Clinical Study Report	
Drug Substance	Olaparib (AZD2281, KU 0059436)
Study Code	D081SC00001 (PROpel)
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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

Study dates:
First subject enrolled: 31 October 2018
Last subject enrolled: 11 March 2020
The analyses presented in this report are based on a clinical data cut-off date of 30 July 2021, and data lock date of 06 September 2021

Phase of development:
Therapeutic confirmatory (III)

International Co-ordinating Investigators:
[redacted]
United Kingdom

[redacted]
Canada

Sponsor's Responsible Medical Officer:
[redacted]
USA

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

2. SYNOPSIS

Study Centres

Patients were randomised at 126 centres in 17 countries ([redacted]): 195 (24.5%) patients in Asia, 350 (44.0%) in Europe, and 251 (31.5%) in North and South America.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 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 [a]	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).

[a] Several exploratory objectives were defined in the protocol, but the results are not reported in this synopsis.

[b] Subsequent systemic anticancer therapies (excluding radiotherapy) were reviewed prior to data unblinding to assess which represented clinically important treatments intended to control prostate cancer. TFST was defined as the time from randomisation to the earlier of 1) the first subsequent anticancer therapy start date following study treatment discontinuation or 2) 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 to be censored at the last known time to have not received subsequent therapy, ie, the last follow-up visit where this was confirmed.

[c] Pain progression defined as: 1) for patients who were asymptomatic at baseline, a ≥ 2 point change from baseline in the average (4-7 days) BPI-SF Item 3 score observed at 2 consecutive evaluations (with ≥ 2 weeks between the end of the initial visit and start of the subsequent visit) OR initiation of opioid use for pain; 2) for patients who are symptomatic at baseline (average BPI-SF Item 3 score > 0 and/or currently taking opioids), a ≥ 2 point change from baseline in the average BPI-SF Item 3 score observed at 2 consecutive visits and average worst pain score ≥ 4, and no decrease in average opioid use (≥ 1-point decrease in AQA score from starting value of 2 or higher) OR any increase in opioid use (eg, 1-point change in AQA score) at 2 consecutive follow-up visits (with ≥ 2 weeks between the end of initial visit and start of subsequent visit). Any patient who had > 2 consecutive visits that were not evaluable for pain progression was to be censored at the last evaluable assessment.

[d] [redacted]

AE, adverse event; AQA, analgesic quantification algorithm; *ATM*, Ataxia-telangiectasia mutated; AUC_{0-8}, area under the plasma concentration-time curve from time zero to 8 hours post-dose; AUC_{ss}, area under the plasma concentration-time curve across the dosing interval at steady state; BP, blood pressure; BPI-SF, Brief Pain Inventory-Short Form; *BRCA1*, Breast Cancer 1 gene; *BRCA2*, Breast Cancer 2 gene; CL_{ss}/F, apparent total body clearance of drug from plasma after extravascular administration at steady state; $C_{max,ss}$, maximum observed plasma (peak) drug concentration at steady state; $C_{min,ss}$, minimum observed plasma (peak) drug concentration at steady state; FAPSI-6, FACT Advanced Prostate Symptom Index 6; FWB, FACT-P Functional Well-Being Subscale; HRQoL, health-related quality of life; HRR, homologous recombination repair; mCRPC, metastatic castration-resistant prostate cancer; NHA, new hormonal agent; PCS, FACT-P Prostate Cancer Subscale; PCWG-3, Prostate Cancer Working Group 3; PK, pharmacokinetic(s); rPFS, radiological progression-free survival; PWB, FACT-P Physical Well-Being Subscale; RECIST 1.1, Response Evaluation Criteria In Solid Tumours version 1.1; SAE, serious adverse event; SSRE, symptomatic skeletal-related event; TFST, time to start of first subsequent anticancer therapy or death; t_{last}, time of last observed (quantifiable) concentration; $t_{max,ss}$, time to reach peak or maximum observed plasma concentration at steady state; TOI, FACT-P Trial Outcome Index; TTPP, time to pain progression.

Study Design

This randomised, double-blind, placebo-controlled, multicentre, international Phase III study was designed to evaluate olaparib in combination with abiraterone versus placebo in combination with abiraterone in patients with metastatic castration-resistant prostate cancer (mCRPC) who had not received prior chemotherapy or new hormonal agent (NHA) at the mCRPC stage (first-line setting). The study was ongoing at the time of writing this synopsis, which reports the results based on the first data cut off (DCO1, 30 July 2021) for the interim analysis of the primary endpoint of radiological progression-free survival (rPFS) and the first interim analysis of overall survival (OS).

Eligible patients were randomised (1:1 ratio) to receive either olaparib in combination with abiraterone, or placebo in combination with abiraterone. Patients were centrally assigned to randomised study treatment using a Randomisation and Trial Supply Management System (Interactive Response Technology). The patient, the investigator, and study centre staff were blinded to study drug allocation.

Radiological PFS was assessed by investigators using the Response Evaluation Criteria In Solid Tumours (RECIST) v1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG-3) (bone) criteria for all randomised patients. A blinded, independent central review (BICR) of all scans used in the assessment of tumours was also conducted. Survival status was assessed every 12 weeks following objective disease progression or treatment discontinuation. Homologous recombination repair (HRR) gene mutation status was determined by testing of circulating tumour DNA (ctDNA) and tumour tissue samples. The Brief Pain Inventory-Short

Form (BPI-SF) and FACT-P PRO questionnaires were electronically administered. Pharmacokinetic (PK) sampling was performed in a subset of patients (~50 patients/treatment arm) at specific timepoints after multiple dosing. Safety assessments included reporting of adverse events (AEs) and SAEs, physical examinations, vital signs (including blood pressure and pulse rate), ECGs, and laboratory tests (including clinical chemistry and haematology).

An external independent data monitoring committee (IDMC) reviewed the interim analysis of rPFS at DCO1, and also reviewed the accumulating study safety data.

Target Population and Sample Size

Eligible patients were biomarker unselected ('all-comers') with confirmed prostate adenocarcinoma and metastatic disease who had not received prior chemotherapy or NHAs for mCRPC (first-line setting). Prior to mCRPC stage, treatment with second-generation antiandrogen agents (except abiraterone) without prostate-specific antigen (PSA) progression/ clinical progression/radiological progression during treatment was allowed, provided it was stopped ≥ 12 months before randomisation. Treatment with first-generation antiandrogen agents before randomisation was allowed if there was a 4-week washout period. Docetaxel was allowed during neoadjuvant/adjuvant treatment for localised prostate cancer and at mHSPC stage, provided there were no signs of failure or disease progression during or immediately after such treatment. Patients had to be candidates for abiraterone therapy with documented evidence of progressive disease defined by PSA progression and/or radiological progression. Both symptomatic and asymptomatic/mildly symptomatic patients were eligible as well as patients with visceral metastases (except brain metastases) as long as they were considered candidates for abiraterone by the investigator. An archival formalin-fixed, paraffin-embedded tumour tissue sample, or a new biopsy taken during the screening window, was required before randomisation.

Approximately 720 patients were planned to be randomised across ~200 study sites in ~20 countries worldwide. As a result of faster than anticipated enrolment, 796 patients were randomised in total. [redacted]. Formal interim analysis of the primary endpoint, rPFS, at DCO1 was planned. A hazard ratio (HR) of 0.68 was assumed for the true treatment effect, corresponding to an assumed increase in median rPFS from 16.5 months (placebo+abiraterone) to 24.3 months (olaparib+abiraterone). Estimated overall dropout rate was 18%. The first DCO was planned to occur when approximately 379 progression or death events had accrued in 796 patients (47.6% of patients had an event [maturity], information fraction 83.7%) and would provide 94.1% power to show a statistically significant difference in rPFS. DCO1 was anticipated to occur ~31 months after the first patient was randomised.

Investigational Product and Comparator(s): Dosage, Mode of Administration, and Batch Numbers

Olaparib (AZD2281, KU 0059436) film-coated tablets (150 mg and 100 mg) were manufactured by AbbVie and AstraZeneca AB, and matching placebo was manufactured by PCI Pharmaceuticals. Patients took olaparib or placebo orally at a dose of 300 mg twice daily (bd) as 2×150 mg tablets. Each dose was to be taken at the same time each day, approximately 12 hours apart with a glass of water, with or without food (except on PK sampling days when the dosing was fasted). The tablets were swallowed whole and not chewed, crushed, dissolved, or divided. The 100 mg and 150 mg tablets were used to manage dose reductions. Batch numbers of olaparib 100 mg, 150 mg, and matching placebo were: [redacted]

Commercially available abiraterone with supportive prednisone or prednisolone was background treatment. Patients were administered abiraterone 1000 mg once daily (qd) in combination with prednisone or prednisolone 5 mg orally bd. In accordance with local prescribing information, abiraterone was taken on an empty stomach; tablets were swallowed whole with water and not crushed or chewed.

Duration of Treatment

Patients started study treatment as soon as possible after randomisation (ideally, within 24 hours post-randomisation), and treatment was to continue until objective radiological disease progression as assessed by the investigator (using RECIST 1.1 for soft tissue lesions and PCWG-3 criteria for bone lesions), occurrence of unacceptable toxicity, severe non-compliance with the protocol, or the patient withdrew consent. Following objective disease progression, further treatment options were at the discretion of the investigator. Crossover from placebo+abiraterone to olaparib+abiraterone was not allowed.

Statistical Methods

The Full Analysis Set (all comers) was the primary population for reporting efficacy, and comprised all randomised patients, analysed according to randomised treatment (intention to-treat principle). The PK Analysis Set included all patients who received ≥ 1 dose of randomised study drug and provided ≥ 1 post-dose analysable plasma sample for PK analysis. The Safety Analysis Set consisted of all randomised patients who received any amount of olaparib, placebo, or abiraterone, and was used for summaries of safety data, according to the treatment received.

[redacted] The 1-sided alpha of 0.025 was allocated to the rPFS assessment. If the result for rPFS was statistically significant, the OS hypothesis was to be

tested in a hierarchical fashion. A multiplicity testing procedure based on the graphical approach in group sequential trials of Maurer and Bretz, analogous to a simple sequential gatekeeping method, strongly controlled the overall familywise 1-sided error rate of 2.5%.

The rPFS endpoint was planned to be tested at DCO1 and DCO2. The OS endpoint was planned to be tested at DCO1, DCO2, [redacted] For each endpoint with an interim analysis, the O'Brien and Fleming spending function calculated based upon actual observed events, was to be used to strongly control the overall type 1 error, with the restriction that alpha spend for the OS interim analysis at DCO1 would not exceed 0.0005.

The rPFS primary endpoint was analysed using a log rank test stratified by the following factors if applicable: Metastases (bone only vs visceral vs other); Docetaxel treatment at mHSPC stage (yes vs no). The HR and corresponding 95% confidence interval (CI) were estimated using a Cox proportional hazards model (with ties = Efron and the stratification variables as covariates) and the 2-sided CI calculated using a profile likelihood approach (a HR < 1 favours olaparib+abiraterone combination therapy).

A sensitivity analysis was conducted using rPFS as assessed for all patients by BICR per RECIST 1.1 and PCWG-3 criteria. Further pre-defined sensitivity analyses of rPFS were also performed including analysis using unequivocal clinical progression in addition to radiological progression. Subgroup analyses were conducted to assess the consistency of the rPFS treatment effect based on the stratification factors, clinical characteristics (ECOG performance status, age at randomisation, region, race, and baseline PSA) and HRR gene mutation status.

The key secondary endpoint, OS, was analysed using the same methodology as for rPFS. Analyses of the other secondary endpoints were not part of the multiplicity strategy, but further describe the efficacy and HRQoL benefits of olaparib+abiraterone compared to placebo+abiraterone.

Safety and tolerability data were summarised using appropriate descriptive measures.

Study Population

This study enrolled 1103 patients, of which 796 were randomised at 126 centres: 399 patients were randomised to olaparib+abiraterone and 397 were randomised to placebo+abiraterone. In total, 794 patients received study treatment; one patient from each treatment group did not receive study treatment. At the time of DCO1, 549 patients (69.0%) were ongoing in the study and 302 patients (38.0%) were still ongoing with combination treatment: 168 patients (42.2%) on the olaparib+abiraterone arm and 134 (33.8%) on the placebo+abiraterone arm.

The randomised treatment arms were generally well balanced in terms of demographic and disease characteristics. Overall, 523 patients (65.7%) had a Gleason score of 8 to 10; 62.7%

had de novo metastases; and 179 (22.5%) had received prior docetaxel at the mHSPC stage. The median time from initial diagnosis was 36.9 months. In total, 149 patients (18.7%) had a BPI-SF Item 3 worst pain score of ≥ 4 at baseline, indicating moderate or severe pain.

Summary of Efficacy Results

Primary endpoint, rPFS based on investigator assessment

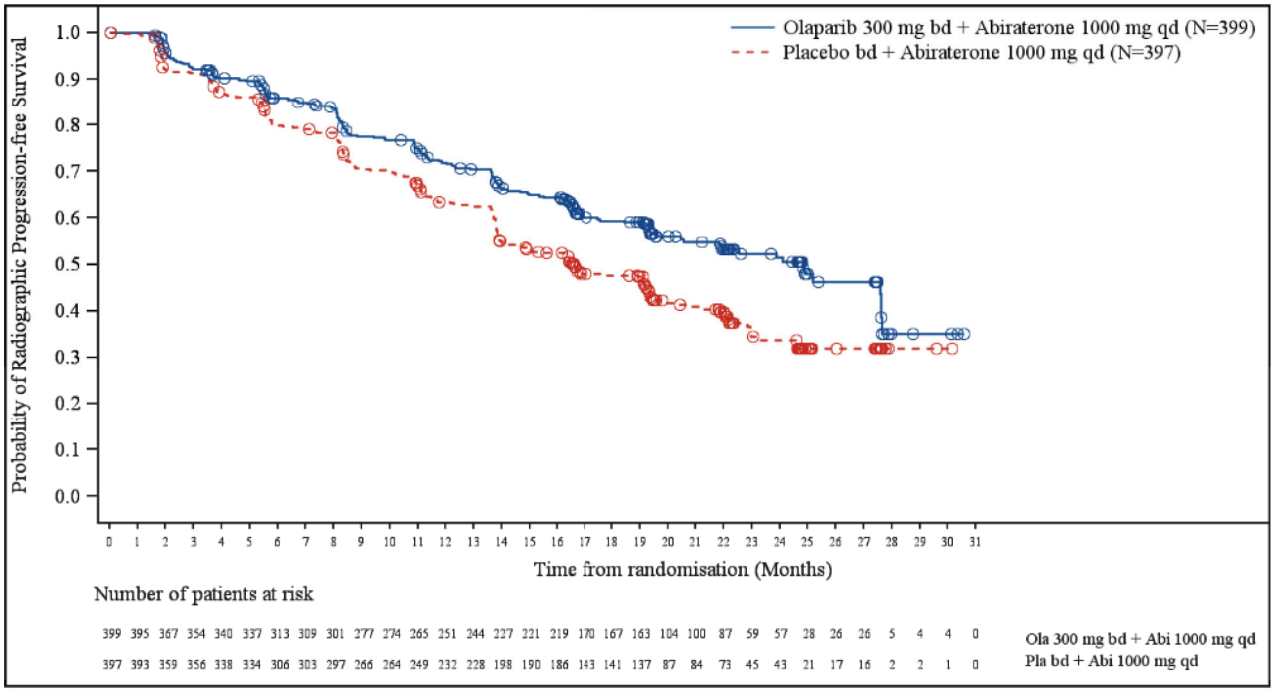
The rPFS data were 49.5% mature at DCO1 (394 events/796 patients). The study met its primary objective, with a p-value of < 0.0001 from the log-rank test (the primary analysis methodology) below the controlled alpha spending allocation at this interim analysis (0.0324 [2-sided]). There was a statistically significant and clinically meaningful 34% reduction in the risk of radiological disease progression or death. An improvement in median rPFS of 8.2 months was observed on the olaparib+abiraterone arm (24.8 months) compared with the placebo+abiraterone arm (16.6 months), with HR 0.66 (95% CI: 0.54, 0.81). Median duration of follow-up in all patients was 16.5 months on the olaparib+abiraterone arm and 14.0 months on the placebo+abiraterone arm. The median follow-up in censored patients of a little over 19 months in both arms allowed appropriate characterisation of the median rPFS observed in both treatment arms.

Based on Kaplan-Meier estimates, at 12 months, 71.8% of patients in the olaparib+abiraterone arm were alive and progression free compared with 63.4% in the placebo+abiraterone arm. At 24 months, 51.4% of patients in the olaparib+abiraterone arm were alive and progression free compared with 33.6% in the placebo+abiraterone arm. The Kaplan-Meier plot (Figure S1) shows a clear separation of the curves in favour of the olaparib+abiraterone arm, apparent from an early time point.

Results of the sensitivity analysis of rPFS based on BICR (HR 0.61, 95% CI: 0.49, 0.74; nominal p < 0.0001), with median rPFS 27.6 months in the olaparib+abiraterone arm vs 16.4 months in the placebo+abiraterone arm, were consistent with the primary analysis (investigator assessment). Results of the other rPFS sensitivity analyses were also consistent with the primary analysis.

Clinical benefit in favour of olaparib+abiraterone was also seen consistently across the pre-defined rPFS exploratory subgroup analyses based on stratification factors and baseline demographic and disease characteristics. There was a clinically meaningful rPFS improvement with olaparib+abiraterone compared with placebo+abiraterone across the HRRm, non-HRRm, and HRRm unknown subgroups. Despite some numerical differences, all observed HR point estimates were associated with a clinically meaningful improvement of at least 5 months in favour of the olaparib+abiraterone arm, irrespective of HRRm status.

Figure S1 Radiological PFS Based on Investigator Assessment, Kaplan-Meier Plot (FAS)



Circle indicates a censored observation.

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 anticancer therapy prior to progression.

DCO1 date: 30 July 2021.

Abi, abiraterone; DCO, data cut-off; FAS, full analysis set; Ola, olaparib; PCWG-3, Prostate Cancer Working Group-3; Pla, placebo; qd, once daily; RECIST, Response Evaluation Criteria in Solid Tumours; rPFS, radiological progression-free survival.

Key Secondary Endpoint, OS

The interim OS data were 28.6% mature (228 events/796 patients), and median OS was not reached in either treatment arm, and thus, should be interpreted with caution. The proportion of events was smaller on olaparib+abiraterone (26.8%) than on placebo+abiraterone (30.5%). The HR point estimate numerically favoured the olaparib+abiraterone vs the placebo+abiraterone arm, suggesting a trend towards improved OS for olaparib+abiraterone-treated patients (HR 0.86; 95% CI: 0.66, 1.12; p = 0.2923), with the Kaplan-Meier curves separating after approximately 22 months. Patients continue to be followed up in this ongoing study. Results of the exploratory subgroup analyses were generally consistent with the FAS. Since the OS data were 28.6% mature at DCO1 and the number of events in some subgroups is small, the results should be interpreted with caution.

Other Secondary Endpoints

Clinical benefit with olaparib+abiraterone was supported by nominally significant and clinically meaningful improvements in the secondary endpoints of TFST and PFS2 at DCO1:

- The TFST data were 50.8% mature (404 events). There was a nominally statistically significant and clinically meaningful improvement in TFST (ie, a delay of 5.1 months) in the olaparib+abiraterone arm vs the placebo+abiraterone arm (HR 0.74, 95% CI: 0.61, 0.90; p = 0.0040; median 25.0 vs 19.9 months, respectively).
- The PFS2 data were 20.6% mature (164 events). There was a nominally statistically significant and clinically meaningful improvement in PFS2 (ie, delay) in the olaparib+abiraterone arm vs placebo+abiraterone arm (HR 0.69, 95% CI: 0.51, 0.94; p = 0.0184; the median was not calculable for either treatment arm.

The TTPP data were not mature at DCO1 (110 events, 13.8%). There was no difference in TTPP in the olaparib+abiraterone arm vs the placebo+abiraterone arm (HR 1.01, 95% CI: 0.69, 1.47; p = 0.9551); median TTPP was not calculable for either treatment arm. The time to opiate use data were not mature at DCO1 (90 events, 11.3%). There was no difference in the time to opiate use for cancer-related pain in the olaparib+abiraterone arm versus the placebo+abiraterone arm (HR 1.08, 95% CI: 0.71, 1.64; p = 0.6510); the median time to opiate use for cancer pain was not calculable for either treatment arm. For time to first symptomatic skeletal-related event (SSRE), there was a total of 84 events (10.6%). There was a numerical improvement (ie, a delay) in time to first SSRE in the olaparib+abiraterone arm vs the placebo+abiraterone arm (HR 0.72, 95% CI: 0.47, 1.11; p = 0.1324; median time to first SSRE was not calculable for either treatment arm. Further follow-up of the secondary endpoints is planned.

HRQoL

The adjusted least squares mean change from baseline in the FACT-P Total and subscale/ index scores showed no overall detriment for the olaparib+abiraterone treatment arm compared with the placebo+abiraterone arm. For the FACT-P total and all subscale/index scores, there was no overall HRQoL detriment in the time to deterioration between the olaparib+abiraterone treatment arm and the placebo+abiraterone arm, with the exception of the Physical Well-Being subscale, which favoured the abiraterone+placebo arm.

The mean change from baseline in BPI-SF scores (worst pain, pain severity, and pain interference) showed no overall differences between the olaparib+abiraterone arm compared with the placebo+abiraterone arm over the treatment period.

Summary of Pharmacokinetic Results

Olaparib absorption was rapid, with median $t_{max,ss}$ of 2.00 hours. Steady state exposure of olaparib co-administered with abiraterone, based on AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$ values, was

39.28 µg·h/mL, 6.281 µg/mL, and 1.014 µg/mL, respectively. Interpatient variability, as indicated by % geometric coefficient of variation (GCV) values, was moderate (25 to 40%) to high (> 40%) for AUC_{ss} and $C_{max,ss}$, and $C_{min,ss}$. Olaparib apparent total body clearance across the dosing interval at steady state was moderate, with an arithmetic mean value of 8.280 L/h.

Absorption of abiraterone was rapid for both treatment arms, with median $t_{max,ss}$ observed between 2.00 and 2.04 hours. Geometric mean (Gmean) abiraterone AUC_{0-8} and $C_{max,ss}$ for patients receiving abiraterone alone were 339.5 ng·h/mL and 105.4 ng/mL, respectively. Gmean abiraterone AUC_{0-8} and $C_{max,ss}$ for patients receiving abiraterone+olaparib were comparable, with values of 393.7 ng/mL and 112.6 ng/mL, respectively. Interpatient variability, as indicated by the %GCV values, was very high for AUC_{ss}, $C_{max,ss}$, and $C_{min,ss}$.

The active metabolite, delta4-abiraterone, appeared rapidly in plasma for both treatment arms, with median $t_{max,ss}$ between 2.01 and 2.58 hours. Gmean delta4-abiraterone AUC_{0-8}, $C_{max,ss}$, and $C_{min,ss}$ for patients receiving abiraterone alone were 14.65 ng·h/mL, 3.903 ng/mL, and 0.7086 ng/mL, respectively. Gmean delta4-abiraterone AUC_{0-8}, $C_{max,ss}$, and $C_{min,ss}$ for patients receiving abiraterone+olaparib were slightly lower, with values of 11.72 ng·h/mL, 3.019 ng/mL, and 0.4907 ng/mL. The slight increase in abiraterone exposure and decrease in delta4-abiraterone exposure when abiraterone was co-administered with olaparib, resulted in metabolite to parent ratios of the exposure parameters ($MRAUC_{0-8}$, $MRC_{max,ss}$, and $MRC_{min,ss}$) approximately 31%, 31%, and 23% lower, respectively, than observed for abiraterone alone.

Summary of Safety Results

The median total duration of exposure to olaparib up to DCO1 was approximately 1.1 times longer than to placebo (17.5 vs 15.7 months, respectively). Median total duration of exposure to abiraterone was approximately 1.2 times longer on the olaparib+abiraterone arm than the placebo+abiraterone arm (18.2 vs 15.7 months, respectively), suggesting that the combination with olaparib did not reduce the planned administration of abiraterone. A higher proportion of patients remained on treatment in the olaparib+abiraterone arm at 18 months (48% on olaparib, 51% on abiraterone) than on the placebo+abiraterone arm (40% on placebo, 41% on abiraterone).

The most common AEs (incidence ≥ 20%) of anaemia, nausea, and fatigue in the olaparib+abiraterone arm are known adverse drug reactions (ADRs) for olaparib. Other common AEs were consistent with the known ADR profiles for olaparib and abiraterone, or considered attributable to the underlying disease.

COVID-19-related AEs were reported at a higher frequency on the olaparib+abiraterone arm vs placebo+abiraterone (8.3% vs 4.5%), and AEs of pulmonary embolism were reported at a higher frequency on the olaparib+abiraterone arm vs placebo+abiraterone (6.5% vs 1.8%).

AEs of CTCAE Grade ≥ 3 were reported for 47.2% of patients on olaparib+abiraterone vs 38.4% on placebo+abiraterone. The most common Grade ≥ 3 AEs on the olaparib+abiraterone arm were anaemia (15.1%) and pulmonary embolism (6.5%); the most common on the placebo+abiraterone arm were anaemia (3.3%) and hypertension (3.3%). Anaemia is a known ADR of olaparib, and hypertension is a known ADR of abiraterone.

AEs of special interest reported for olaparib were balanced between the treatment arms: No events of MDS/AML were reported. Pneumonitis was reported in 3 (0.8%) patients on each treatment arm. New primary malignancies were reported in 12 patients (3.0%) in the olaparib+abiraterone arm and 10 patients (2.5%) in the placebo+abiraterone arm.

Most of the deaths were reported as due to the disease under investigation only (71.0% vs 76.0%, for the olaparib+abiraterone and placebo+abiraterone arms, respectively).

SAEs were reported for 33.9% of patients on olaparib+abiraterone and 27.0% on placebo+abiraterone. The most commonly reported SAE on olaparib+abiraterone was anaemia (5.8%). SAEs with fatal outcome were reported for a similar proportion of patients in the olaparib+abiraterone arm (4.0%) and the placebo+abiraterone arm (4.3%).

AEs leading to discontinuation of olaparib were more frequent than AEs leading to discontinuation of placebo (13.8% vs 7.8%, respectively). AEs leading to olaparib dose reduction were more frequent than AEs leading to placebo dose reduction (20.1% vs 5.6%), and AEs leading to olaparib dose interruption were more frequent than those leading to placebo dose interruption (44.7% vs 25.3%). Anaemia was the most common AE leading to discontinuation, dose reduction, or dose interruption of olaparib.

Except for haemoglobin, changes in haematology parameters were generally mild or moderate and transient. No hepatobiliary or renal safety concerns were identified from review of the laboratory and AE data. No new safety concerns were identified in the safety laboratory data. Two patients on the placebo+abiraterone arm met the biochemical criteria for a Hy's law case; one was considered to be related to abiraterone treatment, for the other, there was an alternative explanation. No clinically meaningful changes were noted in vital signs in patients in either treatment arm during the study. No significant difference between the treatment arms was seen in the ECG data: Similar proportions of patients had abnormal (clinically significant or non-significant) ECG findings between the 2 treatment groups.

Conclusions

The results of the PROpel study based on DCO1 for the primary analysis of rPFS demonstrate a favourable benefit-risk profile for the combination of olaparib with abiraterone, as detailed below:

- There was a statistically significant and clinically meaningful 34% reduction in the risk of radiological disease progression or death (investigator-assessed) for olaparib+abiraterone vs placebo+abiraterone (HR 0.66; 95% CI: 0.54, 0.81; $p < 0.0001$), with an 8.2-month improvement in median rPFS in the olaparib+abiraterone arm compared with placebo+abiraterone (24.8 vs 16.6 months, respectively). The sensitivity analysis of rPFS based on BICR was consistent with the primary analysis (HR 0.61; 95% CI: 0.49, 0.74; nominal $p < 0.0001$).
- The interim OS data were 28.6% mature (228 events); however, the HR point estimate numerically favoured the olaparib+abiraterone vs the placebo+abiraterone arm suggesting a trend towards improved OS with the addition of olaparib to abiraterone (HR 0.86; 95% CI: 0.66, 1.12; $p = 0.2923$), with the Kaplan-Meier curves separating after approximately 22 months. Median OS was not reached in either treatment arm.
- The improvement in clinical benefit was also supported by nominally significant improvements in other secondary endpoints, including delays in TFST (HR 0.74; 95% CI: 0.61, 0.90; $p = 0.0040$) and PFS2 (HR 0.69; 95% CI: 0.51, 0.94; $p = 0.0184$). Results from the PRO analyses indicate that the combination of olaparib+abiraterone had no overall negative impact on the patients' HRQoL. Change from baseline in the FACT-P Total and subscale/index scores showed no overall detriment for the olaparib+abiraterone arm compared with the control arm. Change from baseline in BPI-SF scores (worst pain, pain severity, and pain interference) showed no overall differences between the 2 arms.
- Clinical benefit was also seen consistently across the pre-defined rPFS exploratory subgroup analyses based on stratification factors and baseline demographic and disease characteristics. The treatment effect was also generally consistent with the result for the FAS across the HRRm subgroups, indicating clinical benefit irrespective of HRRm status.
- PK assessments confirmed that there were no clinically relevant PK-based drug-drug interactions between olaparib and abiraterone.
- The safety results show a manageable safety profile for olaparib and abiraterone given in combination, suitable for the treatment of patients with mCRPC:
  - The duration of exposure to study treatment was similar between treatment arms and olaparib did not reduce the extent of exposure to abiraterone.
  - The safety and tolerability of the combination of olaparib+abiraterone appeared to be consistent with the known safety profiles of the olaparib and abiraterone monotherapies in the context of this patient population. Imbalances were noted in venous thromboembolic events and COVID-19-related events, which were more frequently reported with the olaparib+abiraterone combination.