10 November 2022
EMA/941572/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lynparza

International non-proprietary name: olaparib

Procedure No. EMEA/H/C/003726/II/0053

Note

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

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List of abbreviations

Abbreviation	Explanation
ADR	Adverse drug reaction
AE(s)	Adverse event(s)
AML	Acute myeloid leukaemia
AQA	Analgesic Quantification Algorithm
ATM	Ataxia telangiectasia mutated
ATR	Ataxia telangiectasia and Rad3-related protein
AUC	Area under plasma concentration-time curve
AUCss	Area under plasma concentration-time curve during any dosing interval at steady state
BARD1	BRCA1 associated ring domain protein
bd	Blood pressure Twice daily
BICR	Blinded independent central review
BoR	Best overall response
BPI-SF	Brief Pain Inventory Short Form
BRCA	Breast cancer susceptibility gene (in accordance with scientific convention, gene and mutation is italicised whereas protein is not italicised)
BRACAnalysis CDx®	The test consists of gene sequencing and large rearrangement analysis of the *BRCA1* and *BRCA2* genes performed by Myriad Genetics, Inc in their Quality Systems Regulation (QSR) facility
BRCAm	*gBRCA* or *sBRCA* mutated
BRCAwt/VUS	*gBRCA* and *sBRCA* wild type/variant of uncertain significance
BRIP1	BRCA1 interacting protein C-terminal helicase 1
BTD	Breakthrough Therapy Designation
CDK12	Cyclin-dependent kinase 12
CDx	Companion diagnostic
CHEK1	Checkpoint kinase 1
CHEK2	Checkpoint kinase 2
CHMP	Committee for Medicinal Products for Human Use, formerly known as the Committee for Proprietary Medicinal Products (CPMP)
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CrCL	Creatinine clearance
CR	Complete response
CRF	Case report form
CRPC	Castration-resistant prostate cancer
CSR	Clinical study report

CTA	Clinical trial assay
CTC	Circulating tumour cell(s)
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Common technical document
ctDNA	Circulating tumour DNA
CYP	Cytochrome P450
dAUC	Daily AUC
DCO	Data cut-off
DDI	Drug-drug interaction
DDR	DNA damage response
DHPC	Direct Healthcare Professional Communication
DoR	Duration of Response
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EFR	Evaluable for response
EMA	European Medicines Agency
ePRO	Electronic patient reported outcome
EU	European Union
F1CDx	FoundationOne® CDx
FACT	Functional Assessment of Cancer Therapy
FACT-G	Functional Assessment of Cancer Therapy - General
FACT-P	Functional Assessment of Cancer Therapy - Prostate Cancer
FANCL	FA complementation group L
FAPSI-6	FACT Advanced Prostate Symptom Index 6
FAS	Full Analysis Set
FDA	Food and Drug Administration
FIGO	Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics)
FMI	Foundation Medicine Inc.
FMI CLIA HRR CTA	Foundation Medicine Inc CLIA Homologous Recombination Repair Clinical Trial assay. The test uses DNA extracted from formalin-fixed, paraffin-embedded tumour samples and next generation sequencing to detect alterations in a total of 324 genes, including *BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B,*
FWB	Functional well-being
gBRCA	Germline *BRCA*
gBRCAm	Germline *BRCA* mutated
GCP	Good Clinical Practice
Gmean	Geometric mean

h	Hours
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
HRR	Homologous recombination repair
HRRm	Homologous recombination repair gene mutated
IC90	90% inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ILD	Interstitial lung disease
IND	Investigational new drug
ITT	Intention-to-treat
IVIVC	in vitro-in vivo correlation
Ka	Absorption rate constant
MATE	Human Multi-Drug And Toxin Extrusion Transporter
mCRPC	Metastatic castration-resistant prostate cancer
MCV	Mean corpuscular volume
MDS	Myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mHSPC	metastatic Hormono-Sensitive Prostate Cancer
MTP	Multiple testing procedure
N	Total number of patients
n	Number of patients
NA	Not applicable
NHA(s)	New hormonal agent(s)
NR	Not reported
OAT	Organic anion transporter
OATP	Organic anion-transporting polypeptide
OCT	Organic cation-transporter
od	Once daily
OR	Odds ratio
ORR	Objective response rate
OS	Overall survival
PALB2	Partner and localizer of *BRCA2*
PARP	Polyadenosine 5'diphosphoribose polymerase
PBPK	Physiologically-based pharmacokinetic
PBRER	Periodic benefit-risk evaluation report
PCS	Prostate cancer subscale
PCWG3	Prostate Cancer Working Groups 3

PD	Pharmacodynamic
PFS	Progression-free survival
PFS2	Time from randomisation to second progression or death
P-gp	P-glycoprotein
PK	Pharmacokinetic
PPP2R2A	Protein phosphatase 2 regulatory subunit Balpha
PR	Partial response
PRO	Patient reported outcome
PSA	Prostate specific antigen
PSA50	A ≥50% decline in PSA from baseline
PSR	Platinum-sensitive relapsed
PT	Preferred term
PWB	Physical well-being
Q	Quarter
QC	Quality control
QD	Once Daily
QSR	Quality Systems Regulation
QT	ECG interval measured from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia correction
QTcI	QT interval corrected for heart rate using individual-specific correction
RAD51B	RAD51 paralog B
RAD51C	RAD51 paralog C
RAD51D	RAD51 paralog D
RAD54L	RAD54 Like
RECIST	Response Evaluation Criteria in Solid Tumours
rPFS	Radiological progression-free survival
SAE	Serious adverse event
SAP	Statistical analysis plan
SAWP	Scientific Advice Working Party
sBRCA	Somatic *BRCA* (*BRCA* variant found in the tumour but not in the germline)
sBRCAm	Somatic *BRCA* mutated
sBRCA VUS	Somatic *BRCA* variant of uncertain significance
sNDA	Supplemental New Drug Application
SOC	System organ class
SSRE	Symptomatic skeletal-related event
std	Standard deviation

tBRCA	Tumour *BRCA* (mutations detected in the tumour)
tBRCAm	Tumour *BRCA* mutated
TEAE	Treatment emergent adverse event
TTPP	Time to pain progression
UGT	UDP-glucuronosyltransferase
ULN	Upper limit of normal
US/USA	United States/United States of America
vs	Versus
VUS	Variants of uncertain significance
wt	Wild type

1. Background information on the procedure

1.1. Type II group of variations

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, AstraZeneca AB submitted to the European Medicines Agency on 20 December 2021 an application for a variation.

The following variation was requested:

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

Extension of indication to include treatment of adults with metastatic castration resistant prostate cancer (mCRPC), with Lynparza in combination with abiraterone and prednisone or prednisolone, based on the results of the pivotal Phase III study PROpel (D081SC00001) and supportive evidence from Study 8 (D081DC00008). PROpel is a Phase III, randomised, double-blind, placebo-controlled, multicentre study evaluating olaparib vs placebo in combination with abiraterone as first line treatment for men with mCRPC. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC for Lynparza tablets are being updated. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on the updated safety data analysis. The Package Leaflet is updated accordingly. The RMP version 24 has also been submitted.

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

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) **P/0250/2020**, EMEA-002269-PIP01-17-MO1 on the granting of a product-specific) waiver/class waiver.

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP on 12 November 2020 (EMEA/H/SA/1215/5/FU/1/2020/II). The Scientific Advice pertained to clinical aspects development of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Alexandre Moreau Co-Rapporteur: Karin Janssen van Doorn

Timetable	Actual dates
Submission date	20 December 2021
Start of procedure:	23 January 2022
CHMP Rapporteur Assessment Report	25 March 2022
PRAC Rapporteur Assessment Report	25 March 2022
PRAC members comments	30 March 2022
CHMP Co-Rapporteur Critique	4 April 2022
PRAC Outcome	7 April 2022
CHMP members comments	11 April 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	22 April 2022
Request for supplementary information (RSI)	22 April 2022
CHMP Rapporteur Assessment Report	01 July 2022
PRAC Rapporteur Assessment Report	04 July 2022
PRAC members comments	05 July 2022
Updated PRAC Rapporteur Assessment Report	08 July 2022
PRAC Outcome	07 July 2022
CHMP members comments	11 July 2022
Updated CHMP Rapporteur Assessment Report	14 July 2022
Request for supplementary information	21 July 2022
CHMP Rapporteur Assessment Report	13 September 2022
PRAC Rapporteur Assessment Report	16 September 2022
PRAC members comments	21 September 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	29 September 2022
CHMP members comments	03 October 2022
Updated CHMP Rapporteur Assessment Report	10 October 2022
Request for supplementary information	13 October 2022
CHMP Rapporteur Assessment Report	27 October 2022
PRAC Rapporteur Assessment Report	27 October 2022
PRAC members comments	28 October 2022
CHMP members comments	28 October 2022
Updated CHMP Rapporteur Assessment Report	03 November 2022
Updated PRAC Rapporteur Assessment Report	03 November 2022
Opinion	10 November 2022

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Claimed therapeutic indication

The applied indication for Lynparza was, in combination with abiraterone and prednisone or prednisolone, for the treatment of adult patients with metastatic castration resistant prostate cancer.

The recommended indication for Lynparza is, in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (see section 5.1).

Epidemiology

Worldwide in 2020, prostate cancer was estimated to be the fifth most common cause of cancer death in men. In Europe in 2020, prostate cancer was estimated the third most common cause of cancer death (American Cancer Society 2021, Siegel et al 2021, ECIS 2020).

Almost all patients dying from prostate cancer will have mCRPC, and 90% of overall mortality in mCRPC patients is attributable to the underlying malignant disease (Scher et al 2015). For patients diagnosed with metastatic disease, the 5-year survival rate is 30% (American Society of Cancer 2019, Siegel et al 2019).

Clinical presentation, diagnosis and stage/prognosis

Most prostate cancers are adenocarcinomas. Following the initial evaluation and diagnosis, approximately 90% of men undergo primary localized treatment with curative intent (Cooperberg et al, 2010). Androgen deprivation therapy (ADT) (i.e., surgical or medical castration) is often initiated in men with rising prostate-specific antigen (PSA) after primary therapy. Following ADT, the next most frequent clinical state in the current model of prostate cancer progression is that of CRPC, defined as disease progression despite castrate hormone levels (testosterone $\leq$ 50 ng/dL). Men with CRPC can have metastatic or non-metastatic disease. In the majority of patients, metastatic CRPC evolves from non-metastatic CRPC and PSA doubling time has been shown to be a strong predictor of the development of metastases in these patients (Moreira et al, 2015; Scher et al, 2015).Androgen deprivation therapy with luteinising hormone releasing hormone analogues or orchiectomy is usually initially effective at controlling metastatic disease. A good prognostic factor in prostate cancer is when the patients are diagnosed at an early stage and with localised disease.

Almost all patients in advanced stages will ultimately develop mCRPC, which progresses rapidly. Around 60 % of patients with non-metastatic CRPC will developed metastatic disease during the first 5 years (Khirby et al 2011).

Metastatic castration resistant prostate cancer is associated with a range of symptoms but is predominantly characterised by bone pain, fatigue, and urinary dysfunction. Metastasis is predominantly localized in bones (90% of patients with metastatic castration-resistant prostate cancer), causing significant morbidity which requires medical interventions (pain and skeletal-related events, spinal cord compression, pathological fractures, etc).

Between 24% to 30% of mCRPCs have loss of function mutations in genes involved in homologous recombination repair (HRR) of DNA damage response (Abida et al 2017, Armenia et al 2018, Chung et al 2019, Mateo et al 2015, Robinson et al 2015).

In this application, the HRR genes refer to a family of 15 pre-specified genes with a biological rationale for loss of function to predict sensitivity to olaparib.

Management

According to ESMO guideline on cancer of the prostate (2020), the recommended treatments of metastatic CRPC are new hormonal agents (NHAs) such as abiraterone or enzalutamide for asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC, radium-223 for patients with bone-predominant symptomatic metastatic CRPC without visceral metastases, docetaxel and cabazitaxel for patients with metastatic CRPC is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC.

Bone protective agents should be used in men with mCRPC to prevent fractures.

The optimal sequence or combination of these agents (abiraterone, enzalutamide, radium-223, docetaxel and cabazitaxel) is still unknown. In practice, sequencing decisions will be made in the light of the distribution, extent and pace of disease, co-morbidities, patient preferences and drug availability.

Evaluation of a new treatment option that would allow for early intervention in the course of mCRPC and that could also prolong the treatment duration of available therapies, delay disease progression, and improve long-term outcomes in this setting is warranted.

2.1.2. About the product

Lynparza is approved in EU for the treatment of ovarian cancer, breast cancer, adenocarcinoma of the pancreas and prostate cancer.

The MAH applied for a new indication for olaparib tablets formulation in combination with abiraterone and prednisone or prednisolone, as follows:

Lynparza in combination with abiraterone and prednisone or prednisolone is indicated for the treatment of adult patients with metastatic castration resistant prostate cancer.

Olaparib, the active substance of Lynparza, is a potent oral human PARP inhibitor (PARP-1, PARP-2, and PARP-3) that exploits deficiencies in DNA repair pathways to preferentially kill cancer cells with these deficits compared to normal cells.

Abiraterone is a potent, oral inhibitor of testosterone biosynthesis. Abiraterone selectively inhibits the CYP17 enzyme which is required for androgen biosynthesis.

The scientific rationale for the combination of olaparib and abiraterone is based on the preclinical evidence indicating two plausible mechanisms. The first hypothesis involves PARP-1 transcriptional roles: beyond its function in DNA repair, PARP-1 has been implicated in modulation of transcription (Schiewer and Knudsen 2014) which may be especially relevant in hormone dependent cancers, as nuclear hormone receptors have been reported to require catalytically active PARP-1 as a positive co-regulator of target gene expression (Ju et al 2006). The second mechanistic explanation that may account for the activity of olaparib in combination with abiraterone is the induction of an HRR-deficient phenotype through non-genetic mechanisms, via inhibition of AR signalling. Several lines of evidence have been reported that support this possibility, including downregulation of HRR gene transcripts and

protein levels in response to inhibition of AR signalling in prostate cancer correlated with deficient DNA repair and increased DNA damage sensitivity (Goodwin et al 2013, Asim et al 2017, Li et al 2017).

2.2. Non-clinical aspects

2.2.1. Introduction

The non-clinical part of this application is based on literature concerning the efficacy of the combination of olaparib and anti-androgens. No new non-clinical studies have been conducted by the Applicant. A new environmental risk assessment report has been submitted.

Pharmacology

Primary pharmacodynamic studies

Olaparib is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration resistant prostate cancer.

The applicant submitted non-clinical scientific publications that include data from studies conducted *in vitro* and/or *in vivo* (Schiewer and Knudsen 2014; Ju et al 2006; Schiewer et al 2012; Goodwin et al 2013, Asim et al 2017, Li et al 2017). These articles demonstrate the involvement of androgen receptors in promoting the expression of genes involved in DNA repair and highlight the increase in the expression of homologous recombination genes in castration-resistant prostate cancers, promoting the survival of cancer cells. The data from the papers demonstrate that blocking the transcription of androgen receptors leads to a decrease in the expression of DNA repair genes, which would lead to an overactivation of PARP. This would mean that by blocking androgen receptor transcription and inhibiting the PARP enzyme, cell growth and survival would be reduced.

The articles include *in vitro* studies where the combination of anti-androgens with olaparib show to cause an increase in DNA damage with a greater reduction in repair as well as a reduction in cell proliferation compared to monotherapies in cellular models of prostate cancer. *In vivo* and in the absence of HRR mutation, according to the results of the articles, comparable efficacy has been demonstrated for olaparib as monotherapy and for the olaparib + enzlutamide combination.

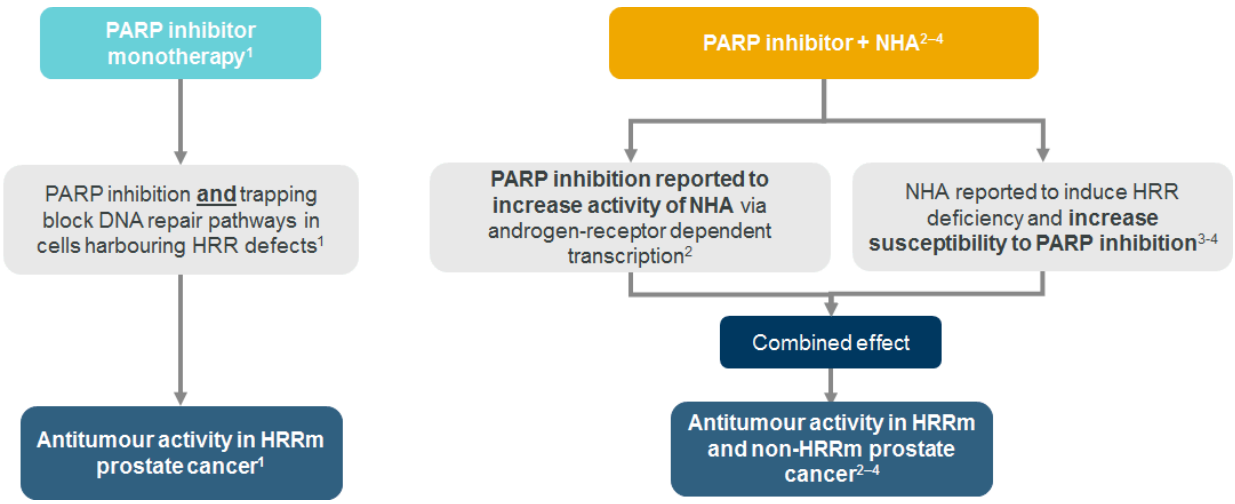


Figure 1: Biological Rationale for PARP Inhibitor and NHA Combination

2.2.2. Ecotoxicity/environmental risk assessment

The potential environmental impact from use of the drug substance olaparib has already been evaluated and supported approval of the capsule (ovarian, fallopian tube, or primary peritoneal cancer) and of the tablet formulation (epithelial ovarian, fallopian tube or primary peritoneal cancer, metastatic adenocarcinoma of the pancreas and metastatic castration-resistant prostate cancer) as a monotherapy.

An updated ERA covering this extension of indication has been submitted.

Substance (INN/Invented Name): *Olaparib*			
CAS-number: *763113-22-0*			
PBT screening		*Result*	***Conclusion***
Bioaccumulation potential-	*OECD107* *(Ref 10)*	*Log Pow = 1.55 at pH 7*	*< 4.5:* ***not PBT or vPvB***
PBT Assessment			
Parameter	***Result relevant for conclusion***		***Conclusion***
Bioaccumulation	*LogPow*	*1.55*	***Not B; therefore: not PBT or vPvB***
Persistence	*DT50 total system*	*251 – 551 days*	
Toxicity	*NOEC*	*0.32 mg/L*	
PBT Statement:	*The compound is not considered as PBT nor vPvB*		
Phase I			
Calculation	***Value***	***Unit***	***Conclusion***
PECsurfacewater, refined	*0.113*	*µg/L*	*> 0.01 µg/L*
Other concerns (e.g. chemical class)			*None*
Phase IIA physical-chemical properties and fate			
Study type	***Test protocol***	***Results***	***Remarks***
Hydrolysis	*OECD 111* *(Ref 14)*	*<10 % (120 hours) at pH 5, 7 and 9*	*Hydrolytically stable.*
Ready Biodegradability Test	*OECD 301F* *(Ref 15)*	*Negligible biodegradation (day 28: <6%)*	*Not readily biodegradable.*
Aerobic Transformation in Aquatic Sediment systems	*OECD 308* *(Ref 1818)*	*DT50 values at 20°C* *LOM DT50water = 7.06*	*Olaparib is very persistent. Olaparib is expected to partition to aquatic*

		days *HOM DT50water = 4.22* *days* *LOM DT50total system = 251 days* *HOM DT50total system = 260 days*	*sediments with no evidence of degradation. As the total radioactivity associated with the sediment exceeded 10% the toxicity of olaparib to sediment- dwelling organisms is investigated in Tier B.*
		DT50 values at 12°C *LOM DT50water = 15.0* *days* *HOM DT50water = 8.96* *days* *LOM DT50total system = 534 days* *HOM DT50total system = 551 days*	
		No metabolites >10% were observed.	
Adsorption-Desorption to two sediments	*OECD 106* *(Ref 1717)*	*HOC sediment mean Kd =* *111; Koc = 1986 L/Kg* *LOC sediment mean Kd =* *3.8; Koc =27487 L/Kg*	
Adsorption-Desorption to sludge	*OPPTS 835.1110* *(Ref 16),*	*Kdsludge(ads) = 25 L/Kg*	*Assessment of olaparib in the terrestrial compartment is not necessary in Tier B.*
Phase IIA effect studies			

Study type	***Test protocol***	***Endpoint***	***Value***	***Unit***	***Remarks***
Algae, Growth Inhibition Test	*OECD 201 (Ref 21)*	*NOEC*	*83*	*mg/L*	*72 hour EC50 > 83 mg/L growth rate*
Daphnia sp. Reproduction Test	*OECD 211 (Ref 22)*	*NOEC*	*0.32*	*mg/L*	*21 day LOEC = 1 mg/L*
Fish, Early Life Stage Toxicity Test	*OECD 210 (Ref 23)*	*NOEC*	*0.32*	*mg/L*	*32 day LOEC = 1 mg/L*
Activated Sludge, Respiration Inhibition Test	*OECD 209 (Ref 20)*	*NOEC*	*100*	*mg/L*	*3 hour EC50 > 100 mg/L*

PNECmicroorganism *= 10 000 µg/L*

PNECsurfacewater *= 32 µg/L*

PECgroundwater *= 0.028 µg/L*

PNECgroundwater *= 32 µg/L*

PECsurfacewater/PNECmicroorganism *= 1.1 × 10^{-5}: Olaparib is unlikely to present a risk to microorganisms*

PECsurfacewater/PNECsurfacewater *= 3.5 × 10^{-3}: Olaparib is unlikely to present a risk to organisms in surface water*

PECgroundwater/PNECgroundwater *= 8.8 × 10^{-4}: Olaparib is unlikely to present a risk to the groundwater environment*

Phase IIB effect studies

Study type	***Test protocol***	***Results***	***Remarks***
Toxicity to Chironomus riparius	*OECD 218 (Ref 24)*	*28 day NOEC = 0.60 mg/kg dry weight*	*NOEC normalised to 10% o.c. = 2.61 mg/Kg*
Toxicity to Lubriculus variegatus	*OECD 225 (Ref 2626)*	*28 day NOEC = 86 mg/kg dry weight*	*-*
Toxicity to Hyalella azteca	*U.S. EPA 600/R-99/064 (Ref 27)*	*28 day NOEC = 89.6 mg/kg dry weight*	*-*

PECsediment *= 13.74 µg/kg (dry weight)*

PNECsediment *= 260 µg/kg (NOEC from the chironomus test (normalised to 10% o.c.) / 10)*

PEC/PNECsediment *= 0.053: Olaparib is unlikely to present a risk to sediment dwelling organisms*

Conclusion
Olaparib is very persistant.

2.2.3. Discussion on non-clinical aspects

The non-clinical part of this application is based on articles concerning the efficacy of the combination of olaparib and anti-androgens. No new non-clinical studies have been submitted by the applicant which is considered acceptable.

The scientific rationale for the combination of abiraterone and olaparib is based on preclinical literature data indicating two plausible mechanisms that may explain the independent biomarker activity of the olaparib-abiraterone combination. The first mechanism of action demonstrates the involvement of PARP in the positive co-regulation of androgen receptor signalling, which would reduce the level of androgen receptor signalling. Studies presented highlight the effect of PARP inhibition which significantly reduces AR expression in a non-clinical model of prostate cancer compared to a positive control. It also appears that PARP inhibitors further reduce AR expression in castrated mice. The level of expression of androgen receptors plays an important role in prostate cancer in terms of cell survival and also resistance to castration. The proposed mechanism seems plausible.

The second mechanism mentioned concerns the decrease in transcription of homologous recombination genes induced by the blocking of androgen receptor transcription. By decreasing the transcription of genes involved in homologous recombination, the activity of the PARP enzyme would be increased, which can justify from a mechanistic point of view the use of the anti-androgen and PARP inhibitor combination.

An updated ERA for Lynparza (olaparib) has been provided. The PECsw for the prostate cancer indications has been updated.

2.2.4. Conclusion on the non-clinical aspects

The scientific rationale for the combination of abiraterone and olaparib is based on the preclinical evidence indicating two plausible mechanisms that may account for the biomarker independent activity of the olaparib-abiraterone combination. Pre-clinical studies in prostate cancer models reported a combined anti-tumour effect when PARP inhibitors and next-generation hormonal agents are administered together. PARP is involved in positive co-regulation of androgen receptor (AR) signalling, which leads to enhanced AR target gene suppression when PARP/AR signalling is co-inhibited. Other pre-clinical studies reported that treatment with NHAs inhibit the transcription of some HRR genes, therefore, inducing HRR deficiency and increased sensitivity to PARP inhibitors via non-genetic mechanisms (see SmPC section 5.1).

The environmental risk file is complete and well-constructed. The PECsw for the prostate cancer indications has been updated for this amendment request as well as the relevant sections of the Phase II Level A and B assessment. Considering the above data, olaparib is not expected to pose a risk to the environment.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

Study **CSR location**	**Study design**	**Subjects**	**Treatments**
D081SC00001 (PROpel) A Randomised, Double-blind, Placebo-controlled, Multicentre Phase III Study of Olaparib Plus Abiraterone Relative to Placebo Plus Abiraterone as First-line Therapy in Men with Metastatic Castration-resistant Prostate Cancer CSR location: Module 5.3.5.1	Randomised; double-blind; multiple centre, multiple dose study	Biomarker unselected patients with mCRPC who had not received prior chemotherapy or NHAs in the mCRPC setting Olaparib + abiraterone (n=399); Placebo + abiraterone (n=397)	Olaparib (300 mg tablet bd) + abiraterone (1000 mg qd) Prednisone/Prednisolone 5mg bd Placebo + abiraterone (1000 mg qd) Prednisone/Prednisolone 5mg bd

Study CSR location	Study design	Subjects	Treatments
D081DC00008 Phase II randomised, double-blind, placebo-controlled, multicentre study to compare the efficacy, safety and tolerability of olaparib versus placebo when given in addition to abiraterone treatment in patients with mCRPC who have received prior chemotherapy containing docetaxel CSR location: Module 5.3.5.1	Randomised; double-blind; multiple centre, multiple dose study	**Part A** Patients with mCRPC - Cohort 1: n=3 - Cohort 2, group 1: n=7 - Cohort 2, group 2: n=6 **Part B** Patients with mCRPC who have received prior chemotherapy containing docetaxel Olaparib + abiraterone: n=71 Placebo + abiraterone: n=71	**Part A** Cohort 1: olaparib 200 mg bd (2 x 100 mg) tablet combined with abiraterone 1000 mg od Prednisone/Prednisolone 5mg bd Cohort 2, group 1: olaparib 300 mg bd (2 x 150 mg) tablet alone, then combined with abiraterone 1000 mg qd Prednisone/Prednisolone 5mg bd Cohort 2, group 2: abiraterone 1000 mg qd alone, then combined with olaparib 300 mg bd (2 x 150 mg) tablet Prednisone/Prednisolone 5mg bd **Part B** Olaparib 300 mg bd (2 x 150 mg) tablet with abiraterone 1000 mg qd Matching placebo with abiraterone 1000 mg od Prednisone/Prednisolone 5mg bd

2.3.2. Pharmacokinetics

Olaparib is a potent, oral inhibitor of PARP that exploits deficiencies in DNA repair pathways and selectively targets cancer cells with these deficiencies compared to normal cells.

In Europe, olaparib as a capsule formulation was approved under the brand name of Lynparza in 2014 for the treatment of patients with advanced ovarian cancer. An oral tablet formulation was subsequently approved for the maintenance treatment of patients with PSR ovarian cancer in addition to other indications in prostate, ovarian, breast and pancreatic cancer.

The tablet formulation of olaparib is being evaluated in all ongoing Phase III studies and consisted of two strengths of film-coated tablets of 100 and 150 mg.

The PK data provided in support of this submission includes:

1. Descriptive, noncompartmental methods of analysis of olaparib PK data from all patients enrolled in the pivotal study **D081SC00001** (PROpel). In addition, abiraterone and delta4-abiraterone PK was investigated in these patients.
2. Descriptive, noncompartmental methods of analysis of olaparib, abiraterone and delta4-abiraterone PK data from all patients enrolled in study **D081DC00008** (Part A). The main objective of Part A was to evaluate the presence of any drug interaction between olaparib and abiraterone.

The additional PK data from the pivotal PROpel study are presented in the section related to PK in target population.

Methods

- ***Analytical methods***

For each analytes a dedicated unique bioanalytical method was developed, and summary results are presented below.

Olaparib

A unique bioanalytical method was used to quantify olaparib in human plasma.

The initial methods for olaparib measurement were developed and validated in human plasma using lithium heparin as anticoagulant. Additional partial validation in K_2EDTA human plasma was conducted. No analytically significant interference from endogenous plasma components was observed at the retention times of olaparib or internal standard in the plasma samples screened. The lower limit of quantification (LLOQ) of the assay was 20.0 ng/mL and the assay was shown to be linear up to 20000 ng/mL. Within-batch precision for olaparib was found to be <8.4% and within-batch accuracy for olaparib was found to be between 91.0% and 101.1%.

The stability of olaparib, in K_2EDTA human plasma was demonstrated for up to four cycles of freezing and thawing. Olaparib in K_2EDTA human plasma was shown to be stable for up to 24 hours when stored at room temperature and for up to 385 days when stored at either approximately -20°C or -80°C.

Abiraterone/Delta4-abiraterone

A unique bioanalytical method (Method ABD4HPP, Report 8394706) was used to quantify abiraterone and its metabolite in human plasma with K_2EDTA as anticoagulant.

Calibration, QC and clinical study samples (50 µL) were spiked with internal standards (abiraterone-d4 for both analytes), processed by liquid-liquid extraction and simultaneously.

Table 1: Results summary

Analytes	AZD2281 (Olaparib) Abiraterone Abiraterone D4A (Delta-4-Abiraterone)
Species	Human
Analytical matrix	EDTA Plasma
Internal standard	[$^2H_8$] AZD2281 ISTD for AZD2281 Abiraterone-d4 ISTD for Abiraterone and Abiraterone D4A
Validated methods	OLBHPP for AZD2281 ABD4HPP for Abiraterone and Abiraterone D4A
Validated ranges	AZD2281: 0.0200 to 20.0 µg/mL Abiraterone: 1.00 to 500 ng/mL Abiraterone D4A: 0.100 to 20 ng/mL
Quality Control levels	AZD2281: 0.0600, 0.800, 14.0 µg/mL Abiraterone: 3.00, 30.0, 200, 400 ng/mL Abiraterone D4A: 0.300, 1.20, 8.00, 16.0 ng/mL
Analytical technique/method of detection	AZD2281: Solid-phase extraction / liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS) Abiraterone and Abiraterone D4A: Liquid-liquid extraction / liquid chromatography followed by tandem mass spectrometric detection (LC-MS/MS)
Sample volume	AZD2281: 100 µL Abiraterone and Abiraterone D4A: 50 µL
Calibration model	AZD2281: Linear regression Abiraterone: Quadratic regression Abiraterone D4A: Linear regression
Weighting factor	AZD2281: 1/x Abiraterone and Abiraterone D4A: $1/x^2$
Number of runs	16 of 17 runs met acceptance criteria. 2 trial runs were also performed but not reported
Total number of samples analysed	AZD2281: 358 Abiraterone and Abiraterone D4A: 781

The lower limit of quantification (LLOQ) of the assay was 1 ng/ml and 0.1 ng/mL for abiraterone and delta4-abiraterone respectively; and the assay was shown to be linear up to 500 ng/ml and 20 ng/mL, for abiraterone and delta4-abiraterone, respectively. Within-batch precision was found to be between 1.0% to 7.3%, and 1.0% to 8.8% for abiraterone and abiraterone D4A respectively. Between-batch precision was found to be between 1.8% and 11.3%, and 3.4% and 7.8% for abiraterone and delta4-abiraterone respectively. Within-batch accuracy was found to be between 86.2% and 111.7%, and 92.9% and 105.0% for abiraterone and delta4-abiraterone respectively. Between-batch accuracy was found to be between 99.2% and 108.0%, and 96.2% and 99.3% for abiraterone and delta4- abiraterone respectively.

Long term stability in plasma at -20°C or -80°C was demonstrated up to 365 days.

Pharmacokinetic data analysis

Standard non-compartmental analysis (NCA) has been performed to estimate PK parameters at steady-state (Cmaxss, Tmaxss, Cminss, AUC_{0-8}) from a subset of patients from Study **D081SC00001** using Phoenix WinNonlin Version 8.1.

Pharmacokinetic in target population

Olaparib and abiraterone/D4-abiraterone PK has been evaluated in two clinical studies **D081SC00001** (PROpel) and **D081DC00008** (presented in the next section)

Study **D081SC00001**

Design

Study **D081SC00001** is a randomised, double-blind, placebo-controlled, multicentre international Phase III study to evaluate olaparib in combination with abiraterone vs placebo in combination with abiraterone as first line therapy in biomarker unselected patients with mCRPC who had not received prior chemotherapy or NHAs for mCRPC.

Patients received oral treatment with olaparib 300 mg BID + abiraterone 1000 mg QD or placebo BID + abiraterone 1000 mg QD. Patients (n=796) were randomized in a 1:1 ratio. Treatment with abiraterone was given as per label and included prednisone or prednisolone 5 mg bd for both treatment groups.

PK sampling consisted of pre-dose, 30 min, 2h, 3h, 5h and 8h post dose on approximately Day 29 of the study. Olaparib plasma concentrations were determined in the olaparib arm whereas abiraterone in both arms. For olaparib, the pre-dose concentration was used as the 12h post-dose concentration to calculate AUCss and CLss/F.

Results

Olaparib

Following multiple dosing to steady state at 300 mg BID, olaparib absorption was rapid with median Tmax,ss of 2.0 hours. Geometric mean AUCss, Cmax,ss and Cmin,ss were 39.3 µg·h/mL, 6.28 µg/mL and 1.01 µg/mL, respectively as shown in ***Table 2***.

Table 2: Olaparib steady-state exposure in PROpel and in other Phase 3 studies

Parameter Gmean (GCV %)	PROpel NCA (N=66)	SOLO2 PPK (N=91)	SOLO3 PPK (N=80)	OlympiA PPK (N=69)	OlympiAD PPK (N=36)	PROfound NCA (N=65)	PROfound PPK (N=72)
$C_{max,ss}$ µg/mL	6.28 (33.7%)	6.83 (32.5%)	7.62 (24.7%)	6.18 (29.2%)	6.48 (40.2%)	7.51 (33.6%)	7.33 (29.9%)
AUC_{ss} µg·h/mL	39.3[a] (42.2%)	41.4 (42.1%)	49.8 (34.8%)	37.3 (38.7%)	42.4 (54.3%)	48.8[b] (46.5%)	48.4 (44.1%)
$C_{min,ss}$ µg/mL	1.01[a] (86.1%)	1.19 (74.6%)	1.62 (69.5%)	1.06 (65.5%)	1.38 (97. 1%)	1.64[b] (87.1%)	1.61 (82.7%)
ECOG* status	0 (75.8%) 1 (24.2%)	0 (78%) 1 (21%)	0 (81.5%) 1 (18.5%)	0 (94.2%) 1 (5.8%)	0 (75%) 1 (25%)	0 (66.2%) 1 (30.8%) 2 (3.08%)	0 (67.6%) 1 (28.4%) 2 (4.05%)

Gmean; geometric mean; GCV: geometric coefficient if variation; * ECOG status is shown as percentage

PPK: analysed by population PK analysis; NCA: analysed by noncompartmental analysis

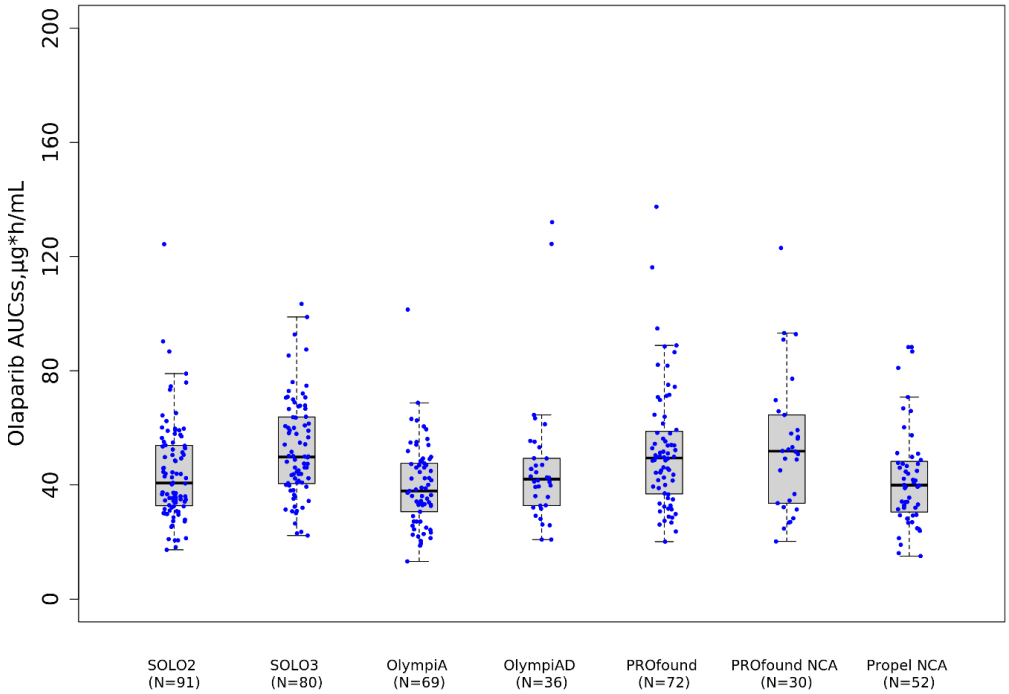
[a] n= 52 for this parameter ; [b] n = 30 for this parameter; n = N for all other parameter

Data source: Table 14.2.14.4 in PROpel CSR; Table 12 in Olaparib-MS-09;
Table 1 in PROfound metabolite PK analysis report

Interpatient variability was moderate (between 25 and 40%) to high (>40%) for AUCss and Cmax,ss and Cmin,ss. Olaparib apparent steady state clearance (CLss/F) was moderate, with an arithmetic mean value of 8.28 L/h.

Steady state PK exposure parameters of olaparib in mCRPC patients when dosed in combination with abiraterone in PROpel were similar to olaparib steady state exposures in other phase III monotherapy studies as shown in Figure 2.

Figure 2: Comparison of olaparib AUCss in Phase 3 studies by boxplot



Abiraterone/D4- Abiraterone

Summary of steady-state PK parameters of abiraterone and its active metabolite are presented in Table 3.

Absorption of abiraterone following multiple dosing was rapid for both treatment groups, with median Tmax,ss observed between 2.00 and 2.04 hours.

Geometric mean abiraterone AUC (0-8), Cmax,ss from patients receiving abiraterone 1000 mg QD administered alone were 339.5 ng·h/mL and 105.4 ng/mL, respectively.

Geometric mean abiraterone AUC (0-8) and Cmax,ss from patients receiving abiraterone 1000 mg QD co-administered with olaparib 300 mg BID for 28 days were comparable with values of 393.7 ng·h/mL and 112.6 ng/mL, respectively.

Interpatient variability, as indicated by the GCV values, was very high for AUCss and Cmax,ss and Cmin,ss.

Delta4-abiraterone appeared rapidly in plasma for both treatment groups, with median Tmax,ss observed between 2.01 and 2.58 hours.

Geometric mean delta4-abiraterone AUC (0-8), Cmax,ss and Cmin,ss from patients receiving abiraterone 1000 mg qd alone were of 14.65 ng·h/mL, 3.903 ng/mL and 0.7086 ng/mL, respectively.

Geometric mean delta4- abiraterone AUC (0-8), Cmax,ss and C,min,ss from patients receiving abiraterone 1000 mg qd coadministered with olaparib 300 mg bd were slightly lower with values of 11.72 ng·h/mL, 3.019 ng/mL and 0.4907 ng/mL.

Table 3: Summary of steady-state PK parameters of abiraterone and its main metabolite

Compound	PK Parameter	Summary Statistic	Placebo bd + Abiraterone 1000 mg qd (N=58)	Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=66)
Abiraterone	$C_{max,ss}$ (ng/mL)	n	56	64
		Gmean	105.4	112.6
		% GCV	105.6	136.9
	$C_{min,ss}$ (ng/mL)	n	44	54
		Gmean	8.454	7.711
		% GCV	95.10	92.41
	$AUC_{(0-8)}$ (ng h/mL)	n	44	54
		Gmean	339.5	393.7
		% GCV	77.99	107.5
	$t_{max,ss}$ (h)	n	56	64
		Median	2.00	2.04
		Minimum	0.00	0.00
		Maximum	8.00	8.00
Delta4-abiraterone	$C_{max,ss}$ (ng/mL)	n	58	65
		Gmean	3.903	3.019
		% GCV	100.3	101.8
	$C_{min,ss}$ (ng/mL)	n	44	54
		Gmean	0.7086	0.4907
		% GCV	68.02	79.39
	$AUC_{(0-8)}$ (ng·h/mL)	n	44	54
		Gmean	14.65	11.72
		% GCV	70.99	80.30
	$t_{max,ss}$ (h)	n	58	65
		Median	2.01	2.58
		Minimum	0.00	0.00
		Maximum	7.00	8.00
	$MRC_{max,ss}$	n	44	54
		Gmean	0.03484	0.02412
		% GCV	65.99	59.32
	$MRC_{min,ss}$	n	43	54
		Gmean	0.08267	0.06364

Compound	PK Parameter	Summary Statistic	Placebo bd + Abiraterone 1000 mg qd (N=58)	Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=66)
		% GCV	80.28	55.31
	$MRAUC_{(0-8)}$	n	44	54
		Gmean	0.04315	0.02976
		% GCV	62.81	53.92

GCV, geometric coefficient of variation; G_{mean}, geometric mean; NA, not available.

Pharmacokinetic interaction studies

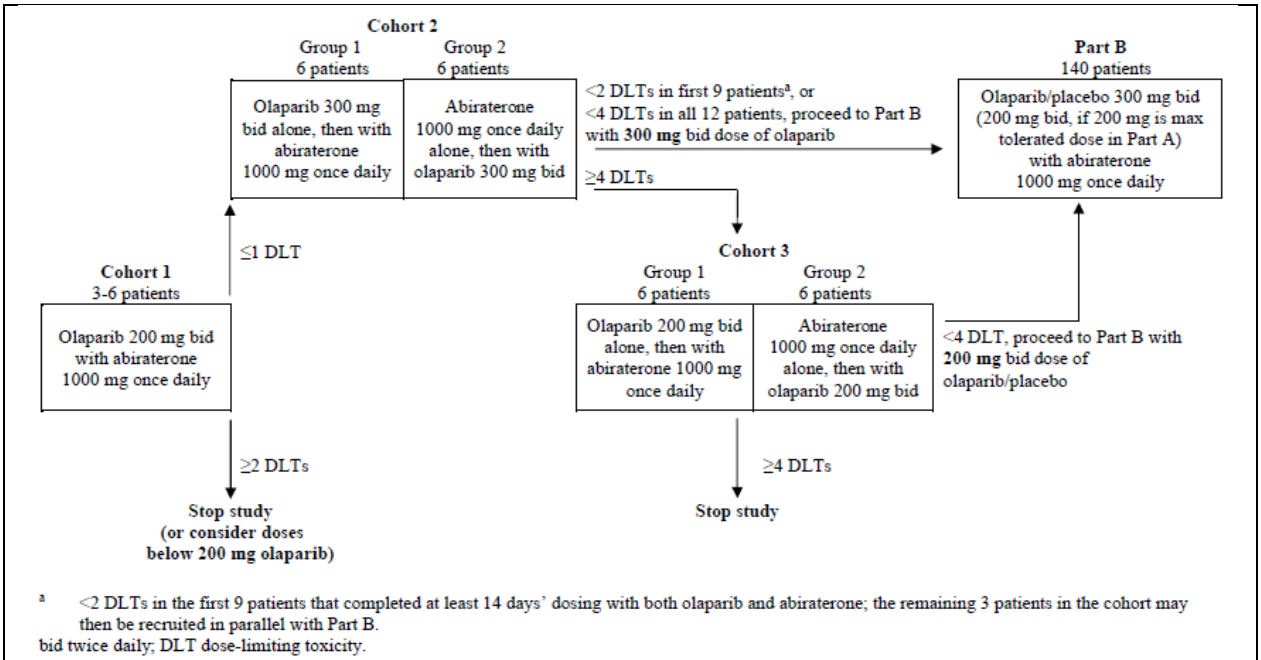
Treatment with abiraterone was given as per label (Zytiga, SmPC) and included prednisone or prednisolone 5 mg bd for both treatment groups for mCRPC treatment.

Potential PK interactions between olaparib and abiraterone has been assessed in two clinical studies: Study D081DC00008, and Study D081SC00001 (PROpel), presented below.

Effect of abiraterone on olaparib pharmacokinetics

Study D081DC00008

Primary Objective	**Safety**: To assess the safety and tolerability of olaparib when given in addition to abiraterone and to recommend, by assessment of dose-limiting toxicities and other safety and tolerability data, a dose of olaparib for further study when given in addition to abiraterone **Efficacy**: To compare the efficacy of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone, by assessment of rPFS (Investigator determined) using RECIST 1.1 and PCWG-2 criteria.
Secondary objective	**Only objective related to PK interactions is reported** **Part 1:** To evaluate the presence of any drug interaction between olaparib and abiraterone by determination of steady state exposure to olaparib in the presence and absence of abiraterone, and determination of steady state exposure to abiraterone in the presence and absence of olaparib.
Design	Phase 2 randomised, double-blind, placebo-controlled Part A was an open-label safety run-in study to assess the safety, tolerability and pharmacokinetics (PK) of olaparib when given in addition to abiraterone 1000 mg once daily. Part B was a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A when given in addition to abiraterone, versus placebo in addition to abiraterone.



[a] <2 DLTs in the first 9 patients that completed at least 14 days' dosing with both olaparib and abiraterone; the remaining 3 patients in the cohort may then be recruited in parallel with Part B.
bid twice daily; DLT dose-limiting toxicity.

Population **N: Entered/** **Analyzed**	PK analysis set For Part A N: 16/13
Treatments	See study design
Sampling	**Olaparib** blood samples were collected predose and at 0.5, 1, 2, 3, 4, 6, 8 and 12 hours after morning dose on each sampling day. Olaparib steady state PK profile collected any day between Days 3 and 7 after morning dose, olaparib PK following abiraterone co-administration may be collected any day between Day 9 and 14. **Abiraterone** blood samples were collected predose and at 0.5, 1, 2, 3, 4, 6, 8, 12 and 24 hours after morning dose on each sampling day. Abiraterone steady state PK profile collected any day between Days 5 and 7 after morning dose, and abiraterone PK following olaparib co-administration may be collecte any day betweent Day 9 and 14.

Pharmacokinetic results

Table 4: Summary of steady state pharmacokinetic parameters of olaparib (PK analysis set)

	Cohort 2, Group 1 (N=7=			**Cohort 2, Group 2 (N=6)**
	Olaparib **(Visit 3) N=6**	**Olaparib+** **abiraterone** **(Visit 4) N=5**	**Ratioa** **(Visit 4:** **Visit 3) N=4**	**Olaparib+** **abiraterone** **(Visit 4) N=6**

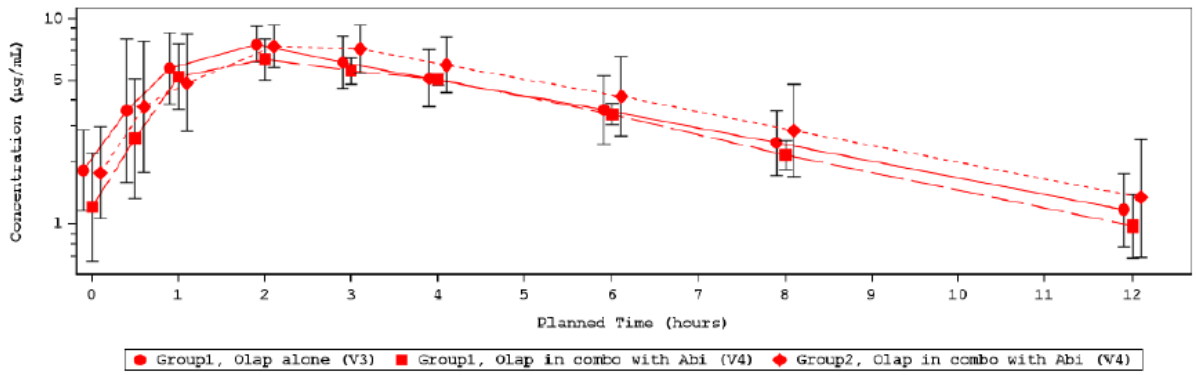
Css,max (µg/mL)[a]	7.781 (25.06%)	6.504 (20.90%)	0.8454 (27.59%)	7.724 (28.05%)
Css,min (µg/mL)[a]	1.264 (46.58%)	0.9170 (31.56%)	0.7848 (35.96%)	1.279 (65.36%)
AUCss (µg·h/mL)[a]	45.27 (31.89%)	40.83 (11.47%)	0.9859 (20.89%)	49.51 (37.30%)
Tmax,ss (h)[c]	2 [1-2.17]	2.080 [2-4]		2.00 [0.5-3.02]
CLss/F (L/h)[b]	6.887 (29.07%)	7.390 (11.52%)		6.372 (32.56%)

a Geometric mean and %GCV are calculated using log transformed data.

b Arithmetic mean, SD and %CV are calculated using untransformed data

c Median, min and max

Figure 8 **Gmean (±GSD) steady state olaparib plasma concentration versus time following 300mg bid dosing: semi logarithmic scale (PK analysis set)**



Cohort 2, Group 1: olaparib 300 mg bid for 3-7 days then olaparib 300 mg bid+abiraterone 1000 mg od for at least 5 days.
Cohort 2, Group 2: abiraterone 1000 mg od for 5-7 days then olaparib 300 mg bid+abiraterone 1000 mg od for at least 3 days.
Gmean, Gmean+GSD and Gmean-GSD were calculated using log transformed data.
Concentrations where actual time deviates more than 10% from scheduled time, or incorrect dosing interval prior to PK sampling, have been excluded.
bid twice daily; Gmean geometric mean; GSD geometric standard deviation; od once daily.
Source: Figure 11.2.1.3.1, page 1.

The data show that when olaparib was co-administered with abiraterone, the Gmean PK parameter ratios of non-log transformed data for Css,max and Css,min were slightly lower (approximately 15% and 22% lower, respectively) and the overall exposure based on AUCss was similar (1.4% lower) compared with olaparib administered as monotherapy. The individual ratio data show that all Css,min ratios were below 1 and that the AUCss and Css,max ratios were distributed both above and below 1 (ranging between 31% lower and 22% higher for Css,max and between 26% lower and 20% higher for AUCss) indicating no clear trend for exposure in combination to be higher or lower than that in monotherapy.

Cross-study analysis

The steady state PK exposure parameters for olaparib in PROpel and in other olaparib phase III monotherapy studies are summarized in Table 5. The results from the table indicate that steady state

exposures based on Cmax,ss, AUCss or Cmin,ss for olaparib in PROpel are similar to olaparib steady state exposures in SOLO2, OlympiA and OlympiAD and are slightly lower to those in SOLO3 and PROfound. Box plots of Olaparib Cmax,ss, AUCss or Cmin,ss as stratified by phase III studies are shown in Figure 3, Figure 4, Figure 5, respectively. The corresponding interquartile ranges for all exposure parameters in PROpel overlap significantly with those from other studies including SOLO3 and PROfound, confirming that olaparib steady state exposures when dosed in combination with abiraterone in PROpel are similar to olaparib steady state exposures in all Phase III monotherapy studies.

Table 5: Olaparib steady state steady exposure in PROpel and in other phase III monotherapy studies

Parameter Gmean (GCV %)	PROpel NCA (N=66)	SOLO2 PPK (N=91)	SOLO3 PPK (N=80)	OlympiA PPK (N=69)	OlympiAD PPK (N=36)	PROfound NCA (N=65)	PROfound PPK (N=72)
$C_{max,ss}$ µg/mL	6.28 (33.7%)	6.83 (32.5%)	7.62 (24.7%)	6.18 (29.2%)	6.48 (40.2%)	7.51 (33.6%)	7.33 (29.9%)
AUC_{ss} µg·h/mL	39.3[a] (42.2%)	41.4 (42.1%)	49.8 (34.8%)	37.3 (38.7%)	42.4 (54.3%)	48.8[b] (46.5%)	48.4 (44.1%)
$C_{min,ss}$ µg/mL	1.01[a] (86.1%)	1.19 (74.6%)	1.62 (69.5%)	1.06 (65.5%)	1.38 (97. 1%)	1.64[b] (87.1%)	1.61 (82.7%)
ECOG* status	0 (75.8%) 1 (24.2%)	0 (78%) 1 (21%)	0 (81.5%) 1 (18.5%)	0 (94.2%) 1 (5.8%)	0 (75%) 1 (25%)	0 (66.2%) 1 (30.8%) 2 (3.08%)	0 (67.6%) 1 (28.4%) 2 (4.05%)

*Gmean; geometric mean; GCV: geometric coefficient if variation; * ECOG status is shown as percentage PPK: analysed by population PK analysis; NCA: analysed by noncompartmental analysis a n= 52 for this parameter ; b n = 30 for this parameter; n = N for all other parameter*

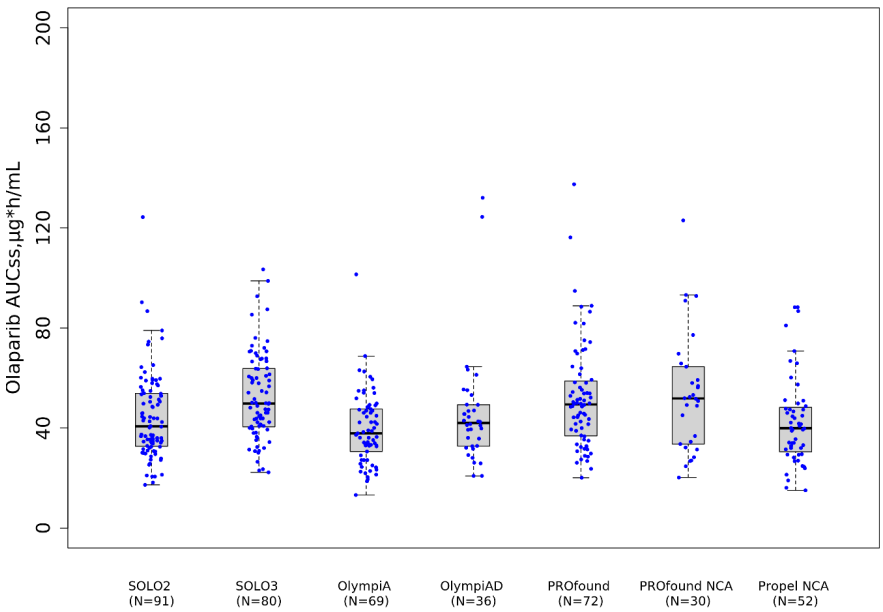


Figure 3: Comparison of olaparib AUCss in phase 3 studies by Box plot

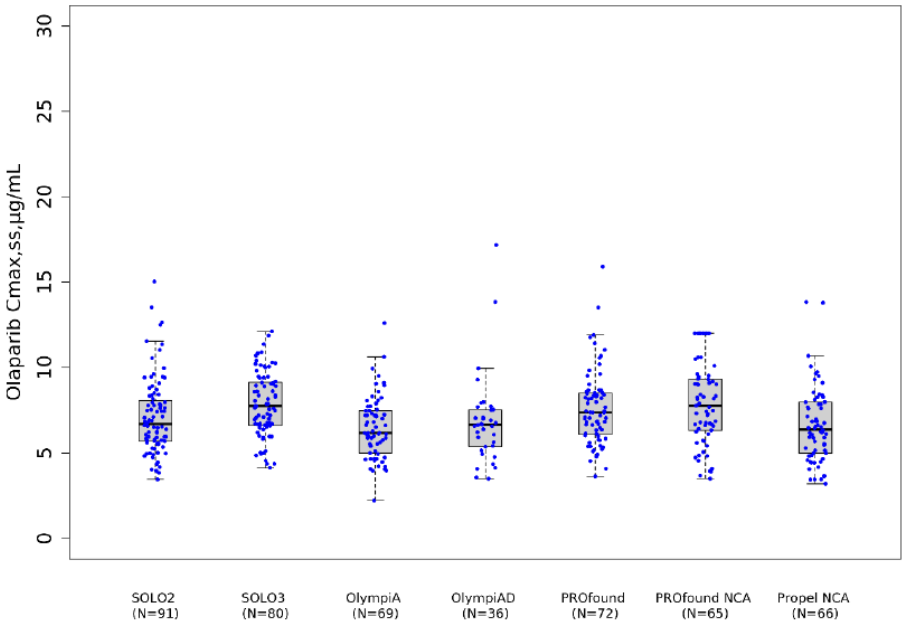


Figure 4: Comparison of olaparib Cmax,ss in phase 3 studies by Box plot

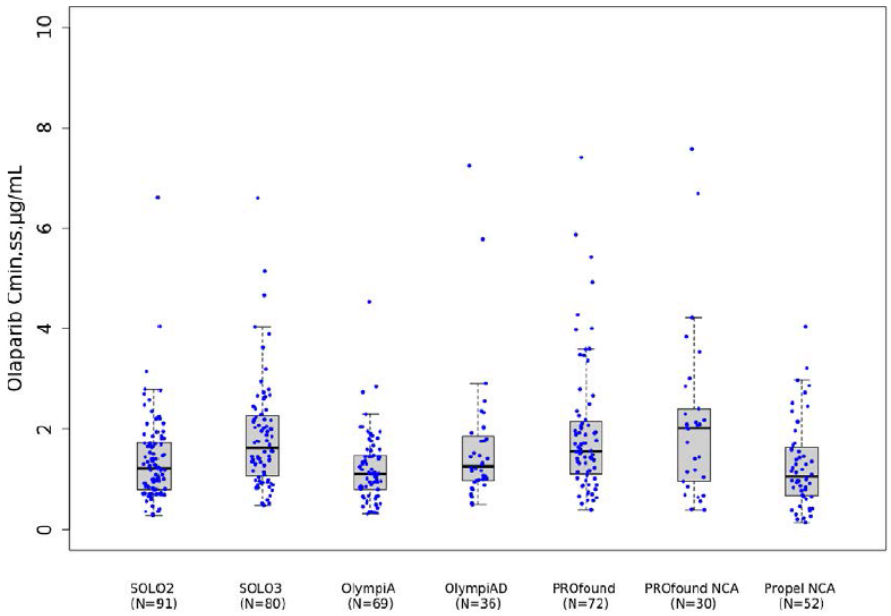


Figure 5: Comparison of olaparib Cmin,ss in phase 3 studies by Box plot

Effect of olaparib on abiraterone PK pharmacokinetics

Study D081DC00008

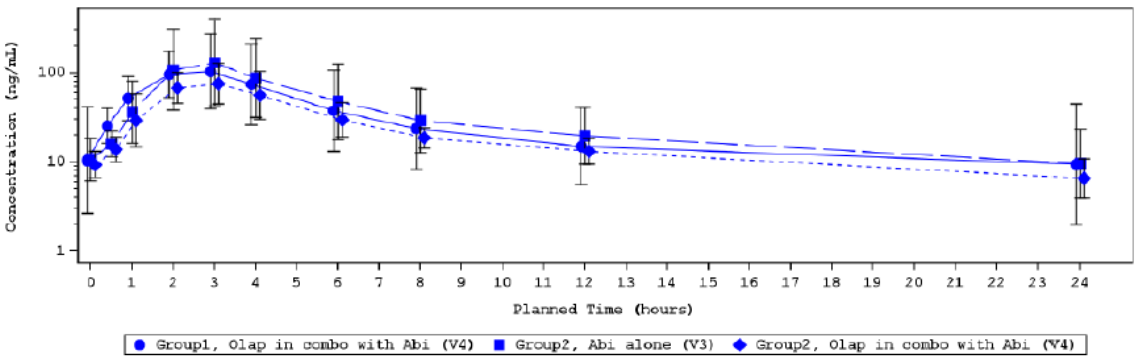
Pharmacokinetic results

Following multiple dosing to steady state of abiraterone 1000 mg od, the Cohort 2 key abiraterone steady state plasma PK parameter results summarised by group and visit are presented in Table 6 and the Gmean plasma concentration-time profiles for all groups and visits are illustrated in Figure 6.

Table 6: Summary of steady state pharmacokinetic parameters of abiraterone (PK analysis set)

	Cohort 2, Group 1 (N=7=			Cohort 2, Group 2 (N=6)
	Abiraterone (Visit 3) N=6	Olaparib+ abiraterone (Visit 4) N=4	Ratio[a] (Visit 4: Visit 3) N=4	Olaparib+ abiraterone (Visit 4) N=6
Css,max (µg/mL)a	145.8 (135.5%)	86.12 (48.88%)	0.8131 (85.06%)	130.7 (68.87%)
Css,min (µg/mL)a	8.376 (96.52%)	6.358 (50.96%)	0.9452 (35.65%)	7.983 (163.3%)
AUCss (µg·h/mL)a	825.5 (105.5%)	524.6 (37.65%)	0.8663 (55.43%)	718.9 (102.0%)
Tmax,ss (h) c	2.525 [1.00-3.00]	2.5 [2.0-3.02]		3.0 [1.08 – 3.0]
CLss/F (L/h)a Arithmetic means	1693 (97.79%)	2013 (40.68%)		1922 (98.08%)

a Geometric mean and %GCV are calculated using log transformed data.
b Arithmetic mean, SD and %CV are calculated using untransformed data
c Median, min, and max



Cohort 2, Group 1: olaparib 300 mg bid for 3-7 days then olaparib 300 mg bid+abiraterone 1000 mg od for at least 5 days.
Cohort 2, Group 2: abiraterone 1000 mg od for 5-7 days then olaparib 300 mg bid+abiraterone 1000 mg od for at least 3 days.
Gmean, Gmean+GSD and Gmean-GSD were calculated using log transformed data.
Concentrations where actual time deviates more than 10% from scheduled time, or incorrect dosing interval prior to PK sampling, have been excluded.
bid twice daily; Gmean geometric mean; GSD geometric standard deviation; od once daily.

Figure 6: Gmean (±GSD) steady state abiraterone plasma concentration versus time following 1000 mg od dosing: semi-logarithmic scale (PK analysis set)

Study D081SC00001 (cut-off date 30/07/2021)

Primary Objective	To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of rPFS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.
Secondary Objective	Only related to PK interactions • To determine steady-state exposure to abiraterone and its active metabolite delta4-abiraterone in the presence and absence of olaparib. • To determine steady-state exposure to olaparib when co-administered with abiraterone.
Design	A phase 3 randomised, double-blind, placebo-controlled, multicentre, international
Population	Randomised received treatments 794

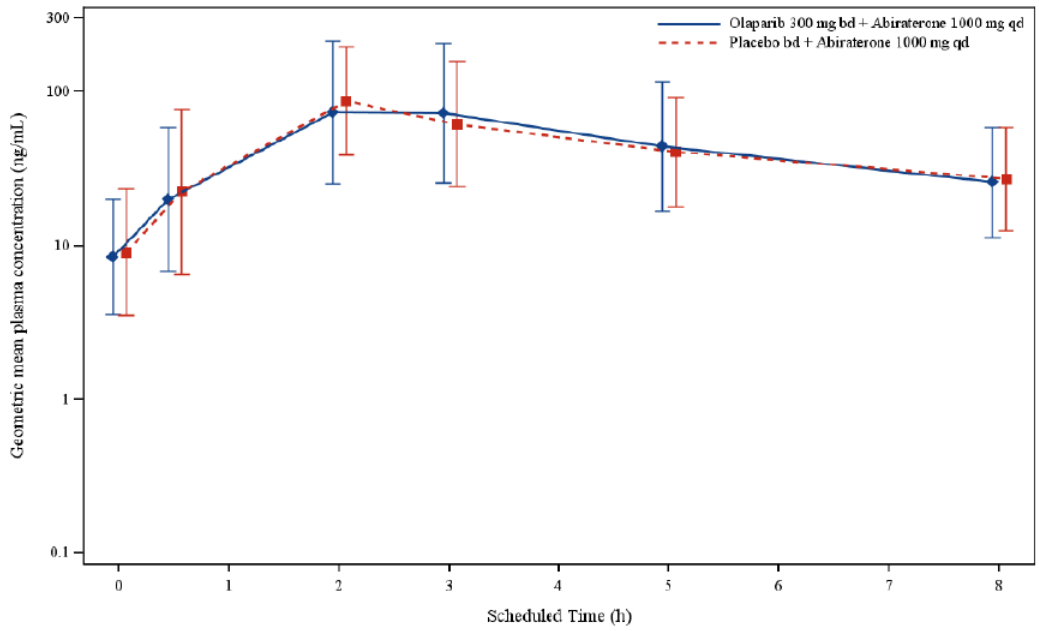
N:Entered/ Analyzed	At cut-off date 30///07/2021, 247 patients completed the study 549 patients on-going PK analysis set N = 124
Treatments	Patients received oral treatment with olaparib 300 mg bd + abiraterone 1000 mg qd, or placebo bd + abiraterone 1000 mg qd. Patients in both treatment arms also received either prednisone or prednisolone 5 mg bd, since abiraterone is indicated in combination with prednisone or prednisolone for treatment of patients with mCRPC
Sampling	At visit 4, samples to be collected at the following times: Pre-dose (- 30 min ± 15 min), and post-dose at 30 min ± 15 min, 2 h ± 0.5 h, 3 h ± 0.5 h, 5 h ± 0.5 h, and 8 h± 1 h

Pharmacokinetic results

Following multiple dosing to steady state of abiraterone 1000 mg qd administered alone or co-administered with olaparib 300 mg bd, the abiraterone steady state plasma PK parameters are summarised in Table 7, and the Gmean ± GSD plasma concentration-time profiles are illustrated in Figure 7. Interpatient variability, as indicated by the %GCV values, was very high for AUCss, Cmax,ss, and Cmin,ss.

Table 7: Summary of Steady State PK Parameters of abiraterone (PK Analysis Set)

Parameter		**Placebo bd + abiraterone 1000 mg qd (N = 58)**	**Olaparib 300 mg bd + abiraterone 1000 mg qd (N = 66)**
$C_{max,ss}$ (ng/mL)	n [a]	56	64
	Geometric	105.4 (105.6)	112.6 (136.9)
$C_{min,ss}$ (ng/mL)	n [a]	44	54
	Geometric	8.454 (95.10)	7.711 (92.41)
AUC_{0-8} (ng·h/mL)	n [a]	44	54
	Geometric	339.5 (77.99)	393.7 (107.5)
$t_{max,ss}$ (h)	n [a]	56	64
	Median	2.00 [0.00 - 8.00]	2.04 [0.00 – 8.00]



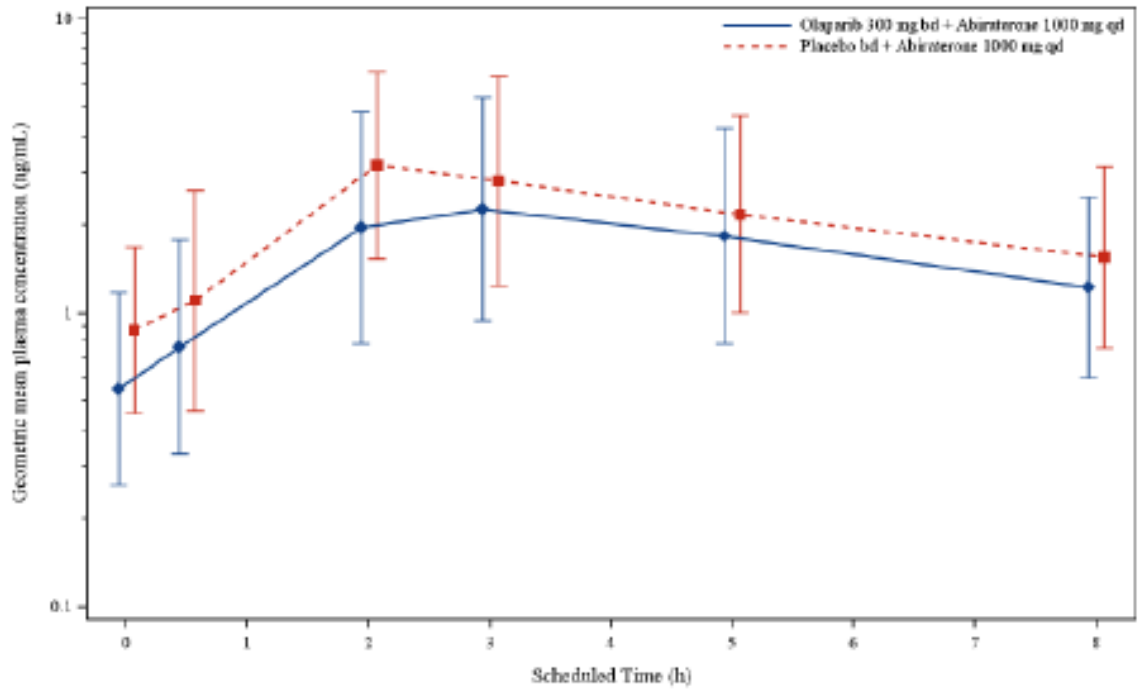
Pre-dose actual sample times are imputed to time = 0 hours.
bd, twice daily; Gmean, geometric mean; GSD, geometric standard deviation; qd, once daily.

Figure 7: Geometric Mean (± GSD Error Bars) Plasma Concentrations (ng/mL) of Abiraterone, Study Day 29 – Semi-logarithmic Plot (PK Analysis Set)

Following multiple dosing to steady state of abiraterone 1000 mg qd administered alone or co-administered with olaparib 300 mg bd, the active metabolite delta4-abiraterone steady state plasma PK parameters are summarised in Table 8, and the Gmean ± GSD plasma concentration-time profiles are illustrated in Figure 8.

Table 8: Summary of Steady State PK Parameters of Delta4-abiraterone (PK Analysis Set)

Parameter		Placebo bd + abiraterone 1000 mg qd	Olaparib 300 mg bd + abiraterone 1000 mg qd (N = 66)
$C_{max,ss}$ (ng/mL)	n [a]	58	65
	Geometric mean	3.903 (100.3)	3.019 (101.8)
$C_{min,ss}$ (ng/mL)	n [a]	44	54
	Geometric mean	0.7086 (68.02)	0.4907 (79.39)
AUC_{0-8}	n [a]	44	54
	Geometric mean	14.65 (70.99)	11.72 (80.30)
$t_{max,ss}$ (h)	n [a]	58	65
	Median	2.01 [0.00 – 7.00]	2.58 [0.00 – 8.00]
$MRC_{max,ss}$	n [a]	44	54
	Geometric mean	0.03484 (65.99)	0.02412 (59.32)
$MRC_{min,ss}$	n[a]	43	54
	Geometric mean	0.08267 (80.28)	0.06364 (55.31)
$MRAUC_{0-8}$	n [a]	44	54
	Geometric mean	0.04315 (62.81)	0.02976 (53.92)



Pre-dose actual sample times are imputed to time = 0 hours.
bd, twice daily; GSD, geometric standard deviation; qd, once daily.

Figure 8: Geometric Mean (± GSD Error Bars) Plasma Concentrations (ng/mL) of Delta4-abiraterone – Study Day 29 – Semi-logarithmic Plot (PK Analysis Set)

The slight increase in abiraterone exposure and the decrease in delta4-abiraterone exposure when abiraterone 1000 mg qd was co-administered with olaparib 300 mg bd, resulted in metabolite to parent ratios of the exposure parameters (MRAUC0-8, MRCmax,ss, and MRCmin,ss) approximately 31%, 31%, and 23% lower, respectively, than that observed for abiraterone 1000 mg qd administered alone.

2.3.3. Pharmacodynamics

No new primary or secondary studies were provided which was considered acceptable by the CHMP.

2.3.4. Discussion on clinical pharmacology

The pharmacokinetic (PK) properties of olaparib have been sufficiently characterized in the initial MAA.

PK data from a pivotal Phase 3 study (PROpel) was submitted. In this study, the PKs of olaparib in the target patients were assessed and compared to other cancer patients (in other indications), by graphical exploration (Figure 2)

Olaparib PK exposure following a 300 mg twice a day (BID) dosing schedule (with combination to abiraterone) in the PROpel study was similar to that observed in previous studies at the same dose. The slight increase in abiraterone exposure and the decrease in delta4-abiraterone exposure when abiraterone 1000 mg qd was co-administered with olaparib 300 mg bd, resulted in metabolite to parent ratios of the exposure parameters lower than that observed for abiraterone 1000 mg qd administered alone. Based on the large variability observed in the steady state exposure parameters of delta4-abiraterone and the low exposure of delta4-abiraterone relative to abiraterone, the small differences in the steady state exposure parameters of delta4-abiraterone observed between the 2

treatment arms were considered clinically not relevant. Steady state exposures (based on Cmax,ss, Cmin,ss, and AUC(0-8) for delta4-abiraterone were slightly lower in the olaparib+abiraterone treatment arm (geometric mean Cmax,ss, Cmin,ss, and AUC(0-8) was 20%, 23%, and 31% lower, respectively). Although delta4-abiraterone is an active metabolite of abiraterone, its steady state plasma concentrations even at Cmax,ss were just slightly above or below 3.5 ng/mL, the concentration required to achieve a 50%-inhibition of CYP17A1 activity (Blanchet et al 2018). Therefore, delta4-abiraterone is unlikely to have meaningful contribution to the overall activity of abiraterone in mCPRC.

Overall the observed olaparib AUCss distribution in the PROpel study overlap with the predicted AUCss from others Phase 3 studies.

One phase 2 study, Study D081DC0008 , was presented to evaluate potential interaction between the two drugs, olaparib 300 mg bid and abiraterone 1000 mg QD indicated for treatment of mCRPC patients.

Based on this phase 2 D081DC00008, and the phase 3 PROpel studies, no clear PK interations on abiraterone PK was showed. Indeed, the phase 2 study (D081DC00008) was not designed to provide quantitative assessment of PK interaction on abiraterone PK following olaparib co-administration with very limited sample size (between treatment comparisons within individual N=4), and the phase 3 study results showed large variability with very small numerical differences in PK parameters (less than 10% increase for Cmax,ss, and 15% increase for AUC0-8h) between the group receiving abiraterone only, and the other group receiving both abirateone and olaparib. In all cases, the observed magnitude of numerical changes after co-administration of olaparib were below 20%.

In summary based on the phase 3 and phase 2 clinical studies, clinically significant PK interactions on abiraterone's PK (co-administered with 10 mg prednisolone) is not expected.

PK interactions between olaparib (300 mg bid) and abiraterone (1000 mg qd) in presence of prednisolone 10 mg per day were assessed in phase 2 D081DC00008 study, and phase 3 PROpel study. The results showed no clinical interactions between the two active substances.

Given abiraterone is already indicated with 10 mg prednisolone daily (5 mg bid) in mCRPC treatment the absence of further documentation of prednisolone interactions with olaparib and abiraterone is deemed acceptable, especially considering cross-study comparisons showed olaparib PK from the phase 3 study D081sc00001 were comparable to previous olaparib phase 3 study administered in monotherapy.

Abiraterone, olaparib, and prednisolone are CYP3A4 substrates. As interaction study with strong CYP3A4 inhibitor was only clinically significant for olaprib, it is likely that the combination of the three drugs with CYP3A4 inhibitors would be driven by olaparib.

Given the overall three drugs perpetrors potentials do not overlap, the combination of the three should not potentiate each drug interaction potentials. Although both olaparib and abiraterone were identified in vitro as CYP1A2 inducer, since abiraterone only slightly induce CYP1A2 in vitro up to 10 µM, it is unlikely the drug combination would result in a greater induction as compared to the drugs taken separately. Therefore, the presented SmPC recommendation on drug interaction is deemed sufficient.

From a mechanistical perspective, CYP3A4/5 are the isozymes predominantly responsible for the metabolic clearance of olaparib and abiraterone is mainly inhibitor of the hepatic drug-metabolising enzymes CYP2D6 and CYP2C8. In this context, no DDI is expected between the two molecules with Olaparib as victim. Prednisolone seems not to have any effect on the PK of CYP3A4 metabolised drugs like midazolam (Marcantonio E. et al. 2014) and therefore an effect is not expected on olaparib.

Finally, no significant PK signal (>20%) is detected when these drugs are taken concomitantly in the phase 2 and phase 3 studies.

The 300 mg BID was selected as the recommended dose of olaparib within the combination as it is consistent with the dose in current SmPC for the approved indications in the monotherapy setting. In study D081DC0008, no dose-limiting toxicities (DLTs) occurred in the combination of either olaparib 200mg or 300mg. The rationale for choosing the higher dose used as monotherapy is barely justified by efficacy or PD data. However, as the pivotal Phase 3 trial was conducted with the dose of 300 mg, it is not known whether similar efficacy could be observed with a lower dose while improving the safety profile.

2.3.5. Conclusions on clinical pharmacology

The current clinical pharmacology package provides sufficient characterisation of the key PK characteristics of Olaparib when combined with abiraterone.

No significant difference in PKs characteristics is observed in the target patients in PROpel study by comparison to the patients already assessed in other olaparib indications.

2.4. Clinical efficacy

Dose response study

No dedicated dose response study was performed. The selected dose of olaparib for the main study was the recommended monotherapy dose approved in its currently approved indication (300 mg BID) with the 150 mg strength tablet.

The selected dose for abiraterone acetate was 1000 mg with 5 mg prednisone (or prednisolone) administered orally qd. The use of olaparib 300 mg bd in combination with abiraterone 1000 mg qd in the current study (PROpel) was also supported by safety and PK data from Study D081DC00008, which evaluated olaparib in combination with abiraterone at the same dose.

2.4.1. Main study

Study D081SC00001 (PROpel)

Methods

This was a Phase III, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy and safety of olaparib or placebo, each combined with abiraterone, as first-line therapy in patients with mCRPC. Patients were biomarker unselected.

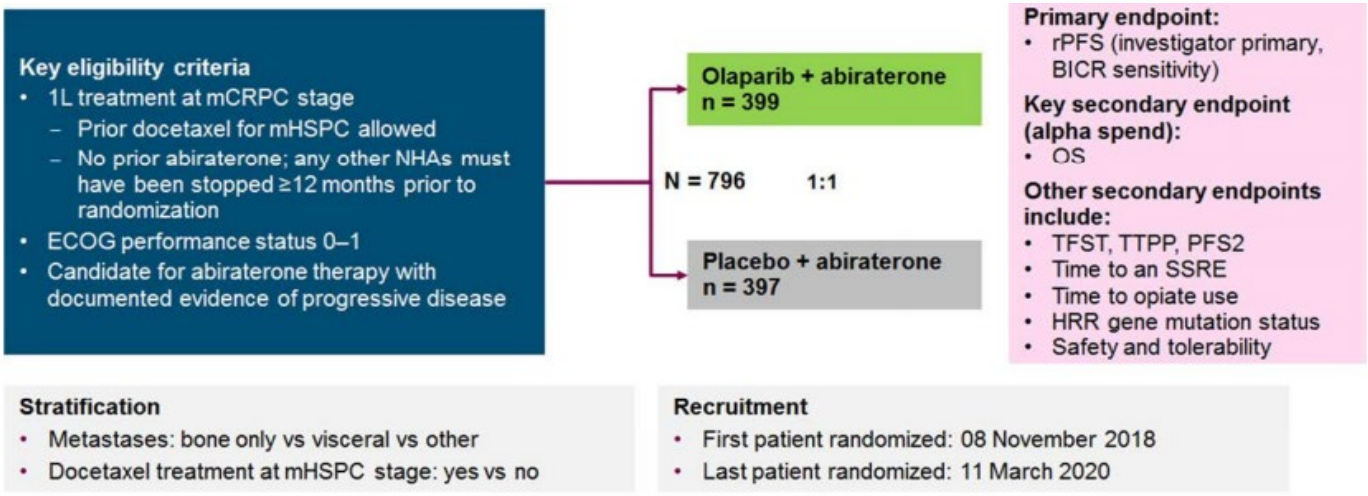
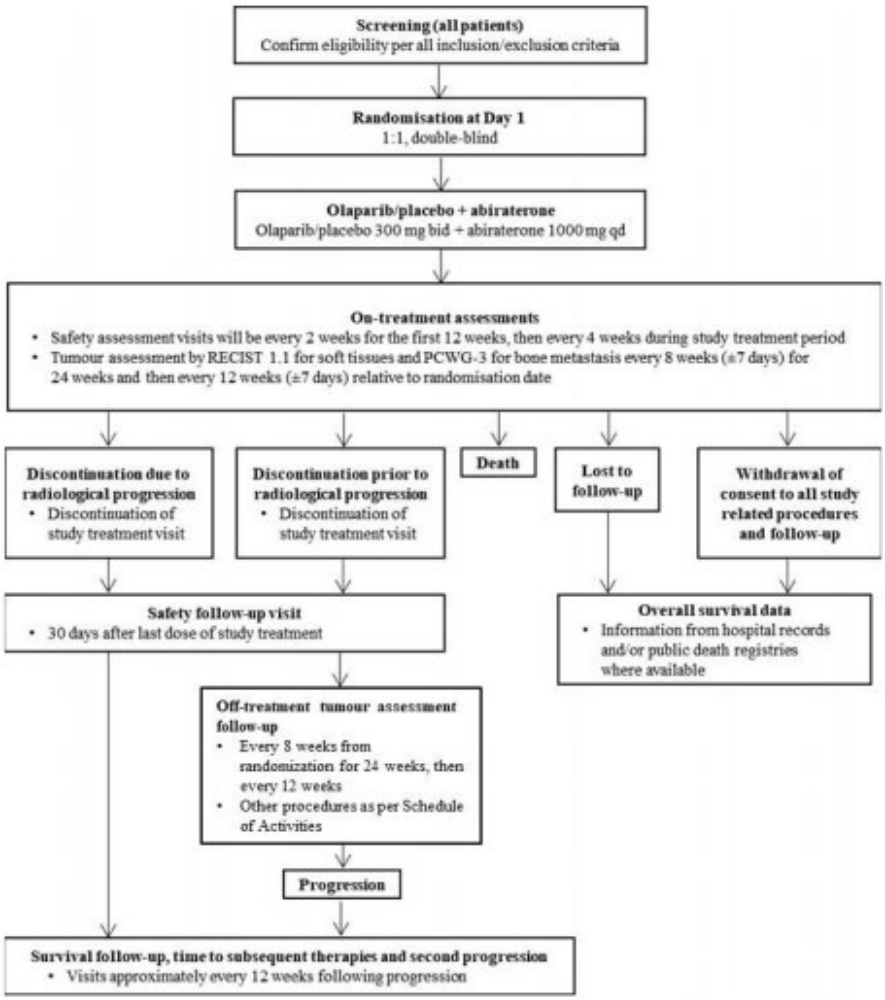


Figure 9: PROpel Study Design



Bid, twice daily; CSR, clinical study report; PCWG-3, Prostate Cancer Working Group 3; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours.
Source: PROpel CSR, Module 5.3.5.1.

Figure 10: PROpel Study Flow Chart

Study participants

Inclusion criteria

1. Male ≥ 18 years of age (or ≥ 19 years of age in South Korea) at the time of signing the informed consent form. For patients enrolled in Japan who were < 20 years of age, written informed consent should have been obtained from the patient and from his legally acceptable representative.

2. Histologically or cytologically confirmed prostate adenocarcinoma.

3. Metastatic status defined as at least 1 documented metastatic lesion on either a bone scan or a CT/MRI scan

4. First-line mCRPCPatients should not have received any cytotoxic chemotherapy, NHA, or other systemic treatment (approved drugs or experimental compounds) in the mCRPC setting. ADT was an exception. Treatment with first-generation antiandrogen agents (eg, bicalutamide, nilutamide, and flutamide) before randomisation was allowed, with a washout period of 4 weeks. Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage, as long as no signs of failure or disease progression occurred during or immediately after such treatment. Prior to mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without PSA progression/clinical progression/radiological progression during treatment was allowed, provided the treatment was stopped at least 12 months before randomisation.

5. Ongoing androgen deprivation with gonadotropin-releasing hormone analogue or bilateral orchiectomy, with serum testosterone with serum testosterone <50 ng/dL (<2.0 nmol/L) within 28 days before randomisation. Patients receiving ADT at study entry should have continued to do so throughout the study.

6. Candidate for abiraterone therapy with documented evidence of progressive disease. Progressive disease at study entry defined as one or more of the following three criteria that occurred while the patient was on androgen deprivation therapy:

   - PSA progression defined by a minimum of two rising PSA levels with an interval of ≥1 week between each determination. The PSA value at the Screening visit should have been ≥1 µg/L (1 ng/mL) (per PCWG-3 criteria);
   - Soft-tissue disease progression defined by RECIST 1.1;
   - Bone progression defined by appearance of 2 or more new lesions on a bone scan (per PCWG-3 criteria).

7. Patients must have had normal organ and bone marrow function measured within 28 days prior to administration of study treatment as defined below:

   Haemoglobin ≥10.0 g/dL with no blood transfusion in the past 28 days.

   Absolute neutrophil count ≥1.5 × 109 /L.

   Platelet count ≥100 × 109 /L.

   Total bilirubin ≤1.5 × institutional ULN. Patients with known Gilbert's disease who had serum bilirubin ≤3 × ULN may have been enrolled.

Serum potassium ≥3.5 mmol/L.

Serum albumin ≥3.0 g/dL.

Aspartate aminotransferase/alanine aminotransferase ≤2.5 × ULN unless liver metastases were present, in which case values must have been ≤5 × ULN.

Creatinine clearance ≥51 mL/min, calculated using the Cockcroft-Gault equation for males or based on a 24-hour urine test: Estimated creatinine clearance = (140-age [years]) x weight (kg)/ serum creatinine (mg/dL) x 72

8. ECOG PS 0-1, with no deterioration over the previous 2 weeks.
9. The participant has, a life expectancy of at least 6 months.
10. Prior to randomisation, sites must have confirmed availability of either an archival formalin fixed, paraffin embedded tumour tissue sample, or a new biopsy taken during the screening window, which met the minimum pathology and sample requirements in order to enable HRR status subgroup analysis of the primary endpoint rPFS.
11. Male patients must have used a condom during treatment and for 3 months after the last dose of olaparib+abiraterone when having sexual intercourse with a pregnant woman or with a woman of childbearing potential. Female partners of male patients should have also used a highly effective form of contraception (see Appendix I, PROpel CSR, Module 5.3.5.1 for acceptable methods) if they were of childbearing potential. Male patients should not have donated sperm throughout the period of taking olaparib and for 3 months following the last dose of olaparib.

Key exclusion criteria included:

1. Had a known additional malignancy that had progression or required active treatment in the last 5 years. Exceptions included basal cell carcinoma of the skin, and squamous cell carcinoma of the skin that had undergone potentially curative therapy.
2. Patients with MDS/AML or with features suggestive of MDS/AML.
3. Clinically significant cardiovascular disease as evidenced by MI or arterial thrombotic events (eg, stroke) in the past 6 months, severe or unstable angina, atrial fibrillation or other cardiac arrhythmia requiring therapy, or New York Heart Association Class II-IV heart failure or cardiac ejection fraction measurement of <50% during screening as assessed by echocardiography or multigated acquisition scan.
4. Planned or scheduled cardiac surgery or percutaneous coronary intervention procedure.
5. Prior revascularisation procedure (significant coronary, carotid, or peripheral artery stenosis).
6. Uncontrolled hypertension (systolic BP ≥ 160 mmHg or diastolic BP ≥ 95 mmHg). Patients with a history of hypertension were allowed provided BP was controlled by antihypertensive treatment.
7. History of uncontrolled pituitary or adrenal dysfunction.
8. Active infection or other medical condition that would have made prednisone/prednisolone use contraindicated.
9. Any chronic medical condition requiring a systemic dose of corticosteroid >10 mg prednisone/prednisolone per day.
10. Patients who were considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease or active, uncontrolled infection. Examples include,

but are not limited to, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, active pneumonitis, extensive interstitial bilateral lung disease on high-resolution CT scan, or any psychiatric disorder that prohibits obtaining informed consent and following the study procedures.

11. Persistent toxicities CTCAEs Grade > 2 caused by previous cancer therapy, excluding alopecia.

12. Patients with brain metastases. A scan to confirm the absence of brain metastases was not required.

13. Patients with spinal cord compression are excluded unless they were considered to have received definitive treatment for this and had evidence of clinically SD for 4 weeks.

14. Patients who were unevaluable for both bone and soft tissue progression as defined by meeting both of the following criteria: – A bone scan referred to as a superscan showing an intense symmetric activity in the bones. – No soft tissue lesion (measurable or nonmeasurable) that can be assessed by RECIST.

15. Patients who were unable to swallow orally administered medication and patients with gastrointestinal disorders likely to interfere with absorption of the study medication.

16. Immunocompromised patients, eg, patients who are known to be serologically positive for human immunodeficiency virus.

17. Patients with known active hepatitis infection (ie, hepatitis B or C).

18. Any previous treatment with PARP inhibitor, including olaparib.

19. Patients receiving any systemic chemotherapy or radiotherapy (except for palliative reasons) within 3 weeks prior to study treatment. Patients who received palliative radiotherapy need to stop radiotherapy 1 week before randomisation.

20. Any previous exposure to a CYP17 (17α-hydroxylase/C17,20-lyase) inhibitor (eg, abiraterone, orteronel).

21. Concomitant use of known strong CYP3A inhibitors (eg, itraconazole, telithromycin, clarithromycin, protease inhibitors boosted with ritonavir or cobicistat, indinavir, saquinavir, nelfinavir, boceprevir, telaprevir) or moderate CYP3A inhibitors (eg, ciprofloxacin, erythromycin, diltiazem, fluconazole, verapamil). The required washout period prior to starting study treatment was 2 weeks.

22. Concomitant use of known strong CYP3A inducers (eg, phenobarbital, enzalutamide, phenytoin, rifampicin, rifabutin, rifapentine, carbamazepine, nevirapine or St John's wort) or moderate CYP3A inducers (eg, bosentan, efavirenz or modafinil). The required washout period prior to starting study treatment was 5 weeks for phenobarbital and enzalutamide and 3 weeks for other agents.

23. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

24. Previous allogenic bone marrow transplant or double umbilical cord blood transplantation.

25. Participation in another clinical study with an investigational product or investigational medical devices within 1 month of randomisation.

26. History of hypersensitivity to olaparib or abiraterone, any of the excipients of olaparib or abiraterone, or drugs with a similar chemical structure or class to olaparib or abiraterone.

Treatments

Patients were randomised in a 1:1 ratio to the treatments as specified below:

1. Olaparib tablets orally 300 mg [2 x 150 mg tablets] twice daily [bd], tablet formulation in combination with abiraterone (1000 mg [2 x 500 mg tablets] once daily)

2. Placebo to match Olaparib in combination with abiraterone 1000 mg

Patients in both arms also received either prednisone or prednisolone 5 mg twice daily.

Treatment was continued until radiological progression of the underlying disease or unacceptable toxicity.

Objectives

Table 9: Objectives and endpoints

Objectives [a]	Endpoints
Primary	
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of rPFS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• rPFS, defined as the time from randomisation to 1) radiological progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first.
Key Secondary	
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of OS in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• OS, defined as the time from randomisation to death from any cause.
Other Secondary	
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to start of first subsequent anticancer therapy or death (TFST) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• TFST, ie, the time from randomisation to: 1) the start of the first subsequent anticancer therapy or 2) death from any cause. [b]
• To determine the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone as assessed by time to pain progression (TTPP) in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• TTPP is defined as the time from randomisation to pain progression based on the BPI-SF Item 3 'worst pain in 24 hours' and opiate analgesic use (AQA score). [c]

Objectives	Endpoints
• To further evaluate the efficacy of the combination of olaparib and abiraterone vs placebo and abiraterone by assessment of time to opiate use, time to an SSRE, and PFS2 in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• Time to opiate use: The time from randomisation to the first opiate use for cancer-related pain. • Time to an SSRE: the time from randomisation to the first SSRE. An SSRE is defined as use of radiation therapy to bone in order to prevent or relieve skeletal complications, occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral, resulting from minimal or no trauma), occurrence of radiologically confirmed spinal cord compression or a tumour-related orthopaedic surgical intervention. • PFS2: The time from randomisation to second progression on next-line anticancer therapy by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression, or death.
• To assess the effect of the combination of olaparib and abiraterone vs placebo and abiraterone on disease related symptoms and HRQoL using BPI-SF and Functional Assessment of Cancer Therapy (FACT) - Prostate Cancer (FACT-P) questionnaires in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• BPI-SF: progression in pain severity domain, change in pain interference domain. • Change in FACT-P total score, FACT-G total score, TOI, FWB, PWB, PCS, and FAPSI-6.
• To evaluate tumour and blood samples collected from patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage for mutations in *BRCA1*, *BRCA2*, *ATM*, and 11 other HRR genes. [d]	• HRR gene mutation status.
• To determine steady-state exposure to abiraterone and its active metabolite delta4-abiraterone in the presence and absence of olaparib. • To determine steady-state exposure to olaparib when co-administered with abiraterone. [d]	• Plasma concentration data at steady state for olaparib, abiraterone, and delta4-abiraterone in the subset of patients evaluable for PK. • If sufficient data are available, PK parameters at steady state (eg, $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, and AUC_{0-8}) will be calculated in the PK patient subset. In addition, AUC_{ss} and CL_{ss}/F for olaparib and the metabolite to parent ratios for $C_{max,ss}$, $C_{min,ss}$ and AUC_{0-8} for Δ4 abiraterone will be determined. t_{last} will also be determined as a diagnostic parameter.
Safety	
• To evaluate the safety and tolerability of the combination of olaparib and abiraterone vs placebo and abiraterone in patients with mCRPC who have received no prior cytotoxic chemotherapy or NHA at mCRPC stage.	• AEs and SAEs, physical examination findings, vital signs (including BP and pulse rate), ECG findings and laboratory test results (including clinical chemistry and haematology parameters).

Sample size

The primary endpoint of the PROpel study was the rPFS at DCO1 (30 July 2021). It was planned to randomise approximately 720 patients (1:1 ratio of olaparib/placebo), with the rPFS analysis occurring once approximately 324 progression or death events had occurred.

It was expected that the targeted sample size of 720 patients with approximately 324 rPFS events (45 % maturity) would provide 89% power to show a statistically significant difference in rPFS at a 1-sided type 1 error rate at 2.5% if the true treatment effect had a hazard ratio (HR) of 0.68, corresponding to an assumed increase in median rPFS from 16.5 months (placebo+abiraterone) to 24.3 months (olaparib+abiraterone).

The primary analysis population was all patients randomised (ITT). A subgroup analysis based on HRR gene mutation status (mutated, wild-type, partially characterised) was conducted to determine whether efficacy in the combination is independent of HRR gene mutation status but this analysis was considered as exploratory compared to the primary analysis in the overall population.

Randomisation

First patient enrolled: 31 October 2018

Last subject enrolled: 11 March 2020

Data cut-off date 1: 30 July 2021

Patients were randomised 1:1 to study treatment with either olaparib in combination with abiraterone or placebo in combination with abiraterone.

Randomisation was stratified by site of distant metastases at baseline (bone only, visceral or other) and docetaxel treatment at the mHSPC stage (yes or no).

Blinding (masking)

PROpel was a double-blind study. Both investigators and patients remained blinded to randomised treatment for the study duration. Patients and investigators were not routinely unblinded to study treatment prior to the final OS analysis.

Statistical methods

- **rPFS**

Primary analysis

The rPFS analysis was planned for when approximately 324 events occurred and was defined as the time from randomisation until the earlier date of objective radiological disease progression, assessed by investigator, according to RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or death (by any cause in the absence of progression), regardless of whether the patient withdrew from randomised therapy or received another anticancer therapy prior to progression.

rPFS was analysed using a log-rank test stratified by site of distant metastases (bone only, visceral or other) and docetaxel treatment at the mHSPC stage (yes or no) to calculate a 2-sided p-value. As a key sensitivity analysis to the primary endpoint of rPFS by investigator assessment, a sensitivity analysis of rPFS using BICR as per RECIST 1.1 and PCWG-3 criteria was assessed using a stratified log-rank test.

Sensitivity analysis

1. A sensitivity analysis will be conducted using rpfs as assessed for all patients by BICR per RECIST 1.1 and PCWG-3 criteria
2. Assessment of possible evaluation-time bias that may be introduced if scans are not performed at the protocol-scheduled time points
3. Assessment of possible attrition bias by repeating the primary rpfs analysis except that the actual rpfs event times, rather than the censored time, of patients who progressed or died in the absence of progression immediately following 2, or more, missed tumor assessments will be included
4. Assessment of possible censoring bias

5. Sensitivity analysis using unequivocal clinical progression in addition to radiological progression (by repeating primary rpfs analysis with the addition of unequivocal progression as an event)

6. Sensitivity analysis for confirmation of bone progression (by repeating primary rpfs analysis with revised confirmation criteria for bone progression where bone progression accompanied by unequivocal clinical progression does not require a confirmatory bone scan)

7. Sensitivity analysis censoring patients with subsequent therapy or discontinuation of study drug (by repeating primary rpfs analysis censoring patients with subsequent therapy or discontinuation of study drug prior to progression)

Subgroup analysis:

The following subgroups of the full analysis set will be analysed for rPFS:

8. Metastases (bone only, visceral or other)

9. Docetaxel treatment at mHSPC stage (yes or no)

10. HRR status subgroup (mutated, wild-type or partially characterised)•

11. Mutation type (germline or somatic)

12. Eastern Cooperative Oncology Group (ECOG) performance status at baseline (0 or 1)

13. Age at randomisation (<65, ≥65)

14. Region (Asia, Europe, North and South America)

15. Race (White, Black/African-American, Asian, Other)

16. Baseline Prostate specific antigen (PSA) (above/below median baseline PSA of the patients across both treatment groups)

Secondary analysis

- **OS**, was defined as the time from randomisation until date of death (due to any cause). Any patient not known to have died at the time of analysis was censored based on the last recorded date on which the patient was known to be alive. Note: Survival calls were made in the week following the date of DCO for the analysis, and if patients were confirmed to be alive or if the death date was post the DCO date these patients were censored at the date of DCO.

- **PFS2**, was defined as the time from randomisation to second progression on next-line anticancer therapy following study treatment discontinuation, by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death, whichever occurred earlier. This definition of PFS2 is in accordance with the EMA draft 'Guideline on the clinical evaluation of anticancer medicinal products' (CHMP Anticancer Guideline 2019).

- **Time to first subsequent anticancer therapy or death,** was defined as the time from randomisation to the earlier of the first subsequent anticancer therapy start date following study treatment discontinuation or death from any cause. Any patient not known to have died at the time of the analysis and not known to have had a further anticancer therapy was censored at the last known time to have not received subsequent therapy, ie, the last visit where this was confirmed.

- **TTPP**, was defined as time from randomisation to pain progression based on the BPI-SF [Item 3] "worst pain in 24 hours" and opiate analgesic use (AQA score).

- **Time to opiate use,** was defined as the time from randomisation to the first opiate use for cancer-related pain.

- **Time to an SSRE,** was defined by any of the following or a combination thereof: • Use of radiation therapy to prevent or relieve skeletal symptoms • Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation was required • Occurrence of spinal cord compression. Radiologic documentation was required • Orthopaedic surgical intervention for bone metastasis.

- CTC conversion rate proportion of patients achieving CTC conversion at any time presented with 95% Cis

- Time to pain severity progression Stratified log-rank test. Hazard ratio using Cox proportional hazard model. KM plot. Logistic regression, adjusting for metastasis category and docetaxel treatment at mHSPC stage

- Pain palliation Proportion of patients with pain palliation at any time presented with 95% Cis. Logistic regression, adjusting for metastasis category and docetaxel treatment at mHSPC stage

- FACT-P Logistic regression, adjusting for metastasis category and docetaxel treatment at mHSPC stage. MMRM. Time to deterioration in FACT-P (FACT-P total score, Fact-G total score, TOI, FWB.PWB,PCS and FAPSI 6). Stratified log-rank test.. Hazard ratio using Cox proportional hazard model. KM plot. Forrest plot

A multiple testing procedure was employed across the primary endpoint of rPFS and the key secondary endpoint of OS. The MTP for the PROpel study is based on analyses at three DCOs. As statistical significance of rPFS was achieved at DCO1, formal rPFS analysis at DCO2 will not be done and analysis of this endpoint at DCO2 will be considered descriptive (with nominal p-values provided). OS was formally analysed at DCO1 (interim analysis), and will be at DCO2 (interim analysis), and DCO3 (final analysis). The 1-sided alpha of 0.025 is fully allocated to rPFS. If the result for rPFS is statistically significant, OS will be tested in a hierarchical fashion. A multiplicity testing procedure based on the graphical approach in group sequential trials of Maurer and Bretz (Maurer and Bretz 2013), analogous to a simple sequential gatekeeping method, strongly controls the overall family-wise 1-sided error rate of 2.5%.

Details of planned analyses at each data cut-off

	DCO1	DCO2	DCO3
Time after first subject randomised	~ 31 months	~ 39 months	~ 48 months
rPFS (overall alpha=0.025)			
Power (%)	94.1	98.2	N/A
Events	379	453	
Information fraction	83.7	100	
Individual alpha	0.014	0.021	
Critical HR/delta (month)	0.799 / 4.2	0.826 / 3.5	
OS (overall alpha=0.025[a])			
Events	230	295	360
Information fraction	63.9	81.9	100.0
Individual alpha	0.00050	0.01295	0.02135
Critical HR/delta (month)	0.648 / 19.6	0.772 / 10.7	0.808 / 8.6

[a] Overall alpha based upon recycling from primary analysis hypothesis test. Assumes an OS median of 36 months in the control arm.

1-sided alpha is presented. DCO, Data cut-off; HR, Hazard ratio; N/A, Not applicable; OS, Overall survival; rPFS, Radiological progression-free survival.

Results

Participant flow

Table 10: PROpel: Patient Disposition (All Patients)

	Number (%) of patients		
	Olaparib+ abiraterone	**Placebo+ abiraterone**	**Total**
Patients enrolled [a]			1103
Patients randomised	**399 (100%)**	**397 (100%)**	**796 (100%)**
Patients who were not randomised			307
Screen failure			284
Patient decision			20
Incorrect enrolment			2
Other			1
Full analysis set	399 (100)	397 (100)	796 (100)
Patients who received treatment	398 (99.7)	396 (99.7)	794 (99.7)
Patients who did not receive treatment	1 (0.3)	1 (0.3)	2 (0.3)
Failure to meet randomisation criteria	1 (0.3)	0	1 (0.1)
Screen failure	0	1 (0.3)	1 (0.1)
Patients ongoing treatment at DCO [b]	180 (45.2)	137 (34.6)	317 (39.9)

	Number (%) of patients		
	Olaparib+ abiraterone	**Placebo+ abiraterone**	**Total**
Patients ongoing both olaparib/placebo and abiraterone [b]	168 (42.2)	134 (33.8)	302 (38.0)
Patients who discontinued olaparib/placebo alone [b]	12 (3.0)	2 (0.5)	14 (1.8)
Patient decision	1 (0.3)	0	1 (0.1)
Adverse event	11 (2.8)	2 (0.5)	13 (1.6)
Due to COVID-19 pandemic	0	0	0
Patients who discontinued abiraterone alone [b]	0	1 (0.3)	1 (0.1)
Adverse event	0	1 (0.3)	1 (0.1)
Due to COVID-19 pandemic	0	0	0
Patients who discontinued treatment [b]	218 (54.8)	259 (65.4)	477 (60.1)
Olaparib/Placebo [b]			
Patient decision	26 (6.5)	16 (4.0)	42 (5.3)
Adverse event	42 (10.6)	26 (6.6)	68 (8.6)
Severe non-compliance to protocol	2 (0.5)	3 (0.8)	5 (0.6)
Objective disease progression	94 (23.6)	147 (37.1)	241 (30.4)
Patient lost to follow-up	0	1 (0.3)	1 (0.1)
Other [c]	54 (13.6)	66 (16.7)	120 (15.1)
Due to COVID-19 pandemic	0	0	0
Abiraterone [b]			
Patient decision	25 (6.3)	18 (4.5)	43 (5.4)
Adverse event	31 (7.8)	28 (7.1)	59 (7.4)
Severe non-compliance to protocol	3 (0.8)	3 (0.8)	6 (0.8)
Objective disease progression	100 (25.1)	143 (36.1)	243 (30.6)
Patient lost to follow-up	0	1 (0.3)	1 (0.1)
Other [c]	59 (14.8)	66 (16.7)	125 (15.7)
Due to COVID-19 pandemic	0	0	0
Patients ongoing study at DCO	282 (70.7)	267 (67.3)	549 (69.0)
Patients who terminated study	117 (29.3)	130 (32.7)	247 (31.0)
Death	104 (26.1)	120 (30.2)	224 (28.1)
Failure to meet randomisation criteria	1 (0.3)	1 (0.3)	2 (0.3)
Screen failure	0	1 (0.3)	1 (0.1)
Patient decision	11 (2.8)	7 (1.8)	18 (2.3)
Other	1 (0.3)	1 (0.3)	2 (0.3)
Due to COVID-19 pandemic	0	0	0

a Informed consent received.
b Percentages are calculated from number of patients who received treatment.
c "Other" reason for discontinuation of treatment as provided by the investigator includes clinical

progression, PSA progression, death, etc.
Unless otherwise stated, percentages are calculated from the number of patients randomised.
Full analysis set - all randomised patients with treatment arms assigned in accordance with the randomisation, regardless of the treatment actually received.
"Due to COVID pandemic" refers to site closure due to pandemic impacting all patients at affected sites.
DCO1 date: 30 July 2021.COVID-19, Coronavirus Disease 2019; CSR, clinical study report; DCO, data cut-off; PSA, prostate specific antigen.

Recruitment

A total of 796 patients with mCRPC were randomised from 126 study centres in 17 countries worldwide : Australia (8 sites), Belgium (1 site), Brazil (7 sites), Canada (10 sites), Chile (4 sites), Czech Republic (4 sites), France (6 sites), Germany (9 sites), Italy (5 sites), Japan (18 sites), Netherlands (3 sites), Slovakia (4 sites), South Korea (6 sites), Spain (6 sites), Turkey (6 sites), United Kingdom (5 sites), United States (24 sites).

First patient enrolled: 31 October 2018

Last subject enrolled: 11 March 2020

Data cut-off date 1: 30 July 2021

The analyses presented in this report are based on the data cut-off 1: 30 July 2021 and the data cut-off 2: 14 March 2022.

Conduct of the study

Protocol amendments:

The global versions of protocol or protocol amendments are presented below.

Global Document Name	Version No	Version Date
First final version of the protocol prior to any amendments	1	02 Jul 2018
Amended CSP	2	05 Jan 2021
Amended CSP	3	14 May 2021

Protocol deviation

The number of patients with important protocol deviations in each treatment arm and overall is summarised below.

Table 11: Important protocol deviations (FAS)

Important protocol deviations [a]	Number (%) of patients Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=399)	Placebo bd + Abiraterone 1000 mg qd (N=397)	Total (N=796)
Number of patients with at least 1 important deviation	29 (7.3)	31 (7.8)	60 (7.5)
Failed inclusion criteria: histologically or cytologically confirmed prostate adenocarcinoma.	1 (0.3)	0	1 (0.1)
Failed inclusion criteria: metastatic status defined as at least one documented metastatic lesion on either a bone scan or a ct/mri scan.	3 (0.8)	7 (1.8)	10 (1.3)
Failed inclusion criteria: first line mcrpc.	5 (1.3)	3 (0.8)	8 (1.0)
Met exclusion criteria: clinically significant cardiovascular disease.	3 (0.8)	5 (1.3)	8 (1.0)
Met exclusion criteria: prior revascularisation procedure (significant coronary, carotid or peripheral artery stenosis).	2 (0.5)	5 (1.3)	7 (0.9)
Patient randomised but did not receive study treatment (olaparib or placebo).	1 (0.3)	1 (0.3)	2 (0.3)
Patient randomised but received their randomised study treatment (olaparib or placebo) at an incorrect dose.	1 (0.3)	1 (0.3)	2 (0.3)
Patient randomised but received an alternative study treatment (olaparib or placebo) to that which they were randomised; includes patients who received study treatment without ixrs	2 (0.5)	0	2 (0.3)
Patient randomised but received other steroid (eg, dexamethasone) than prednisone/prednisolone to support abiraterone treatment prior to study treatment discontinuation.	4 (1.0)	5 (1.3)	9 (1.1)

[a] Important deviations before the start of treatment and during treatment.
Deviation 2 triggering a sensitivity analysis (deviation bias) includes deviation 2.3 and deviation 2.4.
The same patient may have had more than one important protocol deviation.
COVID-19 Coronavirus Disease 2019. IPD Important protocol deviation.

Important protocol deviations [a]	Number (%) of patients Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=399)	Placebo bd + Abiraterone 1000 mg qd (N=397)	Total (N=796)
Patient received prohibited anti-cancer medication/therapy during study treatment period as per the protocol table 7; chemotherapy.	2 (0.5)	1 (0.3)	3 (0.4)
Patient received prohibited anti-cancer medication/therapy during study treatment period as per the protocol table 7; radiotherapy (except palliative).	1 (0.3)	2 (0.5)	3 (0.4)
Patient received prohibited anti-cancer medication/therapy during study treatment period as per the protocol table 7; other novel agents.	0	1 (0.3)	1 (0.1)
Met study treatment interruption or discontinuation criteria but continued study treatment and potentially had major impact to patient safety according to clinical judgement.	3 (0.8)	0	3 (0.4)
Baseline tumor assessment more than 42 days before start date of randomised treatment.	0	1 (0.3)	1 (0.1)
No baseline tumor assessment.	1 (0.3)	0	1 (0.1)

Important protocol deviations [a]	Number (%) of patients Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=399)	Placebo bd + Abiraterone 1000 mg qd (N=397)	Total (N=796)
Number of patients with at least 1 important deviation triggering a sensitivity analysis (deviation bias)	14 (3.5)	13 (3.3)	27 (3.4)
Patients who deviate from key inclusion criteria per the CSP (Deviation 1)	7 (1.8)	5 (1.3)	12 (1.5)
Patients who deviate from key exclusion criteria per the CSP (Deviation 2)	0	0	0
Patients randomised but incorrect treatment or dose received (Deviation 3)	5 (1.3)	6 (1.5)	11 (1.4)
Received prohibited anti-cancer therapy during study treatment period as per the protocol Table 7 (Deviation 4)	1 (0.3)	1 (0.3)	2 (0.3)
Baseline tumor assessments (Deviation 6)	1 (0.3)	1 (0.3)	2 (0.3)
Persistently missing tumor assessments (Deviation 8)	0	0	0

Baseline data

Table 12: PROpel: Summary of Key Demographic and Baseline Characteristics (FAS)

	Olaparib+ abiraterone (N = 399)	Placebo+ abiraterone (N = 397)
Demographics		
Age (years)		
Mean (standard deviation)	68.5 (8.50)	69.8 (7.93)
Median (Min, Max)	69.0 (43, 91)	70.0 (46, 88)
Age group (years), n (%)		
< 65	130 (32.6)	97 (24.4)
≥ 65	269 (67.4)	300 (75.6)
Total	399 (100)	397 (100)
Race n (%)		
White	282 (70.7)	275 (69.3)
Black or African-American	14 (3.5)	11 (2.8)
Asian	66 (16.5)	72 (18.1)
Native Hawaiian or Other Pacific Islander	2 (0.5)	0
American Indian or Alaska Native	1 (0.3)	0
Other	12 (3.0)	9 (2.3)
Missing	22 (5.5)	30 (7.6)
Total	399 (100)	397 (100)
Geographical region		
Europe	178 (44.6)	172 (43.3)
North and South America	130 (32.6)	121 (30.5)

Table 12: PROpel: Summary of Key Demographic and Baseline Characteristics (FAS)

	Olaparib+ abiraterone (N = 399)	Placebo+ abiraterone (N = 397)
Asia	91 (22.8)	104 (26.2)
Previous treatment modalities [a], n (%)		
Patients with any previous treatment modalities	365 (91.5)	380 (95.7)
Immunotherapy	4 (1.0)	3 (0.8)
Hormonal therapy	303 (75.9)	325 (81.9)
Cytotoxic Chemotherapy	98 (24.6)	100 (25.2)
Targeted therapy	0	1 (0.3)
Radiotherapy	206 (51.6)	194 (48.9)
Other	6 (1.5)	4 (1.0)
Prior treatment with second-generation antiandrogen agents prior to mCRPC stage		
Yes	1 (0.3)	0
Enzalutamide	1 (0.3)	0
No	398 (99.7)	397 (100)
Prior docetaxel treatment at mHSPC stage [b]		
Yes	90 (22.6)	89 (22.4)
No	309 (77.4)	308 (77.6)
Prior local therapy with curative intent for prostate cancer		
Yes	134 (33.6)	144 (36.3)
No	265 (66.4)	253 (63.7)

1.Patients can be counted in more than one previous disease related treatment modality. 2.As long as no signs of failure or disease progression occurred during or immediately after docetaxel treatment..3. Baseline pain score is based on a patient completing the BPI-SF questionnaire item #3 (worst pain) at least once during the seven day baseline period and is an average of weekly entries where applicable.

DCO1 date: 30 July 2021. FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle. BPI-SF, Brief Pain Inventory - Short Form; CSR, clinical study report; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; ITT, intention-to-treat; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; Min, minimum; Max, maximum; N, number of patients in treatment; n, number of patients included in analysis; PS, performance status; TNM, tumour, node, metastasis.

Table 13: Disease characteristics at baseline (FAS)

Disease characteristics		
Histology type, n (%)		
Adenocarcinoma	398 (99.7)	397 (100)
Other	1 (0.3)	0
Total Gleason Score, n (%)		
≤ 7	121 (30.3)	134 (33.8)

8 to 10	265 (66.4)	258 (65.0)
Missing	13 (3.3)	5 (1.3)
Distant metastases according to TNM Classification at diagnosis, n (%)		
M0	115 (28.8)	132 (33.2)
MX	26 (6.5)	22 (5.5)
M1	143 (35.8)	139 (35.0)
M1a	11 (2.8)	10 (2.5)
M1b	87 (21.8)	79 (19.9)
M1c	16 (4.0)	14 (3.5)
Missing	1 (0.3)	1 (0.3)
Time from initial diagnosis (months)		
n	399	397
Mean (standard deviation)	54.5 (49.89)	57.5 (50.26)
Median (Min, Max)	33.6 (4, 288)	39.5 (1, 279)
ECOG PS, n (%)		
(0) Normal activity	286 (71.7)	272 (68.5)
(1) Restricted activity	112 (28.1)	124 (31.2)
Missing	1 (0.3)	1 (0.3)
Baseline pain (BPI SF worst pain [Item 3]) score [c], n (%)		
0 (no pain)	133 (33.3)	137 (34.5)
>0-<4 (mild pain)	151 (37.8)	173 (43.6)
4-<6 (moderate pain)	53 (13.3)	36 (9.1)
>=6 (severe pain)	32 (8.0)	28 (7.1)
Missing	30 (7.5)	23 (5.8)
Type of prostate cancer progression, n (%)		
PSA progression	172 (43.1)	173 (43.6)
Radiological progression	92 (23.1)	73 (18.4)
Both	134 (33.6)	150 (37.8)
Missing	1 (0.3)	1 (0.3)
Baseline Prostate Specific Antigen (µg/L)		
Median	17.895	16.805
Min, Max	0.07, 1869.48	0.01, 1888.00
Baseline Haemoglobin (g/L)		
n	397	396
Mean (standard deviation)	131.0 (11.66)	131.3 (12.37)
Baseline S/P-alkaline phosphatase (µkat/L)		
n	396	395

Mean (standard deviation)	3.07 (3.721)	2.83 (2.763)
Baseline S/P-lactate dehydrogenase (µkat/L)		
n	389	392
Mean (standard deviation)	4.43 (3.138)	4.13 (3.445)

Numbers analysed

Table 14: Analysis sets

	Number of patients		
	Olaparib 300 mg bd + Abiraterone 1000 mg qd (N=399)	Placebo bd + Abiraterone 1000 mg qd (N=397)	Total (N=796)
Patients randomised	399	397	796
Patients included in full analysis set	399	397	796
Patients included in safety analysis set	398	396	794
Patients excluded from safety analysis set	1	1	2
Did not receive treatment	1	1	2
Patients included in evaluable for response analysis set (Investigator)	161	160	321
Patients excluded from evaluable for response analysis set (Investigator)	238	237	475
Did not have measurable disease at baseline	238	237	475
Patients included in evaluable for response analysis set (BICR)	162	149	311
Patients excluded from evaluable for response analysis set (BICR)	237	248	485
Did not have measurable disease at baseline	237	248	485
Patients included in PK analysis set	66	58	124
Patients excluded from PK analysis set	333	339	672
Did not receive treatment	1	1	2
No post-dose analysable plasma sample	24	28	52
Major protocol deviations/Adverse event	6	2	8
Patient not selected for PK analysis	302	308	610

HRR testing results

PROpel is an all-comers study and patient enrolment was not based on biomarker status. HRRm status was tested retrospectively using a ctDNA-based test (FoundationOne® Liquid CDx) and a tumour tissue test (FoundationOne® CDx). The reason 2 tests were used to define HRRm status is because despite best efforts, the failure rate of the tumour tissue gene mutation testing in prostate cancer is approximately 30% mainly due to small and poor-quality tumour tissue samples (Abida et al 2017). Accordingly, the tumour tissue test failure rate (31.6%) observed in PROpel was in line with what was observed in PROfound (31%; de Bono et al 2019) and published literature.

Of the 796 randomised patients in PROpel, 782 patients (98.2%) provided tumour samples for analysis with the tumour tissue test. Of the 782 patients with samples available for analysis, 535 patients (68.4%; 535/782) had a valid test result while 247 patients (31.6%; 247/782) failed testing. Adding the 14 patients with no tumour tissue sample, the number of patients with HRRm unknown status was 261 (32.8%). In contrast to the tumour tissue test, ctDNA gene mutation test failure rate was only 7.6% and 734 patients had a valid ctDNA test result.

In PROpel, 198 patients (24.9%) were classified with an HRRm using the ctDNA-based test compared to 118 patients (14.8%) using the tumour tissue test. In the aggregate analysis, there were 226 patients (28.4%) classified as HRRm and 552 patients (69.3%) who were classified as non-HRRm leaving only 18 patients who had no test results from either test and categorised as HRRm unknown.

Table 15: Patient distribution based on HRR gene mutation status by ctDNA-based test and tumor tissue test (FAS)

HRR gene mutation status	Number (%) of patients					
	ctDNA test			Tissue test		
	Olaparib+ abiraterone (N = 399)	Placebo+ abiraterone (N = 397)	Total (N = 796)	Olaparib+ abiraterone (N = 399)	Placebo+ abiraterone (N = 397)	Total (N = 796)
HRRm [a]	98 (24.6)	100 (25.2)	198 (24.9)	62 (15.5)	56 (14.1)	118 (14.8)
Non-HRRm [b]	269 (67.4)	267 (67.3)	536 (67.3)	207 (51.9)	210 (52.9)	417 (52.4)
HRRm unknown [c]	32 (8.0)	30 (7.6)	62 (7.8)	130 (32.6)	131 (33.0)	261 (32.8)
Total	399 (100)	397 (100)	796 (100)	399 (100)	397 (100)	796 (100)

Table 16: Prevalence of HRR alterations in tumour tissue in 535 successfully tested randomised patients in PROpel

Gene	Number of patients within screened population with specific mutation[a]	Prevalence
BRCA1	5	0.9%
BRCA2	45	8.4%
ATM	31	5.8%
BARD1	1	0.2%
BRIP1	0	0.0%
CDK12	35	6.5%
CHEK1	1	0.2%
CHEK2	2	0.4%
FANCL	1	0.2%
PALB2	4	0.7%
RAD51B	0	0.0%
RAD51C	0	0.0%
RAD51D	0	0.0%
RAD54L	3	0.6%

***Table 17*: Prevalence of single HRR alterations in tumour tissue in 535 successfully tested randomised patients in PROpel**

Gene	Number of patients within randomised population with a specific mutation[a]	Prevalence
BRCA1 only	4	0.7%
BRCA2 only	41	7.7%
ATM only	25	4.7%
BARD1 only	0	0.0%
BRIP1 only	0	0.0%
CDK12 only	30	5.6%
CHEK1 only	0	0.0%
CHEK2 only	1	0.2%
FANCL only	1	0.2%
PALB2 only	3	0.6%
RAD51B only	0	0.0%
RAD51C only	0	0.0%
RAD51D only	0	0.0%
RAD54L only	3	0.6%

Table 18 Prevalence of co-occurring HRR alterations in tumour tissue in 535 successfully tested randomised patients in PROpel

Gene	Number of patients within randomised population with a specific mutation[a]	Prevalence
Co-occurring with *BRCA1*	1	0.2%
Co-occurring with *BRCA2*	4	0.7%
Co-occurring with *ATM*	6	1.1%
Co-occurring with *BARD1*	1	0.2%
Co-occurring with *BRIP1*	0	0.0%
Co-occurring with *CDK12*	5	0.9%
Co-occurring with *CHEK1*	1	0.2%
Co-occurring with *CHEK2*	1	0.2%
Co-occurring with *FANCL*	0	0.0%
Co-occurring with *PALB2*	1	0.2%
Co-occurring with *RAD51B*	0	0.0%
Co-occurring with *RAD51C*	0	0.0%
Co-occurring with *RAD51D*	0	0.0%
Co-occurring with *RAD54L*	0	0.0%

Table 19: Prevalence of HRR mutations observed in ctDNA-based testing in PROpel

Gene	Number of patients within screened population with specific mutation[a]	Prevalence
BRCA1	11	1.5%
BRCA2	58	7.9%
ATM	60	8.2%
BARD1	3	0.4%
BRIP1	3	0.4%
CDK12	37	5.0%
CHEK1	0	0.0%
CHEK2	35	4.8%
FANCL	3	0.4%
PALB2	7	1.0%
RAD51B	2	0.3%
RAD51C	0	0.0%
RAD51D	1	0.1%
RAD54L	5	0.7%

Outcomes and estimation

Primary endpoint: radiographic Progression Free Survival (rPFS) based on investigator

The DCO for the analysis of rPFS presented in this CSR (DCO1: 30 July 2021) took place when 394 progression events had occurred (49.5% of maturity), approximately 33 months after the first patient was randomised. For the Full analysis set (FAS), rPFS by BICR at DCO2 (14 March 2022) were provided during the procedure.

The progression status based on investigator, according to RECIST 1.1 at the time of rPFS analysis is presented below

Table 20: PROpel: Summary of Key Efficacy Outcome Variables (FAS) (DCO1: 30 July 2021)

	Olaparib+abiraterone N = 399	Placebo+abiraterone N = 397
rPFS (by investigator assessment) (49.5% maturity)		
Number of events (%)	168 (42.1)	226 (56.9)
Median rPFS (95% CI) (months) [a]	24.84 (20.47, 27.63)	16.59 (13.93, 19.22)
HR (95% CI) [b]	0.66 (0.54, 0.81)	
p-value [c]	p<0.0001	
Patients progression-free at 12 months (%)	71.84	63.44
Patients progression-free at 24 months (%)	51.41	33.59
OS (28.6% maturity)		
Number of events (%)	107 (26.8)	121 (30.5)

	Olaparib+abiraterone N = 399	Placebo+abiraterone N = 397
Median OS (95% CI) (months) [a]	NC (NC, NC)	NC (NC, NC)
HR (95% CI) [b]	0.86 (0.66, 1.12)	
p-value [c]	p=0.2923	
PFS2 (20.6% maturity)		
Number of events (%)	70 (17.5)	94 (23.7)
Median PFS2 (95% CI) (months) [a]	NC (NC, NC)	NC (NC, NC)
HR (95% CI) [b]	0.69 (0.51, 0.94)	
p-value [c, d]	p=0.0184	
TFST (50.8% maturity)		
Number of events (%)	183 (45.9)	221 (55.7)
Median TFST (95% CI) (months) [a]	25.0 (22.2, NC)	19.9 (17.1, 22.0)
HR (95% CI) [b]	0.74 (0.61, 0.90)	
p-value [c, d]	p=0.0040	
TTPP (13.8% maturity)		
Number of events (%) [e]	56 (14.0)	54 (13.6)
Median TTPP (95% CI) (months) [a]	NC (NC, NC)	NC (NC, NC)
HR (95% CI) [b]	1.01 (0.69, 1.47)	
p-value [c, d]	p=0.9551	
Time to opiate use for cancer pain (11.3% maturity)		
Number of events (%) [f]	48 (14.0)	42 (11.9)
Median Time to opiate use (95% CI) (months) [a]	NC (NC, NC)	NC (NC, NC)
HR (95% CI) [b]	1.08 (0.71, 1.64)	
p-value [c, d]	p=0.6510	
Time to first SSRE (10.6% maturity)		
Number of events (%)	37 (9.3)	47 (11.8)
Median Time to first SSRE (95% CI) (months) [a]	NC (NC, NC)	NC (NC, NC)
HR (95% CI) [b]	0.72 (0.47, 1.11)	
p-value [c, d]	p=0.1324	

a. Calculated using the Kaplan-Meier technique. b.The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR <1 favours olaparib 300 mg bd.. c. The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy. d.The p-value presented is nominal as the endpoint is not alpha controlled. e. TTPP defined as time from randomisation to pain progression based on the BPI-SF Item 3 "worst pain in 24 hours" and opiate AQA score. f. Time to opiate use is defined as the time from date of randomisation to the date of first opiate use for cancer related pain. Only patients who are not on opiates at baseline are included.

FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.

AQA, analgesic quantification algorithm; bd, twice daily; BPI-SF, Brief Pain Inventory - Short Form; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; N, number of patients in treatment; NC, not calculable/not calculated; OS, overall survival; rPFS, radiological progression free survival; PFS2, time from randomisation to second progression or death; SSRE, symptomatic skeletal-related event; TFST, time from randomisation to first subsequent therapy or death; TTPP, time to pain progression.

Figure 11: PROpel: Kaplan-Meier Plot of rPFS by Investigator Assessment (FAS) (DCO1: 30 July 2021)

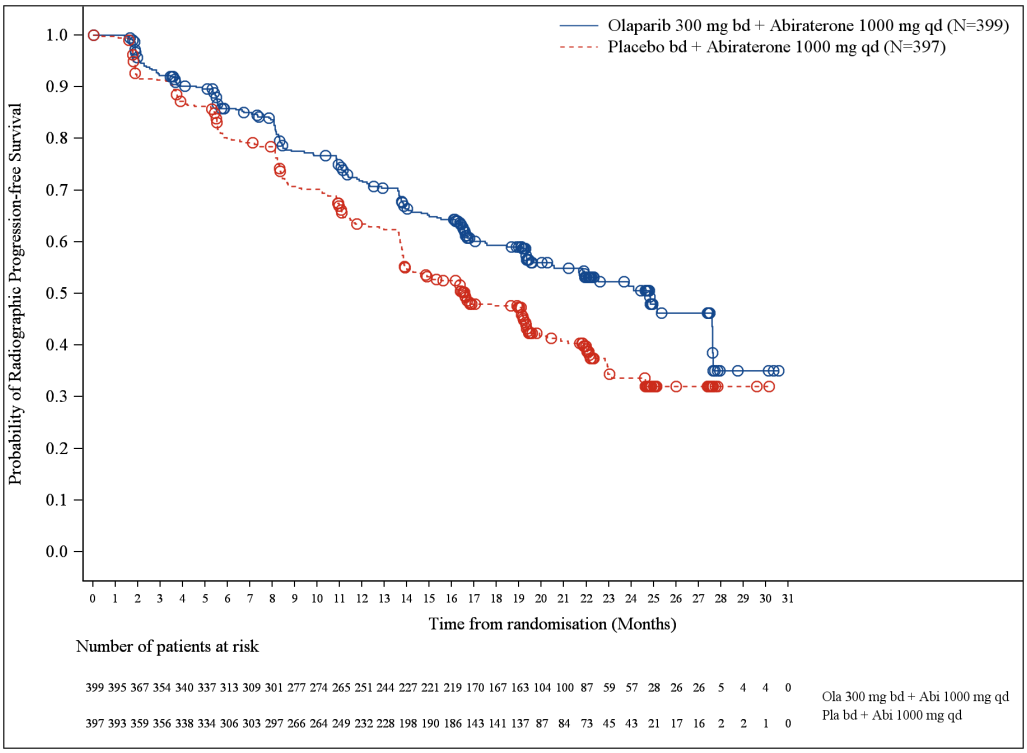


Table 21: PROpel study rPFS Based on Investigator Assessments (Full Analysis Set; DCO1: 30 July 2021 and DCO2: 14 March 2022

Type of Event	Number (%) of patients			
	DCO1		DCO2	
	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Total progression events, n (%)	168 (42.1)	226 (56.9)	199 (49.9)	258 (65.0)
RECIST progression only	73 (18.3)	111 (28.0)	81 (20.3)	128 (32.2)
Bone scan PCWG-3 criteria progression only	65 (16.3)	81 (20.4)	78 (19.5)	91 (22.9)
RECIST and bone scan PCWG-3 progression [a]	2 (0.5)	6 (1.5)	3 (0.8)	7 (1.8)
Death [b]	28 (7.0)	28 (7.1)	37 (9.3)	32 (8.1)
Censored patients, n (%)	231 (57.9)	171 (43.1)	200 (50.1)	139 (35.0)
Censored progression [c]	3 (0.8)	2 (0.5)	4 (1.0)	2 (0.5)
Censored death [d]	20 (5.0)	7 (1.8)	26 (6.5)	14 (3.5)
Progression free at time of analysis [e]	200 (50.1)	156 (39.3)	161 (40.4)	117 (29.5)
Lost to follow-up [f]	0	0	1 (0.3)	0
Withdrawn consent [f]	6 (1.5)	4 (1.0)	6 (1.5)	3 (0.8)

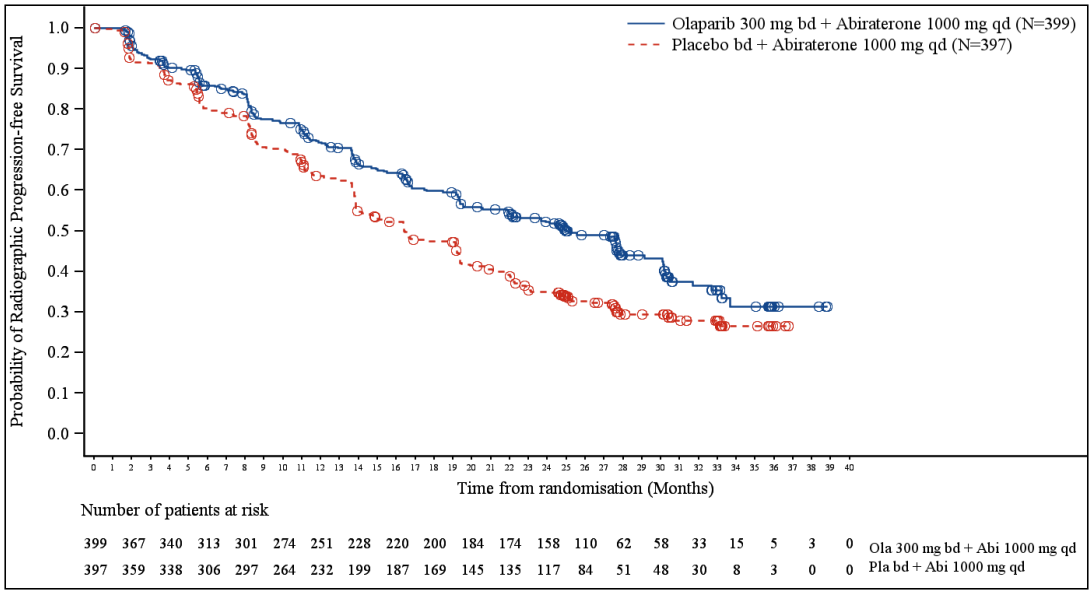
Type of Event	Number (%) of patients			
	DCO1		DCO2	
	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Discontinued study [f]	2 (0.5)	2 (0.5)	2 (0.5)	3 (0.8)
Median progression-free survival (95% CI) (months)	24.84 (20.47, 27.63)	16.59 (13.93, 19.22)	24.97 (20.57, 27.86)	16.39 (13.93, 19.19)
Hazard ratio [g]	**0.66**		**0.67**	
95% CI for hazard ratio [g]	**0.54, 0.81**		**0.56, 0.81**	
2-sided p-value [h]	**<0.0001**		**<0.0001**	
Progression-free survival rate at 6 months (95% CI) (%)	85.82 (81.90, 88.96)	79.94 (75.60, 83.59)	85.82 (81.90, 88.96)	79.94 (75.60, 83.59)
Progression-free survival rate at 12 months (95% CI) (%)	71.84 (66.93, 76.15)	63.44 (58.39, 68.06)	71.84 (66.93, 76.15)	63.44 (58.39, 68.06)
Progression-free survival rate at 18 months (95% CI) (%)	59.37 (54.01, 64.33)	47.65 (42.44, 52.66)	59.85 (54.56, 64.74)	47.46 (42.30, 52.43)
Progression-free survival rate at 24 months (95% CI) (%)	51.41 (45.28, 57.19)	33.59 (27.75, 39.52)	52.14 (46.74, 57.25)	35.04 (30.14, 39.96)
Progression-free survival rate at 30 months (95% CI) (%)	35.02 (24.08, 46.15)	31.95 (26.01, 38.04)	43.16 (37.24, 48.93)	29.46 (24.59, 34.49)
Progression-free survival rate at 36 months (95% CI) (%)	NC (NC, NC)	NC (NC, NC)	31.36 (23.65, 39.35)	26.60 (21.26, 32.21)
Median (range) duration of follow-up in censored patients [i]	19.32 (0.03 - 30.59)	19.35 (0.03 - 30.16)	24.92 (0.03 - 38.80)	27.43 (0.03 - 36.76)
Median (range) duration of follow-up in all patients [i]	16.46 (0.03 - 30.59)	14.00 (0.03 - 30.16)	18.46 (0.03 - 38.80)	14.16 (0.03 - 36.76)

Defined as RECIST and PCWG-3 progression at the same visit. Death in the absence of radiographic progression.RECIST or bone scan PCWG-3 progression event occurred after 2 or more missed visits.Includes patients who died after 2 or more missed visits. Includes patients not known to have progressed (defined as CR, PR, SD or NED by RECIST 1.1, and non-PD, NED or NE by PCWG-3 bone scan). No progression at the last RECIST or bone scan assessment.

The hazard ratio and CI were calculated using a Cox Proportional Hazards model adjusted for the variables selected in the primary pooling strategy: Metastases, Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A hazard ratio <1 favours Olaparib 300 mg bd.

The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy. At DCO2, the p-value is nominal.

Follow-up in months.bd = twice daily; CI = confidence interval; CR = complete response; DCO = data cut-off; mHSPC = metastatic hormone-sensitive prostate cancer; NC = not calculated; NE = not evaluable; PCWG-3 = Prostate Cancer Working Group 3; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid tumours; SD = stable disease.



A circle indicates a censored observation, RECIST version 1.1 and PCWG-3. Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. bd = twice daily; DCO2 = data cut-off 2; Ola = olaparib; PCWG-3 = Prostate Cancer Working Group 3, Pla = placebo; qd = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors v 1.1

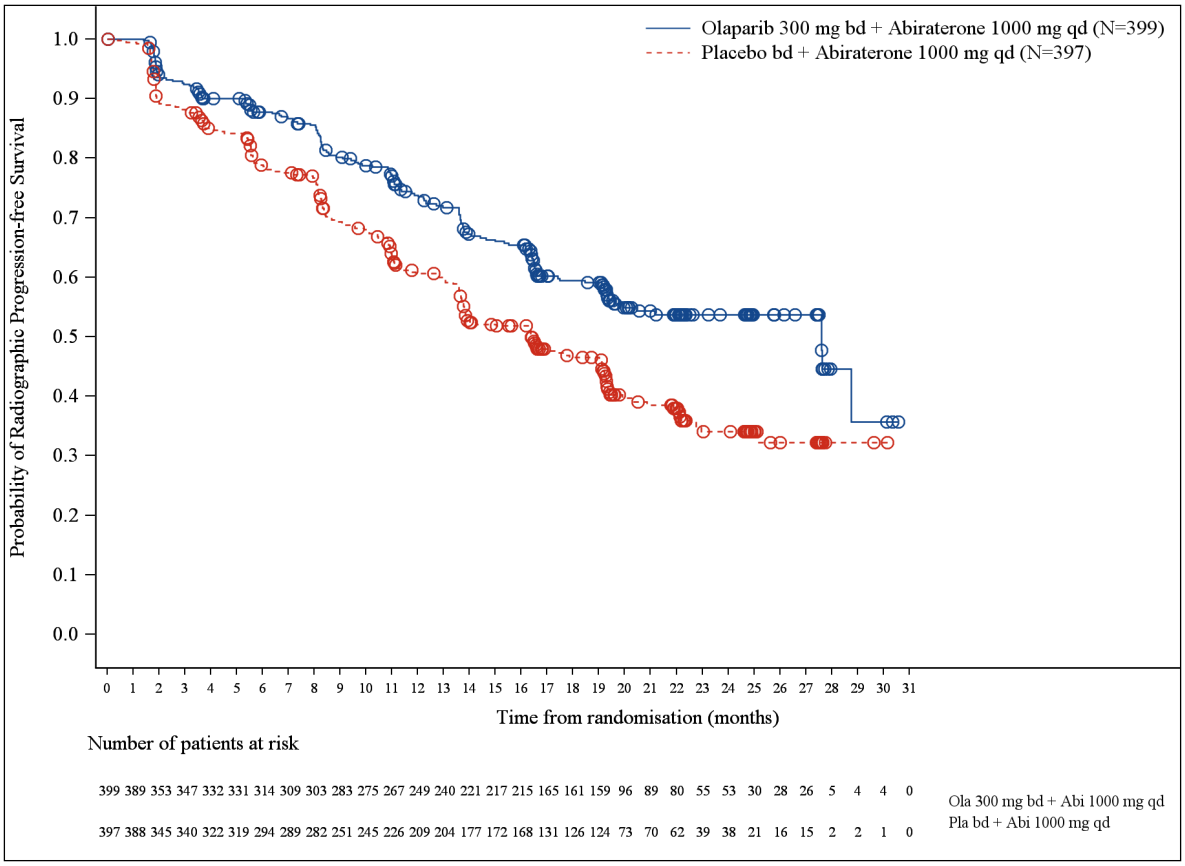
Figure 12: PROpel study rPFS Based on Investigator Assessments, Kaplan-Meier Plot (Full Analysis Set; DCO2: 14 March 2022)

rPFS based on BICR Assessment

Table 22 : PROpel: rPFS based on BICR Assessment (FAS) (DCO1: 30 July 2021)

	Olaparib+abiraterone	Placebo+abiraterone
n (%) of events [a]	157 (39.3)	218 (54.9)
Treatment effect		
Median rPFS (95% CI) [months]	27.6 (19.58, NC)	16.4 (13.77, 19.12)
HR (95% CI) [b]	0.61 (0.49, 0.74)	
2-sided p-valued [c]	p<0.0001	
rPFS at 12 months (%)	73.81	60.61
rPFS at 24 months (%)	53.71	34.11

a.Defined as RECIST and PCWG-3 progression at the same visit.b.The HR and CI were calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A HR < 1 favours olaparib 300 mg bd. C. The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy.



A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.

Progression, as assessed by BICR, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.DCO1 date: 30 July 2021.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.Abi, abiraterone; bd, twice daily; BICR, blinded independent central review; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; ITT, intention-to-treat; N, number of patients in treatment; Ola, olaparib; PCWG-3, Prostate Cancer Working Groups 3; Pla, placebo; qd, once daily; rPFS, radiological progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Figure 13: PROpel: Kaplan-Meier Plot of rPFS by BICR Assessment (FAS) (DCO1: 30 July 2021)

Table 23: PROpel study rPFS Based on Blinded Independent Central Review (BICR) Assessments (Full Analysis Set; DCO1: 30 July 2021 and DCO2: 14 March 2022)

Type of Event	Number (%) of patients			
	DCO1		DCO2	
	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Total progression events, n (%)	157 (39.3)	218 (54.9)	182 (45.6)	242 (61.0)
RECIST progression only	59 (14.8)	109 (27.5)	69 (17.3)	119 (30.0)
Bone scan PCWG-3 criteria progression only	60 (15.0)	77 (19.4)	70 (17.5)	87 (21.9)
RECIST and bone scan PCWG-3 progression [a]	5 (1.3)	7 (1.8)	5 (1.3)	8 (2.0)
Death [b]	33 (8.3)	25 (6.3)	38 (9.5)	28 (7.1)

Table 23: PROpel study rPFS Based on Blinded Independent Central Review (BICR) Assessments (Full Analysis Set; DCO1: 30 July 2021 and DCO2: 14 March 2022)

Type of Event	Number (%) of patients			
	DCO1		DCO2	
	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)	Olaparib + Abiraterone (N=399)	Placebo + Abiraterone (N=397)
Censored patients, n (%)	242 (60.7)	179 (45.1)	217 (54.4)	155 (39.0)
Censored progression [c]	4 (1.0)	2 (0.5)	4 (1.0)	2 (0.5)
Censored death [d]	20 (5.0)	14 (3.5)	30 (7.5)	23 (5.8)
Progression free at time of analysis [e]	210 (52.6)	158 (39.8)	175 (43.9)	126 (31.7)
Lost to follow-up [f]	0	0	0	0
Withdrawn consent [f]	6 (1.5)	3 (0.8)	6 (1.5)	2 (0.5)
Discontinued study [f]	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Median progression-free survival (95% CI) (months)	27.60 (19.58, NC)	16.39 (13.77, 19.12)	27.60 (20.47, 30.16)	16.46 (13.80, 19.15)
Hazard ratio [g]	**0.61**		**0.62**	
95% CI for hazard ratio [g]	**0.49, 0.74**		**0.51, 0.75**	
2-sided p-value [h]	**<0.0001**		**<0.0001**	
Progression-free survival rate at 6 months (95% CI) (%)	87.80 (84.04, 90.72)	78.89 (74.45, 82.65)	88.05 (84.33, 90.94)	79.05 (74.64, 82.78)
Progression-free survival rate at 12 months (95% CI) (%)	73.81 (68.94, 78.04)	60.61 (55.43, 65.39)	73.78 (68.91, 78.02)	61.21 (56.06, 65.95)
Progression-free survival rate at 18 months (95% CI) (%)	59.45 (54.01, 64.46)	46.51 (41.18, 51.66)	59.83 (54.45, 64.79)	47.24 (41.97, 52.33)
Progression-free survival rate at 24 months (95% CI) (%)	53.71 (47.86, 59.20)	34.11 (28.22, 40.07)	54.32 (48.85, 59.47)	35.52 (30.42, 40.64)
Progression-free survival rate at 30 months (95% CI) (%)	35.65 (18.79, 52.92)	32.21 (25.65, 38.93)	46.33 (40.25, 52.18)	32.07 (26.97, 37.28)
Progression-free survival rate at 36 months (95% CI) (%)	NC (NC, NC)	NC (NC, NC)	32.31 (23.21, 41.73)	26.89 (20.92, 33.19)
Median (range) duration of follow-up in censored patients [i]	19.29 (0.03 - 30.59)	19.15 (0.03 - 30.16)	24.80 (0.03 - 38.74)	24.87 (0.03 - 36.80)
Median (range) duration of follow-up in all patients [i]	16.39 (0.03 - 30.59)	13.60 (0.03 - 30.16)	16.53 (0.03 - 38.74)	13.63 (0.03 - 36.80)

[a] Defined as RECIST and PCWG-3 progression at the same visit.

[b] Death in the absence of radiographic progression.

[c] RECIST or bone scan PCWG-3 progression event occurred after 2 or more missed visits.

[d] Includes patients who die after 2 or more missed visits.

[e] Includes patients not known to have progressed (defined as CR, PR, SD or NED by RECIST 1.1, and non-PD, NED or NE by PCWG-3 bone scan).

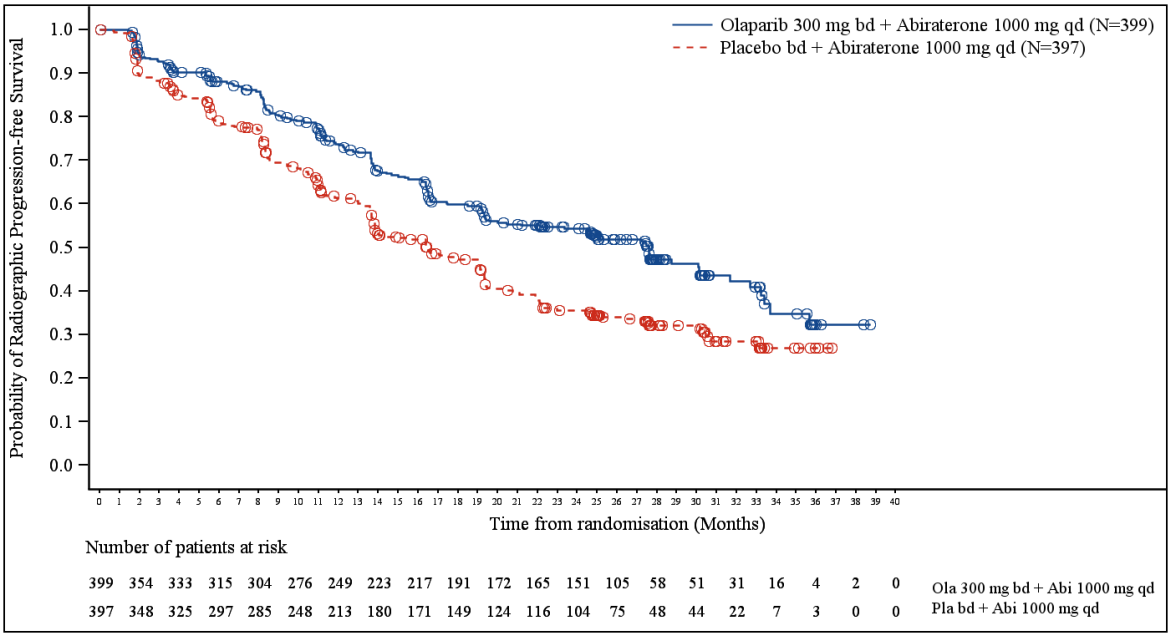
[f] No progression at the last RECIST or bone scan assessment.

[g] The Hazard ratio and CI were calculated using a Cox Proportional Hazards model adjusted for the variables selected in the primary pooling strategy: Metastases, Docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A hazard ratio < 1 favours Olaparib 300 mg bd.

[h] The 2-sided p-value was calculated using the log-rank test stratified by the same variables selected in the primary pooling strategy.

[i] Follow-up in months.

bd = twice daily; BICR = blinded independent central review; CI = confidence interval; CR = complete response; DCO = data cut-off; mHSPC = metastatic hormone-sensitive prostate cancer; NC = not calculated; NE = not evaluable ; PCWG 3 = Prostate Cancer Working Group 3; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid tumours; SD = stable disease.



A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.

Progression, as assessed by BICR, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.

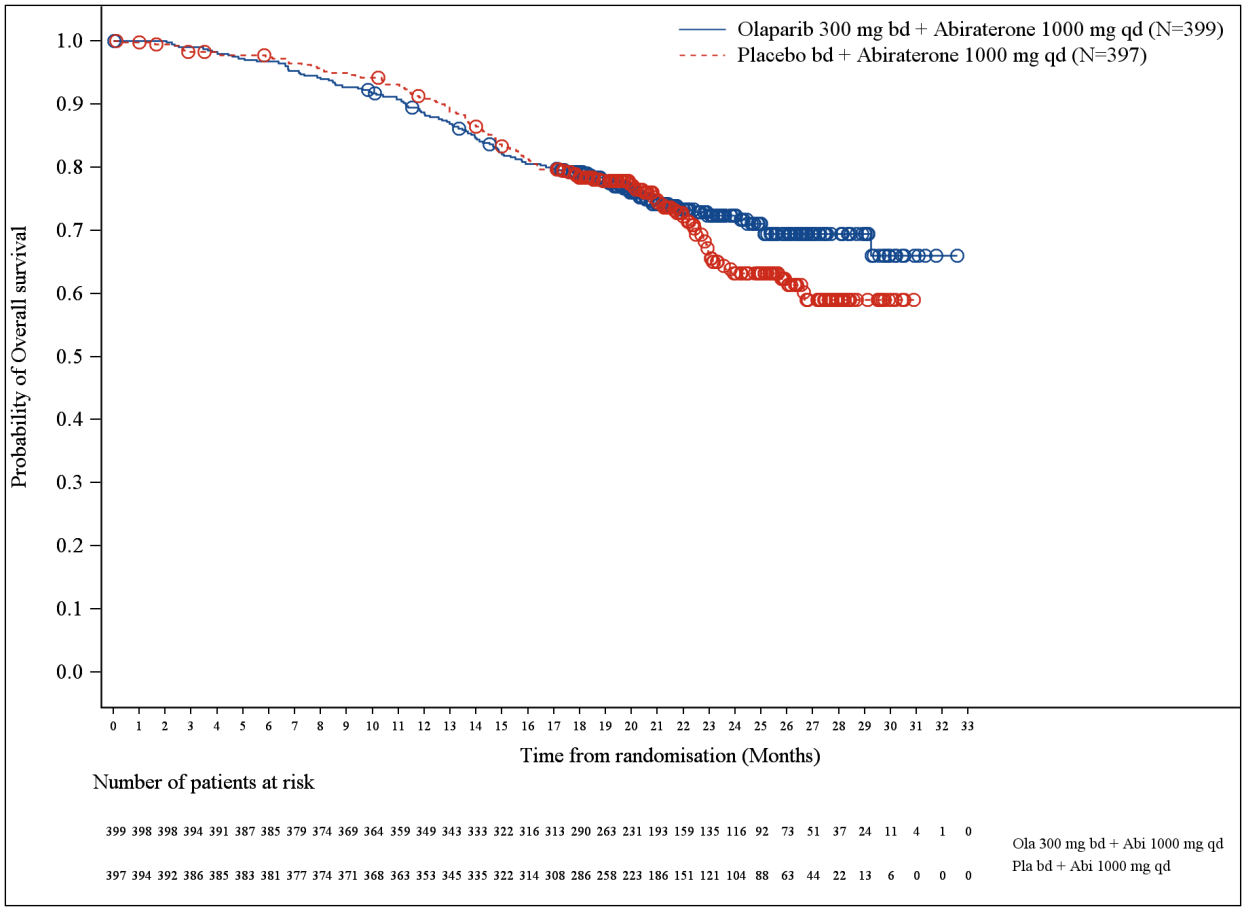
bd = twice daily; BICR = blinded independent central review; DCO2 = data cut-off 2; Ola = olaparib; PCWG-3 = Prostate Cancer Working Group 3, Pla = placebo; qd = once daily; RECIST 1.1 = Response Evaluation Criteria in Solid Tumors v 1.1

Figure 14: PROpel study rPFS Based on BICR, Kaplan-Meier Plot (Full Analysis Set; DCO2: 14 March 2022)

Key secondary endpoint

Overall survival (OS)

At the DCO1 (30 July 2021), the interim analysis OS data (DCO1) were 28.6% mature (228 events out of 796 patients). At the time of the DCO, 70.7% of olaparib+abiraterone-treated patients and 67.3% of the placebo+abiraterone-treated patients were alive and in survival follow-up.



A circle indicates a censored observation.DCO1 date: 30 July 2021.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.Abi, abiraterone; bd, twice daily; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; ITT, intention-to-treat; N, number of patients in treatment; Ola, olaparib; OS, overall survival; Pla, placebo; qd, once daily.

Figure 15: PROpel: Kaplan-Meier Plot of OS (FAS) (DCO1: 30 July 2021)

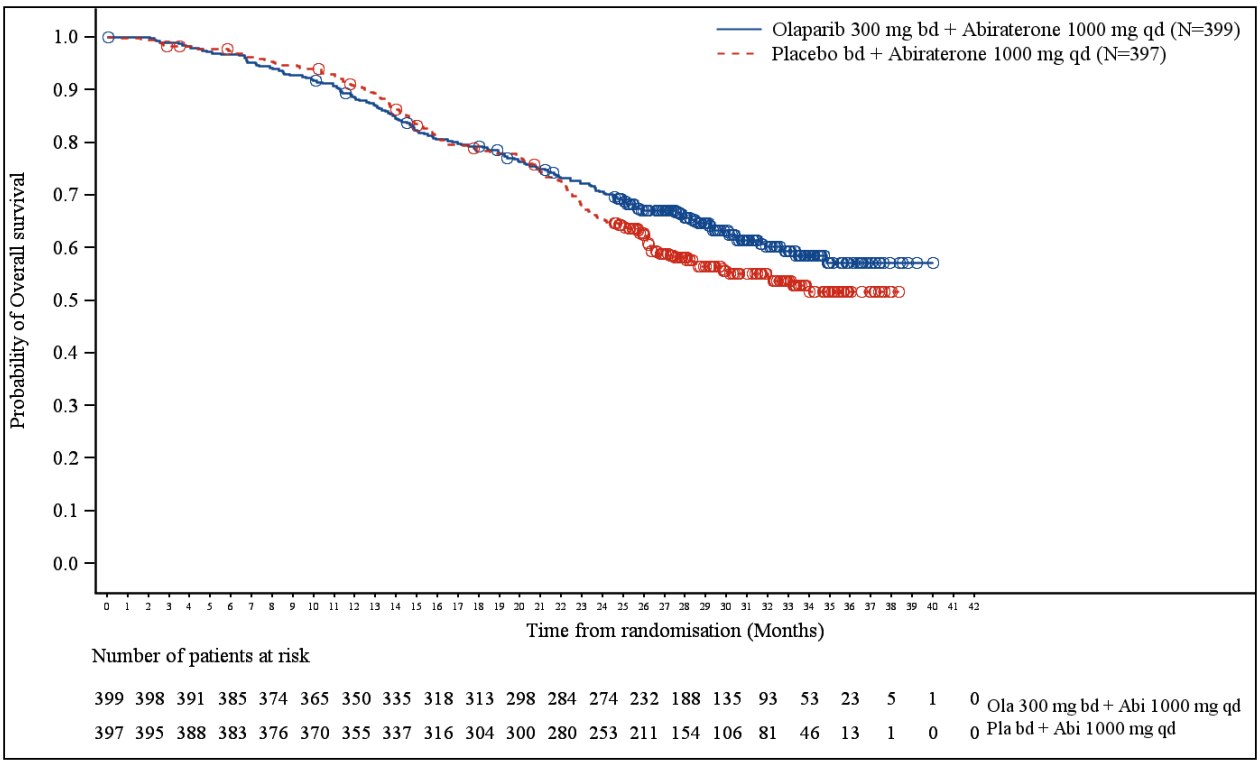
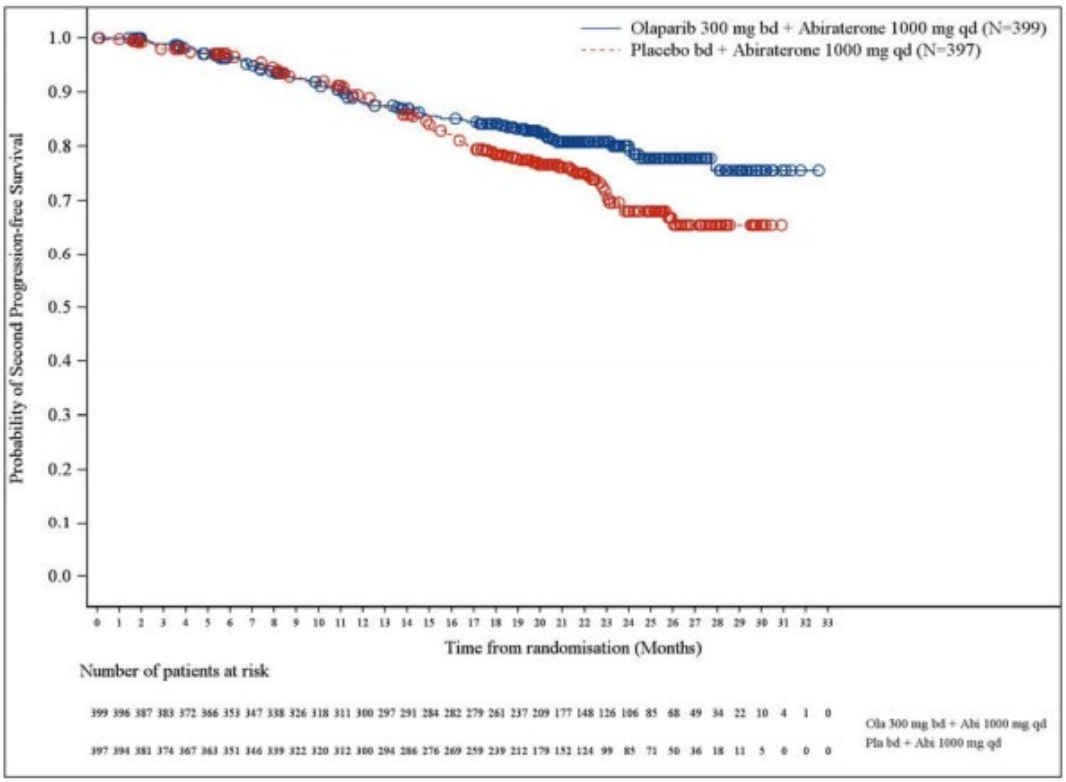


Figure 16 Overall Survival, Kaplan-Meier plot (Full Analysis Set; DCO2: 14 March 2022)

Other secondary endpoints

Time to Second Progression or Death (PFS2)

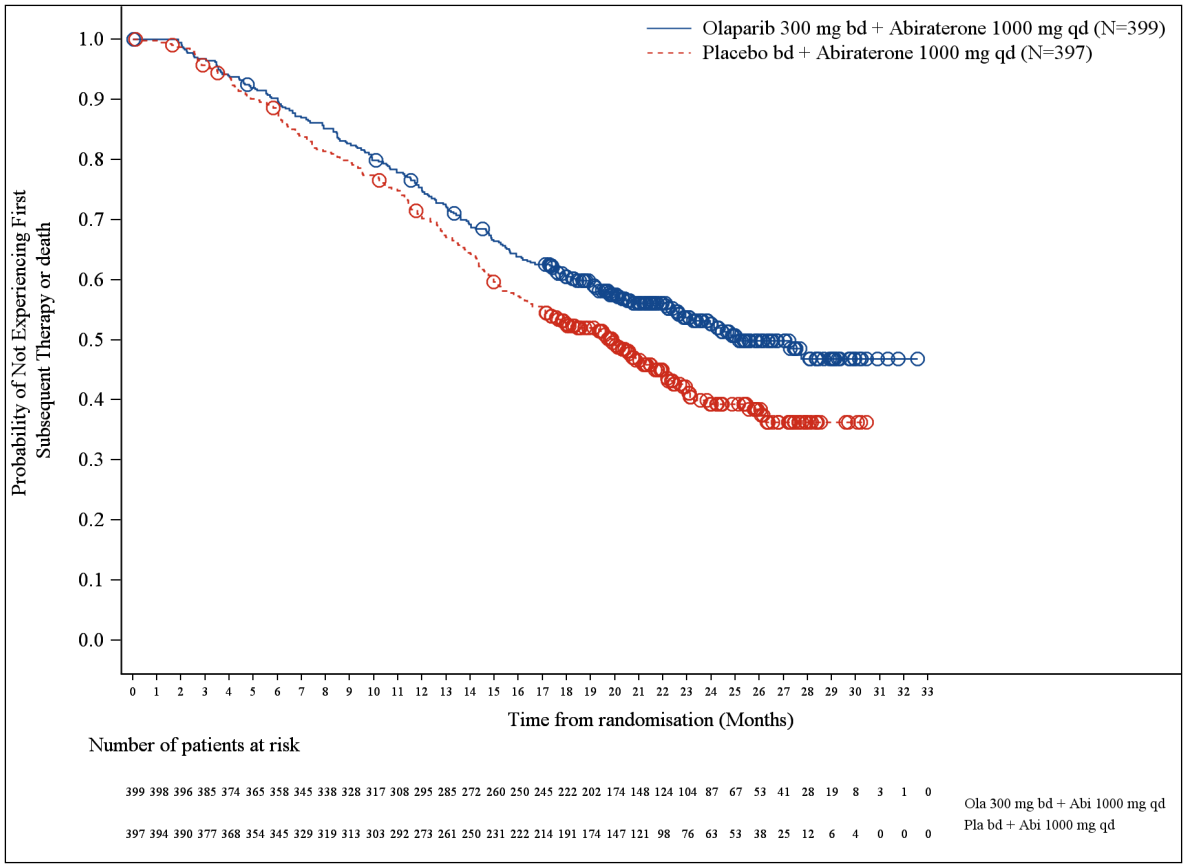
PFS2 data reached 20.6% maturity, with a nominally statistically significant and clinically meaningful improvement in PFS2 (ie, a delay) in the olaparib+abiraterone arm vs placebo+abiraterone arm (HR 0.69; 95% CI: 0.51, 0.94; p=0.0184). Median was not calculable for either treatment arm.



DCO1 date: 30 July 2021.
FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.
Abi, abiraterone; bd, twice daily; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; ITT, intention-to-treat; N, number of patients in treatment; Ola, olaparib; PFS2, time to second progression or death; Pla, placebo; qd, once daily.
Source: Figure 14.2.7.2, PROpel CSR, Module 5.3.5.1.
A circle indicates a censored observation.
Patients who have not had a second disease progression or died at the time of analysis, or who have second progression or die after two or more missed visits, are censored at the latest evaluable assessment where they are last known to be alive and without a second disease progression.

Figure 17 PROpel: Kaplan-Meier Plot of PFS2 (FAS) (DCO1: 30 July 2021)

Time to First Subsequent Therapy or Death (TFST)



A circle indicates a censored observation.TFST (excluding radiotherapy) is defined as the time from randomisation to the earlier of start date of the first subsequent anti-cancer therapy after discontinuation of randomised treatment or death from any cause. Any patient not known to have died at the time of the analysis and not known to have had a further intervention of this type was censored at the last known time to have not received first subsequent therapy, ie, the last follow-up visit where this was confirmed.DCO1 date: 30 July 2021.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.Abi, abiraterone; bd, twice daily; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; ITT, intention-to-treat; Ola, olaparib; Pla, placebo; qd, once daily; TFST, time to first subsequent therapy or death.

Figure 18 PROpel: Kaplan-Meier Plot of TFST (FAS) (DCO1: 30 July 2021)

Table 24: Post-discontinuation anticancer therapy (Full analysis set)

Anticancer therapy [a]	Number (%) of patients		
	Olaparib 300 mg bd + abiraterone 1000 mg qd (N = 399)	Placebo bd + abiraterone 1000 mg qd (N = 397)	Total (N = 796)
Patients with any post-discontinuation anticancer therapy	132 (33.1)	173 (43.6)	305 (38.3)
New hormonal agents			
Abiraterone [b]	19 (4.8)	13 (3.3)	32 (4.0)
Apalutamide	0	1 (0.3)	1 (0.1)
Darolutamide	0	1 (0.3)	1 (0.1)
Enzalutamide	26 (6.5)	36 (9.1)	62 (7.8)
Taxanes			
Cabazitaxel	29 (7.3)	42 (10.6)	71 (8.9)
Docetaxel	68 (17.0)	108 (27.2) [c]	176 (22.1)
Paclitaxel	2 (0.5)	0	2 (0.3)
PARP inhibitors			
Niraparib	0	1 (0.3)	1 (0.1)
Olaparib	0	1 (0.3)	1 (0.1)
Rucaparib	0	1 (0.3)	1 (0.1)

[a] Patients can be counted in > 1 anticancer therapy.

[b] Includes abiraterone acetate.

[c] Includes one docetaxel patient counted under the Systemic Therapy category instead of Cytotoxic Chemotherapy.

bd, twice daily; FAS, full analysis set; PARP, polyadenosine 5'diphosphoribose polymerase; qd, once daily.

Time to Pain Progression (TTPP)

In PROpel, TTPP (based on BPI-SF worst pain [Item 3] and opiate use) data were immature (13.8%), with no difference in TTPP in the olaparib+abiraterone arm vs placebo+abiraterone arm (HR 1.01; 95% CI: 0.69, 1.47; p=0.9551); the median TTPP was not calculable for either treatment arm.

Time to Opiate use for Cancer-related Pain

In PROpel, time to opiate use for cancer-related pain data were immature (11.3%), with no difference in time to opiate use for cancer-related pain in the olaparib+abiraterone arm vs placebo+abiraterone arm (HR 1.08; 95% CI: 0.71, 1.64; p=0.6510); the median time to opiate use was not calculable for either treatment arm.

Time to First Symptomatic Skeletal-Related Event (SSRE)

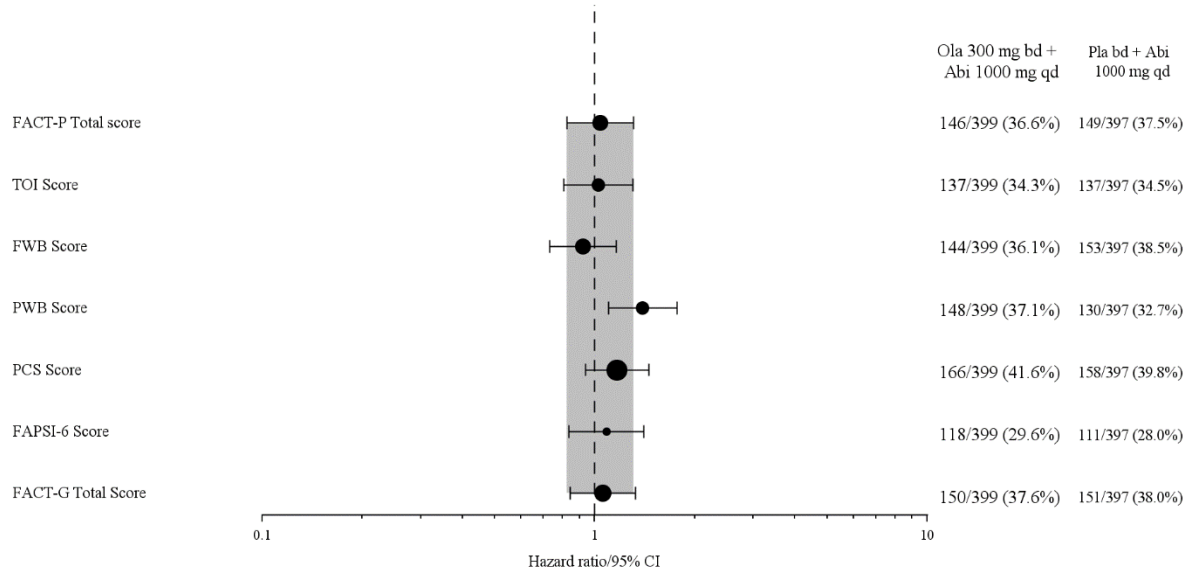
In PROpel, there was a total of 84 events (10.6%) with a numerical improvement (ie, a delay) in time to first SSRE in the olaparib+abiraterone arm vs placebo+abiraterone arm (HR 0.72; 95% CI: 0.47, 1.11; p=0.1324); the median time to first SSRE was not calculable for either treatment arm.

Health Related Quality of Life (HRQoL)

Table 25: PROpel: Overall Adjusted Mean Change From Baseline in FACT-P Total Score and Subscale/Index Scores, MMRM (FAS) (DCO1: 30 July 2021)

FACT-P component	Summary statistic	Olaparib+ abiraterone (N = 399)	Placebo+ abiraterone (N = 397)
FACT-P Total [a]	LS mean (SE)	-4.85 (1.094)	-4.03 (1.089)
	Difference in LS means (95% CI)	-0.82 (-3.56, 1.92)	
	p-value (2-sided)	0.5576	
FACT-G Total [b]	LS mean (SE)	-4.36 (0.806)	-3.60 (0.803)
	Difference in LS means (95% CI)	-0.76 (-2.78, 1.25)	
	p-value (2-sided)	0.4558	
TOI [c]	LS mean (SE)	-3.48 (0.772)	-2.71 (0.770)
	Difference in LS means (95% CI)	-0.77 (-2.71, 1.16)	
	p-value (2-sided)	0.4323	
PWB [d]	LS mean (SE)	-1.53 (0.242)	-1.11 (0.242)
	Difference in LS means (95% CI)	-0.42 (-1.02, 0.18)	
	p-value (2-sided)	0.1691	
FWB [d]	LS mean (SE)	-1.45 (0.283)	-1.09 (0.283)
	Difference in LS means (95% CI)	-0.36 (-1.05, 0.34)	
	p-value (2-sided)	0.3122	
PCS [e]	LS mean (SE)	-0.46 (0.358)	-0.50 (0.358)
	Difference in LS means (95% CI)	0.04 (-0.86, 0.93)	
	p-value (2-sided)	0.9363	
FAPSI-6 [f]	LS mean (SE)	0.15 (0.227)	0.23 (0.227)
	Difference in LS means (95% CI)	-0.08 (-0.64, 0.47)	
	p-value (2-sided)	0.7730	

a. FACT-P total score change from baseline values can be a minimum of -156 and a maximum of 156. b. FACT-G total score is the sum of PWB, SWB, EWB and FWB. FACT-G Total score change from baseline values can be a minimum of -108 and a maximum of 108. c. TOI score is the sum of PWB, FWB and PCS. TOI score change from baseline values can be a minimum of -104 and a maximum of 104. d. PWB score and FWB score change from baseline values can be a minimum of -28 and a maximum of 28.e.PCS score change from baseline values can be a minimum of -48 and a maximum of 48. f. FAPSI-6 score change from baseline values can be a minimum of -24 and a maximum of 24.The analysis was performed using a MMRM with treatment, visit, treatment by visit interaction, baseline FACT-P total score and baseline score by visit interaction, metastases and docetaxel treatment at mHSPC stage as fixed effects. The treatment by visit interaction remains in the model regardless of significance. An unstructured covariance matrix is used to model the within-patient error. The Kenward-Roger approximation is used to estimate degrees of freedom.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.CI, confidence interval; CSR, clinical study report; DCO, data cut-off; EWB, emotional well-being; FACT-G, Functional Assessment of Cancer Therapy – General; FACT P, Functional Assessment of Cancer Therapy – Prostate Cancer; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FAS, full analysis set; FWB, Functional Well-being; ITT, intention-to-treat; LS mean, least squares mean (adjusted mean from model); mHSPC, metastatic hormone-sensitive prostate cancer; MMRM, mixed models for repeated measures; PCS, Prostate Cancer Subscale; PWB, Physical Well-being; SE, standard error; TOI, Trial Outcome Index.



A HR < 1 implies a lower risk of deterioration on olaparib.

The analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction. Size of circle is proportional to the number of events. Grey band represents the 95% confidence interval for the overall (all patients) HR. FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.Abi, abiraterone; bd, twice daily; CSR, clinical study report; DCO, data cut-off; FACT-G, Functional Assessment of Cancer Therapy – General; FACT P, Functional Assessment of Cancer Therapy – Prostate Cancer; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FAS, full analysis set; FWB, Functional Well-being; HR, hazard ratio; ITT, intention-to-treat; Ola, olaparib; PCS, Prostate Cancer Subscale; Pla, placebo; PWB, Physical Well-being; qd, once daily; TOI, Trial Outcome Index.

Figure 19: PROpel: Time to Deterioration in total FACT-P and sub-scales - Forest Plot (FAS) (DCO1: 30 July 2021)

Table 26: PROpel: Overall Adjusted Mean Change from Baseline in BPI-SF Scores, MMRM (FAS)

BPI-SF component	Summary statistic	Olaparib+abiraterone (N = 399)	Placebo+abiraterone (N = 397)
BPI-SF worst pain [a]	LS mean (SE)	-0.17 (0.091)	-0.05 (0.094)
	Difference in LS means (95% CI)	-0.12 (-0.34, 0.11)	
	p-value (2 sided)	0.3044	
BPI-SF pain severity score [a]	LS mean (SE)	-0.14 (0.067)	-0.08 (0.070)
	Difference in LS means (95% CI)	-0.06 (-0.23, 0.10)	
	p-value (2 sided)	0.4437	
BPI-SF pain interference score [a]	LS mean (SE)	-0.04 (0.071)	0.05 (0.074)
	Difference in LS means (95% CI)	-0.09 (-0.26, 0.08)	
	p-value (2 sided)	0.3118	

a. Score change from baseline values can be a minimum of -10 and a maximum of 10.

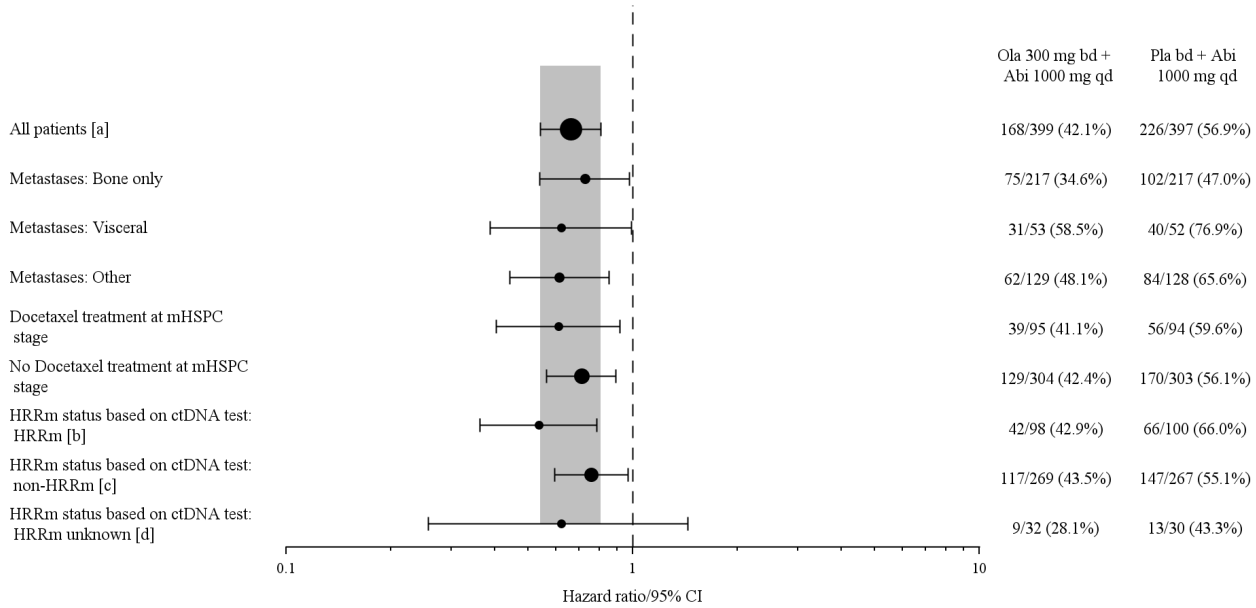
The analysis was performed using a MMRM with treatment, visit, treatment by visit interaction, baseline BPI-SF scores and baseline score by visit interaction, metastases and docetaxel treatment at mHSPC stage as fixed effects. The treatment by visit interaction remains in the model regardless of significance. A Toeplitz with heterogeneity covariance matrix is used to model the within-patient error.The Kenward-Roger approximation is used to estimate degrees of freedom.DCO1 date: 30 July 2021.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.BPI-SF, Brief Pain Inventory - Short Form; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; ITT, intention-to-treat; LS mean, least squares mean (adjusted mean from model); mHSPC, metastatic hormone-sensitive prostate cancer; MMRM, mixed models for repeated measures; SE, standard error.

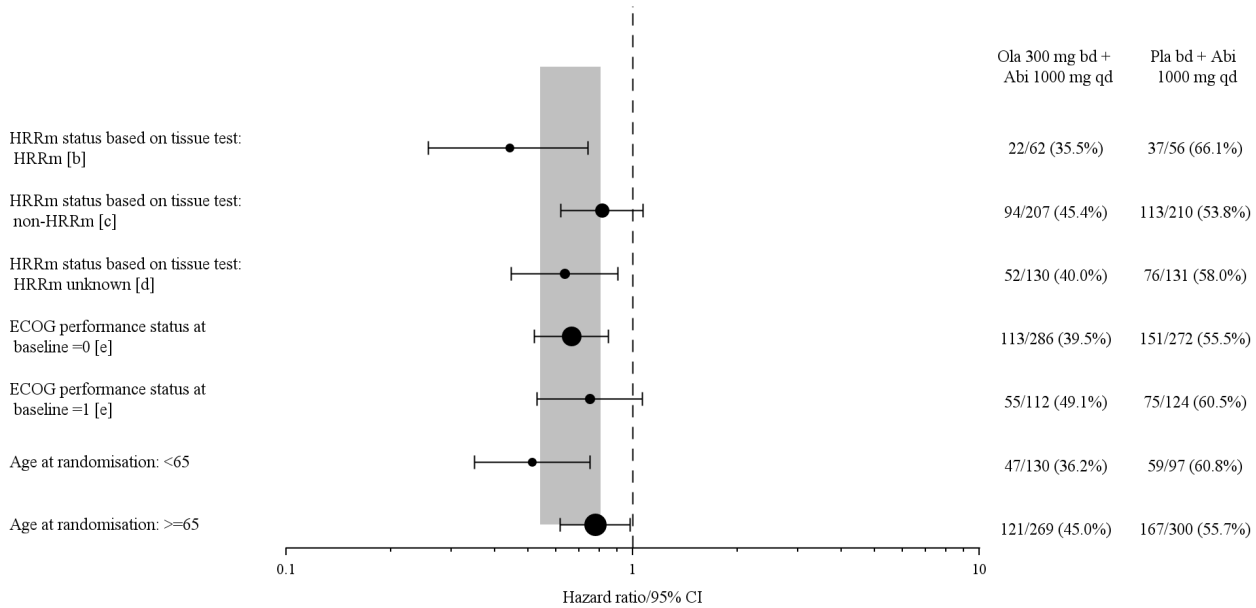
Ancillary analyses

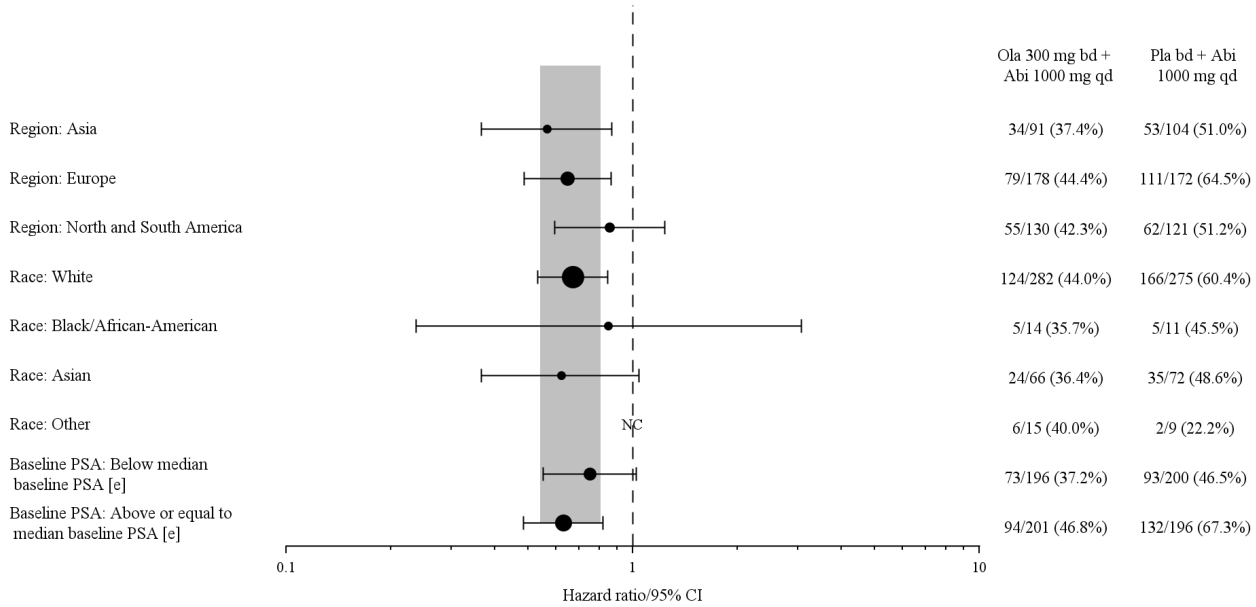
Subgroup Analyses of rPFS (baseline characteristics)

Analyses for the primary endpoint (rPFS by investigator assessment) for 4 pre-specified subgroups were conducted to assess the consistency of treatment effect across potential or expected prognostic factors, baseline characteristics, and HRRm status.

The global interaction test, which compares the fit of a model with no interaction terms to a model with all subgroup interactions included, was not significant at the 10% level (p=0.4129).







a. The analysis performed included the stratification factors selected in the primary pooling strategy as covariates. Each subgroup analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction. A HR < 1 implies a lower risk of progression on olaparib 300 mg bd. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) HR. Progression, as assessed by investigator, defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. b. Defined as: any deleterious or suspected deleterious HRR gene mutation detected. c. Defined as: no deleterious or suspected deleterious HRR gene mutation detected. d. Test failed/sample not analysed. e. Excludes patients with no baseline assessment.Subgroup categories with fewer than 5 events in either treatment arms have NC presented.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.Note: Myriad germline analyses are not available for DCO1.Abi, abiraterone; bd, twice daily; CI, confidence interval; CSR, clinical study report; ctDNA, circulating tumour DNA; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; HRR, homologous recombination repair; HRRm, homologous recombination repair mutation; ITT, intention-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; NC, not calculated; Ola, olaparib; PCWG-3, Prostate Cancer Working Groups 3; Pla, placebo; PS, performance status; PSA, prostate specific antigen; qd, once daily; rPFS, radiological progression-free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Figure 20: PROpel: rPFS Based on Investigator Assessments, Forest Plot, by Subgroup (FAS) (DCO1: 30 July 2021)

Table 27: PROpel: rPFS Exploratory Subgroup Analyses based on Investigator Assessment by Stratification Factors (FAS) (DCO1: 30 July 2021)

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
All patients [a]		
Number of events [b] /total number of patients (%)	168/399 (42.1)	226/397 (56.9)
Median rPFS (months) (95% CI)	24.84 (20.47, 27.63)	16.59 (13.93, 19.22)
HR (95% CI)	0.66 (0.54, 0.81)	
Stratification factors at randomisation (IxRS)		
Site of distant metastases: Bone only		
Number of events [b] /total number of patients (%)	75/217 (34.6)	102/217 (47.0)
Median rPFS (months) (95% CI)	27.63 (24.11, NC)	22.18 (19.12, NC)
HR (95% CI)	0.73 (0.54, 0.98)	
Site of distant metastases: Visceral		
Number of events [b] /total number of patients (%)	31/53 (58.5)	40/52 (76.9)
Median rPFS (months) (95% CI)	13.73 (8.57, NC)	10.91 (5.29, 13.80)
HR (95% CI)	0.62 (0.39, 0.99)	
Site of distant metastases: Other		
Number of events [b] /total number of patients (%)	62/129 (48.1)	84/128 (65.6)
Median rPFS (months) (95% CI)	20.47 (16.59, 27.66)	13.70 (11.07, 16.36)
HR (95% CI)	0.62 (0.44, 0.85)	
Docetaxel treatment at mHSPC stage		
Number of events [b] /total number of patients (%)	39/95 (41.1)	56/94 (59.6)
Median rPFS (months) (95% CI)	27.60 (16.46, NC)	13.83 (10.91, 19.19)
HR (95% CI)	0.61 (0.40, 0.92)	
No Docetaxel treatment at mHSPC stage		
Number of events [b] /total number of patients (%)	129/304 (42.4)	170/303 (56.1)
Median rPFS (months) (95% CI)	24.84 (20.47, 27.63)	16.82 (14.75, 19.45)
HR (95% CI)	0.71 (0.56, 0.89)	

a) HR and 95% CI from a Cox proportional hazards model as used for the primary analysis. An HR < 1 favours olaparib 300 mg bd. CI calculated using the profile likelihood method.

b) Progression, as assessed by the investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Each subgroup analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction.

Subgroups with fewer than 5 events in either treatment group do not have HRs and CIs presented. The IxRS values are used for the stratification factors. AS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.

bd, twice daily; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; IxRS, Interactive voice/web response system; mHSPC, metastatic hormone-sensitive prostate cancer; NC, not calculated; PCWG-3; Prostate Cancer Working Groups 3; rPFS, radiological progression free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Table 28: PROpel: rPFS Exploratory Subgroup Analyses based on Investigator Assessment by Baseline Characteristics (FAS) (DCO1: 30 July 2021)

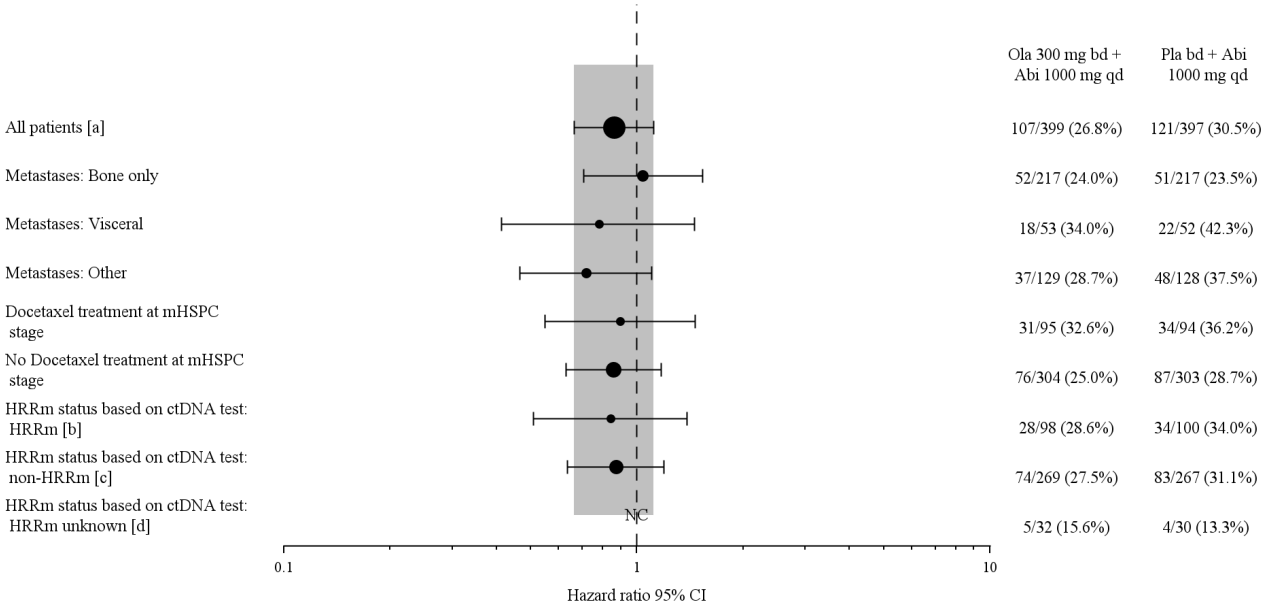
Subgroup	Olaparib+abiraterone	Placebo+abiraterone
All patients [a]		
Number of events [b] /total number of patients (%)	168/399 (42.1)	226/397 (56.9)
Median rPFS (months) (95% CI)	24.84 (20.47, 27.63)	16.59 (13.93, 19.22)

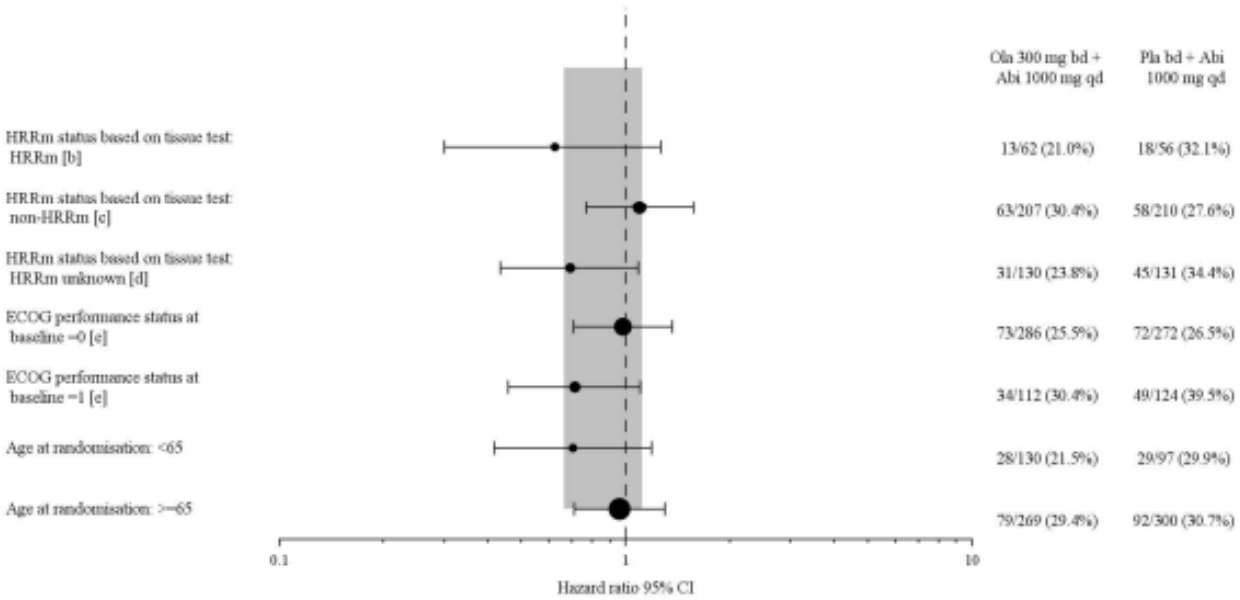
Subgroup	Olaparib+abiraterone	Placebo+abiraterone
HR (95% CI)	0.66 (0.54, 0.81)	
Baseline Characteristics		
ECOG performance status at baseline = 0 [c]		
Number of events [b] /total number of patients (%)	113/286 (39.5)	151/272 (55.5)
Median rPFS (months) (95% CI)	24.87 (21.85, NC)	16.82 (14.26, 20.27)
HR (95% CI)	0.67 (0.52, 0.85)	
ECOG performance status at baseline = 1 [c]		
Number of events [b] /total number of patients (%)	55/112 (49.1)	75/124 (60.5)
Median rPFS (months) (95% CI)	17.48 (13.63, 27.66)	14.59 (11.56, 19.35)
HR (95% CI)	0.75 (0.53, 1.06)	
Age at randomisation: <65		
Number of events [b] /total number of patients (%)	47/130 (36.2)	59/97 (60.8)
Median rPFS (months) (95% CI)	NC (NC, NC)	16.36 (11.70, 20.27)
HR (95% CI)	0.51 (0.35, 0.75)	
Age at randomisation: ≥65		
Number of events [b] /total number of patients (%)	121/269 (45.0)	167/300 (55.7)
Median rPFS (months) (95% CI)	21.95 (19.32, 25.17)	16.66 (13.93, 19.35)
HR (95% CI)	0.78 (0.62, 0.98)	
Region: Asia		
Number of events [b] /total number of patients (%)	34/91 (37.4)	53/104 (51.0)
Median rPFS (months) (95% CI)	27.63 (23.89, NC)	19.12 (13.77, 24.64)
HR (95% CI)	0.57 (0.37, 0.87)	
Region: Europe		
Number of events [b] /total number of patients (%)	79/178 (44.4)	111/172 (64.5)
Median rPFS (months) (95% CI)	21.91 (16.59, 27.63)	13.90 (13.63, 16.66)
HR (95% CI)	0.65 (0.49, 0.87)	
Region: North and South America		
Number of events [b] /total number of patients (%)	55/130 (42.3)	62/121 (51.2)
Median rPFS (months) (95% CI)	NC (NC, NC)	19.38 (14.26, NC)
HR (95% CI)	0.86 (0.60, 1.23)	
Baseline PSA: Below median baseline PSA [c]		
Number of events [b] /total number of patients (%)	73/196 (37.2)	93/200 (46.5)
Median rPFS (months) (95% CI)	25.17 (23.89, 27.66)	22.01 (19.12, NC)
HR (95% CI)	0.75 (0.55, 1.02)	
Baseline PSA: Above or equal to median baseline PSA [c]		
Number of events [b] /total number of patients (%)	94/201 (46.8)	132/196 (67.3)
Median rPFS (months) (95% CI)	18.46 (14.65, NC)	13.77 (11.53, 16.36)
HR (95% CI)	0.63 (0.48, 0.82)	

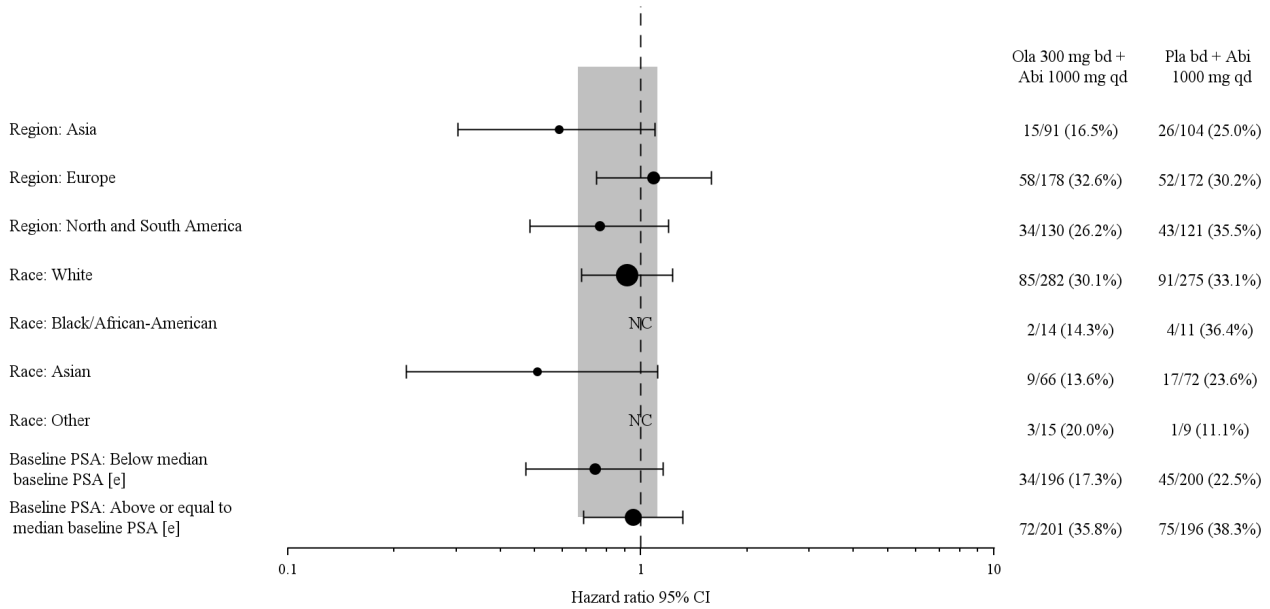
Subgroup	Olaparib+abiraterone	Placebo+abiraterone
Race: White		
Number of events [b] /total number of patients (%)	124/282 (44.0)	166/275 (60.4)
Median rPFS (months) (95% CI)	21.95 (17.58, 27.66)	15.05 (13.77, 19.12)
HR (95% CI)	0.67 (0.53, 0.85)	
Race: Black/African-American		
Number of events [b] /total number of patients (%)	5/14 (35.7)	5/11 (45.5)
Median rPFS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.85 (0.24, 3.06)	
Race: Asian		
Number of events [b] /total number of patients (%)	24/66 (36.4)	35/72 (48.6)
Median rPFS (months) (95% CI)	27.60 (19.55, NC)	19.29 (13.83, NC)
HR (95% CI)	0.62 (0.37, 1.04)	
Race: Other		
Number of events [b] /total number of patients (%)	6/15 (40.0)	2/9 (22.2)
Median rPFS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	NC (NC, NC)	

a. R and 95% CI from a Cox proportional hazards model as used for the primary analysis. An HR < 1 favours olaparib 300 mg bd. CI calculated using the profile likelihood method. b. Progression, as assessed by the investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression. Each subgroup analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction. c. Excludes patients with no baseline assessment. Subgroups with fewer than 5 events in either treatment group do not have HRs and CIs presented. FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle. bd, twice daily; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; NC, not calculated; PCWG-3; Prostate Cancer Working Groups 3; PSA, prostate-specific antigen; rPFS, radiological progression free survival; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1.

Subgroup Analyses of OS (baseline characteristics)







a.The analysis performed included the stratification factors selected in the primary pooling strategy as covariates. Each subgroup analysis was performed using a Cox proportional hazards model that contains a term for treatment, factor and treatment by factor interaction. A HR < 1 implies a lower risk of progression on olaparib 300 mg bd. Size of circle is proportional to the number of events. Grey band represents the 95% CI for the overall (all patients) HR. b.Defined as any deleterious or suspected deleterious HRR gene mutation detected. c. Defined as no deleterious or suspected deleterious HRR gene mutation detected.d. Test failed/sample not analysed. E. Excludes patients with no baseline assessment. Subgroup categories with fewer than 5 events in either treatment group have NC presented.

FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.

Abi, abiraterone; bd, twice daily; CI, confidence interval; CSR, clinical study report; ctDNA, circulating tumour DNA; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; HRR, homologous recombination repair; HRRm, homologous recombination repair mutation; ITT, intention-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; NC, not calculated; Ola, olaparib; Pla, placebo; PS, performance status; PSA, prostate specific antigen; qd, once daily.

Figure 21: PROpel: Overall Survival, Forest Plot, by Subgroup (FAS)

Table 29: PROpel: OS Exploratory Subgroup Analyses by Stratification Factors (FAS)

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
All patients [a]		
Number of events /total number of patients (%)	107/399 (26.8)	121/397 (30.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.86 (0.66, 1.12)	
Stratification Factors		
Site of distant metastases: Bone only		
Number of events /total number of patients (%)	52/217 (24.0)	51/217 (23.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	1.04 (0.71, 1.53)	
Site of distant metastases: Visceral		
Number of events /total number of patients (%)	18/53 (34.0)	22/52 (42.3)
Median OS (months) (95% CI)	NC (NC, NC)	26.68 (18.53, NC)
HR (95% CI)	0.78 (0.41, 1.45)	
Site of distant metastases: Other		

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
Number of events /total number of patients (%)	37/129 (28.7)	48/128 (37.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.72 (0.46, 1.10)	
Docetaxel treatment at mHSPC stage		
Number of events /total number of patients (%)	31/95 (32.6)	34/94 (36.2)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.90 (0.55, 1.46)	
No Docetaxel treatment at mHSPC stage		
Number of events /total number of patients (%)	76/304 (25.0)	87/303 (28.7)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.86 (0.63, 1.17)	
All patients [a]		
Number of events /total number of patients (%)	107/399 (26.8)	121/397 (30.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.86 (0.66, 1.12)	
Baseline Characteristics		
ECOG performance status: ECOG 0 [b]		
Number of events /total number of patients (%)	73/286 (25.5)	72/272 (26.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.98 (0.71, 1.36)	
ECOG performance status: ECOG 1 [b]		
Number of events /total number of patients (%)	34/112 (30.4)	49/124 (39.5)
Median OS (months) (95% CI)	NC (NC, NC)	23.62 (22.47, NC)
HR (95% CI)	0.71 (0.46, 1.10)	
Age at randomisation: <65		
Number of events /total number of patients (%)	28/130 (21.5)	29/97 (29.9)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.70 (0.42, 1.18)	
Age at randomisation: ≥65		
Number of events /total number of patients (%)	79/269 (29.4)	92/300 (30.7)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.96 (0.71, 1.29)	
Region: Asia		
Number of events /total number of patients (%)	15/91 (16.5)	26/104 (25.0)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.59 (0.30, 1.09)	
Region: Europe		
Number of events /total number of patients (%)	58/178 (32.6)	52/172 (30.2)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	1.09 (0.75, 1.58)	

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
Region: North and South America		
Number of events /total number of patients (%)	34/130 (26.2)	43/121 (35.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.76 (0.48, 1.19)	
Baseline PSA: Below median baseline PSA [b]		
Number of events /total number of patients (%)	34/196 (17.3)	45/200 (22.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.74 (0.47, 1.15)	
Baseline PSA: Above or equal to median baseline PSA [b]		
Number of events /total number of patients (%)	72/201 (35.8)	75/196 (38.3)
Median OS (months) (95% CI)	NC (NC, NC)	26.68 (22.97, NC)
HR (95% CI)	0.95 (0.69, 1.31)	
Race: White		
Number of events /total number of patients (%)	85/282 (30.1)	91/275 (33.1)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.91 (0.68, 1.23)	
Race: Black/African-American		
Number of events /total number of patients (%)	2/14 (14.3)	4/11 (36.4)
Median OS (months) (95% CI)	NC (NC, NC)	23.85 (13.70, NC)
HR (95% CI)	NC (NC, NC)	
Race: Asian		
Number of events /total number of patients (%)	9/66 (13.6)	17/72 (23.6)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.51 (0.22, 1.11)	
Race: Other		
Number of events /total number of patients (%)	3/15 (20.0)	1/9 (11.1)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	NC (NC, NC)	

a. HR and 95% CI from a Cox proportional hazards model as used for the primary analysis. A HR <1 favours olaparib 300 mg bd. Subgroups with fewer than five events in either treatment group do not have HRs and CIs presented. The IxRS values are used for the stratification factors.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.

bd, twice daily; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; mHSPC, metastatic hormone-sensitive prostate cancer; NC, not calculated; OS, overall survival.

1. HR and 95% CI from a Cox proportional hazards model as used for the primary analysis. A HR <1 favours olaparib 300 mg bd.
2. Excludes patients with no baseline assessment.

Subgroups with fewer than five events in either treatment group do not have HRs and CIs presented.FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.bd, twice daily; CI, confidence interval; CSR, clinical study report; DCO, data cut-off; ECOG, Eastern Cooperative Oncology Group; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; NC, not calculated; OS, overall survival; PSA, prostate-specific antigen.

Subgroup Analyses of rPFS (HRR mutations)

Table 30: PROpel rPFS Exploratory Subgroup Analyses by HRRm status (FAS) (DCO1: 30 July 2021)

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
All patients		
Number of events [b] /total number of patients (%)	168/399 (42.1)	226/397 (56.9)
Median rPFS (months) (95% CI)	24.84 (20.47, 27.63)	16.59 (13.93, 19.22)
HR (95% CI)	0.66 (0.54, 0.81)	
ctDNA-based test (FoundationOne Liquid CDx)		
HRRm		
Number of events [b]/total number of patients (%)	42/98 (42.9)	66/100 (66.0)
Median rPFS (months)	NC (NC, NC)	13.63 (9.30, 16.59)
HR (95% CI)	0.54 (0.36, 0.79)	
Non-HRRm		
Number of events [b]/total number of patients (%)	117/269 (43.5)	147/267 (55.1)
Median rPFS (months)	24.11 (19.35, 27.63)	18.96 (14.16, 21.19)
HR (95% CI)	0.76 (0.59, 0.97)	
HRRm unknown		
Number of events [b]/total number of patients (%)	9/32 (28.1)	13/30 (43.3)
Median rPFS (months)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.62 (0.26, 1.44)	
Tumour tissue test (FoundationOneCDx)		
HRRm		
Number of events /total number of patients (%)	22/62 (35.5)	37/56 (66.1)
Median rPFS (months)	NC (NC, NC)	16.62 (10.84, 19.38)
HR (95% CI)	0.44 (0.26, 0.74)	
Non-HRRm		
Number of events /total number of patients (%)	94/207 (45.4)	113/210 (53.8)
Median rPFS (months)	22.54 (17.58, 27.60)	16.59 (13.83, 21.19)
HR (95% CI)	0.81 (0.62, 1.07)	
HRRm unknown		
Number of events /total number of patients (%)	52/130 (40.0)	76/131 (58.0)
Median rPFS (months)	24.84 (17.48, NC)	16.39 (13.77, 21.88)
HR (95% CI)	0.64 (0.45, 0.90)	

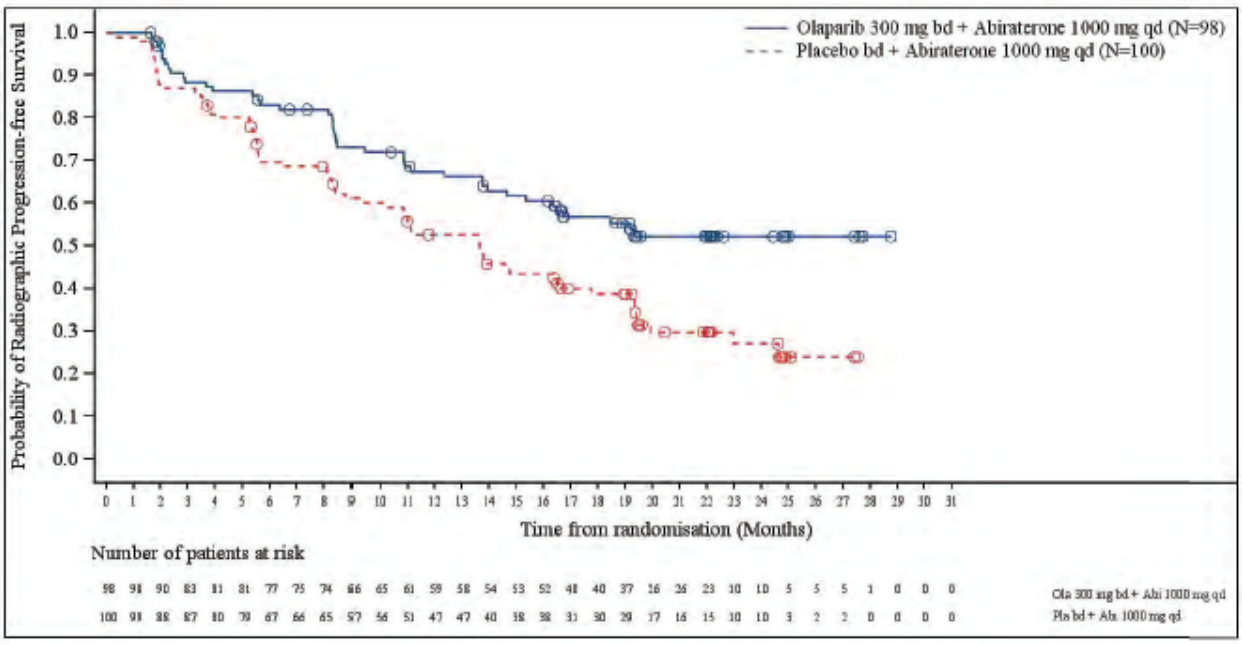
HR and CI are not presented for subgroups with < 5 events in either treatment group.

Note: Myriad germline analyses are not available for DCO1.

DCO1 date: 30 July 2021.

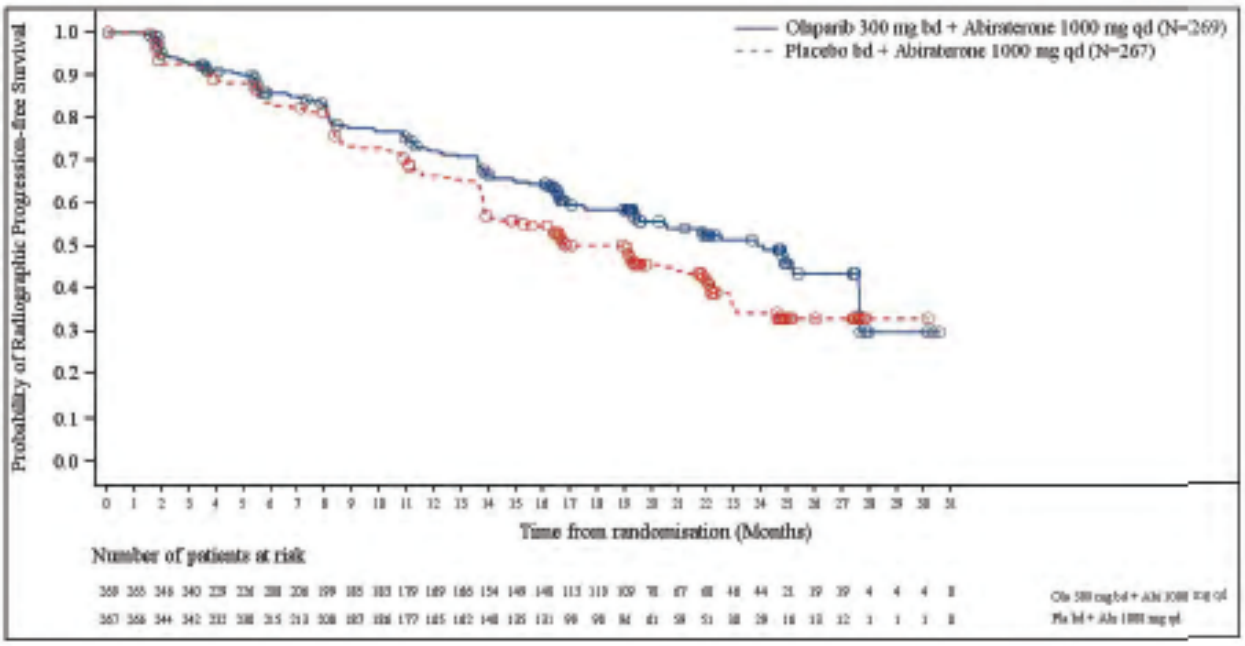
FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.

bd, twice daily; CDx, companion diagnostic; CI, confidence interval; CSR, clinical study report; ctDNA, circulating tumour DNA; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; HRR, homologous recombination repair; HRRm, homologous recombination repair mutation; ITT, intention-to-treat; NC, not calculated; PCWG-3; Prostate Cancer Working Groups 3; rPFS, radiological progression free survival; RECIST, Response Evaluation Criteria in Solid Tumours.



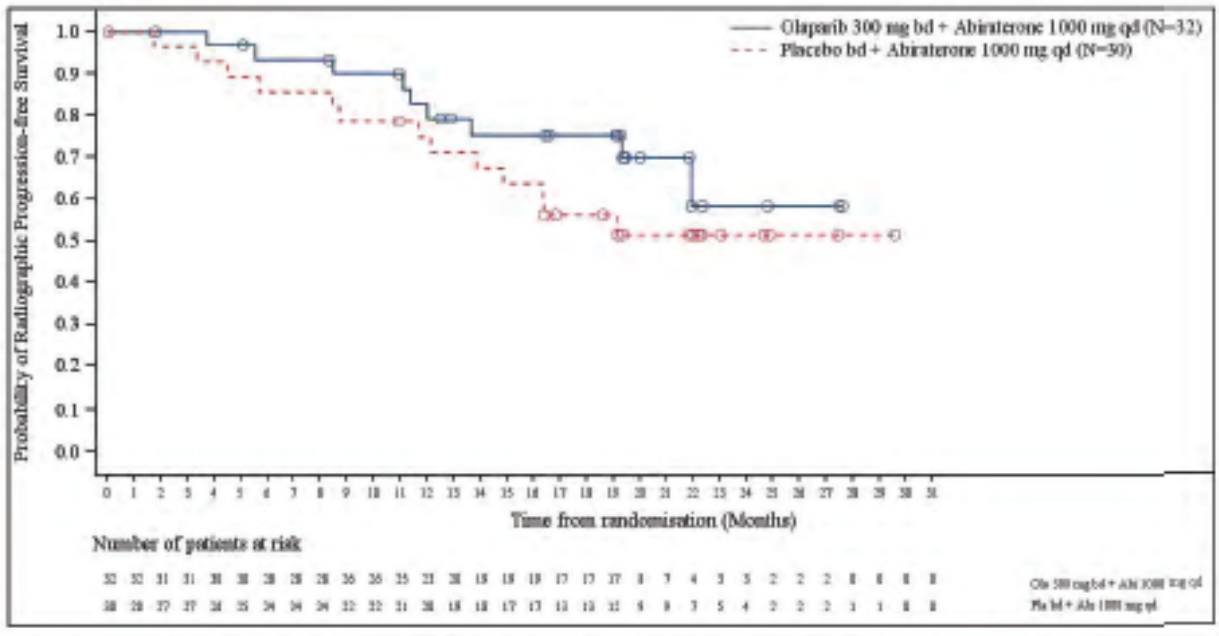
A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.
ctDNA-based test used to derive HRR gene mutation status is FoundationOne®Liquid CDx.

Figure 22: PROpel: rPFS based on investigator assessments in the HRRm subgroup by ctDNA-based test, KM plot (DCO1: 30 July 2021)



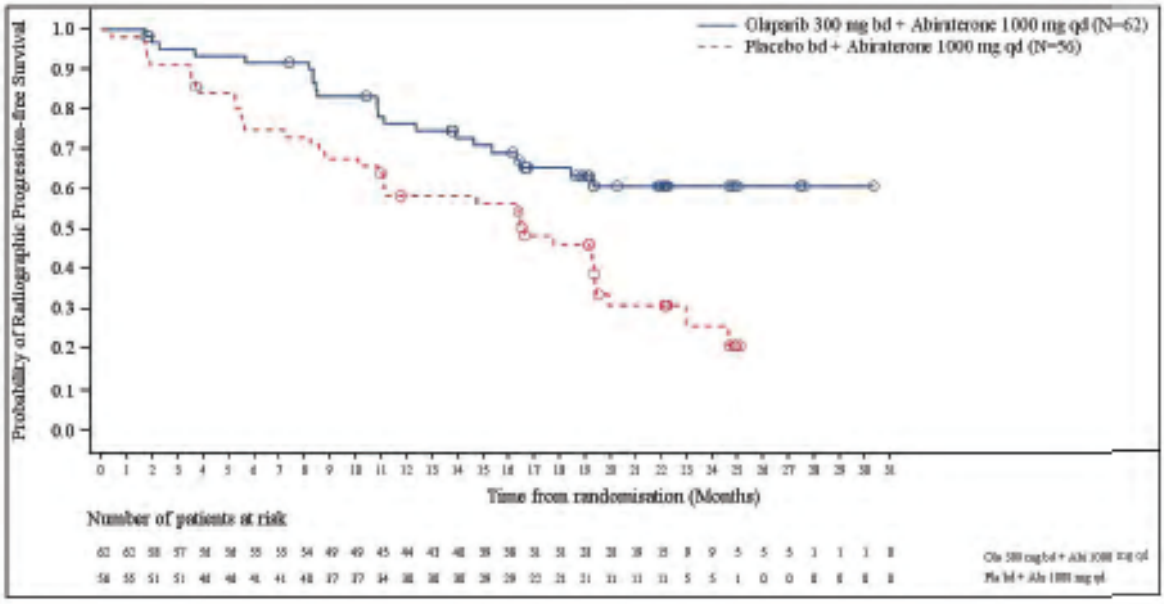
A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.
ctDNA-based test used to derive HRR gene mutation status is FoundationOne®Liquid CDx.

Figure 23: PROpel : rPFS based on investigator assessment in the non-HRRm subgroup by ctDNA test, KM plot (DCO1: 30 July 2021)



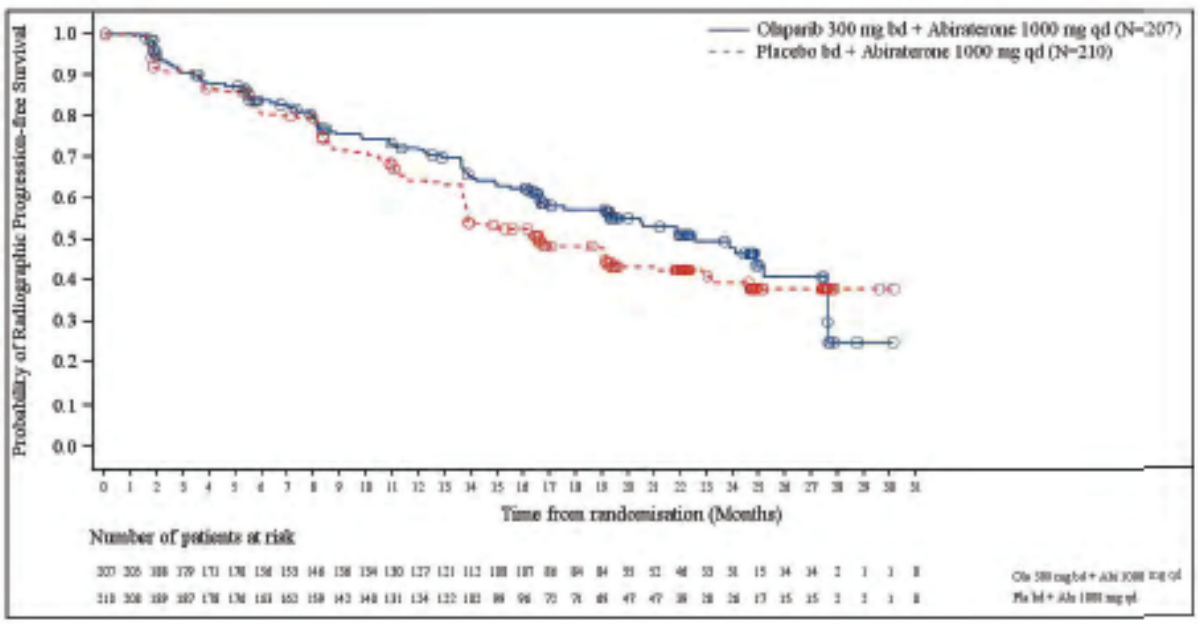
A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.
ctDNA-based test used to derive HRR gene mutation status is FoundationOne®Liquid CDx.

Figure 24: PROpel : rPFS based on investigator assessment in the HRRm unknown subgroup by ctDNA test, KM plot (DCO1: 30 July 2021)



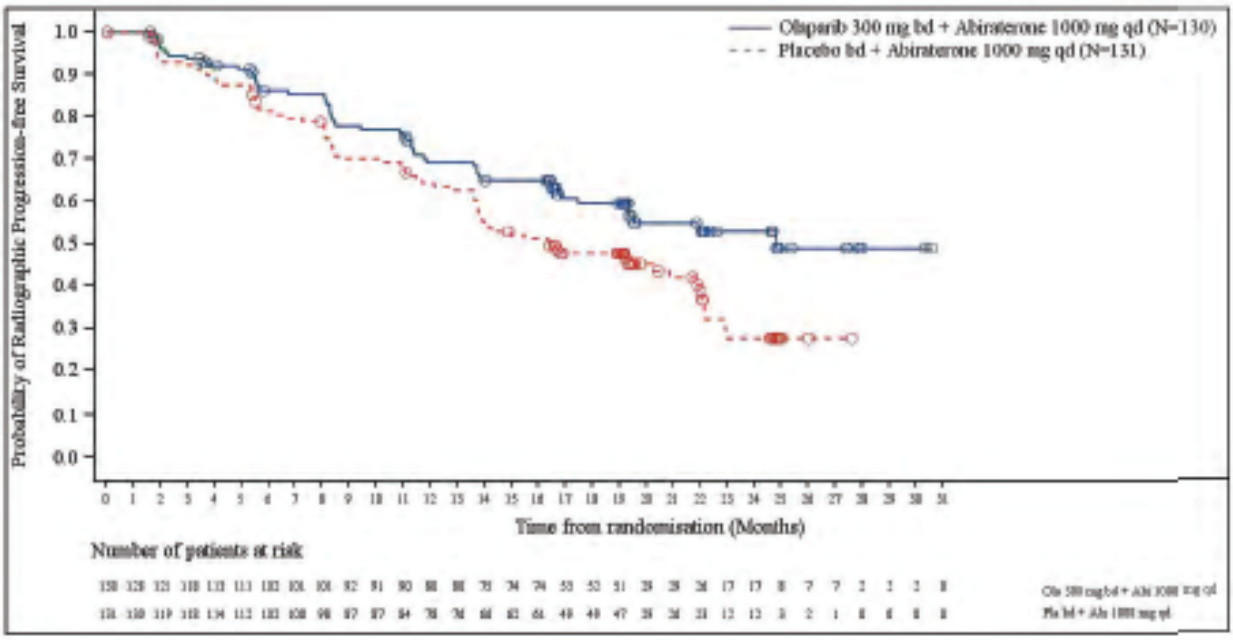
A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.
Tumour tissue test used to derive HRR gene mutation status is FoundationOne®CDx.

Figure 25: PROpel : rPFS based on investigator assessment in the HRRm subgroup by tumor tissue test, KM plot (DCO1: 30 July 2021)



A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.
Tumour tissue test used to derive HRR gene mutation status is FoundationOne®CDx.

Figure 26: PROpel : rPFS based on investigator assessment in the non-HRRm subgroup by tumor tissue test, KM plot (DCO1: 30 July 2021)



A circle indicates a censored observation, RECIST version 1.1 and PCWG-3.
Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death (by any cause in the absence of progression) regardless of whether the patient withdraws from randomised therapy or receives another anti-cancer therapy prior to progression.
Tumour tissue test used to derive HRR gene mutation status is FoundationOne®CDx.

Figure 27: PROpel : rPFS based on investigator assessment in the HRRm unknown subgroup by tumor tissue test, KM plot(DCO1: 30 July 2021)

Subgroup Analyses of OS (HRR mutations)

Table 31: PROpel: OS Exploratory Subgroup Analyses by HRRm status (FAS) (DCO1: 30 July 2021)

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
All patients		
Number of events /total number of patients (%)	107/399 (26.8)	121/397 (30.5)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.86 (0.66, 1.12)	
ctDNA-based test (FoundationOne®Liquid CDx)		
HRRm		
Number of events /total number of patients (%)	28/98 (28.6)	34/100 (34.0)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.84 (0.51, 1.39)	
Non-HRRm		
Number of events /total number of patients (%)	74/269 (27.5)	83/267 (31.1)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.87 (0.64, 1.19)	
HRRm unknown		
Number of events /total number of patients (%)	5/32 (15.6)	4/30 (13.3)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	NC (NC, NC)	
Tumour tissue test (FoundationOne®CDx)		
HRRm		
Number of events /total number of patients (%)	13/62 (21.0)	18/56 (32.1)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.62 (0.30, 1.26)	
Non-HRRm		
Number of events /total number of patients (%)	63/207 (30.4)	58/210 (27.6)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	1.10 (0.77, 1.57)	
HRRm unknown		
Number of events /total number of patients (%)	31/130 (23.8)	45/131 (34.4)
Median OS (months) (95% CI)	NC (NC, NC)	NC (NC, NC)
HR (95% CI)	0.69 (0.43, 1.09)	

Subgroups with fewer than five events in either treatment group do not have HRs and CIs presented.

Note: Myriad germline analyses are not available for DCO1.

FAS: all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle.

bd, twice daily; CDx, companion diagnostic; CI, confidence interval; CSR, clinical study report; ctDNA, circulating tumour DNA; DCO, data cut-off; FAS, full analysis set; HR, hazard ratio; HRR, homologous recombination repair; HRRm, homologous recombination repair gene mutation; ITT, intention-to-treat; NC, not calculated; OS, overall survival.

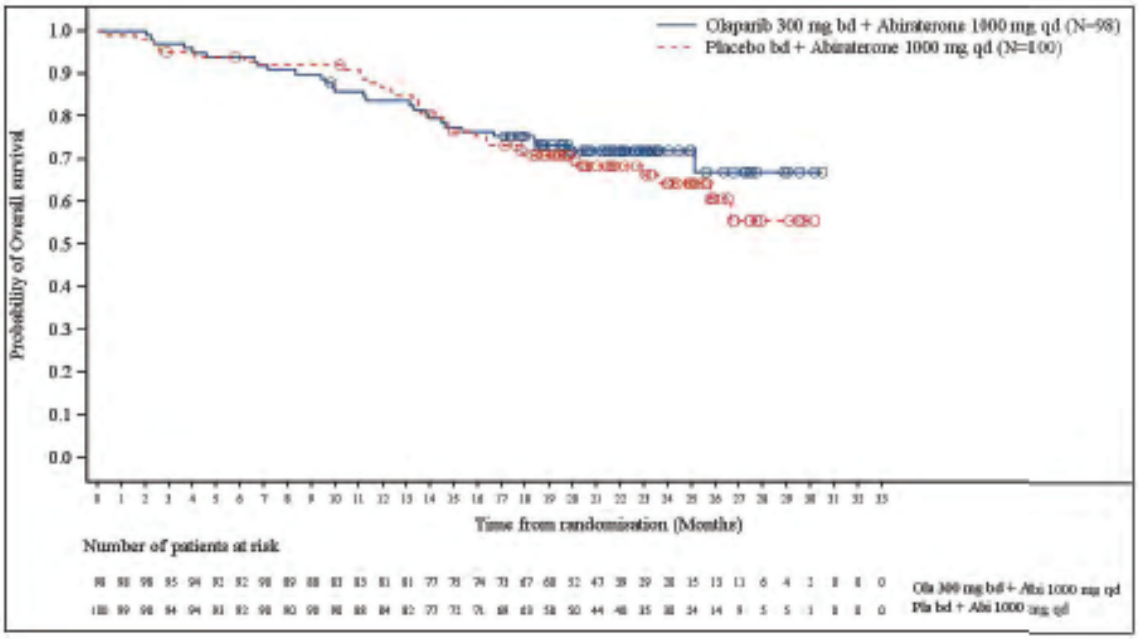


Figure 28: PROpel : OS based on investigator assessment in the HRRm subgroup by ctDNA test, KM plot (DCO1: 30 July 2021)

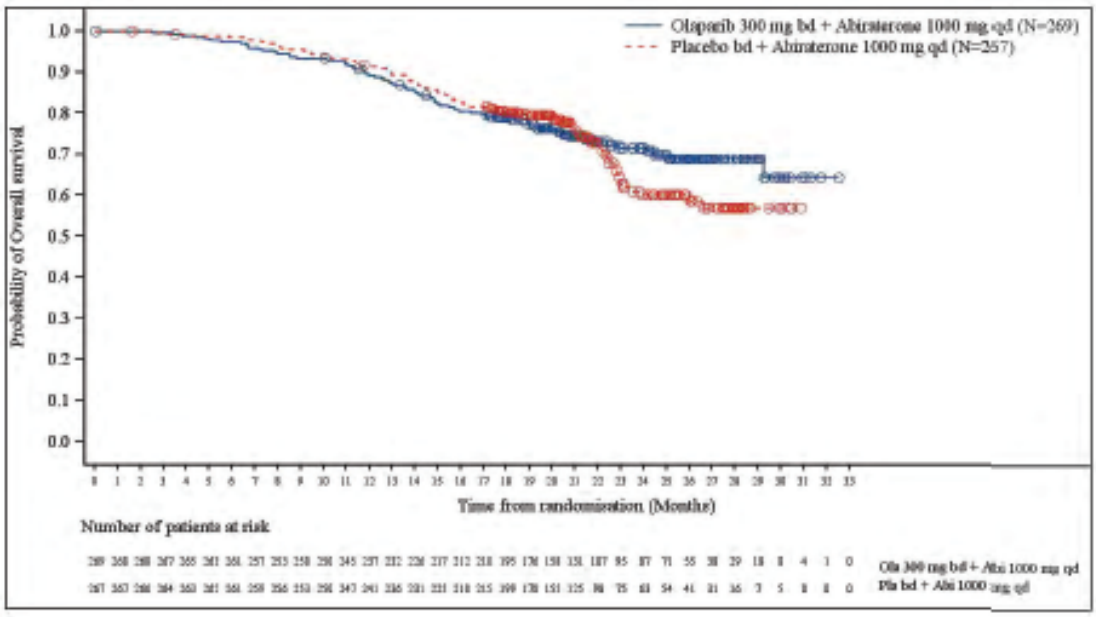


Figure 29: PROpel : OS based on investigator assessment in the non-HRRm subgroup by ctDNA test, KM plot (DCO1: 30 July 2021)

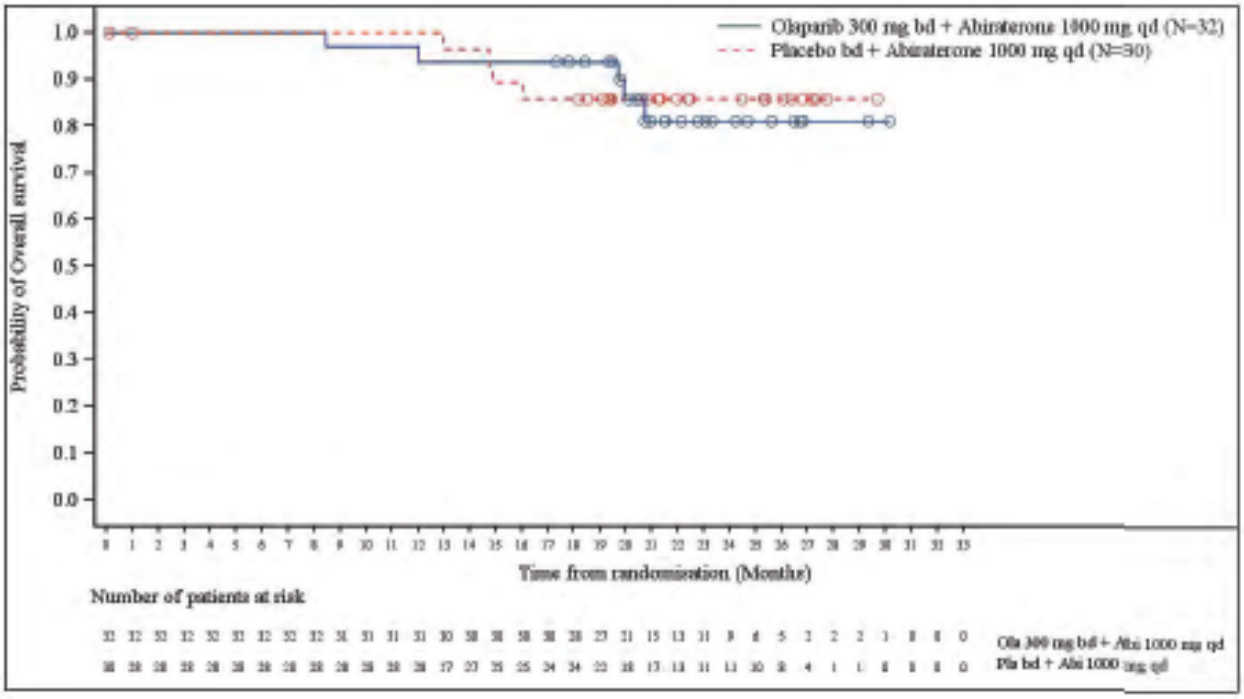


Figure 30: PROpel : OS based on investigator assessment in the HRRm unknown subgroup by ctDNA test, KM plot (DCO1: 30 July 2021)

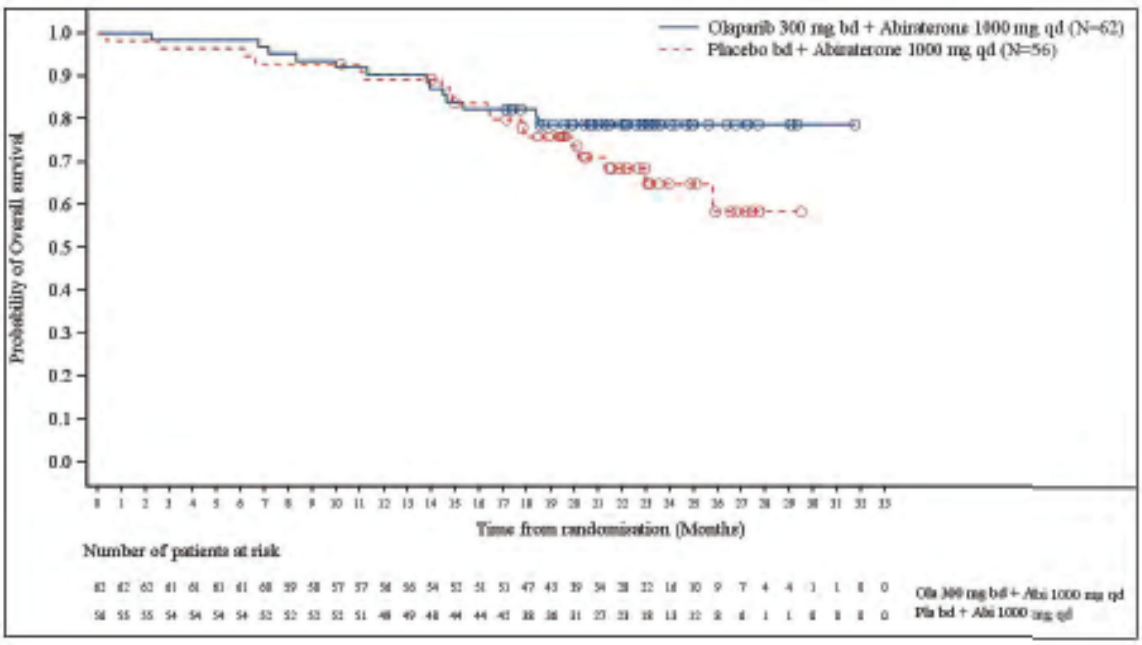


Figure 31: OS based on investigator assessment in the HRRm subgroup by tumor tissue test, KM plot (DCO1: 30 July 2021)

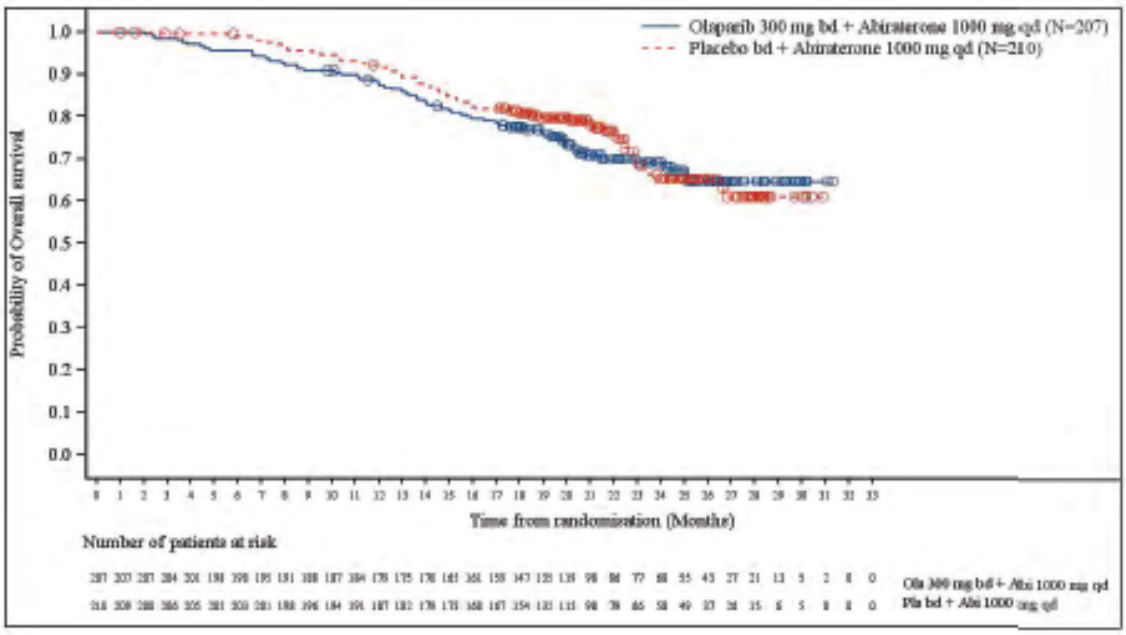


Figure 32: PROpel: OS based on investigator assessment in the non-HRRm subgroup by tumor tissue test, KM plot (DCO1: 30 July 2021)

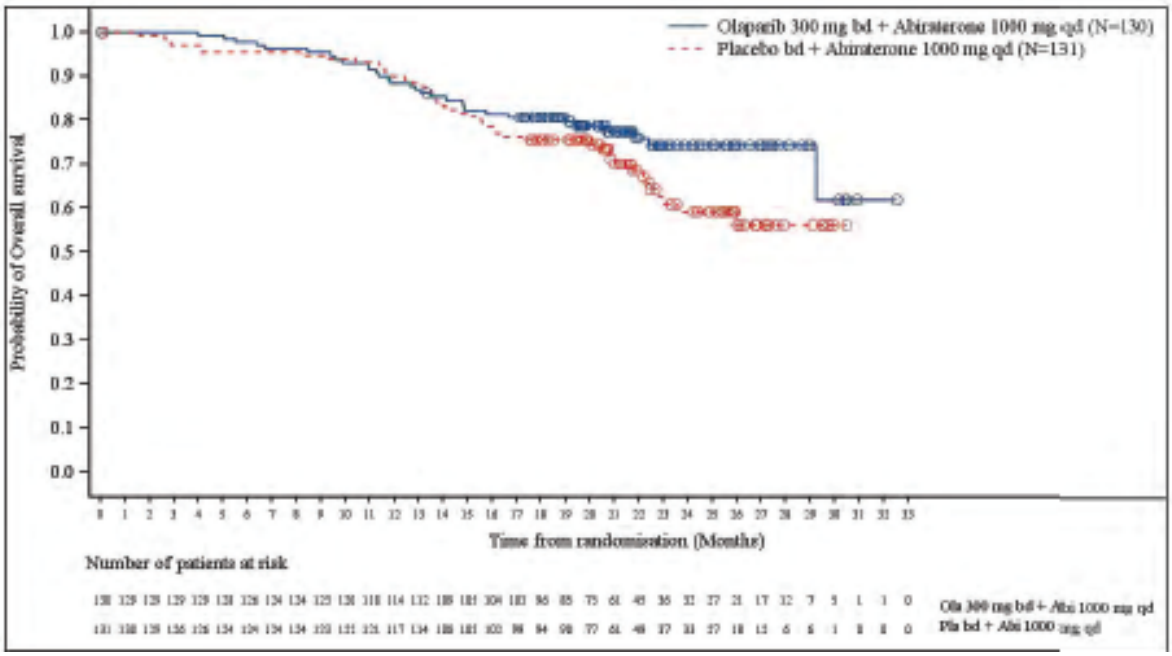


Figure 33: PROpel : OS based on investigator assessment in the HRRm unknown subgroup by tumor tissue test, KM plot (DCO1: 30 July 2021)

Table 32: Aggregate HRRm Subgroup Analyses (DCO1: 30 July 2021)

Subgroup	Treatment Group	Events/Patients (%)	Median (months)	HR (95% CI)
rPFS				
HRRm	Olaparib+abiraterone	43/111 (38.7)	NC	0.50 (0.34, 0.73)
	Placebo+abiraterone	73/115 (63.5)	13.86	
Non-HRRm	Olaparib+abiraterone	119/279 (42.7)	24.11	0.76 (0.60, 0.97)
	Placebo+abiraterone	149/273 (54.6)	18.96	
OS				
HRRm	Olaparib+abiraterone	28/111 (25.2)	NC	0.82 (0.50, 1.35)
	Placebo+abiraterone	35/115 (30.4)	NC	
Non-HRRm	Olaparib+abiraterone	77/279 (27.6)	NC	0.89 (0.65, 1.21)
	Placebo+abiraterone	84/273 (30.8)	NC	

Note: There were 18 patients in HRRm unknown that are not in the model.

Aggregate HRRm subgroups were derived from ctDNA and tissue based HRRm groupings.

rPFS: Progression, as assessed by investigator, is defined by RECIST 1.1 and/or PCWG-3 or death.

The analysis was performed using a Cox proportional hazards model including terms for treatment group, the subgroup factor, and a treatment by subgroup interaction. CIs calculated using profile likelihood method. The HRRm unknown subgroup was excluded from the model. A HR < 1 favors olaparib+abiraterone. Subgroups with fewer than 5 events in either treatment group do not have HR/CIs presented. CI, confidence interval; HR, hazard ratio; HRR, homologous recombination repair; HRRm, homologous recombination repair mutation; NC, not calculable; PCWG-3, Prostate Cancer Working Groups 3; rPFS, radiological progression free survival; OS overall survival; RECIST, Response Evaluation Criteria in Solid Tumours.

Subgroup Analyses of rPFS and OS (according to Prior Docetaxel Use)

Table 33: Radiographic Progression-free Survival Based on Investigator and Overall Survival. Cox proportional Hazard Subgroup Analysis: Prior Docetaxel vs No prior Docetaxel (Full Analysis Set (DC01:30 July 2021 and DCO2: 14 March 2022)

Subgroup	Treatment Group	N	DCO1			DCO2		
			Number (%) of patients with events [a]	Median (95% CI) (months)	Hazard ratio (95% CI)	Number (%) of patients with events [a]	Median (95% CI) (months)	Hazard ratio (95% CI)
rPFS based on investigator assessments								
All patients	Olaparib + Abiraterone	399	168 (42.1)	24.84 (20.47, 27.63)	0.66 (0.54, 0.81)	199 (49.9)	24.97 (20.57, 27.86)	0.67 (0.56, 0.81)
	Placebo + Abiraterone	397	226 (56.9)	16.59 (13.93, 19.22)		258 (65.0)	16.39 (13.93, 19.19)	
Docetaxel treatment at mHSPC stage	Olaparib + Abiraterone	95	39 (41.1)	27.60 (16.46, NC)	0.61 (0.40, 0.92)	46 (48.4)	27.20 (16.46, 31.67)	0.65 (0.44, 0.96)
	Placebo + Abiraterone	94	56 (59.6)	13.83 (10.91, 19.19)		60 (63.8)	13.83 (10.91, 19.35)	
No Docetaxel treatment at mHSPC stage	Olaparib + Abiraterone	304	129 (42.4)	24.84 (20.47, 27.63)	0.71 (0.56, 0.89)	153 (50.3)	24.97 (20.47, 29.14)	0.71 (0.58, 0.88)
	Placebo + Abiraterone	303	170 (56.1)	16.82 (14.75, 19.45)		198 (65.3)	16.72 (14.75, 19.35)	

Subgroup	Treatment Group	N	DCO1			DCO2		
			Number (%) of patients with events [a]	Median (95% CI) (months)	Hazard ratio (95% CI)	Number (%) of patients with events [a]	Median (95% CI) (months)	Hazard ratio (95% CI)
Overall survival								
All patients	Olaparib + Abiraterone	399	107 (26.8)	NC (NC, NC)	0.86 (0.66, 1.12)	148 (37.1)	NC (NC, NC)	0.83 (0.66, 1.03)
	Placebo + Abiraterone	397	121 (30.5)	NC (NC, NC)		171 (43.1)	NC (NC, NC)	
Docetaxel treatment at mHSPC stage	Olaparib + Abiraterone	95	31 (32.6)	NC (NC, NC)	0.90 (0.55, 1.46)	41 (43.2)	34.86 (29.24, NC)	0.76 (0.50, 1.15)
	Placebo + Abiraterone	94	34 (36.2)	NC (NC, NC)		51 (54.3)	27.24 (23.13, NC)	
No docetaxel treatment at mHSPC stage	Olaparib + Abiraterone	304	76 (25.0)	NC (NC, NC)	0.86 (0.63, 1.17)	107 (35.2)	NC (NC, NC)	0.86 (0.67, 1.12)
	Placebo + Abiraterone	303	87 (28.7)	NC (NC, NC)		120 (39.6)	NC (NC, NC)	

[a] Analysis was performed using a Cox Proportional Hazards model that contains a term for treatment, factor, and treatment by factor interaction. HR < 1 favours olaparib + abiraterone. CI calculated using profile likelihood method.

HR and CI are not presented for subgroups with < 5 events in either treatment group. The IXRS values are used for the stratification factors.
CI = confidence interval; DCO = data cut-off; HR = hazard ratio; IXRS = interactive voice/web response system; mHSPC = metastatic hormone-sensitive prostate cancer; NC = not calculated.
Source: PROpel Table 14.2.1.1.1 (DCO1 and DCO2), PROpel Table 14.2.1.4.1 (DCO1 and DCO2), PROpel Table 14.2.4.1 1 (DCO1 and DCO2), PROpel Table 14.2.4.3.1 (DCO1 and DCO2).

Efficacy Subgroup Analyses of rPFS/OS in Patients with Visceral Metastases and/or Symptomatic Disease who had not Received Prior Docetaxel at the mHSPC stage

Table 34: Radiographic Progression-free Survival Based on Investigator and BICR Assessments and Overall Survival, Full Analysis Set and Subgroup Analyses in Patients with Visceral Metastases and/or Symptomatic Disease who had not Received Prior Docetaxel at the mHSPC stage (DCO2: 14 March 2022)

Parameter	Population	Treatment Group	N	Number (%) of patients with events	Median (95% CI) (months)	Hazard ratio (95% CI)
rPFS (assessed by investigator)[a]						
FAS		Olaparib + Abiraterone	399	199 (49.9)	24.97 (20.57, 27.86)	0.67 (0.56, 0.81)
		Placebo + Abiraterone	397	258 (65.0)	16.39 (13.93, 19.19)	
Symptomatic disease and/or visceral metastases, no prior docetaxel [b]		Olaparib + Abiraterone	94	58 (61.7)	16.16 (12.22, 20.57)	0.62 (0.44, 0.87)
		Placebo + Abiraterone	92	73 (79.3)	12.29 (8.11, 15.47)	
rPFS (assessed by BICR) [a]						
FAS		Olaparib + Abiraterone	399	182 (45.6)	27.60 (20.47, 30.16)	0.62 (0.51, 0.75)
		Placebo + Abiraterone	397	242 (61.0)	16.46 (13.80, 19.15)	
Symptomatic disease and/or visceral metastases, no prior docetaxel [b]		Olaparib + Abiraterone	94	52 (55.3)	15.34 (13.60, 23.36)	0.53 (0.37, 0.76)
		Placebo + Abiraterone	92	71 (77.2)	10.97 (8.11, 13.67)	
Overall survival						
FAS		Olaparib + Abiraterone	399	148 (37.1)	NC (NC, NC)	0.83 (0.66, 1.03)
		Placebo + Abiraterone	397	171 (43.1)	NC (NC, NC)	
Symptomatic disease and/or visceral metastases, no prior docetaxel [b]		Olaparib + Abiraterone	94	47 (50.0)	27.86 (22.44, NC)	0.81 (0.55, 1.20)
		Placebo + Abiraterone	92	52 (56.5)	22.97 (18.53, 32.00)	

[a] Progression, as assessed by investigator (or independent assessor for BICR), is defined by RECIST 1.1 and/or PCWG-3 or death.
[b] Symptomatic (BPI-SF item #3 score ≥ 4 and/or opiate use) and/or visceral metastases at baseline, no docetaxel treatment at mHSPC stage.

In the FAS: HR and CI calculated using a Cox proportional hazards model adjusted for the variables selected in the primary pooling strategy: metastases, docetaxel treatment at mHSPC stage. The Efron approach was used for handling ties. A hazard ratio < 1 favours olaparib 300 mg bd.
In the subgroups: each subgroup analysis was performed using a Cox proportional hazards model that contains a term for treatment, subgroup factor and a treatment by subgroup interaction. CIs calculated using profile likelihood method. A hazard ratio < 1 favours olaparib 300 mg bd. Subgroups with fewer than 5 events in either treatment group do not have HR/CIs presented.
BICR = blinded independent central review; BPI-SF = Brief Pain Inventory-Short Form; CI = confidence interval; DCO2 = data cut-off 2; FAS = Full Analysis Set; HR = hazard ratio; mHSPC = metastatic hormone-sensitive prostate cancer; PCWG-3 = prostate cancer working group-3; NC = Not calculated; RECIST = Response evaluation criteria in solid tumours; rPFS = radiographic progression-free survival.
Source: PROpel (DCO2) Tables 14.2.1.4.1, 14.2.1.1.2, 14.2.4.1, PROpel DCO2 IEMT Tables 3380.a1, 3380.a2

Summary of main study

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

Table 35 : Summary of Efficacy for PROpel

Title: Study PROpel Phase III randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy and safety of olaparib (Lynparza™) or placebo, each combined with abiraterone, as first-line therapy in patients with mCRPC			
Study identifier	Study Code - D081SC00001 EudraCT Number - 2018-002011-10		
Design	Phase III, randomised, double-blind, placebo-controlled, multicentre Patients were randomised in a ratio 1:1 : - olaparib + abiraterone - placebo + abiraterone		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		 <not applicable> <not applicable>
Hypothesis	Superiority		
Treatments groups	Olaparib		Olaparib 300 mg bd (tablet formulation) in combination with abiraterone with prednisone or prednisolone 5 mg bd
	Placebo		1000 mg qd administered with prednisone or prednisolone 5 mg bd
Endpoints and definitions	Primary endpoint	rPFS by investigator	The time from randomisation to 1) radiological progression, assessed by investigator per RECIST 1.1 (soft tissue) and PCWG-3 criteria (bone), or 2) death from any cause, whichever occurs first
	Key Secondary endpoint	OS	The time from randomisation until date of death (due to any cause).
	Secondary endpoint	PFS2	The time from randomisation to second progression on next-line anticancer therapy following study treatment discontinuation, by investigator assessment of radiological progression, clinical symptomatic progression, PSA progression or death, whichever occurred earlier.
		TFST	The time from randomisation to the earlier of the first subsequent anticancer therapy start date following study treatment discontinuation or death from any cause.
		TTPP	The time from randomisation to pain progression based on the BPI-SF [Item 3] "worst pain in 24 hours" and opiate analgesic use (AQA score).
		Time to opiate use for cancer related pain	The time from randomisation to the first opiate use for cancer-related pain.

		Time to first SSRE	Time from randomisation to first SSRE was defined by any of the following or a combination thereof: - Use of radiation therapy to prevent or relieve skeletal symptoms - Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral). Radiologic documentation was required - Occurrence of spinal cord compression. Radiologic documentation was required - Orthopaedic surgical intervention for bone metastasis
		BPI-SF	(progression in pain severity domain and change in pain interference domain)
		HRR gene mutation status	Patient enrolment was not based on biomarker selection. Both tumour tissue and blood samples were collected at baseline for retrospective biomarker tests
Database lock	DOC1: 31 July 2021		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	**Full analysis set (FAS):** all patients randomised into the study and analysed according to randomised treatment, ie, ITT principle		
Descriptive statistics and estimate variability	**Treatment group**	**Olaparib + abiraterone**	**Placebo + abiraterone**
	Number of subject	**399**	**397**
	Median rPFS (months)	24.84	16.59
	95% CI	20.47, 27.63	13.93, 19.22
	Median OS	NC	NC
	95% CI	NC, NC	NC, NC
	Median PFS2	NC	NC
	95% CI	NC, NC	NC, NC
	Median TFST	25.0	19.9
	95% CI	22.2, NC	17.1, 22.0
	Median TTPP	NC	NC
	95% CI	NC, NC	NC, NC
	Median Time to opiate use	NC	NC
	95% CI	NC, NC	NC, NC
	Time to first SSRE	NC	NC
	95% CI	NC, NC	NC, NC
Effect estimate per comparison	Primary endpoint rPFS (49.5% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	0.66
		95% CI	0.54, 0.81
		2 sided P-value	<0.0001
	Key secondary endpoint OS (28.6% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	0.86
		95% CI	0.66, 1.12
		2 sided P-value	0.2923
	Secondary endpoint PFS2 (20.6% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	0.69

		95% CI	0.51, 0.94
		2 sided P-value	0.0184
	Secondary endpoint TFST (50.8% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	0.74
		95% CI	0.61, 0.90
		2 sided P-value	0.0040
	Secondary endpoint TTPP (13.8% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	1.01
		95% CI	0.69, 1.47
		2 sided P-value	0.9551
	Secondary endpoint Time to opiate use for cancer pain (11.3% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	1.08
		95% CI	0.71, 1.64
		2 sided P-value	0.6510
	Secondary endpoint Time to first SSRE (10.6% maturity)	Comparison groups	Olaparib + abiraterone vs placebo + abiraterone
		Hazard ratio	0.72
		95% CI	0.47, 1.11
		2 sided P-value	0.1324
Notes	The MTP for the PROpel study is based on analyses at three DCOs. Radiological PFS analyses at DCO1 and DCO2 were planned. As statistical significance of rPFS was achieved at DCO1, formal rPFS analysis at DCO2 will not be done and analysis of this endpoint at DCO2 will be considered descriptive (with nominal p-values provided). OS was formally analysed at DCO1 (interim analysis), and will be at DCO2 (interim analysis), and DCO3 (final analysis). DCO1 was planned when approximately 379 of the 796 patients had an rPFS event (47.6% maturity), which was estimated to occur approximately 31 months after the first patient was randomised in the study. Actual DCO1 was set as 30 July 2021, approximately 33 months after the first patient was randomised, with 394 rPFS events (49.5% maturity) available at the time of the analysis. DCO2 is anticipated to occur approximately 39 months after the first patient was randomised in the study while DCO3 will occur approximately 48 months after the first patient is randomised, when a minimum follow-up of 32 months would be expected.		

Supportive study - Study D081DC00008 (Study 8)

Study D081DC00008 (Study 8) is a Randomised, Double-Blind, Placebo-Controlled, Multicentre Phase II Study to Compare the Efficacy, Safety and Tolerability of Olaparib Versus Placebo When Given in Addition to Abiraterone Treatment in Patients With Metastatic Castrate-Resistant Prostate Cancer Who Have Received Prior Chemotherapy Containing Docetaxel.

Study 8 was a 2-part Phase II study in patients with mCRPC. Part A was an open-label safety run in study for olaparib dose selection, and to assess the safety, tolerability and PK of olaparib when given in addition to abiraterone 1000 mg once daily (Cohort 1, Cohort 2 group 1 and Cohort 2 group 2). Part B was a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A when given in addition to abiraterone, versus placebo in addition to abiraterone. For the purpose of this indication, Study 8 provides supportive efficacy data which are provided by an all-comers population of 142 patients with mCRPC (Part B).

Primary objective: To compare the efficacy of olaparib plus abiraterone with placebo plus abiraterone by assessment of rPFS using RECIST v1.1 and PCWG-2 criteria.

Key secondary objectives: To assess the activity of olaparib in combination with abiraterone, compared with placebo in combination with abiraterone, by PSA, CTCs, ORR (by RECIST 1.1 and PCWG-2 criteria) and malignant soft tissue ORR (by RECIST 1.1), DoR, TFST, TSST, OS, PFS2. To compare the safety and tolerability of olaparib when given in addition to abiraterone, with placebo given in addition to abiraterone.

Design: Study 8 was a 2-part Phase II study in patients with mCRPC. Part A was an open-label safety run in study for olaparib dose selection, and to assess the safety, tolerability and PK of olaparib when given in addition to abiraterone 1000 mg once daily (Cohort 1, Cohort 2 group 1 and Cohort 2 group 2). Part B was a randomised, double-blind, placebo-controlled comparison of the efficacy, safety and tolerability of the dose of olaparib selected from Part A when given in addition to abiraterone, versus placebo in addition to abiraterone.

Patients: A total of 171 patients were enrolled in Part B, and 142 patients were randomised and received treatment with olaparib combined with abiraterone (n = 71) or with placebo combined with abiraterone (n = 71). Patients in the olaparib+abiraterone arm were generally older than those in the placebo+abiraterone arm (median age of 70 years vs 67 years). With the exception of 1 patient in each arm who had an ECOG PS of 2, and 2 patients in the placebo+abiraterone arm with a missing status, all patients had an ECOG PS of 0 or 1. Median (range) baseline PSA was higher in the olaparib+abiraterone arm compared with the placebo+abiraterone arm (86.20 µg/mL [0.2 to 3475.4 µg/mL] versus 46.82 µg/mL [1.4 to 3140.0 µg/mL], respectively). Patients in the olaparib+abiraterone arm had a longer mean time from initial diagnosis of prostate cancer to first dose compared with the placebo+abiraterone arm (respectively, 68.1 months and 59.5 months); the same was seen for time from most recent progression to randomisation (respectively, 67.8 days and 53.1 days). A higher incidence of patients in the olaparib+abiraterone arm had AJCC Stage IV disease at diagnosis compared with the placebo+abiraterone arm (respectively, 50.7% and 38.0%).

Summary of efficacy

A summary of the efficacy data from Part B Study 8 is presented in the table below.

Table 36: Study 8: Summary of Supportive Efficacy Data (FAS)

	Olaparib+abiraterone N = 71	Placebo+abiraterone N = 71
rPFS (by investigator assessment)		
Number of events/total number of patients (%)	46/71 (64.8)	54/71 (76.1)
Median rPFS (months)	13.8	8.2
HR (95% CI)	0.651 (0.438, 0.969)	
p-value (2-sided)	p=0.034	
OS (62% maturity)		
Number of events/total number of patients (%)	43/71 (60.6)	45/71 (63.4)
Median OS (months)	22.7	20.9
HR (95% CI)	0.911 (0.600, 1.384)	
p-value (2-sided)	p=0.662	
PFS2		
Number of events/total number of patients (%)	37/71 (52.1)	45/71 (63.4)
Median PFS2 (months)	23.3	18.5
HR (95% CI)	0.788 (0.511, 1.215)	
p-value (2-sided)	p=0.280	
TFST		
Number of events/total number of patients (%)	57/71 (80.3)	58/71 (81.7)
Median TFST (months)	13.5	9.7
HR (95% CI)	0.781 (0.540, 1.130)	
p-value (2-sided)	p=0.189	
TSST		
Number of events/total number of patients (%)	47/71 (66.2)	52/71 (73.2)
Median TSST (months)	19.6	18.0
HR (95% CI)	0.809 (0.545, 1.201)	
p-value (2-sided)	p=0.294	
Overall radiological ORR		
Number of patients with a response/total number of patients with measurable disease at baseline (%)	9/33 (27.3)	12/38 (31.6)
Odds ratio (95% CI)	0.813 (0.285, 2.261)	
p-value (2-sided)	p=0.617	

FAS: all patients randomised into the study and analysed according to randomised treatment, ie ITT principle.

CI, confidence interval; CSR, clinical study report; FAS, full analysis set; HR, hazard ratio; ITT, intention-to-treat; N, total number of patients; ORR, objective response rate; OS, overall survival; PFS2, time from randomisation to second progression or death; rPFS, radiological progression free survival; TFST, time from randomisation to start of first subsequent therapy or death; TSST, time from randomisation to start of second subsequent therapy or death.

Table 37: Study 8: rPFS Subgroup Analyses by Investigator Assessment by HRR15 Mutation – Final Classification (FAS)

Subgroup	Olaparib+abiraterone	Placebo+abiraterone
HRR positive (HRRm)		
N	11	12
Number of events/total number of patients (%)	8 (72.7)	9 (75.0)
Median rPFS (months) [a, b]	17.8	6.5
HR (95% CI)	0.620 (0.233, 1.649)	
HRR negative (non-HRRm)		
N	35	38
Number of events/total number of patients (%)	24 (68.6)	32 (84.2)
Median rPFS (months) [a, b]	11.6	5.5
HR (95% CI)	0.542 (0.317, 0.926)	
HRR partly characterised (HRRm unknown)		
N	25	21
Number of events/total number of patients (%)	14 (56.0)	13 (61.9)
Median rPFS (months) [a, b]	15.3	13.9
HR (95% CI)	0.952 (0.444, 2.037)	

Final classification HRR15 takes into account all initial data and further test results subsequently available.

Olaparib + abiraterone: olaparib 300 mg bd+abiraterone 1000 mg qd. Placebo + abiraterone: placebo bd+abiraterone 1000 mg qd. The analysis was performed using the log rank test with treatment group as a factor. The HR and CI are estimated from the U and V statistics obtained directly from the LIFETEST model. A HR < 1 implies a lower risk of progression on olaparib 300 mg. bd, twice daily; CI, confidence interval; CSR, clinical study report; FAS, full analysis set; HR, hazard ratio; HRR15, a panel of 15 HRR genes; HRRm homologous recombination repair gene mutation; PCWG-2, Prostate Cancer Working Group 2; qd, once daily; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; rPFS, radiological progression-free survival (investigator determined).

2.4.2. Discussion on clinical efficacy

Design and conduct of clinical studies

The claimed indication is lynparza in combination with abiraterone and prednisone or prednisolone indicated for the treatment of adult patients with metastatic castration resistant prostate cancer. The current application is based on the results of the pivotal study PROpel. This was a Phase III, randomised, double-blind, placebo-controlled, multicentre study to assess the efficacy and safety of olaparib *versus* placebo, each combined with abiraterone and prednisone or prednisolone, as first-line treatment for men with mCRPC.

Patients were randomised 1:1 to receive either olaparib or placebo, each combined with abiraterone and prednisone or prednisolone. All patients had to have evidence of histologically or cytologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan. Patients with brain metastases were not eligible. At the mCRPC stage (first-line setting), patients must have no prior cytotoxic chemotherapy or NHA treatment. Treatment with first-generation antiandrogen agents was allowed provided there was a washout period of 4 weeks. Treatment was continued until objective radiological disease progression or until patients were unable to tolerate study treatment.

Patients were stratified by site of distant metastases (bone only, visceral, or other) and docetaxel treatment at mHSPC stage (yes or no). The stratification based on taxane chemotherapy would avoid

heterogeneous population due to variability in the prior use of docetaxel in HSPC, which is agreed. The other stratification based on site of distant metastases is agreed since symptomatic and asymptomatic/mildly symptomatic patients were eligible in this trial. PROpel is an all-comers study and patient enrolment was not based on biomarker status (HRRm status). Eligibility criteria are considered acceptable according to the claimed indication. Indeed, supported by preclinical evidence (see non-clinical section above), there are two plausible mechanisms of action with biomarkers' independent activity for the olaparib-abiraterone combination explaining that biomarkers are unnecessary for the selection of patients. However, the stratification according to HRR mutation status was recommended by CHMP (EMEA/H/SA/1215/5/2018/II 20 September 2018). Exploratory analyses were performed based on stratification factors, baseline characteristics, and HRRm status to assess the consistency of treatment effect. For HRRm status, both tumour tissue and blood samples were collected at baseline for retrospective biomarker tests. Mutation status was determined using a ctDNA-based test (FoundationOne® Liquid CDx), a tumour tissue test (FoundationOne® CDx), or a germline blood test (Myriad myRisk).

In PROpel, the dose of olaparib used is of 300 mg bd as tablet formulation in combination with abiraterone 1000 mg qd. This choice of dose was supported by safety and PK data from Study D081DC00008, a phase II study which evaluated olaparib in combination with abiraterone at the same dose in mCPRC.

The primary endpoint was rPFS by investigator assessment in the FAS (the FAS comprises all patients randomised into the study and analysed according to the randomised treatment [ie, the ITT principle]) and the key secondary endpoint is OS. The choice of rPFS as primary endpoint instead of OS is acceptable despite the poor prognosis of mCRPC. A blinded, independent central review (BICR) of all scans used in the assessment of tumours was also conducted and used as a sensitivity analysis of the primary endpoint which is acceptable.

The choice of OS as key secondary endpoint is also considered acceptable.

A multiple testing procedure (MTP) was employed across the primary endpoint of rPFS and the key secondary endpoint of OS to control the Type I error at 2.5% (1-sided). Following a hierarchical testing strategy, rPFS was tested first and then OS was tested only if statistical significance was shown for rPFS. The MTP for the PROpel study is based on analyses at three DCOs. Radiological PFS analyses at DCO1 and DCO2 were planned. As statistical significance of rPFS was achieved at DCO1, formal rPFS analysis at DCO2 will not be done and analysis of this endpoint at DCO2 will be considered descriptive (with nominal p-values provided). OS was formally analysed at DCO1 (interim analysis), and will be at DCO2 (interim analysis), and DCO3 (final analysis). DCO2 is planned to be performed at ~56.9% of maturity while DCO3 will occur approximately 48 months after the first patient is randomised, when a minimum follow-up of 32 months would be expected.

Actual DCO1 was set as 30 July 2021, approximately 33 months after the first patient was randomised, with 394 rPFS events (49.5% maturity) available at the time of the analysis. Actual DCO2 was set as 14 March 2022, with 457 rPFS events and 57.4% % of maturity.

Sensitivity analyses were planned in the SAP: assessment of possible evaluation time bias, attrition bias, censoring bias, deviation bias, a sensitivity analysis using unequivocal clinical progression in addition to radiological progression, a sensitivity analysis for confirmation of bone progression and a sensitivity analysis censoring patients with subsequent therapy or discontinuation of study drug.

The comparisons between olaparib and placebo arms associated to abiraterone for all other secondary endpoints (PFS2, TFST, TTPP, time to opiate use, time to SSRE, HRR gene mutation status) in this study were not confirmatory since no multiplicity adjustment plan was set up.

The use of abiraterone+ placebo as comparator is acceptable as recommended by ESMO in the treatment of asymptomatic/mildly symptomatic men with chemotherapy-naïve mCRPC (Cancer of the prostate: ESMO Clinical Practice, Guidelines for diagnosis, treatment and follow-up, volume 31, 25 june 2020). For symptomatic mCRPC patients, the guidelines (ESMO) recommend the use of abiraterone for the treatment of mCRPC in adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen. For this subgroup of patients, abiraterone (in the indication claimed by the MAH) may be suboptimal compared to current valid therapies (chemotherapy). The indication was restricted to be in line with the recommendations and the population that could benefit from the combination olaparib + abiraterone.

The sample size was based on hypothesis to demonstrate a statistically significant difference for the primary endpoint of the study (rPFS) with 89% power at a 1-sided type 1 error rate at 2.5%, which is considered acceptable.

The study was designed to provide at least 89% power to demonstrate statistically significant difference in rPFS at a 1-sided type 1 error rate at 2.5% if the true treatment effect was a hazard ratio (HR) of 0.68, corresponding to an assumed increase in median rPFS from 16.5 months (placebo+abiraterone) to 24.3 months (olaparib+abiraterone).

Efficacy data and additional analyses

Baseline data

Of the 796 patients randomised with mCRPC in the FAS, 70.7% and 69.3% were white in the olaparib+abiraterone arm compared to placebo + abiraterone arm(with a median age of 69.0 years and 71.5% of patients were in the ≥ 65 years age group. A higher proportion of subjects ≥ 65 years old were randomized in placebo + abiraterone arm compared to olaparib + abirterone arm, respectively 75.6% and 67.4%.

The histology (mostly adenocarcinoma), the ECOG PS at baseline (0-1) and the total Gleason Score at diagnosis (8-10) were globally balanced between both arms.

The median baseline PSA was similar between both arms with respectively 17.895 µg/L and 16.805 µg/L in olaparib + abiraterone and placebo + abiraterone arms.

Median times from initial diagnosis (months) were also similar among the olaparib + abiraterone and placebo + abiraterone arms: 33.6 months and 39.5 months, respectively.

The most common site of disease at baseline was bone (86.4%). According to IWRS, 13.2% of patients had visceral metastasis. The presence of distant metastases according to TNM Classification at diagnosis was also well balanced between both arms with: M1: n = 143 (35.8%) for olaparib + abiraterone arm and n = 139 (35.0%) for placebo + abiraterone arm; M0: n = 115 (28.8%) for olaparib + abiraterone arm and n = 132 (32.2%) for placebo + abiraterone arm.

Regarding the previous treatment-related disease, the majority of subjects received a treatment prior to mCRPC stage, 91.5% and 95.7% respectively in olaparib + abiraterone arm and placebo + abiraterone arm. About two-third of randomized subjects received prior hormonal therapy and were well balanced between both arms (75.9% in olaparib+abiraterone arm and 81.9% in placebo+abiraterone arm). Of these subjects, half received radiotherapy in the previous line of treatment (51.6% in the olaparib+abiraterone arm and 48.9% in the placebo+abiraterone arm), and one-quarter received cytotoxic chemotherapy, mostly docetaxel in the mHSPC stage (90/98 in olaparib + abiraterone arm and 89/100 in placebo + abiraterone arm). Only one subject was previously treated with second-generation antiandrogen prior to mCRPC stage. A total of 401/796 (50.4%) subjects received a first-antiandrogen agents, mostly bicalutamide (197/202 subjects).

HRR testing results

Of note, patient enrolment in PROpel study was not based on biomarker selection. Both tumour tissue and blood samples were collected at baseline for retrospective biomarker tests.

The proportion of patients with HRR mutations, non HRR mutation or unknown was well balanced between both arms, regardless of the biomarker tests. The majority of patients randomised were non-HRRm with an incidence of 52.4% when HRRm status was based on tissue test and 67.3% based on ctDNA test. The incidence of HRRm patients was 14.8% when HRRm status was based on tissue test and 24.9% based on ctDNA test. These results are consistent with the epidemiology as approximately 20% of metastatic prostate cancers harbour aberrations in genes involved in DNA damage and repair (*Robinson D, Van Allen EM, Wu YM, et al. Integrative clinical genomics of advanced prostate cancer.Cell. 2015;161:1215e1228).*

Primary endpoint

PROpel study met its primary endpoint with the demonstration of a statistically significative improvement of rPFS based on the investigator's assessment in the FAS with a prolongation of median rPFS of 8.2 months in favor of Olaparib+Abiraterone compared to placebo+Abiraterone at DCO1 (HR : 0.66, 95% 0.54-0.81, p<0.0001). The sensitivity analysis of rPFS by BICR at DCO1 (HR 0.61; 95% CI: 0.49, 0.74; nominal p<0.0001; with median rPFS of 27.6 months in the olaparib+abiraterone arm and 16.4 months in the placebo+abiraterone arm) was consistent with the investigator-based analysis.

At DCO2, a significant rPFS improvement (based on investigator's assessment and BICR) in the olaparib + abiraterone arm is reported, consistent with the data from the first interim analysis.

Key secondary endpoint

The key secondary endpoint, OS, was multiplicity controlled. There is no statistically significant improvement of OS in olaparib + abiraterone with HR of 0.86, 95% CI: 0.66-1.12.

The OS HR point estimate numerically favoured the olaparib+abiraterone compared to the placebo+abiraterone arm suggesting a trend towards improved OS for olaparib+abiraterone-treated patients, with the KM curves separating after approximately 22 months. The median OS was not reached in either treatment arms.

The MAH provided updated OS results from the second planned interim analysis (DCO2 14 March 2022). Median duration of follow-up for OS was 27.56 months in the olaparib + abiraterone arm and 26.32 months in the placebo + abiraterone arm. The OS results showed statistically 17% numerical reduction in the risk of death at any given point in time (HR 0.83, 95% CI: 0.66, 1.03, p=0.1126). As of the 18 months, a higher proportion of patients in the olaparib arm compared with the placebo arm remained alive (18 months [79.32%], 24 months [70.6%], 30 months [63.35%] and 36 months [57.05%] compared with 78.32%, 65.4%, 55.51% and 51.61% respectively). The MAH will provide the final OS data in overall patient population and in subgroups (by BRCAm and HRRm status) and final rPFS and OS Kaplan-Meier curves for the subgroups of BRCAm and non-BRCAm patients from the PROpel study (D081SC00001) as a PAES and this has been reflected in Annex II of the PI.

Other secondary endpoints

The other efficacy endpoints are not adjusted for multiplicity.

There was a favourable trend in PFS2 (20.6% maturity) for the olaparib + placebo arm compared to placebo plus abiraterone arm with HR of 0.69, 95% CI: 0.51-0.94. Median PFS2 was not calculable for either treatment arms.

TFST data reached 50.8% maturity, with a nominally statistically significant and clinically meaningful improvement in TFST (ie, a delay of 5.1 months) in the olaparib+abiraterone arm compared to the placebo+abiraterone arm (HR of 0.74, 95% CI: 0.61-0.90; p=0.0040); the median TFST was 25.0 months and 19.9 months, respectively. The rate of patients with any post-discontinuation anticancer therapy was 33.1% vs. 43.6%. The most commonly reported subsequent treatments included cytotoxic chemotherapy (27.8%) or hormonal therapy (12.8%) which is consistent with clinical practice. Treatment with subsequent PARP inhibitor therapy (olaparib) occurred only for 3 patients (0.8%) in the placebo+abiraterone arm.

Concerning the time to first SSRE, there was a total of 84 events (10.6%) with a numerical improvement in time to first SSRE in the olaparib+abiraterone arm compared to placebo+abiraterone arm with HR of 0.72, 95% CI: 0.47-1.11 (p=0.1324).

The median TTPP based on BPI-SF worst pain [Item 3] and opiate use has not been reached for either treatment arm. No differences were demonstrated in the olaparib+abiraterone arm compared to the placebo+abiraterone arm. TTPP data reached 13.8% maturity with HR of 1.01, 95% CI: 0.6-1.47 (p=0.9551). Time to opiate use for cancer-related pain data reached 11.3% maturity with HR of 1.08, 95% CI: 0.71-1.64 (p=0.6510).

Overall, the PROpel study met its primary endpoint and showed a favourable trend of PFS2, TFST, Time to first SRE for olaparib + abiraterone compared to placebo + abiraterone.

Subgroups analysis

Subgroup's analysis of rPFS based on the stratification factors did not reveal an obvious differential benefit across most of the pre-defined subgroups compared with the overall population.

Regarding subgroup analyses based on HRR status determination, these exploratory analyses did not show a major difference in benefit across most of the mHRR, non-HRRm and unknown HRR subgroups compared with the overall population. At DCO1, the subgroup gene analysis had shown that the benefit of olaparib is higher in HRRm compared to the other non-HRRm and HRR unknown subgroups and shown a favourable trend of rPFS for non-HRRm and unknown subjects but the difference in effect was not explained by the MAH. The applicant provided updated rPFS and OS data from DCO2 of the different HRR mutation subgroups and subgroup analysis in BRCAm vs non-BRCAm patients. Data results of rPFS and OS from DCO2 show a benefit of similar magnitude observed that DCO1. The combination olaparib + abiraterone show a benefit in all HRR mutation subgroups (based on tissue test, cDNAt, aggregate analysis, BRCAm or non-BRCAm/BRCAm unknwown) without detrimental effect and were overall consistent with the FAS. These data, although considered with caution due to the exploratory character of the data as there were no control by multiplicity, demonstrate a potential benefit in the non-BRCAm/ BRCAm unknown status and non-HRRm/HRRm unknown subgroups and do not preclude use in these subpopulations. The benefit at longer term, notably for OS, remains uncertain in non-BRCAm/non-HRRm patients, a PAES is requested. The MAH will provide the final OS data in overall patient population and in subgroups (by BRCAm and HRRm status) and final rPFS and OS Kaplan-Meier curves for the subgroups of BRCAm and non-BRCAm patients from the PROpel study (D081SC00001) as a PAES. Annex II of the SmPC has been updated.

In PROpel study, patients should not have received any cytotoxic chemotherapy, NHA, or other systemic treatment (approved drugs or experimental compounds) in the mCRPC setting. Docetaxel treatment was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage, as long as no signs of failure or disease progression occurred during or immediately after such treatment.

However, despite the indication of abiraterone -which is approved for the treatment of mCRPC adult men who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy in whom

chemotherapy is not yet clinically indicated and in mCRPC adult men whose disease has progressed on or after a docetaxel-based chemotherapy regimen and due to the divergence of US and EU marketing authorisations, both symptomatic and/or with visceral metastasis and asymptomatic or mildly symptomatic mCRPC patients were included in PROpel. Therefore, for the subgroup of patients with visceral metastases and/or symptomatic disease and without docetaxel use at mHSPC stage, the choice of the abiraterone + placebo comparator may be suboptimal, due to the available treatment alternatives in this indication (chemotherapy).

Based on the score on the Brief Pain Inventory-Short Form (BPI-SF) and/or opiate use at baseline, 560 patients with asymptomatic or mildly symptomatic disease were included in PROpel, 183 patients with symptomatic disease, and 53 patients with missing BPI-SF item #3 and no opiate use at baseline. A majority of patients with asymptomatic or mildly symptomatic disease, with symptomatic disease or unknown symptomatic disease status did not receive prior docetaxel treatment at the mHSPC stage (77%, 69.9% and 90.6%, respectively).

RPFS subgroup analyses from DCO1 and DCO2 comparing patients with and without prior docetaxel in the hormone-sensitive disease setting, show no significant difference between the subgroups with respectively a HR of 0.65 (95% CI 0.44-0.96) and 0.71 (95% CI 0.58-0.88) for the subgroup prior treated with docetaxel at mHSPC stage and with no prior docetaxel treatment. Data from rPFS based on investigator assessments in both subgroups were consistent with the FAS and were in favor of the combination olaparib + abiraterone. The subgroup previously treated with docetaxel appears to have a better benefit of the combination olaparib + abiraterone with a median rPFS improvement of 13.37 months vs. approximately 8 months in the subgroup not previously treated with docetaxel at mHSPC. OS data were 28.6% mature at DCO1, and a trend towards improved OS in the FAS was observed for olaparib + abiraterone (hazard ratios [HR]: 0.86; 95% confidence interval [CI]: 0.66-1.12; p = 0.2923). At DCO2, the median follow-up of patients was approximately of 27 months and the maturity was of 40.1%. OS HR point estimate numerically favoured the olaparib + abiraterone vs placebo + abiraterone arm and were consistent with the OS HR point estimate observed in FAS with a HR of 0.76 (95% CI 0.50-1.15) for patients with prior treatment with docetaxel, a HR of 0.86 (95% CI 0.67-1.12) for patients without prior treatment with docetaxel and a HR of 0.83 (95% CI 0.66-1.03) for the FAS.

Post-hoc subgroup analyses for efficacy outcomes (rPFS, OS) and analysis of safety profile of the association abiraterone + olaparib were performed in patients with visceral metastases and/or symptomatic disease who had not received prior docetaxel at the mHSPC stage (at DCO2). The rPFS results indicated that these patients might benefit from the addition of olaparib to abiraterone: median rPFS assessed by investigators 16.16 months (95%CI 12.22, 20.57) for olaparib combination arm vs 12.29 months (95%CI 8.11, 15.47) for placebo combination arm, with HR 0.62 (95%CI 0.44, 0.87). Median OS was 27.86 months (95%CI 22.44, NC) for olaparib combination arm vs 22.97 months (95%CI 18.53, 32.00) for placebo combination arm, with HR 0.81 (95%CI 0.55, 1.20).

These results are consistent with FAS and demonstrate a potential benefit of the association abiraterone + olaparib for all the populations eligible, i.e. in whom the chemotherapy is not clinically indicated at mCRPC, regardless of symptomatic disease status or previous treatment with docetaxel in mHSPC.

The MAH was requested to restrict the indication, to be in line with the recommendations and the population that could benefit from the combination, as follow:

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated.

2.4.3. Conclusions on the clinical efficacy

PROpel study met its primary endpoint rPFS with the demonstration of a statistically significant improvement in rPFS in the olaparib + abiraterone arm compared to placebo + abiraterone, which was supported by the sensitivity analysis of rPFS by BICR. The others secondary endpoints (PFS2, TFST, TSRE) showed a favourable trend for olaparib compared to placebo in combination with abiraterone in the other secondary endpoints except for the TTPP and Time to opiate use for cancer pain.

Symptomatic and/or with visceral metastasis and asymptomatic or mildly symptomatic mCRPC patients with or without prior docetaxel treatment at mHSPC were included in PROpel. For the subgroup of patients with visceral metastases and/or symptomatic disease and without docetaxel use at mHSPC stage, the choice of the abiraterone + placebo comparator may be suboptimal, due to the available treatment alternatives in this indication (chemotherapy). Post-hoc subgroup analyses for efficacy outcomes (rPFS, OS) and analysis of safety profile of the association abiraterone + olaparib were performed in patients with visceral metastases and/or symptomatic disease who had not received prior docetaxel at the mHSPC stage. The rPFS results indicated that these patients might benefit from the addition of olaparib to abiraterone. These results are consistent with FAS and demonstrate a potential benefit of the association abiraterone + olaparib for all the populations eligible, i.e. in whom the chemotherapy is not clinically indicated at mCRPC, regardless of symptomatic disease status or previous treatment with docetaxel in mHSPC.

The benefit of olaparib, in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated can be considered established.

Available data support a potential benefit in the non-BRCAm/ BRCAm unknown status and non-HRRm/HRRm unknown subgroups and do not preclude use in these subpopulations. However, the benefit at longer term, notably for OS, remains uncertain in non-BRCAm/non-HRRm patients, a PAES is requested.

2.5. Clinical safety

2.5.1. Introduction

Across the entire clinical program, as of 15 June 2021, approximately 17923 patients with multiple solid tumors are estimated to have received treatment with olaparib across the dose range 10 mg qd to 600 mg bd in AstraZeneca sponsored studies.

The focus of this application is the PROpel study, in which olaparib 300 mg (or placebo) bd was given in combination with abiraterone as first-line therapy in patients with mCRPC.

Supportive safety data aiming to compare safety observations between PROpel and other AstraZeneca-sponsored studies of Olaparib are given through 2 different pools.

The first pool concerns the association of olaparib and abiraterone (N = 469 patients) and is based on the PROpel study and the supportive study D081DC00008 (Study 8). The Second pool concern patients treated with olaparib in monotherapy: Olaparib 300mg bd pool (N = 3155).

The 2 pools have a common DCO date of 30 July 2021 to match the PROpel interim rPFS analysis DCO but pooled data are based on the DCO dates for the individual studies.

Patient exposure

a. Overall extent of exposure: PROpel

Table 38: Overall Extent of Olaparib/placebo Exposure in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd pool

Month (days)	Number (%) of patients [a]			
	PROpel SAF		Olaparib and abiraterone pool (N = 469)	Olaparib 300 mg bd pool (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
≥ Day 1	398 (100)	396 (100)	469 (100)	3155 (100)
≥ 1 month (30.4 days)	394 (99.0)	392 (99.0)	465 (99.1)	2981 (94.5)
≥ 3 months (91.3 days)	359 (90.2)	365 (92.2)	422 (90.0)	2577 (81.7)
≥ 6 months (182.6 days)	314 (78.9)	321 (81.1)	360 (76.8)	2107 (66.8)
≥ 12 months (365.3 days)	248 (62.3)	237 (59.8)	273 (58.2)	989 (31.3)
≥ 18 months (547.9 days)	191 (48.0)	159 (40.2)	206 (43.9)	548 (17.4)
≥ 24 months (730.5 days)	62 (15.6)	50 (12.6)	72 (15.4)	366 (11.6)
≥ 36 months (1095.8 days)	0	0	0	117 (3.7)
≥ 48 months (1461.0 days)	0	0	0	92 (2.9)
≥ 60 months (1826.3 days)	0	0	0	65 (2.1)
≥ 72 months (2191.5 days)	0	0	0	9 (0.3)

[a] Rows are cumulative and patients were included if they had taken treatment up to that month.
Patients ongoing treatment at study closure may not necessarily appear in the final treatment day category as total treatment duration differs across patients.

Table 39: PROpel - Duration of Olaparib, Placebo and Abiraterone Exposure in each arms

Treatment duration (days)	Olaparib 300 mg bd + abiraterone 1000 mg qd		Placebo bd + abiraterone 1000 mg qd	
	Olaparib (N = 398)	Abiraterone [c] (N = 398)	Placebo (N = 396)	Abiraterone [d] (N = 396)
Total treatment duration [a]				
Mean (standard deviation)	468.8 (258.57)	492.3 (250.75)	448.5 (239.89)	449.4 (241.33)
Median (Min, Max)	531.5 (13, 991)	555.0 (29, 991)	476.5 (12, 927)	477.0 (12, 927)
Total treatment days	186581	195921	177609	177974
Actual treatment duration [b]				
Mean (standard deviation)	452.1 (254.21)	480.2 (248.84)	441.7 (238.80)	444.6 (241.54)
Median (Min, Max)	519.0 (11, 978)	534.0 (28, 988)	464.5 (10, 927)	464.5 (10, 927)
Total treatment days	179916	191133	174907	176063

[a] Total treatment duration = (last dose date - first dose date + 1).[b] Actual treatment duration = (last dose date - first dose date + 1) excluding dose interruptions.[c] Abiraterone for patients that received olaparib.[d] Abiraterone for patients that received placebo.

Proportion of patients with treatment interruptions and dose reductions was higher in Olaparib than in placebo in their respective arms (47.0% *versus* 29.8% and 22.9% *versus* 7.3% respectively for dose reductions and for treatment interruption (Table 65-66).

In both arms, AE was the most common reason for treatment interruption of olaparib/placebo (39.5% olaparib+abiraterone arm and 19.7% in placeo+abiraterone arm) and dose reductions of olaparib/placebo (18.6% olaparib+abiraterone arm *versus* 4.3% in placeo+abiraterone arm).

Median relative dose intensity (percentage of the actual dose delivered relative to the intended dose through to treatment discontinuation) were similar and were >98% in both treatment arms, suggesting that dose intensity was not affected by dose modifications.

The median total duration of exposure to abiraterone was 1.2 times longer in the olaparib+abiraterone arm (555.0 days [18.2 months]) than in the placebo+abiraterone arm (477.0 days [15.7 months]) (Table 37). Combination treatment with olaparib does not appear to reduce the planned administration of abiraterone.

Overall extent of exposure: pools for comparison

Olaparib and abiraterone pool

Exposure to the combination of olaparib 300 mg bd and abiraterone 1000 mg qd in mCRPC concerned 398 patients in the PROpel study and 71 patients in study 8 (supportive study). Thus, pooled data concerned N = 469 patients. This pool provides data for long-term exposure to this treatment association (up to 2 years [24 months]).

As shown in Table 38, compared with the olaparib arm of PROpel, the distribution of cumulative exposure to olaparib was largely similar though there was a lowest proportion of patients remaining on olaparib in the olaparib and abiraterone pool at 6, 12, and 18 months. Consistentlythe median total duration of exposure to olaparib was longer in the olaparib+abiraterone arm of PROpel (531.5 days [17.5 months]; Table 39) than in the olaparib and abiraterone pool (480.0 days [15.8 months]).

Olaparib 300 mg bd pool

Patients in this pool received the same dose and formulation of olaparib as patients in olaparib and abiraterone pool (PROpel + study D081DC00008).

As shown in Table 36 data were pooled from 19 studies with a total of 3155 patients with solid tumours, including 267 patients who had prostate cancer. Among these 19 studies, 8 are phase III studies, 2 are phase II studies and 9 are phase I studies. This pool provides data for long-term exposure to olaparib 300 bd as a monotherapy (up to 72 months).

Table 40: Number of Patients in the Olaparib 300 mg bd pool

Study/pooled dataset	**Number of patients intended for the 300 mg bd cohort and received olaparib (all tumour types)**
Total exposed	**3155**
D081FC00001 (POLO): Phase III *gBRCAm* metastatic pancreatic adenocarcinoma patients whose disease has not progressed on first-line platinum-based chemotherapy	90
D081DC00007 (PROfound): Phase III HRRm metastatic castration-resistant prostate cancer	256
D081CC00006 (OlympiA): Phase III *gBRCA1/2m* and high-risk HER2 negative primary breast cancer patients who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy	911
D0819C00003 (OlympiAD): Phase III HER2-negative breast cancer patients with *gBRCA1/2* mutation	205
D0818C00001 (SOLO1): Phase III FIGO Stage III-IV ovarian cancer SOLO1 China cohort [a]	260 40
D0816C00020 (OPINION): Phase IIIb, patients with platinum-sensitive relapsed non-germline *BRCA* mutated ovarian cancer	279
D0816C00010 (SOLO3): Phase III *gBRCAm* ≥ third line ovarian cancer patients	178
D0816C00002 (SOLO2): Phase III platinum-sensitive serous ovarian cancer SOLO2: China cohort [a]	195 22
D5336C00001 (VIOLETTE): Phase II, second or third line metastatic triple negative breast cancer patients stratified by alterations in HRR related genes (including *BRCA1/2*) (Patient Population E [Stratum A]; olaparib monotherapy)	110
D0816L00003 (LIGHT): Phase II, patients with different HRD tumour status and with platinum-sensitive and endometrioid ovarian, fallopian tube, or primary peritoneal cancer	271
D081CC00001: Phase I anti-hormonal PK study	69
D081BC00002: China PK study	20
D081BC00001: Phase I Japan monotherapy study	19
D0816C00008 (Study 08): Phase I CYP induction	19
D0816C00007 (Study 07): Phase I CYP3A4 inhibition and QT	56
D0816C00006 (Study 06): Phase I renal impairment study	43
D0816C00005: Phase I hepatic impairment study	31
D0816C00004 (Study 04): Phase I food interaction & QT	57
D0810C00024 (Study 24): Phase I relative bioavailability (300 mg tablet bd patients only, Groups 4 and 6)	24

[a] The patients in the China cohorts of SOLO1 and SOLO2 were reported separately to the main clinical study reports for these studies.

As shown in Table 36, compared with the Olaparib+abiraterone arm of PROpel, the proportion of patients remaining on olaparib was lowest in the Olaparib 300 mg bd pool at 1, 3, 6, 12, 18, and 24 months, with the largest difference observed at 12 months and 18 months. A small proportion of patients in the

olaparib 300 mg bd pool remained on olaparib at 36, 48, 60, and 72 months. Consistent with that, the median total duration of exposure to olaparib was longer in the olaparib+abiraterone arm of PROpel (531.5 days [17.5 months];Table 37) than in the olaparib 300 mg bd pool (336.0 days [11.0 months]).

Demographics

PROpel and study 8

The demographic and disease characteristics of patients in PROpel and study 8 were summarised in the efficacy part. Demographic data for patients in these 2 studies have not been pooled, as the studies were in patients with different prior anticancer treatment status.

Olaparib 300 mg bd pool

Demographic data of studies contributing to the olaparib 300 mg bd pool have not been pooled, as the studies were in different patient populations of varying stages of disease. Summaries of the key demographic and baseline patient characteristics for the 19 studies contributing to the pooled dataset are provided in Table 39.

It is important to note that these data are for all patients in these studies and not just those in the olaparib 300 mg bd tablet dose cohorts. The primary tumour location of most patients in the olaparib 300 mg bd pool was breast (40.9%) and ovary (36.2%). Patients with other primary tumour locations, including prostate (8.5%), pancreas (3.2%), fallopian tube (2.6%), and primary peritoneal (2.1%), were also treated in these studies.
Compared with other studies in the olaparib 300 mg bd pool and especially the Phase III PROfound in mCRPC, differences were observed in baseline characteristics. A higher proportion of patients in PROfound study had a ECOG PS score $\geq$1 (restricted activity) and all patients were pre-treated. Whereas, few patients were pre-treated in PROpel, though most of patient in study 8 were pre-treated.
Mean age beetween PROpel, Study 8 and PRofound were similar. However, globaly in the Olaparib 300 mg bd pool, patients were younger than in the Olaparib and Abiraterone pool and mostly composed of female. In addition to these demographics differences, a majority of patients were HRD (BRCA mutated or others) whereas patients in PROpel were included regardless of the HRR status and roughly the majority of patients with known HRR status were HRR non-mutated in both arms.

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D081FC00001 (POLO) N = 154/151 (90 in the pooled dataset)	36 to 84 years (mean age 57.5 years) 70 (45.5%) Female 84 (54.5%) Male 141 (91.6%) White, 6 (3.9%) Asian 5 (3.2%) Black, African American and 2 (1.3%) Other	ECOG PS ≤ 1 103 (66.9%) PS0 48 (31.2%) PS1 (data were missing for 3 patients)	Metastatic pancreatic adenocarcinoma	All pre-treated Median number of prior chemotherapies for metastatic disease was 1.0	All *gBRCAm*
D081DC00007 (PROfound) N = 387/386 (256 in the pooled dataset):	47 to 91 years (mean age 68.6 years) All male 248 (64.1%) White 105 (27.1%) Asian 8 (2.1%) Black, African American, 23 (5.9%) Missing and 3 (0.8%) Other	ECOG PS ≤ 2 186 (48.1%) PS0 183 (47.3%) PS1 17 (4.4%) PS2 (data were missing for one patient)	HRRm metastatic castration-resistant prostate cancer	All pre-treated	All HRRm
D081CC00006 (OlympiA) N=1836/1815 (911 in the pooled dataset)	22 to 78 years (mean age 43.3 years) 1830 (99.7%) Female, 6 (0.3%) Male 1225 (66.7%) White, 531 (28.9%) Asian, 80 (4.4%) Black or African American, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and Other/Missing	ECOG PS ≤1 1628 (88.7%) PS0 208 (11.3%) PS1	Early breast cancer	All pre-treated	All *gBRCAm*
D0819C00003 (OlympiAD) N = 302/296 (205 in the pooled dataset)	22 to 76 years (mean age 45.3 years) 295 (97.7%) Female, 7 (2.3%) Male 197 (65.2%) White, 94 (31.1%) Asian 11 (3.6%) Black, African American and Other	ECOG PS ≤ 1 210 (69.5%) PS0 92 (30.5%) PS1	Metastatic breast cancer	All pre-treated Median number of prior chemotherapies was 1.0	All *gBRCAm*
D0818C00001 (SOLO1) N = 391/390 (260 in the pooled dataset)	29 to 84 years (mean age 53.5 years) All Female 320 (81.8%) White, 59 (15.1%) Asian 12 (3.1%) Black, African American and Other	ECOG PS ≤ 1 305 (78.0%) PS0 85 (21.7%) PS1	Advanced (FIGO Stage III-IV) ovarian cancer	All pre-treated Median number of prior chemotherapies was 1.0	389 *gBRCAm* 2 *sBRCAm*

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D0818C00001 (SOLO1) China cohort N = 64/64 (44 [a] in the pooled dataset)	33 to 67 years (mean age 51.0 years) All Female 64 (100%) Asian	ECOG PS ≤ 1 33 (51.6%) PS0 31 (48.4%) PS1	Advanced (FIGO Stage III-IV) ovarian cancer	All pre-treated Median number of prior chemotherapies was 1.0	All *gBRCAm*
D0816C00020 (OPINION) (279 in the pooled dataset)	40 to 85 years (mean age 64.0 years) All female 273 (97.8%) White 2 (0.7%) Asian 3 (1.1%) Black, African American and Other	ECOG PS ≤ 1 190 (68.1%) PS0 89 (31.9%) PS1	PSR ovarian cancer	All pre-treated Median number of prior chemotherapies was 2.0	34 *sBRCAm* 128 HRD status positive and/or *sBRCAm* 94 HRD status positive non-*BRCAm* 115 HRD status negative non-*BRCAm*
D0816C00010 (SOLO3) N = 266/254 (178 in the pooled dataset)	38 to 85 years (mean age 59.2 years) All Female 223 (83.8%) White, 34 (12.8%) Asian, 6 (2.3%) American Indian or Alaska Native, 2 (0.8%) Black or African American, 1 (0.4%) Other	ECOG PS ≤ 2 198 (74.4%) PS0 67 (25.2%) PS1 1 (0.4%) PS2	Advanced (FIGO Stage III-IV) ovarian cancer	All pre-treated Median number of prior chemotherapies was 2.0 (range 2 – 8)	All *gBRCAm*
D0816C00002 (SOLO2) N = 295/294 (195 in pooled dataset)	28 to 83 years (mean age 56.9 years) All female 264 (89.5%) White, 29 (9.8%) Asian, 1 (0.3%) Black or African American, 1 (0.3%) Other	ECOG PS ≤ 1 239 (81.0%) PS0 54 (18.3%) PS1	PSR ovarian cancer	All treated patients had prior chemotherapy Median number of prior regimens = 2.0 (range 2 – 13)	All *gBRCAm*
D0816C00002 (SOLO2) China Cohort N = 32/32 (22 in pooled dataset)	33 to 67 years (mean age 49.6 years) All female 32 (100%) Asian	ECOG PS ≤ 1	PSR ovarian cancer	All treated patients had prior chemotherapy Median number of prior regimens = 2.0 (range 2 – 4)	All *gBRCAm*

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D5336C00001 (VIOLETTE) N = 273/265 (110 in pooled dataset)	29 to 83 years (mean age 53.6 years) All female 192 (70.3%) White, 44 (16.1%) Asian, 21 (7.7%) missing, 12 (4.4%) Other, 4 (1.5%) Black or African American	ECOG PS ≤ 1 152 (55.7%) PS0 121 (44.3%) PS1	Metastatic triple negative breast cancer	All pre-treated Median number of prior systemic anti-cancer therapies was 2.0 (range 1 - 5)	96 *BRCAm* 47 non *BRCAm* HRRm 130 non HRRm
D0816L00003 (LIGHT) (271 in the pooled dataset)	35 to 91 years (mean age 65.0 years) All female 220 (80.9%) White 28 (10.3%) Asian 17 (6.3%) Black or African American; 7 (2.6%) American Indian or Alaska Native and Other	ECOG PS ≤ 1 181 (66.5%) PS0 90 (33.1%) PS1	High-grade serous or high-grade endometrioid ovarian, fallopian tube, or primary peritoneal cancer	All pre-treated Median number of prior chemotherapies was 2.0	75 *gBRCAm* 25 *sBRCAm* 68 HRD status positive *BRCAwt* 90 HRD status negative *BRCAwt* 13 unassigned
D081CC00001: Anti-hormonal PK interaction study (Part B only) N = 79/79 (69 in pooled dataset)	29 to 79 years (mean age 58.3 years) 64 (81.0%) Female, 15 (19.0%) Male 73 (92.4%) White, 2 (2.5%) Asian, 2 (2.5%) Black or African American, 2 (2.5%) other	ECOG PS ≤ 2 (78 patients [98.7%] were ECOG PS ≤ 1; one patient was PS2)	Patients with advanced solid cancer. The most common primary tumour locations were: ovary (36 patients [45.6%]), and breast (16 patients [20.3%]).	All pre-treated	21 *BRCAm*; 9 *BRCAwt*, 46 patients not tested, 3 missing
D081BC00002 China PK study; N = 47/36 (20 in pooled dataset)	32 to 67 years (mean age 48.4 years). 8 (22.2% male, 28 (77.8%) female. 36 (100%) Asian	35 patients [97.2%] were ECOG PS ≤ 1; one patient was PS2	Patients with advanced solid tumours. Most common locations were breast (21 patients [58.3%]) ovary (6 patients [16.7%]), and gastric (5 patients [13.9%]).	All pre-treated. Median number of regimens of previous chemotherapy at baseline was 4.0	Patients were not tested for *BRCA* mutation status

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D081BC00001 Japan Phase I study (Part B only) N = 23/23 (19 in pooled dataset)	34 to 77 years (mean age 54.1 years) 15 (65.2%) Female, 8 (34.8%) Male 23 (100.0%) Asian	ECOG PS ≤ 2 (18 patients [78.3%] were ECOG PS0)	Patients with advanced solid malignancies. The primary tumour locations in most of the patients were breast (5 patients [21.7%]), ovary (4 patients [17.4%]), cervix and uterus (2 patients [8.7%] each).	The median number of previous chemotherapy regimens at baseline was 3	
D0816C00008 (Study 08) rifampicin interaction study (Part B only) N = 22/19 (19 in pooled dataset)	31 to 79 years (mean age 58.0 years) 16 (84.2%) Female, 3 (15.8%) Male 19 (100.0%) White	ECOG PS ≤ 2 (16 patients [84.2%] were ECOG PS ≤ 1; 3 patients were PS 2)	Patients with advanced solid tumours. The most common primary tumour locations were: breast and ovary (each with 6 patients [26.3%]); colon (2 patients [10.5%]).	All pre-treated	Unknown

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D0816C00007 (Study 07) itraconazole interaction study (Part C) N = 59/54 (56 in pooled dataset including 2 patients from Part B)	34 to 82 years (mean age 61.0 years) 38 (70.4%) Female, 16 (29.6%) Male 51 (94.4%) White, 1 (1.9%) each of Asian, Black or African American, and other race	ECOG PS ≤ 2 (53 patients [98.1%]were ECOG PS ≤ 1; one patient was PS 2)	Patients with advanced solid tumours. The most common primary tumour locations were: ovary (20 patients [37.0%]), pancreas (6 patients [11.1%]), rectal (4 patients [7.4%]), breast, cervix, and head/neck, cervix (3 patients [5.6%] each), biliary tract, colon, colorectal, lung, peritoneum, and uterus (2 patients [3.7%] each).	All pre-treated	6 *BRCAm*; 8 *BRCAwt/VUS*, 45 patients not tested
D0816C00006 (Study 06): renal impairment study (Part B only) N = 44/43 (43 in pooled dataset)	32 to 76 years (mean age 61.9 years) 19 (44.2%) male, 24 (55.8%) female 42 (97.7%) White/ 1 (2.3%) Asian	41 patients (95.3%) were ECOG PS ≤ 1; data for 2 patients were missing	Patients with advanced solid tumours and normal renal function or mild or moderate renal impairment. Most common locations were ovary (12 patients [27.9%]), renal (5 patients [11.6%]) and breast (4 patients [9.3%]).	All pre-treated	3 *BRCAm*; 4 *BRCAwt*, 35 patients not tested

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D0816C00005 Hepatic impairment study N = 31/31 (31 in pooled dataset)	41 to 78 years (mean age 59.7 years) 14 (45.2%) Female, 17 (54.8%) Male 30 (96.8%) White, 1 (3.2%) Asian.	ECOG PS ≤ 2 (12 patients [38.7%] were ECOG PS 0; 17 patients [54.8%] were PS1 and 2 patients were PS2 at the start of Part B of the study)	Patients with advanced solid cancer. The most common primary tumour locations were: liver (8 patients); ovary, colon, and pancreas were also common sites (each in 4 patients). Hepatic function was normal in 13 patients (41.9%); mild impairment in 10 patients (32.3%); moderate impairment in 8 patients (25.8%).	All pre-treated	*BRCA* status was not a requirement for study entry
D0816C00004 (Study 04) Food effect (Part C) N = 60/55 (57 in pooled dataset, including 2 patients from Part B)	36 to 79 years (mean age 60.0 years) 42 (76.3%) Female, 13 (23.6%) Male 54 (98.2%) White, 1 (1.8%) other	ECOG PS ≤ 2 (54 patients [98.2%] were ECOG PS ≤ 1 and data for one patient was missing)	Patients with advanced solid tumours. The most common primary tumour locations were: ovary (19 patients [34.5%]), breast (9 patients [16.3%]), lung (4 patients [7.3%]), colorectal (3 patients [5.5%]), peritoneum (2 patients [3.6%]), and prostate (2 patients [3.6%]).	All pre-treated	5 *BRCAm*; 8 *BRCAwt/VUS*, 47 patients not tested

Table 41: Key Demographic and Baseline Characteristics by Study: Studies in Olaparib 300 mg bd Pool

Study Number of subjects randomised/ treated	Age/sex/race	Performance status	Tumour type	Prior anticancer treatment	Gene mutation status
D0810C00024 (Study 24) bioavailability (groups 4 and 6) N = 197 in whole study/24 in groups 4 and 6 (24 in pooled dataset)	40 to 78 years (mean age 56 years) 23 (95.8%) Female, 1 (4.2%) Male 23 (95.8%) White, 1 (4.2%) Asian	ECOG PS ≤ 2	Breast or ovarian cancer	All had prior chemotherapy Median number of prior regimens in groups 4 and 6 was 4.0	All *gBRCAm*

Please note that 4 of the patients in the China cohort were counted as part of the SOLO1 safety analysis set and are not counted again in the olaparib 300 mg bd pool.

bd, twice daily; BRCA, breast cancer susceptibility gene; BRCAm, BRCA mutated; BRCAwt, BRCA wild type; BRCAwt/VUS, BRCA wild type/variant of uncertain significance; CSR, clinical study report; ECOG, Eastern Cooperative Oncology Group; FIGO, Fédération Internationale de Gynécologie Obstétrique (International Federation of Gynaecology and Obstetrics); gBRCAm, germline BRCA mutated; HRD, homologous recombination deficiency; HRRm, homologous recombination repair mutated; N, total number of patients; PK, pharmacokinetics; PS, performance status; PSR, platinum-sensitive relapsed; sBRCAm, somatic BRCA mutated.

2.5.2. Adverse events

Overview of AEs

Table 42: Number (%) of Patients Who Had at Least One AE in Any Category in PROpel, the Olaparib and Abiraterone pool, and the Olaparib 300 mg bd Pool

AE category	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	387 (97.2)	376 (94.9)	453 (96.6)	3023 (95.8)
Any AE of CTCAE Grade 3 or higher	188 (47.2)	152 (38.4)	223 (47.5)	1153 (36.5)
Any AE with outcome = death	16 (4.0)	17 (4.3)	18 (3.8)	31 (1.0)
Any SAE (including events with outcome = death)	135 (33.9)	107 (27.0)	155 (33.0)	616 (19.5)
Any AE leading to discontinuation of olaparib/placebo [d]	55 (13.8)	31 (7.8)	76 (16.2)	300 (9.5)
Any AE leading to dose reduction of olaparib/placebo [e]	80 (20.1)	22 (5.6)	92 (19.6)	703 (22.3)
Any AE leading to interruption of olaparib/placebo [f]	178 (44.7)	100 (25.3)	196 (41.8)	1193 (37.8)

Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
[b] Includes AEs with an onset date, or worsen, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
[c] Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
[d] AEs leading to discontinuation of olaparib/placebo (regardless of any action taken with abiraterone).
[e] AEs leading to dose reduction of olaparib/placebo (regardless of any action taken with abiraterone).
[f] AEs leading to interruption of olaparib/placebo (regardless of any action taken with abiraterone).

Common Adverse Events

In PROpel, the most commonly reported AEs occurring in ≥5% of patients in either treatment arm, in the Olaparib and Abiraterone pool and in the Olaparib 300 mg bd pools are presented in **Table 43**.

Table 43: Most common AEs (Incidence > 5% in Either Arm of PROpel, the Olaparib and Abiraterone Pool, or the Olaparib 300 mg bd Pool)

	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
MedDRA PT	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Patients with any AE	387 (97.2)	376 (94.9)	453 (96.6)	3023 (95.8)
Anaemia	181 (45.5)	64 (16.2)	202 (43.1)	1086 (34.4)
Fatigue	111 (27.9)	75 (18.9)	125 (26.7)	1238 (39.2)
Nausea	112 (28.1)	50 (12.6)	138 (29.4)	1842 (58.4)
Back pain	68 (17.1)	73 (18.4)	84 (17.9)	339 (10.7)
Constipation	69 (17.3)	55 (13.9)	87 (18.6)	488 (15.5)
Arthralgia	51 (12.8)	70 (17.7)	63 (13.4)	403 (12.8)
Hypertension	50 (12.6)	65 (16.4)	53 (11.3)	88 (2.8)
Diarrhoea	69 (17.3)	37 (9.3)	78 (16.6)	703 (22.3)
Vomiting	52 (13.1)	36 (9.1)	66 (14.1)	904 (28.7)
Oedema peripheral	41 (10.3)	45 (11.4)	55 (11.7)	210 (6.7)
Hot flush	35 (8.8)	49 (12.4)	37 (7.9)	132 (4.2)
Asthenia	44 (11.1)	38 (9.6)	60 (12.8)	365 (11.6)
Decreased appetite	58 (14.6)	23 (5.8)	69 (14.7)	609 (19.3)
Urinary tract infection	41 (10.3)	31 (7.8)	50 (10.7)	240 (7.6)
Dizziness	43 (10.8)	25 (6.3)	47 (10.0)	367 (11.6)
Cough	38 (9.5)	22 (5.6)	49 (10.4)	379 (12.0)
Dyspnoea	35 (8.8)	24 (6.1)	45 (9.6)	303 (9.6)
Headache	34 (8.5)	23 (5.8)	39 (8.3)	516 (16.4)
Pain in extremity	27 (6.8)	30 (7.6)	30 (6.4)	200 (6.3)
Insomnia	25 (6.3)	27 (6.8)	29 (6.2)	215 (6.8)
Musculoskeletal chest pain	25 (6.3)	27 (6.8)	26 (5.5)	98 (3.1)
Muscle spasms	32 (8.0)	19 (4.8)	36 (7.7)	127 (4.0)

MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Hyperglycaemia	24 (6.0)	25 (6.3)	25 (5.3)	50 (1.6)
Lymphocyte count decreased	31 (7.8)	16 (4.0)	32 (6.8)	111 (3.5)
Pyrexia	24 (6.0)	21 (5.3)	34 (7.2)	265 (8.4)
Dyspepsia	27 (6.8)	17 (4.3)	27 (5.8)	282 (8.9)
Hypokalaemia	29 (7.3)	14 (3.5)	35 (7.5)	101 (3.2)
COVID-19	24 (6.0)	17 (4.3)	22 (4.7)	0
Fall	19 (4.8)	22 (5.6)	22 (4.7)	50 (1.6)
Alanine aminotransferase increased	12 (3.0)	28 (7.1)	13 (2.8)	135 (4.3)
Blood alkaline phosphatase increased	19 (4.8)	21 (5.3)	18 (3.8)	59 (1.9)
Myalgia	19 (4.8)	20 (5.1)	21 (4.5)	163 (5.2)
Blood creatinine increased	22 (5.5)	16 (4.0)	25 (5.3)	181 (5.7)
Contusion	25 (6.3)	13 (3.3)	28 (6.0)	36 (1.1)
Upper respiratory tract infection	18 (4.5)	20 (5.1)	20 (4.3)	242 (7.7)
Abdominal pain upper	22 (5.5)	14 (3.5)	23 (4.9)	230 (7.3)
Aspartate aminotransferase increased	13 (3.3)	22 (5.6)	14 (3.0)	112 (3.5)
Weight decreased	23 (5.8)	11 (2.8)	26 (5.5)	99 (3.1)
Abdominal pain	20 (5.0)	13 (3.3)	28 (6.0)	438 (13.9)
Pulmonary embolism	26 (6.5)	7 (1.8)	27 (5.8)	49 (1.6)
White blood cell count decreased	24 (6.0)	8 (2.0)	23 (4.9)	283 (9.0)
Dysgeusia	24 (6.0)	6 (1.5)	27 (5.8)	365 (11.6)
Lymphopenia	22 (5.5)	8 (2.0)	23 (4.9)	71 (2.3)
Nasopharyngitis	14 (3.5)	9 (2.3)	23 (4.9)	186 (5.9)
Neutropenia	18 (4.5)	4 (1.0)	26 (5.5)	259 (8.2)
Thrombocytopenia	12 (3.0)	10 (2.5)	14 (3.0)	167 (5.3)
Neutrophil count decreased	14 (3.5)	7 (1.8)	14 (3.0)	280 (8.9)
Bone pain	15 (3.8)	4 (1.0)	25 (5.3)	59 (1.9)
Stomatitis	10 (2.5)	2 (0.5)	10 (2.1)	207 (6.6)

Patients with multiple AEs are counted once for each PT.Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.PTs are sorted by descending frequency for the total number of AEs in each PT, then alphabetically, in the PROpel SAF.MedDRA Version 24.0.AE, adverse event; bd, twice daily; COVID-19, coronavirus disease 2019; CSR, clinical study report; MedDRA, Medical Dictionary

PROpel

In the olaparib+abiraterone arm, the most common AEs, reported at an incidence ≥ 15%, were anaemia, nausea, fatigue, constipation, diarrhoea, and back pain. In the placebo+Abiraterone arm, they were fatigue, back pain, arthralgia, hypertension, and anaemia.
All AEs of constipation were classed as low grade (CTCAE Grade 1 or 2), and none were classed as serious. The imbalance between treatment arms for constipation was smaller on taking exposure into account. Back pain was observed at a similar incidence in both arms.

Adjusting for treatment exposure did not notably change the differences in AE incidences between arms.

Adverse events reported at an incidence ≥ 2% lower in the olaparib+abiraterone arm than in the placebo+abiraterone arm were diabetes mellitus, arthralgia, hypertension, hot flush, ALT increased, and AST increased. These terms are ADRs of abiraterone, except for hot flush and arthralgia.

Adverse events reported at an incidence ≥ 2% greater in the olaparib+abiraterone arm than in the placebo+abiraterone arm that are not previously known ADRs for olaparib are described below:

Due to disease: constipation, muscle spasms, contusion, weight decreased, dry skin, dehydration, palpitations, bone pain, and neck pain are considered symptoms commonly reported in a mCRPC population. The majority of these AEs were Grade 1 or 2.

Due to treatment with Abiraterone: urinary tract infection, hypokalaemia, atrial fibrillation, and electrocardiogram QT prolonged are ADRs for abiraterone. Although numerical imbalances were observed for these terms, the observed rates are still consistent with labelled frequency for abiraterone.

COVID-19 (COVID-19, suspected COVID-19, and COVID-19 pneumonia)

Newly identified ADR for Olaparib was Pulmonary embolism. This new ADR is discussed in the serious adverse event section.

Comparison of PROpel with pools

In the olaparib+abiraterone arm of PROpel, the most common AEs, reported at an incidence ≥ 15%, were anaemia, nausea, fatigue, constipation, diarrhoea, and back pain. In the Olaparib 300 mg bd pool, they were nausea, fatigue, anaemia, vomiting, diarrhoea, decreased appetite, headache, and constipation (Table 41). These AEs are mostly consistent with the ADR profiles of olaparib and Abiraterone monotherapies. Constipation and back pain were most likely reported due to underlying disease. In general, the most common events with olaparib were mild or moderate in severity, and resolved on continued treatment.

AEs (> 5% incidence in either arm/pool) reported at an incidence > 2% greater in the olaparib+abiraterone arm in PROpel than in the olaparib 300 mg bd pool were anaemia, back pain, hypertension, oedema peripheral, hot flush, urinary tract infection, musculoskeletal chest pain, muscle spasms, hyperglycaemia, lymphocyte count decreased, hypokalaemia, COVID-19, fall, blood alkaline phosphatase increased, contusion, weight decreased, pulmonary embolism, and lymphopenia. Events reported at an incidence > 2% lower in the olaparib+abiraterone arm in PROpel than in the olaparib 300 mg bd pool were fatigue, nausea, diarrhoea, vomiting, decreased appetite, cough, headache, pyrexia, dyspepsia, upper respiratory tract infection, abdominal pain, white blood cell count decreased, dysgeusia, nasopharyngitis, neutropenia, thrombocytopenia, neutrophil count decreased, and stomatitis. The differences in incidence of these AEs, which are mostly ADRs for olaparib or Abiraterone monotherapy, may be attributed to differences in patient population between PROpel and the olaparib 300 mg bd pool.

Table 44 summarize the most common AEs of CTCAE Grade ≥ 3 with an incidence > 1% in either arm of propel, the olaparib and abiraterone pool, or the olaparib 300 mg bd pool.

Table 44: Most Common AEs of CTCAE Grade ≥ 3 (Incidence > 1% in Either Arm of PROpel, the Olaparib and Abiraterone Pool, or the Olaparib 300 mg bd Pool)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Patients with any AE CTCAE grade 3 or higher	188 (47.2)	152 (38.4)	223 (47.5)	1153 (36.5)
Infections and infestations	47 (11.8)	35 (8.8)	54 (11.5)	124 (3.9)
COVID-19	12 (3.0)	7 (1.8)	11 (2.3)	0
Pneumonia	7 (1.8)	3 (0.8)	11 (2.3)	23 (0.7)
Urinary tract infection	8 (2.0)	4 (1.0)	9 (1.9)	24 (0.8)
Blood and lymphatic system disorders	67 (16.8)	21 (5.3)	84 (17.9)	548 (17.4)
Anaemia	60 (15.1)	13 (3.3)	75 (16.0)	462 (14.6)
Lymphopenia	7 (1.8)	2 (0.5)	8 (1.7)	17 (0.5)
Neutropenia	4 (1.0)	1 (0.3)	5 (1.1)	85 (2.7)
Thrombocytopenia	2 (0.5)	1 (0.3)	3 (0.6)	37 (1.2)
Metabolism and nutrition disorders	30 (7.5)	21 (5.3)	34 (7.2)	72 (2.3)
Hyperglycaemia	7 (1.8)	6 (1.5)	7 (1.5)	7 (0.2)
Hypokalaemia	7 (1.8)	2 (0.5)	9 (1.9)	16 (0.5)
Cardiac disorders	15 (3.8)	10 (2.5)	21 (4.5)	26 (0.8)
Acute myocardial infarction	3 (0.8)	3 (0.8)	5 (1.1)	1 (0.0)
Atrial fibrillation	5 (1.3)	3 (0.8)	5 (1.1)	3 (0.1)
Vascular disorders	18 (4.5)	13 (3.3)	19 (4.1)	49 (1.6)
Hypertension	14 (3.5)	13 (3.3)	15 (3.2)	20 (0.6)
Respiratory, thoracic and mediastinal disorders	31 (7.8)	11 (2.8)	36 (7.7)	82 (2.6)
Pulmonary embolism	26 (6.5)	7 (1.8)	26 (5.5)	32 (1.0)
Gastrointestinal disorders	14 (3.5)	10 (2.5)	17 (3.6)	178 (5.6)
Nausea	1 (0.3)	1 (0.3)	2 (0.4)	34 (1.1)
Vomiting	4 (1.0)	1 (0.3)	5 (1.1)	35 (1.1)
General disorders and administration site conditions	15 (3.8)	11 (2.8)	17 (3.6)	132 (4.2)
Asthenia	5 (1.3)	3 (0.8)	8 (1.7)	39 (1.2)
Fatigue	4 (1.0)	3 (0.8)	5 (1.1)	75 (2.4)
Investigations	38 (9.5)	33 (8.3)	41 (8.7)	205 (6.5)
Alanine aminotransferase increased	4 (1.0)	9 (2.3)	4 (0.9)	22 (0.7)
Amylase increased	3 (0.8)	5 (1.3)	3 (0.6)	3 (0.1)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Blood alkaline phosphatase increased	2 (0.5)	6 (1.5)	2 (0.4)	7 (0.2)
Lymphocyte count decreased	13 (3.3)	5 (1.3)	13 (2.8)	23 (0.7)
Neutrophil count decreased	9 (2.3)	3 (0.8)	9 (1.9)	93 (2.9)
White blood cell count decreased	7 (1.8)	2 (0.5)	7 (1.5)	57 (1.8)

[a] Patients with multiple adverse events are counted once by the maximum CTCAE grade for each SOC/PT.
[b] Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
[c] Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Comparison of PROpel with pools

AEs of CTCAE Grade ≥ 3 occurred in a higher proportion of patients in the Olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool (Table 42), as discussed in the Overview of AEs Section.In the olaparib+abiraterone arm of PROpel, the most common AEs of CTCAE Grade ≥ 3, reported in ≥ 2% of patients, were anaemia, pulmonary embolism, hypertension, lymphocyte count decreased, COVID-19, neutrophil count decreased, and urinary tract infection. In the olaparib 300 mg bd pool, they were anaemia, neutrophil count decreased, neutropenia, and fatigue.

AEs of CTCAE Grade ≥ 3 reported at an incidence > 1% greater in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool were COVID-19, pneumonia, urinary tract infection, lymphopenia, hyperglycaemia, hypokalaemia, atrial fibrillation, hypertension, pulmonary embolism, and lymphocyte count decreased. Events reported at an incidence > 1% lower in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool were neutropenia and fatigue.

Adverse drug reaction for Abiraterone

Abiraterone ADRs reported at an incidence > 2% greater in the olaparib and abiraterone pool than in the placebo and abiraterone pool were embolic and thrombotic events, venous (SMQ), Cardiac arrhythmia terms (including bradyarrhythmia and tachyarrhythmias) (SMQ), Torsades de pointes/QT prolongation (SMQ), and hypokalaemia (grouped term). Although numerical imbalances were observed between the pools in the incidence of cardiac arrhythmia, Torsades de pointes/QT prolongation, and hypokalaemia, the rates were still consistent with the labelled frequency for abiraterone.

Table 45 summarizes the incidence of abiraterone ADRs in the olaparib and abiraterone pool, and the placebo and abiraterone pool.

Table 45: Olaparib and Abiraterone Pool: Incidence of Abiraterone ADRs

SMQ or grouped term	Number (%) of patients [a]			
	Olaparib and abiraterone pool (N = 469)		Placebo and abiraterone pool [b] (N = 467)	
	Any grade	CTCAE Grade ≥ 3	Any grade	CTCAE Grade ≥ 3
Cardiac failure [c]	8 (1.7)	6 (1.3)	6 (1.3)	1 (0.2)
Embolic and thrombotic events				
Arterial	13 (2.8)	11 (2.3)	10 (2.1)	8 (1.7)
Vessel type unspecified and mixed arterial and venous	7 (1.5)	3 (0.6)	8 (1.7)	4 (0.9)
Venous	30 (6.4)	27 (5.8)	14 (3.0)	8 (1.7)
Haemodynamic oedema, effusions and fluid overload	71 (15.1)	0	69 (14.8)	2 (0.4)
Myocardial infarction	8 (1.7)	8 (1.7)	5 (1.1)	5 (1.1)
Other ischaemic heart disease [c]	7 (1.5)	2 (0.4)	2 (0.4)	1 (0.2)
Cardiac arrhythmia terms (incl bradyarrhythmia and tachyarrhythmias)	42 (9.0)	10 (2.1)	30 (6.4)	5 (1.1)
Torsades de pointes/QT prolongation [c]	14 (3.0)	3 (0.6)	2 (0.4)	1 (0.2)
Hypertension [d]	55 (11.7)	15 (3.2)	73 (15.6)	13 (2.8)
Hypokalaemia [d]	41 (8.7)	9 (1.9)	20 (4.3)	2 (0.4)

[a] Patients with multiple events in the same category were counted only once in that category. [b] Comprises 396 patients in PROpel and 71 patients in Study 8 who received placebo bd and abiraterone 1000 mg qd. [c] Narrow SMQ.[d] Grouped term.

Serious adverse event

Table 46: Most Common SAEs (Incidence ≥ 1% in either Arm of PROpel, the Olaparib and Abiraterone Pool, or the Olaparib 300 mg bd Pool)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Patients with any SAE	135 (33.9)	107 (27.0)	155 (33.0)	616 (19.5)
Infections and infestations	52 (13.1)	37 (9.3)	58 (12.4)	122 (3.9)
COVID-19	12 (3.0)	9 (2.3)	11 (2.3)	0
Pneumonia	8 (2.0)	4 (1.0)	12 (2.6)	29 (0.9)
Urinary tract infection	8 (2.0)	3 (0.8)	10 (2.1)	21 (0.7)
Urosepsis	5 (1.3)	2 (0.5)	4 (0.9)	4 (0.1)
Blood and lymphatic system disorders	29 (7.3)	5 (1.3)	35 (7.5)	164 (5.2)
Anaemia	23 (5.8)	2 (0.5)	28 (6.0)	137 (4.3)
Febrile neutropenia	4 (1.0)	2 (0.5)	5 (1.1)	8 (0.3)
Nervous system disorders	12 (3.0)	14 (3.5)	14 (3.0)	41 (1.3)
Ischaemic stroke	1 (0.3)	4 (1.0)	2 (0.4)	1 (0.0)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Syncope	4 (1.0)	2 (0.5)	4 (0.9)	8 (0.3)
Cardiac disorders	13 (3.3)	11 (2.8)	19 (4.1)	27 (0.9)
Acute myocardial infarction	3 (0.8)	3 (0.8)	5 (1.1)	1 (0.0)
Atrial fibrillation	3 (0.8)	4 (1.0)	3 (0.6)	3 (0.1)
Respiratory, thoracic and mediastinal disorders	18 (4.5)	7 (1.8)	21 (4.5)	64 (2.0)
Pulmonary embolism	13 (3.3)	3 (0.8)	13 (2.8)	18 (0.6)
Musculoskeletal and connective tissue disorders	11 (2.8)	5 (1.3)	11 (2.3)	31 (1.0)
Back pain	4 (1.0)	2 (0.5)	5 (1.1)	6 (0.2)
Renal and urinary disorders	6 (1.5)	9 (2.3)	5 (1.1)	26 (0.8)
Acute kidney injury	3 (0.8)	4 (1.0)	3 (0.6)	3 (0.1)

[a] Patients with multiple SAEs are counted once for each SOC/PT.
[b] Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
[c] Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

PROpel

Serious AEs were reported in a higher proportion for olaparib+abiraterone-treated patients than placebo+abiraterone-treated patients (**Table 46**).
In the olaparib+abiraterone arm, the most common SAEs, reported at an incidence ≥ 2%, were anaemia, pulmonary embolism, COVID-19, pneumonia, and urinary tract infection. In the placebo+abiraterone arm, this was COVID-19.

Serious AEs reported at an incidence > 1% greater in the olaparib+abiraterone arm than in the placebo+abiraterone arm were urinary tract infection, anaemia, and pulmonary embolism. Urinary tract infection is a known ADR for abiraterone, and anaemia is a known ADR for olaparib. Pulmonary embolism is a newly identified ADR for Olaparib. No events were reported at an incidence > 1% lower in the olaparib+abiraterone arm than in the placebo+abiraterone arm.

Venous Thromboembolism

VTE was identified as a new ADR for Olaparib.
Across the entire clinical programme an imbalance of VTEs disfavouring the olaparib treatment arm has been noted in PROfound, PROpel and PAOLA-1 studies. Although the incidence and event rate of VTEs are lower in other monotherapy studies, there is a slightly higher incidence of VTEs in the olaparib arms in SOLO2 and SOLO1.

Although most emboli are thought to arise from lower extremity proximal veins, pelvic or abdominal veins, the frequency of VTEs was low. In general, the VTEs reported from these clinical studies did not report any additional confounders (other than the presence of advanced cancer and concurrent treatment with androgen deprivation treatments or bevacizumab) and showed no pattern in time to onset. No

apparent baseline imbalance can be noted relating to baseline risk factors that would explain the observed imbalances.

In PROpel, a higher proportion of venous thromboembolism, mostly pulmonary embolism, was reported in the Olaparib+Abiraterone arm than in the placebo+Abiraterone arm (Table 47). Others VTEs included deep vein thrombosis, portal vein thrombosis and thrombophlebitis superficial.

VTE were mostly grade ≥ 3 in both arms, less than half of the cases were serious including 1 outcome of death in the Olaparib+Abiraterone arm. In few cases, VTE resulted in dose interruption of Olaparib/placebo. However, no dose reduction in either arms and only 1 treatment discontinuation in the placebo+Abiraterone arm were reported (Table 47).

Table 47: PROpel: Patients Who Had at Least One AE of Embolic and Thrombotic Events, Venous (SMQ) Grouped Term

AE category	Number (%) of patients [a]	
	Olaparib+ abiraterone (N = 398)	Placebo+ abiraterone (N = 396)
Any AE	29 (7.3)	13 (3.3)
Any AE of CTCAE Grade 3 or higher	27 (6.8)	8 (2.0)
Any AE with outcome = death	1 (0.3)	0
Any SAE (including events with outcome = death)	14 (3.5)	4 (1.0)
Any AE leading to discontinuation of olaparib/placebo	0	1 (0.3)
Any AE leading to dose reduction of olaparib/placebo	0	0
Any AE leading to dose interruption of olaparib/placebo	8 (2.0)	2 (0.5)

[a] Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories. Includes AEs with an onset date, or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.

Pulmonary embolism was the most severe and most frequent AE among VTEs AE. All the olaparib dose interruption in the olaparib+abiraterone arm were due to pulmonary embolism. Pulmonary embolism was reported as causally related by the investigator in 7 patients (1.8%) in the olaparib+abiraterone arm. All pulmonary embolism events were reported as CTCAE Grade ≥ 3, in accordance with CTCAE version 4.03, whereby any pulmonary embolism is categorised as Grade ≥ 3. In the olaparib+abiraterone arm, the majority of patients who developed pulmonary embolism recovered or were recovering (17 of 26 patients) from the event at the time of DCO and 8 patients had not recovered. One patient in the olaparib+abiraterone arm had an AE of pulmonary embolism with fatal outcome. The investigator considered the event to be unrelated to olaparib and Abiraterone.

The median time to onset of pulmonary embolism was similar between the treatment arms (209 and 248 days in the olaparib+abiraterone and placebo+abiraterone arms, respectively). The majority of pulmonary embolism AEs were detected incidentally on radiographic imaging in both treatment arms (69.2% and 71.4% in the olaparib+abiraterone and placebo+Abiraterone arm, respectively).

In either arm of PROpel there were confounding factors that could explain pulmonary embolism AEs including immobilisation, hospitalisation due to appendicitis, and hip fracture in the placebo+abiraterone arm (3 patients in the placebo+abiraterone arm), and previous immobilisation and history of pulmonary embolism or other VTEs prior to starting study treatment in the olaparib+abiraterone arm (7 patients). None of the patients with history of VTEs in the olaparib+abiraterone arm (4 patients) were on long term anticoagulant treatment prior to developing pulmonary embolism. Overall, considering baseline risk

factors, there was a slightly higher number of patients who had a history of VTEs in the olaparib+abiraterone arm, compared to the placebo+abiraterone arm.

In Study 8, the frequency of VTE events was low: pulmonary embolism was reported in 2 patients (2.8%) in the olaparib+abiraterone arm, and pulmonary embolism and thrombosis were reported in 1 patient (1.4%) each in the placebo+abiraterone arm

Comparison of PROpel with pools

Serious AEs occurred in a higher proportion of patients in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool.

In the olaparib+abiraterone arm of PROpel study, the most common SAEs, reported in ≥ 2% of patients, were anaemia, pulmonary embolism, COVID-19, pneumonia, and urinary tract infection. In the olaparib 300 mg bd pool, this was anaemia.

Serious AEs reported at an incidence > 1% greater in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool were COVID-19, pneumonia, urinary tract infection, urosepsis, anaemia, and pulmonary embolism. No SAEs were reported at an incidence > 1% lower in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool.

Deaths

PROpel

The majority of reported deaths in both arms were attributed by the investigator to progression of the disease under investigation. The incidence of AEs with outcome of death was balanced between treatment arms. (**Table 48**)

Table 48: PROpel: All Deaths

Category	Number (%) of patients	
	Olaparib+abiraterone (N = 399)	Placebo+abiraterone (N = 397)
Total number of deaths	107 (26.8)	121 (30.5)
Death related to disease under investigation only	76 (19.0)	92 (23.2)
AE with outcome of death only	15 (3.8)	11 (2.8)
AE with outcome of death only (AE start date after 30-day follow-up period)	1 (0.3)	0
Number of patients with death related to disease under investigation and an AE with outcome of death	1 (0.3)	6 (1.5)
Other deaths [a]	14 (3.5)	12 (3.0)

[a] Patients who died and are not captured in the earlier categories.
Death related to disease under investigation is determined by the investigator.
Rows are mutually exclusive; patients are only reported in 1 category.

Comparison of PROpel with pools

Across the datasets, the most common reason for death was disease under investigation, as determined by the investigator. Adverse events with outcome of death occurred in a higher proportion of patients in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool (Table 48). A detailed review of AEs with outcome death identified no safety concerns.

Table 49: All Deaths in PROpel, the Olaparib and Abiraterone pool, and the Olaparib 300 mg bd Pool

Category	Number (%) of patients			
	PROpel FAS		Olaparib and abiraterone pool (N = 469)	Olaparib 300 mg bd pool (N = 3155)
	Olaparib +abiraterone (N = 399)	Placebo +abiraterone (N = 397)		
Total number of deaths	107 (26.8)	121 (30.5)	150 (32.0)	942 (29.9)
Death related to disease under investigation only	76 (19.0)	92 (23.2)	110 (23.5)	842 (26.7)
AE with outcome death only	15 (3.8)	11 (2.8)	17 (3.6)	21 (0.7)
AE with outcome death only (AE start date falling after 30 day follow-up period)	1 (0.3)	0	3 (0.6)	9 (0.3)
Number of patients with death related to disease and an AE with outcome of death	1 (0.3)	6 (1.5)	1 (0.2)	11 (0.3)
Other deaths [a]	14 (3.5)	12 (3.0)	19 (4.1)	59 (1.9)

[a] Patients who died and are not captured in the earlier categories. Death related to disease under investigation is determined by the investigator. Rows are mutually exclusive, patients are only reported in one category.

Table 50: Listing of Key Information for AEs With outcome Death in Study 8 from the Olaparib and Abiraterone Pool

Study/patient	Sex/Age (years) [a]	AE (MedDRA PT)	Causally related to olaparib [b]	Time from start of treatment to AE onset (days)	Dose last taken before death (mg/day)	Time from last dose to death (days)	Time from start of treatment to death (days)
D081DC00008 (Study 8)/ E0503201	M/79	Pneumonitis	Yes	342	600	1	354
D081DC00008 (Study 8)/ E4102205	M/79	Cardiac failure	No	91	600	5	91
D081DC00008 (Study 8)/ E6201201	M/79	Ischaemic stroke	No	542	600	1	542
D081DC00008 (Study 8)/ E6202206	M/71	Mediastinitis		504	600	1	621

Important potential risks for Olaparib

Pneumonitis and New Primary Malignanices (NPM) other than MDS/AML have been classified in the RMP as important potential risks.

Since pneumonitis and NPMs occur at low frequency, to improve the sensitivity and precision of estimates to characterise these important potential risks, information has been drawn from larger pools of olaparib studies, in addition to PROpel. To gain a complete clinical picture of patients with uncommon events that are important potential risks for olaparib, information from multiple data sources was used.

Generally, where the events were reported as SAEs, they were recorded on both the clinical database (a validated database that was locked for the purpose of the study analysis) and the AstraZeneca Patient Safety database (a 'live' database, with data subject to change as new information is provided to the data entry site).

Some reports are taken from the AstraZeneca Patient Safety database where events occurred after the end of the safety follow-up period for a given patient, after the DCO for an ongoing study or after study closure. These reports are supplemented with demography, baseline medical history, AE and clinical laboratory data from the clinical database.

New Primary Malignancies

For the majority of studies with olaparib, reports for events of NPM continue to be collected beyond 30 days after the last dose of olaparib; investigators are asked during the regular follow-up for OS if the patient had developed an NPM and prompted to report any cases to the Sponsor.

Considering the different risk characteristics, more favourable outcome, and the difficulty in estimating true background incidence rates of non-melanoma skin cancers, these cases have been excluded from the analysis of NPM cases. Non-melanoma skin cancers have distinct risk factors, such as ultraviolet light, ionising radiation, immunosuppression, and their incidence is influenced by geographic factors, age, and ethnicity. No direct mechanism has been described to link PARP inhibition to the occurrence of basal cell carcinoma or squamous cell skin cancer. Non-melanoma skin cancers tend to have a better outcome when diagnosed early, compared to malignant melanoma.

PROpel

Adverse events in the SOC 'Neoplasms benign, malignant and unspecified' were reported for 23 patients in the olaparib+abiraterone arm versus 18 in the placebo+abiraterone arm.

NPMs were identified by review of this SOC, to exclude PTs relating to cancer or tumour pain, benign events, and events of squamous cell skin cancer, Bowen's disease, basal cell carcinoma, and external ear neoplasm malignant (reported as 'Squamous Cell Carcinoma Left ear pinna [skin]'). Events with a date of onset on treatment, or during and after the 30-day safety follow up period are included in the summary of new primary malignancies.

In PROpel, NPMs were reported in 12 patients (3.0%) in the olaparib+abiraterone arm and 10 patients (2.5%) in the placebo+abiraterone arm (Table 50).

Table 51: New Primary Malignancies (in PROpel)

	Number (%) of patients [a]	
	Olaparib+ abiraterone (N = 398)	**Placebo+ abiraterone (N = 396)**
Number of patients with any new primary malignancy	12 (3.0)	10 (2.5)
Bladder cancer	3 (0.8)	0
Colon cancer	1 (0.3)	1 (0.3)
Colorectal cancer	0	1 (0.3)
Diffuse large B-cell lymphoma	0	1 (0.3)
Gastric cancer	1 (0.3)	
Lung adenocarcinoma	1 (0.3)	2 (0.5)

	Number (%) of patients [a]	
	Olaparib+ abiraterone (N = 398)	Placebo+ abiraterone (N = 396)
Malignant melanoma	1 (0.3)	0
Malignant melanoma in situ	1 (0.3)	0 [b]
Neoplasm skin	1 (0.3)	0
Neuroendocrine carcinoma of the skin	1 (0.3)	0
Neuroendocrine carcinoma	0	1 (0.3)
Non-small cell lung cancer	0	1 (0.3)
Oesophageal neoplasm	0	1 (0.3)
Oropharyngeal cancer	0	1 (0.3)
Rectal cancer	1 (0.3)	0
Small intestine adenocarcinoma	1 (0.3)	0
Transitional cell carcinoma	0	1 (0.3)

Pooled data from Olaparib clinical programme

Table 51 shows the AEs of NPM in PROpel compared with other studies in the clinical programme and provides incidence rates. When larger populations of olaparib-treated patients are considered, the incidence remains ≤ 1%.

Table 52: Summary of AEs of New Primary Malignancies Occurring Across the Olaparib Programme

	Olaparib		Comparator [a]	
	Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
Olaparib and abiraterone pool N = 469 olaparib+abiraterone	12	2.5%	NA	NA
Olaparib monotherapy combined therapeutic dose pool N = 4098 olaparib	42	1.0%	NA	NA
Entire clinical programme [d] N = 17923 olaparib	115	0.6%	NA	NA

Of the 44 AEs (reported in 42 patients) in the olaparib monotherapy combined therapeutic dose pool, the reported malignancies were breast cancers (n = 18), GI cancers (n = 8), thyroid cancer (n = 4), lung cancer (n = 3), malignant melanoma (n = 2), plasma cell myeloma, Burkitt lymphoma, bladder cancer, glioma, squamous cell carcinoma of the oral cavity, squamous cell carcinoma of the tongue, lip and/or oral cavity cancer, endometrial adenocarcinoma, and lymphoma (n = 1 each). Of the 42 patients in the olaparib monotherapy combined therapeutic dose pool with NPMs, 35 patients had a documented BRCA mutation, 3 patients were gBRCAwt and in 4 patients, the BRCA mutation status was unknown.

All patients in the olaparib monotherapy combined therapeutic dose pool had other potential factors that offer alternative explanations for the development of the NPM, such as: a history of smoking, alcohol

consumption or exposure to strong sunlight; a documented breast cancer gene (BRCA1 or 2) mutation; a medical history of previous cancers; exposure to previous chemotherapy agents including multiple cycles of platinum containing chemotherapies that are known DNA-damaging agents and taxanes, anthracyclines and other alkylating and DNA-damaging agents; and prior radiotherapy.

Among the entire clinical development, NPM was reported in 115 over 17923 patients (incidence of 0.6%). There have also been reports of NPM from post-marketing surveillance, consistent with the characterisation of the events reported from monotherapy clinical studies.

Pneumonitis

Adverse events of pneumonitis are routinely collected on-treatment and during the 30-day follow-up period only per protocol; pneumonitis AEs are not actively solicited beyond the end of the 30-day follow up period.

PROpel

From the start of PROpel (first patient randomised 08 November 2018) up to the DCO of 30 July 2021, pneumonitis was reported at similar incidence between both arms, that incidence being of 0.8%.

Pooled data from Olaparib clinical programme

Table 52 shows the AEs of pneumonitis in PROpel compared with other studies in the clinical programme and provides incidence rates. When larger populations of olaparib-treated patients are considered, the incidence is approximately 1%.

Table 53: Summary of AEs of Pneumonitis Occurring Across the Olaparib Programme

		Olaparib		Comparator [a]	
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
D081SC00001 (PROpel) N = 398 olaparib+abiraterone N = 396 placebo+abiraterone	Prostate cancer	3	0.8%	3	0.8%
Olaparib and abiraterone pool N = 469 olaparib+abiraterone		5	1.1%	NA	NA
Olaparib monotherapy combined therapeutic dose pool N = 4098 olaparib		37	0.9%	NA	NA

Pneumonitis has been reported in 0.9% of patients treated with olaparib in clinical studies in the olaparib monotherapy combined therapeutic dose pool (Table 52). Considering the entire olaparib clinical programme 122 case reports have been received up to 15 June 2021 (crude incidence 122/17923; 0.7%). Overall, the majority of pneumonitis AEs reported in the olaparib monotherapy therapeutic dose pool were mild or moderate, non-serious, and resolved without treatment discontinuation. Although there were slightly higher rates reported in patients receiving olaparib in SOLO1, SOLO2, and POLO, these studies were designed with a 2:1 randomisation and the exposure (and therefore observation time) on the olaparib arm was longer, which could potentially explain the observed difference.

Main other significant adverse drug reactions for Olaparib

Haematological Toxicities

Anaemia

Anaemia is the most common haematological effect reported with olaparib treatment. The proposed product information includes anaemia as an adverse reaction of olaparib therapy.

The majority of AEs of anaemia were mild or moderate in severity. Onset was early with a median time to first onset of 1.89 months in the olaparib+abiraterone arm of PROpel. The risk of developing anaemia remained constant from around 3 months of treatment, with no evidence of cumulative effect. AEs of anaemia were manageable by interrupting or reducing the olaparib dose or giving blood transfusions or growth factors in accordance with local practice. Regarding the resolution a total of 53% of patients in the olaparib+abiraterone arm who had an AE of anaemia had a first event with a resolution date. The median time to resolution for a first event in the olaparib+abiraterone arm was 4.19 months.

In PROpel, anaemia events any grade, of CTCAE Grade ≥ 3 severity (though no CTCAE Grade 4 haemoglobin values were reported in either treatment arm), SAEs and events leading to discontinuation, dose reduction, or interruption of olaparib/placebo occurred in a higher proportion in the olaparib+abiraterone-treated patients compared to the placebo+abiraterone-treated patients (Table 53). Given that, a higher proportion were treated for the AE in the olaparib+abiraterone arm (34.1%) than in the placebo+abiraterone arm (21.5%). A total of 15.6% of patients in the olaparib+abiraterone arm received at least one blood transfusion, compared to 3.8% of patients in the placebo+abiraterone arm. Proportion of patients in PROpel requiring treatment for anaemia was consistent with the proportion of patients with CTCAE Grade ≥ 3 AEs of anaemia.

The overall incidence of anaemia was higher in the olaparib+abiraterone arm of PROpel (46%) than in the olaparib 300 mg bd pool (35.2%) Table 53). The high proportion of bone metastases (87.5%) might have contributed to the observed higher overall incidence of anaemia in the olaparib+abiraterone arm of PROpel. Across AE categories, the incidence and severity of anaemia events following olaparib+abiraterone treatment in PROpel were consistent with the known safety profile of Olaparib.

Table 54: Patients Who Had at Least One AE of Anaemia (Grouped Term) in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
AE category	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	183 (46.0)	65 (16.4)	205 (43.7)	1109 (35.2)
Any AE of CTCAE Grade 3 or higher	60 (15.1)	13 (3.3)	75 (16.0)	466 (14.8)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	23 (5.8)	2 (0.5)	28 (6.0)	142 (4.5)
Any AE leading to discontinuation of olaparib/placebo [d]	15 (3.8)	3 (0.8)	19 (4.1)	67 (2.1)
Any AE leading to dose reduction of olaparib/placebo [e]	42 (10.6)	2 (0.5)	48 (10.2)	350 (11.1)
Any AE leading to interruption of olaparib/placebo [f]	61 (15.3)	7 (1.8)	64 (13.6)	516 (16.4)

Neutropenia, Thromvytopenia, Lymphopenia, Leukopenia

The incidence of other haematological AEs associated with olaparib such as the grouped terms neutropenia, thrombocytopenia, leukopenia, and lymphopenia were low in PROpel (all < 15%). These events are known ADRs for olaparib and were reported with a higher incidence in olaparib+abiraterone-treated patients compared to the placebo+abiraterone-treated patients. These events were predominantly mild or moderate in severity in severity, were manageable by using a combination of olaparib dose modification and supportive therapies, resolved whilst on treatment and rarely led to permanent discontinuation of treatment.

In PROpel, AEs of neutropenia were more common in the olaparib+abiraterone arm than in the placebo+abiraterone arm. Events of CTCAE Grade ≥ 3 severity occurred in a higher proportion of olaparib+abiraterone-treated patients than placebo+abiraterone-treated patients.

The AE category tables below show consistent pattern though slight differences in proportion of neutropenia, thrombocytopenia, lymphopenia, and leukopenia AEs between PROpel and the Olaparib 300 mg bd pool. These differences may be attributed to differences in patient population between PROpel and the olaparib 300 mg bd pool.

Table 55: Patients Who Had at Least One AE of Neutropenia (Grouped Term) in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
AE category	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	33 (8.3)	14 (3.5)	41 (8.7)	535 (17.0)
Any AE of CTCAE Grade 3 or higher	15 (3.8)	7 (1.8)	17 (3.6)	182 (5.8)
Any AE with outcome = death	0	0	0	1 (0.0)
Any SAE (including events with outcome = death)	6 (1.5)	2 (0.5)	7 (1.5)	23 (0.7)
Any AE leading to discontinuation of olaparib/placebo [d]	1 (0.3)	0	1 (0.2)	22 (0.7)
Any AE leading to dose reduction of olaparib/placebo [e]	1 (0.3)	0	3 (0.6)	92 (2.9)
Any AE leading to interruption of olaparib/placebo [f]	9 (2.3)	2 (0.5)	11 (2.3)	211 (6.7)

[a] Patients with multiple events reported in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
[c] Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
[d] AEs leading to discontinuation of olaparib/placebo (regardless of any action taken with abiraterone).
[e] AEs leading to dose reduction of olaparib/placebo (regardless of any action taken with abiraterone).
[f] AEs leading to interruption of olaparib/placebo (regardless of any action taken with abiraterone).

Table 56: Patients Who Had at Least One AE of Thrombocytopenia (Grouped Term) in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

AE category	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	22 (5.5)	14 (3.5)	26 (5.5)	299 (9.5)
Any AE of CTCAE Grade 3 or higher	3 (0.8)	1 (0.3)	5 (1.1)	66 (2.1)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	1 (0.3)	0	1 (0.2)	16 (0.5)
Any AE leading to discontinuation of olaparib/placebo [d]	1 (0.3)	0	0	23 (0.7)
Any AE leading to dose reduction of olaparib/placebo [e]	1 (0.3)	0	1 (0.2)	35 (1.1)
Any AE leading to interruption of olaparib/placebo [f]	3 (0.8)	2 (0.5)	3 (0.6)	85 (2.7)

[a] Patients with multiple events reported in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
[c] Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
[d] AEs leading to discontinuation of olaparib/placebo (regardless of any action taken with abiraterone).
[e] AEs leading to dose reduction of olaparib/placebo (regardless of any action taken with abiraterone).
[f] AEs leading to interruption of olaparib/placebo (regardless of any action taken with abiraterone).

Table 57: Patients Who Had at Least One AE of Lymphopenia (Grouped Term) in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

AE category	Number (%) of patients [a]			
	PROpel SAF		Olaparib and abiraterone pool (N = 469)	Olaparib 300 mg bd pool (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	52 (13.1)	22 (5.6)	54 (11.5)	179 (5.7)
Any AE of CTCAE Grade 3 or higher	20 (5.0)	7 (1.8)	21 (4.5)	40 (1.3)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	1 (0.3)	0	1 (0.2)	0
Any AE leading to discontinuation of olaparib/placebo [b]	4 (1.0)	1 (0.3)	4 (0.9)	1 (0.0)
Any AE leading to dose reduction of olaparib/placebo [c]	0	0	0	6 (0.2)
Any AE leading to interruption of olaparib/placebo [d]	10 (2.5)	3 (0.8)	10 (2.1)	24 (0.8)

[a] Patients with multiple events reported in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] AEs leading to discontinuation of olaparib/placebo (regardless of any action taken with abiraterone).
[c] AEs leading to dose reduction of olaparib/placebo (regardless of any action taken with abiraterone).
[d] AEs leading to interruption of olaparib/placebo (regardless of any action taken with abiraterone).

Table 58: Patients Who Had at Least One AE of Leukopenia (Grouped Term) in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

AE category	Number (%) of patients [a]			
	PROpel SAF		Olaparib and abiraterone pool (N = 469)	Olaparib 300 mg bd pool (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	32 (8.0)	8 (2.0)	33 (7.0)	431 (13.7)
Any AE of CTCAE Grade 3 or higher	10 (2.5)	1 (0.3)	10 (2.1)	83 (2.6)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	3 (0.8)	0	3 (0.6)	4 (0.1)
Any AE leading to discontinuation of olaparib/placebo [b]	1 (0.3)	0	1 (0.2)	10 (0.3)
Any AE leading to dose reduction of olaparib/placebo [c]	2 (0.5)	0	2 (0.4)	43 (1.4)
Any AE leading to interruption of olaparib/placebo [d]	6 (1.5)	1 (0.3)	6 (1.3)	110 (3.5)

[a] Patients with multiple events reported in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] AEs leading to discontinuation of olaparib/placebo (regardless of any action taken with abiraterone).
[c] AEs leading to dose reduction of olaparib/placebo (regardless of any action taken with abiraterone).
[d] AEs leading to interruption of olaparib/placebo (regardless of any action taken with abiraterone).

Myelodysplastic Syndrome/acute Myeloid Leukaemia

MDS/AML is an ADR for olaparib treatment (following the evaluation of the results of the SOLO2 study). MDS/AML is considered an AESI and an important identified risk for olaparib and events are collected beyond the 30-day safety follow-up for the duration of the survival follow-up. A summary of AEs of MDS/AML occurring in PROpel (DCO = 30 July 2021) together with cases in other pivotal studies, in the olaparib and abiraterone pool, the olaparib monotherapy combined therapeutic dose pool, and across the entire clinical programme (DCO = 15 June 2021) is shown in Table 58.

Table 59: Summary of AEs of MDS/AML Occurring Across the Olaparib Programme

		Olaparib		Comparator [a]	
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
D081SC00001 (PROpel) N = 398 olaparib+abiraterone N = 396 placebo+abiraterone	Prostate cancer	0	0%	0	0%

		Olaparib		Comparator [a]	
		Number of patients with AEs	Incidence [b]	Number of patients with AEs	Incidence [b]
D081FC00001 (POLO) N = 90 olaparib N = 61 placebo	Pancreatic cancer, prior platinum	0	0	0	0
D081DC00007 (PROfound) N = 256 olaparib N = 130 investigators choice of NHA	Prostate cancer	1	0.4%	0	0
D081CC00006 (OlympiA) N = 911 olaparib N = 904 placebo	Breast cancer	2	0.2%	3	0.3%
D0819C00003 (OlympiAD) N = 205 olaparib N = 91 physician's choice	Breast cancer, prior platinum	0	0	0	0
D0818C00001 (SOLO1) N = 260 olaparib N = 130 placebo	Ovarian cancer	3	1.2%	0	0
D0816C00010 (SOLO3) N = 178 olaparib N = 76 chemotherapy	Ovarian cancer	5	2.8%	3	3.9%
D0816C00002 (SOLO2) N = 195 olaparib N = 99 placebo	Ovarian cancer	16	8.2%	4 [c]	4.0%
Olaparib and abiraterone pool N = 469 olaparib+abiraterone		0	0%	NA	NA
Olaparib monotherapy combined therapeutic dose pool N = 4098 olaparib		34	0.8%	NA	NA
Entire clinical programme [c] N = 17923 olaparib		96	0.5%	NA	NA

[a] The comparator was physician's choice of chemotherapy in OlympiAD (which consisted of either capecitabine, eribulin or vinorelbine) and SOLO3 (which consisted of either pegylated liposomal doxorubicin, paclitaxel, gemcitabine or topotecan). The comparator was NHA (enzalutamide or Abiraterone acetate with prednisone) in PROfound.
[b] The percentage of patients experiencing any event of MDS/AML.
[c] One of the 4 placebo patients had received olaparib treatment 3 months prior to developing AML.

General disorders

Fatigue and Asthenia

Fatigue and asthenia have both been identified as ADRs with olaparib treatment. In general, reported events of fatigue and asthenia for olaparib monotherapy treatment are mild or moderate in severity, chronic in nature, but rarely lead to treatment discontinuation. Dose interruption or reduction are rarely required; some events resolve whilst on treatment.

In PROpel, AEs of fatigue and asthenia were reported for a higher percentage of patients in the Olaparib+abiraterone arm than in the placebo+abiraterone arm. The proportion of events that were CTCAE Grade ≥ 3 in severity was low in both arms (Table 59). Onset of fatigue and asthenia was early, with median time to first onset of 1.84 months in the olaparib+abiraterone arm

Notably, AEs of fatigue and asthenia occurred at a lower incidence in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool despite the combined therapy and the older population of

PROpel patients compared to the patients in the Olaparib 300 mg bd pool. The risk of developing fatigue and asthenia remained constant from around 3 months of treatment, with no evidence of cumulative effect. A total of 34.7% of patients in the olaparib+abiraterone arm who had an AE of fatigue and asthenia had a first event with a resolution date. The median time to resolution was 5.13 months for a first event in the olaparib+abiraterone arm.

Table 60: Patients Who Had at Least One AE of Fatigue or Asthenia in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

AE category	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Any AE	148 (37.2)	112 (28.3)	175 (37.3)	1563 (49.5)
Any AE of CTCAE Grade 3 or higher	9 (2.3)	6 (1.5)	12 (2.6)	111 (3.5)
Any AE with outcome = death	0	0	0	0
Any SAE (including events with outcome = death)	5 (1.3)	2 (0.5)	5 (1.1)	12 (0.4)
Any AE leading to discontinuation of olaparib/placebo [d]	3 (0.8)	3 (0.8)	4 (0.9)	32 (1.0)
Any AE leading to dose reduction of olaparib/placebo [e]	9 (2.3)	3 (0.8)	12 (2.6)	109 (3.5)
Any AE leading to interruption of olaparib/placebo [f]	13 (3.3)	6 (1.5)	15 (3.2)	121 (3.8)

[a] Patients with multiple events reported in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
[b] Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
[c] Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
[d] AEs leading to discontinuation of olaparib/placebo (regardless of any action taken with abiraterone).
[e] AEs leading to dose reduction of olaparib/placebo (regardless of any action taken with abiraterone).
[f] AEs leading to interruption of olaparib/placebo (regardless of any action taken with abiraterone).

Gastro-intestinal

Nausea and Vomiting

Nausea and vomiting have both been identified as ADRs with olaparib treatment. In general, reported events of nausea and vomiting for olaparib treatment are mild or moderate in severity, rarely lead to treatment discontinuation, are manageable, and resolve whilst on treatment.

Adverse events of nausea and vomiting were reported for a higher percentage of patients in the olaparib+abiraterone arm than in the placebo+abiraterone arm. Nearly all events were CTCAE Grade ≤ 2 in severity and not serious.

Adverse events of nausea and vomiting overall and leading to interruption of olaparib occurred at a lower incidence in the olaparib+abiraterone arm of PROpel than in the olaparib 300 mg bd pool.

Adverse events of special interests for Abiraterone

The incidence of abiraterone ADRs in the olaparib and abiraterone pool and the placebo and abiraterone pool is summarized in Table 60. The placebo and abiraterone pool comprise 396 patients in PROpel and 71 patients in Study 8 who received placebo bd and abiraterone 1000 mg qd.

Table 61: Olaparib and Abiraterone Pool: Incidence of Abiraterone ADRs

SMQ or grouped term	Number (%) of patients [a]			
	Olaparib and abiraterone pool (N = 469)		Placebo and abiraterone pool [b] (N = 467)	
	Any grade	CTCAE Grade ≥ 3	Any grade	CTCAE Grade ≥ 3
Cardiac failure [c]	8 (1.7)	6 (1.3)	6 (1.3)	1 (0.2)
Embolic and thrombotic events				
Arterial	13 (2.8)	11 (2.3)	10 (2.1)	8 (1.7)
Vessel type unspecified and mixed arterial and venous	7 (1.5)	3 (0.6)	8 (1.7)	4 (0.9)
Venous	30 (6.4)	27 (5.8)	14 (3.0)	8 (1.7)
Haemodynamic oedema, effusions and fluid overload	71 (15.1)	0	69 (14.8)	2 (0.4)
Myocardial infarction	8 (1.7)	8 (1.7)	5 (1.1)	5 (1.1)
Other ischaemic heart disease [c]	7 (1.5)	2 (0.4)	2 (0.4)	1 (0.2)
Cardiac arrhythmia terms (incl bradyarrhythmia and tachyarrhythmias)	42 (9.0)	10 (2.1)	30 (6.4)	5 (1.1)
Torsades de pointes/QT prolongation [c]	14 (3.0)	3 (0.6)	2 (0.4)	1 (0.2)
Hypertension [d]	55 (11.7)	15 (3.2)	73 (15.6)	13 (2.8)
Hypokalaemia [d]	41 (8.7)	9 (1.9)	20 (4.3)	2 (0.4)

a Patients with multiple events in the same category were counted only once in that category.
b Comprises 396 patients in PROpel and 71 patients in Study 8 who received placebo bd and abiraterone 1000 mg qd.
c Narrow SMQ.
d Grouped term.
Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Abiraterone ADRs reported at an incidence > 2% greater in the olaparib and abiraterone pool than in the placebo and abiraterone pool were Embolic and thrombotic events, venous (SMQ), Cardiac arrhythmia terms (including bradyarrhythmia and tachyarrhythmias) (SMQ), Torsades de pointes/QT prolongation (SMQ), and hypokalaemia (grouped term). Except for AEs reported in the Embolic and thrombotic events, venous SMQ (CTCAE Grade ≥3 AEs of VTEs were reported in a higher percentage of patients in the olaparib+abiraterone arm [5.8%] compared with the placebo+abiraterone arm [1.7%]), AEs of CTCAE Grade ≥3 were reported in a similar percentage of patients in both treatment arms.

The observed imbalance in venous embolic and thrombotic events is further discussed in Section "Serious adverse event" of this report and VTE is now identified as a new ADRs for Olaparib.

Although numerical imbalances were observed between the pools in the incidence of cardiac arrhythmia, Torsades de pointes/QT prolongation, and hypokalaemia, the rates were still consistent with the labelled frequency for abiraterone.

One abiraterone ADR was reported at an incidence > 2% lower in the olaparib and abiraterone pool than in the placebo and abiraterone pool: hypertension.

Following the DBL for PROpel, no new ADRs for abiraterone were observed, nor did the combination treatment appear to increase the known ADRs of abiraterone.

Laboratory findings

Haematology

No additional safety concern for olaparib was identified in the haematology data from PROpel.

Changes in the laboratory values for the haematology parameters of haemoglobin, neutrophils, platelets, and lymphocytes are considered adverse drugs reactions (ADRs) for olaparib and are presented in the hemalogical toxicity section of identified AEs. The number and proportion of patients with maximum overall CTCAE grades during treatment for selected haematology values in PROpel are shown in Table 61.

Table 62: PROpel: Number (%) of Patients With Maximum Overall CTCAE Grades During Treatment for Key Haematological Parameters

	Total evaluable at baseline [a]	Maximum overall CTCAE grade during treatment (%) [b]				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Haemoglobin						
Olaparib+abiraterone	397 (100)	12 (3.0)	247 (62.2)	95 (23.9)	43 (10.8)	0
Placebo+abiraterone	396 (100)	80 (20.2)	270 (68.2)	41 (10.4)	5 (1.3)	0
Platelets						
Olaparib+abiraterone	396 (100)	309 (78.0)	76 (19.2)	6 (1.5)	3 (0.8)	2 (0.5)
Placebo+abiraterone	396 (100)	317 (80.1)	73 (18.4)	5 (1.3)	1 (0.3)	0
Leukocytes						
Olaparib+abiraterone	397 (100)	244 (61.5)	89 (22.4)	50 (12.6)	8 (2.0)	6 (1.5)
Placebo+abiraterone	396 (100)	345 (87.1)	39 (9.8)	11 (2.8)	1 (0.3)	0
Neutrophils						
Olaparib+abiraterone	397 (100)	311 (78.3)	36 (9.1)	33 (8.3)	11 (2.8)	6 (1.5)
Placebo+abiraterone	396 (100)	370 (93.4)	16 (4.0)	8 (2.0)	2 (0.5)	0
Lymphocytes						
Olaparib+abiraterone	397 (100)	122 (30.7)	61 (15.4)	129 (32.5)	77 (19.4)	8 (2.0)
Placebo+abiraterone	396 (100)	214 (54.0)	65 (16.4)	78 (19.7)	34 (8.6)	5 (1.3)

[a] Patients with a baseline value and at least one on-treatment value. Percentages have been calculated using the number of patients with a baseline value and a post-baseline value.
[b] Includes assessments on or after the date of first dose and up to and including 30 days following the date of last dose of randomised treatment, and is the maximum CTCAE grade (low/high) - patients with no low/high graded assessments during treatment are excluded.

Clinical chemistry

No additional safety concern for olaparib was identified in the clinical chemistry data from PROpel.

A summary of maximum overall CTCAE grade during treatment for key clinical chemistry parameters (creatinine, bilirubin, ALT, AST, and ALP) is presented in Table 62. Changes in clinical chemistry parameters were generally mild or moderate and transient. In the majority of patients, the maximum CTCAE Grade was 0, 1, or 2 in both treatment arms. The proportion of patients with Grade 3 or 4 values

was similar in the olaparib and placebo treatment arms. As a reminder, increase in creatinine is an ADR for Olaparib and increase in AST, ALT and decrease in kaliemia are known ADR of Abiraterone.

Table 63: PROpel: Number (%) of Patients With Maximum Overall CTCAE Grades During Treatment for Clinical Chemistry Parameters

	Total evaluable at baseline [a]	Maximum overall CTCAE grade during treatment (%) [b]				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
ALT						
Olaparib+abiraterone	397 (100)	318 (80.1)	70 (17.6)	2 (0.5)	6 (1.5)	1 (0.3)
Placebo+abiraterone	396 (100)	279 (70.5)	85 (21.5)	10 (2.5)	20 (5.1)	2 (0.5)
AST						
Olaparib+abiraterone	395 (100)	289 (73.2)	94 (23.8)	9 (2.3)	3 (0.8)	0
Placebo+abiraterone	392 (100)	272 (69.4)	97 (24.7)	7 (1.8)	12 (3.1)	4 (1.0)
ALP						
Olaparib+abiraterone	396 (100)	177 (44.7)	141 (35.6)	40 (10.1)	36 (9.1)	2 (0.5)
Placebo+abiraterone	394 (100)	160 (40.6)	142 (36.0)	51 (12.9)	36 (9.1)	5 (1.3)
Bilirubin						
Olaparib+abiraterone	396 (100)	294 (74.2)	76 (19.2)	25 (6.3)	1 (0.3)	0
Placebo+abiraterone	394 (100)	308 (78.2)	65 (16.5)	19 (4.8)	1 (0.3)	1 (0.3)
Creatinine						
Olaparib+abiraterone	397 (100)	4 (1.0)	326 (82.1)	65 (16.4)	2 (0.5)	0
Placebo+abiraterone	395 (100)	33 (8.4)	325 (82.3)	34 (8.6)	3 (0.8)	0
Magnesium (low) [c]						
Olaparib+abiraterone	389 (100)	336 (86.4)	44 (11.3)	5 (1.3)	3 (0.8)	1 (0.3)
Placebo+abiraterone	391 (100)	346 (88.5)	37 (9.5)	5 (1.3)	2 (0.5)	1 (0.3)
Magnesium (high) [c]						
Olaparib+abiraterone	388 (100)	344 (88.7)	40 (10.3)	0	4 (1.0)	0
Placebo+abiraterone	391 (100)	360 (92.1)	25 (6.4)	0	6 (1.5)	0
Potassium (low) [c]						
Olaparib+abiraterone	397 (100)	306 (77.1)	81 (20.4)	0	10 (2.5)	0
Placebo+abiraterone	394 (100)	323 (82.0)	63 (16.0)	0	8 (2.0)	0
Potassium (high) [c]						
Olaparib+abiraterone	395 (100)	298 (75.4)	76 (19.2)	20 (5.1)	0	1 (0.3)
Placebo+abiraterone	396 (100)	293 (74.0)	83 (21.0)	17 (4.3)	3 (0.8)	0
Sodium (low) [c]						
Olaparib+abiraterone	394 (100)	293 (74.4)	87 (22.1)	0	13 (3.3)	1 (0.3)
Placebo+abiraterone	396 (100)	309 (78.0)	71 (17.9)	0	15 (3.8)	1 (0.3)
Sodium (high) [c]						
Olaparib+abiraterone	393 (100)	328 (83.5)	64 (16.3)	1 (0.3)	0	0

	Total evaluable at baseline [a]	Maximum overall CTCAE grade during treatment (%) [b]				
		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Placebo+abiraterone	395 (100)	332 (84.1)	61 (15.4)	2 (0.5)	0	0

[a] Patients with a baseline value and at least one on-treatment value. Percentages have been calculated using the number of patients with a baseline value and a post-baseline value.
[b] Includes assessments on or after the date of first dose and up to and including 30 days following the date of last dose of randomised treatment. For magnesium, potassium, and sodium, is the maximum CTCAE grade (low/high) - patients with no low/high graded assessments during treatment are excluded.
[c] CTCAE grades can worsen in 2 directions; low and high are associated with hypo and hyper directional shifts, respectively.

Inogram

No clinically meaningful difference between the 2 treatment arms was observed for change from baseline in CTCAE grades for potassium, magnesium, or sodium.

Increase in Creatinine

Mild elevations in serum creatinine have been observed without any apparent clinical sequelae and renal impairment. The onset was rapid with a return to baseline after olaparib discontinuation. These data are Altogether this informations are consistent with the finding that olaparib is known to be an inhibitor of OCT2 and MATE1.

In PROpel, AEs of increased creatinine were reported for a similar proportion of patients in both treatment arms except for grade 2 that was higher in the olaparib+abiraterone arm compared to the placebo+abiraterone arm (respectively, 16.4% and 8.6%). There were no CTCAE Grade 4 or serious events in either treatment arm.

Noteworthy, no renal safety concerns were identified from a review of laboratory and AE data. There is no evidence to suggest that olaparib impairs renal function.

Assessment of the Potential for Drug-induced Liver Injury

Both ALT increased and AST increased are ADRs for abiraterone. No hepatobiliary safety concerns were identified from a review of laboratory and AE data in PROpel. There is no evidence to suggest that olaparib causes DILI. Two cases of DILI were reported, both in the placebo+abiraterone arm. One was a confirmed Hy's law case, attributed to abiraterone. The other was a potential Hy's law case (with choledocholithiasis as an alternative explanation for the elevated liver function test results), considered unrelated to placebo and abiraterone.

A lower proportion of olaparib+abiraterone-treated patients in PROpel (3.8%) had hepatic metastases at baseline compared with Study 8 (5.6%) and with olaparib-treated patients in most of the studies that contributed most of the safety data for the olaparib 300 mg bd: PROfound (9.8%), OlympiAD (38.5%), SOLO1 (5.0%), OPINION (8.6%), SOLO3 (12.4%), SOLO2 (13.8%), and LIGHT (7.0%).

Laboratory abnormalities for ALT and AST

At baseline, the proportion of patients with ALT or AST values of CTCAE Grade ≥ 1 was similar and low in PROpel (75 patients; 19%), the olaparib and abiraterone pool (82 patients; 17.4%), and the olaparib 300 mg bd pool (629 patients; 20.1%).

The proportion of patients with maximum on-treatment combined AST or ALT $\leq 3 \times$ ULN was similar and high in the olaparib+abiraterone arm of PROpel, the olaparib and abiraterone pool, and the olaparib 300 mg bd pool. (Table 63)

Table 64: Maximum Value During Continuous Treatment for ALT and AST in PROpel, the Olaparib and Abiraterone Pool, and the Olaparib 300 mg bd Pool

Combined ALT or AST	Number (%) of patients			
	PROpel SAF		Olaparib and abiraterone pool (N = 469)	Olaparib 300 mg bd pool (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
≤ 3 × ULN	383 (96.2)	362 (91.4)	452 (96.4)	2981 (95.4)
> 3 × ULN to ≤ 5 × ULN	7 (1.8)	9 (2.3)	8 (1.7)	85 (2.7)
> 5 × ULN to ≤ 10 × ULN	5 (1.3)	14 (3.5)	6 (1.3)	38 (1.2)
> 10 × ULN to ≤ 20 × ULN	2 (0.5)	6 (1.5)	2 (0.4)	17 (0.5)
> 20 × ULN	1 (0.3)	5 (1.3)	1 (0.2)	5 (0.2)

Percentages are calculated out of the number of patients with ALT or AST values during continuous treatment phase.
Derived from laboratory assessments between the start of continuous treatment and 30 days following the date of last dose of continuous treatment.

The incidence of CTCAE Grade ≥ 3 elevations for ALT and AST was similar and low in the olaparib+abiraterone arm of PROpel (1.8% and 0.8% respectively), the olaparib and abiraterone pool (1.5% and 0.9% respectively), and the olaparib 300 mg bd pool (1.3% and 1.5% respectively). The incidence in the placebo+abiraterone arm of PROpel was higher than in the olaparib+abiraterone arm and both pools (5.6% and 4.1% respectively). Consistent with that, the proportion of patients with CTCAE Grade ≥ 3 AEs of ALT or AST increased was similar and low in the olaparib+abiraterone arm of PROpel (1.0% and 0.5% respectively), the olaparib and abiraterone pool (0.9% and 0.6% respectively), and the olaparib 300 mg bd pool (0.7% and 0.6% respectively). A higher proportion was observed in the placebo+abiraterone arm of PROpel (2.3% and 1.0% respectively).

Concomitant elevations of ALT/AST and bilirubin

No concurrent elevations of AST or ALT > 3 × ULN and total bilirubin >2 × ULN, irrespective of ALP, were observed in the olaparib+abiraterone arm of PROpel. Cases meeting these criteria were uncommon in the placebo+abiraterone arm of PROpel (2 patients [0.5%]), the olaparib and abiraterone pool (1 patient [0.2%]), and the olaparib 300 mg bd pool (28 patients [0.9%]).

Safety in special populations

As PROpel have not been conduct in specials population such as pregnant or breast feading women and hepatic or renal impaired patients, no new data are available for these special populations.

The olaparib and abiraterone pool and the olaparib 300 mg bd pool have been used as the data sources for this section, rather than PROpel.

Effect of gender

As all patients in PROpel were male, an analysis of the effects of gender has been conducted in the olaparib 300 mg bd pool.

Owing to the imbalance in the number of male and female patients, differences between genders should be interpreted with caution. In addition, it should be noted that 256 of the 410 male patients had mCRPC and were recruited in the PROfound study. The mean age of the male patients in the PROfound study was 68.6 years, older than that of the ovarian and breast cancer patients in the 300 mg bd pool (OlympiA: 43.3 years; SOLO1: 53.5 years; SOLO2: 57.0 years; SOLO3: 58.5 years; and OlympiAD: 45.3

years). In addition, the percentage of patients in PROfound with a baseline ECOG PS of ≥1 was 51.7%, which is notably higher than that observed in either OlympiA (11.3%), SOLO1 (21.7%), SOLO2 (18.3%), or SOLO3 (25.6%).

The incidence of AEs across most categories was higher for male patients than female patients (Table 64).

Table 65: Olaparib 300 mg bd Pool: Number (%) of Patients Reporting at Least One AE by Gender

AE category	Number (%) of patients [a]	
	Male (N = 410)	Female (N = 2745)
Any AE	397 (96.8)	2626 (95.7)
Any AE CTCAE Grade ≥ 3	190 (46.3)	963 (35.1)
Any AE with outcome = death	12 (2.9)	19 (0.7)
Any SAE (including events with outcome = death)	131 (32.0)	485 (17.7)
Any AE leading to discontinuation of olaparib	60 (14.6)	240 (8.7)
Any AE leading to dose reduction of olaparib	77 (18.8)	626 (22.8)
Any AE leading to dose interruption of olaparib	166 (40.5)	1027 (37.4)

[a] Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.
Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.

Common AEs (> 10% incidence overall) reported at an incidence > 5% greater in male patients than in female patients were anaemia and decreased appetite. Events reported at an incidence > 5% lower in male patients than in female patients were nausea, fatigue, vomiting, headache, abdominal pain, and dysgeusia. These imbalances are likely to be related to differences in the disease under treatment, the majority of female patients being treated for breast or ovarian cancer.

Within the context of a low number of male patients compared with female patients in the olaparib 300 mg bd pool, no clinically meaningful gender-related differences in the safety profile of olaparib have been identified.

Effect of Age

Owing to the imbalance in the number of patients per age group in either the olaparib and abiraterone pool and the olaparib 300 mg bd pool, differences between groups should be interpreted with caution. In particular, limited conclusions can be drawn for the ≥ 85 years age group, which comprised only 1.7% and 0.4% of patients respectively.

In both pools, the incidence of SAEs driven by the proportion of patients who were hospitalised or had prolonged hospitalization, of AEs leading to discontinuation, AEs of anaemia and decreased appetite increased with age. Additionally, asthenia, oedema peripheral, Cardiac disorders, Infections and infestations increased with age in the Olaparib and Abiraterone pool while constipation, accidents and injuries, orthostatic hypotension, fall and loss of consciousness, syncope, dizziness, ataxia and fractures AEs increased with age in the Olaparib 300 mg bd pool.

Effect of Race

Taking the imbalance in size of subgroups into account, no clinically significant differences in the safety profile of olaparib in White versus Asian patients have been observed in either pool. In addition, no effect of race on the PK of olaparib has been identified

Safety related to drug-drug interactions and other interactions

No new data are available.

Discontinuation due to adverse events

Most common AEs leading to discontinuation with an incidence of ≥0.5% in either arm of propel, the olaparib and abiraterone pool, or the olaparib 300 mg bd pool are presented in Table 65.

Table 66: Most Common AEs Leading to Discontinuation (Incidence ≥0.5% in Either Arm of PROpel, the Olaparib and Abiraterone Pool, or the Olaparib 300 mg bd Pool)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Patients with any AE leading to discontinuation of olaparib/placebo [d]	55 (13.8)	31 (7.8)	76 (16.2)	300 (9.5)
Infections and infestations	10 (2.5)	0	10 (2.1)	16 (0.5)
COVID-19	2 (0.5)	0	2 (0.4)	0
Pneumocystis jirovecii pneumonia	2 (0.5)	0	2 (0.4)	1 (0.0)
Pneumonia	2 (0.5)	0	2 (0.4)	6 (0.2)
Blood and lymphatic system disorders	17 (4.3)	3 (0.8)	21 (4.5)	89 (2.8)
Anaemia	15 (3.8)	3 (0.8)	19 (4.1)	67 (2.1)
Metabolism and nutrition disorders	3 (0.8)	2 (0.5)	3 (0.6)	9 (0.3)
Decreased appetite	1 (0.3)	2 (0.5)	1 (0.2)	6 (0.2)
Cardiac disorders	4 (1.0)	4 (1.0)	6 (1.3)	5 (0.2)
Acute myocardial infarction	1 (0.3)	2 (0.5)	1 (0.2)	0
Atrial fibrillation	2 (0.5)	1 (0.3)	2 (0.4)	0
Gastrointestinal disorders	2 (0.5)	2 (0.5)	5 (1.1)	60 (1.9)
Nausea	1 (0.3)	0	4 (0.9)	33 (1.0)
Vomiting	0	0	1 (0.2)	18 (0.6)
Musculoskeletal and connective tissue disorders	1 (0.3)	4 (1.0)	4 (0.9)	10 (0.3)
Arthralgia	0	2 (0.5)	0	6 (0.2)
Musculoskeletal chest pain	0	2 (0.5)	0	0
General disorders and administration site conditions	4 (1.0)	4 (1.0)	6 (1.3)	39 (1.2)
Asthenia	0	2 (0.5)	1 (0.2)	8 (0.3)
Fatigue	3 (0.8)	1 (0.3)	3 (0.6)	25 (0.8)
Investigations	5 (1.3)	5 (1.3)	5 (1.1)	27 (0.9)
Alanine aminotransferase increased	1 (0.3)	2 (0.5)	1 (0.2)	2 (0.1)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Lymphocyte count decreased	2 (0.5)	1 (0.3)	2 (0.4)	0

a Patients with multiple AEs leading to discontinuation are counted once for each SOC/PT.
b Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
c Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
d Action taken: study treatment permanently discontinued. Study treatment refers to olaparib/placebo.

AEs leading to Dose Reduction

AEs leading to dose reduction of olaparib/placebo with an incidence of ≥0.5% in either arm of propel, the olaparib and abiraterone pool, or the olaparib 300 mg bd pool are presented in Table 66.

Table 67: Adverse Events Leading to Dose Reduction (Incidence ≥ 0.5% in Either Arm of PROpel, the Olaparib and Abiraterone Pool, or the Olaparib 300 mg bd Pool)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Patients with any AE leading to dose reduction [d]	80 (20.1)	22 (5.6)	92 (19.6)	703 (22.3)
Blood and lymphatic system disorders	43 (10.8)	2 (0.5)	50 (10.7)	385 (12.2)
Anaemia	41 (10.3)	2 (0.5)	47 (10.0)	348 (11.0)
Leukopenia	1 (0.3)	0	1 (0.2)	17 (0.5)
Neutropenia	1 (0.3)	0	2 (0.4)	37 (1.2)
Thrombocytopenia	1 (0.3)	0	1 (0.2)	19 (0.6)
Metabolism and nutrition disorders	5 (1.3)	0	6 (1.3)	15 (0.5)
Decreased appetite	3 (0.8)	0	4 (0.9)	14 (0.4)
Vascular disorders	0	2 (0.5)	0	2 (0.1)
Hypertension	0	2 (0.5)	0	0
Gastrointestinal disorders	5 (1.3)	2 (0.5)	7 (1.5)	136 (4.3)
Nausea	4 (1.0)	1 (0.3)	6 (1.3)	93 (2.9)
Vomiting	2 (0.5)	1 (0.3)	2 (0.4)	36 (1.1)
Renal and urinary disorders	4 (1.0)	2 (0.5)	4 (0.9)	10 (0.3)
Renal impairment	2 (0.5)	2 (0.5)	2 (0.4)	5 (0.2)
General disorders and administration site conditions	10 (2.5)	4 (1.0)	13 (2.8)	124 (3.9)
Asthenia	6 (1.5)	3 (0.8)	8 (1.7)	29 (0.9)
Fatigue	3 (0.8)	0	5 (1.1)	80 (2.5)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Investigations	15 (3.8)	9 (2.3)	15 (3.2)	111 (3.5)
Alanine aminotransferase increased	1 (0.3)	2 (0.5)	1 (0.2)	5 (0.2)
Blood creatinine increased	5 (1.3)	3 (0.8)	5 (1.1)	23 (0.7)
Creatinine renal clearance decreased	3 (0.8)	4 (1.0)	3 (0.6)	5 (0.2)
Electrocardiogram QT prolonged	2 (0.5)	0	2 (0.4)	0
Glomerular filtration rate decreased	2 (0.5)	0	2 (0.4)	3 (0.1)
Neutrophil count decreased	0	0	0	53 (1.7)
Platelet count decreased	0	0	0	16 (0.5)
White blood cell count decreased	1 (0.3)	0	1 (0.2)	26 (0.8)

a Patients with multiple AEs leading to dose reduction are counted once for each SOC/PT.
b Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
c Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
d Action taken, dose reduced.

AEs leading to Treatment Interruption

AEs leading to treatment interruption of olaparib/placebo with an incidence of ≥0.5% in either arm of propel, the olaparib and abiraterone pool, or the olaparib 300 mg bd pool are presented in Table 67.

Table 68: Adverse Events Leading to Treatment Interruption (Incidence ≥ 0.5% in Either Arm of PROpel, the Olaparib and Abiraterone Pool, or the Olaparib 300 mg bd Pool)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Patients with any AE leading to dose interruption [d]	178 (44.7)	100 (25.3)	196 (41.8)	1193 (37.8)
Infections and infestations	38 (9.5)	27 (6.8)	45 (9.6)	149 (4.7)
COVID-19	10 (2.5)	8 (2.0)	10 (2.1)	0
Upper respiratory tract infection	4 (1.0)	1 (0.3)	4 (0.9)	14 (0.4)
Urinary tract infection	2 (0.5)	3 (0.8)	5 (1.1)	12 (0.4)
Blood and lymphatic system disorders	67 (16.8)	12 (3.0)	71 (15.1)	602 (19.1)
Anaemia	61 (15.3)	7 (1.8)	64 (13.6)	509 (16.1)
Leukopenia	4 (1.0)	0	4 (0.9)	47 (1.5)
Lymphopenia	4 (1.0)	0	4 (0.9)	11 (0.3)

SOC MedDRA PT	Number (%) of patients [a]			
	PROpel SAF [b]		Olaparib and abiraterone pool [c] (N = 469)	Olaparib 300 mg bd pool [c] (N = 3155)
	Olaparib +abiraterone (N = 398)	Placebo +abiraterone (N = 396)		
Neutropenia	6 (1.5)	1 (0.3)	8 (1.7)	110 (3.5)
Thrombocytopenia	3 (0.8)	2 (0.5)	3 (0.6)	51 (1.6)
Metabolism and nutrition disorders	17 (4.3)	7 (1.8)	17 (3.6)	25 (0.8)
Decreased appetite	7 (1.8)	0	7 (1.5)	13 (0.4)
Cardiac disorders	12 (3.0)	7 (1.8)	12 (2.6)	13 (0.4)
Atrial fibrillation	4 (1.0)	2 (0.5)	4 (0.9)	0
Respiratory, thoracic and mediastinal disorders	15 (3.8)	5 (1.3)	17 (3.6)	78 (2.5)
Dyspnoea	1 (0.3)	0	1 (0.2)	31 (1.0)
Pulmonary embolism	8 (2.0)	1 (0.3)	8 (1.7)	8 (0.3)
Gastrointestinal disorders	26 (6.5)	21 (5.3)	28 (6.0)	354 (11.2)
Abdominal pain	2 (0.5)	1 (0.3)	2 (0.4)	43 (1.4)
Diarrhoea	8 (2.0)	5 (1.3)	8 (1.7)	60 (1.9)
Nausea	9 (2.3)	4 (1.0)	10 (2.1)	155 (4.9)
Vomiting	5 (1.3)	4 (1.0)	6 (1.3)	132 (4.2)
General disorders and administration site conditions	22 (5.5)	10 (2.5)	25 (5.3)	195 (6.2)
Asthenia	6 (1.5)	5 (1.3)	7 (1.5)	33 (1.0)
Fatigue	8 (2.0)	1 (0.3)	9 (1.9)	91 (2.9)
Pyrexia	3 (0.8)	3 (0.8)	4 (0.9)	42 (1.3)
Investigations	29 (7.3)	22 (5.6)	30 (6.4)	205 (6.5)
Amylase increased	4 (1.0)	2 (0.5)	4 (0.9)	2 (0.1)
Aspartate aminotransferase increased	3 (0.8)	4 (1.0)	3 (0.6)	17 (0.5)
Blood creatinine increased	4 (1.0)	3 (0.8)	5 (1.1)	18 (0.6)
Electrocardiogram QT prolonged	5 (1.3)	1 (0.3)	5 (1.1)	1 (0.0)
Lymphocyte count decreased	6 (1.5)	3 (0.8)	6 (1.3)	13 (0.4)
Neutrophil count decreased	3 (0.8)	0	3 (0.6)	101 (3.2)
Platelet count decreased	0	0	0	35 (1.1)
White blood cell count decreased	2 (0.5)	1 (0.3)	2 (0.4)	64 (2.0)

a Patients with multiple AEs leading to dose interruption are counted once for each SOC/PT.
b Includes AEs with onset date or worsening, on or after the date of first dose and up to and including 30 days following discontinuation of randomised treatment.
c Includes AEs with an onset date between the date of first dose of continuous treatment and 30 days following the last dose of continuous treatment.
d 'Action taken, dose interrupted' for the PROpel SAF. ;'Action taken, drug interrupted. Dose reduced and interrupted' for the pooled data.

Post marketing experience

Olaparib (both capsule and tablet formulations) have been approved for use in a number of countries worldwide for a range of indications across multiple tumour types.

AstraZeneca has comprehensive processes for signal detection, regular safety reviews, identifying and evaluating issues potentially affecting patient safety, and developing safety recommendations (including changes to the reference safety information). In addition, these processes enable the identification of safety topics that need to be kept under close surveillance. The safety signal detection activities include review of reported AEs from post-marketing sources, and a review of the published literature relevant to olaparib. The post-marketing data for olaparib are regularly reviewed for new findings or trends.

Acces Programme and Ongoing Studies

As of 15 June 2021, a total of 1904 patients have been dosed with olaparib capsules or tablets in the following Global Access Programmes: Named Patient Supply Scheme, French Authorisation of Temporary Use, Turkish Compassionate Use Programme, UK Early Access to Medicines Scheme, UK Compassionate Use Programme, German Compassionate Use Programme, Dutch Compassionate Use Programme, and USA Early Access programme. In addition, there are a number of ongoing clinical studies in which patients have been dosed with either olaparib tablets or a blinded comparator agent.

2.5.3. Discussion on clinical safety

The safety assessment is mainly based on 469 patients treated with olaparib 300 mg bd and abiraterone 1000 mg qd in the PROpel study and in the supportive study, D081DC00008 study 8. These data provide a significant amount of safety data, with long-term exposure (up to 2 years).

These data were thereafter compared with a large pool of 3155 patients which received the same dose of olaparib as monotherapy in other indications. The pool was composed of 19 studies in various cancer types (n=3155) including 8 phase III studies among which PROfound (n=256) is the only study with the same targeted patient population, as the one of this application, mCRPC.

Safety and tolerability findings were consistent between the olaparib+abiraterone arm of PROpel and the olaparib and abiraterone pool.

Polled data are based on the DCO dates for the individual studies.

Exposure

The summary of clinical safety for the currently applied indication, mCRPC, describes the results with a DCO date of 30 July 2021 to match the date of the PROpel interim rPFS analysis.

In Propel study, at the time of the DCO, almost all patients randomised had received study treatments 794/796 patients. The number of patients still on treatment began to diverge between arms after 18 months in favor of the olaparib+abiraterone arm. Therefore, the median total duration of exposure was longer in the olaparib+abiraterone arm compared to the placebo+abiraterone arm (17.5 months and 15.7 months, respectively). Of note, the combination treatment with olaparib does not appear to reduce the planned administration of abiraterone.

In the Olaparib and Abiraterone pool, the overall extent of exposure was largely similar between the pool and the olaparib+abiratone arm of PROpel however with slightly lower indicators of exposure in the olaparib and abiraterone pool driven by a lower exposure to Olaparib in study 8.

Adverse events

Overall, the safety profile of olaparib is well characterised and is consistent with previous data from olaparib monotherapy. The overall safety profile of olaparib from PROpel study is similar to the one identified previously in other indications. Most commonly AE reported belonged to the SOC Hematologic disorders, gastro-intestinal disorders, General disorders and respiratory disorders and Nervous system disorders.

In PROpel study, the majority of patients exposed to olaparib+abiraterone reported AEs (96.6%), which were approximately equally distributed between ≤ CTCAE Grade 2 (52.5%) ≥ CTCAE Grade 3 (47.5%) in severity with very few AEs leading to death (3.8%) or treatment discontinuation (16.2%). Of note, anaemia was the only AE leading to olaparib treatment discontinuation with an incidence > 1% higher when Olaparib was taken in association to abiraterone than when olaparib or abiraterone were taken as a monotherapy.

The toxicity of olaparib associated to abiraterone was thus most often manageable including by dose interruptions (41.8%), dose reductions (19.6%) and standard supportive treatment as required. The most frequent reason for treatment interruption and treatment dose reduction was anaemia with respectively 13.6% and 10.0% of incidence, slightly lower to the ones for olaparib 300 mg bf pool (respectively, 16.1% and 11%).

Overall, the safety findings in the Olaparib and abiraterone pool had higher frequency than in the Olaparib 300 mg bd pool and in the placebo+abiraterone arm of PROpel, excepted for AEs leading to dose reduction of Olaparib with a slight imbalance in favor of the Olaparib 300 mg bd pool (22.3% *versus* 19.6% for the Olaparib and abiraterone pool) and for AE with outcome of death with an imbalance in favour of the placebo+abiraterone arm (4.3% *versus* 3.8% for the Olaparib and abiraterone pool).

More precisely, a higher incidence of cytopenia AEs (including anaemia ≥ CTCAE Grade 3), fatigue, nausea and pulmonary embolism (always considered as CTCAE grade 3 in accordance with CTCAE version 4.03) was reported in the olaparib and abiraterone pool than in the placebo+abiraterone arm of PROpel. This suggesting a heavier treatment for mCRPC patient population when treated with the association of abiraterone and olaparib compared to when treated with abiraterone in monotherapy. Cytopenia and pulmonary embolism were also reported at higher incidence in the olaparib and abiraterone pool than in the Olaparib 300 mg bd pool, potentially attributed to differences in patient population between pools (i.e, patient's age).

SAEs were reported in higher proportion in the Olaparib+abiraterone arm (33.9%) compared to the placebo+abiraterone arm (27.0%) and SAEs reported at an incidence > 1% greater in the olaparib+abiraterone arm than in the placebo+abiraterone arm were urinary tract infection, anaemia, and pulmonary embolism. Urinary tract infection and anaemia are known ADR for abiraterone and olaparib respectively. Pulmonary embolism is a newly identified ADR for Olaparib as discussed before.

In accordance with PROpel study, incidence of SAEs was higher in the Olaparib and abiraterone pool (33.0%) than in the Olaparib 300 mg bd pool (19.5%) and the SEAs reported with an incidence > 1% greater in the Olaparib and abiraterone pool where mostly known ADRs for abiraterone and olparib. Others may be attributed to differences in patient population between pools.

The majority of reported deaths in both arms were attributed by the investigator to progression of the disease under investigation (168 of 228 deaths [73.7%]); 76 in the olaparib+abiraterone arm and 92 in the placebo+abiraterone arm. The incidence of AEs with outcome of death was higher in the olaparib+abiraterone treated patients compared to placebo+abiraterone treated patients (respectively 4.1% and 2.8% with AE start date during and after the 30 days-follow up period). In addition, only 1 death in PROpel study were considered related to study treatment by investigator, it was in the olaparib+abiraterone arm and due to interstitial lung disease.

Interstitial lung disease and pneumonitis are known AESI of olaparib.
In Olaparib 300 mg bd pool, the incidence of AE with outcome death was higher in compared to Olaparib and abiraterone pool (respectively, 3.6% and 0.7%). This difference could be explained by difference in patient population between pools. Over 30 AE with outcome of deaths, 16 was judged related to olaparib treatment. In the majority of study, the reason was a myelodysplastic syndrome (14) with time from start of treatment to days ranging between (313 days to 2053 days). Interestingly, in PROfound the death was due pneumonia and neutropenia in the same patient (1) without any hematological malignancy (MDS/AML). However, one leukemia led to the death of one patient in PROfound but was considered unrelated to study treatment by the investigator.

Dose interruptions and dose reductions

AE leading to any study treatment (Olaparib, placebo, Abiraterone or prednisone/prednisolone) discontinuation, reduction and interruption were more frequent in Olaparib+Abiraterone arm than in placebo+Abiraterone arm (respectively, 14.3% and 10.1%; 25.1% and 13.1%; 47.5 and 29.8%). However, this did not affect significantly the treatment duration in the Olaparib+Abiraterone arm as the median total treatment duration was similar to the actual treatment duration both for olaparib (respectively 531.5 days and 519.0 days) and abiraterone (respectively 555.0 and 534.0 days). Neither was impacted the dose intensity of Olaparib and Abiraterone in the Olaparib+abiratarone arm as the median relative dose intensity was respectively of 98.3% and 96.5%.

Dose interruptions and dose reductions of Olaparib or Placebo were reported respectively in 44.7% and 20.1% of patients in the olaparib+abiraterone arm and respectively in 25.3% and 5.6% of patients in the placebo+abiratone arm.

Incidence of reported AEs leading to discontinuation of treatment was higher in the olaparib+abiraterone arm than in the placebo+abiraterone arm (respectively, 13.8% and 7.8%). Anaemia was the only AEs leading to discontinuation of olaparib/placebo at an incidence > 1% greater in the olaparib+abiraterone arm than in the placebo+abiraterone arm.

ADRs and AESI

Generally, commons AEs experienced by mCRPC patient treated with the association olaparib and abiraterone (anaemia, fatigue, nausea, back pain, constipation, diarrhoa, etc.) were corresponding to known ADRs of olaparib and abiraterone as per SmPC, and potential symptoms of the underlying disease. No new ADRs was identified for abiraterone.

However, AEs in the Venous thromboenlism events (VTEs) SOC driven by pulmonary embolism were classified as newly ADRs for Olaparib following PROpel study. In PROpel study, VTEs were reported at a higher incidence in the olaparib+abiraterone arm (29 patients; 7.3%) compared to the placebo+abiraterone arm (13 patients; 3.3%) with respectively 93% (27 patients) and 61.5% (8 patients) of VTEs that were pulmonary embolism. Among all VTEs cases in the olaparib+abiraterone and the placebo+abiraterone arms of PROpel respectively, 48.3% (14 patients) and 30.8% (4 patients) were considered as serious, 27.6% (8 patients) and 15.4% (2 patients) led to treatment dose interruption. There was 1 VTE with outcome of death in the olaparib+abiraterone arm of PROpel that was considered unrelated to treatments by the investigator. VTEs were identified in previous phase III studies (PROfound and PAOLA-1) where olaparib 300 mg bd was used as monotherapy. VTEs reported from these clinical studies did not identify any additional confounders other than the presence of advanced cancer and concurrent treatment with androgen deprivation treatments or bevacizumab and showed no pattern in time to onset. No apparent baseline imbalance can be noted relating to baseline risk factors that would explain the observed imbalances.

Currently there is no evidence to support a potential biologic-pharmacologic plausibility between olaparib and VTEs, however the consistent imbalance of VTEs and the lack of apparent alternative explanation suggest that there is at least a reasonable possibility for a causal association between Olaparib and VTEs and is included in section 4.4 of the SmPC.

The adverse events of special interest (AESIs) for olaparib are pneumonitis, Myelodysplastic Syndrome/Acute Myeloid Leukaemia (MDS/AML) and new primary malignancies (NPMs).

MDS/AML are known ADR for olaparib meanwhile a causal relationship between olaparib treatment and the development or acceleration of new primary malignancies and pneumonitis has not been established.

Investigators in PROpel were required to record new primary malignancies and MDS/AML events beyond 30 days after the last dose of olaparib at any point in survival follow-up. The applicant will provide an analysis of long-term safety data, including new primary malignancies and any new cases of myelodysplastic syndrome/acute myeloid leukaemia in PROpel at the time of data cut-off 2 (DCO2) and also at the final overall survival (OS) analysis.

In the entire clinical programme, 96 patients experienced an MDS/AML with 1 event occurred in PROfound study with outcome death, but the investigator didn't judge the event to be related to the study treatment. No MDS/AML was reported in any arm or PROpel neither in the Olaparib and Abiraterone pool. However, the follow-up period of PROpel and Study 8 at the current DCO are shorter than the studies in Olaparib monotherapy combined therapeutic dose pool or in the entire clinical programme.

Frequency of NPMs in PROpel study (3.0%) and in the Olaparib and Abiraterone pool (2.5%) is overall in line with previous experiences. However, the follow-up period of PROpel and Study 8 at the current DCO are shorter than the monotherapy combined therapeutic pool and the entire clinical programme pool. No NPM occured in study 8. Contributory factors to NPMs in PROpel aren't clear as the majority of patients in PROpel were HRR non mutated (67.3 according to ctDNA testing and 52.4% according to tissue testing with respectively 7.8% or 32.8% of unknown status) and naïve from chemotherapy (75.4%). The applicant imputed the slightly higher rate of NPM AEs in this patient population, compared with other studies, to the higher age (mean age 69 and 70 years in the olaparib + abiraterone and placebo + abiraterone arms, respectively) of the patients in PROpel study.

Given the lower life expectancy of mCRPC patients compared to patients with breast or ovarian cancer for which Olaparib already has a marketing authorization the importance of AML/MDS and NPMs could be counterbalanced by the time to onset of these 2 AESI for Olaparib. The applicant confirms to provide an analysis of long-term safety data, including new primary malignancies and any new cases of myelodysplastic syndrome/acute myeloid leukaemia in PROpel at the time of data cut-off 2 (DCO2) and also at the final overall survival (OS) analysis.

Concerning pneumonitis, with the largest and youngest population OlympiA study provide the most robust data source to assess the contribution of olaparib to the risk of this AESI. There was no difference in the incidence of pneumonitis between the olaparib (9 patients; 1.0%) and placebo arm (11 patients, 1.2%) of Olympia. The incidence of pneumonitis in PROpel substantiate the findings of OlympiA with an equal incidence of pneumonitis of 0.8% in both arms.

Overall, the majority of pneumonitis AEs reported in the olaparib monotherapy therapeutic dose pool were mild or moderate, non-serious, and resolved without treatment discontinuation.

Laboratory parameters

A decrease in all laboratory values for haematological parameters (including haemoglobin, platelets, leukocytes, neutrophils and lymphocytes) was observed when patients were treated with olaparib and abiraterone. Incidence of patients with a maximum CTCAE Grade of 3 or 4 was generally low

(neutronpenia 4.3%, leukopenia 3.5%, lymphopenia 21.4% and thrombocytopenia 1.3%) at the exception of anaemia and lymphopenia (respectively, 10.8% and 21.4%). Lymphopenia led to treatment discontinuation in few cases and in both arms (0.5% and 0.3% in the olaparib+abiraterone arm and placebo+abiraterone arm, respectively). However, these changes in haematological parameters are generally mild or moderate, manageable, and reversible.

Increases in creatinine have been identified as an ADR with olaparib treatment. AEs of increased creatinine were predominantly CTCAE grade 1 in severity with a slight imbalance for grade 2 in the olaparib+abiraterone arm compared to the placebo+abiraterone arm but didn't lead to permanent discontinuation of treatment. The lab observations of elevated serum creatinine were not associated with renal impairment and had no significant clinical sequelae.

Both ALT increase and AST increase are known ADRs for abiraterone. No concurrent elevations of AST or ALT > 3 × ULN and total bilirubin >2 × ULN, irrespective of ALP, were observed in the olaparib+abiraterone arm of PROpel. The incidence of CTCAE Grade $\geqslant$ 3 elevations for ALT and AST was higher in the placebo+abiraterone arm of PROpel (5.6% and 4.1% respectively) compared to the ones in the olaparib+abiraterone arm of PROpel (respectively, 1.8% and 0.8%) and in the olaparib and abiraterone pool (respectively, 1.5% and 0.9%) that both remained low. ALT increase led to treatment discontinuation in few cases and in both arms (0.3% and 0.5% in the olaparib+abiraterone arm and placebo+abiraterone arm, respectively). However, these changes in hepatobiliary parameters were generally mild or moderate, manageable, and reversible.

No hepatobiliary or renal safety concerns were identified from a review of laboratory and AE data in PROpel

Special populations

All patients in PROpel were male, white and older than most of patients in Olaparib 300 mg bd pool (except for PROfound study).

Assessment of the safety of olaparib in patient subgroups among the 300 mg bd pool has showed a higher incidence of AEs across categories for male and higher incidence of SAEs, AEs leading to discontinuation, AEs of anaemia and decreased appetite in older patients. No significant differences were found in White *versus* Asian patients.

These results must be interpreted with caution owing to the imbalance in the number of patients per groups in the Olaparib 300 mg bd pool. However, these results are consistent with the findings in PROpel study and Olaparib and Abiraterone pool.

Post marketing experience

Based on post-marketing data, angioedema and erythema nodosum were recently added as ADRs for olaparib. There were no events of angioedema, nor be reported AEs of erythema nodosum in either arm of PROpel and in the olaparib and abiraterone pool (PROpel + Study 8).

Acces Programme and Ongoing Studies

From all the ongoing studies or patient access programme no new or important safety information resulting in changes to the safety profile of olaparib has been identified.

Cumulative post-marketing data and safety data from the ongoing studies are available in the PBRER.

2.5.4. Conclusions on clinical safety

Overall, the safety profile of olaparib is well characterised and is consistent with previous data from olaparib monotherapy. However, a new ADR was added for Olaparib that is venous thromboembolism events (VTEs), in particular pulmonary embolism.

In PROpel, the incidence of AEs any category, SAEs and AEs of CTCAE Grade ≥ 3 was higher in the Olaparib+Abiraterone arm compared to the placebo+Abiraterone arm. The incidence of cytopenia, fatigue, nausea and pulmonary embolism was higher in the Olaparib+Abiraterone arm compared to the placebo+Abiraterone arm as well.

Even though the combined therapy of Olaparib and Abiraterone represents a heavier treatment for mCRPC patients compared to abiraterone alone with rapid anaemia, chronic asthenia and nausea, the toxicity of the association was most often manageable including by dose interruptions (41.8%), dose reductions (19.6%) and standard supportive treatment as required.Moreover, these treatments modifications due to AEs did not affect significantly the treatment duration and the dose intensity of both Olaparib and Abiraterone drugs in the Olaparib+Abiraterone arm.

2.5.5. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.>

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

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

The PRAC considered that the risk management plan version 26.2 is acceptable.

The CHMP endorsed the Risk Management Plan version 26.2 with the following content:

Safety concerns

Summary of Safety Concerns

Important identified risks	Myelodysplastic syndrome/acute myeloid leukaemia
Important potential risks	New primary malignancies Effects on embryofoetal survival and abnormal development
Missing information	Long term exposure to/potential toxicity to olaparib

Pharmacovigilance plan

The PRAC, having considered the data submitted, is of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures

Risk minimisation measures

Summary Table of Pharmacovigilance Activities and Risk Minimisation Activities by Safety Concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
MDS/AML	Routine risk minimisation measures: • SmPC Section 4.4 and 4.8 • PL Section 2 and 4	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire • Cumulative assessment (provided within each annual PBRER)
New primary malignancy	None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Follow-up targeted safety questionnaire
Effects on embryofoetal survival and abnormal development	Routine risk minimisation measures: • SmPC Sections 4.4, 4.6 • PL Section 2	Routine
Long term exposure to/potential toxicity to olaparib	None	Routine

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.8, 5.1, of the SmPC have been updated. Particularly, a new warning with regard to Venous Thromboembolic Events has been added to

the product information. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on the updated safety data analysis The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: Overall, the wording in the PL is similar to that already tested previously during the MA applications. Therefore, it is justified to consider the Package Leaflet User Testing report provided during review of the MA application procedure as relevant for this application, and that no updated document is needed for this submission.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (see section 5.1).

3.1.2. Available therapies and unmet medical need

According to ESMO guideline on cancer of the prostate (2020), the recommended treatment of metastatic CRPC are abiraterone or enzalutamide for asymptomatic/mildly symptomatic men with chemotherapy-naïve metastatic CRPC, radium-223 for men with bone-predominant symptomatic metastatic CRPC without visceral metastases, docetaxel and cabazitaxel for men with metastatic CRPC is an option in asymptomatic/mildly symptomatic patients with chemotherapy-naïve metastatic CRPC.

The optimal sequence or combination of these agents (abiraterone, enzalutamide, radium-223, docetaxel and cabazitaxel) has not been established yet. In practice, sequencing decisions will be made in the light of the distribution, extent and pace of disease, co-morbidities, patient preferences and drug availability.

Evaluation of new treatment options that would allow for early intervention in the course of mCRPC and that could also prolong the treatment duration of available therapies, delay disease progression, and improve long-term outcomes in this setting is warranted.

3.1.3. Main clinical studies

The current application is based on results from the ProPEL study, a Phase III, randomised, double-blind, placebo-controlled, multicentre study designed to assess the efficacy and safety of olaparib *versus* placebo, each combined with abiraterone and prednisone or prednisolone, as first-line treatment for men with mCRPC. Patients were randomised 1:1 to receive either olaparib or placebo, each combined with abiraterone and prednisone or prednisolone. All patients had to have evidence of histologically or cytologically confirmed prostate adenocarcinoma and metastatic status defined as at least one documented metastatic lesion on either a bone or CT/MRI scan. At the mCRPC stage (first-line setting), patients must have no prior cytotoxic chemotherapy or NHA treatment. PROpel is an all-comers study and patient enrolment was not based on biomarker status (HRRm status).

3.2. Favourable effects

The primary endpoint of the pivotal study is met with a statistically significant improvement of rPFS in the FAS with a prolongation of median rPFS of 8.2 months in favor of Olaparib+Abiraterone arm

compared to the placebo+Abiraterone arm at DCO1 (respectively, 24.84 months and 16.59 months). Data at DCO2 were consistent, with a benefit of similar magnitude observed and a median rPFS improvement of 8.6 months for olaparib + abiraterone compared with that for placebo + abiraterone (24.97 vs 16.39 months). OS results from DCO2 showed median duration of follow-up of 27.56 months in the olaparib + abiraterone arm and 26.32 months in the placebo + abiraterone arm. The OS results showed statistically 17% numerical reduction in the risk of death at any given point in time (HR 0.83, 95% CI: 0.66, 1.03, p=0.1126).

There was a favourable trend in PFS2 (20.6% maturity) for the olaparib + placebo arm compared to placebo + abiraterone arm with HR of 0.69 [95% CI: 0.51-0.94].

The other secondary endpoints (TFST, TSRE) showed a favourable trend for olaparib compared to placebo in combination with abiraterone.

Data results of rPFS and OS based on BRCAm and HRRm status from DCO2 show a benefit of similar magnitude as observed at DCO1. The combination olaparib + abiraterone showed a clear benefit in all HRR mutation subgroups (based on tissue test, cDNAt, aggregate analysis, BRCAm or non-BRCAm/BRCAm unknwown) without detrimental effect and were overall consistent with the FAS.

3.3. Uncertainties and limitations about favourable effects

The benefit of olaparib + abiraterone compared to placebo + abiraterone is uncertain in patients with mCRPC with non-HRRm/ unknown HRR taking into account:

- The study was not powered to assess efficacy within subgroups based on HRR gene mutations despite CHMP recommendations (2018), and the results of the subgroup studies should be taken with caution as they are exploratory.

- The non-HRRm subgroup by tumour tissue test OS HR 1.10 (95% CI: 0.77, 1.57) does not appear consistent with the rest of the HRRm subgroup OS results.

- The benefit at longer term, notably for OS, remains uncertain in non-BRCAm/non-HRRm patients. In order to further characterise the long-term efficacy of olaparib in the patients with mCRPC in D081SC00001 (PROpel) study, the MAH should provide the final OS data analyses in overall patient population and in all biomarker subgroups (by BRCAm and HRRm status) including rPFS and OS KM curves for all the subgroups.as a PAES.

3.4. Unfavourable effects

Overall, the safety profile of olaparib is well characterised and is consistent with previous data from olaparib monotherapy. The overall safety profile of olaparib from PROpel study is similar to the one identified previously in other indications. Most commonly reported AEs belonged to the SOC Hematologic disorders, gastro-intestinal disorders, General disorders and respiratory disorders and Nervous system disorders.

In PROpel, the incidence of AEs, SAEs and AEs of CTCAE Grade ≥ 3 were slightly higher in the olaparib+abiraterone arm than in the placebo+abiraterone arm (respectively, 97.2% and 94.9% for AEs, 33.9% and 27% for SAEs and 47.2% and 38.4% for AEs of CTCAE Grade ≥ 3) though a similar rate of AEs with outcome death (respectively 4% and 4.3%). These differences between the Olaparib+Abiraterone arm and the placebo+Abiraterone arm were mainly driven by AEs of anaemia, nausea, fatigue and pulmonary embolism with incidence respectively of 45.5% and 16.2; 28.1% and 12.6%; 27.9% and 18.9% and 6.5% and 1.8%. These AEs are previously known ADR for Olaparib except for venous thromboembolism (VTE) which is a new ADR for Olaparib.

Altogether, even though the combined therapy of Olaparib and Abiraterone represents a heavier treatment for mCRPC patients compared to abiraterone alone, the toxicity of the association was most often manageable including by dose interruptions (41.8%), dose reductions (19.6%) and standard supportive treatment as required.

AE leading to any study treatment (Olaparib, placebo, Abiraterone or prednisone/prednisolone) discontinuation, reduction and interruption were more frequent in Olaparib+Abiraterone arm than in placebo+Abiraterone arm (respectively, 14.3% and 10.1%; 25.1% and 13.1%; 47.5 and 29.8%). However, this did not affect significantly the treatment duration in the Olaparib+Abiraterone arm as the median total treatment duration was similar to the actual treatment duration both for olaparib (respectively 531.5 days and 519.0 days) and abiraterone (respectively 555.0 and 534.0 days). Neither was impacted the dose intensity of Olaparib and Abiraterone in the Olaparib+abiratarone arm as the median relative dose intensity was respectively of 98.3% and 96.5%.

3.5. Uncertainties and limitations about unfavourable effects

MDS/AML are known ADR for olaparib meanwhile a causal relationship between olaparib treatment and the development or acceleration of new primary malignancies and pneumonitis has not been established.

Investigators in PROpel were required to record new primary malignancies and MDS/AML events beyond 30 days after the last dose of olaparib at any point in survival follow-up. The applicant will provide an analysis of long-term safety data, including new primary malignancies and any new cases of myelodysplastic syndrome/acute myeloid leukaemia in PROpel at the final overall survival (OS) analysis.

3.6. Effects Table

Table 69 : Effects Table for Olaparib associated with abiraterone in first-line setting of mCRPC

Effect	Short description	Unit	Treatment (olaparib + abiraterone) N=399	Control (placebo + abiraterone) N=397	Uncertainties / Strength of evidence	References
Favourable Effects (DCO 30 July 2021)						
rPFS	Time from randomisation to radiological progression or death	HR (95% CI)	0.66 (0.54, 0.81)			PROpel study
		Median (Months)	24.8 (20.5, 27.6)	16.6 (13.9, 19.2)		
OS	Time from randomisation until death	HR (95% CI)	0.86 (0.66, 1.12) p=0.2923 28.6% mature			
Favourable Effects (DCO 14 March 2022)						
Interim OS	Time from randomisation until death	HR (95% CI)	0.83 (0.66-1.03) p=0.1126 40.1% mature			PROpel study
Unfavourable Effects						
AE of CTCAE Grade ≥3		%	52.8	40.4		PROpel
AE with death outcome		%	5.8	4.5		
Serious AEs		%	38.7	29.5		
AEs leading to		%	16.3	10.4		

Effect	Short description	Unit	Treatment (olaparib + abiraterone) N=399	Control (placebo + abiraterone) N=397	Uncertainties / Strength of evidence	References
discontinuation of study treatment						
AEs leading to dose reduction of study treatment		%	26.9	13.6		
AEs leading to interruption of study treatment		%	50.5	31.6		
Pulmonary embolism	From DCO 30 July 2021	%	6.5	1.8	not available at DCO 14 March 2022	

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

PROpel study met its primary endpoint with the demonstration of a statistically significant improvement in rPFS in the olaparib + abiraterone arm compared to placebo + abiraterone. PROpel study showed an improvement of median rPFS of 8.2 months with olaparib + abiraterone treatment compared to the placebo + abiraterone (HR = 0.66, 95% 0.54-0.81, p<0.0001). The sensitivity analysis of rPFS by BICR (HR 0.61; 95% CI: 0.49, 0.74; nominal p<0.0001; median rPFS was 27.6 months in the olaparib+abiraterone arm and 16.4 months in the placebo+abiraterone arm) was consistent with the investigator-based analysis. PROpel study showed a favourable trend of PFS2, TFST, Time to first SRE for olaparib + abiraterone compared to placebo + abiraterone.

The MAH provided updated OS results from the second planned interim analysis (DCO2 14 March 2022). Median duration of follow-up for OS were of 27.56 months in the olaparib + abiraterone arm and 26.32 months in the placebo + abiraterone arm. The OS results showed statistically 17% numerical reduction in the risk of death at any given point in time (HR 0.83, 95% CI: 0.66, 1.03, p=0.1126). The MAH will provide the final OS data in overall patient population (see Annex II).

Subgroup's analysis of rPFS based on the stratification factors did not reveal an obvious differential benefit across most of the pre-defined subgroups compared with the overall population.

The indication was restricted to patients with mCRPC in whom chemotherapy is not clinically indicated to be in line with the recommendations and the population that could benefit from the study's combination olaparib + abiraterone (see Efficacy discussion).

Overall, the safety profile of olaparib is well characterised and is consistent with previous data from olaparib monotherapy. However, venous thromboembolism events (VTEs), in particular pulmonary embolism, was added as new ADR for Olaparib (see Product information).

In PROpel study, the incidence of AEs any category, SAEs and AEs of CTCAE Grade ≥ 3 was higher in the Olaparib+Abiraterone arm compared to the placebo+Abiraterone arm. The incidence of cytopenia, fatigue, nausea and pulmonary embolism was also higher in the Olaparib+Abiraterone arm compared to the placebo+Abiraterone arm.

3.7.2. Balance of benefits and risks

Olaparib has demonstrated a statistically significant and clinical relevant improvement in rPFS in adult patients with mCRPC after failure of androgen deprivation therapy in whom chemotherapy is not clinically indicated, supported by the secondary endpoints.

Even though there are currently uncertainties on the magnitude of the benefit in terms of OS in the non-BRCAm/non-HRRm patients, the results are considered clinically relevant and sufficient to conclude on clinical benefit in the intended treatment setting. The benefit at longer term, notably for OS, will be submitted in a post-approval measure (PAES).

Overall, the safety profile of olaparib is well characterised and is consistent with previous data from olaparib monotherapy. It can be concluded that the benefits outweigh the risks.

3.7.3. Additional considerations on the benefit-risk balance

None

3.7.4. Conclusions

The overall B/R of Lynparza is positive in the following indication: Lynparza is indicated in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with mCRPC in whom chemotherapy is not clinically indicated (see section 5.1).

The following measures are considered necessary to address issues related to efficacy:

Post authorisation efficacy study (PAES)**:** In order to further characterise the long-term efficacy of olaparib in the patients with mCRPC in D081SC00001 (PROpel) study, the MAH should provide the final OS data analyses in overall patient population and in all biomarker subgroups (by BRCAm and HRRm status) including rPFS and OS KM curves for all the subgroups.

4. Recommendations

Outcome

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

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

Extension of indication to include the use of Lynparza in combination with abiraterone and prednisone or prednisolone for the treatment of adult patients with metastatic castration-resistant prostate cancer in whom chemotherapy is not clinically indicated. Consequently, sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC and Annex II are updated. In addition, sections 4.4 and 4.8 of the SmPC for Lynparza hard capsules are revised based on the updated safety data analysis. The Package Leaflet is updated accordingly. The RMP version 26.2 has also been submitted.

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

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **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 long-term efficacy of olaparib in the patients with mCRPC in D081SC00001 (PROpel) study, the MAH should provide the final OS data analyses in overall patient population and in all biomarker subgroups (by BRCAm and HRRm status) including rPFS and OS KM curves for all the subgroups.	April 2023