	0	1 (0.5%)	1 (0.3%)	0
Acute myocardial infarction	1 (0.5%)	0	0	0
Cardiac arrest	0	0	1 (0.3%)	0
Cardiac failure	0	0	1 (0.3%)	0
Myocardial infarction	2 (0.9%)	0	0	0
Myocardial ischaemia	0	0	1 (0.3%)	0
General disorders and administration site conditions	0	1 (0.5%)	2 (0.5%)	0
Adverse drug reaction	0	1 (0.5%)	1 (0.3%)	0
General physical health deterioration	0	0	1 (0.3%)	0
Psychiatric disorders	0	1 (0.5%)	1 (0.3%)	0
Completed suicide	0	1 (0.5%)	1 (0.3%)	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.5%)	2 (0.5%)	1 (1.1%)
Dyspnoea	0	1 (0.5%)	1 (0.3%)	0
Pulmonary embolism	0	0	1 (0.3%)	0
Respiratory failure	0	0	0	1 (1.1%)
Injury, poisoning and procedural complications	0	0	0	1 (1.1%)
Road traffic accident	0	0	0	1 (1.1%)
Nervous system disorders	1 (0.5%)	0	0	0
Cerebral arteriosclerosis	1 (0.5%)	0	0	0
Vascular disorders	1 (0.5%)	0	0	1 (1.1%)
Circulatory collapse	1 (0.5%)	0	0	0
Hypovolaemic shock	0	0	0	1 (1.1%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

Table 104. Treatment-emergent Adverse Events Leading to Death by System Organ Class and Preferred Term; Integrated Safety (for BRCA and HRR) Analysis Set– IA2 Clinical Cutoff 17 June 2022

	MAGNITUDE Cohort 1 (SAC)				Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE		MAGNITUDE Cohort 3 FDC	
	BRCA		All HRR		BRCA	All	BRCA	All HRR
	Placebo + AAP	Niraparib + AAP	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety (for BRCA and HRR)	112	113	211	212	130	378	52	95
Subjects with 1 or more AEs leading to death	4 (3.6%)	10 (8.8%)	9 (4.3%)	20 (9.4%)	10 (7.7%)	26 (6.9%)	2 (3.8%)	4 (4.2%)
System organ class Preferred term								
Infections and infestations	1 (0.9%)	8 (7.1%)	2 (0.9%)	13 (6.1%)	8 (6.2%)	14 (3.7%)	1 (1.9%)	2 (2.1%)
COVID-19	0	3 (2.7%)	0	6 (2.8%)	3 (2.3%)	7 (1.9%)	0	0
COVID-19 pneumonia	0	3 (2.7%)	0	4 (1.9%)	3 (2.3%)	4 (1.1%)	0	0
Pneumonia	0	1 (0.9%)	0	1 (0.5%)	1 (0.8%)	1 (0.3%)	1 (1.9%)	1 (1.1%)
Septic shock	0	1 (0.9%)	0	1 (0.5%)	1 (0.8%)	1 (0.3%)	0	1 (1.1%)
Sepsis	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0
Suspected COVID-19	1 (0.9%)	0	2 (0.9%)	0	0	0	0	0
Cardiac disorders	1 (0.9%)	1 (0.9%)	4 (1.9%)	3 (1.4%)	1 (0.8%)	6 (1.6%)	0	0
Cardio-respiratory arrest	0	1 (0.9%)	0	1 (0.5%)	1 (0.8%)	1 (0.3%)	0	0
Acute myocardial infarction	1 (0.9%)	0	2 (0.9%)	1 (0.5%)	0	1 (0.3%)	0	0
Cardiac arrest	0	0	0	0	0	1 (0.3%)	0	0
Cardiac failure	0	0	0	0	0	1 (0.3%)	0	0
Cor pulmonale	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0
Myocardial infarction	0	0	2 (0.9%)	0	0	0	0	0
Myocardial ischaemia	0	0	0	0	0	1 (0.3%)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.9%)	1 (0.5%)	1 (0.5%)	1 (0.8%)	2 (0.5%)	0	0
Dyspnoea	0	1 (0.9%)	0	1 (0.5%)	1 (0.8%)	1 (0.3%)	0	0
Pulmonary embolism	0	0	1 (0.5%)	0	0	1 (0.3%)	0	0
General disorders and administration site conditions	0	0	0	2 (0.9%)	0	3 (0.8%)	0	0
Adverse drug reaction	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0
General physical health deterioration	0	0	0	0	0	1 (0.3%)	0	0
Sudden death	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (1.9%)	1 (1.1%)
Road traffic accident	0	0	0	0	0	0	1 (1.9%)	1 (1.1%)
Nervous system disorders	1 (0.9%)	0	1 (0.5%)	0	0	0	0	0
Cerebral arteriosclerosis	1 (0.9%)	0	1 (0.5%)	0	0	0	0	0
Psychiatric disorders	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0
Completed suicide	0	0	0	1 (0.5%)	0	1 (0.3%)	0	0
Vascular disorders	1 (0.9%)	0	1 (0.5%)	0	0	0	0	1 (1.1%)
Circulatory collapse	1 (0.9%)	0	1 (0.5%)	0	0	0	0	0
Hypovolaemic shock	0	0	0	0	0	0	0	1 (1.1%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.
Note: Combined SAC Group (All) = 212 (MAGNITUDE Cohort 1) + 123 (MAGNITUDE Cohort 2) + 19 (Bedivere) + 24 (QUEST2) = 378
Note: Combined SAC Group (BRCA) = 113 (MAGNITUDE Cohort 1) + 0 (MAGNITUDE Cohort 2) + 0 (Bedivere) + 17 (QUEST2) = 130
[TSFAE09_HRR_BRCA.RTF] [JNJ-64091742/Z_SCS/DBR_PCR3001SCS/RE_PCR3001SCSIA2/PROD/TSFAE09_HRR_BRCA.SAS] 08NOV2022, 16:21

Table 105. Summary of Death during Follow-up; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: safety	211	212
Subjects died in follow-up [a]	40 (19.0%)	36 (17.0%)
Adverse event	0	1 (0.5%)
Progressive disease	31 (14.7%)	29 (13.7%)
Other	9 (4.3%)	6 (2.8%)

Key: AAP=abiraterone acetate plus prednisone; HRR=homologous recombination repair
[a]Follow-up death is defined as the death occurs more than 30 days after the last dose of study drug.

Table 106. Summary of Death during Follow-up; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001) – IA2 Clinical Cutoff 17 June 2022

Table 69 of the Day 180 AR: Summary of Death during Follow-up; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001) – IA2 Clinical Cutoff 17 June 2022		
	Placebo + AAP	Niraparib + AAP
Analysis set: safety	211	212
Subjects died in follow-up [a]	66 (31.3%)	61 (28.8%)
Adverse event	1 (0.5%)	2 (0.9%)
COVID-19 related	0	2 (0.9%)
Progressive disease	53 (25.1%)	51 (24.1%)
Other	12 (5.7%)	8 (3.8%)
COVID-19 related	3 (1.4%)	0

Key: AAP = abiraterone acetate plus prednisone.
[a]Follow-up death is defined as the death occurs more than 30 days after the last dose of study drug.

Adverse Events of Special Interest (AESI)

Table 107. TEAEs of Special Interest (by Grouped Term); Cohort 1 All HRR Safety Analysis Set (Study64091742PCR3001)

TEAE Grouped Term	Placebo + AAP (N=211)			Niraparib + AAP (N=212)		
	Overall	Grade 3	Grade 4	Overall	Grade 3	Grade 4
Anaemia	43 (20.4%)	16 (7.6%)	0	98 (46.2%)	60 (28.3%)	3 (1.4%)
Thrombocytopenia	18 (8.5%)	5 (2.4%)	0	45 (21.2%)	6 (2.8%)	8 (3.8%)
Neutropenia	12 (5.7%)	3 (1.4%)	0	29 (13.7%)	11 (5.2%)	3 (1.4%)
Hypokalemia	20 (9.5%)	6 (2.8%)	0	30 (14.2%)	6 (2.8%)	0
Fluid retention/edema	28 (13.3%)	0	0	28 (13.2%)	2 (0.9%)	0
Hypertension	47 (22.3%)	30 (14.2%)	0	67 (31.6%)	33 (15.6%)	0
Arrhythmia	12 (5.7%)	3 (1.4%)	0	27 (12.7%)	5 (2.4%)	0
Cardiac failure	4 (1.9%)	1 (0.5%)	0	4 (1.9%)	1 (0.5%)	1 (0.5%)
Hepatotoxicity	26 (12.3%)	10 (4.7%)	0	25 (11.8%)	3 (1.4%)	1 (0.5%)
Cerebrovascular disorders	2 (0.9%)	0	0	6 (2.8%)	2 (0.9%)	0
Ischemic heart disease	8 (3.8%)	3 (1.4%)	0	4 (1.9%)	3 (1.4%)	1 (0.5%)
Osteoporosis[a]	2 (0.9%)	0	0	1 (0.5%)	0	0
AML	1 (0.5%)	0	1 (0.5%)	0	0	0
Rhabdomyolysis/myopathy	1 (0.5%)	0	0	0	0	0

Key: AAP=abiraterone acetate plus prednisone; AML=acute myeloid leukemia; N=number; TEAE=treatment-emergent adverse event
[a] Including osteoporosis-related fractures

- Anaemia

Table 108. Characteristics of the AESI of Anaemia (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	43 (20%)	98 (46%)	177 (47%)	37 (39%)
Grade 3 Incidence*	16 (7.6%)	60 (28%)	115 (30%)	17 (18%)
Grade 4 Incidence*	0	3 (1.4%)	4 (1.1%)	0
Grade 5 Incidence	0	0	0	0
Serious	2 (0.9%)	12 (5.7%)	31 (8.2%)	2 (2.1%)
Treatment Discontinuation	1 (0.5%)	5 (2.4%)	8 (2.1%)	0
Dose Interruption	7 (3.3%)	49 (23%)	92 (24%)	14 (15%)
Dose Reduction	1 (0.5%)	28 (13%)	53 (14%)	3 (3.2%)

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

*Per NCI-CTCAE, Grade 3 anemia is defined as hemoglobin<8.0 g/dL, <4.9 mmol/L, or <80 g/L with transfusion indicated; Grade 4 includes life-threatening consequences with urgent intervention indicated (NCI-CTCAE 2017).

- Thrombocytopenia

Table 109. Characteristics of the AESI of Thrombocytopenia (preferred term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	18 (8.5%)	45 (21%)	86 (23%)	11 (12%)
Grade 3 Incidence	5 (2.4%)	6 (2.8%)	19 (5.0%)	4 (4.2%)
Grade 4 Incidence	0	8 (3.8%)	12 (3.2%)	1 (1.1%)
Grade 5 Incidence	0	0	0	0
Serious	0	4 (1.9%)	6 (1.6%)	0
Treatment Discontinuation	0	1 (0.5%)	5 (1.3%)	0
Dose Interruption	4 (1.9%)	20 (9.4%)	39 (10%)	3 (3.2%)
Dose Reduction	2 (0.9%)	6 (2.8%)	13 (3.4%)	2 (2.1%)

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Neutropenia

Table 110. Characteristics of the AESI of Neutropenia (preferred term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	12 (5.7%)	29 (14%)	54 (14%)	8 (8.4%)
Grade 3 Incidence	3 (1.4%)	11 (5.2%)	23 (6.1%)	3 (3.2%)
Grade 4 Incidence	0	3 (1.4%)	7 (1.9%)	1 (1.1%)
Grade 5 Incidence	0	0	0	0
Serious	0	3 (1.4%)	3 (0.8%)	1 (1.1%)
Treatment Discontinuation	0	0	1 (0.3%)	0
Dose Interruption	2 (0.9%)	14 (6.6%)	27 (7.1%)	5 (5.3%)
Dose Reduction	0	3 (1.4%)	6 (1.6%)	0

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Hypertension

Table 111. Characteristics of the AESI of Hypertension (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	47 (22%)	67 (32%)	120 (32%)	19 (20%)
Grade 3 Incidence*	30 (14%)	33 (16%)	62 (16%)	10 (11%)
Grade 4 Incidence*	0	0	1 (0.3%)	0
Grade 5 Incidence	0	0	0	0
Serious	0	0	1 (0.3%)	0
Treatment Discontinuation	0	0	1 (0.3%)	1 (1.1%)
Dose Interruption	3 (1.4%)	3 (1.4%)	12 (3.2%)	1 (1.1%)
Dose Reduction	0	1 (0.5%)	4 (1.1%)	1 (1.1%)

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

*In the studies, hypertension was graded according to NCI-CTCAE criteria, which used more stringent criteria than clinical staging. For example, NCI-CTCAE grade 2 hypertension (systolic 140-159 mm or diastolic 90-99 mm) and grade 3 hypertension (systolic>160 mm or diastolic>100 mm) taken together equate to clinical stage 2 hypertension (systolic>140 mm or diastolic>90 mm). NCI-CTCAE Grade 4 mostly corresponds to the clinical stage of hypertensive crisis (NCI-CTCAE 2017, Whelton 2018).

Events of Mineralocorticoid Excess (Hypokalemia, Fluid Retention/Oedema)

- Hypokalemia

Table 112. Characteristics of the AESI of Hypokalemia (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	20 (9.5%)	30 (14%)	50 (13%)	10 (11%)
Grade 3 Incidence	6 (2.8%)	6 (2.8%)	10 (2.6%)	2 (2.1%)
Grade 4 Incidence	0	0	1 (0.3%)	2 (2.1%)
Grade 5 Incidence	0	0	0	0
Serious	1 (0.5%)	2 (0.9%)	3 (0.8%)	1 (1.1%)
Treatment Discontinuation	0	0	0	1 (1.1%)
Dose Interruption	1 (0.5%)	6 (2.8%)	13 (3.4%)	4 (4.2%)
Dose Reduction	0	1 (0.5%)	2 (0.5%)	1 (1.1%)

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Fluid Retention/Oedema

Table 113. Characteristics of the AESI of Fluid retention/Oedema (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	28 (13%)	28 (13%)	49 (13%)	2 (2.1%)
Grade 3 Incidence	0	2 (0.9%)	3 (0.8%)	0
Grade 4 Incidence	0	0	0	0
Grade 5 Incidence	0	0	0	0
Serious	0	1 (0.5%)	4 (1.1%)	1 (1.1%)
Treatment Discontinuation	0	0	0	0
Dose Interruption	1 (0.5%)	3 (1.4%)	6 (1.6%)	2 (2.1%)
Dose Reduction	1 (0.5%)	0	1 (0.3%)	0

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

MACE (Arrhythmias, Ischemic Heart Disease, Cardiac Failure)

- Arrhythmias

The most common arrhythmia was tachycardia (including the PTs sinus tachycardia, supraventricular tachycardia and atrial tachycardia). No event of TdP was reported.

Table 114. Characteristics of the AESI of Arrhythmias (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	12 (5.7%)	27 (13%)	52 (14%)	12 (13%)
Grade 3 Incidence	3 (1.4%)	5 (2.4%)	10 (2.6%)	1 (1.1%)
Grade 4 Incidence	0	0	0	0
Grade 5 Incidence	0	1 (0.5%)	2 (0.5%)	0
Serious	2 (0.9%)	3 (1.4%)	6 (1.6%)	0
Treatment Discontinuation	0	1 (0.5%)	3 (0.8%)	0
Dose Interruption	3 (1.4%)	4 (1.9%)	7 (1.9%)	0
Dose Reduction	0	0	0	1 (1.1%)

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Cardiac Failure

Table 115. Characteristics of the AESI of Cardiac Failure (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	4 (1.9%)	4 (1.9%)	12 (3.2%)	1 (1.1%)
Grade 3 Incidence	1 (0.5%)	1 (0.5%)	4 (1.1%)	0
Grade 4 Incidence	0	1 (0.5%)	2 (0.5%)	0
Grade 5 Incidence	0	1 (0.5%)	2 (0.5%)	0
Serious	1 (0.5%)	3 (1.4%)	7 (1.9%)	0
Treatment Discontinuation	0	1 (0.5%)	4 (1.1%)	0
Dose Interruption	0	3 (1.4%)	4 (1.1%)	0
Dose Reduction	0	0	0	0

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Ischemic Heart Disease

Table 116. Characteristics of the AESI of Ischemic Heart Disease (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	8 (3.8%)	4 (1.9%)	8 (2.1%)	3 (3.2%)
Grade 3 Incidence	3 (1.4%)	3 (1.4%)	4 (1.1%)	1 (1.1%)
Grade 4 Incidence	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Grade 5 Incidence	3 (1.4%)	0	1 (0.3%)	0
Serious	6 (2.8%)	4 (1.9%)	6 (1.6%)	2 (2.1%)
Treatment Discontinuation	3 (1.4%)	1 (0.5%)	2 (0.5%)	0
Dose Interruption	0	2 (0.9%)	3 (0.8%)	1 (1.1%)
Dose Reduction	0	1 (0.5%)	1 (0.3%)	0

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Cerebrovascular Disorders

Table 117. Characteristics of the AESI of Cerebrovascular Disorders (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	2 (0.9%)	6 (2.8%)	11 (2.9%)	0
Grade 3 Incidence	0	2 (0.9%)	3 (0.8%)	0
Grade 4 Incidence	0	0	2 (0.5%)	0
Grade 5 Incidence	1 (0.5%)	0	0	0
Serious	2 (0.9%)	2 (0.9%)	7 (1.9%)	0
Treatment Discontinuation	1 (0.5%)	0	0	0
Dose Interruption	0	2 (0.9%)	4 (1.1%)	0
Dose Reduction	0	0	0	0

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- Hepatotoxicity

Table 118. AESI of Hepatoxicity (grouped term) by Preferred Term; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: safety set	211	212
Hepatotoxicity	26 (12.3%)	25 (11.8%)
Aspartate aminotransferase increased	20 (9.5%)	11 (5.2%)
Alanine aminotransferase increased	22 (10.4%)	10 (4.7%)
Hyperbilirubinaemia	2 (0.9%)	7 (3.3%)
Gamma-glutamyl transferase increased	1 (0.5%)	2 (0.9%)
Hepatotoxicity	0	2 (0.9%)
Aspartate aminotransferase abnormal	0	1 (0.5%)
Hepatic cytolysis	0	1 (0.5%)
Hepatic failure	1 (0.5%)	1 (0.5%)
Hepatitis acute	0	1 (0.5%)

Key: AAP=abiraterone acetate plus prednisone, AESI=adverse event of special interest, MedDRA=Medical Dictionary of Regulatory Activities
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

Table 119. Characteristics of the AESI of Hepatotoxicity (grouped term)

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
Adverse Event Characteristic	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Incidence (All Grades)	26 (12%)	25 (12%)	39 (10%)	6 (6.3%)
Grade 3 Incidence	10 (4.7%)	3 (1.4%)	7 (1.9%)	1 (1.1%)
Grade 4 Incidence	0	1 (0.5%)	1 (0.3%)	0
Grade 5 Incidence	0	0	0	0
Serious	1 (0.5%)	2 (0.9%)	2 (0.5%)	0
Treatment Discontinuation	2 (0.9%)	1 (0.5%)	3 (0.8%)	0
Dose Interruption	8 (3.8%)	3 (1.4%)	7 (1.9%)	2 (2.1%)
Dose Reduction	6 (2.8%)	2 (0.9%)	4 (1.1%)	1 (1.1%)

Combined SAC Group includes MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE
Treatment discontinuation, dose interruption, and dose reduction due to any component of therapy

- AML/MDS

For the AESI of AML, no event of AML was reported for subjects treated with nira+AAP combination therapy, either in MAGNITUDE Cohort 1, the Combined SAC Group, or MAGNITUDE Cohort 3. However, there was 1 subject with an event of AML in the PBO+AAP arm of MAGNITUDE Cohort 1.

For the AESI of MDS, no subjects reported an event in any of the 3 groupings.

2.6.8.4. Laboratory findings

Haematology

The majority of patients had no haematologic test abnormalities during treatment (Grade 0: 51.9% - 100%) across both arms of the MAGNTUDE cohort 1 study and the supportive studies, with the exception of anaemia (Grade 0: 14.0% - 28.4%).

Table 120. Summary of Haematology Worst US NCI-CTCAE Toxicity Grade During Treatment; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

TEAE PT	Placebo + AAP (N=211)		Niraparib + AAP (N=212)	
	Grade 1-2 N (%)	Grade 3-4 N (%)	Grade 1-2 N (%)	Grade 3-4 N (%)
Anaemia	136 (64.5%)	15 (7.1%)	124 (58.5%)	57 (26.9%)
Lymphocyte Count Decreased	43 (20.4%)	21 (9.9%)	64 (30.2%)	38 (17.9%)
Neutrophil Count Decreased	27 (12.8%)	5 (2.4%)	45 (21.2%)	15 (7.1%)
Platelet Count Decreased	37 (17.5%)	4 (1.9%)	66 (31.1%)	15 (7.1%)
White Blood Cell Decreased	36 (17.1%)	2 (0.9%)	74 (34.9%)	10 (4.7%)

Key: AAP=abiraterone acetate plus prednisone; N=number; NCI-CTCAE=National Cancer Institute – Common Terminology Criteria for Adverse Events; PT=preferred term; TEAE=treatment-emergent adverse event

Table 121. Most Common Hematologic Laboratory Test Abnormalities (Grade 3 or 4) During Treatment

	MAGNITUDE Cohort 1		Combined SAC Group*	MAGNITUDE Cohort 3
	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Anemia				
Grade 3	7.1%	27%	29%	18%
Grade 4	0	0	0	0
Decreased Lymphocyte Count				
Grade 3	9.0%	17%	16%	14%
Grade 4	0.9%	1.4%	0.8%	1.1%
Decreased Neutrophil Count				
Grade 3	2.4%	5.7%	7.2%	3.2%
Grade 4	0	1.4%	1.9%	1.1%
Decreased Platelet Count				
Grade 3	1.9%	3.3%	5.0%	3.2%
Grade 4	0	3.8%	3.2%	2.1%
Decreased White Blood Cell				
Grade 3	0.9%	4.7%	5.3%	1.1%
Grade 4	0	0	0.3%	1.1%

Source: Mod5.3.5.3/ISS/TSFLAB02

Hematologic Laboratory Test Parameters with a Grade 3 occurrence >3% in any grouping or Grade 4 occurrence >1% in any grouping are included in Table 36.

Chemistry

The majority of patients had no chemistry laboratory abnormalities during treatment (Grade 0: 58.1% -93.6%) across both arms of the MAGNTUDE cohort 1 study and the supportive studies. Recorded test abnormalities were mostly Grade 1 or 2 across the studies and no major shifts (>10% of patients) in the CTCAE baseline values (grade 0 or 1 to grade 3 or 4) occurred for any chemistry laboratory abnormality.

Table 122. Summary of Chemistry and Haematology Worst US NCI-CTCAE Toxicity Grade (Grouped) During Treatment; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP Worst US NCI-CTCAE Toxicity Grade During Treatment				Niraparib + AAP Worst US NCI-CTCAE Toxicity Grade During Treatment			
	N	Grade >0	Grade 1 or 2	Grade 3 or 4	N	Grade >0	Grade 1 or 2	Grade 3 or 4
Analysis set: Safety	211				212			
Chemistry								
Alanine Aminotransferase Increased	210	48 (22.9%)	37 (17.6%)	11 (5.2%)	211	40 (19.0%)	38 (18.0%)	2 (0.9%)
Alkaline Phosphatase Increased	210	70 (33.3%)	68 (32.4%)	2 (1.0%)	211	88 (41.7%)	81 (38.4%)	7 (3.3%)
Aspartate Aminotransferase Increased	210	55 (26.2%)	50 (23.8%)	5 (2.4%)	211	49 (23.2%)	46 (21.8%)	3 (1.4%)
Blood Bilirubin Increased	210	19 (9.0%)	17 (8.1%)	2 (1.0%)	211	23 (10.9%)	23 (10.9%)	0
Creatinine Increased	210	36 (17.1%)	33 (15.7%)	3 (1.4%)	211	64 (30.3%)	63 (29.9%)	1 (0.5%)
Hyperkalemia	210	48 (22.9%)	42 (20.0%)	6 (2.9%)	211	56 (26.5%)	51 (24.2%)	5 (2.4%)
Hypoalbuminemia	210	19 (9.0%)	18 (8.6%)	1 (0.5%)	211	16 (7.6%)	15 (7.1%)	1 (0.5%)
Hypoglycemia	210	30 (14.3%)	29 (13.8%)	1 (0.5%)	211	14 (6.6%)	14 (6.6%)	0
Hypokalemia	210	38 (18.1%)	32 (15.2%)	6 (2.9%)	211	49 (23.2%)	40 (19.0%)	9 (4.3%)
Hematology								
Anemia	211	151 (71.6%)	136 (64.5%)	15 (7.1%)	212	181 (85.4%)	124 (58.5%)	57 (26.9%)
Hemoglobin Increased	211	0	0	0	212	2 (0.9%)	2 (0.9%)	0
Leukocytosis	211	0	0	0	212	0	0	0
Lymphocyte Count Decreased	211	64 (30.3%)	43 (20.4%)	21 (10.0%)	212	102 (48.1%)	64 (30.2%)	38 (17.9%)
Lymphocyte Count Increased	211	18 (8.5%)	14 (6.6%)	4 (1.9%)	212	15 (7.1%)	14 (6.6%)	1 (0.5%)
Neutrophil Count Decreased	211	32 (15.2%)	27 (12.8%)	5 (2.4%)	212	60 (28.3%)	45 (21.2%)	15 (7.1%)
Platelet Count Decreased	211	41 (19.4%)	37 (17.5%)	4 (1.9%)	212	81 (38.2%)	66 (31.1%)	15 (7.1%)
White Blood Cell Decreased	211	38 (18.0%)	36 (17.1%)	2 (0.9%)	212	84 (39.6%)	74 (34.9%)	10 (4.7%)

Key: AAP = abiraterone acetate plus prednisone, NCI-CTCAE = National Cancer Institute – Common Terminology Criteria for Adverse Events
Note: N is the number of subjects with at least 1 postbaseline assessment for the specific lab test within the time period.
[TSFLAB03_HRR.RTF] [JNJ-64091742\PCR3001\DBR_CSR\RE_CSR\PROD\TSFLAB03.SAS] 12NOV2021, 20:03

Table 123. Most Common Chemistry Laboratory Test Abnormalities (Grade 3 or 4) During Treatment

	MAGNITUDE Cohort 1		Combined SAC Group	MAGNITUDE Cohort 3
	PBO+AAP n=211	nira+AAP SAC n=212	nira+AAP SAC n=378	FDC+P n=95
Increased ALT				
Grade 3	5.2%	0.5%	0.8%	0
Grade 4	0	0.5%	0.3%	0
Increased ALP				
Grade 3	0.5%	3.3%	2.1%	0
Grade 4	0.5%	0	0	0
Hyperkalemia				
Grade 3	2.9%	1.4%	1.3%	1.1%
Grade 4	0	0.9%	1.1%	0
Hypokalemia				
Grade 3	2.9%	3.8%	4.2%	4.3%
Grade 4	0	0.5%	0.5%	2.1%

Source: Mod5.3.5.3/ISS/TSFLAB02
Chemistry Laboratory Test Parameters with a Grade 3 occurrence >3% in any grouping or Grade 4 occurrence >1% in any grouping are included in Table 37.

Hepatic function

No subjects met the criteria for Hy's Law. For further details, see the section on 'AESIs' above.

Vital signs and Physical Examination Findings

Vital signs were measured at baseline and regularly during treatment, according to the schedule noted in the protocol. Among the vital signs collected, only BP was noted as markedly abnormal.

In the nira+AAP group, there were 46 subjects (21.8%) with systolic BP of >160 mm Hg and with a >20 mm Hg increase from baseline (classified as Grade 3 by CTCAE criteria), however only 31 subjects (14.6%) were considered to have a clinically significant value for a TEAE of hypertension to be reported as Grade 3. Alternatively, in the PBO+AAP group, there were 31 subjects (14.8%) with systolic BP of >160 mm Hg and with a >20 mm Hg increase from baseline (classified as Grade 3 by CTCAE criteria), with 26 subjects (12.3%) considered clinically significant for a TEAE of hypertension to be reported as Grade 3. No Grade 4 or 5 hypertension events were reported.

Table 124. Markedly Abnormal Vital Signs during Treatment; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP	Niraparib + AAP
Analysis set: safety	211	212
Systolic blood pressure		
N (no. subjects with baseline and any postbaseline measurement)	210 (99.5%)	211 (99.5%)
<90 mm Hg and with >20 mm Hg decrease from baseline	1 (0.5%)	3 (1.4%)
>160 mm Hg and with >20 mm Hg increase from baseline	31 (14.8%)	46 (21.8%)
Diastolic blood pressure		
N (no. subjects with baseline and any postbaseline measurement)	210 (99.5%)	211 (99.5%)
<50 mm Hg and with >10 mm Hg decrease from baseline	2 (1.0%)	1 (0.5%)
>100 mm Hg and with >10 mm Hg increase from baseline	18 (8.6%)	21 (10.0%)

Key: AAP = abiraterone acetate plus prednisone.
Note: Percent for abnormal rows is calculated based on the total number subjects with baseline and any postbaseline measurement as denominator. Each subject is counted only once based on the max decrease or increase during treatment.

2.6.8.5. In vitro biomarker test for patient selection for safety

See clinical pharmacology section

2.6.8.6. Safety in special populations

Age

Age distribution in the different studies was comparable with only a slightly lower age distribution in the placebo + AAP arm of the MAGNITUDE cohort 1. In general, the incidence of AEs including Grade 3 and 4 AEs, SAEs and AEs leading to discontinuation of a study agent was higher in the age group > 75 years within the niraparib + AAP arm and placebo + AAP arm in the MAGNITUDE cohort 1 and across

the supportive studies (Combined SAC group and MAGNITUDE cohort 3) compared to the younger age groups. The safety profiles in the different age categories in the Combined SAC group were consistent with the safety profile in the niraparib + AAP arm of cohort 1.

Table 125. Overall Summary of Treatment-emergent Adverse Events by Age Group; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP			Niraparib + AAP		
	<65	≥ 65- <75	≥ 75	<65	≥ 65- <75	≥ 75
Analysis set: safety	62	100	49	61	88	63
Subjects with 1 or more:						
AEs	58 (93.5%)	92 (92.0%)	49 (100.0%)	61 (100.0%)	86 (97.7%)	63 (100.0%)
Related AEs [a]	34 (54.8%)	52 (52.0%)	30 (61.2%)	52 (85.2%)	62 (70.5%)	48 (76.2%)
Niraparib/Placebo related AEs	23 (37.1%)	40 (40.0%)	21 (42.9%)	47 (77.0%)	53 (60.2%)	46 (73.0%)
Abiraterone acetate related AEs	21 (33.9%)	40 (40.0%)	23 (46.9%)	33 (54.1%)	45 (51.1%)	32 (50.8%)
AEs leading to death [b]	2 (3.2%)	1 (1.0%)	4 (8.2%)	0	7 (8.0%)	5 (7.9%)
Serious AEs	9 (14.5%)	23 (23.0%)	20 (40.8%)	16 (26.2%)	29 (33.0%)	31 (49.2%)
Related serious AEs [a]	0	4 (4.0%)	2 (4.1%)	4 (6.6%)	7 (8.0%)	13 (20.6%)
Niraparib/Placebo related serious AEs	0	4 (4.0%)	1 (2.0%)	3 (4.9%)	7 (8.0%)	11 (17.5%)
Abiraterone acetate related serious AEs	0	1 (1.0%)	1 (2.0%)	1 (1.6%)	3 (3.4%)	6 (9.5%)
AEs leading to discontinuation of study agent [c]	1 (1.6%)	5 (5.0%)	7 (14.3%)	3 (4.9%)	7 (8.0%)	13 (20.6%)
AEs leading to discontinuation of Niraparib/Placebo	1 (1.6%)	3 (3.0%)	6 (12.2%)	3 (4.9%)	7 (8.0%)	13 (20.6%)
AEs leading to discontinuation of Abiraterone acetate	1 (1.6%)	5 (5.0%)	6 (12.2%)	3 (4.9%)	7 (8.0%)	9 (14.3%)
Grade 3 or 4 AEs	27 (43.5%)	48 (48.0%)	23 (46.9%)	38 (62.3%)	58 (65.9%)	46 (73.0%)
COVID-19 AEs	5 (8.1%)	3 (3.0%)	1 (2.0%)	3 (4.9%)	9 (10.2%)	2 (3.2%)
COVID-19 SAEs	3 (4.8%)	1 (1.0%)	1 (2.0%)	2 (3.3%)	6 (6.8%)	2 (3.2%)
COVID-19 non-serious AEs	3 (4.8%)	2 (2.0%)	0	2 (3.3%)	3 (3.4%)	0

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event
[a]An AE is categorized as related if assessed by the investigator as related to niraparib, abiraterone acetate or prednisone.
[b]AEs leading to death are based on AE outcome of Fatal.
[c]An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.

Race

Patients in the clinical studies were predominantly White (71-74%) across the studies with the second largest group being Asians (15%-17%). The category 'Others' represented 9.5%-12% of the patients.

Table 126. Overall Summary of Treatment-emergent Adverse Events by Race; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP			Niraparib + AAP		
	Asian	White	Other	Asian	White	Other
Analysis set: safety	41	153	17	29	160	23
Subjects with 1 or more:						
AEs	38 (92.7%)	144 (94.1%)	17 (100.0%)	28 (96.6%)	159 (99.4%)	23 (100.0%)
Related AEs [a]	23 (56.1%)	79 (51.6%)	14 (82.4%)	21 (72.4%)	125 (78.1%)	16 (69.6%)
Niraparib/Placebo related AEs	15 (36.6%)	59 (38.6%)	10 (58.8%)	21 (72.4%)	111 (69.4%)	14 (60.9%)
Abiraterone acetate related AEs	15 (36.6%)	57 (37.3%)	12 (70.6%)	12 (41.4%)	86 (53.8%)	12 (52.2%)
AEs leading to death [b]	1 (2.4%)	6 (3.9%)	0	1 (3.4%)	10 (6.3%)	1 (4.3%)
Serious AEs	13 (31.7%)	37 (24.2%)	2 (11.8%)	11 (37.9%)	60 (37.5%)	5 (21.7%)
Related serious AEs [a]	0	5 (3.3%)	1 (5.9%)	5 (17.2%)	18 (11.3%)	1 (4.3%)
Niraparib/Placebo related serious AEs	0	5 (3.3%)	0	4 (13.8%)	16 (10.0%)	1 (4.3%)
Abiraterone acetate related serious AEs	0	1 (0.7%)	1 (5.9%)	5 (17.2%)	5 (3.1%)	0
AEs leading to discontinuation of study agent [c]	3 (7.3%)	8 (5.2%)	2 (11.8%)	3 (10.3%)	15 (9.4%)	5 (21.7%)
AEs leading to discontinuation of Niraparib/Placebo	2 (4.9%)	6 (3.9%)	2 (11.8%)	3 (10.3%)	15 (9.4%)	5 (21.7%)
AEs leading to discontinuation of Abiraterone acetate	3 (7.3%)	7 (4.6%)	2 (11.8%)	3 (10.3%)	12 (7.5%)	4 (17.4%)
Grade 3 or 4 AEs	15 (36.6%)	77 (50.3%)	6 (35.3%)	20 (69.0%)	106 (66.3%)	16 (69.6%)
COVID-19 AEs	0	9 (5.9%)	0	0	12 (7.5%)	2 (8.7%)
COVID-19 SAEs	0	5 (3.3%)	0	0	9 (5.6%)	1 (4.3%)
COVID-19 non-serious AEs	0	5 (3.3%)	0	0	4 (2.5%)	1 (4.3%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event
[a]An AE is categorized as related if assessed by the investigator as related to niraparib, abiraterone acetate or prednisone.
[b]AEs leading to death are based on AE outcome of Fatal.
[c]An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.

Geographical Region

Table 127. Overall Summary of Treatment-emergent Adverse Events by Geographical Region; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP			Niraparib + AAP		
	Asia-PAC	Europe	North and South America	Asia-PAC	Europe	North and South America
Analysis set: safety	52	120	39	43	128	41
Subjects with 1 or more:						
AEs	49 (94.2%)	112 (93.3%)	38 (97.4%)	42 (97.7%)	128 (100.0%)	40 (97.6%)
Related AEs [a]	32 (61.5%)	57 (47.5%)	27 (69.2%)	35 (81.4%)	95 (74.2%)	32 (78.0%)
Niraparib/Placebo related AEs	20 (38.5%)	43 (35.8%)	21 (53.8%)	33 (76.7%)	83 (64.8%)	30 (73.2%)
Abiraterone acetate related AEs	22 (42.3%)	46 (38.3%)	16 (41.0%)	22 (51.2%)	62 (48.4%)	26 (63.4%)
AEs leading to death [b]	1 (1.9%)	6 (5.0%)	0	1 (2.3%)	9 (7.0%)	2 (4.9%)
Serious AEs	16 (30.8%)	30 (25.0%)	6 (15.4%)	15 (34.9%)	48 (37.5%)	13 (31.7%)
Related serious AEs [a]	0	5 (4.2%)	1 (2.6%)	6 (14.0%)	13 (10.2%)	5 (12.2%)
Niraparib/Placebo related serious AEs	0	4 (3.3%)	1 (2.6%)	5 (11.6%)	11 (8.6%)	5 (12.2%)
Abiraterone acetate related serious AEs	0	2 (1.7%)	0	5 (11.6%)	3 (2.3%)	2 (4.9%)
AEs leading to discontinuation of study agent [c]	3 (5.8%)	10 (8.3%)	0	3 (7.0%)	15 (11.7%)	5 (12.2%)
AEs leading to discontinuation of Niraparib/Placebo	2 (3.8%)	8 (6.7%)	0	3 (7.0%)	15 (11.7%)	5 (12.2%)
AEs leading to discontinuation of Abiraterone acetate	3 (5.8%)	9 (7.5%)	0	3 (7.0%)	13 (10.2%)	3 (7.3%)
Grade 3 or 4 AEs	21 (40.4%)	57 (47.5%)	20 (51.3%)	28 (65.1%)	87 (68.0%)	27 (65.9%)
COVID-19 AEs	0	8 (6.7%)	1 (2.6%)	0	11 (8.6%)	3 (7.3%)
COVID-19 SAEs	0	4 (3.3%)	1 (2.6%)	0	8 (6.3%)	2 (4.9%)
COVID-19 non-serious AEs	0	4 (3.3%)	1 (2.6%)	0	3 (2.3%)	2 (4.9%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event
[a]An AE is categorized as related if assessed by the investigator as related to niraparib, abiraterone acetate or prednisone.
[b]AEs leading to death are based on AE outcome of Fatal.
[c]An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.

ECOG Performance Status

Table 128. Overall Summary of Treatment-emergent Adverse Events by Baseline ECOG performance status; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP		Niraparib + AAP	
	0	1	0	1
Analysis set: safety	146	65	130	82
Subjects with 1 or more:				
AEs	138 (94.5%)	61 (93.8%)	128 (98.5%)	82 (100.0%)
Related AEs [a]	80 (54.8%)	36 (55.4%)	104 (80.0%)	58 (70.7%)
Niraparib/Placebo related AEs	52 (35.6%)	32 (49.2%)	92 (70.8%)	54 (65.9%)
Abiraterone acetate related AEs	57 (39.0%)	27 (41.5%)	69 (53.1%)	41 (50.0%)
AEs leading to death [b]	2 (1.4%)	5 (7.7%)	2 (1.5%)	10 (12.2%)
Serious AEs	32 (21.9%)	20 (30.8%)	40 (30.8%)	36 (43.9%)
Related serious AEs [a]	4 (2.7%)	2 (3.1%)	16 (12.3%)	8 (9.8%)
Niraparib/Placebo related serious AEs	4 (2.7%)	1 (1.5%)	14 (10.8%)	7 (8.5%)
Abiraterone acetate related serious AEs	1 (0.7%)	1 (1.5%)	7 (5.4%)	3 (3.7%)
AEs leading to discontinuation of study agent [c]	5 (3.4%)	8 (12.3%)	10 (7.7%)	13 (15.9%)
AEs leading to discontinuation of Niraparib/Placebo	4 (2.7%)	6 (9.2%)	10 (7.7%)	13 (15.9%)
AEs leading to discontinuation of Abiraterone acetate	5 (3.4%)	7 (10.8%)	8 (6.2%)	11 (13.4%)
Grade 3 or 4 AEs	63 (43.2%)	35 (53.8%)	82 (63.1%)	60 (73.2%)
COVID-19 AEs	5 (3.4%)	4 (6.2%)	6 (4.6%)	8 (9.8%)
COVID-19 SAEs	2 (1.4%)	3 (4.6%)	3 (2.3%)	7 (8.5%)
COVID-19 non-serious AEs	4 (2.7%)	1 (1.5%)	4 (3.1%)	1 (1.2%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event
[a]An AE is categorized as related if assessed by the investigator as related to niraparib, abiraterone acetate or prednisone.
[b]AEs leading to death are based on AE outcome of Fatal.
[c]An AE is counted as leading to discontinuation of study agent if it leads to withdrawal of niraparib, abiraterone acetate or prednisone.

Hepatic impairment

The assessment of treatment with niraparib + AAP in patients with hepatic impairment was based on PK studies which were conducted with the individual agents as part as their respective monotherapy program. No PK studies were conducted for the niraparib + AAP combination in this patient population. For further details on the assessment of clinical pharmacology, see section 2.6.2.

Renal impairment

No formal studies for niraparib or the niraparib + AAP combination (either as SAC or FDC) have been conducted in patients with renal impairment.

2.6.8.7. Safety related to drug-drug interactions and other interactions

No clinical trial evaluating drug interactions has been performed using nira+AAP. See PK/PD section.

2.6.8.8. Discontinuation due to adverse events

Discontinuation due to adverse events

Complete discontinuation of treatment due to TEAEs occurred in 19 patients in the niraparib + AAP arm (9%) and 8 patients in the placebo + AAP arm (3.8%) of MAGNITUDE Cohort 1.

Table 129. Treatment-emergent Adverse Events Leading to Discontinuation of Any Component of Nira/AA/P by System Organ Class and Preferred Term; Integrated Safety

	MAGNITUDE Cohort 1 (SAC)		Combined (SAC) MAGNITUDE Cohorts 1 and 2 + QUEST Combination 2 + BEDIVERE	MAGNITUDE Cohort 3 FDC
	Placebo + AAP	Niraparib + AAP	Niraparib + AAP	Niraparib + AAP
Analysis set: Integrated safety	211	212	378	95
Subjects with 1 or more AEs leading to discontinuation of any of Nira/AA/P	13 (6.2%)	23 (10.8%)	47 (12.4%)	9 (9.5%)
System organ class Preferred term				
Infections and infestations	1 (0.5%)	8 (3.8%)	10 (2.6%)	2 (2.1%)
COVID-19	0	4 (1.9%)	5 (1.3%)	0
COVID-19 pneumonia	0	2 (0.9%)	2 (0.5%)	0
Herpes zoster	0	1 (0.5%)	1 (0.3%)	0
Pneumonia	0	1 (0.5%)	2 (0.5%)	1 (1.1%)
Septic shock	0	0	0	1 (1.1%)
Suspected COVID-19	1 (0.5%)	0	0	0
Blood and lymphatic system disorders	1 (0.5%)	6 (2.8%)	12 (3.2%)	0
Anaemia	1 (0.5%)	5 (2.4%)	8 (2.1%)	0
Thrombocytopenia	0	1 (0.5%)	5 (1.3%)	0
Neutropenia	0	0	1 (0.3%)	0
Gastrointestinal disorders	0	4 (1.9%)	9 (2.4%)	3 (3.2%)
Vomiting	0	3 (1.4%)	7 (1.9%)	0
Nausea	0	2 (0.9%)	6 (1.6%)	0
Abdominal pain	0	1 (0.5%)	1 (0.3%)	1 (1.1%)
Ileus	0	0	0	1 (1.1%)
Stomatitis	0	0	0	1 (1.1%)
General disorders and administration site conditions	1 (0.5%)	4 (1.9%)	7 (1.9%)	0
Asthenia	0	3 (1.4%)	5 (1.3%)	0
Fatigue	0	1 (0.5%)	2 (0.5%)	0
General physical health deterioration	1 (0.5%)	0	0	0
Cardiac disorders	3 (1.4%)	3 (1.4%)	8 (2.1%)	0
Acute coronary syndrome	0	1 (0.5%)	1 (0.3%)	0
Atrial fibrillation	0	1 (0.5%)	2 (0.5%)	0
Cor pulmonale	0	1 (0.5%)	1 (0.3%)	0
Acute myocardial infarction	1 (0.5%)	0	0	0
Cardiac arrest	0	0	1 (0.3%)	0
Cardiac failure	0	0	2 (0.5%)	0
Cardiac failure congestive	0	0	1 (0.3%)	0
Coronary artery disease	1 (0.5%)	0	0	0
Myocardial infarction	1 (0.5%)	0	0	0
Myocardial ischaemia	0	0	1 (0.3%)	0
Psychiatric disorders	0	2 (0.9%)	2 (0.5%)	0
Anxiety	0	1 (0.5%)	1 (0.3%)	0
Completed suicide	0	1 (0.5%)	1 (0.3%)	0
Respiratory, thoracic and mediastinal disorders	0	2 (0.9%)	3 (0.8%)	1 (1.1%)
Dyspnoea	0	2 (0.9%)	3 (0.8%)	0
Respiratory failure	0	0	0	1 (1.1%)
Hepatobiliary disorders	1 (0.5%)	1 (0.5%)	1 (0.3%)	0
Hepatitis acute	0	1 (0.5%)	1 (0.3%)	0
Hyperbilirubinaemia	1 (0.5%)	0	0	0
Musculoskeletal and connective tissue disorders	2 (0.9%)	1 (0.5%)	1 (0.3%)	1 (1.1%)
Arthralgia	0	1 (0.5%)	1 (0.3%)	0
Back pain	1 (0.5%)	0	0	0
Musculoskeletal chest pain	1 (0.5%)	0	0	1 (1.1%)

Reproductive system and breast disorders	0	1 (0.5%)	1 (0.3%)	0
Pelvic pain	0	1 (0.5%)	1 (0.3%)	0
Endocrine disorders	0	0	0	1 (1.1%)
Adrenal insufficiency	0	0	0	1 (1.1%)
Injury, poisoning and procedural complications	0	0	1 (0.3%)	1 (1.1%)
Cardiac valve rupture	0	0	1 (0.3%)	0
Road traffic accident	0	0	0	1 (1.1%)
Investigations	3 (1.4%)	0	2 (0.5%)	0
Alanine aminotransferase increased	2 (0.9%)	0	0	0
Aspartate aminotransferase increased	2 (0.9%)	0	1 (0.3%)	0
Eastern Cooperative Oncology Group performance status worsened	1 (0.5%)	0	0	0
Gamma-glutamyltransferase increased	0	0	1 (0.3%)	0
Metabolism and nutrition disorders	0	0	0	3 (3.2%)
Decreased appetite	0	0	0	1 (1.1%)
Hypokalaemia	0	0	0	1 (1.1%)
Hyponatraemia	0	0	0	1 (1.1%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (0.9%)	0	0	0
Acute myeloid leukaemia	1 (0.5%)	0	0	0
Lung neoplasm malignant	1 (0.5%)	0	0	0
Nervous system disorders	1 (0.5%)	0	2 (0.5%)	0
Cerebral arteriosclerosis	1 (0.5%)	0	0	0
Cognitive disorder	0	0	1 (0.3%)	0
Dysgeusia	0	0	1 (0.3%)	0
Lethargy	0	0	1 (0.3%)	0
Renal and urinary disorders	1 (0.5%)	0	1 (0.3%)	0
Acute kidney injury	0	0	1 (0.3%)	0
Urinary retention	1 (0.5%)	0	0	0
Vascular disorders	1 (0.5%)	0	1 (0.3%)	2 (2.1%)
Circulatory collapse	1 (0.5%)	0	0	0
Hypertension	0	0	1 (0.3%)	1 (1.1%)
Hypovolaemic shock	0	0	0	1 (1.1%)

Key: AAP = abiraterone acetate plus prednisone, AE = adverse event, FDC=fixed-dose combination
Note: Subjects are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 24.0.

TEAEs leading to discontinuation of study agent in 2 or more subjects

Table 130. TEAEs Leading to Discontinuation of Study Agent reported in at least 2 Subjects; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP (N=211)			Niraparib + AAP (N=212)		
	Placebo	AA	Prednisone	Niraparib	AA	Prednisone
Subjects with ≥1 AE leading to D/C	10 (4.7%)	12 (5.7%)	11 (5.2%)	23 (10.8%)	19 (9.0%)	19 (9.0%)
TEAE PT						
COVID-19	0	0	0	4 (1.9%)	4 (1.9%)	4 (1.9%)
COVID-19 pneumonia	0	0	0	2 (0.9%)	2 (0.9%)	2 (0.9%)
Anaemia	1 (0.5%)	1 (0.5%)	1 (0.5%)	5 (2.4%)	2 (0.9%)	2 (0.9%)
Nausea	0	0	0	2 (0.9%)	2 (0.9%)	2 (0.9%)
Vomiting	0	0	0	3 (1.4%)	2 (0.9%)	2 (0.9%)
Asthenia	0	0	0	3 (1.4%)	2 (0.9%)	2 (0.9%)
Dyspnoea	0	0	0	2 (0.9%)	2 (0.9%)	2 (0.9%)
ALT increased	0	2 (0.9%)	1 (0.5%)	0	0	0
AST increased	0	2 (0.9%)	1 (0.5%)	0	0	0

Key: AA=abiraterone acetate; AAP=AA plus prednisone; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19=Coronavirus Disease 2019; D/C=discontinuation; N=number; PT=preferred term; TEAE=treatment-emergent AE

Adverse events leading to dose interruption

In MAGNITUDE Cohort 1, dose interruption of any study agent occurred more frequently in the niraparib/AAP arm compared with the placebo/AAP arm in the pivotal MAGNITUDE cohort 1 study (45.8% vs. 23.2%).

In MAGNITUDE Cohort 3, the most common TEAEs leading to dose interruption was anaemia in 14 patients (15%).

With nira+AAP treatment, the majority of patients (>90%) with dose interruptions due to the preferred term of anaemia was able to remain on treatment. In MAGNITUDE Cohort 1, anaemia caused dose interruption in 49 patients but only led to treatment discontinuation in 5 patients. (Table 131).

Table 131. TEAEs Leading to Dose Interruption of Study Agent reported in at least 5 Subjects; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP (N=211)			Niraparib + AAP (N=212)		
	Placebo	AA	Prednisone	Niraparib	AA	Prednisone
Subjects with ≥1 AE leading to dose interruption	48 (22.7%)	38 (18.0%)	28 (13.3%)	92 (43.4%)	63 (29.7%)	47 (22.2%)
TEAE PT						
Anaemia	7 (3.3%)	3 (1.4%)	3 (1.4%)	47 (22.2%)	15 (7.1%)	14 (6.6%)
Thrombocytopenia	4 (1.9%)	0	0	20 (9.4%)	1 (0.5%)	1 (0.5%)
Neutropenia	2 (0.9%)	0	0	14 (6.6%)	2 (0.9%)	2 (0.9%)
Fatigue	2 (0.9%)	2 (0.9%)	1 (0.5%)	7 (3.3%)	7 (3.3%)	4 (1.9%)
Asthenia	1 (0.5%)	1 (0.5%)	1 (0.5%)	5 (2.4%)	1 (0.5%)	1 (0.5%)
Vomiting	1 (0.5%)	0	0	6 (2.8%)	6 (2.8%)	6 (2.8%)
Nausea	1 (0.5%)	1 (0.5%)	0	4 (1.9%)	5 (2.4%)	3 (1.4%)
COVID-19	3 (1.4%)	3 (1.4%)	2 (0.9%)	6 (2.8%)	6 (2.8%)	5 (2.4%)
Dyspnoea	1 (0.5%)	1 (0.5%)	1 (0.5%)	5 (2.4%)	3 (1.4%)	1 (0.5%)
ALT increased	8 (3.8%)	7 (3.3%)	3 (1.4%)	1 (0.5%)	1 (0.5%)	1 (0.5%)
AST increased	5 (2.4%)	5 (2.4%)	2 (0.9%)	1 (0.5%)	2 (0.9%)	1 (0.5%)
Hypokalaemia	1 (0.5%)	1 (0.5%)	0	1 (0.5%)	6 (2.8%)	1 (0.5%)

Key: AA=abiraterone acetate; AAP=AA plus prednisone; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; COVID-19=Coronavirus disease 2019; N=number; PT=preferred term; TEAE=treatment-emergent AE

Adverse events leading to dose reduction

TEAEs leading to dose reduction of any component of combination therapy (niraparib/placebo, AA, or prednisone) occurred in 58 patients in the nira+AAP arm (27%) and 20 patients in the PBO+AAP arm (9.5%) in MAGNITUDE Cohort 1.

In the nira+AAP arm, anaemia caused dose reduction in 28 patients (13.2%) only for niraparib (without modification of AAP) and led to treatment discontinuation in 5 patients (2.4%).

Table 132. TEAEs Leading to Dose Reduction of Study Agent reported in at least 2 Subjects; Cohort 1 All HRR Safety Analysis Set (Study 64091742PCR3001)

	Placebo + AAP (N=211)			Niraparib + AAP (N=212)		
	Placebo	AA	Prednisone	Niraparib	AA	Prednisone
Subjects with ≥1 AE leading to dose reduction	7 (3.3%)	7 (3.3%)	12 (5.7%)	42 (19.8%)	6 (2.8%)	19 (9.0%)
TEAE PT						
Anaemia	1 (0.5%)	0	0	28 (13.2%)	0	0
Thrombocytopenia	2 (0.9%)	0	0	6 (2.8%)	0	0
Neutropenia	0	0	0	3 (1.4%)	0	0
Leukopenia	0	0	0	2 (0.9%)	0	0
Fatigue	0	0	0	4 (1.9%)	0	1 (0.5%)
Asthenia	1 (0.5%)	1 (0.5%)	0	2 (0.9%)	0	0
Blood creatinine increased	0	0	0	2 (0.9%)	0	0
ALT increased	2 (0.9%)	4 (1.9%)	0	1 (0.5%)	1 (0.5%)	0
AST increased	2 (0.9%)	3 (1.4%)	0	1 (0.5%)	0	0
Nausea	0	0	0	2 (0.9%)	0	0
Diabetes mellitus	0	0	2 (0.9%)	0	0	0
Type 2 diabetes mellitus	0	0	2 (0.9%)	0	0	0
Hyperglycaemia	0	0	1 (0.5%)	0	1 (0.5%)	3 (1.4%)
Contusion	0	0	1 (0.5%)	0	0	3 (1.4%)

Key: AA=abiraterone acetate; AAP=AA plus prednisone; AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; N=number; PT=preferred term; TEAE=treatment-emergent AE

2.6.9. Discussion on clinical safety

Patient exposure

At the DCO (8th October 2021), a higher proportion of patients remained on treatment in the niraparib arm of MAGNITUDE Cohort 1 compared with the placebo arm: 54.2% vs. 41.7% . The most frequently reported reason for treatment discontinuation in both arms was progressive disease (34.0% in the niraparib arm vs. 51.2% in the placebo arm). This suggests that the addition of niraparib has a positive impact in terms of decreasing the probability of experiencing progressive disease. However, it should be noted that a considerably higher proportion of patients in the niraparib arm discontinued the treatment due to AEs in comparison with the placebo arm (9.0% vs. 3.8%), which implies that the addition of niraparib, although apparently decreasing the percentage of patients suffering from progressive disease, it also significantly increases the toxicity of the combination.

The duration of study treatment (median) was slightly longer in the niraparib arm compared to the placebo arm: 13.8 months vs. 12.1 months. Only 16 patients (7.5%) received the study treatment for 24 months or longer. Considering that the proposed fixed-dose combination is intended for long term treatment until progression or unacceptable toxicity, the Applicant was requested to submit updated safety data from the MAGNITUDE study, with a longer follow up to clarify remaining uncertainties concerning unfavourable effects. The submitted safety data included 378 subjects, who received individual products, referred to as niraparib and AAP single-agent combination (nira+AAP SAC) and 95 subjects, who received niraparib/AA FDC tablets plus prednisone (FDC+P). Taking into account the available information on the SAC and the established safety profiles of the single agents, the submitted safety data for the FDC is considered acceptable.

Regarding baseline characteristics, overall, the demographic characteristics were balanced between the treatment arms, except for a slightly higher proportion of patients ≥ 75 years old (29.7% vs. 23.2%), ECOG PS of 1 and with visceral disease in the niraparib arm compared to the placebo arm.

Adverse events

Safety data supporting the current application are based on studies in a low number of patients, restricting the possibility to detect less common ADRs. Further, due to the overall short treatment duration, especially in the FDC cohort, long-term safety data are limited. This translates in uncertainties when characterising the safety profile of Akeega however these limitations are to a certain extent counterbalanced by the well-characterized safety profiles of the individual compounds (abiraterone and niraparib) which are comparable, in terms of ADRs, with the safety profile of Akeega. Of note, only two new ADRs have been identified in the present application (lymphophenia and pulmonary embolism), which is indicative of this consistency. The percentages experiencing an AE or AEs considered as related by the investigator in the MAGNITUDE Cohort 3 (FDC) were similar or lower than the percentages reported in the niraparib arm of MAGNITUDE Cohort 1, which is reassuring because it suggests that the administration of the FDC does not translate into a worse tolerability profile. However, the significantly shorter treatment exposure in Cohort 3, should be taken into account in this respect. The percentages of patients who reported causally-related AEs, SAEs and causally-related SAEs, and G3-4 AEs were considerably higher in the niraparib arm compared to the placebo arm. The difference between arms was around 10% in the case of SAEs, and around 20% in the case of causally-related AEs and G3-4 AEs.

Concerning treatment-related adverse events, no major changes were identified, between the two arms, regardless of causality assessment. The safety profile remained consistent with already known safety profile of the individual components of the FDC.

The higher frequency of Grade 3-4 TEAEs in the niraparib arm compared to the placebo arm (67% vs. 46.4%) in MAGNITUDE Cohort 1 was mainly due to higher incidences of TEAEs in the SOC 'Blood and lymphatic system disorders' (33% vs. 9.0%) and in particular anaemia (30% vs. 7.6%) and neutropenia (6.6% vs. 1.4%). Haematological adverse events, including anaemia and neutropenia, are well-known ADRs associated with niraparib and other PARP inhibitors. Similar findings were observed in the Combined SAC Group and MAGNITUDE Cohort 3.

There were 99.1% of patients in the niraparib arm vs. 94.3% in the placebo arm that reported 1 or more AEs occurring with frequency of at least 5%. AEs belonging to "Gastrointestinal disorders" SOC were the AEs most commonly reported in the niraparib arm, accounting for 59.0% in this arm, vs. 45.5% in the placebo arm. The differences were especially marked in the following PTs: constipation (30.7% in the niraparib arm vs. 13.7% in the placebo arm), nausea (23.6% vs. 13.7%) and vomiting (13.2% vs. 6.6%). AEs belonging to "Blood and lymphatic system disorders" were the second AEs most commonly reported in the niraparib arm, accounting for 56.1% in this arm, vs. 28% in the placebo arm. Of note, some of the differences between arms were considerably marked: anaemia was reported in 46.2% patients in the niraparib arm vs. 20.4% patients in the placebo arm, thrombocytopenia in 21.2% vs. 8.5% patients, neutropenia in 13.7% vs. 5.7% patients, leukopenia in 10.4% vs. 2.4% patients, and lymphopenia in 9.0% vs. 1.9% patients. Other common (≥20%) adverse events reported in the niraparib arm were hypertension (31.1% in the niraparib arm vs. 20.9% in the placebo arm) and fatigue (26.4% vs. 16.6%).

It should be noted that TEAEs in the SOC "Infections and infestations" were more frequent (39.6%) in the niraparib arm of (Cohort 1) than in the placebo arm (26.1%), which was also consistent with the higher incidence of grade 3-4 TEAEs (14.6% vs. 6.2%). Therefore, it seems that patients in the niraparib arm were more vulnerable to infections and had a more serious outcome than patients in the placebo group. While hematological toxicities associated with PARP inhibitors (in particular neutropenia and leukopenia) may increase the risk of infections and exacerbate disease progression, no clinical link between haematological events (neutropenia) and the higher incidence of infections, including with serious outcomes, in the niraparib arm of the MAGNITUDE study, was identified. However, scientific

research has established critical roles of the PARP enzyme family including PARP1, the main target of niraparib, in regulating innate and adaptive immune responses, in particular viral infections by multifaceted mechanisms. Consequently, a causative mechanistic link between niraparib and the increased risk of serious infections, which is not related to neutropenia or leukopenia events, could theoretically be plausible. Therefore, a warning has been included in section 4.4 of the SmPC, including mitigating measures concerning this risk.

Generally, common AEs experienced by mCRPC patient treated with niraparib and abiraterone were consistent with the known ADRs of niraparib and abiraterone monotherapies, as described in their respective SmPCs, and potential symptoms of the underlying disease. However, two new ADRs were identified: lymphophenia and pulmonary embolism.

Lymphopenia was included as an ADR due to the significantly higher frequency occurring in the niraparib arm compared with the placebo arm in MAGNITUDE Cohort 1 (9.0% vs. 1.9%). No concurrent event of infection was reported within 7 days.

Pulmonary embolism was reported with a higher frequency in the niraparib arm (4.7%) as compared with the placebo arm (0.9%) in MAGNITUDE Cohort 1. Pulmonary embolism occurred approximately 5 times more frequently in the niraparib arm of the MAGNITUDE cohort 1 study, which is further reflected in the higher incidence of serious cases of pulmonary embolism in the treatment arm compared with the placebo arm (1.9% vs. 0.5 %). Likewise, other forms of embolism were more frequent in the niraparib arm than the placebo arm; TEAEs: 4 patients (1.9%) vs 1 (0.5%); and SAEs: 1 patient (0.5%) vs. no patient. However, it does not seem that any other thromboembolic event in particular was reported with a marked higher frequency in the niraparib arm vs. the placebo arm. Since pulmonary embolism can constitute a serious to life-threatening condition if not discovered and treated timely, a warning has been included in section 4.4 of the SmPC.

Serious adverse events (SAEs)

In MAGNITUDE Cohort 1 SAEs were reported with more than 10% of difference between arms: 35.8% vs. 24.6%. In the context of an aged population (median age: 69.0) this increase is not negligible and highlights the fact that the addition of niraparib implies a considerable worse toxicity profile.

In MAGNITUDE Cohort 1, the higher incidence of serious TEAEs in the niraparib arm compared with the placebo arm was mainly driven by the SOC "Infections and infestations" (11.3% in the niraparib arm vs. 6.6% in the placebo arm), "Blood and lymphatic systems disorders" (8% vs. 1.9%) and "Cardiac disorders" (4.7% vs. 3.8%). The most frequently reported SAE in the niraparib arm was anaemia (5.7% vs. 0.9% in the placebo arm) and pneumonia (3.3% vs. 1.9% in the placebo arm). In the placebo arm only two SAEs occurred >1% (pneumonia: 1.9% and myocardial infarction: 1.4%).

The higher incidence of pulmonary embolism in the MAGNITUDE cohort 3 (3.2%) compared to MAGNITUDE Cohort 1 (1.9%) and the Combined SAC Pool (2.1%) is noted.

Deaths

Deaths during treatment were reported with a similar frequency in both arms (9.0%). However, there were more subjects who had TEAEs leading to death in the niraparib arm than in the placebo arm: 5.7% vs. 3.3%. Of those deaths, only one ,in the niraparib arm, was considered as related to the study agent,. Of note, there were no on-treatment deaths due to "unknown cause" in any arm.

In terms of SOCs, no particular trend was observed. Importantly, deaths belonging to "cardiac disorders" SOC were balanced between the two arms. However, it should be noted that an imbalance in the "infections and infestations" SOC is observed (3.3% vs. 0.9%), mainly driven by COVID-19 deaths. The trend towards a higher rate of infections with severe outcome (including deaths) was further confirmed by the updated safety data provided by the Applicant during the assessment, where

8 additional FU months were provided. Of note, during the period of time between October 2021 and June 2022 there were 6 additional deaths reported in this SOC in the niraparib arm, vs. no additional death reported in the placebo arm; and 4 of those additional deaths were due to "COVID-19" or "COVID-19 pneumonia". As such, it is clear that there is an imbalance between the two arms, which has been further confirmed after a longer follow-up (6.1% vs. 0.9%). A warning has been included in in section 4.4.

Additionally, in the niraparib arm there was a death due to completed suicide which suggested a potential link to niraparib, also taking into account that "depression" is listed in section 4.8 of the SmPC of niraparib. However, after reviewing additional evidence provided by the Applicant, it has been considered very complicated to isolate niraparib's contribution to the occurrence of suicidal behaviours / thoughts, considering the emotional impact that metastatic cancer can have on patients' mental well-being.

A death caused by pulmonary embolism (accompanied by acute heart failure and acute pulmonary failure) occurred in the Combine SAC Pool, which was not categorised as related to the study treatment by the investigator. After further assessment, it was agreed that there were too many confounding factors to draw any conclusion on the causal role of niraparib. Its potential role or at least partial contribution could not be fully discarded.

Adverse Events of Special Interest (AESI)

AESIs were more common with combination therapy compared to the monotherapies, occurring in 80% of the niraparib+abiraterone arm and 58% of the placebo+abiraterone arm in MAGNITUDE Cohort 1, 79% of the Combined SAC Group, and 60% of MAGNITUDE Cohort 3.

Overall, the AESIs are sufficiently addressed in the section "Description of selected adverse reactions" in 4.8 of the SmPC.

Cerebrovascular events were initially reported with a higher frequency in the niraparib arm than in the placebo arm (2.8% vs. 0.9%). With the safety update, these events were reported in 3.3% patients in the niraparib arm vs. 1.9% in the placebo arm. 2 out of 7 incidences of cerebrovascular events in the niraparib arm were considered serious, however not related to the study drug. The remaining 5 incidences of cerebrovascular events were considered non-serious, and all except one were assessed to be not related.

Despite some differences, the safety profile of BRCA and Non-BRCA subgroups was overall comparable.

Discontinuation due to AEs

As expected, treatment discontinuations were higher in the niraparib+abiraterone arm.

Laboratory findings

Regarding haematology laboratory abnormalities during treatment, all parameters (including G1-2 and G3-4 events) were significantly increased in the niraparib arm compared with the placebo arm. Anaemia was the most commonly reported G3-abnormality in the niraparib arm.

Chemistry laboratory abnormalities that occurred during treatment were mostly Grade 1 or 2. It is noted that grade 3 increased ALT was markedly more frequent in the placebo arm (5.2%) than in the niraparib arm (0.5%). In general, there was a higher frequency of the grade 3 or 4 hepatotoxicity laboratory findings ("ALT increased" and "AST increased") in the placebo than in the niraparib arm. Regarding these data, the Applicant confirmed that no additional toxicity was observed with the combination of nira+AAP compared to placebo+AAP and found the difference to be coincidental.

Safety in special populations

Concerning age, no significant differences were observed among subgroups. As expected, the percentage of SAEs and AEs leading to death increases in both arms as patients are older. It is noted that the number of patients especially in the higher age groups are low, which makes the results uncertain.

Regarding race and geographical region no conclusion could be drawn due to the difference in the size of subgroups.

Regarding hepatic impairment, no PK studies were conducted for the niraparib+abiraterone combination in patient with moderate and severe hepatic impairment. Based on the SmPC of the mono-component Niraparib (Zejula) and Abiraterone (Zytiga), in line with the Guideline On Summary Of Product Characteristics (SmPC) Rev.2, a contraindication in patients with severe hepatic impairment is reflected in the SmPC of Akeega.

Updated safety data

Updated safety data have been provided for Cohort 1, with 8.2 months of additional follow-up (median treatment duration 17.9 months in the nira+AAP arm and 15.2 months in the placebo+AAP arm). Overall, the updated safety data are in line with the data already provided, although frequencies were overall higher than previously reported and some increased considerably in the niraparib arm (AEs leading to death, SAEs, AEs leading to discontinuation of study agent, G3-4 AEs, COVID AEs and COVID SAEs). An increase in the incidence of infections and infestations was observed (24.1% in the niraparib arm and 15.2% in the placebo arm in IA2, compared with 17.5% in the niraparib arm and 10.0% in the placebo arm). This difference was mainly driven by COVID cases.

The Applicant submitted updated safety data from Cohort 3 of the MAGNITUDE study with a median duration of the study treatment of 17.5 months. Data submitted were consistent with the data previously reported for this cohort with overall only a very slight increase in overall AEs, grade 3 and 4 AEs, SAEs and AESIs compared to the previous CCO (IA2) and in line with the reported data for Cohort 1. The Applicant is recommended to provide the final safety data from MAGNITUDE Cohort 3 post-approval **(PAM-REC).**

2.6.10. Conclusions on the clinical safety

The addition of niraparib to abiraterone translates into a worse tolerability profile, with an increase in treatment-related AEs, SAEs, Aes of grade 3-4 and Aes leading to treatment discontinuation.

Overall, the safety profile of the combination appears quite consistent with the already known safety profile of the mono-components. Of note, several of the well-known toxicities of both agents overlap, while some haematological events, such as anaemia, considerably exacerbated. However, overall, it seems that G4 events / SAEs due to this overlapping toxicity are not frequent, and that they can be properly managed by means of dose modifications or interruptions. Two new ADRs have been identified for the combination: pulmonary embolism and lymphopenia.

In terms of deaths no particularly worrisome trend is observed, apart from the imbalance of COVID-related deaths for which a warning is included in section 4.4 of the SmPC. The combination of niraparib and abiraterone/prednisone is associated with a worsening of the toxicity profile of abiraterone/prednisone alone, although it seems to be acceptable and manageable.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 133: Summary of Safety Concerns

Important Identified Risks	Severe hypertension
Important Potential Risks	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) Second primary malignancies (SPM) other than MDS and AML
Missing Information	Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV heart disease or cardiac ejection fraction measurement of <50%

2.7.2. Pharmacovigilance plan

Table 134: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	Summary of Objectives	Safety Concerns Addressed	Milestones	Due Dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA Planned	• Primary: To estimate the incidence rate of SPM, including MDS/AML, in patients with mCRPC treated with AKEEGA. • Secondary: To evaluate the distribution of SPM/MDS/AML events across different risk factors such as age, prior chemotherapy, and other relevant factors.	Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML) Second primary malignancies (SPM) other than MDS and AML	Feasibility	Within 3 months of CHMP opinion
			Draft protocol	Within 6 months of CHMP opinion
			Interim reports	Provided annually
			Final report of study results	5 years following study initiation

2.7.3. Risk minimisation measures

Table 135: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Important Identified Risks		
Severe hypertension	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Recommendations to adequately control pre-existing hypertension before starting AKEEGA treatment, to monitor BP during treatment in accordance with a monitoring schedule, and to correct and control hypertension are provided in SmPC Sections 4.2, 4.4, and 4.8, and PL Section 2. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • An instruction to permanently discontinue AKEEGA and to institute appropriate medical management in patients developing PRES is provided in SmPC Section 4.4. • Patients who experience a sudden increase in BP, which may be a medical emergency that could lead to organ damage or can be life-threatening, should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None
Important Potential Risks		

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML)	Routine risk minimization measures: • SmPC Section 4.4 • PL Section 2 • Instructions to refer the patient to a hematologist for further evaluation in case of suspected MDS/AML or prolonged hematological toxicity that has not resolved with treatment interruption or dose reduction, to permanently discontinue AKEEGA treatment if MDS or AML is confirmed, and to treat the patient appropriately are provided in SmPC Section 4.4 and PL Section 2. • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA (final report of study results: 5 years following study initiation)
Second primary malignancies (SPM) other than MDS and AML	Routine risk minimization measures: • Legal status Additional risk minimization measures: • None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA (final report of study results: 5 years following study initiation)
Missing Information		
Use in patients with cardiovascular disease as evidenced by myocardial infarction, or arterial and venous thrombotic events in the past 6 months, severe or unstable angina, or NYHA Class III or IV	Routine risk minimization measures: • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4 • Advice to use AKEEGA with caution in patients with a history	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • None

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
heart disease or cardiac ejection fraction measurement of <50%	of cardiovascular disease is provided in SmPC Section 4.4. • A recommendation to optimize cardiac function and treatment for cardiac risk factors before starting treatment with AKEEGA is provided in SmPC Section 4.4 and PL Section 2. • A recommendation to monitor patients during treatment for signs and symptoms of cardiac dysfunction in accordance with a monitoring schedule and to correct abnormalities is provided in SmPC Section 4.4. • An instruction for treatment interruption and management of patients developing Grade ≥3 adverse reactions is provided in SmPC Section 4.2. • A recommendation to consider treatment discontinuation in case of a clinically significant decrease in cardiac function is provided in SmPC Section 4.4.	
	• Patients who experience muscle weakness, muscle twitches, or a pounding heart beat (palpitations) should stop taking AKEEGA and seek medical attention immediately, as described in PL Section 4. • Legal status Additional risk minimization measures: • None	

2.7.4. Conclusion

The CHMP considers that the risk management plan version 1.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the IBD to determine the forthcoming Data Lock Points. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request an alignment of the PSUR cycle with the international birth date (IBD). The IBD is not determined yet**.**

2.9. Product information

2.9.1. User consultation

A full user consultation has been performed on the Akeega 100mg/500 mg film-coated tablets patient leaflet. Three rounds of testing have been performed. Based on the results from round 2, amendments to the package leaflet to improve readability of one of the key safety messages was implemented. These amendments were tested in round 3, meeting the requirements set.

A bridging report was submitted for the 50mg/500mg patient leaflet. Overall, the user consultation presented by the Applicant met the requirements for user testing and is considered acceptable

3. Benefit-Risk Balance

3.1. Therapeutic Context

The finally approved indication for the fixed-dose combination (FDC) of niraparib plus abiraterone acetate is the following:

"Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated."

Disease or condition

Worldwide, prostate cancer is the second most common cancer and the fifth leading cause of cancer death in men (IARC 2020). In Europe, prostate cancer is the most common cancer in men, representing 20.2% of all cancers in men and 10% of cancer deaths in 2020.

Patients diagnosed at an early stage are amenable to curative therapy, however advanced stages are life-threatening. For patients diagnosed with metastatic disease, the 5-year survival rate is 30% (American Cancer Society 2021, Siegel 2021).

3.1.1. Available therapies and unmet medical need

Treatment options for patients with mCRPC include abiraterone acetate (with prednisone or prednisolone) and enzalutamide for chemotherapy naïve patients who are asymptomatic or mildly symptomatic and in whom chemotherapy is not yet clinically indicated (ESMO 2020; NCCN 2022). For symptomatic patients or patients with signs of rapid progression or visceral metastases despite lack of symptoms, initial use of docetaxel may be preferred. The radionuclide radium-223 may be used in patients with bone-predominant symptomatic metastatic CRPC. In the post-docetaxel setting, cabazitaxel is also a treatment option, as well as abiraterone and enzalutamide.

In patients with bone metastasis, use of bisphosphonate or denosumab is recommended to prevent skeletal-related events.

Patients with HRR gene alterations who have not received therapy for mCRPC (first line treatment) and are currently managed in the same manner as other patients with mCRPC who do not harbour an HRR alteration. Of note, olaparib, a PARPi, is currently approved in the EU in the second line setting (i.e., following prior therapy with new hormonal agents) in patients with BRCA1/2 mutations and in combination with abiraterone and prednisone/prednisolone for the treatment of patients with mCRPC in whom chemotherapy is not clinically indicated.

3.1.2. Main clinical studies

The evidence in support of this application is based on the results of the **Study 64091742PRC3001 (MAGNITUDE)**. This is a randomized, double-blind, placebo-controlled, multicenter study of niraparib in combination with AA and prednisone daily (nira+AAP) compared with placebo plus AAP (pbo+AAP) daily in subjects with mCRPC who had not received prior systemic therapy in the mCRPC setting.

The study consists of three cohorts. Data presented below correspond to the 225 **patients with BRCA1/2 mutations** included in **Cohort 1**, who were randomised (1:1) to receive either nira+AAP (n=113) or pbo+AAP (n=112). Cohort 3 (n=95), open-label, provides evidence on the efficacy and safety of the fixed-dose combination (FDC).

3.2. Favourable effects

In the BRCA subgroup, the primary endpoint rPFS (BICR) showed a statistically significant effect favouring nira+AAP over pbo+AAP (**HR 0.533; 95% CI: 0.361, 0.789**). Median rPFS was 16.56 months in the nira+AAP arm and 10.87 months in the pbo+AAP arm.

Secondary endpoints TCC and TSP also favoured the nira+AAP arm, with a HR of 0.558(95% CI: 0.346,0.900) and 0.544 (95% CI: 0.347, 0.853), respectively. For what concern OS, no statistically significant differences were observed between treatment arms for OS in the BRCA subgroup (HR 0.961; 95% CI: 0.565, 1.633) at the 1IA but a trend in favour of the nira+AAP was observed at 2IA (~42% maturity) although statistical significance was not reached.

In Cohort 3 (FDC), which included a proportion of BRCA mutations were comparable in Cohort 1 (approx. 53%) and Cohort 3 (approx. 55%), the event-free rates for rPFS by BICR and OS at 1 year were comparable to those obtained for Cohort 1. 'The

With regards to the relevance of the FDC formulation, bioequivalence of the regular strength (niraparib 100 mg/abiraterone acetate 500 mg) to single agent combination has been adequately demonstrated.

3.3. Uncertainties and limitations about favourable effects

At the time of the DCO for the primary analysis OS data were immature (25.9% events in the nira+AAP arm and 28.0% in the pbo+AAP arm) and no statistically significant differences were observed between treatment arms in the BRCA subgroup (HR 0.961; 95% CI: 0.565, 1.633). Updated data, based on the 2IA for OS (~42% maturity) showed a trend in favour of the nira+AAP, although statistical significance was not reached and uncertainties remain on the long term efficacy. To further evaluate the efficacy of Akeega, the MAH should submit the final clinical study report, including the final analysis of overall survival results and other long-term endpoints from the MAGNITUDE study (PAES).

For what concern the biomarker assessment, the description of primary endpoint and relevant secondary endpoints according to central biomarker analytic method (tissue vs ctDNA), including K-M plots, has been provided. Trends in primary and secondary endpoints are considered comparable in both biomarker methods (tissue vs ctDNA) to overall findings, nevertheless the clinical validity of ctDNA test of will be determined when the survival data are mature. According to the protocol, exploratory biomarker assays may be performed (where allowed by local regulations) to better define changes in tumour status over time. Results of these exploratory analyses should be provided once available (**REC)**.

For what concern the results of key efficacy endpoints provided for Cohort 3 of Magnitude study (FDC), at the time of the DCO, with a median follow-up of 5.5 months, data were immature with high censoring. To address this uncertainty the Applicant is recommended to submit the efficacy data (i.e., rPFS by BICR, TSP, TCC and OS) post-approval **(REC)**.

3.4. Unfavourable effects

Overall, the safety profile of the combination appears quite consistent with the already known safety profile of the mono-components. Of note, several of the well-known toxicities of both agents overlap, leading to an increased frequency of some AEs, especially haematological toxicities and hypertension: anaemia was reported in 46.2% patients vs. 20.4% patients, thrombocytopenia in 21.2% vs. 8.5% patients, neutropenia in 13.7% vs. 5.7% patients, leukopenia in 10.4% vs. 2.4% patients, lymphopenia in 9.0% vs. 1.9% patients, and hypertension in 31.1% vs. 20.9% patients. However, overall it seems that G4 events / SAEs due to this overlapping toxicity are not frequent, and that they can be properly managed by means of dose modifications or interruptions.

Two new ADRs were identified for the combination treatment in the MAGNITUDE study (niraparib vs placebo-arm): lymphopenia (9.0% vs 1.9%)) and pulmonary embolism (4.7% vs 0.9%)). Pulmonary embolism has also been previously reported for other PARP inhibitors.

The percentages of patients who reported causally-related AEs, SAEs and causally-related SAEs, and G3-4 AEs were markedly higher in the niraparib arm than in the placebo arm.

The incidence of Grade 3-4 AEs was of 67% in the niraparib arm and 46.4% in the placebo arm. Anaemia (30% vs. 7.6%) and hypertension (15% vs. 12%) were the most commonly reported in the niraparib arm (≥10%). SAEs were reported 36% in the niraparib arm vs. 25% in the placebo arm. By PT, the most frequently reported SAE in the niraparib arm was anaemia (5.7% vs. 0.9%), followed by pneumonia (3.3% vs. 1.9%) and COVID-19 (4.72% vs. 1.4%; including COVID-19 pneumonia).

Regarding deaths, treatment emergent adverse events leading to death occurred in 12 (5.7%) patients in the niraparib arm and 7 (3.3%) patients in the placebo arm. Of note, an imbalance in the "infections and infestations" SOC is observed (3.3% vs. 0.9%), mainly driven by COVID-19 deaths.

A higher percentage of patients in the niraparib arm had 1 or more AEs leading to discontinuation of any component of the combination: 10.8% vs. 6.2%. The most frequently reported SOC in the niraparib arm was "Infections and infestations" (3.8%), mainly driven by "COVID-19" and "COVID-19 pneumonia". Of note, "anaemia" was the reason for discontinuation of 2.4% of patients in the niraparib arm vs. 0.5% in the placebo arm.

TEAEs leading to dose reduction and interruption of any study treatment (niraparib, placebo, abiraterone or prednisone/prednisolone), were more frequent in the niraparib arm than in the placebo arm of MAGNITUDE cohort 1 (27.4% vs. 9.5%; 45.8% vs. 23.2%, respectively), driven mainly by haematologic events with anaemia accounting for dose interruptions in 49 patients (23%) and for dose reductions in 28 patients (13%).

3.5. Uncertainties and limitations about unfavourable effects

Uncertainties about unfavourable effects remain for the FDC treatment due to the premature nature of the safety data set in the MAGNITUDE FDC cohort 3. Updated safety data are expected to be provided post-approval (REC).

The pharmacokinetic properties of niraparib and abiraterone as a fixed-dose combination have been characterised using several clinical studies in healthy subjects and cancer patients. Several issues were identified regarding the demonstration of bioequivalence for the LS-FDC and some uncertainties remain regarding the potential higher exposure of abiraterone with the LS-FDC. This potential higher exposure is adequately communicated in the SmPC.

3.6. Effects Table

Table 136. ***Effects Table for Akeega in the 1st line setting of mCRPC – Study MAGNITUDE (data cut-off for primary endpoint: 8 October 2021; data cut-off for key secondary endpoints 17 June 2022)***

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Primary endpoint (Cohort 1 BRCA subgroup; n=225))						
rPFS	Radiographic progression free survival. BICR assessment					
			Akeega	**Placebo**		
		Median, months (95% CI)	16.56 (13.86, NE)	10.87 (8.31, 13.80)		Results based on the 1IA
		HR[b]	0.533 (95%CI: 0.361,0.789); P[a]= 0.0014			
Key secondary endpoints (Cohort 1 – BRCA subgroup)						

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
TPS	Time-to-symptomatic progression	Median, months (95% CI)	NE (NE, NE)	23.6 (17.9, 30.6)		
		HR[b]	0.544 (95%CI: 0.347, 0.853); P[a] =0.0071		Statistical significance not reached (pre-specified p=0.012)	
OS	Overall survival	HR[b]	0.881 (0.582, 1.335		p[c]= 0.5505	
Unfavourable Effects						
AEs of Grade⩾3	Adverse events of CTCAE Grade ≥3	%	67.0	46.4		Results based on Cohort 1 (CSR).
SAEs	Serious adverse events	%	35.8	24.6		
Deaths	Adverse events leading to death	%	5.7	3.3		
AEs leading to discontinuation	Adverse events leading to discontinuation of study treatment	%	10.8	6.2		

Abbreviations: CI=confidence interval; HR=hazard ratio; NE=not estimable

Notes:

[a] p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no) and prior AAP use (yes versus no).

[b] Hazard ratio is from stratified proportional hazards model. Hazard ratio <1 favours niraparib + AAP treatment.

[c] p-value is from a log-rank test stratified by stratification factors: past taxane-based chemotherapy exposure (yes versus no), prior AAP use (yes versus no), and gene alteration group (BRCA1 or BRCA2 versus all other HRR).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

In the MAGNITUDE study the combination of niraparib + AAP demonstrated a statistically significant improvement in rPFS (BICR) compared with AAP alone in patients with mCRPC with BRCA 1/BRCA 2 mutations. A trend in favour of the experimental arm was also observed in the key secondary endpoints of TCC and TSP, although statistical significance was only reached for TSP. Sensitivity analyses were overall consistent with the primary analysis.

Even if OS data were still immature no differences were observed between treatment arms at the 1IA and a trend in favour of the nira+AAP was observed in the updated OS data submitted. To further characterize the efficacy of niraparib in combination with abiraterone acetate, the Applicant will provide the final clinical study report, including the final analysis of overall survival results and other long-term endpoints from the MAGNITUDE study by 1 Q of 2024 (**see Annex II**).

The submitted efficacy and safety data for the FDC (MAGNITUDE cohort 3) showed results in line with Cohort 1, however, updated efficacy and safety data are recommended to be submitted post-approval **(REC).**

From a safety point of view, the safety profile of the combination appears consistent with the already known safety profile of the mono-components nevertheless the addition of niraparib to abiraterone translates into a worse tolerability profile, with an increase in treatment-related AEs, SAEs, AEs of grade 3-4 and AEs leading to treatment discontinuation and overlapping of toxicities. Two new ADRs have been identified and included in the SmPC (pulmonary embolism and lymphopenia).

3.7.2. Balance of benefits and risks

Niraparib + abiraterone has demonstrated a statistically significant and clinically relevant improvement in rPFS in patients with mCRPC and *BRCA1/2 mutations* supported by secondary endpoints. Even though there are currently uncertainties on the magnitude of the benefit in terms of OS, the results are considered clinically relevant and sufficient to conclude on clinical benefit in the intended treatment setting.

The safety profile of niraparib plus abiraterone is well characterize and is consistent with the safety profile of the mono-components except for two new ADRs identified and included in the SmPC. It can be concluded that the benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

Establishing the benefit of the combination in HRR subgroups is challenging, due to the small sample that leads to wide CIs. Although data are still immature, a detrimental effect in OS cannot be ruled out in the non-BRCA patients. Therefore, the indication has been restricted to the population with BRCA alterations, in which a clear benefit is established.

3.8. Conclusions

The overall benefit /risk balance of Akeega with prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations in whom chemotherapy is not clinically indicated is positive.

The following measures are considered necessary to address issues related to efficacy:

In order to further characterise the efficacy of Akeega to be used in combination with prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated, the MAH should submit the final overall survival data and other long-term endpoints from the MAGNITUDE study.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus decision that the benefit-risk balance of AKEEGA is favourable in the following indication:

Akeega is indicated with prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC) and BRCA 1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated.

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Post authorisation efficacy study (PAES): In order to further characterise the efficacy of Akeega to be used in combination with prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer (mCRPC) and BRCA1/2 mutations (germline and/or somatic) in whom chemotherapy is not clinically indicated, the MAH should submit the final overall survival data and other long-term endpoints from the MAGNITUDE study.	Q1 2024