Clinical Study Report Addendum Synopsis	
Drug Substance	Olaparib
Study Code	D081DC00007
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EudraCT Number	2016-000300-28
NCT Number	NCT02987543

A Phase III, Open Label, Randomized Study to Assess the Efficacy and Safety of Olaparib (Lynparza™) Versus Enzalutamide or Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer Who Have Failed Prior Treatment with a New Hormonal Agent and Have Homologous Recombination Repair Gene Mutations (PROfound)

Final Analysis of Overall Survival and Safety Update

Study dates: First patient enrolled: 6 February 2017
Last patient enrolled: 18 September 2018
The analyses presented in this report are based on a data cut of date of 20 March 2020 and a database lock date of 17 April 2020.

Phase of development: Therapeutic confirmatory (III)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

This is a clinical study report (CSR) addendum to the CSR for Study D081DC00007 (hereafter referred to as PROfound). The results of the radiological progression-free survival (rPFS) analysis were based on the data cut-off (DCO) date of 04 June 2019 and were reported along with the data for the secondary efficacy endpoints (including interim OS), health-related quality of life, pharmacokinetics, and safety data in the CSR for the rPFS analysis (23 October 2019).

This CSR addendum reports the final analyses of the key secondary endpoint of overall survival (OS), along with updated patient disposition and safety data, based on a DCO date of 20 March 2020, for the overall study population and for the subsets of patients who had their homologous recombination repair gene mutated (HRRm) status confirmed by the germline breast cancer susceptibility gene (*gBRCA*) mutation (*gBRCAm*) and) tests.

Study Centres

This was an international multicentre study conducted in 206 study centres in 20 countries (of these, 139 centres randomised patients): Argentina (6 sites), Australia (10 sites), Austria (5 sites), Brazil (14 sites), Canada (12 sites), Denmark (1 site), France (13 sites), Germany (15 sites), Israel (6 sites), Italy (10 sites), Japan (30 sites), Netherlands (6 sites), Norway (1 site), South Korea (9 sites), Spain (7 sites), Sweden (2 sites), Taiwan (9 sites), Turkey (8 sites), United Kingdom (5 sites) and United States (37 sites).

Publications

- de Bono J et al. N Engl J Med. 2020 May 28;382(22):2091-2102.
- Thiery-Vuillemin A et al. J Clin Oncol. 2020;38(suppl abstr 5539).
- Saad F et al. J Clin Oncol. 2020;38(suppl abstr 5538).
- Hussain M et al. J Clin Oncol. 2020;38(suppl 6): abstr 195.
- de Bono JS et al. J Clin Oncol. 2020;38(suppl 6): abstr 134.
- Hussain M et al. Ann Oncol. 2019;30(suppl 5): abstr LBA12_PR.
- Hussain M et al. Ann Oncol. 2019;30(suppl 5): abstr 847PD.

Objectives and Criteria for Evaluation

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description [a]**
Primary	Efficacy	To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with mCRPC with *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A). [b]	rPFS by BICR: the time from randomisation until the date of objective radiological disease progression (by RECIST 1.1 and PGWG-3) or death (by any cause in the absence of progression) regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy prior to progression
Key secondary	Efficacy	To determine the efficacy (as assessed by ORR) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A). [b]	Confirmed ORR in soft tissue and bone: the number of patients with a CR and PR by BICR divided by the number of patients in the treatment group in the FAS with measurable disease at baseline
Key secondary	Efficacy	To determine the efficacy (as assessed by rPFS) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations (Cohort A+B). [b] Note: this objective is not applicable for the potential future China cohort.	rPFS by BICR
Key secondary	Efficacy	To determine the efficacy (as assessed by time to pain progression) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A). [b]	TTPP: the time from randomisation to time point at which worsening in pain (based on BPI-SF worst pain [Item 3] and opiate analgesic use [AQA score]) is observed for asymptomatic patients and symptomatic patients (at baseline)

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description [a]**
Key secondary	Efficacy	To determine the efficacy (as assessed by overall survival) of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A).	OS: the time from the date of randomisation until death due to any cause regardless of whether the patient withdrew from randomised therapy or received another anti-cancer therapy. 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.
Other secondary	Efficacy	To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A). [b]	• Time to first SSRE: the time from randomisation to first use of radiation therapy to prevent or relieve skeletal symptoms, occurrence of new symptomatic pathological bone fractures, occurrence of spinal cord compression or orthopaedic surgical intervention for bone metastasis • DoR: the time from the date of first documented confirmed response (by BICR using RECIST 1.1 and PCWG-3) until date of documented progression (by BICR) or death in the absence of disease progression • Time to opiate use for cancer-related pain: the time from randomisation to the date of opiate use for cancer-related pain in patients who have not received any opiates at baseline • Confirmed ORR in soft tissue • PSA_{50} response: the proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later • CTC conversion rate: the proportion of patients achieving a decline in the

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Objective			Outcome Variable
Priority	**Type**	**Description**	**Description [a]**
			number of CTCs from ≥5 cells/7.5 mL at baseline to <5 cells/7.5 mL post baseline • PFS2: the time from the date of randomisation to the earliest of the investigator-assessed progression events (subsequent to that used for the primary variable of rPFS) or death
Other secondary	Efficacy	To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying gene mutations (Cohort A) on disease-related symptoms and HRQoL. [b]	• Time to pain severity progression (BPI-SF pain severity domain and opiate use): the time from the date of randomisation to increase in the BPI-SF pain severity domain or increased opiate use • Change from baseline in BPI-SF pain interference score • Time to deterioration and change from baseline in pre-specified FACT-P Total and subscale scores: FACT-P is a questionnaire composed of the following subscales: physical, social/family, emotional and functional well-being as well as the additional concerns scales consisting of specific prostate cancer symptoms. • Pain palliation: proportion of patients with pain (BPI-SF worst pain [Item 3]) score ≥4 points at baseline who have a decrease of ≥2 points in pain (BPI-SF worst pain [Item 3]) and without ≥1 point increase in analgesic score (AQA score) at 12 weeks, confirmed at least 3 weeks later

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description [a]**
Other secondary	Efficacy	To assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations other than *BRCA1*, *BRCA2* or *ATM* (Cohort B). [c] Note: this objective is not applicable for the potential future China cohort.	• rPFS by BICR • Confirmed ORR in soft tissue and bone • TTPP (BPI-SF worst pain [Item 3] and opiate analgesic use [AQA score]) • OS
Other secondary	Efficacy	To further assess the efficacy of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations (Cohort A+B). [c]	• Confirmed ORR in soft tissue and bone • Time to first SSRE • DoR • Time to opiate use for cancer-related pain • Confirmed ORR in soft tissue • PSA_{50} response • CTC conversion • PFS2 • OS
Other secondary	Efficacy	To further assess the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying gene mutations (Cohort A+B) on disease-related symptoms and HRQoL. [b]	• TTPP (BPI-SF worst pain [Item 3] and opiate analgesic use [AQA score]) • Time to pain severity progression (BPI-SF pain severity domain and opiate use) • Change from baseline in BPI-SF pain interference score. • Time to deterioration and change from baseline in pre-specified FACT-P Total and subscale scores. • Pain palliation (BPI-SF worst pain [Item 3])
Other secondary	Pharmacokinetics	To determine the exposure to olaparib in a subset of subjects receiving olaparib. [b] Note: this objective is not applicable for the potential future China cohort.	Olaparib plasma concentration data

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Objective			Outcome Variable
Priority	**Type**	**Description**	**Description** [a]
Safety	Safety	To evaluate the safety and tolerability of olaparib versus investigator choice of enzalutamide or abiraterone acetate.	AEs, SAEs, DAEs, OAEs, laboratory, vital signs and ECGs
Exploratory	Other	To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate on patient-reported treatment tolerability and overall health status. [b]	• PRO-CTCAE: a questionnaire consisting of 8 pre-selected items considered relevant to the study treatments that assesses tolerability from the patient's perspective. • PGIC: a single-item questionnaire that assesses the change in overall health status of patients since the start of study treatment.
Exploratory	Efficacy	To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A) based on prior receipt of taxane. [b]	Subgroup analysis of rPFS in patients with or without prior taxane
Exploratory	Efficacy	To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with either germline or somatic *BRCA1*, *BRCA2* or *ATM* qualifying mutations (Cohort A). [b]	Subgroup analysis of rPFS based on whether the qualifying mutation is a germline mutation or only in the tumour (somatic)
Exploratory	Efficacy	To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with *BRCA1*, *BRCA2*, or *ATM* qualifying mutations as detected by ctDNA analysis. [b] Note: this objective is not applicable for the potential future China cohort.	rPFS analysis in patients with qualifying mutation identified by ctDNA test

Table S1 Objectives and Outcome Variables

Objective			Outcome Variable
Priority	**Type**	**Description**	**Description** [a]
Exploratory	Efficacy	To compare the effect of olaparib versus investigator choice of enzalutamide or abiraterone acetate in subjects with HRR qualifying mutations as detected by ctDNA analysis. [b] Note: this objective is not applicable for the potential future China cohort.	rPFS analysis in patients with qualifying mutation identified by ctDNA test
Exploratory	Efficacy	To explore methods of estimating OS adjusting for the impact of the control arm receiving subsequent PARP inhibitors (including olaparib), platinum compounds or imbalances between the treatment arms for other potentially active agents.	OS adjusted for impact of subsequent PARP inhibitors (or other potentially active investigational agents)
Exploratory	Pharmacogenetics	To compare the tumour HRR gene mutation status in all screened subjects with evaluable results from plasma. [b] Note: this objective is not applicable for the potential future China cohort.	Comparison of HRR gene mutation status between tumour DNA and plasma derived ctDNA
Exploratory	Pharmacogenetics	Future exploratory research into factors that may influence development of cancer and/or response to study treatment (where response is defined broadly to include efficacy, tolerability or safety) may be performed on the collected and stored archival tumor samples that were mandatory for entry onto the study or on blood samples. [b] Note: this objective is not applicable for the potential future China cohort.	• Evaluate loss of heterozygosity of HRR genes in tumours • Evaluation of ctDNA collected from plasma at baseline and at progression • CTCs (EPIC assay)

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Objective			Outcome Variable
Priority	**Type**	**Description**	**Description** [a]
Exploratory	Pharmacogenetics	To collect and store DNA (according to each country's local and ethical procedures) for future exploratory research into genes/genetic variation that may influence response (ie, distribution, safety, tolerability and efficacy) to study treatments and or susceptibility to disease (optional). [b]	Blood sample pharmacogenetics analysis
Exploratory	Health economics	To investigate the health economic impact of treatment and the disease on hospital related resource use and health state utility. [b]	• Number, type and reason of hospitalisations and hospital attendances, procedures conducted and hospital length of stay (HOSPAD) • EQ-5D-5L: a questionnaire comprising 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort and anxiety/depression)

[a] Endpoints that are included in multiple objectives are described at their first appearance only.

[b] Objective is reported outside of this CSR addendum.

[c] Only the OS endpoint of this objective is reported in this CSR addendum.

Cohort A+B comprises all patients randomised in Cohort A and Cohort B.

AE = adverse event; *ATM* = ataxia telangiectasia mutated; AQA = Analgesic Quantification Algorithm; BICR = blinded independent central review; BPI-SF = Brief Pain Inventory – Short Form; *BRCA* = breast cancer susceptibility gene; CR = complete response; CTC = circulating tumour cell; CSR = clinical study report; ctDNA = circulating tumour DNA; DAE = discontinuation of study treatment due to adverse event; DoR = duration of response; ECG = electrocardiogram; EQ-5D-5L = EuroQoL 5-dimension, 5-level Health State Utility Index; FACT-P = Functional Assessment of Cancer Therapy – Prostate Cancer; FAS = full analysis set; HOSPAD = Hospital Admission; HRQoL = health related quality of life; HRR = homologous recombination repair; mCRPC = metastatic castration-resistant prostate cancer; OAE = other significant adverse event; ORR = objective response rate; OS = overall survival; PCWG-3 = Prostate Cancer Working Group 3; PFS2 = time from randomisation to second progression; PARP = polyadenosine 5'diphosphoribose polymerase; PGIC = Patient Global Impression of Change; PR = partial response; PRO-CTCAE = Patient Reported Outcomes - Common Terminology Criteria for Adverse Events; PSA = prostate-specific antigen; PSA_{50} = a ≥50% decline in PSA from baseline; RECIST = Response Evaluation Criteria in Solid Tumours; rPFS = radiological progression-free survival; SAE = serious adverse event; SSRE = symptomatic skeletal-related event; TTPP = time to pain progression.

Study Design

PROfound was a Phase III, randomised, open-label, multicentre trial to assess the efficacy and safety of olaparib monotherapy in patients with metastatic castration-resistant prostate cancer (mCRPC) that have qualifying homologous recombination repair (HRR) gene mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have failed prior treatment with a new hormonal agent (NHA). Eligible patients were those with HRRm mCRPC, who had progressed following prior treatment with an NHA. All patients must have had a qualifying HRR mutation assessed via the FMI Clinical Trial Improvement Amendments (CLIA) HRR clinical trial assay (CTA) to be randomised. Qualifying HRR gene mutations were *BRCA1*, *BRCA2* and *ATM* for Cohort A, and *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and *RAD54L* for Cohort B. Patients must have received a prior NHA (eg, abiraterone acetate and/or enzalutamide) for the treatment of metastatic prostate cancer and/or castration-resistant prostate cancer (CRPC) and, in the opinion of the investigator, progressed on this treatment. Patients without prior surgical castration must have been taking and willing to continue luteinizing hormone-releasing hormone analog (agonist or antagonist) therapy throughout the duration of study treatment. Patients must have been candidates for treatment with enzalutamide or abiraterone acetate with documented current evidence of metastatic castration-resistant prostate cancer, where metastatic status was defined as at least one documented metastatic lesion on either bone scan or computed tomography/magnetic resonance imaging scan. Patients known to have an HRR gene mutation via the commercially available FoundationOne® assay prior to randomisation could enter the study based on this result, however, residual DNA (stored at FMI) from the original FoundationOne® test was used to confirm the presence of a qualifying HRR gene mutation using the FMI CLIA HRR CTA. Subjects who did not have sufficient residual DNA from their original test were analysed in silico for qualifying HRR gene mutations, according to the criteria in place for determining eligible mutations in PROfound, based on their original FoundationOne® test data, but were required to provide a sufficient formalin-fixed, paraffin embedded tumour sample to carry out retrospective central confirmation using the FMI CLIA HRR CTA. In addition, patients must have consented to provide a blood sample for exploratory biomarker research. Patients were randomised using an interactive voice response system/interactive web response system in a 2:1 ratio to the treatments as specified below:

- Olaparib tablets orally 300 mg twice daily (bd)
- Investigators choice of NHA with either enzalutamide 160 mg orally once daily (od) or abiraterone acetate 1000 mg orally od with prednisone 5 mg orally bd (prednisolone was permitted for use instead of prednisone, if necessary)

Target Subject Population and Sample Size

It was intended to randomise a total of approximately 240 patients in Cohort A and 100 patients in Cohort B (2:1 ratio) with mCRPC that had qualifying HRR mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who had failed prior treatment with an NHA.

The DCO for the rPFS analysis (04 June 2019) took place when 174 progression events had occurred in Cohort A (71.0% maturity). The DCO for the final OS analysis (20 March 2020) took place when 148 OS events had occurred in Cohort A (60.4% maturity).

Investigational Product and Comparators: Dosage, Mode of Administration and Batch Numbers

Olaparib tablets were manufactured by [redacted] on behalf of AstraZeneca, as 150 mg and 100 mg green, film-coated tablets. A mixed sourcing model was used for abiraterone acetate, prednisone/prednisolone and enzalutamide, allowing for both central and local supply. Abiraterone acetate tablets were manufactured by [redacted] or [redacted] (on behalf of manufacturing licence holder [redacted], as 500 mg or 250 mg tablets. Prednisone tablets were manufactured by [redacted] and prednisolone tablets were manufactured by [redacted], both as 5 mg tablets. Enzalutamide capsules were manufactured by [redacted] as 40 mg capsules. Use of enzalutamide 40 mg tablets, supplied locally, was also permitted. Olaparib tablets were dosed orally at 300 mg bd. Abiraterone acetate was dosed orally at 1000 mg od, in combination with oral prednisone or prednisolone 5 mg bd. Enzalutamide was dosed orally at 160 mg od. The following batch numbers of centrally-sourced olaparib, abiraterone acetate, prednisone and enzalutamide were used:

- Olaparib: 1000073096, 1000086265, 1000088520, 1000110206, 1000112671, 1000126303, 1000126304, 1000127645, 1000149956, 1000149959, 1000149961
- Abiraterone acetate: 21443.1, A0052, GDZSF00, HAZSK00, IBZVZ00
- Prednisone: GF4958
- Enzalutamide: 15K09/15, 17C06/18, 17I01/12, 17K07/08

Duration of Treatment

Patients were to continue to receive study treatment until objective radiological disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 and Prostate Cancer Working Group 3 (PCWG-3) as assessed by blinded independent central view (BICR), or by investigator assessment if after the DCO for the primary analysis, as long as they did not meet any other discontinuation criteria. Once patients receiving investigators choice of NHA were determined to have objective radiological progression by BICR, or by investigator assessment if after the date of DCO for the primary analysis, they were eligible to switch to treatment with olaparib. Patients who switched to olaparib were able to continue treatment

with olaparib as long as in the investigator's opinion they were benefiting from treatment and did not meet any other discontinuation criteria.

Statistical Methods

The final OS analysis was performed with a DCO date of 20 March 2020.

In the OS analysis, p-values were calculated using a log-rank test stratified by the stratification factors determined by the pooling strategy and with the Breslow method for handling ties. The hazard ratio (HR) and confidence interval (CI) were estimated using a Cox proportional hazards model with the stratification factors determined by the pooling strategy being used as covariates and the Efron approach being used for handling ties. The 2-sided 95% CIs were calculated using the profile likelihood method with a HR less than 1 favouring olaparib. Subgroup analyses of OS were conducted to assess the consistency of treatment effect across potential or expected prognostic factors.

Sensitivity analyses adjusting for the effect of subsequent olaparib on the investigators choice of NHA arm were conducted using a Rank Preserving Structural Failure Time Model approach. The primary analyses for OS was also repeated excluding any patients who did not have a qualifying gene mutation according to the testing quality control metrics and mutation clarification process approved for the [redacted] test or a *BRCA1/2* mutation confirmed by the [redacted] (where these tests have been performed to support companion diagnostic development).

In order to describe the nature of the benefits of olaparib treatment, hypotheses were tested using a multiple testing procedure with an alpha-exhaustive recycling strategy. Upon achieving statistical significance on the primary endpoint rPFS in Cohort A at the DCO for the rPFS analysis (04 June 2019), testing of each of the key secondary endpoints, objective response rate (Cohort A), rPFS (Cohort A+B), time to pain progression (Cohort A) and interim OS (Cohort A) were performed sequentially with the 2-sided 5% level of alpha recycled from the primary rPFS (Cohort A) endpoint. Interim OS in Cohort A was tested at this DCO, spending 0.010 alpha and statistical significance was not achieved with an observed OS p-value in Cohort A of 0.0173. At the DCO for the final OS analysis (DCO 20 March 2020), final OS in Cohort A was tested with 0.047 alpha.

Subject Population

A total of 4425 patients with mCRPC who had failed treatment with a prior NHA, were enrolled (ie, gave informed consent) at 206 centres in 20 countries. Of these, 139 centres randomised patients. Patients with an available FFPE tumour sample were screened for qualifying HRR gene mutations using the FMI CLIA HRR CTA. Of the 245 patients with qualifying HRR gene mutations (*BRCA1*, and/or *BRCA2* and/or *ATM*) that were randomised into Cohort A, 162 patients received olaparib and 83 patients received investigators choice of

NHA. Of the 142 patients with qualifying HRR gene mutations (*BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/or *RAD54L*) that were randomised into Cohort B, 94 patients received olaparib and 47 patients received investigators choice of NHA; one patient randomised to the investigators choice of NHA arm did not receive study treatment. Of the 387 patients with qualifying HRR gene mutations (*BRCA1*, *BRCA2*, *ATM*, *BARD1*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51C*, *RAD51D* and/or *RAD54L*) that were randomised into Cohort A+B, 256 patients received olaparib and 130 patients received investigators choice of NHA.

In Cohort A and Cohort A+B at the time of the DCO for the final OS analysis (20 March 2020), a higher percentage of patients in the olaparib compared with the investigators choice of NHA arms were still receiving study treatment and a higher percentage of patients in the investigators choice of NHA arm compared with the olaparib arm discontinued treatment. In Cohort B at the time of the DCO for the final OS analysis (20 March 2020), a similar percentage of patients in the olaparib and investigators choice of NHA arms were still receiving study treatment and a similar percentage of patients in the olaparib and investigators choice of NHA arms discontinued treatment. For all cohorts, the majority of patients who discontinued study treatment did so due to objective radiographic progression or unequivocal clinical progression. A lower percentage of patients discontinued study treatment due to objective radiographic progression in the olaparib arm compared with the investigators choice of NHA arm. A higher percentage of patients discontinued study treatment due to AEs in the olaparib arm compared with the investigators choice of NHA arm. A similar percentage of patients in the olaparib and investigators choice of NHA arms decided to voluntarily discontinue treatment.

In Cohort A, the 2 treatment arms were well balanced in terms of age, race and ethnicity. Median age was 68 years in the olaparib arm and 67 years in the investigators choice of NHA arm in Cohort A. The majority of patients were White and one quarter of patients were Asian. The patient demographics were similar between the treatment groups and in line with expectations. Baseline characteristics of the target population of patients were generally well balanced between the two treatment arms in Cohort A. Bone was the most common site of disease. All patients received a prior NHA as per the PROfound study inclusion criteria, but data were missing for 2 patients. Overall, 43.7% of patients received prior enzalutamide, 36.7% of patients received prior abiraterone, and 18.8% of patients had received both treatments previously. In addition, two thirds of patients received a prior taxane (34.3% had docetaxel alone, 2.4% had cabazitaxel alone and 18.0% had both docetaxel and cabazitaxel). The majority of patients had an ECOG performance status of 0 or 1 in both treatment arms. The majority of patients had a total Gleason score of 7 to 9 in both treatment arms and median baseline PSA was higher in the investigators choice of NHA arm compared with the olaparib arm. Of the 224 patients in Cohort A with a single mutation, 62.5% of patients had a *BRCA1*

or *BRCA2* mutation alone and 37.5% of patients had a *ATM* mutation alone. For Cohort A, 21 patients had co-occurring mutations.

In Cohort B, the 2 treatment arms were well balanced in terms of age, race, and ethnicity. Median age was 69 years in the olaparib arm and 69.5 years in the investigators choice of NHA arm. The majority of patients were White and approximately 30% of patients were Asian. The patient demographics were similar between the treatment groups and in line with expectations. Baseline characteristics of the target population of patients were generally well balanced between the two treatment arms in Cohort B. Bone was the most common site of disease. All patients received a prior NHA as per the PROfound study inclusion criteria, but data were missing for 3 patients. Overall, 35.2% of patients received prior enzalutamide, 43.0% of patients received prior abiraterone and 19.7% of patients had received both treatments previously. In addition, two thirds of patients received a prior taxane (41.5% had docetaxel alone, 6.3% had cabazitaxel alone and 12.7% had both docetaxel and cabazitaxel). The majority of patients had an ECOG performance status of 0 or 1 in both treatment arms. The majority of patients had a total Gleason score of 7 to 9 in both treatment arms and median baseline PSA was higher in the investigators choice of NHA arm compared with the olaparib arm. Of the 135 patients in Cohort B with a single mutation, 65.9% of patients had a *CDK12* mutation alone and 31.9% of patients had a single mutation in 1 of 9 HRR genes (*BARD1*, *BRIP1*, *CHEK1*, *CHEK2*, *PALB2*, *PPP2R2A*, *RAD51B*, *RAD51D* and *RAD54L*). Four patients were incorrectly assigned to Cohort B (1 *BRCA2* [olaparib], 1 *BRCA2+CDK12* (investigators choice of NHA) and 2 *ATM* [both olaparib]). No patients in Cohort B had a *FANCL* or *RAD51C* mutation alone or co-occurring with other mutations. For Cohort B, 7 patients had co-occurring mutations.

Summary of Efficacy Results

At the time of the DCO for the rPFS analysis (04 June 2019), statistically significant results were achieved for the following endpoints: rPFS (BICR) in Cohort A, ORR (BICR) in Cohort A, rPFS (BICR) in Cohort A+B, and time to pain progression in Cohort A, as per the pre-specified multiple testing framework. Interim OS in Cohort A was tested at this DCO, spending 0.010 alpha and statistical significance was not achieved with an observed OS p-value in Cohort A of 0.0173. At the DCO for the final OS analysis (DCO 20 March 2020), final OS in Cohort A was tested with 0.047 alpha. The observed final OS analysis p-value in Cohort A was 0.0175 and thus statistical significance can be claimed. Therefore, all endpoints pre-specified in the hierarchical testing procedure for PROfound were statistically significant.

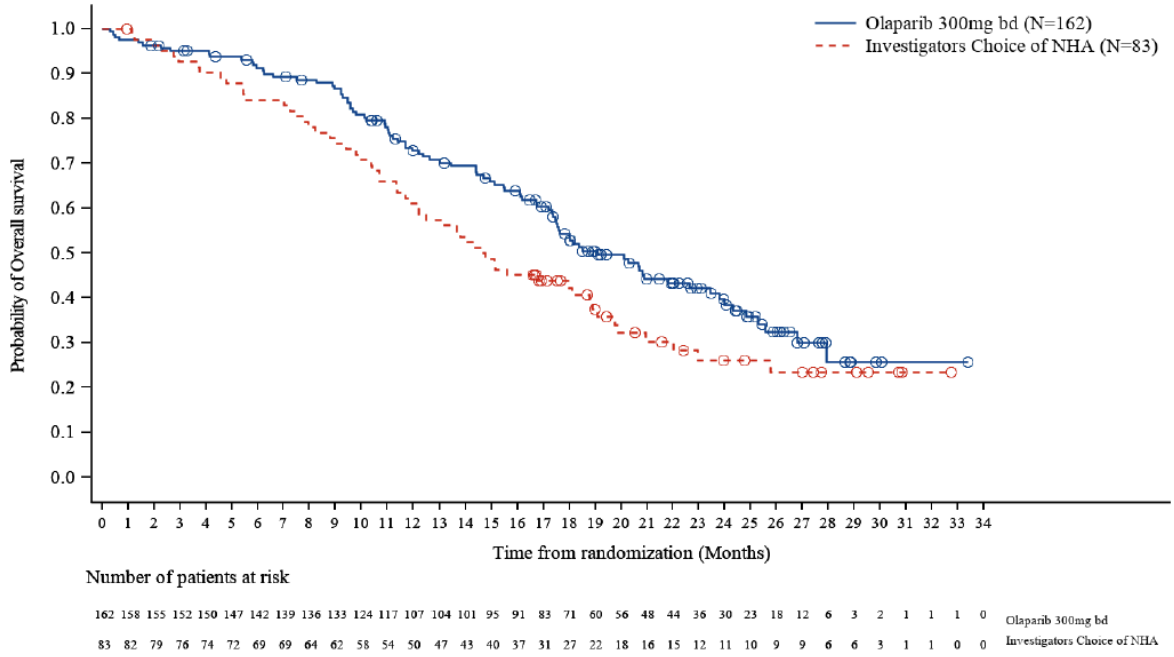
Key Secondary Variable: Overall Survival in Cohort A

The final OS data were 60.4% mature (148 events out of 245 patients). At the time of the DCO, 30.2% of olaparib-treated patients and 25.3% of investigators choice of NHA-treated patients were known to be alive and were in survival follow-up.

There was a statistically significant and clinically meaningful OS benefit in olaparib-treated patients compared with investigators choice of NHA treated patients in Cohort A, with a median OS improvement of 4.4 months in the olaparib arm vs the investigators choice of NHA arm (HR=0.69; 95% CI 0.50, 0.97; p=0.0175; median OS 19.1 vs 14.7 months, respectively).

The Kaplan-Meier plot for OS in Cohort A is presented in Figure S1. Clinical benefit was demonstrated by clear separation of the curves in favour of the olaparib arm vs the investigators choice of NHA arm; this separation was first observed at approximately 3 months and was maintained throughout the study.

Figure S1 Overall Survival, Kaplan-Meier Plot (FAS; Cohort A)



A circle indicates a censored observation.
bd = twice daily; FAS = full analysis set; NHA = new hormonal agent.

The OS subgroup data were generally consistent with that of the overall population in Cohort A.

In Cohort A, 56 out of 83 patients (67.5%) in the investigators choice of NHA arm received subsequent treatment with olaparib. A pre-specified sensitivity analysis of OS adjusting for investigators choice of NHA-treated patients receiving subsequent olaparib was conducted for Cohort A; the HR from this analysis was 0.42 (95% CI 0.19, 0.91), favouring olaparib treatment. These data further support the clinical benefit of olaparib seen in Cohort A and

suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.

Overall survival in the confirmed [redacted] subset was consistent with the FAS in Cohort A.

Other Secondary Variables

Overall Survival in Cohort B

The final OS data were 70.4% mature (100 events out of 142 patients). At the time of the DCO, 20.2% of olaparib-treated patients and 25.0% of investigators choice of NHA-treated patients were known to be alive and were in survival follow-up.

The median OS was 14.1 months in the olaparib arm and 11.5 months in the investigators choice of NHA arm, equating to a median OS improvement of 2.6 months in the olaparib arm vs the investigators choice of NHA arm. The HR numerically favoured olaparib vs the investigators choice of NHA arm and suggested no detriment for OS in olaparib-treated patients (HR=0.96; 95% CI 0.63, 1.49).

In Cohort B, 30 out of 48 patients (62.5%) in the investigators choice of NHA arm received subsequent treatment with olaparib. A pre-specified sensitivity analysis of OS adjusting for investigators choice of NHA-treated patients receiving subsequent olaparib was conducted for Cohort B; the HR from this analysis was 0.83 (95% CI 0.11, 5.98), favouring olaparib treatment. These data further support the clinical benefit of olaparib seen in Cohort B and suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.

Contrary to the expectation at the time of the PROfound study design, preclinical data generated by AstraZeneca does not support the role of *PPP2R2A* as a gene involved in the HRR process; deleterious mutations in this gene are therefore unlikely to confer sensitivity to olaparib or any other PARP inhibitor. In Cohort B, there were 6 patients in the olaparib arm and 4 patients in the investigators choice of NHA arm with a mutation in the *PPP2R2A* gene only. An ad hoc subgroup analysis of OS excluding these patients was conducted for Cohort B; the HR from this analysis was 0.83 (95% CI 0.54, 1.31), favouring olaparib treatment.

Overall survival in the confirmed [redacted] subset was consistent with the FAS in Cohort B.

Overall Survival in Cohort A+B

The final OS data were 64.1% mature (248 events out of 387 patients). At the time of the DCO, 26.6% of olaparib-treated patients and 25.2% of investigators choice of NHA-treated patients were known to be alive and were in survival follow-up.

There was a trend for OS benefit in olaparib-treated patients compared to investigators choice of NHA-treated patients, with a median OS improvement of 3.3 months in the olaparib arm vs the investigators choice of NHA arm (HR=0.79; 95% CI 0.61, 1.03; median OS 17.3 vs 14.0 months).

The OS subgroup data were generally consistent with that of the overall population in Cohort A+B. With regards to the OS subgroup analysis by gene (based on analyses of patients with mutations in a single HRR gene), the benefit of olaparib over investigators choice of NHA was maintained for patients with a *BRCA1* or *BRCA2* mutation. The HR suggested no detriment for olaparib treated patients with a mutation in an *ATM*, *CDK12*, or *CHEK2* gene only. Hazard ratios were not calculated for some of the Cohort B genes (*BARD1*, *BRIP1*, *CHEK1*, *PALB2*, *RAD51B*, *RAD51D*, and *RAD54L*) due to the small number of events (<5 events) in these subgroups. There were no patients enrolled with *FANCL* or *RAD51C* mutations. No clinical benefit in OS for *PPP2R2A* was observed, in line with the data at the time of the DCO for the rPFS analysis (04 June 2019).

In Cohort A+B, 86 out of 131 patients (65.6%) in the investigators choice of NHA arm received subsequent treatment with olaparib. A pre-specified sensitivity analysis of OS adjusting for investigators choice of NHA-treated patients receiving subsequent olaparib was conducted for Cohort A+B; the HR from this analysis was 0.55 (95% CI 0.29, 1.06), favouring olaparib treatment. These data further support the clinical benefit of olaparib seen in Cohort A+B and suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.

In Cohort A+B, there were 6 patients in the olaparib arm and 4 patients in the investigators choice of NHA arm with a mutation in the *PPP2R2A* gene only. An ad hoc subgroup analysis of OS excluding these patients was conducted for Cohort A+B; the HR from this analysis was 0.75 (95% CI 0.58, 0.98), favouring olaparib treatment.

Overall survival in the confirmed [redacted] and confirmed [redacted] *gBRCAm* subsets was consistent with the FAS in Cohort A+B.

Summary of Safety Results

Overall, the median total duration of exposure to olaparib was approximately 1.9 times longer than in the investigators choice of NHA arm (230 days [7.6 months] vs 120 days [4.0 months]), consistent with the delayed time to disease progression. In the olaparib arm, the most common AEs (reported by ≥20% patients) of anaemia, nausea, decreased appetite, fatigue, and diarrhoea are known adverse drug reactions. In the investigators choice of NHA arm, the most common AEs (reported by ≥20% of patients) were fatigue and nausea.

Oedema peripheral was the only AE which occurred at a ≥5% greater frequency in the olaparib arm than the investigators choice of NHA arm that was not an ADR. All AEs of

oedema peripheral were classed as low grade (Common Terminology Criteria for Adverse Events [CTCAE] Grade 1 or 2) and none were classed as serious. The exposure adjusted event rate was similar between the treatment arms (176.47 vs 168.64 events per 1000 patient years, respectively), and therefore these events are most likely due to underlying disease.

Smaller imbalances (reported at a ≥3.5% greater frequency in the olaparib arm compared with the investigators choice of NHA arm) were noted in the incidence of lymphopenia (5.1% vs 0.8%, respectively), headache (6.3% vs 2.3%, respectively), stomatitis (5.1% vs 1.5%, respectively), and white blood cell count decreased (4.7% vs 0%, respectively), all of which are known ADRs for olaparib, and also in constipation (19.1% vs 14.6%, respectively) and pulmonary embolism (4.7% vs 0.8%, respectively) that are not recognised as part of the known safety profile of olaparib. After adjustment for duration of exposure, constipation was reported at a higher rate in the investigators choice of NHA arm compared with the olaparib arm (354.50 vs 264.23 events per 1000 patient years, respectively). The imbalance in pulmonary embolism was discussed in detail in Section 12.2.2 of the CSR for the rPFS analysis. Since the DCO for the rPFS analysis (04 June 2019), one additional event of pulmonary embolism was reported in the olaparib arm.

Adverse events of CTCAE Grade ≥3 were reported in 52.0% of olaparib-treated patients and 40.0% of the investigators choice of NHA-treated patients. Anaemia was the only AE of CTCAE Grade ≥3 reported in ≥5% of patients (22.7% of olaparib-treated patients vs 5.4% of investigators choice of NHA-treated patients).

The most common SAEs were anaemia in 23 (9.0%) olaparib-treated patients and urinary tract infection in 4 (3.1%) of investigators choice of NHA-treated patients. Sixteen patients had an AE with outcome of death: Three patients in the olaparib arm and 2 patients in the investigators choice of NHA arm had AEs of pneumonia which led to death, and 2 patients in the olaparib arm had AEs of cardiopulmonary failure which led to death; all other AEs leading to death occurred in one patient each. The majority of deaths were due to disease under investigation. In total, 248 patients died during the study; 160 (62.5%) in the olaparib arm and 88 (67.2%) in the investigators choice of NHA arm.

Adverse events leading to discontinuation of study treatment occurred in 19.9% of olaparib-treated patients and 8.5% of investigators choice of NHA-treated patients. The most common AE leading to discontinuation of olaparib treatment (reported in ≥5% of patients) was anaemia (20 patients [7.8%]); all other events occurred in ≤2% of patients.

Adverse events of special interest in this study were the important identified risk of myelodysplastic syndrome (MDS)/acute myeloid leukaemia (AML), and the important potential risks of new primary malignancies and pneumonitis (grouped term: pneumonitis, interstitial lung disease, and radiation pneumonitis). Since the DCO for the rPFS analysis, there were no new events of new primary malignancies or pneumonitis in either arm. One

patient (0.4%) in the olaparib arm reported an event of MDS/AML (reported term: leukemia [LMA]) that occurred after the 30-day follow-up period.

Eighty-three of the 130 patients randomised to receive investigators choice of NHA switched to olaparib after radiographic progression. The median duration of treatment of olaparib was 4.8 months. The safety and tolerability profile of olaparib in these patients was consistent with that observed in patients randomised to olaparib in PROfound.

Conclusions

As of the DCO for the final OS analysis (20 March 2020), PROfound continued to demonstrate a positive benefit/risk profile for olaparib 300 mg bd monotherapy in patients with mCRPC that have qualifying HRR gene mutations that were predicted to be deleterious or suspected deleterious (known or predicted to be detrimental/lead to loss of function) who have failed prior treatment with an NHA. This is evidenced by the following:

- In Cohort A, there was a statistically significant and clinically meaningful OS benefit in olaparib-treated patients compared with investigators choice of NHA-treated patients, with a median OS improvement of 4.4 months in the olaparib arm vs the investigators choice of NHA arm (HR=0.69; 95% CI 0.50, 0.97; p=0.0175; median OS 19.1 vs 14.7 months, respectively).
  - The OS subgroup data were generally consistent with that of the overall population in Cohort A.
  - A pre-specified sensitivity analysis of OS adjusting for investigators choice of NHA-treated patients receiving subsequent olaparib was conducted for Cohort A; the HR from this analysis was 0.42 (95% CI 0.19, 0.91) favouring olaparib treatment. These data further support the clinical benefit of olaparib seen in Cohort A and suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.
- In Cohort B, the HR numerically favoured olaparib vs the investigators choice of NHA arm and suggested no detriment for OS in olaparib-treated patients (HR=0.96; 95% CI 0.63, 1.49), with a median OS improvement of 2.6 months in the olaparib arm vs the investigators choice of NHA arm (median OS 14.1 vs 11.5 months, respectively).
  - A pre-specified sensitivity analysis of OS adjusting for investigators choice of NHA-treated patients receiving subsequent olaparib was conducted for Cohort B; the HR from this analysis was 0.83 (95% CI 0.11, 5.98) favouring olaparib treatment. These data further support the clinical benefit of olaparib seen in Cohort B and suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.
  - An ad hoc subgroup analysis of OS excluding patients with a mutation in the *PPP2R2A* gene only was conducted for Cohort B; the HR from this analysis was 0.83 (95% CI 0.54, 1.31), favouring olaparib treatment.
- In Cohort A+B, there was a trend for OS benefit in olaparib-treated patients compared to investigators choice of NHA-treated patients, with a median OS improvement of

3.3 months in the olaparib arm vs the investigators choice of NHA arm (HR=0.79; 95% CI 0.61, 1.03; median OS 17.3 vs 14.0 months, respectively).

  - The OS subgroup data were generally consistent with that of the overall population in Cohort A+B.
  - A pre-specified sensitivity analysis of OS adjusting for investigators choice of NHA-treated patients receiving subsequent olaparib was conducted for Cohort A+B; the HR from this analysis was 0.55 (95% CI 0.29, 1.06), favouring olaparib treatment. These data further support the clinical benefit of olaparib seen in Cohort A+B and suggest that the true effect of olaparib is likely to be greater than observed in the unadjusted final OS analysis.
  - An ad hoc subgroup analysis of OS excluding patients with a mutation in the *PPP2R2A* gene only was conducted for Cohort A+B; the HR from this analysis was 0.75 (95% CI 0.58, 0.98), favouring olaparib treatment.

- The olaparib safety and tolerability profile in this study was consistent with that observed at the DCO for the rPFS analysis (04 June 2019) and in previous studies of olaparib.